Berek & Novak's Gynecology

SIXTEENTH EDITION



Wolters Kluwer

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To Deborah—together in life and in print.

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FOREWORD

Emil Novak of Johns Hopkins University School of Medicine and Hospital edited the ***Textbook of Gynecology***, which was first published in 1941, and remained the standard in the field for many years thereafter. The 14th edition of that landmark text, published in 2007, was given a new title, ***Berek and Novak's Gynecology***, honoring both Dr. Jonathan S. Berek and the late Dr. Novak, whose significant contributions sustained and, where necessary, recalibrated the work through several previous editions, thereby preserving its vitality and relevance for new generations of physicians. The book retains its prominence as one of the major comprehensive textbooks in the discipline, a status it is certain to maintain in the 16th edition.

For this 16th edition, Dr. Berek again assembled an impressive array of contributors—clinicians and researchers, leaders in their respective fields—who bring insightful knowledge and valuable perspectives to their respective areas of expertise. The result is a comprehensive treatment of current practice—but with an eye toward future developments—in the science and practice of gynecology and its related subspecialties. Innovative developments in research and clinical practice are treated in detail. For example, in keeping with the expansion of one gynecologic subspecialty the section on Urogynecology with its chapters on the urinary tract, prolapse, and anorectal are necessary reading for comprehension of this discipline. The substantially expanded field of minimally invasive gynecologic surgery is covered thoroughly in the chapters dealing with endoscopy, hysterectomy, and robotics. Not surprising, given Dr. Berek's reputation as a leader and innovator in gynecology and gynecologic oncology, this textbook indisputably remains the definitive encyclopedia on that subject. The basic science section is intertwined beautifully with the principles of practice, promoting an understanding of the many changes in clinical medicine in recent years. Compassion and sensitivity are evident throughout the work, especially in the sections dealing with sexuality and related sexual issues. In keeping with sensitivity, the chapter on violence toward women is critical for the care of women and it has now become an even greater responsibility of ours.

The traditional areas of gynecology are presented in an exciting format with all the information the practicing gynecologist requires in order to provide excellent patient care. Another attractive feature is that it is published with substantial full-color

illustrations and graphics that greatly enhance the readability and accessibility of the material.

Practitioners of the medical specialty of gynecology, both clinicians and researchers, are wholly dedicated to the care and well-being of women. As both a teaching tool and reference, this new edition of ***Berek and Novak's Gynecology*** will prove to be, as previous editions were, an invaluable asset to them as they ply their important work.

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PREFACE

The first edition of ***Novak's Textbook of Gynecology***, written by the distinguished Dr. Emil Novak of Johns Hopkins, became an essential international reference for the practice of gynecology. This 16th edition is the carefully nurtured descendant of that book and retains the useful format of my four previous editions of the text, enhanced by full-color illustrations and photographic reproductions.

As with the prior editions, the goal is to provide a comprehensive summary of the specialty of gynecology. All chapters were thoroughly revised to provide timely information and references. The illustrations and photographs were updated and made more accessible and informative.

This textbook, originated by the faculty of the Johns Hopkins University School of Medicine, continues to reflect the contributions of that great institution. After the 5th edition and the subsequent death of Dr. Novak in 1957, many physicians from Johns Hopkins, and some members of the Vanderbilt faculty, helped carry the torch—Dr. Edmund R. Novak through the ninth edition in 1979; Drs. Howard W. Jones, Jr. and Georgeanna Seegar Jones through the 10th edition in 1981; and Drs. Howard W. Jones, III, Lonnie S. Burnett, and Anne Colston Wentz through the 11th edition in 1988. These editors, assisted by contributors from the faculty at Johns Hopkins, especially Drs. J. Donald Woodruff and Conrad G. Julian, helped define the specialty of gynecology during the latter half of the 20th century and shaped the practice of gynecology as we know it today—its surgical and medical therapies, reproductive endocrinology, assisted reproductive technologies, gynecologic oncology, urogynecology, and infectious diseases. As a graduate of Johns Hopkins University School of Medicine, I am honored to contribute to that rich tradition.

Berek & Novak's Gynecology, 16th edition, is presented in eight sections. The first section, General Principles, includes the initial assessment of the gynecologic patient, her medical history and physical examination, and techniques to improve physician communication skills. This section addresses ethical principles of patient care, quality assessment and improvement, clinical research, and the epidemiology of gynecologic conditions, with chapters that summarize the scientific basis for the specialty—anatomy and embryology, molecular biology and genetics, and reproductive physiology. The

second section, Gynecology Topics, covers puberty, pediatric and adolescent gynecology, adult gynecology, chapters on benign diseases of the female reproductive tract—the evaluation of pelvic infections, uterine fibroids, pain, intraepithelial diseases, the function of the female reproductive tract from puberty through menopause, and the evaluation of benign breast disease. A new chapter on a sensitive and consequential topic appears in this section—violence against women and sexual assault. The third section, Primary Medical Care, emphasizes the importance of primary health care for women: preventive care and screening, and psychiatric care and complementary medicine. The fourth section, Operative Gynecology, covers perioperative care and the operative management of benign gynecologic conditions using endoscopy, hysterectomy, and robotics. The fifth section, Urogynecology, contains chapters on the urinary tract, prolapse, and anorectal problems. The sixth section, Early Pregnancy Issues, includes the management of early pregnancy loss and ectopic pregnancy. The seventh section, Reproductive Endocrinology and Infertility, summarizes the management of amenorrhea, major endocrine disorders, and infertility. The eighth section, Gynecologic Oncology, covers malignant diseases of the female reproductive tract and breast cancer.

I am especially grateful to my talented content editor, Deborah Berek, who diligently evaluated and assisted the entire project from the initial manuscripts through page proofs. I appreciate the many people at Lippincott Williams & Wilkins who helped me, especially Charley Mitchell, whom I consider the best editor in medical book publishing and with whom I worked for more than a quarter of a century. I gratefully acknowledge the many individuals who contributed to this book and extend my gratitude to Ashley Fischer and Kayla Smull for their dedication and commitment to enthusiastically and skillfully shepherd the manuscript during the editorial process. I acknowledge the outstanding work of Chris Miller at Aptara who diligently and expertly worked with me to accomplish the final page layout and formatting of this book. I offer my admiration and thanks to Tim Hengst, an outstanding medical illustrator, for the excellent illustrations, anatomic drawings, and thematic designs for all the editions under my guidance. I acknowledge the invaluable support of my mentors—Dean Sherman Mellinkoff, Drs. J. Donald Woodruff, Kenneth J. Ryan, J. George Moore, and William J. Dignam—and I extend my gratitude to my colleagues Drs. Isaac Schiff, Beverly Mitchell, and Dean Emeritus Philip Pizzo. Each of these physicians and scholars graciously provided essential guidance and encouragement. My special thanks to Laurie Lacob, Nicole Kidman and Keith Urban, Trisha Yearwood and Garth Brooks for their support of the Stanford Women's Cancer Center—and for the help, encouragement, and friendship that stimulated this project.

After 12 years as Chair of the Department of Obstetrics and Gynecology at the Stanford

University School of Medicine, I stepped away from the position in 2017 to pursue other academic activities at Stanford University and the Stanford University School of Medicine. The powerful generosity of spirit and commitment to causes that support women and their health guides the work of my colleagues at Stanford and has been a source of pleasure and inspiration for me. The community surrounding the university shares this commitment to improving the health and welfare of women, and I am gratified by their efforts on behalf of women and their families.

I look forward to the specialty's continued positive impact on the health of women throughout the world. It is my fervent hope that our work will benefit all women, reducing the numbers of those who are afflicted with diseases of the female reproductive tract and breast, preserving their ability to participate in their families and communities. To that end, this book is offered as a resource to assist and encourage all who study the specialty of gynecology.

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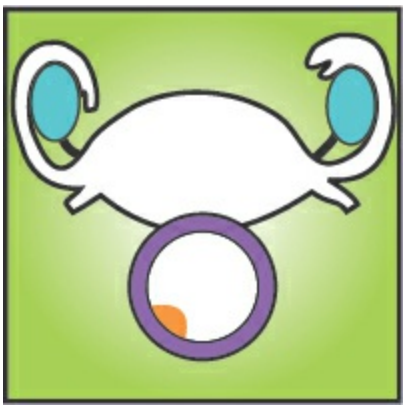
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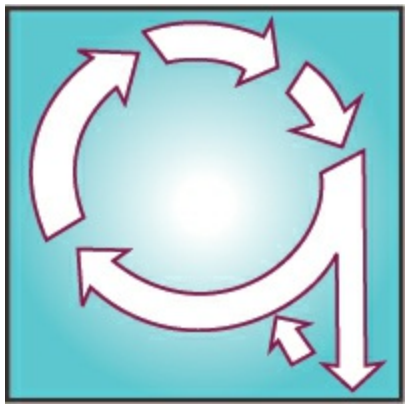
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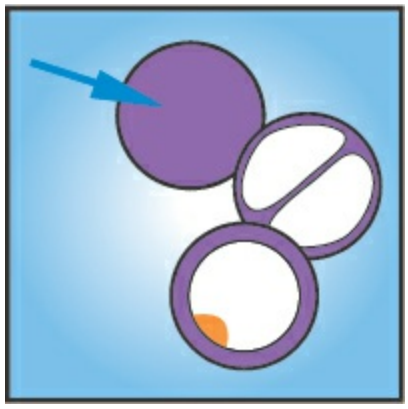
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CHAPTER 1

Initial Assessment and Communication



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Summary

KEY POINTS

1 We are all products of our environment, our background, and our culture. The importance of ascertaining the patient's general, social, and familial situation cannot be overemphasized. The physician should avoid being judgmental, particularly with respect to questions about sexual practices, gender identity, and sexual orientation.

2 Good communication is essential to patient assessment and treatment. The foundation of communication is based on key skills: empathy, attentive listening, expert knowledge, and rapport. These skills can be learned and refined.

3 The concepts of medical professionalism initially codified in the Hippocratic Oath demand that physicians be circumspect with all patient-related information. For physician–patient communication to be effective, the patient must feel that she is able to discuss her problems in depth and in confidence.

4 Different styles of communication may affect the physician's ability to perceive the patient's status and achieve the goal of optimal assessment and successful treatment. The intimate and highly personal nature of many gynecologic conditions requires particular sensitivity to evoke an honest response.

5 Some patients lack accurate information about their illnesses. Incomplete or inadequate understanding of an illness can produce increased anxiety, dissatisfaction with medical care, distress, coping difficulties, unsuccessful treatment, and poor treatment response.

6 After a dialogue is established, the patient assessment proceeds with obtaining a complete history and typically, performing a physical examination. Both of these aspects of the assessment rely on good patient–physician interchange and attention to details.

7 At the completion of the physical examination, the patient should be informed of the findings. When the results of the examination are normal, the patient can be reassured accordingly. When there is a possible abnormality, the patient should be informed immediately; this discussion should take place after the examination, with the patient clothed.

The practice of gynecology requires many skills. In addition to medical knowledge, the gynecologist should develop interpersonal and communication skills that promote patient– physician interaction and trust. The assessment must be of the "whole patient," rather than confined to her general medical status. It should include any apparent medical conditions and the psychological, social, and family aspects of her situation. **To view the patient in the appropriate context, environmental and cultural issues that affect the patient must be taken into account.** This approach is valuable in routine assessments, and in the evaluation of specific medical conditions, providing opportunities for preventive care and counseling on an ongoing basis.

VARIABLES THAT AFFECT PATIENT STATUS

Many external variables exert an influence on the patient and on the care she receives. Some of these factors include the patient's "significant others"—her family, friends, and personal and intimate relationships (Table 1-1). **These external variables include psychological, genetic, biologic, social, and economic issues.** Factors that affect a patient's perception of disease and pain and the means by which she has been taught to cope with illness include her education, attitudes, understanding of human reproduction and sexuality, and family history of disease (1–3). Cultural factors, socioeconomic status, religion, ethnicity, language, age, gender identity, and sexual orientation are important considerations in understanding the patient's response to her care.

Table 1-1 Variables That Influence the Status of the Patient

Patient
Age
History of illness
Attitudes and perceptions
Sexual orientation
Habits (e.g., use of alcohol, tobacco, and other drugs)
Family
Patient's status (e.g., married, separated, living with a partner, divorced)
Caregiving (e.g., young children, children with disabilities, aging parents)
Siblings (e.g., number, ages, closeness of relationship)
History (e.g., disease)
Environment
Social environment (e.g., community, social connectedness)
Economic status (e.g., poverty, insuredness)
Religion (e.g., religiosity, spirituality)
Culture and ethnic background (e.g., first language, community)
Career (e.g., work environment, satisfaction, responsibilities, stress)

We are all products of our environment, our background, and our culture. The importance of ascertaining the patient's general, social, and familial situation cannot be overemphasized (4,5). Cultural sensitivity may be particularly important in providing reproductive health care (6).

[1] The context of the patient's support system and family can and should be ascertained directly. The family history should include a careful analysis of those who had significant illnesses, such as cancer or an illness that the patient perceives to be a potential explanation for her own symptoms. The patient's perspective of her illness can provide important information that guides the physician's judgment; specific questioning to elicit this perspective can improve satisfaction with the interaction (4,7). The patient's understanding of key events in the family medical history and how they relate to her is important. The patient's sexual history, sexual orientation, relationships, and practices should be understood, and her functional level of satisfaction in these areas should be determined. **The physician should avoid being judgmental, particularly**

with respect to questions about sexual practices, gender identity, and sexual orientation (see Chapter 17).

COMMUNICATION

[2] Good communication is essential to patient assessment and treatment. The patient–physician relationship is based on communication conducted in an open, honest, and careful manner that allows the patient's situation and problems to be accurately understood and effective solutions developed collaboratively. Good communication requires patience, dedication, and practice and involves careful listening and attention to verbal and nonverbal communication.

The foundation of communication is based on four key skills: empathy, attentive listening, expert knowledge, and the ability to establish rapport. These skills can be learned and refined (4,5,8). When the initial relationship with the patient is established, the physician must vigilantly pursue interviewing techniques that continue to create opportunities to foster an understanding of the patient's concerns. Trust is the fundamental element that encourages open communication of the patient's feelings, concerns, and thoughts, rather than withholding information (9).

One very basic element of communication—sharing a common language and culture—may be missing when a clinician interacts with a patient of limited or no English proficiency. Language concordance between the physician and patient is assumed in many discussions of communication. More than 21% of Americans speak a language other than English at home, and of these 41% reported to the Census Bureau that they speak English less than very well (10). Language barriers are associated with limited health literacy, compromised interpersonal care, and lower patient satisfaction in health care encounters (11,12). While language-concordant health care professionals are optimal, in-person medical interpreters can mitigate these effects; video and telephonic interpretation provide technologic solutions that help mitigate communication challenges with individuals of limited English proficiency (13). The State of California recognized the importance of communication in patient–physician interactions through a provision in the Health and Safety Code that states "where language or communication barriers exist between patients and the staff of any general acute care hospital, arrangements shall be made for interpreters or bilingual professional staff to ensure adequate and speedy communication between patients and staff" (14). Training future physicians to work with interpreters is receiving increasing attention in US medical schools and will contribute to improved clinical practice and reduce health care disparities (15).

[3] Although there are many styles of interacting with patients, each physician must determine and develop the best way that she or he can relate to patients. Physicians must convey that they are able and willing to listen and that they receive the information with

utmost confidentiality (1,4). **The concepts of medical professionalism initially codified in the Hippocratic Oath demand that physicians be circumspect with all patient-related information.** The Health Insurance Portability and Accountability Act (HIPAA), which took effect in 2003, established national standards intended to protect the privacy of personal health information. Initial fears expressed about the impact of HIPAA regulations and the potential for legal liability led to discussions of appropriate communication and physicians' judgments based on the ethical principles of confidentiality in providing good medical care (16,17) (see Chapter 2).

Communication Skills

It is essential for the physician to communicate with a patient in a manner that allows her to continue to seek appropriate medical attention. The words used, the patterns of speech, the manner in which words are delivered, even body language and eye contact, are all important aspects of the patient–physician interaction. The traditional role of the physician was paternalistic, with the physician expected to deliver direct commands or "orders" and specific guidance on all matters (5). Now patients appropriately demand and expect more balanced communication with their physicians. Although they may not have equivalent medical expertise, they do expect to be treated with appropriate deference, respect, and a manner that acknowledges their personhood as equal to that of the physician. Doctor–patient communication is receiving more attention in medical education and is being recognized as a major task of lifelong professional learning and a key element of successful health care delivery (18).

Patients with rare or unusual conditions sometimes have more specific medical knowledge of a given medical problem than the physician does. When this is the case, the physician must avoid reacting defensively. A 2013 poll indicated that one-third of Americans had researched symptoms or diagnoses online; 46% of those individuals reported that their online research led them to seek medical care, while 38% decided to manage their suspected health conditions without consulting a clinician (19). The patient often lacks broader knowledge of the context of the problem, awareness of the variable reliability of electronic sources of information, the ability to assess a given study or journal report within a historical context or in comparison with other studies on the topic, knowledge of drug interactions, an ability to maintain objective intellectual distance from the topic, or essential experience in the art and science of medicine. The physician possesses these skills and extensive knowledge, whereas the patient has an intensely focused personal interest in her specific medical condition. Surveys of physicians' perceptions of the impact of Internet-based health information on the doctor–patient relationship found positive and negative perceptions; physicians express concerns about a hindrance to efficient time management during an office visit, but a positive perception of the potential effects on the quality of care and patient outcomes

(20). **A collaborative relationship that allows patients greater interactive involvement in the doctor–patient relationship can potentially lead to better health outcomes** (21–23).

Physician–Patient Interaction

The pattern of the physician's speech can influence interactions with the patient. Some important components of effective communication between patients and physicians are presented in Table 1-2. There is evidence that scientifically derived and empirically validated interview skills can be taught and learned, and conscientious use of these skills can result in improved outcomes (24). A list of such skills is found in Table 1-3.

[3] For physician–patient communication to be effective, the patient must feel that she is able to discuss her problems in depth and in confidence. Time constraints imposed by the pressures of office scheduling to meet economic realities make this difficult; both the physician and the patient frequently need to reevaluate their priorities. If the patient perceives that she participates in decision making and that she is given as much information as possible, she will respond to the mutually derived treatment plan with lower levels of anxiety and depression, embracing it as a collaborative plan of action. She should be able to propose alternatives or modifications to the physician's recommendations that reflect her own beliefs and attitudes. There is ample evidence that patient communication, understanding, and treatment outcomes are improved when discussions with physicians are more dialogue than lecture. When patients feel they have some room for negotiation, they tend to retain more information regarding health care recommendations. The concept of collaborative planning between patients and physicians is embraced as a more effective alliance than the previous model in which physicians issued orders. The patient thus becomes more vested in the process of determining health care choices. For example, decisions about the risks and benefits of menopausal hormone therapy must be discussed in the context of an individual's health and family history, including her personal beliefs and goals. The woman decides whether the potential benefits outweigh the potential risks, and she is the one to determine whether or not to use such therapy. Whereas most women prefer shared decision making in the face of uncertainty, with an evidence-based discussion of her risks and benefits, others may want a more directive approach (25). **The physician's challenge is to be able to personalize the interaction and communication.**

Table 1-2 Important Components of Communication Between the Patient and Physician: The Physician's Role

The Physician Is:
A good listener

Empathetic
Compassionate
Honest
Genuine
Respectful
Fair
Facilitative
The Physician Uses:
Understandable language
Appropriate body language
A collaborative approach
Open dialogue
Appropriate emotional content
Humor and warmth
The Physician Is Not:
Confrontational
Combative
Argumentative
Condescending
Overbearing
Dogmatic
Judgmental
Paternalistic

Table 1-3 Behaviors Associated With the 14 Structural Elements of the Interview[a]

Preparing the Environment
Create privacy
Eliminate noise and distractions
Provide comfortable seating at equal eye level

Provide access
Preparing Oneself
Eliminate distractions and interruptions
Focus
Self-hypnosis
Meditation
Constructive imaging
Let intrusive thoughts pass through
Observation
Create a personal list of categories of observation
Practice in a variety of settings
Notice physical signs
Presentation
Affect
What is said and not said
Greeting
Create a personal stereotypical beginning
Introduce oneself
Check the patient's name and how it is said
Create a positive social setting
Introduction
Explain one's role and purpose
Check the patient's expectation
Negotiate about differences in perspective
Be sure expectations are congruent with the patient's
Detecting and Overcoming Barriers to Communication
Develop personal list of barriers to look for
Include appropriate language
Physical impediments such as deafness, delirium

Include cultural barriers
Recognize the patient's psychological barriers, such as shame, fear, and paranoia
Surveying Problems
Develop personal methods of initiation of problem listing
Ask "What else?" until problems are elicited
Negotiating a Priority Problem
Ask the patient for priorities
State own priorities
Establish mutual interests
Reach agreement on order of addressing issues
Developing a Narrative Thread
Develop personal ways of asking the patient to tell her story
Ask when last felt healthy
Ask about entire course of illness
Ask about recent episode or typical episode
Establishing the Life Context of the Patient
Use first opportunity to inquire about personal and social details
Flesh out developmental history
Learn about the patient's support system
Learn about home, work, neighborhood, safety
Establishing a Safety Net
Memorize complete review of systems
Review issues as appropriate to specific problem
Presenting Findings and Options
Be succinct
Ascertain the patient's level of understanding, cognitive style
Ask the patient to review and state understanding
Summarize and check
Tape record and give the tape to the patient

Ask the patient's perspectives
Negotiating Plans
Activate the patient
Agree on what is feasible
Respect the patient's choices whenever possible
Closing
Ask the patient to review plans and arrangements
Clarify what to do in the interim
Schedule next encounter
Say goodbye

[a]**Lipkin M Jr**. Physician–patient interaction in reproductive counseling. *Obstet Gynecol* 1996;88:31S–40S. Derived from **Lipkin M, Frankel RM, Beckman HB, et al.** Performing the interview. In: **Lipkin M, Putnam SM, Lazare A,** eds. *The Medical Interview: Clinical Care, Education, and Research*. New York: Springer-Verlag; 1995:65–82.

There is evidence that when patients are heard and understood, they become more vocal and inquisitive and their health improves. Participation facilitates investment and empowerment. **Good communication is essential to the maintenance of a relationship between the patient and physician that will foster ongoing care.** Health maintenance, therefore, can be linked directly to the influence of positive interactions between the physician and patient. Women who are comfortable with their physician may be more likely to raise issues or concerns and convey information about potential health risks and be more receptive to the physician's recommendations. This degree of rapport may promote the effectiveness of health interventions, including behavior modification. It helps ensure that patients return for regular care because they feel the physician is genuinely interested in their welfare and they have confidence in the quality of treatment and guidance they receive.

When patients are ill, they feel vulnerable, physically and psychologically exposed, and powerless. The physician, by virtue of his or her knowledge and status, has power that can be intimidating. It is essential that the physician be aware of this disparity and ensure that the "balance of power" does not shift too far away from the patient. Shifting it back from the physician to the patient may help improve outcomes (1,22). Physicians' behaviors can suggest that they are not respectful of the patient. Such actions as failing to maintain scheduled appointment times, routinely holding substantive discussions when the patient is undressed, or speaking to her from a standing position while she is lying down or in the lithotomy position can emphasize the imbalance of

power in the relationship.

In assessing the effects of the patient–physician interaction on the outcome of chronic illness, three characteristics associated with better health care outcomes were identified (26):

1. **An empathetic physician and a high level of patient involvement in the interview.**
2. **Expression of emotion by the patient and physician.**
3. **Provision of information by the physician in response to the patient's inquiries.**

Among patients with diabetes, these characteristics resulted in improved diastolic blood pressure and reduction of HgA1c. The best responses were achieved when an empathetic physician provided as much information and clarification as possible, responded to the patients' questions openly and honestly, and expressed a full range of emotions, including humor. Responses improved when the relationship was not dominated by the physician (26).

Studies of gender and language have shown that men tend to dominate conversations, interrupt more frequently, and control the topics of the conversation (27). As a result, male physicians may tend to take control, and this imbalance of power may be magnified in the field of obstetrics and gynecology, in which all the patients are women. Male physicians may be more assertive than female physicians. Men's speech tends to be characterized by interruptions, command, and lectures, and women's speech is characterized by silence, questions, and proposals (27,28). Some patients may feel more reticent in the presence of a male physician, whereas others may be more forthcoming with a male than a female physician (29). Women's preference for a male or female physician may be based on gender as well as experience, age, competency, communication styles, and other skills (30–32). Although these generalizations clearly do not apply to all physicians, they can raise awareness about the various styles of communication and how they shape the physician–patient relationship (28). These patterns indicate that **[4] all physicians, regardless of their gender, need to be attentive to their style of speech because it may affect their ability to elicit open and candid responses from their patients** (33,34). Women tend to express their feelings in order to validate, share, and establish an understanding of their concerns or establish a shared understanding of their concerns (27,35).

Different styles of communication may affect the physician's ability to perceive the patient's status and to achieve the goal of optimal assessment and successful treatment. The intimate and highly personal nature of many gynecologic conditions requires particular sensitivity to evoke an honest patient response.

Style

The art of communication and persuasion is based on mutual respect and fosters the development of the patient's understanding of the circumstances of her health. Insight is best achieved when the patient is encouraged to question her physician and not pressured to make decisions. Patients who feel "backed into a corner" have the lowest compliance with recommended treatments (36).

Following are techniques to help achieve rapport with patients:

1. **Use positive language (e.g., agreement, approval, and humor)**.
2. **Build a partnership (e.g., acknowledgment of understanding, asking for opinions, paraphrasing, and interpreting the patient's words).**
3. **Ask rephrased questions.**
4. **Give complete responses to the patient's questions.**

The manner in which a physician guides a discussion with a patient will determine the patient's level of understanding and her ability to successfully complete therapy. The term *compliance* has long been used in medicine; it suggests that the patient will follow the physician's recommendations or "orders." The term is criticized as being overly paternalistic; an alternative term, *adherence* to therapy, is preferable (37,38). This term still implies that the physician will dictate the therapy. A more collaborative approach is suggested by the phrase *successful use* of therapy, which can be credited mutually to the physician and the patient. With this phrase, the ultimate success of the therapy appropriately accrues to the patient (39). If a directive is given to take a prescribed medication without a discussion of the rationale for its use, patients may not comply, particularly if the instructions are confusing or difficult to follow. Barriers to adherence may result from practical considerations: Nearly everyone finds a four times daily (qid) regimen more difficult than daily use. A major factor in successful use is the simplicity of the regimen (40,41). Practical factors that affect successful use include financial considerations, insurance coverage, and literacy (42). A discussion and comprehension of the rationale for therapy, along with the potential benefits and risks, are necessary components of successful use; but they may not be sufficient in the face of practical barriers. The specifics of when and how to take medication, including what to do when medication is missed, have an impact on successful use. Positive physician–patient communication is correlated with patient adherence to medical advice (43).

[7] The presentation style of the information is key to its effectiveness. As noted, the physician should establish a balance of power in the relationship, including conducting serious discussions about diagnosis and management strategies when the patient is fully clothed and face-to-face with the physician in a private room. Body language is important during interactions with patients. The physician should avoid an

overly casual manner, which can communicate a lack of respect or compassion. The patient should be viewed directly and spoken to with eye contact so that the physician is not perceived as "looking off into the distance."

Laughter and Humor

Humor is an essential component that promotes open communication. It can be either appropriate or inappropriate. Appropriate humor allows the patient to diffuse anxiety and understand that (even in difficult situations) laughter can be healthy (44,45). Inappropriate humor would horrify, disgust, offend, or generally make a patient feel uncomfortable or insulted. Laughter can be used as an appropriate means of relaxing the patient and making her feel better.

Laughter is a "*metaphor for the full range of the positive emotions.*" It is the response of human beings to incongruities and one of the highest manifestations of the cerebral process. It helps to facilitate the full range of positive emotions—love, hope, faith, the will to live, festivity, purpose, and determination (44). Laughter is a physiologic response, a release that helps us feel better and allows us to accommodate the collision of logic and absurdity. Illness, or the prospect of illness, heightens our awareness of the incongruity between our existence and our ability to control the events that shape our lives and our outcomes. We use laughter to combat stress, and stress reduction is an essential mechanism used to cope with illness.

Table 1-4 Importance Attached to the Patient–Physician Relationship[a]

Rank	Physicians' Support Services	Always or Often (%)	Rarely or Never (%)
1	Answering the patient's questions about the disease and its treatment, side effects, and possible outcomes	99	1
2	Making sure that the patient clearly understands the explanation of the medical treatment procedures	99	1
3	Encouraging the patient to develop an attitude of hope and optimism concerning treatment outcome	95	5
4	Adjusting treatment plans to enhance compliance when the patient exhibits noncompliance	88	12
5	Directly counseling family members	87	13
6	Continuing to serve as primary physician when the patient receives supplementary treatment at another facility	85	15
7	Providing referral to social support groups	83	17
8	Providing the patient with educational materials	81	19
9	Helping the patient develop methods to improve the quality of his or her life	74	26
10	Assisting the patient in determining which of his or her coping mechanisms are most productive and helping to activate them	62	38
11	Providing referral to psychological counseling services	57	43

[a]Results of a physician survey of 649 oncologists in regard to patient–physician communication.

Modified from **Cousins N.** *Head First: The Biology of Hope and the Healing Power of the Human Spirit.* New York: Penguin Books; 1989:220, with permission.

Strategies for Improving Communication

All physicians should appreciate the importance of the art of communication during the medical interview. It is essential that interactions with patients are professional, honorable, and honest. Issues that were reported to be important to physicians regarding patient–physician interactions are presented in Table 1-4. Similarly, patients suggested the importance of many of these same issues in facilitating participatory decision making (46).

Following are some general guidelines that can help improve communication:

1. **Listen more and talk less.**
2. **Encourage the pursuit of topics introduced by and important to patients.**
3. **Minimize controlling speech habits such as interrupting, issuing commands, and lecturing.**
4. **Seek out questions and provide full and understandable answers.**
5. **Become aware of any discomfort that arises in an interview, recognize when it originates in an attempt by the physician to take control, and redirect that attempt.**
6. **Assure patients that they have the opportunity to discuss their problem fully.**
7. **Recognize when patients may be seeking empathy and validation of their feelings rather than a solution. Sometimes all that is necessary is to be there as a compassionate human being.**

In conducting interviews, it is important for the physician to understand the patient's concerns. Given the realities of today's busy office schedules, an additional visit may be required to discuss some issues in sufficient depth. In studies of interviewing techniques it was shown that although clinicians employ many divergent styles, the successful ones tend to look for "windows of opportunity" (i.e., careful, attentive listening with replies or questions at opportune times). This communication skill is particularly effective for exploring psychological and social issues during brief interviews. The chief skill essential to allow the physician to perceive problems is the ability to listen attentively.

An interview that permits maximum transmission of information to the physician is best achieved by the following approach (9):

1. **Begin the interview with an open-ended question.**
2. **As the patient begins to speak, pay attention to her answers, her emotions, and her general body language.**
3. **Extend a second question or comment, encouraging the patient to talk.**
4. **Allow the patient to respond without interrupting, perhaps by employing silence, nods, or small facilitative comments, encouraging the patient to talk while the**

physician is listening.

5. **The physician should periodically summarize his or her understanding of the history to confirm accuracy.**
6. **Expressions of empathy and understanding at the completion of the interview along with a summary of the planned assessments and recommendations will facilitate the closure of the interview.**

Attentiveness, rapport, and collaboration characterize good medical interviewing techniques. Open-ended questions (*"How are you doing?" "How are things at home?" "How does that make you feel?"*) are generally desirable, particularly when they are coupled with good listening skills (47).

Premature closure of an interview and an inability to get complete information from the patient may occur for several reasons. They may result from failure to recognize the patient's particular concern, from not providing appropriate opportunity for discussion, from the physician's discomfort with sharing the patient's emotion, or perhaps from the physician's lack of confidence that he or she can deal with the patient's concern. One of the principal factors undermining the success of the interview is lack of time. This is a realistic concern perceived by physicians, but skilled physicians can facilitate considerable interaction even in a short time by encouraging open communication.

[5] Some patients lack accurate information about their illnesses. Incomplete or inadequate understanding of an illness can produce dissatisfaction with medical care and increased anxiety, distress, and coping difficulties, resulting in unsuccessful treatment and poor treatment response. As patients increasingly request more information about their illnesses and more involvement in decisions about their treatment, and as physicians attempt to provide more open interactive discussions, there is an even greater need to provide clear and effective communication. Although patients vary in their intellectual abilities, medical sophistication, anxiety, denial, and the ability to communicate, the unfortunate occurrence of impaired patient comprehension can be the product of poor physician communication techniques, lack of consultation time, and in some cases, the withholding of information considered detrimental to patient welfare.

If clinical findings or confirmatory testing strongly suggests a serious condition (e.g., malignancy), the gravity and urgency of this situation must be conveyed in a manner that does not unduly alarm or frighten the individual. Honest answers should be provided to any specific questions the patient may want to discuss (48).

Allowing time for questions is important, and scheduling a follow-up visit to discuss treatment options after the patient has an opportunity to consider the options and recommendations is often valuable. The patient should be encouraged to bring a partner or family member with her to provide moral support, serve as another

listener to absorb and digest the discussion, and assist with questions. The patient should be encouraged to write down any questions or concerns she may have and bring them with her to a subsequent visit; important issues may not come to mind easily during an office visit. If the patient desires a second opinion, it should always be facilitated. Physicians should not feel threatened by patient attempts to gain information and knowledge.

Valuable information can be provided by interviews with ancillary support staff and by providing pamphlets and other materials produced for patient education. Some studies demonstrated that the use of pamphlets is highly effective in promoting an understanding of the condition and treatment options. Others showed that the use of audiotapes, videotapes, or information on an Internet site has a positive impact on knowledge and can decrease anxiety.

There are numerous medical Web sites that can be accessed, although the accuracy of the information is variable and must be carefully reviewed by physicians before recommending sites to patients. Physicians should be familiar with Internet sources offering accurate information and be prepared to provide the addresses of these sites if the patient expresses interest (49).

The relationship between the patient and her physician, as with all aspects of social interaction, is subject to constant change. The state of our health is dynamic and it affects our ability to communicate with others, including conversations between patients and physicians. **Open communication between patient and physician can help achieve maximum effectiveness in the diagnosis, treatment, and compliance for all patients.**

Talk to the heart, speak to the soul.

Look to the being and embrace the figure's form.
Reach deeply, with hands outstretched.
Talk intently, to the seat of wisdom,
as life resembles grace.

Achieve peace within a fragile countenance.
Seek the comfort of the placid hour
Through joyous and free reflection
know the other side of the flesh's frame.
JSB

HISTORY AND PHYSICAL EXAMINATION

[6] After a dialogue is established, the patient assessment proceeds with obtaining a complete history and, if indicated, performing a physical examination. Both of these aspects of the assessment rely on good patient–physician interchange and attention to details. During the history and physical examination, risk factors that

may require special attention should be identified. These factors should be reviewed with the patient when developing a plan for her future care (see Chapter 21).

Depending on the setting—ambulatory office, inpatient hospitalization, or outpatient surgical center—record keeping is typically facilitated by forms or templates (increasingly, electronic templates as a component of the electronic medical record [EMR]), which provide prompts for important elements of the medical, family, and social history. One challenge is that paper forms and electronic records do not always "mesh," and these paper and electronic records may be periodically unavailable. Efforts to develop patient-held medical records are not yet widely adopted, although the increasing use of smart phones with health applications ("apps") facilitates patient record keeping of data such as blood pressure readings, medication lists, and activity records. Menstrual-cycle tracking is now part of the movement that has been termed the "quantified self" (50,51).

History

After the chief complaint and characteristics of the present illness are ascertained, the medical history of the patient should be updated. Increasingly, this information is available electronically in the EMR, but should be confirmed with the patient. The record should include her complete medical and surgical history, her reproductive history (including menstrual and obstetric history), her current use of medications (including over-the-counter and complementary and alternative medications), and a thorough family and social history.

A technique for obtaining information about the present illness is presented in Table 1-5. **The physician should consider which other members of the health care team might be helpful in completing the evaluation and providing care. Individuals who interact with the patient in the office—from the receptionists to medical assistants, nurses, advance practice nurses (nurse practitioners or nurse midwives)—can contribute to the patient's care and may provide additional information or insight or be appropriate clinicians for providing follow-up. In some teaching hospitals, residents or medical students may provide care and participate in an office setting. The role that each of these individuals plays in a given office or health care setting may not be apparent to the patient; care should be taken that each individual introduces her- or himself at the opening of the interaction and explains his or her role on the team. It may be necessary to discuss the roles and functions of each individual member of the team.** In some cases, referral to a nutritionist, physical or occupational therapist, social worker, psychologist, psychiatrist, or sex counselor would be helpful. Referral to or consultations with these clinicians and with physicians in other specialty areas should be addressed as needed. The nature of the relationship between the obstetrician-gynecologist and the patient should be clarified. Some women

have a primary clinician whom they rely on for primary care. Other women, particularly healthy women of reproductive age, consider their obstetrician-gynecologist their primary clinician. The individual physician's comfort with this role should be discussed and clarified at the initial visit and revisited periodically as required in the course of care. These issues are covered in Section III, Preventative Health Care and Primary Care (see Chapters 21 and 22). Laboratory testing for routine care and high-risk factors is presented in Chapter 21.

Physical Examination

A thorough gynecologic physical examination is typically performed at the time of the initial visit, periodically, and as needed throughout the course of treatment (Table 1-6). The extent of the physical examination during the gynecologic visit is often dictated by the patient's primary concerns and symptoms. For example, for healthy teens without symptoms who are requesting oral contraceptives before the initiation of intercourse, a gynecologic examination is not necessarily required.

Gynecologists have traditionally recommended an annual pelvic examination to screen for asymptomatic conditions, although the evidence for the utility of the screening examination has been called into question (52,53). The American College of Obstetricians and Gynecologists continues to strongly recommend an annual visit as an opportunity for a woman and her ob-gyn to discuss whether an examination is appropriate for her (54). While strongly supporting shared decision making around annual pelvic examinations for asymptomatic women, those with symptoms suggestive of gynecologic disease, including menstrual problems, vaginal discharge, incontinence, infertility, or pelvic pain, should have a pelvic examination (54). Some aspects of the examination—such as assessment of vital signs and measurement of height, weight, blood pressure, and calculation of a body mass index—should be performed routinely during most office visits. Typically, examination of the breasts and abdomen and a complete examination of the pelvis are considered to be essential parts of the gynecologic examination.

Prior to performing the female pelvic examination, and while the patient is still fully clothed, she should be questioned about previous experiences with the examination. Is this her first gynecologic examination? Have previous examinations been difficult or painful? Has she experienced past physical or sexual abuse? While attention should always be given to performing a gentle and atraumatic examination, for individuals with a past history of trauma, the gynecologic examination can trigger flashbacks or can retraumatize. Women should be informed that if the examination is too difficult for them, they can request that it be discontinued. For women who are undergoing their first gynecologic examination, it may be useful to ask what they have heard about the gynecologic examination or to state: *"Most women are nervous before their first exam,*

but afterward, most describe it as 'uncomfortable.'"

Abdominal Examination

With the patient in the supine position, an attempt should be made to encourage her to relax as much as possible. Her head should be leaned back and supported gently by a pillow so that she does not tense her abdominal muscles. Flexion of the knees may facilitate relaxation.

The abdomen should be inspected for signs of an intra-abdominal mass, organomegaly, or distention that would, for example, suggest ascites or intestinal obstruction. Auscultation of bowel sounds, if deemed necessary to ascertain the nature of the bowel sounds, should precede palpation. The frequency of intestinal sounds and their quality should be noted. In a patient with intestinal obstruction, "rushes," and the occasional high-pitched sound, can be heard. Bowel sounds associated with an ileus may occur less frequently but at the same pitch as normal bowel sounds.

Table 1-5 Technique of Taking the History of the Present Illness

1. **The technique used in taking the history of the present illness varies with the patient, the patient's problem, and the physician. Allow the patient to talk about her chief symptom.** Although this symptom may or may not represent the real problem (depending on subsequent evaluation), it is usually uppermost in the patient's mind and most often constitutes the basis for the visit to the physician.

   During the phase of the interview, establish the temporal relation of the chief symptom to the total duration of the illness. Questions such as, *"Then up to the time of this symptom, you felt perfectly well?"* may elicit other symptoms that may antedate the chief one by days, months, or years. In this manner, the patient may recall the date of the first appearance of illness.

   Encourage the patient to talk freely and spontaneously about her illness from the established date of onset. Do not interrupt the patient's account, except for minor promptings such as, *"When did it begin?"* and *"How did it begin?,"* which will help in developing the chronologic order in the patient's story.

   After the patient has furnished her spontaneous account (and before the next phase of the interview), it is useful to employ questions such as, *"What other problems have you noticed since you became ill?"* The response to this question may reveal other symptoms not yet brought forth in the interview.

   Thus, in the first phase of the interview, the physician obtains an account of the symptoms as the patient experiences them, without any bias being introduced by the examiner's direct questions. Information about the importance of the symptoms to the patient and the patient's emotional reaction to her symptoms are also revealed.

2. **Because all available data regarding the symptoms are usually not elicited by the aforementioned techniques, the initial phase of the interview should be followed by a series of direct and detailed questions concerning the symptoms described by the patient.** Place each symptom in its proper chronologic order and then evaluate each in accordance with the directions for analyzing a symptom.

   In asking direct questions about the details of a symptom, take care not to suggest the nature of

the answer. This particularly refers to questions that may be answered “yes” or “no.” If a leading question should be submitted to the patient, the answer must be assessed with great care. Subject the patient to repeated cross-examination until you are completely satisfied that the answer is not given just to oblige you.

Finally, before dismissing the symptom under study, inquire about other symptoms that might reasonably be expected under the clinical circumstances of the case. Symptoms specifically sought but denied are known as negative symptoms. These negative symptoms may confirm or rule out diagnostic possibilities suggested by the positive symptoms.

3. **The data secured by the techniques described in the first two phases of the interview should now suggest several diagnostic possibilities.** Test these possibilities further by inquiring about other symptoms or events that may form part of the natural history of the suspected disease or group of diseases.

4. **These techniques may still fail to reveal all symptoms of importance to the present illness, especially if they are remote in time and seemingly unrelated to the present problem.** The review of systems may then be of considerable help in bringing forth these data. A positive response from the patient on any item in any of the systems should lead immediately to further detailed questioning.

5. **Throughout that part of the interview concerning the present illness, consider the following factors:**

a. **The probable cause of each symptom or illness, such as emotional stress, infection, neoplasm.** Do not disregard the patient’s statements of causative factors. Consider each statement carefully, and use it as a basis for further investigation. When the symptoms point to a specific infection, direct inquiry to water, milk, and foods eaten; exposure to communicable diseases, animals, or pets; sources of sexually transmitted disease; or residence or travel in the tropics or other regions where infections are known to exist. In each of the above instances, ascertain, if possible, the date of exposure, incubation period, and symptoms of invasion (prodromal symptoms).

b. **The severity of the patient’s illness, as judged either by the presence of systemic symptoms, such as weakness, fatigue, loss of weight, or by a change in personal habits.** The latter includes changes in sleep, eating, fluid intake, bowel movements, social activities, exercise, or work. Note the dates the patient discontinued her work or took to bed. Is she continuously confined to bed?

c. **Determine the patient’s psychological reaction to her illness (anxiety, depression, irritability, fear) by observing how she relates her story as well as her nonverbal behavior.** The response to a question such as, *“Have you any particular theories about or fear of what may be the matter with you?”* may yield important clues relative to the patient’s understanding and feeling about her illness. The reply may help in the management of the patient’s problem and allow the physician to give advice according to the patient’s understanding of her ailment.

Modified with permission from **Hochstein E, Rubin AL**. *Physical Diagnosis*. New York: McGraw-Hill; 1964:9–11.

The abdomen is palpated to evaluate the size and configuration of the liver,

spleen, and other abdominal contents. Percussion prior to palpation may suggest organomegaly. Evidence of fullness or mass effect should be noted. This is particularly important in evaluating patients who may have a pelvic mass and in determining the extent of omental involvement, for example, with metastatic ovarian cancer. A fullness in the upper abdomen could be consistent with an "omental cake." All four quadrants should be carefully palpated for any evidence of mass, firmness, irregularity, or distention. A systematic approach should be used (e.g., clockwise, starting in the right upper quadrant). If there is an area of particular tenderness, the examination typically focuses on this area last. The patient should be asked to inhale and exhale during palpation of the edge of the liver. With a history of acute pain, rebound tenderness (suggesting peritoneal irritation) should be ascertained.

Table 1-6 Method of the Female Pelvic Examination

The patient is instructed to empty her bladder. She is placed in the lithotomy position (Fig. 1-1) and draped properly. The examiner's right or left hand, depending on his or her preference, is gloved. The pelvic area is illuminated well, and the examiner faces the patient. The following order of procedure is suggested for the pelvic examination:
A. **External Genitalia**
1. Inspect the mons pubis, labia majora, labia minora, perineal body, and anal region for characteristics of the skin, distribution of the hair, contour, and swelling. Palpate any abnormality.
2. Separate the labia majora with the index and middle fingers of the gloved hand and inspect the epidermal and mucosal characteristics and anatomic configuration of the following structures in the order indicated below:
a. Labia minora
b. Clitoris
c. Urethral orifice
d. Vaginal outlet (introitus)
e. Hymen
f. Perineal body
g. Anus
3. If disease of the Skene glands is suspected, palpate the gland for abnormal excretions by milking the undersurface of the urethra through the anterior vaginal wall. Examine the expressed excretions by microscopy and cultures. If there is a history of labial swelling, palpate for a diseased Bartholin gland with the thumb on the posterior part of the labia majora and the index finger in the vaginal orifice. In addition, sebaceous cysts, if present, can be felt in the labia minora.
B. **Introitus**

With the labia still separated by the middle and index fingers, instruct the patient to bear down. Note the presence of the anterior wall of the vagina when a cystocele is present or bulging of the posterior wall when a rectocele or enterocele is present. Bulging of both may accompany a complete prolapse of the uterus.

The supporting structure of the pelvic outlet is evaluated further when the bimanual pelvic examination is done.

C. **Vagina and Cervix**

Inspection of the vagina and cervix using a speculum should always precede palpation.

The instrument should be warmed with tap water—not lubricated—if vaginal or cervical smears are to be obtained for the test or if cultures are to be performed.

Select the proper size of speculum **(Fig. 1-2)**, warmed and lubricated (unless contraindicated). Introduce the instrument into the vaginal orifice with the blades oblique, closed, and pressed against the perineum. Carry the speculum along the posterior vaginal wall, and after it is fully inserted, rotate the blades into a horizontal position and open them. Maneuver the speculum until the cervix is exposed between the blades. Gently rotate the speculum around its long axis until all surfaces of the vagina and cervix are visualized.

1. Inspect the vagina for the following:
    a. The presence of blood
    b. Discharge. This should be studied to detect trichomoniasis, monilia, and clue cells and to obtain cultures, primarily for gonococci and chlamydia.
    c. Mucosal characteristics (i.e., color, lesions, superficial vascularity, and edema). The lesion may be:
        i. Inflammatory—redness, swelling, exudates, ulcers, vesicles
        ii. Neoplastic
        iii. Vascular
        iv. Pigmented—bluish discoloration of pregnancy (Chadwick sign)
        v. Miscellaneous (e.g., endometriosis, traumatic lesions, and cysts)
    d. Structural abnormalities (congenital and acquired)
2. Inspect the cervix for the same factors listed above for the vagina. Note the following comments relative to the inspection of the cervix:
    a. Unusual bleeding from the cervical canal, except during menstruation, merits an evaluation for cervical or uterine neoplasia.
    b. Inflammatory lesions are characterized by a mucopurulent discharge from the os and redness, swelling, and superficial ulcerations of the surface.
    c. Polyps may arise either from the surface of the cervix projecting into the vagina or from the cervical canal. Polyps may be inflammatory or neoplastic.
    d. Carcinoma of the cervix may not dramatically change the appearance of the cervix or may appear as lesions similar in appearance to an inflammation. Therefore, a biopsy should be

performed if there is suspicion of neoplasia.

D. **Bimanual Palpation**

The pelvic organs can be outlined by bimanual palpation; the examiner places one hand on the lower abdominal wall and the finger(s) (one or two) (see **Fig. 1-3**) of the other hand in the vagina (or vagina and rectum in the rectovaginal examination) (see **Fig. 1-4**). Either the right or left hand may be used for vaginal palpation. The number of fingers inserted into the vagina should be based on what can comfortably be accommodated, the size and pliability of the vagina, and the weight of the patient. For example, adolescent, slender, and older patients might be best examined with a single-finger technique.

1. Introduce the well-lubricated index finger and, in some patients, both the index and the middle finger into the vagina at its posterior aspect near the perineum. Test the strength of the perineum by pressing downward on the perineum and asking the patient to bear down. This procedure may disclose a previously concealed cystocele or rectocele and descensus of the uterus.
   Advance the fingers along the posterior wall until the cervix is encountered. Note any abnormalities of structure or tenderness in the vagina or cervix.
2. Press the abdominal hand, which is resting on the infraumbilical area, very gently downward, sweeping the pelvic structures toward the palpating vaginal fingers.
   Coordinate the activity of the two hands to evaluate the body of the uterus for:
   a. Position
   b. Architecture, size, shape, symmetry, tumor
   c. Consistency
   d. Tenderness
   e. Mobility

   Tumors, if found, are evaluated for location, architecture, consistency, tenderness, mobility, and number.
3. Continue the bimanual palpation, and evaluate the cervix for position, architecture, consistency, and tenderness, especially on mobility of the cervix. Rebound tenderness should be noted at this time. The intravaginal fingers should then explore the anterior, posterior, and lateral fornices.
4. Place the “vaginal” finger(s) in the right lateral fornix and the “abdominal” hand on the right lower quadrant. Manipulate the abdominal hand gently downward toward the vaginal fingers to outline the adnexa.
   A normal tube is not palpable. A normal ovary (about 4 × 2 × 3 cm in size, sensitive, firm, and freely movable) is often not palpable. If an adnexal mass is found, evaluate its location relative to the uterus and cervix, architecture, consistency, tenderness, and mobility.
5. Palpate the left adnexal region, repeating the technique described previously, but place the vaginal fingers in the left fornix and the abdominal hand on the left lower quadrant.
6. Follow the bimanual examination with a rectovaginal–abdominal examination.
   Insert the index finger into the vagina and the middle finger into the rectum very gently. Place the other hand on the infraumbilical region. The use of this technique makes possible higher exploration of the pelvis because the cul-de-sac does not limit the depth of the examining finger.
7. In patients who have an intact hymen, examine the pelvic organs by the rectal–abdominal

technique.

E. **Rectal Examination**

1. Inspect the perianal and anal area, the pilonidal (sacrococcygeal) region, and the perineum for the following aspects:
    a. Color of the region (Note that the perianal skin is more pigmented than the surrounding skin of the buttocks and is frequently thrown into radiating folds.)
    b. Lesions
        i. The perianal and perineal regions are common sites for itching. Pruritus ani is usually indicated by thickening, excoriations, and eczema of the perianal region and adjacent areas.
        ii. The anal opening often is the site of fissures, fistulae, and external hemorrhoids.
        iii. The pilonidal area may present a dimple, a sinus, or an inflamed pilonidal cyst.
2. Instruct the patient to “strain down” and note whether this technique brings into view previously concealed internal hemorrhoids, polyps, or a prolapsed rectal mucosa.
3. Palpate the pilonidal area, the ischiorectal fossa, the perineum, and the perianal region before inserting the gloved finger into the anal canal.
   Note the presence of any concealed induration or tenderness in any of these areas.
4. Palpate the anal canal and rectum with a well-lubricated, gloved index finger. Lay the pulp of the index finger against the anal orifice and instruct the subject to strain downward. Concomitant with the patient’s downward straining (which tends to relax the external sphincter muscle), exert upward pressure until the sphincter is felt to yield. Then, with a slight rotary movement, insinuate the finger past the anal canal into the rectum. Examine the anal canal systematically before exploring the rectum.
5. Evaluate the anal canal for:
    a. Tonus of the external sphincter muscle and the anorectal ring at the anorectal junction.
    b. Tenderness (usually caused by a tight sphincter, anal fissure, or painful hemorrhoids).
    c. Tumor or irregularities, especially at the pectinate line.
    d. Superior aspect: Reach as far as you can. Mild straining by the patient may cause some lesions, which are out of reach of the finger, to descend sufficiently low to be detected by palpation.
    e. Test for occult blood: Examine the finger after it is withdrawn for evidence of gross blood, pus, or other alterations in color or consistency. Smear the stool to test for occult blood (guaiac).
6. Evaluate the rectum:
    a. Anterior wall
        i. Cervix: size, shape, symmetry, consistency, and tenderness, especially on manipulation
        ii. Uterine or adnexal masses

iii. Rectouterine fossa for tenderness or implants
In patients with an intact hymen, the examination of the anterior wall of the rectum is the usual method of examining the pelvic organs.

b. Right lateral wall, left lateral wall, posterior wall, superior aspect; test for occult blood

Modified with permission from **Hochstein E, Rubin AL.** *Physical Diagnosis*. New York: McGraw-Hill; 1964:342–353.

Pelvic Examination

The pelvic examination is usually performed with the patient in the dorsal lithotomy position (Fig. 1-1). The patient's feet should rest comfortably in stirrups with the edge of the buttocks at the lower end of the table so that the vulva can be readily inspected and the speculum can be inserted in the vagina without obstruction from the table. Raising the head of the examination table, if possible, may facilitate relaxation. Drapes should be placed to provide a measure of cover for the patient's legs but should be depressed over the abdomen to allow observation of the patient's expression and to facilitate communication.

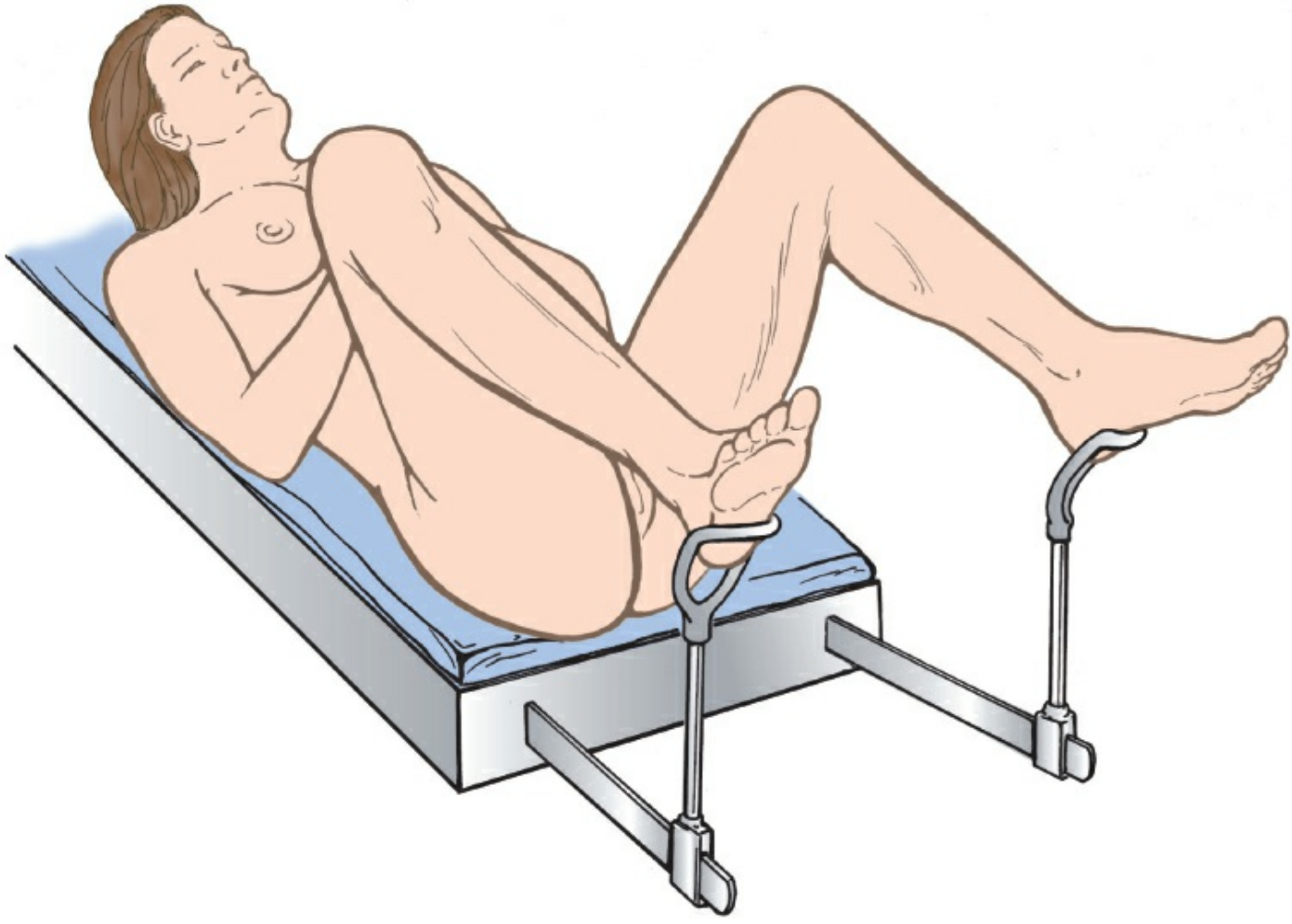


FIGURE 1-1 The lithotomy position for the pelvic examination.

Before each step of the examination, the patient should be informed of what she will feel next: "*First you'll feel me touch your inner thighs; next I'll touch the area around the outside of your vagina*." The vulva and perineal area should be carefully inspected. Evidence of any lesions, erythema, pigmentation, masses, or irregularity should be noted. The skin quality should be noted and any signs of trauma, such as excoriations or ecchymosis. Areas of erythema or tenderness are noted, particularly in women with vulvar burning or pain, as might be seen with vulvar vestibulitis or localized provoked vulvodynia. The presence of any visible lesions should be quantitated and carefully described with regard to their full appearance and characteristics on palpation (i.e., mobility, tenderness, consistency). A drawing of the location of skin lesions is helpful. Ulcerative or purulent lesions of the vulva should be evaluated and tested for infection as outlined in subsequent chapters, and biopsy should be planned for any lesions if the diagnosis is not apparent on inspection. It may be helpful to ask the patient if she is aware of any vulvar lesions and to offer a mirror to demonstrate any lesions.

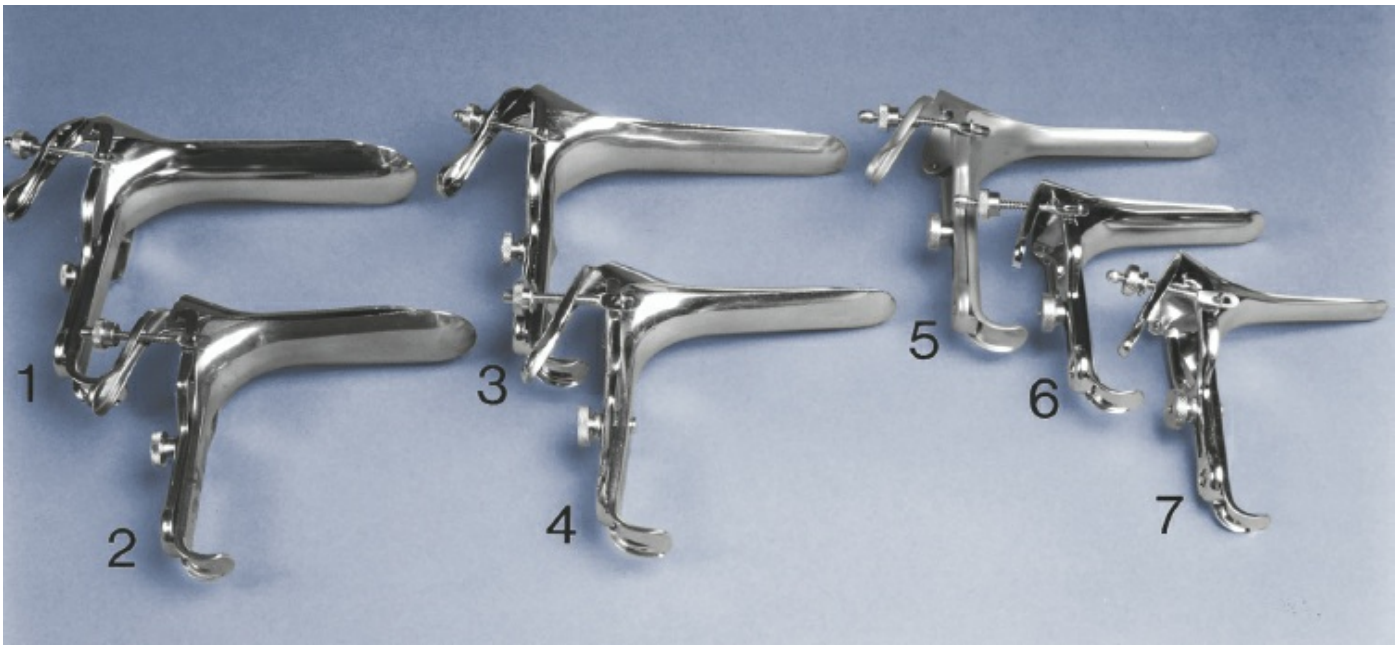


FIGURE 1-2 Vaginal specula: (*1*) Graves extra long; (*2*) Graves regular; (*3*) Pederson extra long; (*4*) Pederson regular; (*5*) Huffman "virginal"; (*6*) pediatric regular; and (*7*) pediatric narrow.

After thorough visualization and palpation of the external genitalia, including the mons pubis and the perianal area, a speculum is inserted into the vagina. In a healthy adult who is sexually active, a Pederson speculum is usually appropriate. The types of specula that are used in gynecology are presented in Figure 1-2.

The smallest-width speculum necessary to produce adequate visualization should be used. The larger Graves speculum may be required in women who have lax vaginal walls, are pregnant, or will be undergoing cervical or endometrial biopsies or

procedures. In some women, a longer speculum (either Pederson or Graves) may facilitate visualization of the cervix in a manner that is less uncomfortable to the patient. If any speculum other than the typically sized specula is used, the patient should be informed and documented in the medical record. It can be helpful to encourage the patient to remind the clinician before her next examination. The speculum should be warmed before it is inserted into the vagina; a heating pad or speculum warmer should be placed under the supply of specula. **If lubrication is required, warm water generally is sufficient or a small amount of lubricant can be used without interfering with cervical cytology testing.** The patient should be asked to relax the muscles of her distal vagina before the insertion of the speculum to facilitate the placement and to avoid startling her by this portion of the examination. After insertion, the cervix and all aspects of the vagina should be carefully inspected. Particular attention should be paid to the vaginal fornices, because lesions (e.g., warts) may be present in those areas and may not be readily visualized.

The appropriate technique and frequency for cervical cytology testing are presented in Chapter 16. **Biopsy should be performed on any obvious lesions on the cervix or in the vagina.** An endometrial biopsy usually is performed with a flexible cannula (see Chapter 10). Any purulence in the vagina or cervix should be cultured (see Chapter 15). **Testing for sexually transmitted diseases should be performed routinely in adolescents and young adults as recommended by the Centers for Disease Control and Prevention.**

After the speculum is removed, lubrication is applied to the examination glove, and **one or two (the index or index and middle) fingers are inserted gently into the vagina to palpate the uterus and adnexal areas.** In general, in right-handed physicians, the fingers from the right hand are inserted into the vagina and the left hand is placed on the abdomen to provide counter pressure as the pelvic viscera are moved **(Fig. 1-3)**. In patients with pelvic pain, a stepwise "functional pelvic examination" involves the sequential palpation of anatomic structures, including the vaginal introitus, pelvic floor muscles, bladder, rectum, cervix, and cul-de-sac. These areas are assessed for tenderness and a specific source of pain. Pelvic floor muscle spasm is a common concomitant of pelvic pain. The vagina, its fornices, and the cervix are palpated carefully for any masses or irregularities. One or two fingers are placed gently into the posterior fornix so the uterus can be moved. With the abdominal hand in place, the uterus usually can be palpated just above the surface pubis. In this manner, the size, shape, mobility, contour, consistency, and position of the uterus are determined. The patient is asked to provide feedback about any areas of tenderness, and her facial expressions are observed during the examination.

The adnexa are palpated gently on both sides, paying particular attention to any enlargements. The size, shape, mobility, and consistency of any adnexal structures

should be carefully noted.

When indicated, a rectovaginal examination should be performed to evaluate the rectovaginal septum, the posterior uterine surface, the adnexal structures, the uterosacral ligaments, and the posterior cul-de-sac. Uterosacral nodularity or posterior uterine tenderness associated with pelvic endometriosis or cul-de-sac implants of ovarian cancer can be assessed in this manner. Hemorrhoids, anal fissures, sphincter tone, rectal polyps, or rectal lesions including carcinoma may be detected. A single stool sample for fecal occult blood testing obtained in this manner is not adequate for the detection of colorectal cancer and is not recommended **(Fig. 1-4)** (55).

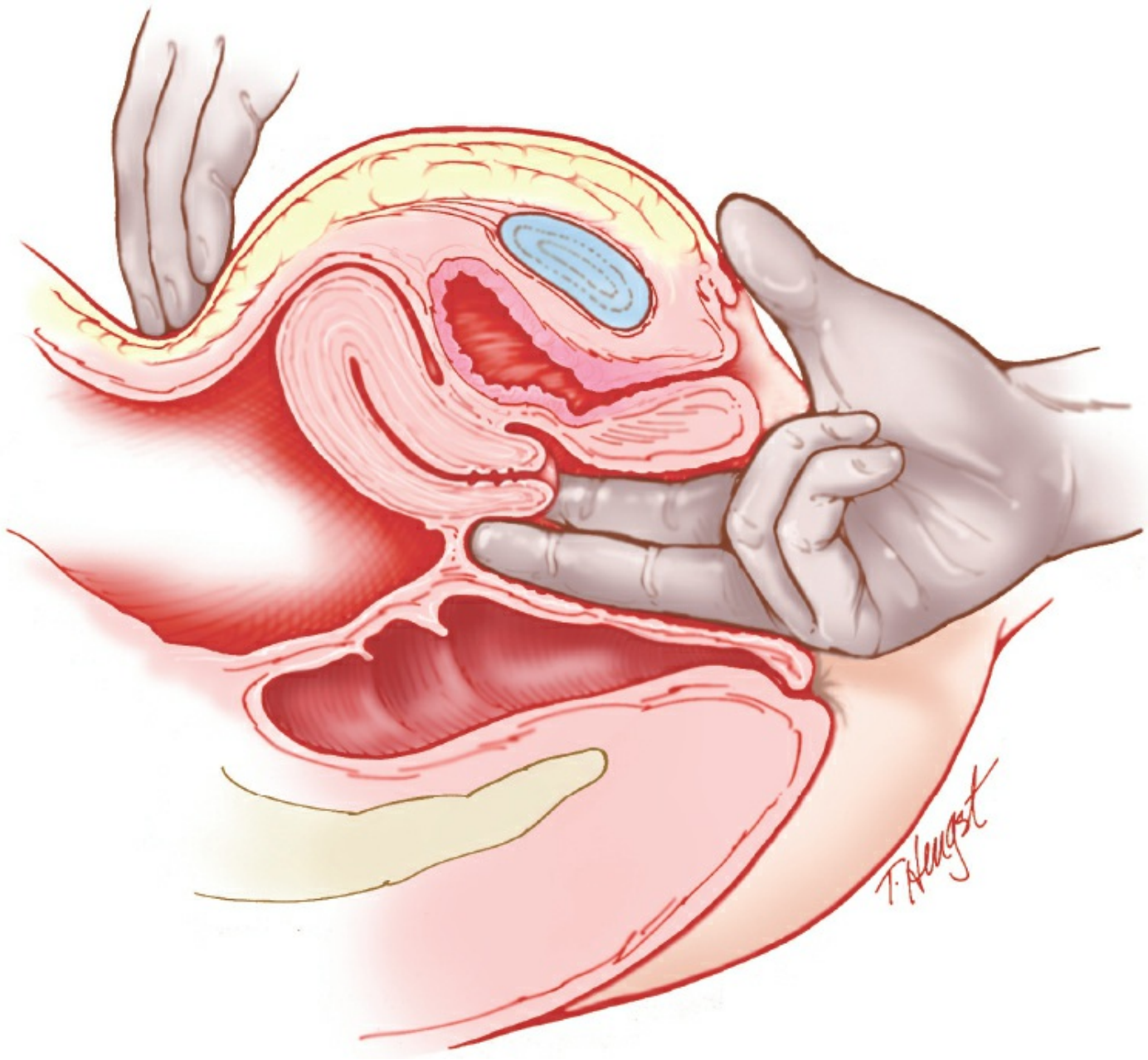


FIGURE 1-3 The bimanual examination.

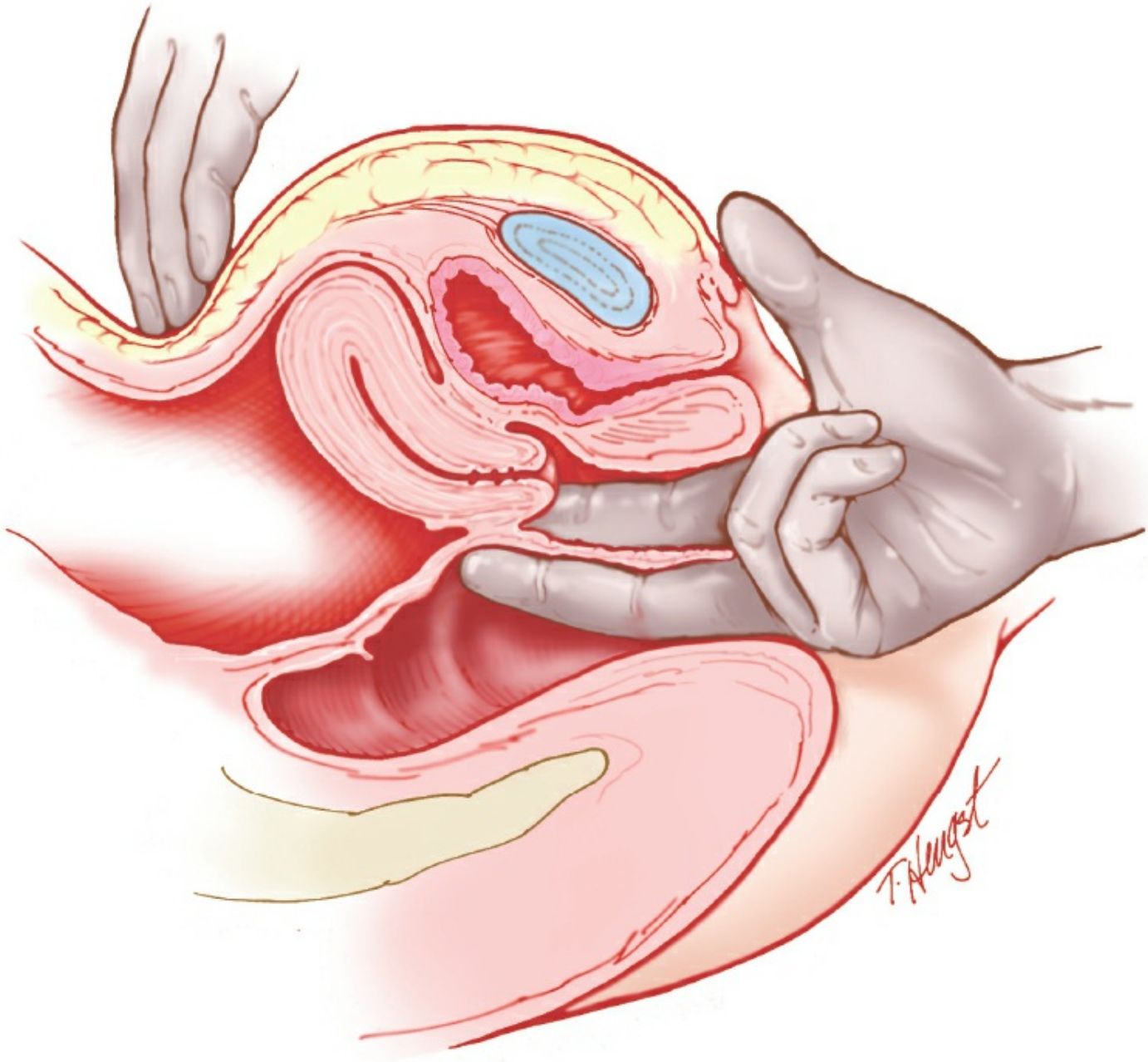


FIGURE 1-4 The rectovaginal examination.

At the completion of the physical examination, the patient should be informed of the findings. When the results of the examination are normal, the patient can be reassured accordingly. When there is a possible abnormality, the patient should be informed immediately; this discussion should take place after the examination with the patient clothed. A plan to evaluate the findings should be outlined briefly and in clear, understandable language. The implications and timing of any proposed procedure (e.g., biopsy) should be discussed, and the patient should be informed when the results of any tests will be available.

Pediatric Patients

A careful examination is indicated when a child presents with genital symptoms such as itching, discharge, burning with urination, or bleeding. The examiner should be familiar with the normal appearance of the prepubertal genitalia. The normal unestrogenized hymenal ring and vestibule can appear mildly erythematous. The technique of examination is different from that used for examining an adult and may need to be tailored to the individual child based on her age, size, and comfort with the examiner.

A speculum examination should not be performed in a prepubertal child in the office. A young child usually can be examined best in a "frog leg" or "butterfly leg" position on the examining table. Some very young girls (toddlers or infants) do best when held in their mother's arms. Sometimes, the mother can be positioned, clothed, on the examination table (feet in stirrups, head of table elevated) with the child on her lap, the child's legs straddling her mother's legs. The knee–chest position may be helpful for the examination (56). The child who is relaxed and warned about touching will usually tolerate the examination satisfactorily. An otoscope can be used to examine the distal vagina if indicated. Two percent *lidocaine* jelly may be used as a topical anesthetic to facilitate the examination if needed.

Some children who were abused, who had particularly traumatic previous examinations, or who are unable to allow an examination may need to be examined under anesthesia, although a gentle office examination should almost always be attempted first. If the child had bleeding and no obvious cause of bleeding is visible externally or within the distal vagina, an examination under anesthesia is indicated to visualize the vagina and cervix completely. A hysteroscope, cystoscope, or other endoscopic instruments can be used to provide magnification and as a light source for vaginoscopy, which should be performed under anesthesia.

Adolescent Patients

A pelvic examination may be less revealing in an adolescent than in an older woman, particularly if it is the patient's first examination or if it takes place on an emergency basis. **An adolescent who presents with excessive bleeding should have a pelvic examination if she had intercourse, if the results of a pregnancy test are positive, if she has abdominal pain, if she is markedly anemic, or if she is bleeding heavily enough to compromise hemodynamic stability.** The pelvic examination occasionally may be deferred in young teenagers who have a classic history of irregular cycles soon after menarche, who have normal hematocrit levels, who deny sexual activity, and who will reliably return for follow-up. A pelvic examination may be deferred in adolescents who present to the office requesting oral contraceptives before the initiation of intercourse or at the patient's request, even if she has had intercourse. Newer testing methods using DNA amplification techniques allow noninvasive urine testing for gonorrhea and chlamydia (57). Guidelines recommend that cervical cytology testing in

most adolescents be initiated at age 21 for virtually all young women, with the exception of those who are HIV-infected or otherwise immunocompromised (58).

Other diagnostic techniques (such as a transabdominal pelvic ultrasound) can substitute for or supplement an inadequate examination. An examination usually is required when there is a question of pelvic pain, genital anomaly, pregnancy-related condition, or possibility of pelvic infection. **The key to a successful examination in an adolescent lies in earning the patient's trust, explaining the components of her examination, performing only the essential components, and using a very careful and gentle technique.** It is helpful to ascertain whether the patient has had a previous pelvic examination, how she perceived the experience, and what she heard about a pelvic examination from her mother or friends.

Before a first pelvic examination is performed, a brief explanation of the planned examination (which may or may not need to include a speculum), instruction in relaxation techniques, and the use of *lidocaine* jelly at the vaginal introitus/ hymenal ring can be helpful. An explanation should be provided to the patient (and her mother, if the patient chooses), about the anatomy of the hymen, noting that after menarche, the hymen is elastic and typically easily distensible, and that a gynecologic examination does nothing to impact virginity (59). The patient should be encouraged to participate in the examination by voluntary relaxation of the introital muscles or by using a mirror if she wishes. If significant trauma is suspected or the patient finds the examination too painful and is truly unable to cooperate, an examination under anesthesia may be necessary. The risks of general anesthesia must be weighed against the value of information that would be obtained by the examination.

Confidentiality is an important issue in adolescent health care. A number of medical organizations, including the American Medical Association, the American Academy of Pediatrics, and the American College of Obstetrics and Gynecologists, endorsed adolescents' rights to confidential medical care. Particularly with regard to issues as sensitive as sexual activity, it is critical that the adolescent be interviewed alone, without a parent in the room. After assurances of confidentiality (with the caveats dictated by state law relating to mandatory reporting of suspected physical or sexual abuse), the patient should be asked whether she engaged in sexual intercourse, whether she used any method of contraception, used condoms to minimize the risks of sexually transmitted diseases, or she feels there is any possibility of pregnancy.

Follow-Up

Arrangements should be made for the ongoing care of patients, regardless of their health status. Patients with no evidence of disease should be counseled regarding health behaviors and the need for routine care. For those with signs and symptoms of a medical disorder, further assessments and a treatment plan should be discussed. The

physician must determine whether she or he is equipped to treat a particular problem or whether the patient should be directed to another health professional, either in obstetrics and gynecology or another specialty, and how that care should be coordinated. If the physician believes it is necessary to refer the patient elsewhere for care, the patient should be reassured that this measure is being undertaken in her best interests and that continuity of care will be ensured. Patients deserve a summary of the findings of the visit, recommendations for preventive care and screening, an opportunity to ask any additional questions, and a recommendation for the frequency of any follow-up or ongoing care visits. Ideally, the recommendations for care should be transmitted to the patient in written form, as an "after visit summary" noting diagnoses, medications prescribed, and recommendations for testing such as blood tests or imaging and follow-up visits.

SUMMARY

The management of patients' gynecologic symptoms, and abnormal findings and signs detected during examination, requires the full use of a physician's skills and knowledge. Physicians are challenged to practice the art of medicine in a manner that leads to effective alliances with their patients. The value of skilled medical history taking cannot be overemphasized. **Physicians should listen carefully to what patients are saying about the nature and severity of their symptoms.** They should listen to what patients may not be expressing: their fears, anxieties, and personal experiences that lead them to react in a certain manner when faced with what is often, to them, a crisis (such as the diagnosis of an abnormality on examination, laboratory testing, or pelvic imaging).

Physicians should supplement their formal education and clinical experience by constantly seeking valid new information and honing their communication skills. To meet the challenges posed by the complexities of patient care, physicians must learn to practice evidence-based medicine, derived from the very latest data of highest quality. Computers make the world of information management accessible to both physicians and patients. Physicians need to search the medical literature to acquire knowledge that can be applied, using the art of medicine, to patient care that maintains health, prevents disease, alleviates suffering, and manages and cures illness.

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CHAPTER 2

Principles of Patient Care



Susan L. Zweizig, Joanna M. Cain

Patient and Physician: Professionalism
- Disclosing Medical Errors and Unanticipated Outcomes
- Confidentiality
  - *Record Keeping*
  - *Legal Considerations*
- Informed Consent
  - *Autonomy*
  - *Surrogate Decision Makers*
- Beneficence and Nonmaleficence
  - *Medical Futility*
  - *Quality of Life*

Professional Relations
- Conflict of Interest
  - *Health Care Payors*
  - *Legal Problems*
- Harassment
- Stress Management, Burnout and Prevention

Society and Medicine
- Justice
- Health Care Reform

KEY POINTS

1 Professionalism is the foundation of patient care and is as much an ongoing educational endeavor as is learning new procedures or techniques.

2 The right to privacy prohibits a physician from revealing information regarding the patient unless the patient waives that privilege.

3 Informed consent is a process whereby the physician educates the patient about the medical condition, associated risks and benefits of treatment, explains reasonable medical alternatives, and explores her values in this context.

4 The concept of autonomy does not allow a patient's wishes to take precedence over good medical judgment.

5 For children, parents are the surrogate decision makers, except in circumstances in which their decision is life threatening and might not be the choice a child would make later, when individual adult beliefs and values are formed.

6 Creating a highly professional environment of safe culture, lack of harassment, high professional behavior standards, and disclosure of unexpected outcomes benefit patients and health professionals.

7 Prevention of burnout and maintenance of physician wellness are ethical responsibilities of the health care system and are vital to the fiduciary relationship between a physician and their patients.

The practice of gynecology, as with all branches of medicine, is based on ethical principles that guide patient care. These principles and concepts create a framework for ethical decision making that applies to all aspects of practice:

- **Autonomy: a person's right to self-rule, to establish personal norms of conduct, and to choose a course of action based on a set of personal values and principles derived from these concepts**
- **Confidentiality: a person's right to autonomy in deciding how and to whom personal medical information will be communicated**
- **Beneficence: the obligation to promote the well-being of others or, in medicine, to act in the best interest of the patient, defined by meeting a goal of medicine through the care offered**
- **Covenant: an agreement or commitment between two or more parties for the performance of some action**
- **Fiduciary relationship: a relationship founded on faith and trust and the obligation to act in a trustworthy manner**
- **Informed consent: the patient's acceptance of a medical intervention after adequate discussion and consideration of the nature of the procedure, its risks, benefits, and alternatives**
- **Justice: medical resources should be distributed fairly and individuals or groups have the right to claim what is due to them based on certain personal properties or characteristics**
- **Nonmaleficence: obliges health professionals to avoid doing harm, assuring that benefits of interventions outweigh the potential harms of intervention**

PATIENT AND PHYSICIAN: PROFESSIONALISM

Health care providers fulfill a basic need—to preserve and advance the health of human beings. Despite the challenges imposed by the commercial aspects of the medical environment, for most physicians, the practice of medicine remains very much a "calling," a giving of oneself to the greater good. The behavior of health professionals is evaluated in accordance with these ethical principles and concepts by other professionals and the public who share the belief in the "calling" of medicine. There are examples of unprofessional behaviors that mar this professional image. They are demonstrably easier to see in others than ourselves, including unprofessional behavior in shouting at or mistreating others, lack of recognition of conflicts of interest that could affect patient care, or inappropriate interactions with students, patients, or colleagues. These behaviors, such as boundary violations or learner abuse, erode the professional standing of the physician. Lapses do not always represent inherent flaws in professionals, "*most lapses represent deficiencies in judgment and skill. They occur when the physician in question fails to recognize the presence of a challenge to professionalism or lacks the skill to handle a challenge at the time it occurs*" (1). As Lucey and Souba note, **[1]** the solution to unprofessional behavior is not recrimination but development of a set of skills that allow professionals to recognize and address these professional challenges—and those skills need to be developed and reinforced by individuals and by the whole community of practicing physicians throughout their professional careers (1). Professionalism is as much an ongoing educational endeavor as is learning new procedures or techniques, and "*we should assume that our peers want to be professional and that they will welcome interventions from a trusted colleague when circumstances suggest that a lapse is imminent*" (1). **[6]** Creating an environment where we can help one another in this way improves the quality and safety of the care for our patients by preventing unprofessional behavior. **An environment without fear of recrimination, harassment, or unprofessional behavior fosters ease in speaking up for patients' interests and promotes safer environments for everyone. This is a fundamental principle of excellence in patient care (2).**

Professionalism has to balance the differences between fiduciary and contractual relationships between physician and patient: "*The kind of minimalism that a contractualist understanding of the professional relationship encourages produces a professional too grudging, too calculating, too lacking in spontaneity, too quickly exhausted to go the second mile with his patients along the road of their distress*" (3). There is a relationship between physician and patient that extends beyond a contract and assumes the elements of a fiduciary relationship—a covenant between parties. **The physician, having knowledge about the elements of health care, assumes a trust relationship with the patient where her interests are held paramount. Both the**

patient and the physician have rights and responsibilities in this relationship, and both are rewarded when those rights and responsibilities are upheld. Honesty, disclosure, confidentiality, and informed consent are expressions of that trust or covenantal relationship. This cannot be accomplished without some self-awareness on the physicians' part. Health care systems and the governing bodies of medicine have a similar obligation to patients in maintaining physician health through the identification and prevention of provider burnout or dysfunction.

Disclosing Medical Errors and Unanticipated Outcomes

[6] In creating a trustworthy and safe environment, the timely and appropriate disclosure of unanticipated outcomes improves the trust patients have in their health care team and, with complete documentation and reporting, ensures that all medical errors or near misses are used to improve the environment of care. If we are obligated as professionals by our trust relationship with our patients, then patients should expect truthfulness, including being made aware of individual or systemic errors, which, as Kohn et al. noted in *To Err Is Human*, are inevitable in the delivery of health care (4). **[6] A climate that supports a no-fault discussion of errors creates an environment conducive to restructuring the systems or procedures that make it possible for errors to occur and is critical in the development of a safety culture.**

Medical errors can create a keen sense of shame, humiliation, and failed responsibility in health professionals, and efforts have begun to identify and develop the skills and methods for disclosing and learning from them. Support for individuals facing these feelings and preparing to disclose is critical in this development. **[6] Skills that seem common to disclosure are explaining medical facts with honesty and truthfulness (responsibility and answering questions), empathy (and apology), stating how future errors will be prevented, and using good communication skills (5). These are skills that require training and development and should not be taken for granted.** Many institutions have risk management groups or other support groups that can be helpful in development of skills and can accompany or lead such a discussion in the absence of those skills. Disclosure and apology cause apprehension for physicians—particularly in the discipline of obstetrics and gynecology where litigation has adversely affected practice patterns (defensive medicine) and heightened a reluctance to disclose medical errors for fear of litigation (6,7). Apology raises particular anxiety about implying culpability and inciting litigation, so help with framing an apology is always appropriate. **The obligation of trust (fiduciary relationship) that we have with our patients is an important part of healing—and we owe it to our patients and ourselves to develop the robust curricula and support at all levels of medical care to make disclosure the step toward solution and healing that it can be**

for physician and patient.

Confidentiality

The patient seeking assistance from a health professional has the right to assurance that the information exchanged during that interaction is kept private. [2] **Privacy is essential to the trust relationship between doctor and patient. Discussions are privileged information. The right to privacy prohibits a physician from revealing information regarding the patient unless the patient waives that privilege.** Privileged information belongs to the patient except when it impinges on the legal and ethical rights of institutions and society at large, regardless of the setting. In a court situation, for example, physicians cannot reveal information about their patients unless the patient waives that privilege. If privilege is waived, the physician may not withhold such testimony.

[2] **A physician applying the principle of autonomy will respect a patient's privacy and maintain a process that protects confidentiality. The right of privacy must be maintained even when it does not seem intrinsically obvious. A patient's family, friend, or spiritual guide, for example, has no right to medical information regarding the patient unless the patient specifically approves it, except when the patient is unable to provide that guidance because of their medical circumstance.** In that circumstance, health providers must exercise their judgment based on their assessment of the involvement of that particular person with the patient's health. This may seem obvious, but often can be overlooked, such as when a health care giver receives a call from a concerned relative inquiring about the status of a patient. The response may be a natural attempt to reassure and inform a caring individual about the patient's status. However, for her own reasons, the patient may not want certain individuals informed of her medical condition. Thus, confidentiality can unintentionally be breached. It is wise to ask patients about who may be involved in decision making and who may be informed about their status. [2] **If a health care giver is unclear of the patient's wishes regarding the person requesting information, the reply should indicate that the patient's permission is necessary before discussing her status. When trying to contact patients for follow-up of medical findings, it is never appropriate to reveal the reason for contact to an individual other than the patient.**

Record Keeping

Health care professionals are a part of record-keeping organizations. Those records are used for multiple purposes in medicine and are a valuable tool in patient care. There is an increasing tendency for ancillary organizations to collect, maintain, and disclose information about individuals with whom they have no direct connection. Health care professionals must be aware of this practice and its ramifications. Patients sign a

document, often without understanding its meaning, upon registering with a health care institution or insurance plan. That document waives the patient's privilege to suppress access and gives insurers, and often other health care providers who request it, access to the medical record. The consequences of such disclosure for patients can be significant in terms of insurance coverage and potential job discrimination. Even with health care reform and improved attention to pre-existing conditions as part of that reform (8), this continues to be a concern because individuals may have shifts in the pools of insurance available to them and their costs may vary. This concern must be weighed against the need for all health care providers involved with an individual to be informed about past or present diseases or activities that may interfere with or complicate management. The use of illegal drugs, a positive HIV test result, genetic testing results, and even a history of cancer or psychiatric illness are all exceptionally important to health care providers in evaluating individual patients. When revealed to outside institutions, these factors may affect the patient's ability to obtain medical care, insurance, or even credit. **Everything that is written in a patient's record should be important to the medical care of that patient, and extrinsic information should be avoided.** It is appropriate for physicians to discuss with patients the nature of medical records and their release to other parties so that patients can make an informed choice about such release.

The Health Insurance Portability and Accountability Act (HIPAA) was enacted in 1996 and effective compliance of the "privacy rule" was instituted in April 2003. This rule imposed additional requirements for access to patient records for clinical research and guidelines for protecting electronic medical records. Although the intent of the act was laudable, the extent to which privacy is improved is still unknown. The potential harm to the public from misunderstanding of HIPAA requirements or the cost of those requirements that may inhibit critical research is also unknown. Exceptions from the requirement to obtain patient authorization to share health information include areas such as patient treatment, payment, operations (quality improvement, quality assurance, and education), disclosure to public health officials and health oversight agencies, and legal requirements (9). It is important that researchers understand the influence of these rules in all settings; preplanning for clinical database research to include consent for research database efforts when the patient first enters the office or institution will make this critical research possible. **The security of medical records is a concern for individual patients and physicians and for health systems and researchers.**

Legal Considerations

The patient's privilege to keep their records or medical information private can be superseded by the needs of society, but only in rare circumstances. The classic legal decision quoted for the needs of others superseding individual patient rights is that of *Tarasoff v. Regents of the University of California* (10). That decision establishes that

the special relationship between a patient and doctor may support affirmative duties for the benefit of third persons. It requires disclosure if "*necessary to avert danger to others*" but still in a fashion "*that would preserve the privacy of the patient to the fullest extent compatible with the prevention of the threatened danger.*" This principle is compatible with the various codes of ethics that allow physicians to reveal information to protect the welfare of the individual or the community. In other words, "the protective privilege ends where the public peril begins" (11).

Legislation can override individual privilege. The most frequent example is the recording of births and deaths, which is the responsibility of physicians. Various diseases are required to be reported depending on state law (e.g., HIV status may or may not be reportable in individual states, whereas AIDS is reportable in all states). Reporting any injuries caused by lethal weapons, rapes, and battering (e.g., elder and child abuse) is mandatory in some states and not others. The regulations for the reporting of these conditions are codified by law and can be obtained from the state health department. **[4]** These laws are designed to protect the individual's privacy as much as possible while still serving the public's interest. **Particularly in the realm of abuse, physicians have a complex ethical role regardless of the law. Victims of abuse must feel supported and assured that the violent act they survived will not have an adverse effect on how they are treated as people.** Their sense of vulnerability and their actual vulnerability may be so great that reporting an incident may increase their risk for medical harm.

Informed Consent

[3] Informed consent is a process that involves an exchange of information directed toward reaching mutual understanding and informed decision making. Ideally, informed consent should be the practical manifestation of respect for individual patient preferences and autonomy (12). An act of informed consent is often misunderstood to be getting a signature on a document. The intent of the individual involved in the consent process is often the protection of the physician from liability. Nothing could be further from either the legal or ethical meaning of this concept.

[3] Informed consent begins with a conversation between physician and patient that teaches the patient about the medical condition, explores her values, and informs her about the reasonable medical alternatives. Informed consent is an interactive discussion in which one participant has greater knowledge about medical information and the other participant has greater knowledge about that individual's value system and circumstances affected by the information. This process does not require an arduous lecture on the medical condition or extensive examination of the patient's psyche. It does require adjustment of the information to the educational level of the patient and respectful elicitation of concerns and questions. Fear that the information

may frighten patients, fear of hearing the information by the patient, a lack of ability to comprehend technical information, the accuracy of the information given, and an inability to express that lack are among the many barriers facing physicians and patients engaging in this conversation (13). [1] **Communication skills are part of the art of medicine,** and observation of good role models, practices, and positive motivation can help to instill this ability in physicians.

Autonomy

[4] **Informed consent arises from the principle of autonomy.** Pellegrino defines an autonomous person as "*one who, in his thoughts, work, and actions, is able to follow those norms he chooses as his own without external constraints or coercion by others*" (14). This definition contains the essence of what health care providers must consider as informed consent. The choice to receive or refuse medical care must be in concert with the patient's values and be freely chosen, and the options must be considered in light of the patient's values.

[4] **Autonomy is not respect for a patient's wishes against good medical judgment.** Consider the example of a patient with inoperable, advanced-stage cervical cancer who demands surgery and refuses radiation therapy. [4] **The physician's ethical obligation is to seek the best for the patient's survival (beneficence) and avoid the harm (nonmaleficence) of surgery, even if that is what the patient wishes.** Physicians are not obligated to offer treatment that is of no benefit, and the patient has the right to refuse treatment that does not fit into her values. Thus, this patient could refuse treatment for her cervical cancer, but she does not have the right to be given any treatment she wishes, which in this case is a treatment that would cause harm and no benefit.

Surrogate Decision Makers

[5] **If the ability to make choices is diminished by extreme youth, mental processing difficulties, extreme medical illness, or loss of awareness, surrogate decision making may be required. In all circumstances, the surrogate must make every attempt to act as the patient would have acted (15).** The hierarchy of surrogate decision makers is specified by statutory law in each state and differs slightly from state to state. For adults, the first surrogate decision maker in the hierarchy is usually a court-appointed guardian if one exists and second is a durable power of attorney for health care if it exists, followed by relatives by degree of presumed familiarity (e.g., spouse, adult children, parents). For lesbian couples, this presents issues in some states even with changes in federal law that make marriage for same-sex couples legal. In this situation, the creation of a durable power of attorney can address this issue proactively. **Physicians should make sure their patients are aware of the need to have clear instructions about who they would want to speak for them if they are not able—in some cases it is not the person specified by the state guidelines.** For example,

elderly women may not want their elderly (and slightly senile) spouse making decisions and prefer a friend or children—and should have a durable power of attorney for health care that ensures that will be the case.

[5] For children, parents are the surrogate decision makers, except in circumstances in which the decision is life threatening and might not be the choice a child would make later, when individual adult beliefs and values are formed. The classic example of this is the Jehovah's Witness parents who refuse life-saving transfusions for their child (16). Although this case is the extreme, it illustrates that the basic principle outlined for surrogate decision making should apply to parents. Bias that influences decision making (in protection of parental social status, income, or systems of beliefs) needs to be considered by physicians because the potential conflict may lead parents to decisions that are not in the best interest of the child. If there is a conflicting bias that does not allow decisions to be made in the best interest of the child or that involves a medical threat to a child, legal action to establish guardianship (normally through a child protective agency by the courts) may be necessary. This action can destroy the patient (child)–physician relationship and the parent–physician relationship. It may affect the long-term health and well-being of the child, who must return to the care of the parents. Such decisions should be made only after all attempts to educate, clarify, and find alternatives are exhausted.

[5] The legal age at which adolescents may make their own decisions regarding their health care varies by state and national laws. There is a growing trend to increase the participation of adolescents who are capable of decision making for their own health care. Because minors often have developed a value system and the capacity to make informed choices, their ability to be involved in decisions should be assessed individually rather than relying solely on the age criteria of the law and their parents' views (17).

A unique area for consideration of informed consent is providing care or conducting clinical research in foreign settings or caring for individuals from other countries who have differing viewpoints regarding individual autonomy. For example, if the prevailing standard for decision making by a woman is that her closest male relative makes it for her, how is that standard accommodated within our present autonomy-based system? In international research, these issues presented major concerns when women were assigned to placebo or treatment groups and consent was accepted from male relatives (18). The potential of coercion when no other access to health care is available creates real questions about the validity and freedom of choice for participants in entering clinical research studies in order to access health care in under-resourced areas (19). When caring for patients from different cultures and countries in daily practice, it is important to recognize that these issues exist in a microcosm. **Ensuring that the patient can make the choice herself or that she freely chooses to have a relative make it for her remains an important element of**

informed consent.

Beneficence and Nonmaleficence

[1] The principles of beneficence and nonmaleficence are the basis of medical care—the "to do good and no harm" of Hippocrates. These issues can be clouded by other decision makers, consultants, family members, and sometimes financial constraints or conflicts of interest. Of all the principles of good medical care, benefit is the one that continually must be reassessed. Simple questions can help clarify choices. What is the medical indication? How does the proposed therapy address this issue? How much will this treatment benefit the patient? How much will it extend the patient's life? Does it meet a goal of medicine, such as curing a disease, ameliorating symptoms, reducing suffering, or educating about a disease? When confronted with multiple medical problems and consultants, physicians should ask how much treatment will be of benefit given all the patient's problems (e.g., failing kidneys, progressive cardiomyopathy, HIV-positive status, and respiratory failure) rather than considering treatment of one problem without acknowledging that the overall benefit is limited by the presence of all the other problems.

An additional area of balancing beneficence and nonmaleficence is ensuring that the medicine we practice is the safest and of the highest quality relative to medical evidence. The safety and quality agenda in medicine is growing and necessitates consideration of the role of experience (number of procedures, simulation for ongoing maintenance of skills and development of skills, team training) in ensuring that our patients have access to the highest quality of care. When evidence shows improved outcomes for specific interventions—for example, with timing difference in preoperative antibiotics—health care professionals must participate in and embrace efforts to achieve those metrics on behalf of their patients as part of their fiduciary duty and their obligation to seek the benefit of their patients. Steps specific to this in obstetrics and gynecology are listed by the American College of Obstetricians and Gynecologists as **developing the commitment to encourage a culture of patient safety, implementing safe medication practices, reducing the likelihood of surgical errors, improving communication with health care providers and patients, and working with patients to improve safety** (20).

The benefit or futility of the treatment, along with quality-of-life considerations, should be evaluated for all aspects of patient care. It is best to weigh all of the relevant issues in a systematic fashion. Some systematic approaches depend on a sequential gathering of all the pertinent information in four domains: medical indications (benefit and harm), patient preferences (autonomy), quality of life, and contextual issues (justice) (11). Other approaches identify decision makers, followed by facts, and then ethical principles. **It is important for physicians to select an ethical model of**

analysis under which to practice, one that will provide sufficient experience with an ethics-based analytic system in order to help clarify the issues when confronting troubling and complex decisions.

Medical Futility

The essence of good medical care in sometimes challenging situations is to attempt to be as clear as possible about the outcomes of the proposed interventions. If the proposed intervention (e.g., continued respiratory support or initiating support) has a slight or highly unlikely chance of success, intervention might be considered futile. **Physicians have no obligation to continue or initiate therapies that are not of benefit** (21). The decision to withdraw or withhold care is one that must be accompanied by an effort to ensure that the patient or her surrogate decision maker is educated about the decision and agrees with it. Other issues, such as family concerns, can and should modify decisions if the overall well-being of the patient and of the family is best served. For example, waiting (within reason) to withdraw life support may be appropriate to allow a family to reach consensus or a distant family member to see the patient for the last time.

Quality of Life

Quality of life is a much used, often unclear, term. In the care of patients, quality of life is the effect of therapy on the patient's experience of living based on her perspective. It is perilous to assume that health care givers know what quality of life represents for a particular patient (11). It is instructive to attempt to understand what is important to an individual patient's quality of life and seek the patient's perspective. The results may be surprising. For example, when offered a new drug for ovarian cancer, a patient might prefer to decline the treatment because the side effects may not be acceptable, even when there may be a reasonable chance that her life may be slightly prolonged. Conversely, the physician may believe that further treatment offers little benefit but the patient finds joy and fulfillment in entering a phase I clinical trial because it adds meaning to her life to give information to others about the possibilities of a new treatment. Informing patients of the experiences of others who have faced these choices may help in decision making, but it is never a substitute for the choice of the individual patient.

PROFESSIONAL RELATIONS

Conflict of Interest

All professionals have multiple interests that affect their decisions. Contractual and covenantal relationships between physician and patient are intertwined and complicated by health care payers and colleagues, which create considerable

pressure. The conflict with financial considerations directly influences patients' lives, often without their consent. Rennie described that pressure eloquently: "*Instead of receiving more respect (for more responsibility), physicians feel they are being increasingly questioned, challenged, and sued. Looking after a patient seems less and less a compact between two people and more a match in which increasing numbers of spectators claim the right to interfere and referee*" (22). One response to this environment is for the physician to attempt to protect his or her efforts by assuming that the physician–patient relationship is only contractual in nature. For example, a pre-existing contract, insurance, a relationship with a particular hospital system, or a managed care plan may discourage referral to a specialist, removing the physician's responsibility. All health care professionals will experience this tension between a covenantal or contractual relationship. However, the ethical requirement to put the patient's best interests forward and to provide trustworthy information about options remains.

Health Care Payers

An insurance coverage plan may demand that physicians assume the role of gatekeeper and administrator. Patients can be penalized for a lack of knowledge about their future desires or needs and the lack of alternatives to address the changes in those needs. Patients are equally penalized when they develop costly medical conditions that would not be covered if they moved from plan to plan. These situations often place the physician in the position of being the arbiter of patients' coverage rather than acting as an advocate and adviser. It is an untenable position for physicians because often they cannot change the conditions or structure of the plan but are forced to be the administrators of it.

In an effort to improve physician interest in and compliance with decreasing costs, intense financial conflicts of interest can be brought to bear on physicians by health care plans or health care systems. If a physician's profile on costs or referral is too high, he or she might be excluded from the plan, thus decreasing his or her ability to earn a living or to provide care to certain patients with whom a relationship has developed. Conversely, a physician may receive a greater salary or bonus if their management of patients causes the plan or the health system to be more profitable.

These conflicts are substantially different from those of fee-for-service plans, although the ultimate effect on the patient can be the same. In fee-for-service plans, financial gain conflicts of interest have the potential to result in failure to refer a patient or to restrict referral to those cases in which the financial gain is derived by return referral of other patients (23). Patients who have poor insurance coverage may be referred differently from those who have better coverage. Patients may be unaware of these underlying conflicts of interest, a situation that elevates conflict of interest to an ethical problem. A patient has a right to know what her plan covers, to whom she is

being referred and why, and the credentials of those to whom she is referred. The reality is that health care providers make many decisions under the pressure of multiple conflicts of interest. Physicians can be caught between self-interest and professional integrity. Failure to recognize and address conflicts of interest that impact decision making harm the relationship of individuals and society to health care providers. **[6] Focusing clearly on the priority of the patient's best interest and responsibly rejecting choices that compromise the patient's needs are ethical requirements.**

Legal Problems

[6] Abuses of the system (e.g., referral for financial gain) led to proposals and legislation, often referred to as Stark I and II, affecting physicians' ability to send patients to local laboratories and facilities in which they have a potential for financial gain. There were clearly documented abuses, but the same legislation would negatively affect rural clinics and laboratories whose sole source of financial support is rural physicians. States vary on the statutory legislation regarding this issue. Regardless of the laws, it is ethically required that financial conflicts of interest are revealed to patients (24–26).

Another abuse of the physician–patient relationship caused by financial conflicts of interest is fraudulent Medicare and Medicaid billings. This activity resulted in the Fraud and Abuse Act of 1987 (42 U.S.C. at 1320a–7b), which prohibits any individual or entity making false claims or soliciting or receiving any remuneration in cash or any kind, directly or indirectly, overtly or covertly, to induce a referral. Indictments under these laws are felonies, with potential fines, jail sentences, and loss of the license to practice medicine. Physicians should be aware of the legal ramifications of their referral and billing practices.

Harassment

The goal of medicine is excellence in the care of patients and, often, research and education that will advance the practice of medicine. Everyone involved in the process should be able to pursue the common goal on equal footing and without harassment that interferes with employees', learners', or colleagues' ability to work or be promoted equally in that environment. Every office and institution should have an assessment strategy to ensure that the work environment is conducive to focusing on work and learning and not hostile to individuals.

Every office and institution must have written policies on discrimination and sexual harassment that detail inappropriate behavior and state-specific steps to be taken to correct an inappropriate situation and make sure they are widely accessible and available. The goal is to ensure appropriate reporting and procedures for taking appropriate action and protecting victims, educating or rehabilitating an

offender, and preventing the reoccurrence of the behavior.

In the United States, the legal support for this right is encoded in both statutory law through the Civil Rights Act of 1964 (42 U.S.C.A. at 2000e–2000e–17 [West 1981 and Supp. 1988]) and reinforced with judicial action (case or precedent law) by state and U.S. Supreme Court decisions. Charges of sexual harassment can be raised as a result of unwelcome sexual conduct or a hostile workplace. Employees are not the only ones to experience sexual or other harassment; learners such as medical students or nursing students can experience it and have a high reported prevalence of it. Sexual or other harassment for students can interfere with the educational process and trigger federal discrimination liability, including loss of federal funds encoded in Title IX protections (27).

Stress Management, Burnout and Prevention

[7] **In addition to the acknowledged stress of the time pressures and responsibility of a career in medicine, the health care environment is associated with an increasing incidence of physician burnout, a serious threat to physician wellness and the safety and quality of care that their workforce provides.** Addressing this problem is a shared responsibility of the physicians themselves and the health care systems where they work. Individual physician responsibility should include awareness and education about this issue, addressing professional priorities, and having a plan for work–life balance that includes self-care and wellness.

Burnout is a work-related syndrome characterized by emotional exhaustion, depersonalization, and feelings of low personal accomplishment. Practitioners who are burned out have been found to have higher rates of depression, alcohol abuse, and suicidal ideation and are more likely to have experienced medical errors in their practice (28–30). Physician burnout is associated with absenteeism, lapses in professionalism, and early retirement. There is a widening gap in satisfaction with work–life balance and increase in burnout among US physicians, with burnout in obstetrician–gynecologists measured over 50%, second only to emergency medicine physicians (31). This level of distress puts the field of obstetrics and gynecology at risk for depletion of qualified providers, with physicians and others retiring early or leaving medicine entirely.

Addressing burnout in our specialty requires support for physicians through focus on the workplace drivers of this problem, of which there are many. Time spent directly with patients is an important source of reward for physicians and this time is limited by organizational and regulatory demands that are compounded by market forces. Loss of physician autonomy and resultant excessive administrative tasks consume already limited time, distancing physicians from the meaning and value of their work, thereby diminishing the rewards associated with work. In a study of obstetrics and gynecology

providers done in collaboration with the AMA, the strongest single predictor of emotional resilience and sense of accomplishment for individual physicians was control over schedule and hours worked (32).

[6] Alignment of values between the worker and the **[7]** workplace, enhancing communication, establishing a culture of respect, mutual support, and expressing appreciation, have all been shown to improve efficiency, reduce errors, and improve workflow in physician practices and are most effective when supported by leadership. High-quality leaders prioritize improvement of workplace culture and creation of community along with nurturing support for flexibility and physician work–life balance. Strength in leadership, measured by composite leadership scores, is strongly correlated with decrease in burnout (33,34). The personal experience of burnout frequently involves loss of meaning and joy in one's work, isolation, and lack of community. For busy clinicians, isolation has become an occupational hazard and mindfulness or reflective practice in groups can be a very effective outlet. Some data reflect that getting physicians together for a meeting or a meal improves camaraderie and decreases burnout (34,35).

[7] All physicians should develop personal awareness and a commitment to a plan for self-care. Various strategies have been advocated and studied to prevent burnout, and there is no uniform approach that will be successful for every physician. Definition of values or what is most important in life can clarify priorities and facilitate setting limits, establishing time away from work, and planning time for relationships or other revitalizing activities. Many preventative measures and interventions involve wellness practices, stress reduction, and reconnection with the meaning of work and the reasons why physicians entered medical careers. Contemplative practices including mindfulness meditation, cultivation of awareness, and narrative medicine are interventions that have been studied in prevention or amelioration of physician burnout (36). Writing a mission statement reflecting why the physician chose medicine has been recommended as a simple strategy to refocus on the meaning of work.

Though formal mindfulness practice is not for everyone, focusing on the moment, the self, or the breath can allow for regrouping and improve one's sense of being grounded and more in control. Small actionable steps such as improving sleep and exercise and setting boundaries on work time can help. Specific wellness practices and their relationship to burnout have been studied in US surgeons. Incorporating a strategy that prioritized work–life balance, focusing on what is most important in life, and finding meaning in one's work were all found to be helpful in reducing burnout (37). General health habits such as exercise and attending primary care visits have also been found to be important.

Women's health care providers have a significant risk for burnout and face poorer personal, mental, and physical health; increased medical errors; disengagement; and resultant early retirement. Professional well-being is important for our patients and for

the career, personal, and family life of the individual physician.

SOCIETY AND MEDICINE

Justice

[1] Some of the ethical and legal problems in the practice of gynecology relate to the fair and equitable distribution of burdens and benefits. How benefits are distributed is a matter of great debate. There are various methods of proposed distribution:

- **Equal shares** (everyone has the same number of health care dollars per year)
- **Need** (only those people who need health care get the dollars)
- **Queuing** (the first in line for a transplant gets it)
- **Merit** (those with more serious illnesses receive special benefits)
- **Contribution** (those who have paid more into their health care fund get more health care)

Each of these principles could be appropriate as a measure of just allocation of health care dollars, but each will affect individual patients in different ways. Just distribution has become a major issue in health care. The principles of justice apply only when the resource is desired or beneficial and to some extent scarce (38).

The traditional approach to medicine was for practitioners to accept the intense focus on the individual patient. Changes in medicine will alter the focus from the patient to a population: "*in the emerging medicine, the presenting patient, more than ever before, will be a representative of a class, and the science that makes possible the care of the patient will refer prominently to the population from which that patient comes*" (39). Physicians increasingly have accumulating outcomes data (population statistics) to modify the treatment of an individual in view of the larger population statistics. If, for example, the outcome of radical ovarian cancer debulking is only 20% successful in a patient with a certain set of medical problems, that debulking may be offered instead to someone who has an 85% chance of success. Theoretically, the former individual might have a successful debulking and the procedure might fail in the latter, but population statistics were used to allocate this scarce resource. The benefit was measured by statistics that predict success, not by other forms of justice allocation by need, queuing, merit, or contribution. This approach represents a major change in the traditional dedication of health care solely to the benefits, however small, of individual patients. With scarce resources, the overall benefits for all patients are considered in conjunction with the individual benefits for one patient.

There was always inequity in the distribution of health care access and resources. This inequity is not seen by those health care providers who do not care for the patients who are unable to gain access, such as those who lack transportation, live in

rural areas, or where limits are imposed by lack of health care providers, time, and financial resources. Social discrimination leads to inequity in the distribution of health care. Racial and ethnic minorities are less likely to see private physicians or specialists, with clear impacts on outcomes of care, regardless of their income or source of health care funding (40). Thus, health care is rationed by default.

To reform the health care system requires judicial, legislative, business mandates, and attention to the other social components that can pose obstacles to the efforts to expand health care beyond a focus on individual patients.

Health Care Reform

The tension between understanding health as an inherently individual matter (in which the receipt of health care is critical to individual well-being) and as a communal resource (in which distribution of well-being throughout society is the goal) underpins much of the political and social debate surrounding health care reform (41). The questions of health care reform are twofold: (1) What is the proper balance between individual and collective good? and (2) Who will pay for basic health care? Because much of health care reform requires balancing competing goals, legislation to achieve reform should specifically address how this balance can be achieved. The role of government can be:

- Regulating access of individuals to health care
- Regulating potential harms to the public health (e.g., smoking, pollution, drug use)
- Promoting health practices of benefit to large populations (e.g., immunization, fluoridation of water)

Even with the changes in health care structure in the United States, health care payers, not individual providers, often make decisions regarding the distribution of and access to coverage and resources. The health insurance industry determines what are "reasonable and customary" charges and what will be covered. The government decides (often with intense special-interest pressure) what Medicare and Medicaid will cover. These decisions directly affect patient care. For that reason, health care providers cannot ethically remain silent when the health and well-being of their individual patients and their communities are adversely affected by health care reform decisions.

Research on the outcomes of care provided by gynecologists or affected adversely by systems for financing health care (financial aspects, safety, quality-of-life measures, survival, morbidity, and mortality) will allow the discipline to have a voice in determining choices for women's health care. This is an ethically important responsibility for all women's health care providers.

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CHAPTER 3

Quality, Safety, and Performance Improvement



John P. Keats, Joseph C. Gambone

What Is Quality Care?
- Patient-Centered Care
- Clinical Variation in Patient Care
- Role of Organizational Leadership
- Communication
- Operating Room Safety
- Application of Safety Technology
- Disruptive Provider Behavior
- Disclosure and Apology for Adverse Events
- Safety in the Office Setting
- High Reliability
- A Process for Performance Improvement
- The Business Case for Quality and Safety

KEY POINTS

1 Quality is the degree to which health services increase the likelihood of desired health outcomes.

2 Every physician assumes responsibility for safety and excellence of care in their own practice environment.

3 Communication problems are the most frequently identified root cause of serious adverse events in hospitals.

4 Drills and rehearsals for emergency situations improve outcomes and enhance safety.

5 Disruptive behavior in the hospital setting can have adverse effects on patient safety and overall quality of care.

6 There is mounting evidence that improving quality and safety in health care can reduce cost and increase value.

WHAT IS QUALITY CARE?

Nearly two decades ago, the Institute of Medicine (IOM) published two seminal works in the fields of patient safety and medical care quality: *To Err Is Human* and *Crossing the Quality Chasm* (1,2). Despite the heightened awareness and increased public focus on the crucial issues of quality and safety raised by these publications, there is limited published evidence of significant progress toward improving the safety and quality of this country's health care (3). This slow progress caused some leaders in the patient safety movement to call for a redesign of education for health care professionals in order to equip these individuals with the essential knowledge, skill, and attitude required to function safely and effectively in the health care delivery environment of the 21st century. Although this imperative affects all health professions, it is particularly compelling for medical education because physicians' actions and decisions dictate the parameters of care to be provided by most other health care professionals (4). Recent changes in reimbursement methods for health care services that put a greater emphasis on value (better clinical outcomes and avoidance of complications) rather than volume (fee-for-service) are creating more interest in clinical performance improvement (5).

[1] The IOM defined quality as "the degree to which health services for the individual and populations increase the likelihood of desired health outcomes . . . consistent with current professional knowledge" (6). This assertion acknowledges that health care quality is important and applicable to entire groups of people and each individual patient. Implicit is the obligation to be sensitive to the flexible meaning of "desired health outcomes" because desired outcomes may differ from the perspective of hospitals, physicians, patients, and their families. Adherence to the definition includes rigorous application of accepted standards of knowledge and therapy to any clinical problem, a process now referred to as evidence-based medical practice (7). The IOM summarizes its definition of quality care in "Six Aims for Improvement" **(Table 3-1)**.

Patient-Centered Care

Many industries have recognized that one of the best definitions of quality is meeting customer expectations. The "centering" of patient care requires a focus on meeting appropriate expectations. The involvement of patients in health care decision making is traditionally restricted to the legal requirement for informed consent where the discussion tends to be limited to the benefits and risks of a plan or procedure. A more complete discussion of individual expectations, appropriate patient preferences, and the

inclusion of all reasonable alternatives for care encourages a more collaborative process.

The PREPARED checklist (Table 3-2) is one method that may be used for guiding informed collaborative choice and patient-centered care (Table 3-2) (8).

Table 3-1 Six Aims for Quality Health Care

Care should be:	
Safe (first among equals)	Timely
Effective	Efficient
Patient-centered	Equitable

Clinical Variation in Patient Care

Individual patients receiving identical diagnoses might not be given identical treatments. This is known as clinical variation and can be broadly categorized as falling into two types. One is *necessary* clinical variation, an alteration in medical practice that is required by the differing needs of individual patients. This modification may be in response to differences in the patients themselves because of age, overall health status, or other clinical characteristics; or it may be caused by differing desired outcomes as part of a patient-centered approach to care (9). This kind of variation is expected in any system of care. The other type is *unexplained* clinical variation, which comprises differences in medical care and patient management that are not accounted for by differences in patient symptoms, objective findings, or patients' goals for care. **These treatment discrepancies could account for wide variations in the cost of care without any demonstrable difference in outcomes as measured by achievement of therapeutic goals, morbidity, or mortality** (10–12). Often this unexplained variation is the result of management choices made by physicians in cases that fall into areas of discretion in clinical judgment, where no single course is clearly correct. Sometimes this variation is unexplained and unintended. It is this unexplained or unintended variation that is considered one of the greatest barriers to the delivery of consistent, high-quality care (13). The specialty of gynecology is subject to this treatment inconsistency. Significant geographic variations in hysterectomy rates, largely unexplained by the clinical characteristics of those local populations, have been reported (14,15). Further study and reduction of unnecessary variation in these rates could contribute to making medical care more efficient and equitable.

Table 3-2 PREPARED Checklist Process for Informed Communication and Patient-Centered Care

Plan:	Course of action being considered

Reason:	Indication or rationale
Expectation:	Chances of benefit and failure
Preferences:	Patient-centered priorities
Alternatives:	Other reasonable options/plans
Risks:	Potential harms from considered plans
Expenses:	Direct and indirect costs
Decision:	Fully informed collaborative choice

Role of Organizational Leadership

[2] Creating a safe environment for the delivery of medical care requires the active participation of organizational leadership. Each physician assumes a significant responsibility for safety and excellent care in his or her own practice environment. Inadequate leadership around safety issues erodes physician and staff morale and can contribute to the occurrence of patient harm and adverse clinical outcomes (16). In the hospital, oversight for issues of safety and quality is shared by the hospital board, executive leadership, and medical staff leadership, including physicians who serve as chief medical officer, vice president of medical affairs, or department chairs. A new position being adopted by many hospitals is the patient safety officer (17). This individual takes direct responsibility for overseeing all aspects of the hospital patient safety program and reports to the hospital chief executive officer or board of directors. It is an emerging role for physicians who want to make patient safety the focus of their professional lives.

An important method for improving the safety environment in a hospital is the adoption of the tenets of a safety construct referred to as "Just Culture" (18). **Just Culture recognizes that human error cannot be completely eliminated from any complex system such as health care.** People sometimes make mistakes. They can be held accountable for following procedural rules to reduce harm to patients resulting from human error. **Adverse outcomes and near misses encourage the organization to examine its processes of care with an eye to continuous improvement. With such a system in place, the reporting of safety problems and concerns will often increase dramatically.** This permits the hospital or other health care organizations to initiate programs that address these issues and make "first, do no harm" a priority.

Communication

[3] An assessment of the factors leading up to serious adverse events in hospitals

revealed that communication problems were the most frequently identified root cause, occurring in almost three-fourths of cases (19). Assuring clear and timely communication between all caregivers is perhaps the single most important measure to improve the safety and quality of medical care. Structured communication techniques in the health care setting are referred to under the title "team resource management." The basic principle of team resource management is to foster an atmosphere conducive to enabling individuals with different roles to achieve a successful outcome to a complex operation (20). Despite differing roles, training, and ranking within a perceived hierarchy and the inclusion of some individuals who may not have worked together as a team before, it is understood that each participant shares an overarching responsibility. That responsibility is to communicate with all team members whenever they see anything that is potentially unsafe or when other team members are not acting appropriately in a given situation. This concept is particularly applicable in the operating room, which is by nature a highly complex environment. **Everyone present—physicians, nurses, house staff, and technicians—must keep patient safety foremost in their minds. No one should hesitate to raise questions and concerns when an unsafe situation is observed.**

Certain situations in health care are particularly prone to miscommunication. One example is during the stress of emergency situations, when a physician may be rapidly ordering medications, blood transfusions, or initiating procedures. A technique referred to as "call-outs" helps ensure that critical orders are correctly received. The person to whom the verbal order is directed repeats the order verbatim to acknowledge that it is accurately received and accepts responsibility for carrying it out. Hearing this call-out assures the ordering physician that the order was received, who will be performing it, and creates an opportunity to correct the order if it was misheard. Telephone orders are well known to be sources of misinterpretation of physicians' treatment intentions (21). Check-back is a technique to minimize errors in this medium. In a typical situation, a doctor calls a nurse to order a medication for a patient. Check-back has three components. First, the physician gives the medication order to the nurse. Second, the nurse repeats the order back to the physician, specifying medication name, dose, route, and timing of administration. Lastly, the physician confirms to the nurse that the order was correctly received. When a handoff of a patient from one physician to another occurs, that presents a third opportunity for miscommunication. A relay team approach to care is occurring more frequently in medical education as a result of residency work-hour restrictions (22). To minimize errors in this setting, it is wise to use a structured script for communicating critical clinical information. One such script is from a program published by the Agency for Healthcare Research and Quality (AHRQ) called Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS). It is the mnemonic I PASS the BATON, which is essentially a checklist of clinical items to be related to the person assuming the care of the patient **(Fig. 3-1)**

(23). The key point is that management handoffs should be a formal process that does not rely on memory to convey crucial information.

I	Introduction	Introduce yourself and your role/job (include patient)
P	Patient	Name, identifiers, age, sex, location
A	Assessment	Present chief complaint, vital signs, symptoms, and diagnosis
S	Situation	Current status/circumstances, including code status, level of (un)certainty, recent changes, and response to treatment
S	SAFETY Concerns	Critical lab values/reports, socioeconomic factors, allergies, and alerts (falls, isolation, etc.)
THE		
B	Background	Comorbidities, previous episodes, current medications, and family history
A	Actions	What actions were taken or are required? Provide brief rationale
T	Timing	Level of urgency and explicit timing and prioritization of actions
O	Ownership	Who is responsible (person/team) including patient/family?
N	Next	What will happen next? Anticipated changes? What is the plan? Are there contingency plans?

FIGURE 3-1 I PASS the BATON. (From Team STEPPS Program of the U.S. Agency for Healthcare Research and Quality [AHRQ]).

An important feature of team resource management is the ability of any team member to "stop the line"—that is, to halt the process or procedure when they perceive a risk to patient safety. One recommended technique is the "CUS" method.

This acronym represents three possible sets of "code words" that any team member may use to stop the procedure until the safety concern is addressed. The letters in the acronym stand for "I'm *C*oncerned"; "I'm *U*ncomfortable"; and "I have a *S*afety concern." Another method is the "Two-Challenge Rule." This indicates that when a team member has a safety concern, he or she should bring it to the attention of the physician in charge of the procedure. If the concern is not acknowledged or adequately addressed, the team member should address it a second time. If the concern is still unanswered or uncorrected, the team member is obligated to go up the chain of command to a supervisor or higher-ranking physician to have his or her concerns satisfied.

All of these techniques can contribute to a safer environment for patient care in the operating room, emergency department, and in hospital rooms. However, none of them can be very effective without practice. **[4]** The use of drills and simulations in training programs to rehearse these techniques in mock emergency situations in anesthesia (24) and other surgical disciplines (25,26) is well established. The use of simulators to teach basic surgical techniques including laparoscopy and robotic surgery are becoming more common (27,28). **Drills and rehearsals for emergency situations improve outcomes and enhance safety** (29,30).

Operating Room Safety

The operating room is by its nature a highly complex health care environment. It is a potential site for adverse events, which can be catastrophic. These include wrong patient surgeries, wrong site surgeries, and retained foreign objects. All of these occur in hospitals, despite recognition that these events should never take place (31,32). The Joint Commission, a national accrediting body for hospitals, has developed the Universal Protocol™ that all surgeons and operating rooms should follow (33). There are three major components of the Universal Protocol. **First is to conduct a preprocedure verification process** that confirms the identity of the patient and his or her understanding of what procedure is to be performed. **Second is marking of the operative site** by the surgeon, which is especially critical in cases involving bilateral structures. This is to be done in the preoperative area with the patient awake as a confirmation of accuracy. **Third is the performance of a surgical "time-out"** in the operating room prior to the start of the surgery to confirm the correct patient identity and correct planned procedure. **Failure to perform any of these steps increases the risk of performing the wrong operation on the wrong patient.**

The traditional use of checklists resulted in dramatic increases in the safety of aviation (34). Their use in medicine is demonstrated to significantly decrease complications when used consistently to verify that procedural steps are not overlooked. A simple five-step checklist for central-line placement in the intensive care unit was shown to reduce the incidence of catheter-related sepsis to almost zero

(35,36). Similarly, checklists are advocated for use in the surgical suite to ensure that critical steps for error prevention and patient safety are not overlooked. The World Health Organization (WHO) released a surgical checklist in 2009 under their "Safe Surgery Saves Lives" program (37). It involves items to be reviewed and documented before the induction of anesthesia, before the skin incision, and before the patient leaves the operating room. Use of the WHO checklist was shown to reduce major complications of surgery from 11% to 7% and the major surgery inpatient death rate from 1.5% to 0.8% (38). The use of checklists such as this to improve patient safety in the operating room should become more widespread.

The inadvertent retention of foreign bodies such as sponges, instruments, or other objects at the conclusion of surgery is a continuing source of patient harm. Risk factors associated with retained foreign bodies are emergency surgery, unexpected change in surgical procedure, high patient body mass index (BMI), and failure to perform sponge and instrument counts (39). Systems must be established to prevent these occurrences, and surgeons need to be aware of the contributing risk factors listed above (40). **The most commonly retained item is a surgical sponge. Strict adherence to guidelines for tracking surgical sponges is necessary to reduce the incidence of this serious complication.** One comprehensive program to assist in adherence is called "Sponge Accounting" (41,42). It involves standardized counting and recording of sponges at the start of the case and as additional sponges are added to the surgical field. At the conclusion of the surgery, all sponges are placed in special transparent holders to allow visual confirmation that all sponges were taken out of the patient. Other systems employ radiofrequency tagging of all sponges so that retained sponges can be detected easily before the surgical wound is closed (43).

Application of Safety Technology

Computerized physician (prescriber) order entry system (CPOE) is a prescription ordering system where the prescriber enters ordering information directly into a computer, typically as part of a hospital or office electronic medical record. Most modern systems can check for errors and make suggestions based on preprogrammed guidelines and protocols. CPOE is known to reduce serious medical errors and prevent otherwise undetected adverse drug events (ADEs) (44). When CPOE systems are properly designed and implemented, they can improve workflow efficiency by supplying real-time dosing information and other decision-support protocols and guidelines. Poorly designed or improperly implemented CPOE systems, however, have the potential to decrease efficiency and increase medication error.

Medication safety is a high priority for quality improvement initiatives. Avoiding abbreviations that may lead to medication error increases patient safety (45). **Avoiding abbreviations that can be misread is an important and effective**

improvement, especially when orders are handwritten. One easily remembered and important rule about the written medication order is "always lead and never follow" a decimal point when using zeros. An order that is written as .1 mg should be written as 0.1 mg—an example of leading with a zero. It can be very dangerous for the written period to be missed, resulting in 1 mg being given to a patient rather than 0.1 mg. The leading zero should alert to the correct dosage. An order that is written as 1.0 mg should be written as 1 mg—never following with a zero, so that a patient is not mistakenly given 10 mg of a drug if the period is missing or not seen. Exclusive use of properly designed and implemented CPOE systems can eliminate misread written orders.

Disruptive Provider Behavior

In 2009, as part of its accreditation standards, the Joint Commission proposed that all health care organizations with professional staffs develop and implement a Code of Conduct Policy along with an education program that addresses disruptive behavior. **[5]** Disruptive physician (provider) behaviors include inappropriate conduct in the hospital setting, resulting in conflict or confrontation. These behaviors can range from verbal or physical abuse to sexual harassment. In recent years disruptive behavior in the hospital setting has become more evident, if not more common. One study showed that the vast majority of surveyed physicians, nurses, and administrators had witnessed disruptive behavior by physicians (46). Nurses and other hospital employees also commit disruptive behavior, but it is far less common than disruptive physician behavior. **Disruptive behavior in the hospital setting can have adverse effects on patient safety and overall quality of care.**

Team building that encourages collegial interaction and a sense that all members of the health care team are important to the process and present valuable contributions can promote a culture that reduces the likelihood of disruptive behavior.

Disclosure and Apology for Adverse Events

Organized medicine is increasing its focus on the prevention of medical error. A controversial issue involving medical error is the prompt disclosure and apology for any medical errors that occur. In the past many, if not most, health care organizations focused on managing the legal risk of medical error. The conventional wisdom was that any disclosure and apology for error would promote litigation and bigger payouts. **The Joint Commission and other professional organizations require or endorse active disclosure to the patient when adverse events occur, including those caused by error** (47).

Lucian Leape, one of the fathers of the modern patient safety movement, pointed out

that a patient has an ethical right to full disclosure of medical error (48). Although an apology is not an ethical right, it is a therapeutic necessity, according to Leape. Three programs are worth noting in any discussion of disclosure and apology for medical error. First is the University of Michigan's patient safety program, which addresses the need to disclose medical error in several publications (49). Important points are made about a patient's rights concerning disclosure of medical error and that an apology for errors can be a productive benevolent gesture rather than an admission of fault. The authors point out several fallacies about disclosure, including that disclosing medical error always leads to litigation and that error always means negligence.

Secondly, several programs are under way to test the assertion that disclosure and apology can decrease the likelihood of litigation. COPIC, a Colorado medical insurance company, found that full disclosure results in small early settlements and dramatically reduced law suits and payouts (50).

Table 3-3 Medical Director Responsibilities in an Office Setting

• Motivation of staff to create a "safety culture"
• Credentialing and privileging for office procedures
• Developing/updating/enforcing office policies
• Conducting regular mock safety drills
• Tracking and reporting adverse events
• Establishing a nonpunitive quality improvement process

Lastly, The Sorry Works! Coalition, a coalition of doctors, insurers, and patient advocates, urges the use of full disclosure and apology for medical errors (51). They point out that the current tort system has failed, resulting in higher and higher malpractice premiums without decreasing the rate of medical error. Demands for caps on malpractice awards and greater disciplinary measures for providers are largely ineffective. The Sorry Works! Coalition advocates early disclosure with apology and financial settlements without litigation as the way to deal with medical error.

Safety in the Office Setting

Thus far, most efforts to improve safety involved activities that occur in the inpatient setting. This is a logical initial approach because most risky procedures and tests are performed in the hospital setting. There is a trend to adapt some invasive procedures and tests to be offered in the office setting. Gynecologic procedures such as hysteroscopy and loop excision of the cervix are examples of this. It is anticipated that there will be increasing numbers of "risky" invasive procedures performed in the office setting. The American College of Obstetricians and Gynecologists (ACOG) established

a Task Force on Patient Safety in the Office Setting in 2009.

The charge to the task force was to "assist, inform, and enable Fellows of the College to design and implement processes that will facilitate a safe and effective environment for the more invasive technologies currently being introduced into the office setting." The task force produced a monograph and an article containing an executive summary of their work and recommendations (52,53). The task force addressed issues of leadership in the office setting; competency and assessment; teamwork and communication; anesthesia safety; measurement (of processes and outcomes); and tools such as checklists, time-outs, and drills.

In the hospital setting, leadership for safety is provided at multiple levels, starting with the department chair, with assistance from designated personnel in risk management and quality assurance. In the office setting, this responsibility must be assumed by one individual in a solo practice and one or several in a group practice. One individual should be designated as medical director and his or her responsibilities are outlined in Table 3-3.

The process of competency assessment should be similar to the credentialing and privileging systems that hospitals use. The determination that a provider is qualified (credentialed) and competent to perform specific procedures (privileged) is equally important in the office setting. Procedures initially performed solely in an inpatient setting should be converted to the office setting only after the provider has demonstrated competency in an accredited operating room setting.

Effective communication with office personnel and with patients was identified by the task force as an essential element for creating a culture of safety in the office setting. Regular meetings should be held with all office staff to establish and implement patient safety and quality improvement protocols.

Anesthesia safety is critical for avoiding adverse outcomes in the office setting. As office-based procedures become more invasive, many practices have incorporated certified anesthesia personnel into the office team. The level of anesthesia achieved, not the agents used, should be the primary issue regarding anesthesia safety. When nonanesthesia-certified providers are managing the patient, appropriate credentialing and privileging should be documented.

The task force strongly recommends the use of checklists, drills, and time-outs to verify the appropriate progress of office-based procedures. Checklists improve safety and effectiveness in other industries besides health care (34,36). Verifying that the correct procedure is being performed on the correct patient during a time-out for confirmation is useful in the office setting, and drills and simulations are essential activities in high reliability organizations. Advances in technology are expected to move many more invasive procedures into the office setting, and patients and providers will expect that these are performed with high reliability and safety.

Through the Presidential Task Force Report, ACOG provided a blueprint for

improving patient safety in the office setting (52,53).

High Reliability

Patient care delivery is often as consequential and error prone as running a nuclear power plant or operating an aircraft carrier. The science of high reliability which is applied in those two activities is being introduced into health care, particularly in the hospital setting. The ability to operate highly complex and hazardous technologic systems essentially without error over long periods of time is the hallmark of a "High Reliability Organization" (54,55). Using techniques such as simulations, checklists, and situational awareness, delivery of care is increasingly managed by medical teams who work together to reduce medical error to very low levels (56). The concept of "Six Sigma" is meant to define an ideal of restricting errors to one error in about one million events (57). Although this may be an unreachable goal in something as complex as patient care, the concept is meant to establish a very high standard.

A Process for Performance Improvement

Professional organizations like ACOG and others have been partnering with their fellows and fellows' institutions to address clinical performance issues such as high cesarean delivery and other surgical rates by organizing courses in basic and advanced patient safety. One protocol that has been successfully implemented in ACOG's advanced course is illustrated in Table 3-4. The protocol outlines and emphasizes the need for proper planning of any performance improvement effort and the need for ongoing monitoring in order to sustain the positive changes. Participating leadership teams have used these worksheets to create a roadmap for institutional change to achieve a variety of goals in patient safety and quality improvement.

The Business Case for Quality and Safety

[6] How can the application of the quality and safety principles outlined above result in cost savings in the delivery of health care? The business case for quality and safety is built on the concept of the elimination of waste in medical care. Brent James, executive director for the Institute for Healthcare Delivery Research at Intermountain Healthcare in Salt Lake City, identifies two main types of waste in health care (58). The first is *quality waste*, which can be thought of as rework or scrap. This is the failure to achieve the desired outcome of medical care the first time around. This would include such diverse events as medication errors that result in patient harm, hospital-acquired infections, wrong site surgeries, and retained foreign objects at surgery. The second type is *inefficiency waste*. This refers to excessive resource consumption to achieve an outcome when a different alternative is available to more

efficiently achieve a similar outcome. An example would be performing an inpatient hysterectomy for menorrhagia that could be treated equally well with outpatient medication or endometrial ablation. James estimated that together these two sources account for as much as 50% of the expenditures on health care in this country (58). While many experts considered this a wild exaggeration, this view was given some credence in 2012 in a comprehensive review of the American health care delivery system by the IOM (59). This publication estimated that in 2009, waste in the medical delivery system resulted in the loss of $750 billion from productive use, enough to provide health insurance coverage to 150 million people. The conclusions from this group are shared by proponents of value-based delivery of patient care (60), where emphasis is put on obtaining the best clinical outcomes while using the most efficient amount of resources (the value equation). The Centers for Medicare and Medicaid (CMS) have adopted payment methods that are based upon this value equation (61). Combating all sources of wasted health care dollars will require a widespread adoption of the principles discussed: the use of evidence-based medical treatments and safety technology; the elimination of unexplained clinical variation in our processes of care; the direct involvement of patients in monitoring their own care; improved teamwork and communication between providers in different disciplines; and all of these under the guidance of committed health care leadership able to rally support for these efforts. The twin aims of improving the safety and quality of medical care are goals that all physicians should actively pursue.

Table 3-4 ACOG Process of Performance Improvement*

STEP I) Identify a Performance Improvement or Patient Safety Problem:				
Identify areas of concern/interest for performance improvement or patient safety within your department/organization				
Search and review	Departmental/organizational data for areas of concern with respect to performance or patient safety. This may be based on a recent incident that has occurred or one that is suggested in the literature	**Have any surveys been done to identify areas of concern? Has data been collected over time to measure the number of adverse events that have occurred due to this problem/issue?**	**What is the current level of error/satisfaction in your organization? Numerator and Denominator?**	**What is the goal for improving the level of performance/safety?** **Has any benchmarking been done to establish realistic goals?**
Checklist for identifying the safety problem:				
1. Identify a performance improvement/patient safety problem that is of concern in your department/organization. a. Determine that this is a performance/safety problem that has widespread interest in the department/organization. b. Why is it important to accomplish this change now? c. What is the basis of comparison (benchmark)?				
2. List the adverse event(s) associated with this problem. a. How was this decided on? b. What measures will be used to assess the change project?				
3. How will the department/organization support the change? a. What resources will be required? b. How will the sponsor demonstrate their support?				
STEP II) Plan for Measurement of Results:				
SMART goals				
Specific	Define as narrowly and unambiguously as possible what it is that you are targeting in your improvement project. Your specific target or goal must be expressed in quantitative terms.			
Measurable	Your target has to be something quantifiable. See below for more details to be assessed for this item.			
Attainable	Your target must be realistic in terms of your organization's ability to achieve it. In general, goals of 100% or "never" are not realistic.			
Relevant	The parameter you are trying to improve must be something perceived as important and desirable to key stakeholders, such as physicians, nurses, administration, and patients. Make the case as to why this is relevant to each group.			
Time-bound	Determine a specific end point for the improvement project by which time you will achieve the amount of improvement decided on in "Specific" above.			
Checklist for Measurement of Results:				
1. What is currently being measured in this area at your institution? a. Is this the best metric to follow? What others may be important?				
2. How will you define what you want to improve? a. Definition should be unambiguous (e.g., "improving neonatal outcome" is ambiguous; "reducing the percentage of newborns with 5-minute Apgar less than 7" is not)				
3. In what format will you measure what you want to improve? a. Will you use simple counts? Percentages? Rates? i. If percentages or rates, what will you use as numerator and denominator? b. Do you need to design a new measurement tool or can you use one already in place? c. How are measurements currently being presented? Are run charts or control charts routinely used?				
4. Do you need to develop a data collection plan? a. How will the data be stratified? b. Will the data collection require sampling?				
STEP III) Identify All Stakeholders for Safety Problem or Improvement Opportunity:				
Identify all those who have a stake (may cause or be affected by the consequences) in the project				
Stakeholders	Identify all those who have a stake in the project, either who create or are affected by the consequences of the care process.	**List all those who could cause or who could be affected by the consequences of the care process?**	**Do they understand the responsibilities of their role in the care process?**	**How can these stakeholders be incented to improve outcomes?**

Clinical stakeholders	Identify all providers and nursing staff who will participate in the clinical care involved with the project. This should also include the patient.			
Nonclinical stakeholders	Identify others, such as administrators, who could have a stake in the outcomes of the care process.			
Checklist for identifying all stakeholders:				
1. Identify all individuals who are involved in the clinical and overall care. a. Anyone who could create consequences or be affected by the consequences of the care is a stakeholder in the process. b. Are all stakeholders identified?				
2. Include both clinical and nonclinical individuals who may be stakeholders. a. Are all clinical stakeholders identified? b. Are all nonclinical stakeholders identified?				
3. Is the patient included as a stakeholder? a. Can the patient become an active stakeholder (e.g., patient signs correct operative site for surgery) in the care process? b. How will this be accomplished?				
STEP IV) Identify Required Roles:				
Identify individuals who will assume key roles in your change process				
Sponsor(s)	Sanction change from a leadership level. Must agree to be a highly visible supporter of change effort. Preferably has authority to commit resources to the project. Consider developing sponsorship at multiple levels.	**Who could play this role?**	**Do they understand the responsibilities of this role?**	**If not, who will coach them?**
Agents(s)	Support the sponsors and facilitate change. Needs knowledge of the change process and be trusted by physicians. Will be responsible for gathering and reviewing data and provide support to those coping with the change.			
Champion(s)	Respected opinion leaders who agree to be "early adopters" of the change. Best if they are seen as frontline practitioners and not part of management.			
Checklist for aligning the change team:				
1. Create the "burning platform" and/or the vision. a. What is the problem to be corrected or the opportunity for improvement that exist? b. Why is it important to accomplish this change now?				
2. What is the proposed change? a. How was this decided on? b. What measures will be used to assess the change project?				
3. How will the sponsors support the change? a. What resources will be required? b. How will the sponsor demonstrate their support?				

(*continued*)

4. How will the agents support the change? a. How will they communicate and support the change process? b. How will they deal with resistance?				
5. How will the champions support the change? a. What does it mean for them to cross the bridge first? b. How will they communicate their experience to others?				
STEP V) Plan for Dealing With Resistance (In Advance):				
Identify areas where resistance to the planned change(s) is likely				
Search and review	Departmental/organizational data for experiences in the past when change was proposed	Minutes of departmental meetings may be helpful to identify individuals who do not like change or who generally oppose making changes	Information from interviewing present and past opinion leaders; careful that "personality issues" are not involved	The literature for information from other locations where the same or similar change(s) were made
Checklist for identifying individuals/departments who may resist the planned change(s):				
1. Review past improvement efforts for clues as to who may oppose any change a. Start with individuals/departments who are most likely to be affected by the change(s) b. Brainstorm about individuals who are generally opposed to any/all changes c. Send out information about the proposed change(s) and the reason(s) for them				
2. Ask for feedback in writing by a certain date				
3. Follow up with phone calls/e-mails getting "buy in" or reasons for opposition from those who have not responded				
4. Consider modifying the change(s) based on the feedback from those who may oppose or who are only "lukewarm" about the proposed change(s) a. What are the possible compromises? b. Will the proposed change(s) still be effective if suggested modifications are made?				
STEP VI) Plan for Monitoring, Follow-up, and Sustainability of Change:				
Measuring change	a. How will you measure change once the process is in place? b. How often and to whom will you report the data? c. What will your criteria be for determining the success of the project and deciding how to adjust it if goals are not being met?			
Follow-up	a. How will you expand the process beyond your pilot setting?			
Sustainability	a. How will you celebrate short-term wins? b. How will you incorporate measures of this process into the standard quality reporting functions of department or hospital leadership? c. Who will be responsible for monitoring that any improvement is sustained?			
Checklist for monitoring, follow-up, and sustainability of change:				
1. Who will pilot your change? a. Select a single unit or small group of physicians to initially institute the change process b. Decide how long the pilot will run and intervals at which you will gather and report data				

*Keats and Gambone (2014). American College of Obstetricians and Gynecologists (ACOG) Advanced Course in Patient Safety and Quality Improvement.

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CHAPTER 4

Clinical Research



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KEY POINTS

1 *Clinical research* includes all research involving human participants and represents a range of research disciplines and approaches, including patient-oriented research, clinical trials, epidemiology, and outcomes research.

2 *Clinical trials* are a subset of clinical research where human participants are prospectively assigned to an intervention.

3 *Randomized clinical trials are a subset of clinical trials* that use a controlled experimental design to assess the effectiveness of an intervention on an outcome.

4 *Outcomes research* and *health services research* include studies that seek to identify the most effective and efficient intervention, treatments, and services for patient care.

5 Study designs include *experimental studies* (clinical trials), *observational studies* (cohort studies, case-control studies, and cross-sectional studies), and *descriptive studies* (case reports and case series).

6 *Scientific validity* of a research study is evaluated by understanding the study question, how the study was designed, and whether chance, bias, or confounding could have accounted for the findings.

7 All study designs have inherent strengths and weaknesses and the quality of the methods of the individual study and its scientific validity must be evaluated to determine the study's overall quality of evidence.

STUDY DESIGNS

Medical practice is evolving to include complex options for patient treatment and preventive care, in part because clinical research methods and techniques to guide patient care have advanced. To evaluate whether new treatments and diagnostic approaches should be integrated into clinical practice or decide whether study results reported in the literature are valid, clinicians should understand the fundamental strengths and limitations of clinical research methods and the level of evidence different types of studies provide.

[1] Clinical research, which encompasses all research involving human participants, includes patient-oriented research involving understanding mechanisms of human disease, studies of therapies or interventions for disease, clinical trials, and epidemiology (1). It does not include secondary studies using publicly available datasets or studies using **[2]** existing biologic specimens. Clinical trials, a subset of clinical research, are studies that evaluate the effects of an intervention on participants by prospectively assigning participants to intervention groups (1).

Epidemiologic methods and behavioral research are used in clinical research to examine the distribution of disease and the factors that affect health and how people make [4] health-related decisions. Outcomes research and health services research include studies that seek to identify the most effective and efficient intervention, treatments, and services for patient care.

The purpose of a research study is to test a hypothesis and to measure an

association between *exposure (or treatment)* and an outcome (e.g., disease occurrence, prevention, symptom score, quality of life). The type of study design influences the way the study results should be interpreted. Selection of study design should be based on the specific research question being addressed.

[5] *Analytic studies are often subdivided into experimental studies (clinical trials) and observational studies (cohort studies, case-control studies, and cross-sectional studies).*

Descriptive studies **(case reports and case series) can provide useful information for informing future analytic studies.**

The common types of clinical research study methods, strengths and weaknesses of the specific study method, and interpretation of the results are presented. **Well-designed and executed clinical trials have been presumed to represent the highest level of evidence for evaluating health interventions; however, work in evidence-based medicine has urged that study design is only one of several factors that drives the [7]quality of evidence within a study.** It should be noted that all study designs have inherent strengths and weaknesses and the quality of the methods of the individual study and its scientific validity must be evaluated to determine the study's overall quality of evidence (2,3). **[6] *Scientific validity* of a research study is evaluated by understanding the study question, how the study was designed, and whether chance, bias, or confounding could have accounted for the findings.**

ANALYTIC STUDIES

Clinical Trials

[2] Clinical trials include any study where participants are prospectively assigned to receive an intervention or treatment (which may include being assigned to a control group) and the outcomes to be measured are clearly defined at the time the trial is designed. **[4] Features of *randomized clinical trials* include randomization (in which participants are randomly assigned to exposures), unbiased assessment of outcome, and analysis of all participants based on the assigned exposure (an "intention to treat" analysis).**

There are many different types of clinical trials, including studies designed to evaluate treatments, prevention techniques, community interventions, quality-of-life improvements, and diagnostic or screening approaches (4). Investigators conducting randomized clinical trials are expected to register the trial to comply with mandatory registration and results reporting requirements (5,6).

Clinical Trial Phases

New investigational drugs or treatments are usually evaluated by clinical trials in

phases which begin with small trials designed to determine treatment safety (phase 1) and progress to large-scale studies designed to determine efficacy and side effects (phase 3) (Table 4-1) (7).

Randomized Controlled Double-Blinded Clinical Trial

The *randomized controlled double-blinded clinical trial* design minimizes bias when evaluating the effect of an intervention on an outcome because randomizing treatment assignment minimizes the influence of confounders and *blinding* both the participant and the investigator minimizes the possibility that ascertainment of the outcome is influenced by treatment group assignment. When studies are not randomized or blinded, bias may result from preferential assignment of treatment based on patient characteristics or an unintentional imbalance in baseline characteristics between treatment groups, leading to *confounding* (8).

Although not all studies can be designed with blinding, the efforts used in the trial to minimize bias from nonblinding should be explained. Investigators are expected to provide evidence that the factors that might influence outcome, such as age, stage of disease, medical history, and symptoms, are similar in patients assigned to the study protocol compared with patients assigned to placebo or traditional treatment. Published reports from the clinical trial are expected to include a table showing a comparison of the treatment groups with respect to potential confounders and to demonstrate that the groups did not differ in any important ways before the study began.

CONSORT Checklist

Clearly defining the outcome or criteria for successful treatment helps ensure unbiased assessment of the outcome. A well-designed clinical trial has a sufficient number of subjects enrolled to ensure that a "negative" study (one that does not show an effect of the treatment) has enough statistical power to evaluate the predetermined (a priori), expected treatment effect. **The Consolidated Standards of Reporting Trials (CONSORT) Statement is an evidence-based, minimum set of recommendations for reporting on randomized controlled trials developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials.** The 25-item CONSORT checklist (Table 4-2) and flow diagram (Fig. 4-1) offer a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation (9).

Table 4-1 Phases of Clinical Trials

Stage of Testing	Trial Aim	Numbers of Participants

Phase 1	Evaluate treatment safety, determine safe dosage range. Data are collected on the treatment (dose, when, and how it is taken) and how participants respond (in terms of effects and side effects).	Involve 20–100 healthy volunteers or people with the disease or condition
Phase 2	Evaluate treatment efficacy, further evaluate safety and tolerability.	Involve up to several hundred people with the disease or condition
Phase 3	Definitively determine the efficacy of treatment for the intended population, compare with other available treatments, assess adverse events and side effects.	Involve 30–3,000 participants, often within randomized clinical trials
Phase 4	Evaluate for uncommon serious side effects and adverse effects, optimal use including identifying subgroups that may benefit more or less from the treatment under study. These trials are particularly important for identifying rare adverse events when medications and devices are utilized in larger populations. These studies are conducted after the intervention has been approved by the FDA.	Large trials or observations studies, registries, with thousands of participants

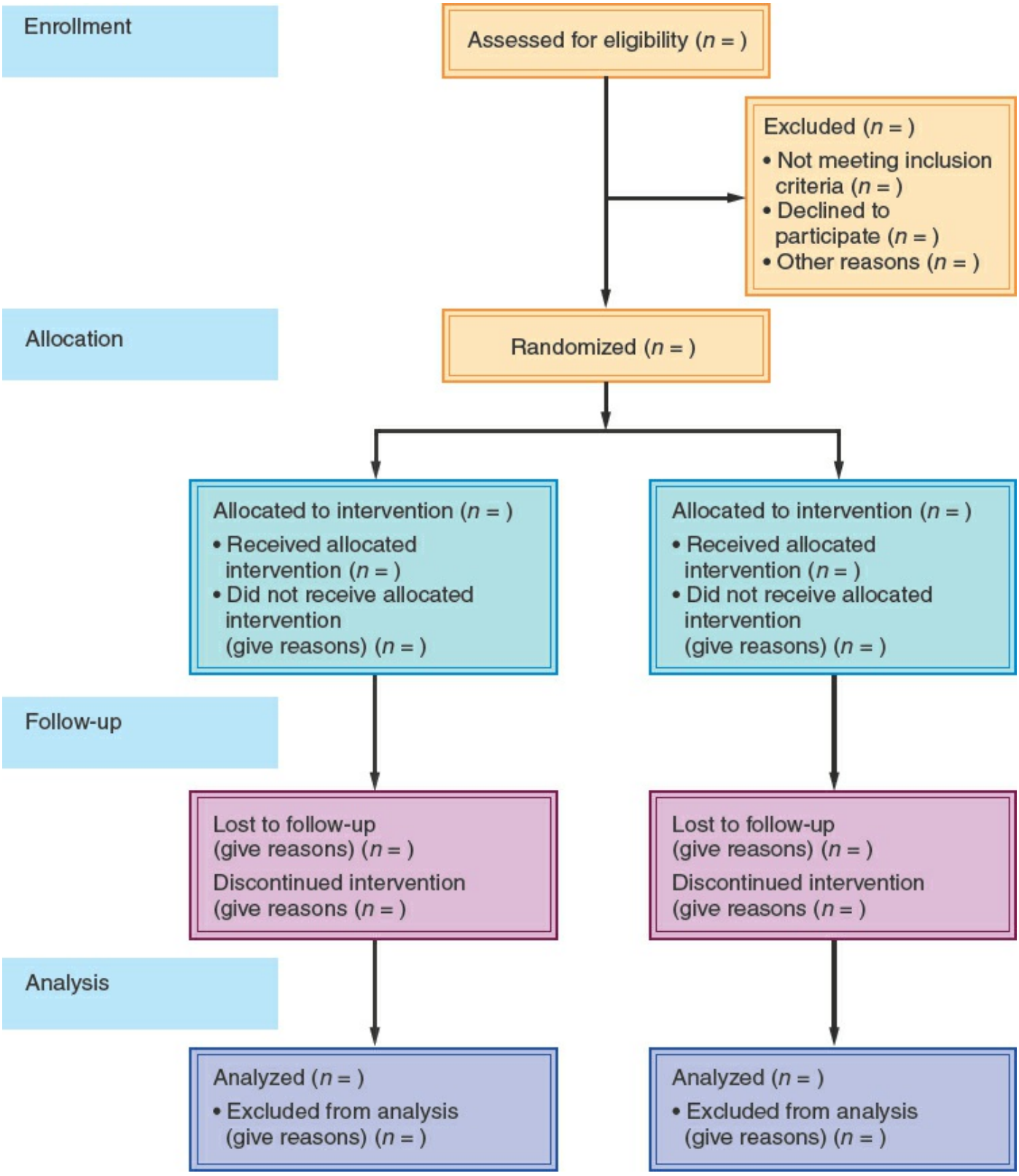


FIGURE 4-1 CONSORT flow diagram.

Clinical Trial Design Considerations

[3] Well-designed and correctly performed clinical trials can clearly determine the efficacy of an intervention and identify causal relationships, because they provide

information about the relative and absolute risks and minimize concerns about bias and confounding (see section Presenting and Understanding the Results of Analytic Studies). Potential weaknesses of clinical trials include cost restraints, length of time required to complete the study, feasibility of recruitment and implementation, and issues with applicability to populations outside of the strictly controlled study environment. Some clinical research questions are not amenable to clinical trials because of ethical issues with assigning patients to treatment groups, nature of the exposure being studied (such as socioeconomic status, weight, environmental exposures, and other patient characteristics), and urgent and emerging medical issues (e.g., the impact of Zika virus on pregnancy outcomes) (2).

When evaluating the results from a clinical trial, consider how restrictive inclusion and exclusion criteria may narrow the participant population to an extent that there may be concerns about external validity or generalizing the results. Other concerns include blinding, loss to follow-up, and clearly defining the outcome of interest. When the results of a randomized controlled trial do not show a significant effect of the treatment or intervention, the methods should be evaluated to understand what assumptions (expected power and effect size) were made to determine the necessary sample size for the study.

Intention-to-Treat Analysis

Randomized controlled trials should be evaluated with an intention-to-treat analysis, which means that all of the people randomized at the initiation of the trial should be accounted for in the analysis with the group to which they were assigned. Unless part of the overall study design, even if a participant stopped participating in the assigned treatment or "crossed over" to another treatment during the study, they should be analyzed with the group to which they were initially assigned. All of these considerations help to minimize bias in the design, implementation, and interpretation of a clinical trial (8).

Table 4-2 CONSORT Checklist

Section/Topic	Item No.	Checklist Item	Reported on Page No.
Title and Abstract			
	1a	Identification as a randomized trial in the title	_____
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[a]	_____
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	_____
	2b	Specific objectives or hypotheses	_____
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	_____
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	_____
Participants	4a	Eligibility criteria for participants	_____
	4b	Settings and locations where the data were collected	_____
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	_____
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	_____
	6b	Any changes to trial outcomes after the trial commenced, with reasons	_____
Sample size	7a	How sample size was determined	_____
	7b	When applicable, explanation of any interim analyses and stopping guidelines	_____
Randomization: sequence generation	8a	Method used to generate the random allocation sequence	_____
	8b	Type of randomization; details of any restriction (such as blocking and block size)	_____
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	_____
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	_____
Blinding	11a	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes) and how	_____
	11b	If relevant, description of the similarity of interventions	_____
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	_____
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	_____
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	_____
	13b	For each group, losses and exclusions after randomization, together with reasons	_____
Recruitment	14a	Dates defining the periods of recruitment and follow-up	_____
	14b	Why the trial ended or was stopped	_____
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	_____
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	_____
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	_____
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	_____

(*continued*)

Section/Topic	Item No.	Checklist Item	Reported on Page No.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	_____
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)[a]	_____
Discussions			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses	_____
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	_____
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	_____
Other Information			
Registration	23	Registration number and name of trial registry	_____
Protocol	24	Where the full trial protocol can be accessed, if available	_____
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	_____

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacologic treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

Observational Studies

Observational studies can evaluate exposures and outcomes that are not amenable to an experimental design (e.g., exposure is known or suspected to have harmful effects). Not all research questions can be addressed with clinical trials because of ethical issues (unethical to willingly subject participants to known harmful exposures), the nature of the exposures being studied (inherent participant characteristics), and feasibility issues (rare outcomes such as unusual adverse events and diseases).

Observational studies, including cohort, case-control, and cross-sectional studies, are analytic studies that take advantage of "natural experiments" in which exposure is not assigned by the investigator; rather, the individuals are assessed by the investigator for a potential exposure of interest (present or absent) and outcomes (present or absent). The timing of the evaluation of the exposure and outcome defines the study type.

Cohort Studies

Cohort studies often are referred to as longitudinal studies. Cohort studies involve identifying a group of exposed and unexposed individuals and following both groups over time to compare the rate of disease (or outcome) in the groups. Cohort studies may be prospective, meaning that the exposure is identified before outcome, or retrospective, in which the exposure and outcome have already occurred when the study is initiated. **Even in a retrospective cohort study, the study is defined by the fact that the cohorts were identified based on the exposure (not the outcome), and individuals should be free of disease (outcome) at the beginning time point for the**

cohort study (Fig. 4-2).

In a study that includes a survival analysis, the two cohort groups (exposed and unexposed) begin with a population that is 100% well (or alive) at the beginning of the study. The groups are followed over time to calculate the percentage of the cohort that is still well (or alive) at different time points during the study and at the end of the study. Although a survival analysis typically describes mortality after disease (i.e., cancer patients who died within 5 years), it can be adapted to other events and outcomes (e.g., the percentage of women who become pregnant while using long-acting contraceptives).

Cohort Study Design

Strengths of cohort studies include the ability to obtain attributable and relative risks (RRs) because the occurrence of the outcome is being compared in two groups (see section Presenting and Understanding the Results of Analytic Studies). In these studies, only associations can be established, not causality. Because randomization is not part of the study design, the investigator must consider that a factor associated with the exposure may lead to the outcome rather than the exposure itself. Misclassifying the exposure or the outcome and confounding variables are potential sources of bias in cohort studies.

Given that truly prospective cohort studies can be expensive and take a long time for completion, there should be compelling evidence for the public health importance of the exposure(s) and association(s) being addressed. Issues related to sample size and participant retention in the study protocol are as important in cohort studies as they are in randomized controlled trials.

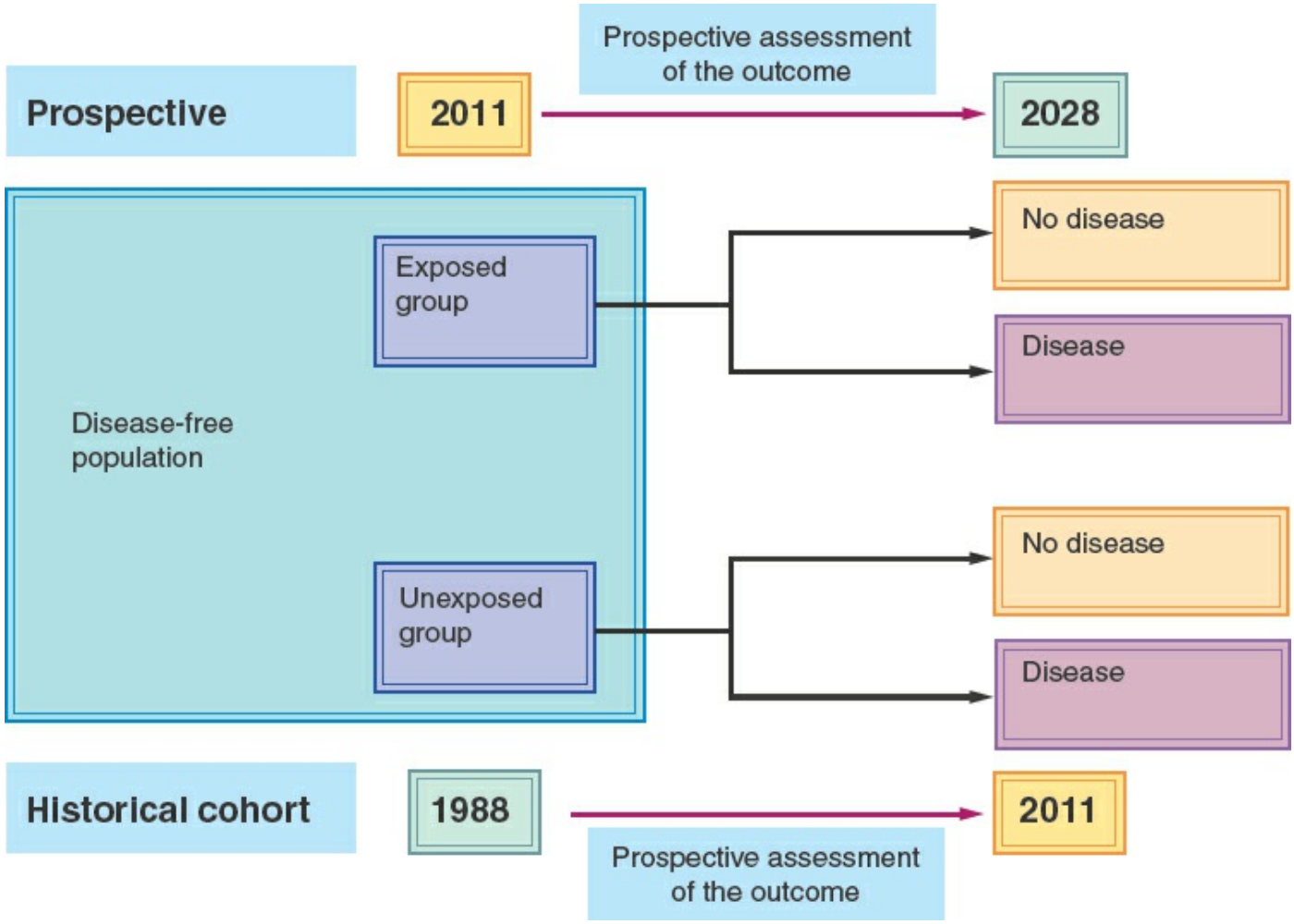


FIGURE 4-2 Schematic of prospective and retrospective cohort study designs.

Case-Control Studies

A case-control study starts with the identification of individuals with a disease or outcome of interest and a suitable control population without the disease or outcome of interest. The controls should represent a sample of the population from which the cases arose and who were at risk for the disease or outcome but did not develop it. The relationship between a particular attribute or exposure to the disease is retrospectively studied by comparing how the cases and controls differed in that exposure **(Fig. 4-3)**.

Odds Ratio

The measure of association for a case-control study is the odds ratio (OR), which is the ratio of exposed cases to unexposed cases, divided by the ratio of exposed to unexposed controls (see section Presenting and Understanding the Results of Analytic Studies). **If an entire population could be characterized by its exposure and disease status, the exposure OR would be identical to the RR obtainable from a cohort study of the same population.** Although the RR cannot be calculated directly from a

case-control study, it can be used as an estimate of the RR when the sample of cases and controls are representative of all people with or without the disease and when the disease being studied is uncommon. Attributable risk is not directly obtainable in a case-control study.

Case-Control Study Considerations

The advantages of case-control studies are that they are lower in cost and easier to conduct than other analytic studies. Case-control studies are most feasible for examining the association between a relatively common exposure and a relatively rare disease. Disadvantages include greater potential for selection bias, recall bias, and misclassification bias.

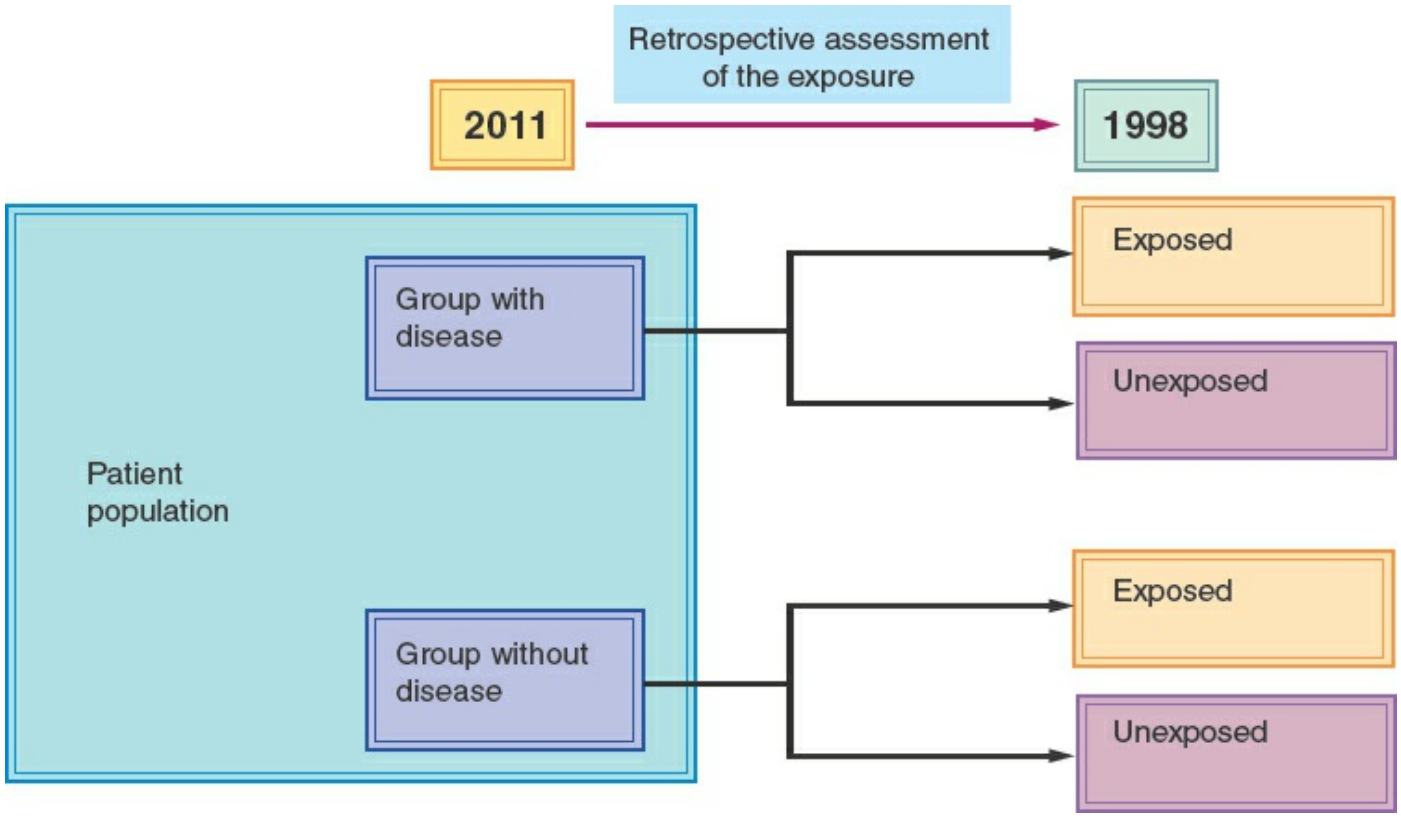


FIGURE 4-3 Schematic of case-control study design.

Case-control studies may be especially prone to selection bias and recall bias. Investigators need to understand sampling issues around which cases and controls were selected for their study and how these may have affected exposure rates. Subtle issues, such as interviewer technique, may affect the likelihood that cases may recall or report exposures more readily than controls.

Cross-Sectional Studies

Cross-sectional studies assess both the exposure and the outcome at the same point in time. Individuals are surveyed to provide a "snapshot" of health events in the

population at a particular time. Cross-sectional studies are often called prevalence studies because the disease exists at the time of the study, and the longitudinal follow-up and disease duration are not known. **Prevalence (PR) is the existing number of cases at a specific point in time.**

Cross-sectional studies are often done to evaluate a diagnostic test. The value of the test (predictor) is compared with the outcome (disease). The results of these evaluations are often presented as *sensitivity* and *specificity*. The sensitivity and specificity represent the characteristics of a given diagnostic test and do not vary by population characteristics. In contrast, the negative predictive value (NPV) and positive predictive value (PPV) of a test do vary with the baseline characteristics of a population such as PR of a disease **(Fig. 4-4)**.

Cross-Sectional Study Considerations

Although cross-sectional studies are primarily descriptive, they may contribute information about suggested risk factors for a disease by showing how that disease varies by age, sex, race, or geography. In *ecologic studies*, disease rates in various populations are correlated with other characteristics measured at the population level (such as diet, ultraviolet radiation exposure, work or home environment).

Caution must be used in interpreting findings from a cross-sectional study because there is no temporal relationship between the exposure and the outcome; therefore, causality cannot be established. Cross-sectional data can be valuable in informing analytic study designs or used as supporting data for documenting the consistency of an association.

DESCRIPTIVE STUDIES

Descriptive studies, case reports and case series, do not include comparison groups.

Case Reports and Case Series

In a case report or case series, the characteristics of individuals who have a particular exposure or outcome are described. Examples include series of patients with a particular disease, patients who had a particular surgical procedure, or an adverse outcome (such as ureteral injury at the time of hysterectomy). A case report usually describes an unusual clinical scenario or procedure in a single patient, whereas a case series usually includes a larger group of patients with similar exposures or outcomes. Although **members of a case series share a particular characteristic, it cannot be assumed that there is a cause-and-effect relationship.**

Hypotheses about exposures and disease may be developed from descriptive studies that should be explored in analytic studies. Because a case series has no

comparison group, statistical tests of association between the exposure and outcome cannot be performed. A case series usually does not yield any measure of association other than estimates of the frequency of a particular characteristic among members included in the case series.

PRESENTING AND UNDERSTANDING THE RESULTS OF ANALYTIC STUDIES

To present the results of clinical trials or observational studies, a variety of rates and measures may be derived, as summarized below. **To judge the scientific validity of the results of clinical studies, an investigator needs to consider whether the finding could have occurred simply by chance, by performing appropriate statistical testing, or if there are other possible explanations for the reported association, including bias or confounding.** Besides statistical significance and freedom from bias or confounding, there are several additional criteria that can be applied to judge whether the treatment truly did affect disease outcome or whether an exposure truly caused the outcome, as outlined below.

Rates and Measures

The terminology associated with rates and measures include the following (Fig. 4-5):

- ***Incidence (IR)*—frequency of newly identified disease or event (outcome).**
- ***Prevalence (PR)*—frequency of an existing disease or outcome during a specified period or point in time.**
- ***Odds Ratios (OR)*—ratio of the probability of an exposure in one group (cases) compared with probability of the exposure in another group (controls).**
- ***Relative Risk (RR)*—ratio of risk in the exposed group compared with the risk in the unexposed group.** If the RR = 1 (or not significantly different from 1) then the risk in the exposed group is equal to the risk in the unexposed group. RR >1 may suggest a positive association with the exposed group having greater risk than the unexposed group, whereas RR <1 implies a negative association with the exposed group having less risk than the unexposed group.
- ***Absolute Risk Reduction (ARR)*—the difference in risk between the unexposed (control) group and the exposed (treatment) group.**
- ***Relative Risk Reduction (RRR)*—the percentage of reduction in the risk comparing the unexposed (control) group to the exposed (treatment) group.**

- ***Number Needed to Treat (NNT)*—represents the number of people who would need treatment (or the intervention) to prevent one additional outcome (to calculate the NNT, take the inverse of the ARR, i.e., 1 ï ARR).**
- ***Sensitivity*—among the people who have the outcome, this is the proportion who have a positive test.**
- ***Specificity*—among the people who do not have the outcome, this is the proportion who have a negative test.**
- ***Negative Predictive Value (NPV)*—among the people who have a negative test, this is the proportion who do not have the outcome.**
- ***Positive Predictive Value (PPV)*—among the people who have a positive test, this is the proportion who have the outcome.**

	Disease +	Disease −	
Test +	95 (a)	5 (b)	100
Test −	5 (c)	95 (d)	100
	100	100	200

Prevalence of disease is 50%

Sensitivity (a/a + c): 95/100 = 95%
Specificity (d/b + d): 95/100 = 95%
PPV (a/a + b): 95/100 = 95%
NPV (d/c + d): 95/100 = 95%

	Disease +	Disease −	
Test +	95	50	145
Test −	5	950	955
	100	1,000	1,100

Prevalence of disease is 9%

Sensitivity: 95/100 = 95%
Specificity: 950/1,000 = 95%
PPV: 95/145 = 65.5%
NPV: 950/955 = 99.5%

FIGURE 4-4 Comparison of sensitivity, specificity, and predictive values when the prevalence of the disease varies.

	Outcome +	Outcome –
Exposure +	a	b
Exposure –	c	d
	100	100

- **Overall incidence rate (IR):** (a + c) ÷ (a + b + c + d)
- **Odds ratio (OR):** (a/b) ÷ (c/d)
- **Relative risk (RR):** (a/(a + b) ÷ (c/c + d))
- **Relative risk reductions (RRR):** 1-RR x 100%
- **Absolute risk reduction (ARR):** (a/(a + b)) – (d/(c + d))
- **Number needed to treat (NNT):** 1 ÷ ARR

FIGURE 4-5 Calculating rates and measures.

Statistical Testing

Statistical testing is used in clinical research for hypothesis testing in which the investigator is evaluating the study results against the null hypothesis (that there is

no difference between the groups). Results from statistical testing allow the investigator to evaluate how likely it is that the study result is caused by chance rather than an intervention or exposure (*p* value). In the case where a study failed to find a significant difference, it is equally important to describe the likelihood that the study conclusion was wrong and that a difference truly exists. Finally, it is important to provide as precise a measure of the treatment effect or association as possible and convey to the reader the plausible range in which the "true" effect resides (or confidence interval [CI]).

p Value and Statistical Significance

The *p* value is a reflection of the probability of a *type I error (alpha).* This reflects the probability that a difference between study groups could have arisen by chance alone. In other words, it is the probability that there is a difference between therapies, interventions, or observed groups when a true difference does not exist.

Historically in the medical literature, a *p* value of less than or equal to 0.05 was used to determine statistical significance. This reflects a probability of 1 in 20 that the null hypothesis was incorrectly rejected based on the results from the study sample. This *p* value may be adjusted downward if multiple associations are being tested and the chances of false discovery are high. In genome-wide association studies, in which hundreds of thousands of genetic variants are tested between groups, *p* values are frequently set at 10^{-7} (0.0000001).

Beta Error and Power

***Type II (or beta) error* reflects the probability of failing to reject the null hypothesis when in reality it is incorrect (i.e., there truly was a treatment effect or a difference between the observed groups).** In clinical trials it is important for the investigator to address the beta error, even in the design stage of the study. Study planners should determine the *power* (or 1 - the *beta error*) that they would like their study to have to detect an association and, given assumptions made about the differences expected between treatments, design the study size accordingly. Be aware that small clinical trials cited as evidence for "no effect of therapy," may not have an adequate sample size to address the study question; in essence, the study is not powered to detect the difference.

Confidence Intervals

CI provide the investigator an estimated range in which the true statistical measure (e.g., mean, proportion, and RR) is expected to occur. A 95% CI implies that if the study were to be repeated within the same sample population numerous times, the CI estimates would contain the true population parameter 95% of the time. In other words, the probability of observing the true value outside of this

range is less than 0.05. When evaluating measures of association, such as OR or RR with 95% CI, values that include 1 (no difference) are not considered statistically significant.

Meta-analysis

Meta-analysis is a quantitative study design that involves the systematic collection of data from previous studies, evaluation of the data, and combination of the data (where appropriate). Meta-analyses can improve precision of the effect measure and narrow the CI by aggregating treatment effects data from several clinical trials to provide a summary measure. Commonly performed by the Cochrane Collaboration within their systematic evidence reviews, well-designed meta-analyses can provide high-quality evidence that can be used for clinical decision making (10). There are important considerations in interpreting the meta-analysis, including whether studies were similar enough in their design, study population, and outcome measurement to be aggregated and whether or not there were sufficient good-quality studies available for analyses (2). Guides for systematic reviews and meta-analysis that involve randomized controlled trials (i.e., the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement) and observational studies (i.e., the Meta-analysis Of Observational Studies in Epidemiology [MOOSE] guidelines) are excellent resources for the investigator and the reviewer (11,12).

Bias

***Bias* is a systematic error in the design, conduct, or analysis of a study that can result in invalid conclusions.** It is important for an investigator to anticipate the types of bias that might occur in a study and correct them during the design of the study, because it may be difficult or impossible to correct for them in the analysis.

- ***Information bias* occurs when participants are classified incorrectly with respect to exposure or disease.** This may occur if records are incomplete or if the criteria for exposure or outcome were poorly defined, leading to misclassification.
- ***Recall bias* is a specific type of information bias that may occur if cases are more likely than controls to remember or to reveal past exposures.** In addition to establishing well-defined study criteria and accessing complete records, information bias may be reduced by blinding interviewers to a participant's study group.
- ***Selection bias* may occur when choosing cases or controls in a case-control study and when choosing exposed or unexposed subjects in a cohort study. A systematic error in selecting participants may influence the outcome by distorting the measure of association between the exposure and the**

outcome. Including an adequately large study sample and obtaining information about nonparticipants may reduce bias or provide information to evaluate potential selection bias.

Confounding

A *confounder* is a factor that is associated with the outcome (e.g., disease) and the exposure. The confounder may account for the apparent effect of the exposure on the disease or mask a true association. Confounders have unequal distributions between the study groups.

- Age, race, and socioeconomic status are potential confounders in many studies. Results may be adjusted for these variables by using statistical techniques such as stratification or multivariable analysis. Adjusting for confounding variables aids in understanding the association between the outcome and exposure if the confounding variables were constant.
- Multivariable analysis is a statistical technique commonly used in epidemiologic studies that simultaneously controls a number of confounding variables. The results from an adjusted analysis include the adjusted OR or RR that reflects an association between the exposure and the outcome and accounts for the specific known confounders that were included in the analysis.

Causality and Generalizability

The criteria needed to establish a causal relationship between two factors, especially exposure and disease, are defined (13). Although there are nine separate criteria for judging whether an association is likely to be causal, several of these criteria are most relevant for clinical studies.

- ***Biologic gradient*** *or* ***dose response*** refers to a relationship between exposure and outcome such that a change in the duration, amount, or intensity of the exposure is associated with a corresponding increase or decrease in disease risk.
- ***Plausibility*** refers to knowledge of the pathologic process of the disease or biologic effects of the exposure that would reasonably support an association. Plausibility overlaps with another concept, *coherence*, which also refers to compatibility with the known biology of the disease.
- ***Experiment*** refers to the evidence that the disease or outcome can be prevented or improved by an experiment that eliminates, reduces, or otherwise counters the exposure.
- ***Consistency*** refers to whether the association was repeatedly observed by different investigators, in different locations and circumstances.

- ***Temporality*** refers to the concept that cause must precede effect. For example, is it possible in a case-control study that symptoms of preclinical disease could lead to the exposure? Investigators must demonstrate that the exposure was present before the disease developed.
- ***Strength*** refers to the strength of association. The further the deviation of the RR or OR from 1, the stronger the association and the easier it is to accept that the study results are real. For example, studies have shown that the possession of a BRCA1 mutation may increase the lifetime risk for breast cancer by 14- to greater than 30-fold (varies by age) (14).

SUMMARY

Reviewing the medical literature is part of the ongoing education for those who provide clinical care. Incorporating research findings into clinical care is enhanced by understanding different study designs, their strengths and weaknesses, and the measures of association they are able to provide. Evaluating whether there is enough evidence available to support changing a specific medication, procedure, or protocol used to care for patients is the cornerstone to improving clinical practice. In a field that is rapidly progressing, understanding clinical research helps physicians provide optimal care for the women they treat every day.

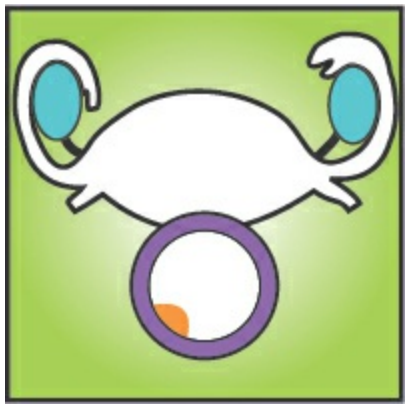
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CHAPTER 5

Anatomy and Embryology



Shannon L. Wallace, Eric R. Sokol

Embryonic Development
- Urinary System
  - *Kidneys, Renal Collecting System, Ureters*
- Genital System
  - *Internal Reproductive Organs*
  - *External Genitalia*
- Clinical Correlations
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  - *Pelvic Bone Articulations*
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  - *Lateral Wall*
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- Blood Vessels
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Pelvic Viscera

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The Genital Tract and Its Relations

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- Peritoneal Cavity
- Ureter
- Pelvic Floor
- Endopelvic Fascia
- Obturator Space

Summary

KEY POINTS

1 Approximately 10% of infants are born with some abnormality of the genitourinary system, and anomalies in one system are often mirrored by anomalies in another system that provide special

implications in pelvic surgery.

2 An understanding of the development of pelvic floor disorders and their safe and effective management requires a comprehensive knowledge of the interrelationships between the bony pelvis and its ligaments, pelvic muscles and fasciae, nerves and blood vessels, and pelvic viscera.

3 A comprehensive knowledge of pelvic anatomy is crucial for the pelvic surgeon. This understanding of specific anatomic relationships is required for safe and successful surgery, as well as the development of new clinical and surgical techniques.

4 There is significant variation in the branching pattern of pelvic blood vessels between individuals, and patterns of blood flow may be asymmetric from side to side in the same individual. The pelvic surgeon should be prepared for deviations from "textbook" vascular patterns.

5 About 75% of all iatrogenic injuries to the ureter result from gynecologic procedures, most commonly laparoscopic hysterectomy; risk is increased with distortions of pelvic anatomy, including adnexal masses, endometriosis, other pelvic adhesive disease, or fibroids.

6 An understanding of the embryologic development and anatomy of the female pelvis is fundamental to the knowledge base of a practicing gynecologist.

The anatomy of the fundamental supporting structures of the pelvis, including the genital, urinary, and gastrointestinal viscera, are presented in this chapter. Because significant variation has developed in the names of many common anatomic structures, the terms used here reflect current nomenclature according to the *Nomina Anatomica*; other commonly accepted terms are included in parentheses (1).

EMBRYONIC DEVELOPMENT

The female urinary and genital tracts are closely related, anatomically and embryologically. Both are derived largely from primitive mesoderm and endoderm, and there is evidence that the embryologic urinary system has an important inductive [1] influence on the developing genital system. **About 10% of infants are born with some abnormality of the genitourinary system, and anomalies in one system are often mirrored by anomalies in another system (2).**

Developmental defects may play a significant role in the differential diagnosis of certain clinical conditions and have special implications in pelvic surgery (2–7). **Thus, it is important for gynecologists to have a basic understanding of embryology.**

Following is a presentation of the urinary system, internal reproductive organs, and external genitalia in order of their initial appearance, although much of the development of each of these three regions proceeds synchronously at an early embryologic age (Table 5-1).

Urinary System

Kidneys, Renal Collecting System, Ureters

The kidneys, renal collecting system, and ureters derive from the longitudinal mass

of mesoderm (known as the nephrogenic cord) found on each side of the primitive aorta. This process gives rise to three successive sets of increasingly advanced urinary structures, each developing more caudal to its predecessor.

The *pronephros*, or "first kidney," is rudimentary and nonfunctional; it is succeeded by the "middle kidney," or *mesonephros*, which is believed to function briefly before regressing. Although the *mesonephros* is transitory as an excretory organ, its duct, the *mesonephric (wolffian) duct*, is of singular importance for the following reasons:

1. It grows caudally in the developing embryo to open, for the first time, an excretory channel into the primitive cloaca and the "outside world."
2. It serves as the starting point for development of the metanephros, which becomes the definitive kidney.
3. It ultimately differentiates into the sexual duct system in the male.
4. Although regressing in female fetuses, there is evidence that the mesonephric duct may have an inductive role in development of the paramesonephric or müllerian duct (3).

The ureteric buds, which sprout from the distal mesonephric ducts, initiate the development of the *metanephros*; these buds extend cranially and penetrate the portion of the nephrogenic cord known as the *metanephric blastema.* The ureteric buds begin to branch sequentially, with each growing tip covered by metanephric blastema. Ultimately, the metanephric blastema forms the renal functional units (the nephrons), whereas the ureteric buds become the collecting duct system of the kidneys (collecting tubules, minor and major calyces, renal pelvis) and the ureters. Although these primitive tissues differentiate along separate paths, they are interdependent on inductive influences—neither can develop alone.

The kidneys initially lie in the pelvis but subsequently ascend to their permanent location, rotating almost 90 degrees in the process as the more caudal part of the embryo in effect grows away from them. Their blood supply, which first arises as branches of the middle sacral and common iliac arteries, comes from progressively higher branches of the aorta until the definitive renal arteries form and previous vessels regress. **The definitive kidneys become functional in the late 7th to early 8th weeks of gestation.**

Table 5-1 Development of Genital and Urinary Tracts by Embryologic Age

Weeks of Gestation	Genital Development	Urinary Development
4–6	Urorectal septum	Pronephros
	Formation of cloacal folds,	Mesonephros/mesonephric duct

	genital tubercle	
	Ureteric buds, metanephros	
	Genital ridges	Exstrophy of mesonephric ducts and ureters into bladder wall
6–7	End of indifferent phase of genital development	Major, minor calyces form
	Development of primitive sex cords	Kidneys begin to ascend
	Formation of paramesonephric ducts	
	Labioscrotal swellings	
8–11	Distal paramesonephric ducts begin to fuse	Kidney becomes functional
	Formation of sinuvaginal bulbs	
12	Development of clitoris and vaginal vestibule	
20	Canalization of vaginal plate	
32	Renal collecting duct system complete	

Bladder and Urethra

The cloaca forms as the result of dilation of the opening to the fetal exterior. During the 7th week of gestation, the cloaca is partitioned by the mesenchymal urorectal septum into an anterior urogenital sinus and a posterior rectum. The bladder and urethra form from the most superior portion of the urogenital sinus, with surrounding mesenchyme contributing to their muscular and serosal layers. The remaining inferior urogenital sinus is known as the *phallic* or *definitive urogenital sinus*. Concurrently, the distal mesonephric ducts and attached ureteric buds are incorporated into the posterior bladder wall in the area that will become the bladder trigone. As a result of the absorption process, the mesonephric duct ultimately opens independently into the urogenital sinus below the bladder neck.

The *allantois*, which is a vestigial diverticulum of the hindgut that extends into the umbilicus and is continuous with the bladder, loses its lumen and becomes the fibrous band known as the *urachus* or *median umbilical ligament*. **In rare instances, the urachal lumen remains partially patent, with formation of urachal cysts, or completely patent, with the formation of a urinary fistula to the umbilicus** (4).

Genital System

Although genetic gender is determined at fertilization, the early genital system is indistinguishable between the two genders in the embryonic stage. This is known as the "indifferent stage" of genital development, during which both male and female fetuses have gonads with prominent cortical and medullary regions, dual sets of genital ducts, and external genitalia that appear similar. Male sexual differentiation is an "active" process requiring the presence of the SRY gene (gender-determining region), located on the short arm of the Y chromosome. Clinically, **gender is not apparent until about the 12th week of embryonic life and depends on the elaboration of testis-determining factor and, subsequently, androgens by the male gonad.** Female development is called the "basic developmental path of the human embryo," requiring not estrogen but the absence of testosterone.

Internal Reproductive Organs

The *primordial germ cells* migrate from the yolk sac through the mesentery of the hindgut to the posterior body wall mesenchyme at about the 10th thoracic level, which is the initial site of the future ovary (Figs. 5-1 and 5-2). When the germ cells reach this area, they induce proliferation of cells in the adjacent mesonephros and celomic epithelium to form a pair of *genital ridges* medial to the mesonephros. This occurs during the 5th week of gestation. The development of the gonad is absolutely dependent on this proliferation because these cells form a supporting aggregate of cells (the primitive sex cords) that invest the germ cells and without which the gonad would degenerate.

Müllerian Ducts

The *paramesonephric or müllerian ducts* form lateral to the mesonephric ducts; they grow caudally and then medially to fuse in the midline. They contact the urogenital sinus in the region of the posterior urethra at a slight thickening known as the *sinus tubercle.* Subsequent sexual development is controlled by the presence or absence of testis-determining factor, encoded on the Y chromosome and elaborated by the somatic sex cord cells. Testis-determining factor causes the degeneration of the gonadal cortex and differentiation of the medullary region of the gonad into Sertoli cells.

The Sertoli cells secrete a glycoprotein known as *anti-müllerian hormone* (AMH), which causes regression of the paramesonephric duct system in the male embryo and is the likely signal for differentiation of Leydig cells from the surrounding mesenchyme. The Leydig cells produce testosterone and, with the converting enzyme 5α-reductase, dihydrotestosterone. Testosterone is responsible for evolution of the mesonephric duct system into the vas deferens, epididymis, ejaculatory ducts, and seminal vesicle. At puberty, testosterone leads to spermatogenesis and changes in primary and secondary sex characteristics. Dihydrotestosterone triggers the

development of the male external genitalia and the prostate and bulbourethral glands. In the absence of testis-determining factor, the medulla regresses, and the cortical sex cords break up into isolated cell clusters (the primordial follicles).

The germ cells differentiate into oogonia and enter the first meiotic division as primary oocytes, at which point development is arrested until puberty. In the absence of AMH, the mesonephric duct system degenerates, although in at least one-fourth of adult women, remnants may be found in the mesovarium (*epoophoron, paroophoron*) or along the lateral wall of the uterus or vagina (*Gartner duct cyst*) (5).

The paramesonephric duct system subsequently develops. The inferior fused portion becomes the *uterovaginal canal*, which later becomes the epithelium and glands of the uterus and the upper vagina. The endometrial stroma and myometrium differentiate from surrounding mesenchyme. The cranial unfused portions of the paramesonephric ducts open into the celomic (future peritoneal) cavity and become the *fallopian tubes*.

The fusion of the paramesonephric ducts brings together two folds of peritoneum, which become the broad ligament and divide the pelvic cavity into a posterior rectouterine and anterior vesicouterine pouch or cul-de-sac. Between the leaves of the broad ligament, mesenchyme proliferates and differentiates into loose areolar connective tissue and smooth muscle.

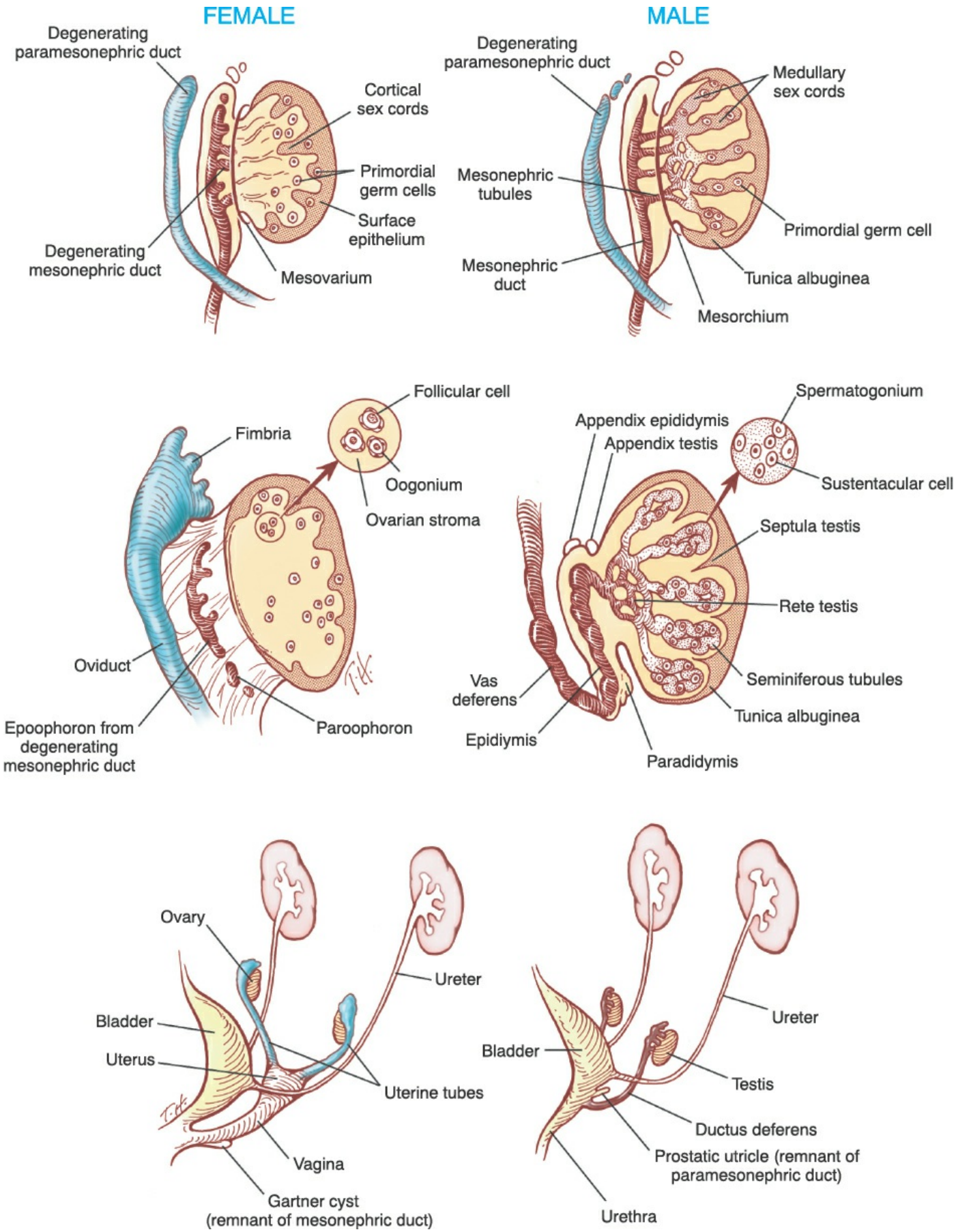

FEMALE
MALE
Degenerating paramesonephric duct
Cortical sex cords
Primordial germ cells
Surface epithelium
Degenerating mesonephric duct
Mesovarium
Degenerating paramesonephric duct
Medullary sex cords
Mesonephric tubules
Primordial germ cell
Mesonephric duct
Tunica albuginea
Mesorchium
Follicular cell
Fimbria
Oogonium
Ovarian stroma
Oviduct
Epoophoron from degenerating mesonephric duct
Paroophoron
Spermatogonium
Appendix epididymis
Appendix testis
Sustentacular cell
Septula testis
Rete testis
Seminiferous tubules
Vas deferens
Tunica albuginea
Epidiymis
Paradidymis
Ovary
Ureter
Bladder
Uterus
Uterine tubes
Vagina
Gartner cyst (remnant of mesonephric duct)
Ureter
Bladder
Testis
Ductus deferens
Prostatic utricle (remnant of paramesonephric duct)
Urethra

FIGURE 5-1 The comparative changes of the female and male during early embryonic development.

Vagina

The *vagina* forms in the 3rd month of embryonic life. While the uterovaginal canal is forming, the endodermal tissue of the sinusal tubercle begins to proliferate, forming a pair of *sinovaginal bulbs*, which become the inferior 20% of the vagina. The most inferior portion of the uterovaginal canal becomes occluded by a solid core of tissue (the *vaginal plate*), the origin of which is unclear. Over the subsequent 2 months, this tissue elongates and canalizes by a process of central desquamation, and the peripheral cells become the vaginal epithelium. The fibromuscular wall of the vagina originates from the mesoderm of the uterovaginal canal. The hymen is a thin fold of membrane that remains to a varying degree between the dilated, canalized, fused sinovaginal bulbs and the urogenital sinus.

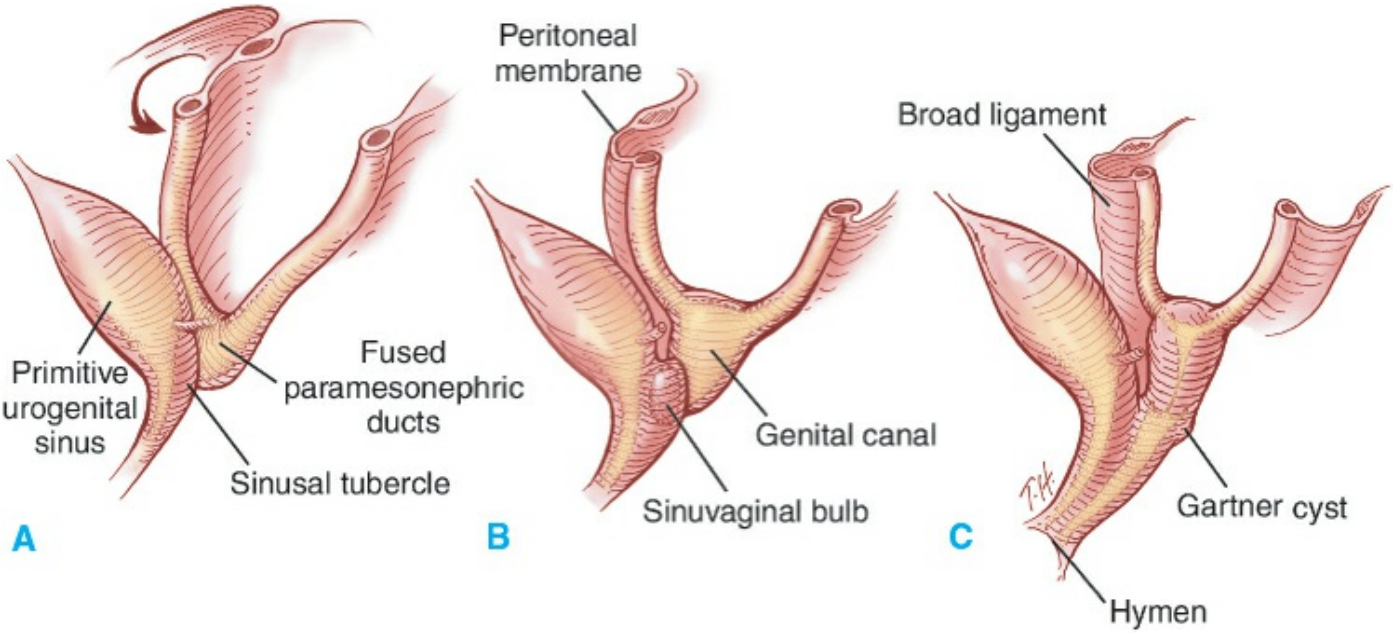


FIGURE 5-2 The embryonic development of the female genital tract. The formation of the uterus and vagina. **A:** The uterus and superior end of the vagina begin to form as the paramesonephric ducts fuse together near their attachment to the posterior wall of the primitive urogenital sinus. **B,C:** The ducts then zipper together in a superior direction between the 3rd and 5th months. As the paramesonephric ducts are pulled away from the posterior body wall, they drag a fold of peritoneal membrane with them, forming the broad ligaments of the uterus. **A–C:** The inferior end of the vagina forms from the sinovaginal bulbs on the posterior wall of the primitive urogenital sinus.

Accessory Genital Glands

The female accessory genital glands develop as outgrowths from the urethra (*paraurethral* or *Skene*) and the definitive urogenital sinus (*greater vestibular* or *Bartholin*). Although the ovaries first develop in the thoracic region, they ultimately arrive in the pelvis by a complicated process of descent. This descent by differential

growth is under the control of a ligamentous cord called the *gubernaculum*, which is attached to the ovary superiorly and to the fascia in the region of the future labia majora inferiorly. The gubernaculum becomes attached to the paramesonephric ducts at their point of superior fusion so that it becomes divided into two separate structures. As the ovary and its mesentery (the mesovarium) are brought into the superior portion of the broad ligament, the more proximal part of the gubernaculum becomes the *ovarian ligament*, and the distal gubernaculum becomes the *round ligament*.

External Genitalia

Early in the 5th week of embryonic life, folds of tissue form on each side of the cloaca and meet anteriorly in the midline to form the genital tubercle (Fig. 5-3). With the division of the cloaca by the urorectal septum and consequent formation of the perineum, these cloacal folds are known anteriorly as the *urogenital folds* and posteriorly as the *anal folds*. The genital tubercle begins to enlarge. In the female embryo, its growth gradually slows to form the clitoris, and the urogenital folds form the labia minora. In the male embryo, the genital tubercle continues to grow to form the penis, and the urogenital folds are believed to fuse to enclose the penile urethra. Lateral to the urogenital folds, another pair of swellings develops, known in the indifferent stage as *labioscrotal swellings*. In the absence of androgens, they remain largely unfused to become the labia majora. The definitive urogenital sinus gives rise to the vaginal vestibule, into which open the urethra, vagina, and greater vestibular glands.

Clinical Correlations

Developmental abnormalities of the urinary and genital systems can be explained and understood by a consideration of female and male embryologic development. [1] The intertwined development of these two systems may cause abnormalities in one to be associated with abnormalities in the other (6).

Urinary System

Urinary tract anomalies arise from defects in the ureteric bud, the metanephric blastema, or their inductive interaction with each other.

Renal Agenesis

Renal agenesis occurs when one or both ureteric buds fail to form or degenerate, and the metanephric blastema is therefore not induced to differentiate into nephrons. Bilateral renal agenesis is incompatible with postnatal survival, but infants with only one kidney usually survive, and the single kidney undergoes compensatory hypertrophy. **Unilateral renal agenesis is often associated with absence or abnormality of fallopian tubes, uterus, or vagina—the paramesonephric duct derivatives**.

Abnormalities of Renal Position

Abnormalities of renal position result from disturbance in the normal ascent of the kidneys. A malrotated pelvic kidney is the most common result; a horseshoe kidney, in which the kidneys are fused across the midline, occurs in about 1 in 600 individuals and has a final position lower than usual because its normal ascent is prevented by the root of the inferior mesenteric artery.

Duplication of the Upper Ureter and Renal Pelvis

Duplication of the upper ureter and renal pelvis is relatively common and results from premature bifurcation of the ureteric bud. If two ureteric buds develop, there will be complete duplication of the collecting system. In this situation, one ureteric bud will open normally into the posterior bladder wall, and the second bud will be carried more distally within the mesonephric duct to form an ectopic ureteral orifice into the urethra, vagina, or vaginal vestibule; incontinence is the primary presenting symptom. Most of the aforementioned urinary abnormalities remain asymptomatic unless obstruction or infection supervenes. In that case, anomalous embryologic development must be included in the differential diagnosis.

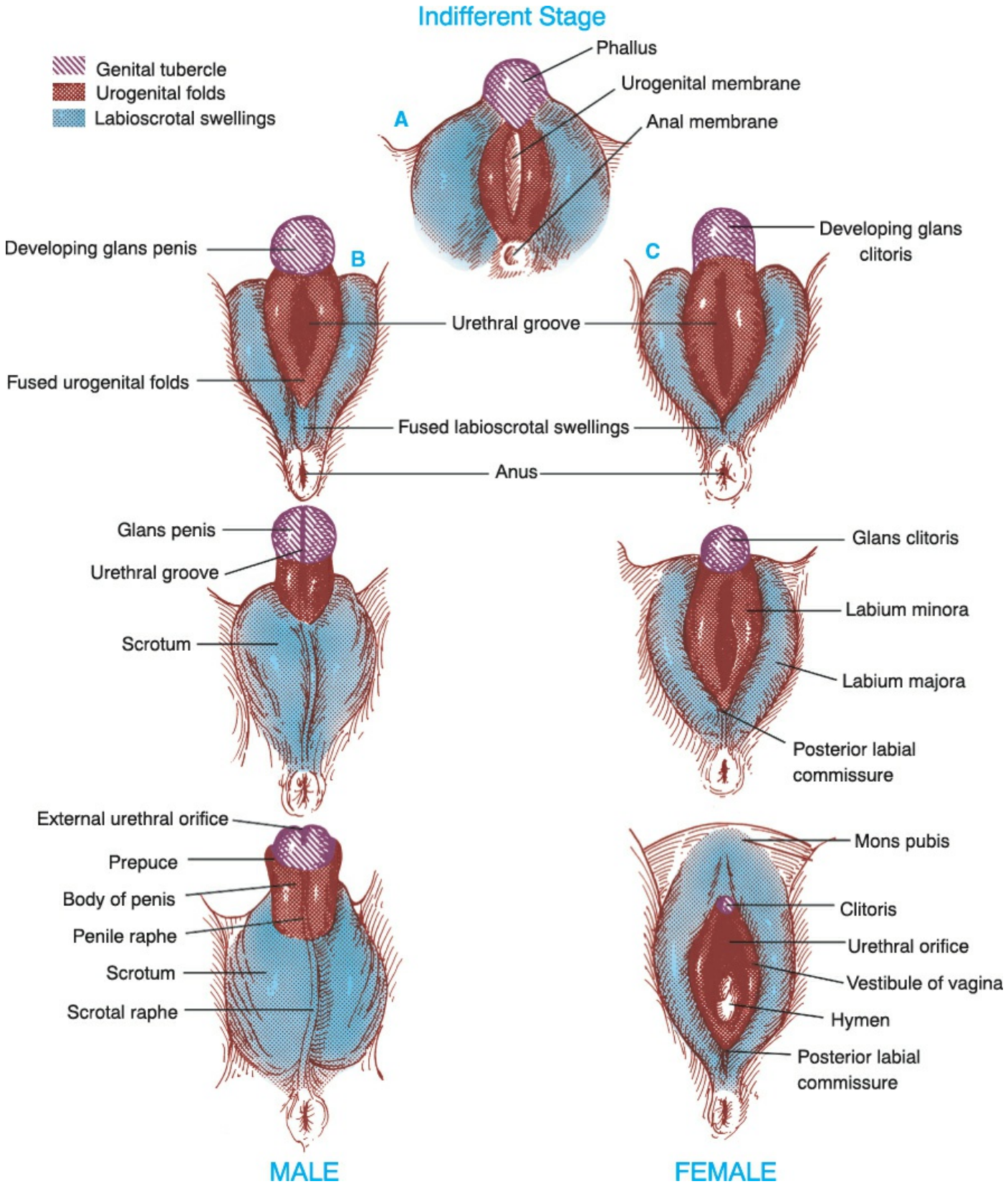


FIGURE 5-3 The comparative development of the female and male external genitalia. **A:** In both sexes, the development follows a uniform pattern through the 7th week and thereafter begins to differentiate. **B:** The male external genitalia. **C:** The female external genitalia.

Because the early development of the genital system is similar in both sexes, congenital defects in sexual development, usually arising from a variety of chromosomal abnormalities, tend to present clinically with ambiguous external genitalia. These conditions are known as *intersex conditions* or *hermaphroditism* and are classified according to the histologic appearance of the gonads.

True Hermaphroditism

Individuals with true hermaphroditism have both ovarian and testicular tissue, most commonly as composite ovotestes but occasionally with an ovary on one side and a testis on the other. In the latter case, a fallopian tube and a single uterine horn may develop on the side with the ovary because of the absence of local AMH. True hermaphroditism is an extremely rare condition associated with chromosomal mosaicism, mutation, or abnormal cleavage involving the X and Y chromosomes.

Pseudohermaphroditism

In individuals with pseudohermaphroditism, the genetic gender indicates one gender, whereas the external genitalia have characteristics of the other gender. Males with pseudohermaphroditism are genetic males with feminized external genitalia, most commonly manifesting as hypospadias (urethral opening on the ventral surface of the penis) or incomplete fusion of the urogenital or labioscrotal folds. Females with pseudohermaphroditism are genetic females with virilized external genitalia, including clitoral hypertrophy and some degree of fusion of the urogenital or labioscrotal folds. Both types of pseudohermaphroditism are caused either by abnormal levels of sex hormones or abnormalities in the sex hormone receptors.

Another major category of genital tract abnormalities involves various types of uterovaginal malformations, which occur in 0.16% of women (Fig. 5-4) (7). These malformations are believed to result from one or more of the following situations:

1. Improper fusion of the paramesonephric ducts
2. Incomplete development of one paramesonephric duct
3. Failure of part of the paramesonephric duct on one or both sides to develop
4. Absent or incomplete canalization of the vaginal plate

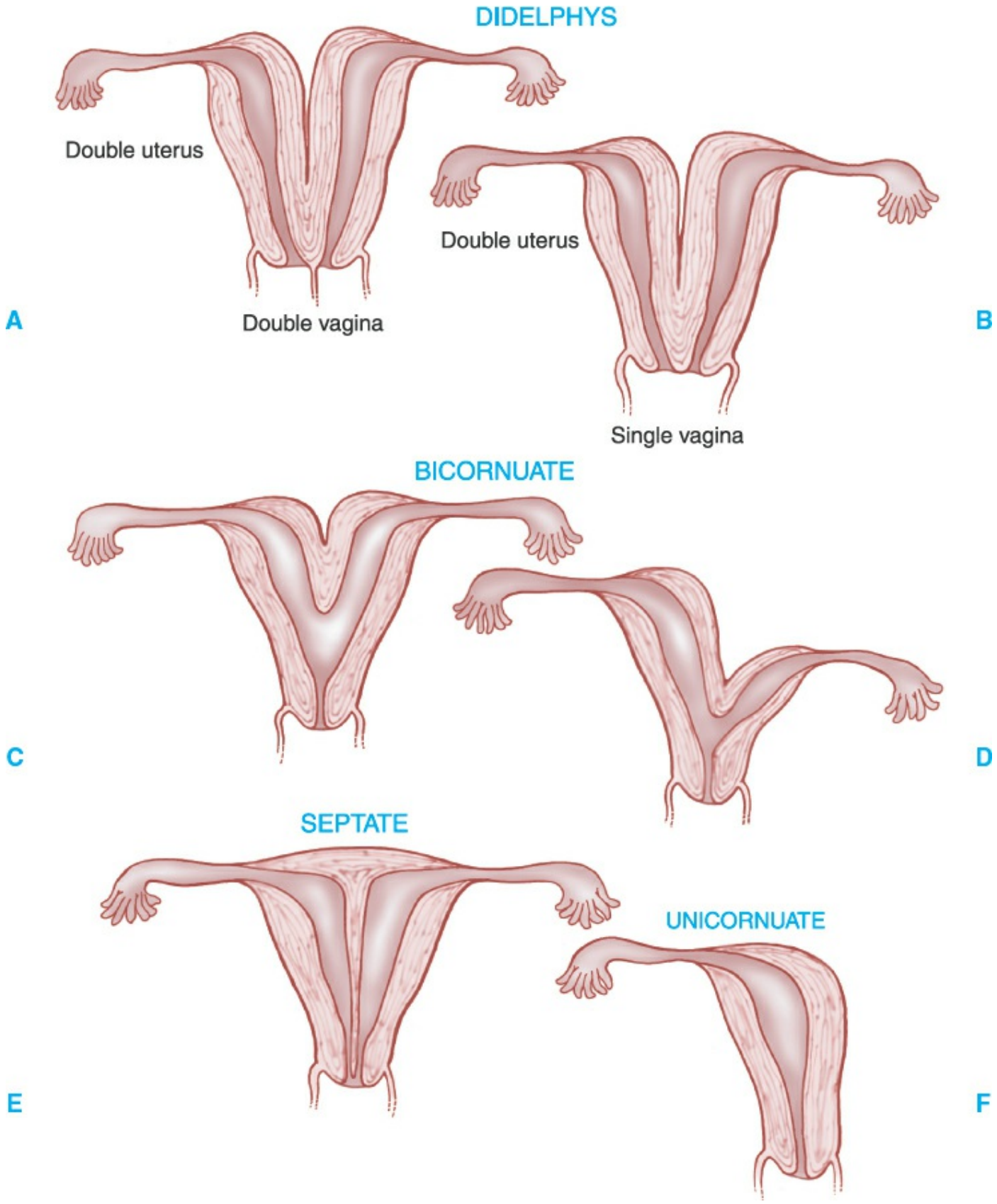


FIGURE 5-4 Types of congenital abnormalities. **A:** Double uterus (uterus didelphys) and double vagina. **B:** Double uterus with single vagina. **C:** Bicornuate uterus. **D:** Bicornuate uterus with a rudimentary left horn. **E:** Septate uterus. **F:** Unicornuate uterus.

PELVIC STRUCTURE

Bony Pelvis

The skeleton of the pelvis is formed by the sacrum and coccyx and the paired hip bones (coxal, innominate), which fuse anteriorly to form the symphysis pubis. Figure 5-5 illustrates the bony pelvis as well as its ligaments and foramina.

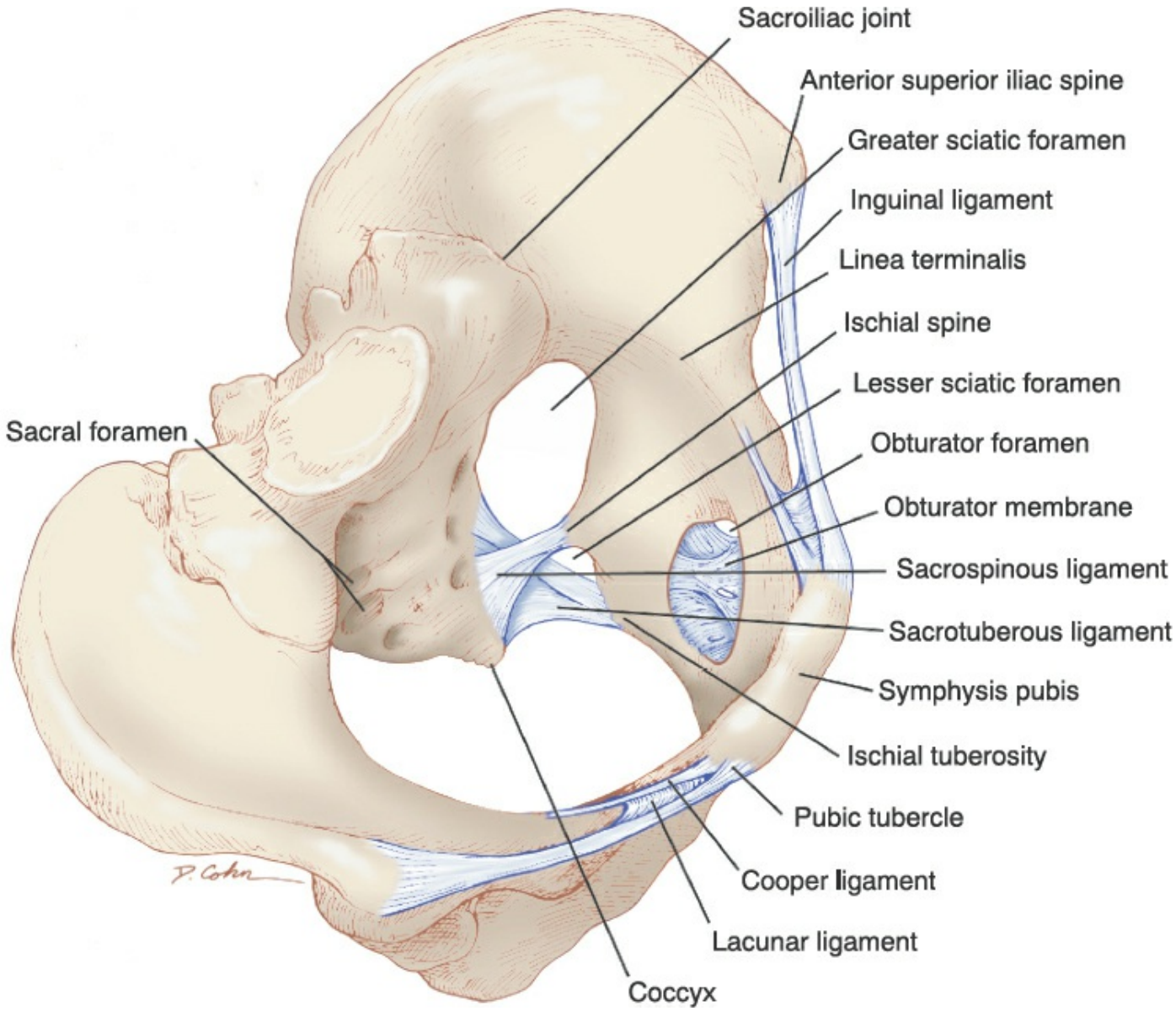


FIGURE 5-5 The female pelvis. The pelvic bones (the innominate bone, sacrum, and coccyx) and their joints, ligaments, and foramina.

Sacrum and Coccyx

The sacrum and coccyx are an extension of the vertebral column resulting from the five fused sacral vertebrae and the four fused coccygeal vertebrae. They are joined by a symphyseal articulation (sacrococcygeal joint), which allows some movement.

The essential features of the sacrum and coccyx are as follows:

1. **Sacral promontory**—the most prominent and anterior projection of the sacrum; this is an important landmark for insertion of a laparoscope and for sacrocolpopexy. It is located just below the level of bifurcation of the common iliac arteries.
2. **Four paired anterior and posterior sacral foramina—**exit sites for the anterior and posterior rami of the corresponding sacral nerves; the lateral sacral vessels also traverse the anterior foramina.
3. **Sacral hiatus—**results from incomplete fusion of the posterior lamina of the fifth sacral vertebra, offering access to the sacral canal, which is clinically important for caudal anesthesia.

Laterally, the alae ("wings") of the sacrum offer auricular surfaces that articulate with the hip bones to form synovial sacroiliac joints.

Os Coxae

The paired *os coxae*, or hip bones, have three components: the ilium, the ischium, and the pubis. These components meet to form the acetabulum, a cup-shaped cavity that accommodates the femoral head.

Ilium

1. **Iliac crest**—provides attachments to the iliac fascia, abdominal muscles, and fascia lata.
2. **Anterior superior and inferior spine**—superior spine provides the point of fixation of the inguinal ligament and is clinically important as a lateral landmark for laparoscopic entry.
3. **Posterior superior and inferior spine**—superior spine is the point of attachment for the sacrotuberous ligament and the posterior sacroiliac ligament.
4. **Arcuate line**—marks the pelvic brim and lies between the first two segments of the sacrum.
5. **Iliopectineal eminence (linea terminalis)**—the junction line of the ilium and the pubis.
6. **Iliac fossa**—the smooth anterior concavity of the ilium, covered by the iliacus muscle.

Ischium

1. **Ischial spine**—delineates the greater and lesser sciatic notch above and below it. It is the point of fixation for the sacrospinous ligament and the arcus tendineus fasciae pelvis (white line); the ischial spine represents an important landmark in the performance of pudendal nerve block and sacrospinous ligament vaginal suspension;

vaginal palpation during labor allows detection of progressive fetal descent.

2. **Ischial ramus**—joins the pubic rami to encircle the obturator foramen; provides the attachment for the inferior fascia of the urogenital diaphragm and the perineal musculofascial attachments.
3. **Ischial tuberosity**—the rounded bony prominence upon which the body rests in the sitting position; a clinical landmark for the passage of the inferior arm of anterior vaginal mesh kit systems.

Pubis

1. **Body**—formed by the midline fusion of the superior and inferior pubic rami.
2. **Symphysis pubis**—a fibrocartilaginous symphyseal joint where the bodies of the pubis meet in the midline, allows for some resilience and flexibility, which is critical during parturition.
3. **Superior and inferior pubic rami**—join the ischial rami to encircle the obturator foramen; provide the origin for the muscles of the thigh and leg; provide the attachment for the inferior layer of the urogenital diaphragm; the inferior rami is a clinical landmark for transobturator incontinence sling passage.
4. **Pubic tubercle**—a lateral projection from the superior pubic ramus, to which the inguinal ligament, rectus abdominis, and pyramidalis attach.

Clinical Considerations

[2] Studies using magnetic resonance imaging (MRI) or computed tomography (CT) pelvimetry found an association between the architecture of the bony pelvis, specifically a wider transverse inlet (distance between the most superior aspects of the iliopectineal line), a shorter obstetric conjugate (shortest distance between the sacral promontory and the pubic symphysis), a larger pelvic floor area, and the occurrence of pelvic floor disorders (8,9). Pelvic dimensions can increase the likelihood of pelvic floor damage during childbirth and predispose some women to structural failure later in life. It is theorized that women with a wide pelvic inlet may be more likely to suffer neuromuscular and connective tissue injuries during labor and delivery, increasing the risk of developing pelvic neuropathy, pelvic organ prolapse, or both (8,9). A loss of lumbar lordosis and a pelvic inlet that is less vertically oriented are more common in women who develop genital prolapse than in those who do not (10,11). A less vertical orientation of the pelvic inlet is thought to result in an alteration of the intra-abdominal forces that are normally directed anteriorly to the pubic symphysis such that a greater proportion is directed toward the pelvic viscera and their connective tissue and muscular supports. Recent studies have shown that a larger pelvis with a larger cross-sectional area is subject to more downward intra-abdominal force (12,13). This research complements previous theories that smaller pelvises may be protective (8).

Studies have demonstrated a decreased risk of pelvic floor disorders for African American women, which may be mediated by their relatively narrower pelvises (14). However, the understanding of pelvic shape is still rudimentary. One MRI study, in which only white women were enrolled to remove race as a potential confounder, found that bony pelvis dimensions were similar at the level of the muscular pelvic floor with and without pelvic organ prolapse (15).

Pelvic Bone Articulations

The pelvic bones are joined by four articulations (two pairs):

1. **Two cartilaginous symphyseal joints—the sacrococcygeal joint and the symphysis pubis**—these joints are surrounded by strong ligaments anteriorly and posteriorly, which are responsive to the effect of relaxin and facilitate parturition.
2. **Two synovial joints—the sacroiliac joints**—these joints are stabilized by the sacroiliac ligaments, the iliolumbar ligament, the lateral lumbosacral ligament, the sacrotuberous ligament, and the sacrospinous ligament.

The pelvis is divided into the *greater* and *lesser pelvis* by an oblique plane passing through the sacral promontory, the *linea terminalis* (*arcuate line of the ilium*), the pectineal line of the pubis, the pubic crest, and the upper margin of the symphysis pubis. This plane lies at the level of the superior pelvic aperture (*pelvic inlet*) or pelvic brim. The inferior pelvic aperture or *pelvic outlet* is irregularly bound by the tip of the coccyx, the symphysis pubis, and the ischial tuberosities. The dimensions of the superior and inferior pelvic apertures have important obstetric implications.

Ligaments

Four ligaments—inguinal, Cooper's, sacrospinous, and sacrotuberous—of the bony pelvis are of special importance to the gynecologic surgeon.

Inguinal Ligament

The inguinal ligament is important surgically in the repair of inguinal hernia. The inguinal ligament:

1. Is formed by the lower border of the aponeurosis of the external oblique muscle folded back upon itself.
2. Is fused laterally to the iliacus fascia and inferiorly to the fascia lata.
3. Flattens medially into the lacunar ligament, which forms the medial border of the femoral ring.

Cooper Ligament

Cooper ligament is used in bladder suspension procedures. Cooper ligament:

1. **Is a strong ridge of fibrous tissue extending along the pectineal line—also known as the pectineal ligament.**
2. **Merges laterally with the iliopectineal ligament and medially with the lacunar ligament.**

Sacrospinous Ligament

The sacrospinous ligament is often used for vaginal suspension. This ligament offers the advantage of a vaginal surgical route. The sacrospinous ligament:

1. **Extends from the ischial spine to the lateral aspect of the sacrum.**
2. **Is separated from the rectovaginal space by the rectal pillars.**
3. **Lies anterior to the pudendal nerve and the internal pudendal vessels at its attachment to the ischial spine.**

The inferior gluteal artery, with extensive collateral circulation, is found between the sacrospinous and sacrotuberous ligaments and may be injured during sacrospinous suspension (Fig. 5-6) (16). **[2]** Injury to the inferior gluteal artery, and to the pudendal nerve and internal pudendal vessels, during sacrospinous ligament suspension may be minimized by careful and controlled retraction and suture placement, at least two fingerbreadths medial to the ischial spine.

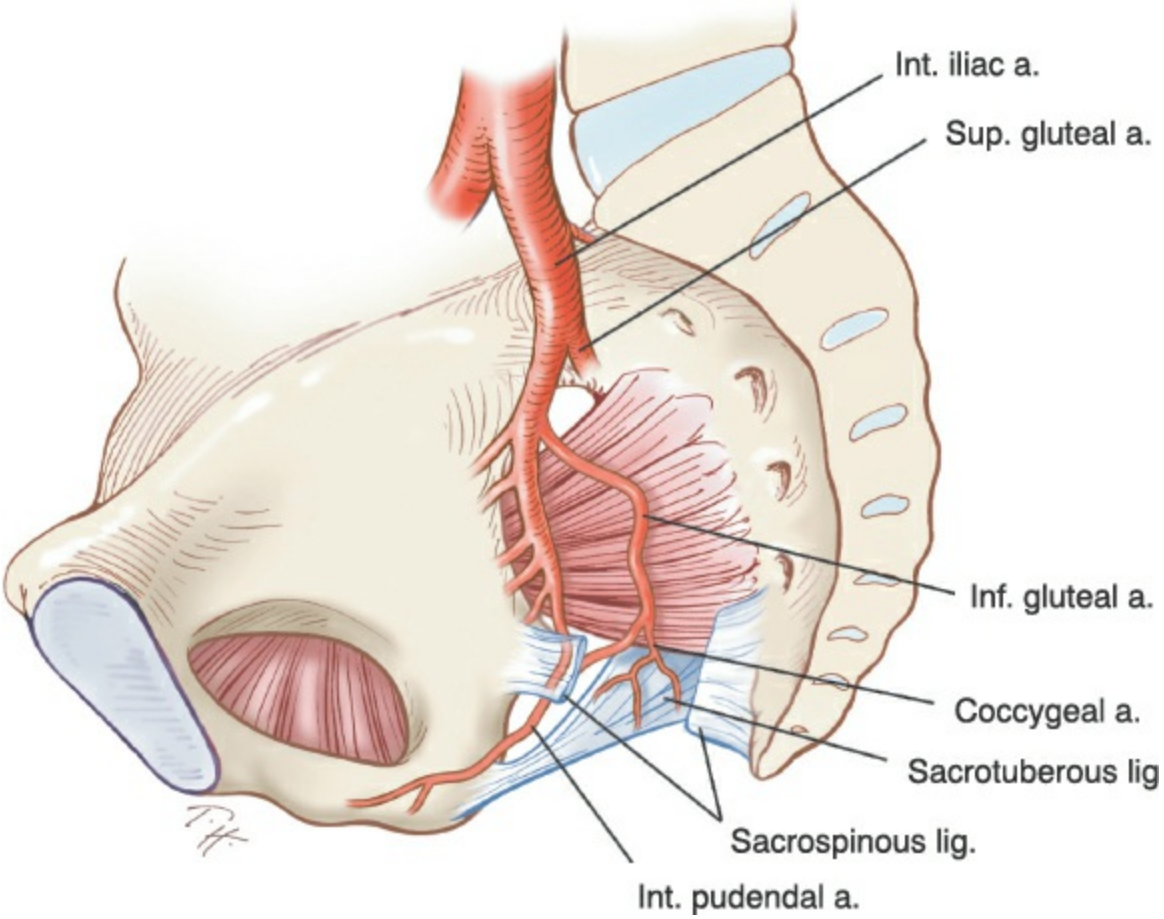


FIGURE 5-6 Tone drawing of left hemipelvis with sacrospinous ligament reflected. a., artery; Inf., inferior; lig., ligament; n., nerve; Sacrosp., sacrospinous; Sacrotub., sacrotuberous. (Redrawn from **Thompson JR, Gibbs JS, Genadry R, et al**. Anatomy of pelvic arteries adjacent to the sacrospinous ligament: importance of the coccygeal branch of the inferior gluteal artery. *Obstet Gynecol* 1999;94:973–977, with permission.)

Sacrotuberous Ligament

The sacrotuberous ligament is occasionally used as a point of fixation for vaginal vault suspension, sometimes inadvertently during attempted sacrospinous suspension. The sacrotuberous ligament:

1. **Extends from the ischial tuberosity to the lateral aspect of the sacrum**
2. **Merges medially with the sacrospinous ligament**
3. **Lies posterior to the pudendal nerve and the internal pudendal vessels**

Foramina

The bony pelvis and its ligaments delineate three important foramina that allow the passage of the various muscles, nerves, and vessels to the lower extremities.

Greater Sciatic Foramen

The greater sciatic foramen transmits the following structures: the piriformis muscle, the

superior gluteal nerves and vessels, the sciatic nerve along with the nerves of the quadratus femoris, the inferior gluteal nerves and vessels, the posterior cutaneous nerve of the thigh, the nerves of the obturator internus, and the internal pudendal nerves and vessels.

Lesser Sciatic Foramen

The lesser sciatic foramen transmits the tendon of the obturator internus to its insertion on the greater trochanter of the femur. The nerve of the obturator internus and the pudendal vessels and nerves reenter the pelvis through the lesser sciatic foramen.

Obturator Foramen

[3] The obturator foramen transmits the obturator nerves and vessels. The obturator neurovascular bundle can be injured during transobturator tape placement, a procedure for treatment of urinary incontinence. Older trocar-based mesh kits for anterior and apical vaginal prolapse were often passed through the obturator membrane, just lateral to the descending ischiopubic ramus but medial to the obturator foramen. Injury to the obturator nerves and vessels can be prevented during these procedures by careful identification of anatomic landmarks and placement away from the obturator foramen.

Muscles

The muscles of the pelvis include those of the lateral wall and those of the pelvic floor (Fig. 5-7; Table 5-2).

Lateral Wall

The muscles of the lateral pelvic wall pass into the gluteal region to assist in thigh rotation and adduction. They include the piriformis, the obturator internus, and the iliopsoas.

Pelvic Floor

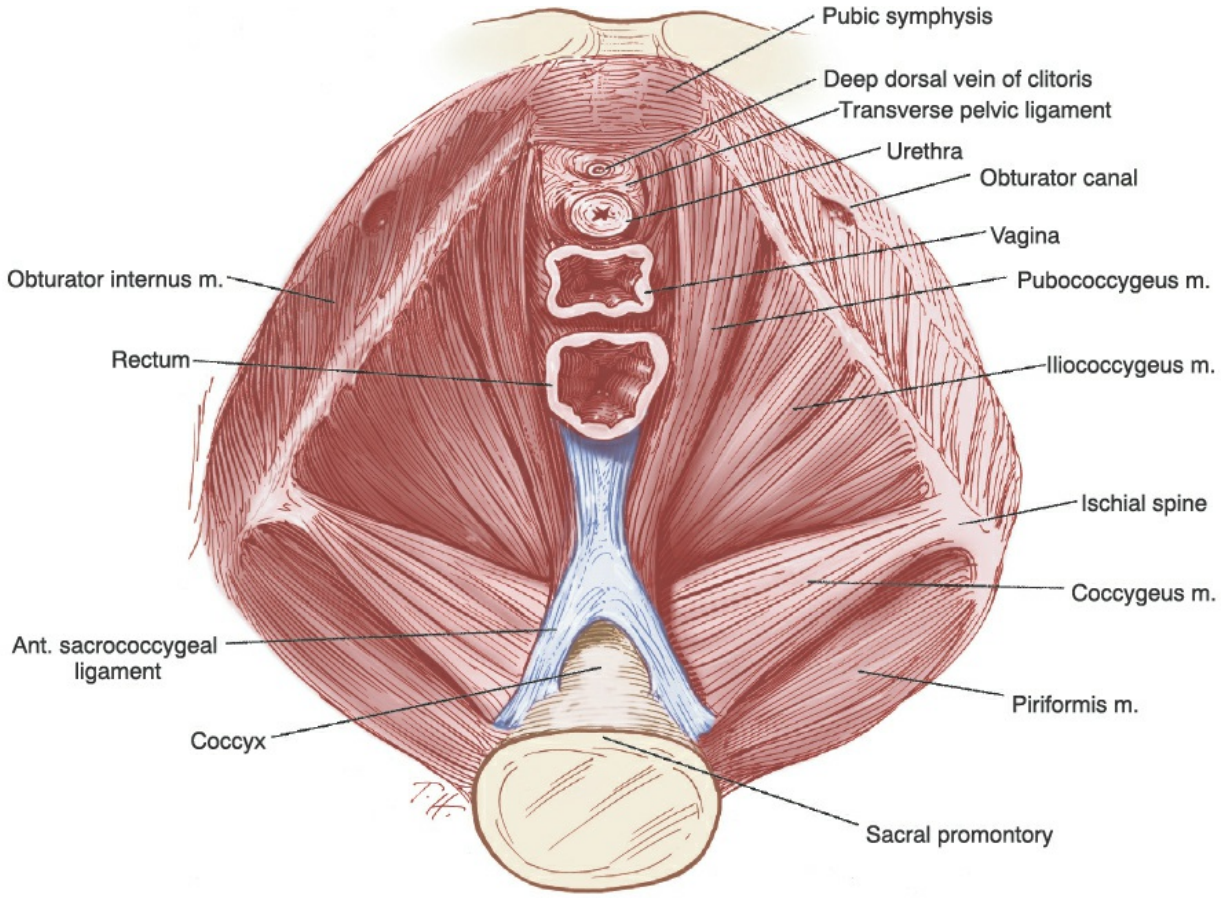
Pelvic Diaphragm

The pelvic diaphragm is a funnel-shaped fibromuscular partition that forms the primary supporting structure for the pelvic contents (Fig. 5-8). It is composed of the levator ani (pubococcygeus, puborectalis, iliococcygeus) and the coccygeus muscles, along with their superior and inferior fasciae (Table 5-2 on page 61). It forms the ceiling of the ischiorectal fossa.

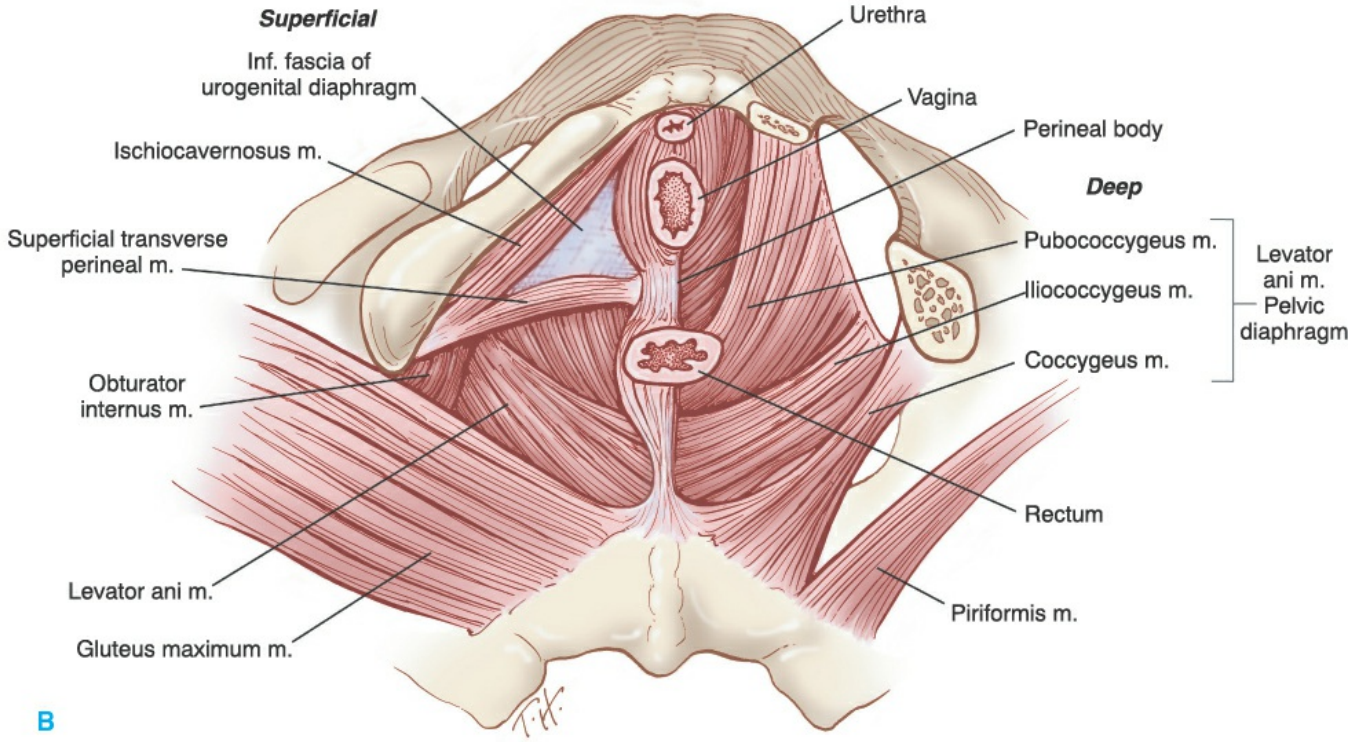
Levator Ani

The levator ani muscles are composed of the pubococcygeus (including the pubovaginalis and pubourethralis), puborectalis, and the iliococcygeus. The levator

ani is a broad, curved sheet of muscle stretching anteriorly from the pubis and posteriorly from the coccyx and from one side of the pelvis to the other. It is perforated by the urethra, vagina, and anal canal. Its origin is from the tendinous arch extending from the body of the pubis to the ischial spine. **This tendinous arch, called the *arcus tendineus levator ani*, is formed by a thickening of the obturator fascia and serves as a lateral landmark and point of attachment for some vaginal suspension procedures**. The levator ani is inserted into the central tendon of the perineum, the wall of the anal canal, the anococcygeal ligament, the coccyx, and the vaginal wall.


Pubic symphysis
Deep dorsal vein of clitoris
Transverse pelvic ligament
Urethra
Obturator canal
Vagina
Obturator internus m.
Pubococcygeus m.
Rectum
Iliococcygeus m.
Ischial spine
Coccygeus m.
Ant. sacrococcygeal ligament
Piriformis m.
Coccyx
Sacral promontory

A


Superficial
Urethra
Inf. fascia of urogenital diaphragm
Vagina
Perineal body
Ischiocavernosus m.
Deep
Superficial transverse perineal m.
Pubococcygeus m.
Levator ani m.
Pelvic diaphragm
Iliococcygeus m.
Obturator internus m.
Coccygeus m.
Rectum
Levator ani m.
Piriformis m.
Gluteus maximum m.

B

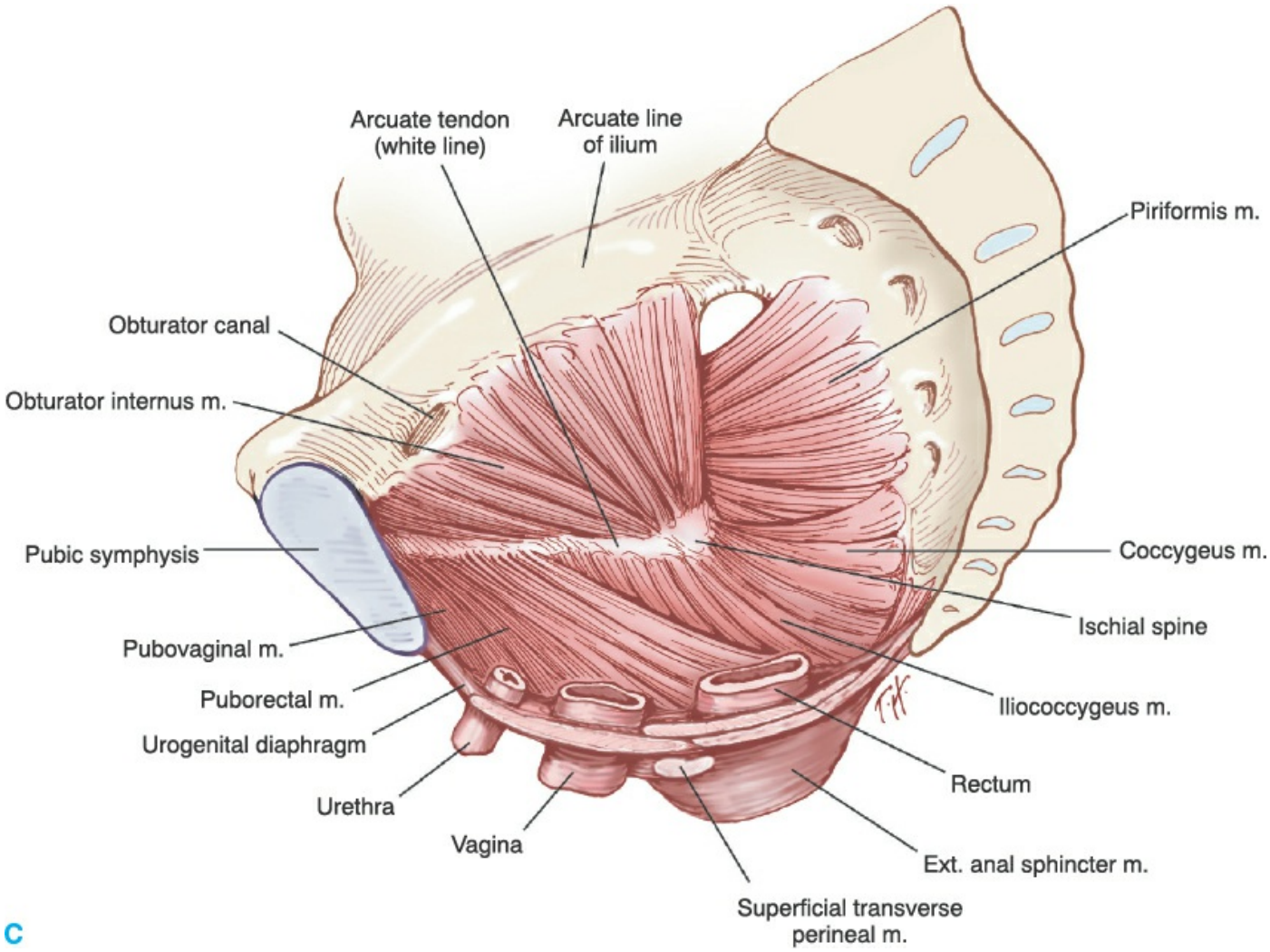


FIGURE 5-7 The pelvic diaphragm. **A:** A view into the pelvic floor that illustrates the muscles of the pelvic diaphragm and their attachments to the bony pelvis. **B:** A view from outside the pelvic diaphragm illustrating the divisions of the levator ani muscles (superficial plane removed on the right). **C:** A lateral, sagittal view of the pelvic diaphragm and superior fascia of the urogenital diaphragm. The muscles include the deep transverse perineal and sphincter urethrae.

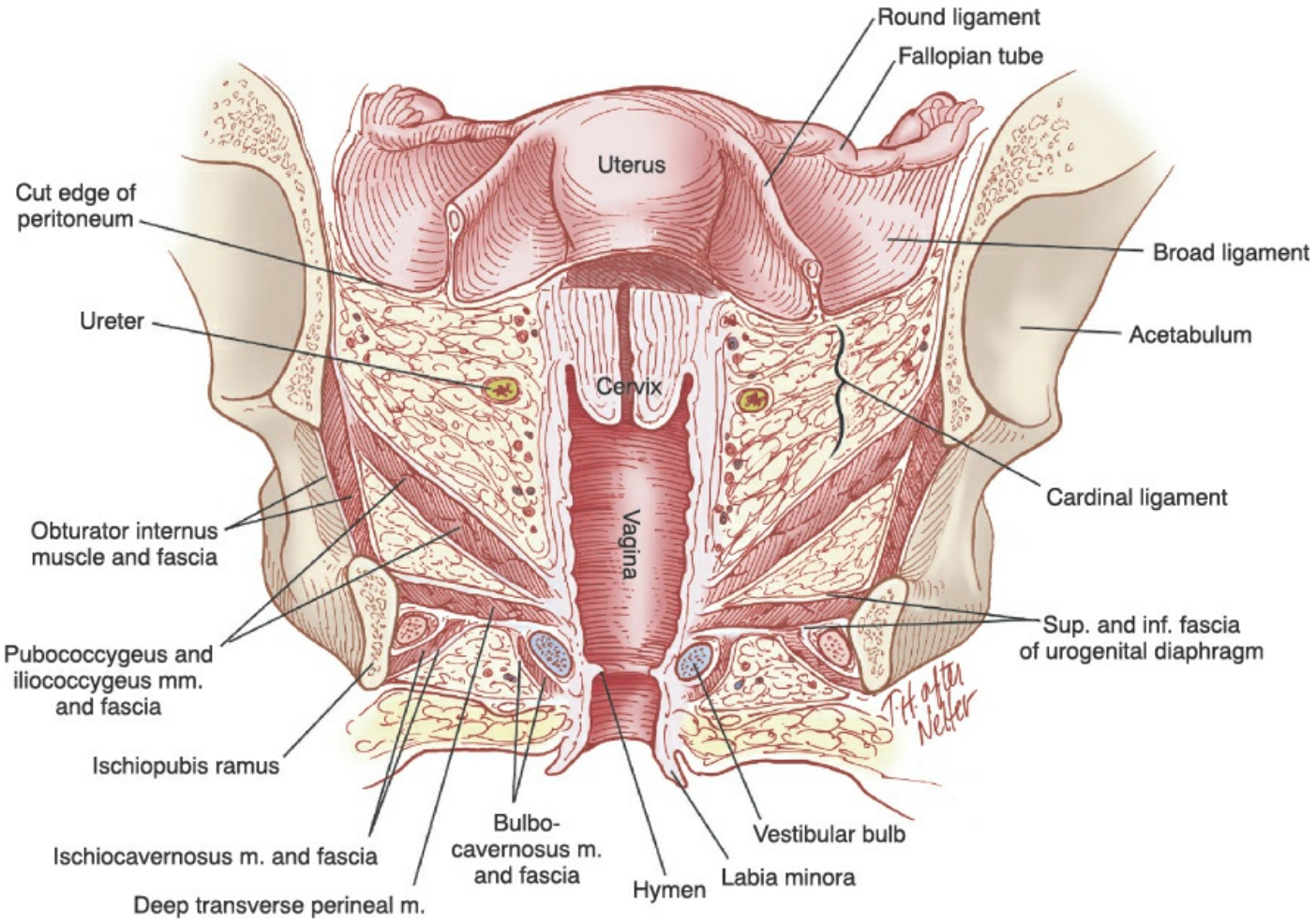


FIGURE 5-8 The ligaments and fascial support of the pelvic viscera.

Table 5-2 Muscles of the Pelvic Floor

	Origin	Insertion	Action	Innervation
Lateral Pelvic Wall				
Piriformis	Anterior aspect of S2–S4 and sacrotuberous ligament	Greater trochanter of the femur	Lateral rotation, abduction of thigh in flexion; holds head of femur in acetabulum	S1–S2; forms a muscular bed for the sacral plexus
Obturator internus	Superior and inferior pubic rami	Greater trochanter of the femur	Lateral rotation of thigh in flexion; assists in holding head of femur in acetabulum	(L5, S1) Obturator internus nerve
Iliopsoas	Psoas from the lateral margin of the lumbar vertebrae; iliacus from the iliac fossa	Lesser trochanter of the femur	Flexes thigh and stabilizes trunk on thigh; flexes vertebral column or bends it unilaterally	(L1–L3) Psoas–ventral rami of lumbar nerve (L2–L3) Iliacus–femoral nerve contains the lumbar plexus within its muscle body
Pelvic Floor				
Pelvic Diaphragm				
Levator ani Pubococcygeus Pubovaginalis Puborectalis	From the tendinous arch, extending from the body of the pubis to the ischial spine	Central tendon of the perineum; wall of the anal canal; anococcygeal ligament; coccyx; vaginal wall	Assists the anterior abdominal wall muscles in containing the abdominal and pelvic contents; supports the posterior wall of the vagina; facilitates defecation; aids in fecal continence; during parturition, supports the fetal head during cervical dilation	S3–S4; the inferior rectal nerve
Coccygeus	Ischial spine and sacrospinous ligament	Lateral margin of the fifth sacral vertebra and coccyx	Supports the coccyx and pulls it anteriorly	S4–S5
Urogenital Diaphragm				
Deep transverse perineal	Medial aspect of the ischiopubic rami	Lower part of the vaginal wall; anterior fibers blend with those of the sphincter urethrae	Steadies the central perineal tendon	S2–S4; perineal nerve
Sphincter urethrae	Medial aspect of the ischiopubic rami	Urethra and vagina	Compresses the urethra	S2–S4; perineal nerve

The levator ani assists the anterior abdominal wall muscles in containing the abdominal and pelvic contents. It supports the vagina, facilitates defecation, and aids in maintaining fecal continence. During parturition, the levator ani supports the fetal head while the cervix dilates. A simulated vaginal delivery model demonstrated that the pubococcygeus muscle stretches more than three times its original length (17). The anterior portion of the levator ani complex serves to close the urogenital hiatus and pull the urethra, vagina, perineum, and anorectum toward the pubic bone, whereas the horizontally oriented posterior portion (levator plate) serves as a supportive diaphragm or "backstop" behind the pelvic viscera. Loss of normal levator ani tone, through denervation or direct muscle trauma, results in laxity of the urogenital hiatus, loss of the horizontal orientation of the levator plate, and a more bowl-like configuration. These

changes can be bilateral or asymmetric (18). Such configurations are seen more often in women with pelvic organ prolapse than in those with normal pelvic organ support (19).

The levator ani is composed of striated muscle fibers with predominantly type I (slow-twitch) fibers that maintain a constant state of resting contraction. The baseline activity of the levator ani keeps the urogenital hiatus narrowed and draws the distal parts of the urethra, vagina, and rectum toward the pubic bones. Type II (fast-twitch) muscle fibers allow for involuntary reflex muscle contraction elicited by sudden increase in abdominal pressure and for voluntary contractions, as with Kegel exercises. Relaxation of these muscles occurs only briefly and intermittently during the process of evacuation (voiding, defecation, and during parturition).

Traditional teaching is that the levator ani muscles are innervated by the pudendal nerve on the perineal surface and direct branches of the sacral nerves on the pelvic surface. Evidence indicates that the levator ani muscles are innervated solely by a nerve traveling on the superior (intrapelvic) surface of the muscles without the contribution of the pudendal nerve (20–25). This nerve, referred to as the *levator ani nerve*, originates from S3, S4, and/or S5 and innervates both the coccygeus and the levator ani muscle complex (20). After exiting the sacral foramina, it travels 2 to 3 cm medial to the ischial spine and arcus tendineus levator ani across the coccygeus, iliococcygeus, pubococcygeus, and puborectalis. Occasionally, a separate nerve comes directly from S5 to innervate the puborectalis muscle independently. Given its location, the levator ani nerve is susceptible to injury through parturition and pelvic surgery, such as during sacrospinous or iliococcygeus vaginal vault suspensions.

Urogenital Diaphragm

The muscles of the urogenital diaphragm anteriorly reinforce the pelvic diaphragm and are intimately related to the vagina and the urethra. They are enclosed between the inferior and superior fascia of the urogenital diaphragm. The muscles include the deep transverse perineal and sphincter urethrae **(Table 5-2)**.

Blood Vessels

The pelvic blood vessels supply genital structures and the following:

- Urinary and gastrointestinal tracts
- Muscles of the abdominal wall, pelvic floor and perineum, buttocks, and upper thighs
- Fasciae, other connective tissue, and bones
- Skin and other superficial structures

Classically, vessels supplying organs are known as *visceral vessels* and those supplying supporting structures are called *parietal vessels*.

Major Blood Vessels

The course of the major vessels supplying the pelvis is illustrated in Figure 5-9; their origin, course, branches, and venous drainage are presented in Table 5-3. In general, the venous system draining the pelvis closely follows the arterial supply and is named accordingly. Not infrequently, a vein draining a particular area may form a plexus with multiple channels. Venous systems, which are paired, mirror each other in their drainage patterns, with the notable exception of the ovarian veins. Unusual features of venous drainage are also listed in Table 5-3.

General Principles

"Control blood supply" and "maintain meticulous hemostasis" are two of the most common exhortations to young surgeons. In developing familiarity with the pattern of blood flow in the pelvis, several unique characteristics of this vasculature should be understood because of their potential implications for surgical practice:

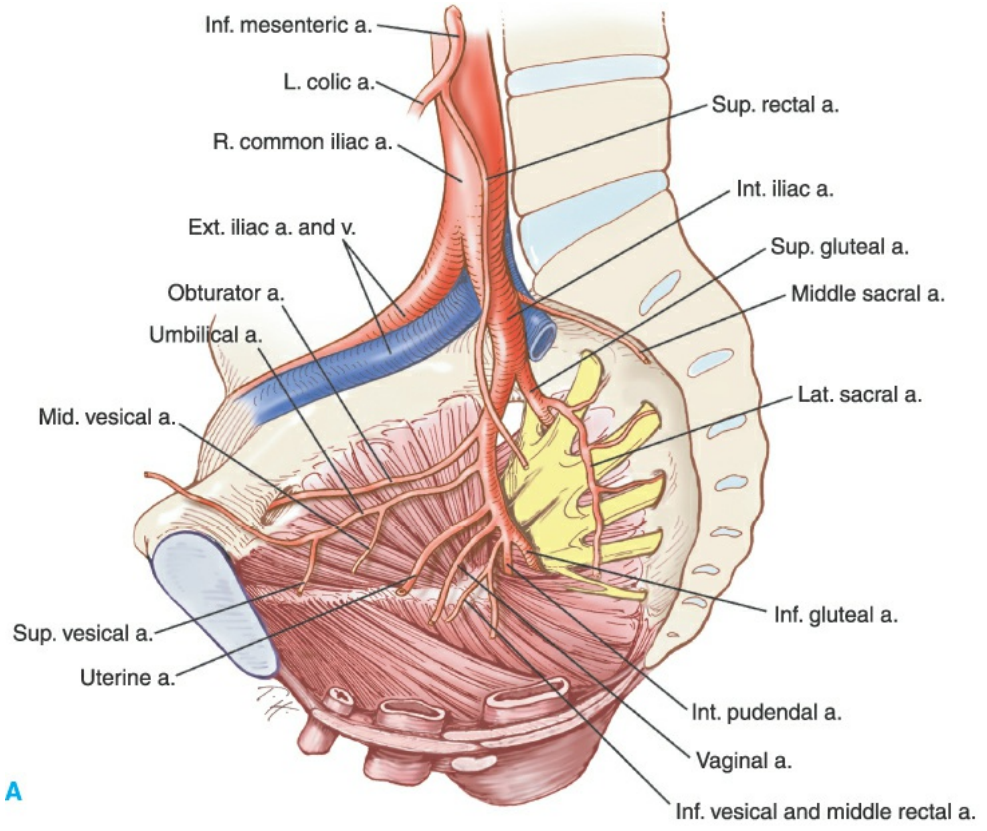
1. **The pelvic vessels play an important role in pelvic support.** They provide condensations of endopelvic fascia that act to reinforce the normal position of pelvic organs (26).
2. **[4] There is significant anatomic variation between individuals in the branching pattern of the internal iliac vessels.** There is no constant order in which branches divide from the parent vessel; some branches may arise as common trunks or may spring from other branches rather than from the internal iliac. Occasionally, a branch may arise from another vessel entirely (e.g., the obturator artery may arise from the external iliac or inferior epigastric artery). This variation may be found in the branches of other major vessels; the ovarian arteries are reported to arise from the renal arteries or as a common trunk from the front of the aorta on occasion. The inferior gluteal artery may originate from the posterior or the anterior branch of the internal iliac (hypogastric) artery. Patterns of blood flow may be asymmetric from side to side, and structures supplied by anastomoses of different vessels may show variation from person to person in the proportion of vascular support provided by the vessels involved (26). The pelvic surgeon must be prepared for deviations from "textbook" vascular patterns.
3. **The pelvic vasculature is a high-volume, high-flow system with enormous expansive capabilities throughout reproductive life.** Blood flow through the uterine arteries increases to about 500 mL/min in late pregnancy. In nonpregnant women, certain conditions, such as uterine fibroids or malignant neoplasms, may be associated with neovascularization and hypertrophy of existing vessels and a corresponding increase in pelvic blood flow. Understanding the volume and flow characteristics of the pelvic vasculature in different clinical situations will enable the surgeon to anticipate problems and take appropriate pre- and intraoperative

measures (including blood and blood product availability) to prevent or manage hemorrhage.

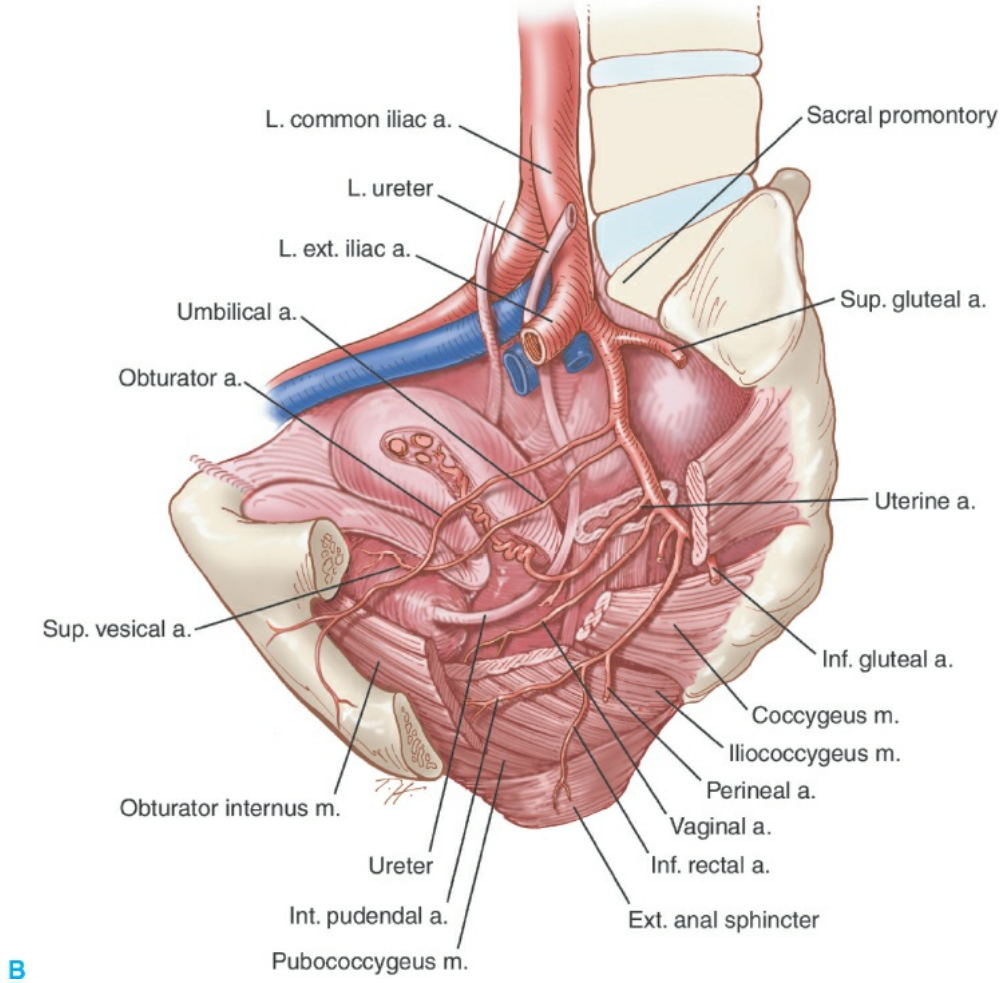
4. **[4] The pelvic vasculature is supplied with an extensive network of collateral connections that provides a rich anastomotic communication between different major vessel systems (Fig. 5-10 on page 66).** This degree of redundancy is important to ensure adequate supply of oxygen and nutrients in the event of major trauma or other vascular compromise. Hypogastric artery ligation continues to be used as a strategy for management of massive pelvic hemorrhage when other measures have failed. Bilateral hypogastric artery ligation, particularly when combined with ovarian artery ligation, dramatically reduces pulse pressure in the pelvis, converting flow characteristics from that of an arterial system to a venous system and allowing use of collateral channels of circulation to continue blood supply to pelvic structures. The significance of collateral blood flow is demonstrated by reports of successful pregnancies occurring after bilateral ligation of both hypogastric and ovarian arteries (27). **Table 5-4 on page 67** lists the collateral channels of circulation in the pelvis.

Special Vascular Considerations

During laparoscopy, vascular injury most commonly occurs during abdominal entry. To avoid injury to vascular structures and resultant hemorrhage while inserting a trocar into the anterior abdominal wall, the surgeon should keep in mind certain anatomic relationships. The most common vascular injury is laceration of the inferior epigastric artery during placement of lateral trocars. The inferior epigastric artery is a branch of the external iliac artery, arising from the parent vessel at the medial border of the inguinal ligament and coursing cephalad lateral to and posterior to the rectus sheath at the level of the arcuate line. It lies about 1.5 cm lateral to the medial umbilical fold, which marks the site of the obliterated umbilical artery. **During laparoscopy, the inferior epigastric artery almost always can be visualized between the obliterated umbilical artery medially and the insertion of the round ligament through the inguinal canal laterally**. This artery can be traced visually cephalad under transillumination, allowing for safe insertion of the lateral port site. The distal aorta, which lies directly underneath the umbilicus, and the right common iliac artery, which crosses the midline, are particularly prone to injury during umbilical laparoscopic trocar insertion. The aortic bifurcation occurs at the level of L4 to L5, just above the sacral promontory. Palpation of the sacral promontory to guide trocar insertion allows the surgeon to avoid the major vascular structures in this area (see **Fig. 26-11** in Chapter 26). **[3] The left common iliac vein lies medial to the artery and is at risk of injury during dissection for sacrocolpopexy.**


Inf. mesenteric a.
L. colic a.
R. common iliac a.
Ext. iliac a. and v.
Obturator a.
Umbilical a.
Mid. vesical a.
Sup. vesical a.
Uterine a.
Sup. rectal a.
Int. iliac a.
Sup. gluteal a.
Middle sacral a.
Lat. sacral a.
Inf. gluteal a.
Int. pudendal a.
Vaginal a.
Inf. vesical and middle rectal a.

A


L. common iliac a.
L. ureter
L. ext. iliac a.
Umbilical a.
Obturator a.
Sup. vesical a.
Obturator internus m.
Ureter
Int. pudendal a.
Pubococcygeus m.
Sacral promontory
Sup. gluteal a.
Uterine a.
Inf. gluteal a.
Coccygeus m.
Iliococcygeus m.
Perineal a.
Vaginal a.
Inf. rectal a.
Ext. anal sphincter

B

FIGURE 5-9 The blood supply to the pelvis. **A:** The sagittal view of the pelvis without the viscera. **B:** The blood supply to one pelvic viscus.

Table 5-3 The Major Blood Vessels of the Pelvis

Artery	Origin	Course	Branches	Venous Drainage
Ovarian	Arises from ventral surface of aorta just below the origin of the renal vessels	Crosses over common iliac vessels; in proximity to ureter over much of its course, crosses over ureter while superficial to the psoas muscle and runs just lateral to the ureter when entering the pelvis as part of the infundibulopelvic ligament	To ovaries, fallopian tubes, broad ligament; often small branches to ureter	Right side drains into the inferior vena cava; left drains into the left renal vein
Inferior mesenteric artery (IMA)	Unpaired left-sided retroperitoneal artery arising from the aorta 2–5 cm proximal to its bifurcation	IMA and its branches pass over the left psoas muscle and common iliac vessels; IMA courses anterior to the ureter and ovarian vessels above the pelvic brim	1. *Left colic*—originates above pelvic brim; supplies left transverse colon, splenic flexure, descending colon 2. *Sigmoid*—several branches; supply sigmoid colon 3. *Superior rectal (hemorrhoidal)*—divides into two terminal branches to supply rectum	Inferior mesenteric vein empties into the splenic vein
Common iliac artery	Terminal division of the aorta at fourth lumbar vertebra	Oblique and lateral course, about 5 cm in length	1. *External iliac* 2. *Internal iliac*	Lie posterior and slightly medial to arteries; drain into inferior vena cava
External iliac femoral artery	Lateral bifurcation of common iliac, begins opposite the lumbosacral joint	Along the medial border of the psoas muscle and lateral pelvic side wall; becomes femoral artery after passing under the inguinal ligament to supply lower extremities	1. *Superficial epigastric*—supplies skin and subcutaneous tissue of lower anterior abdominal wall 2. *External pudendal*—supplies skin and subcutaneous tissue of mons pubis and anterior vulva 3. *Superficial circumflex iliac*—supplies skin/subcutaneous tissues of the flank 4. *Inferior epigastric*—supplies musculofascial layer of lower anterior abdominal wall 5. *Deep circumflex iliac*—supplies musculofascial layer of lower abdominal wall	Lie posterior and then medial to the artery as it enters the anterior thigh; drain into common iliac veins
Internal iliac (hypogastric) artery	Medial bifurcation of common iliac artery, begins opposite the lumbosacral joint; is major blood supply to the pelvis	Descends sharply into the pelvis; divides into an anterior and posterior division 3–4 cm after origin	*Posterior division:* 1. *Iliolumbar*—anastomoses with lumbar and deep circumflex iliac arteries; helps supply lower abdominal wall, iliac fossa 2. *Lateral sacral*—supplies contents of sacral canal, piriformis muscle 3. *Superior gluteal*—supplies gluteal muscles *Anterior division:* 1. *Obturator*—supplies iliac fossa, posterior pubis, obturator internus muscle 2. *Internal pudendal* 3. *Umbilical*—remnant of fetal umbilical artery; after giving off branches, as the medial umbilical ligament 4. *Superior, middle, inferior vesical*—supply bladder and one or more branches to the ureter 5. *Middle rectal (hemorrhoidal)*—supplies rectum, branches to midvagina 6. *Uterine*—supplies uterine corpus and cervix, with branches to upper vagina, tube, round ligament, and ovary 7. *Vaginal*—supplies vagina 8. *Inferior gluteal*—supplies gluteal muscles, muscles of posterior thigh	Deep to arteries, from complex plexus; drain into common iliac veins
Internal pudendal artery	Internal iliac artery; provides the major blood supply to the perineum	Leaves the pelvis through the greater sciatic foramen, courses around the ischial spine, and enters the ischiorectal fossa through the lesser sciatic foramen. In its path to the perineum, lies with the pudendal nerve within Alcock canal, a fascial tunnel over the obturator internus muscle	1. *Inferior rectal (hemorrhoids)*—supplies anal canal, external anal sphincter, perianal skin, with branches to levator ani 2. *Perineal*—supplies perineal skin, muscles of superficial perineal compartment (bulbocavernosus, ischiocavernosus, superficial transverse perineal) 3. *Clitoral*—supplies clitoris, vestibular bulb, Bartholin gland, and urethra	Drain into internal iliac veins
Middle sacral artery	Midline unpaired vessel arising from posterior terminal aorta	Courses over lower lumbar vertebrae, sacrum, and coccyx	Supplies bony and muscular structures of posterior pelvic wall	Paired middle sacral veins usually drain into left common iliac vein
Lumbar arteries	Segmental branches arising at each lumbar level from posterior aorta	Pass around the side of the four superior lumbar vertebrae, divide into anterior and posterior branches	Supplies abdominal wall musculature (external/internal oblique, transversus abdominis)	Drains into inferior vena cava

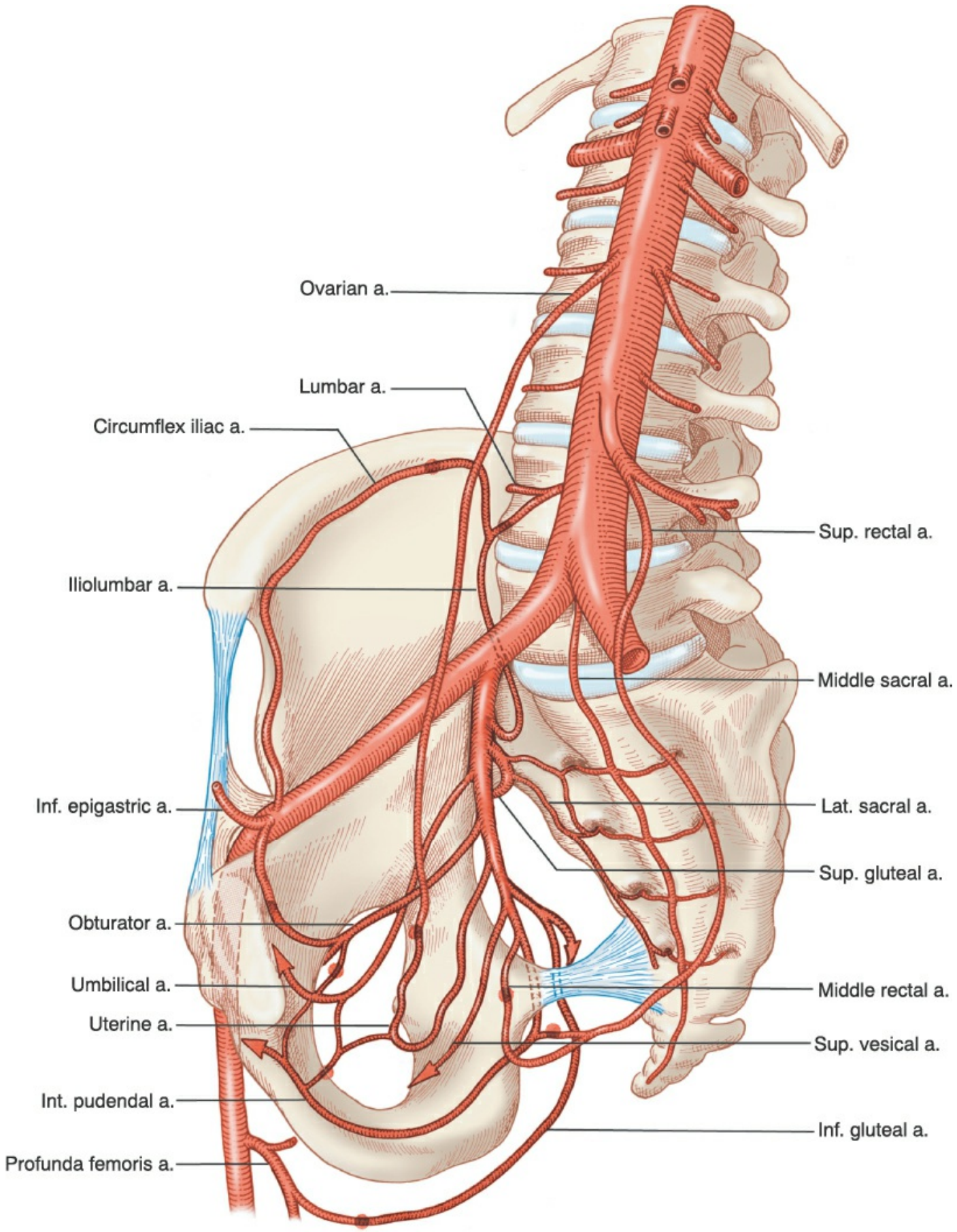

Ovarian a.
Lumbar a.
Circumflex iliac a.
Sup. rectal a.
Iliolumbar a.
Middle sacral a.
Inf. epigastric a.
Lat. sacral a.
Sup. gluteal a.
Obturator a.
Umbilical a.
Middle rectal a.
Uterine a.
Sup. vesical a.
Int. pudendal a.
Inf. gluteal a.
Profunda femoris a.

FIGURE 5-10 The collateral blood vessels of the pelvis. (Modified from **Kamina P**. *Anatomie Gynécologique et Obstétricale*. Paris, France: Maloine Sa Éditeur; 1984:125.)

Table 5-4 Collateral Arterial Circulation of the Pelvis

Primary Artery	Collateral Arteries
Aorta	
Ovarian artery	Uterine artery
Superior rectal artery (inferior mesenteric artery)	Middle rectal artery
	Inferior rectal artery (internal pudendal)
Lumbar arteries	Iliolumbar artery
Vertebral arteries	Iliolumbar artery
Middle sacral artery	Lateral sacral artery
External Iliac	
Deep iliac circumflex artery	Iliolumbar artery
	Superior gluteal artery
Inferior epigastric artery	Obturator artery
Femoral	
Medial femoral circumflex artery	Obturator artery
	Inferior gluteal artery
Lateral femoral circumflex artery	Superior gluteal artery
	Iliolumbar artery

Lymphatics

The lymphatic system absorbs and transports interstitial fluid from tissues, including larger molecules like protein and cellular debris. Small lymphatic capillaries drain organs and form larger vessels that drain into lymph nodes. **The pelvic lymph nodes are generally arranged in groups or chains and follow the course of the larger pelvic vessels, for which they are usually named. Smaller nodes that lie close to the visceral structures are usually named for those organs.** Lymph nodes in the pelvis receive afferent lymphatic vessels from pelvic and perineal visceral and parietal structures and send efferent lymphatics to more proximal nodal groups. The number of lymph nodes and their exact location are variable; however, certain nodes tend to be relatively constant:

1. Obturator nodes in the obturator foramen, close to the obturator vessels and nerve
2. Nodes at the junction of the internal and external iliac veins
3. Ureteral nodes in the broad ligament near the cervix, where the uterine artery crosses over the ureter
4. The *Cloquet* or Rosenmüller node—the highest of the deep inguinal nodes that lies within the opening of the femoral canal

Figure 5-11 illustrates the pelvic lymphatic system. Table 5-5 outlines the major lymphatic chains of relevance to the pelvis and their primary afferent connections from major pelvic and perineal structures. There are extensive interconnections between lymph vessels and nodes; usually more than one lymphatic pathway is available for drainage of each pelvic site. Bilateral and crossed extension of lymphatic flow may occur, and entire groups of nodes may be bypassed to reach more proximal chains.

The natural history of most genital tract malignancies directly reflects the lymphatic drainage of those structures, although the various interconnections, different lymphatic paths, and individual variability make the spread of malignancy somewhat unpredictable. Regional lymph node metastasis is one of the most important factors in formulation of treatment plans for gynecologic malignancies and prediction of eventual outcome.

Nerves

The pelvis is innervated by both the autonomic and somatic nervous systems. The autonomic nerves include both *sympathetic* (adrenergic) and *parasympathetic* (cholinergic) fibers and provide the primary innervation for genital, urinary, and gastrointestinal visceral structures and blood vessels.

Somatic Innervation

The *lumbosacral plexus* and its branches provide motor and sensory somatic innervation to the lower abdominal wall, the pelvic and urogenital diaphragms, the perineum, and the hips and lower extremities (Fig. 5-12). The nerves originating from the muscles, the lumbosacral trunk, the anterior divisions of the upper four sacral nerves (*sacral plexus*), and the anterior division of the coccygeal nerve and fibers from the fourth and fifth sacral nerves (*coccygeal plexus*) are found on the anterior surface of the piriformis muscle and lateral to the coccyx, respectively, deep in the posterior pelvis. In Table 5-6 each major branch is listed by spinal segment and structures innervated. In addition to these branches, the lumbosacral plexus includes nerves that innervate muscles of the lateral pelvic wall (obturator internus, piriformis), posterior hip muscles, and the pelvic diaphragm. A visceral component, the pelvic splanchnic nerve, is included.

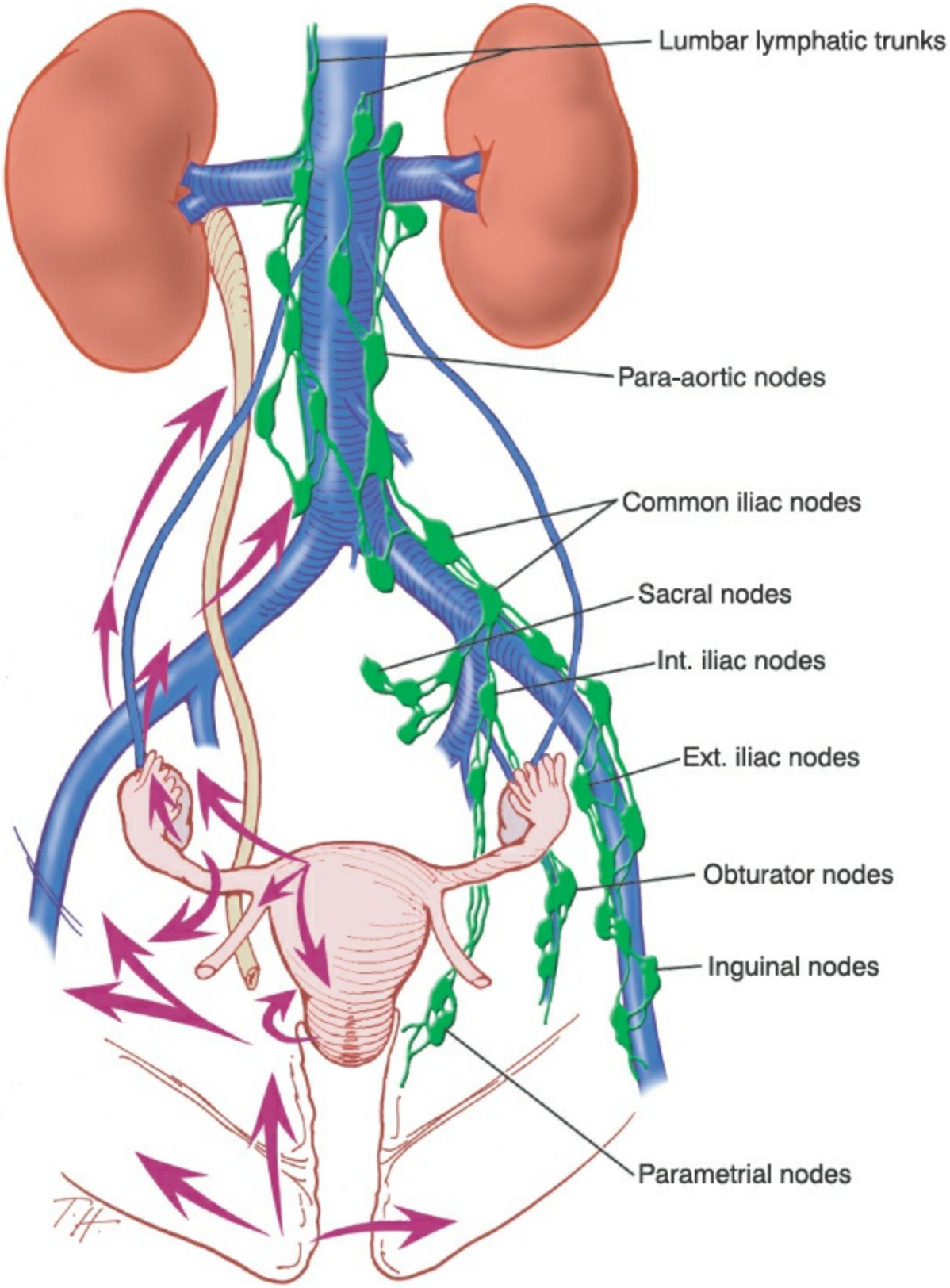


FIGURE 5-11 The lymphatic drainage of the female pelvis. The vulva and lower vagina drain to the superficial and deep inguinal nodes, sometimes directly to the iliac nodes (along the dorsal vein of the clitoris) and to the other side. The cervix and upper vagina drain laterally to the parametrial, obturator, and external iliac nodes and posteriorly along the uterosacral ligaments to the sacral nodes. Drainage from these primary lymph node groups is upward along the infundibulopelvic ligament, similar to drainage of the

ovary and fallopian tubes to the para-aortic nodes. The lower uterine body drains in the same manner as the cervix. Rarely, drainage occurs along the round ligament to the inguinal nodes.

Table 5-5 Primary Lymph Node Groups Providing Drainage to Genital Structures

Nodes	Primary Afferent Connections
Aortic/para-aortic	Ovary, fallopian tube, uterine corpus (upper); drainage from common iliac nodes
Common iliac	Drainage from external and internal iliac nodes
External iliac	Upper vagina, cervix, uterine corpus (upper); drainage from inguinal
Internal iliac	Upper vagina, cervix, uterine corpus (lower)
Lateral sacral	
Superior gluteal	
Inferior gluteal	
Obturator	
Vesical	
Rectal	
Parauterine	
Inguinal	Vulva, lower vagina (rare: uterus, tube, ovary)
Superficial	
Deep	

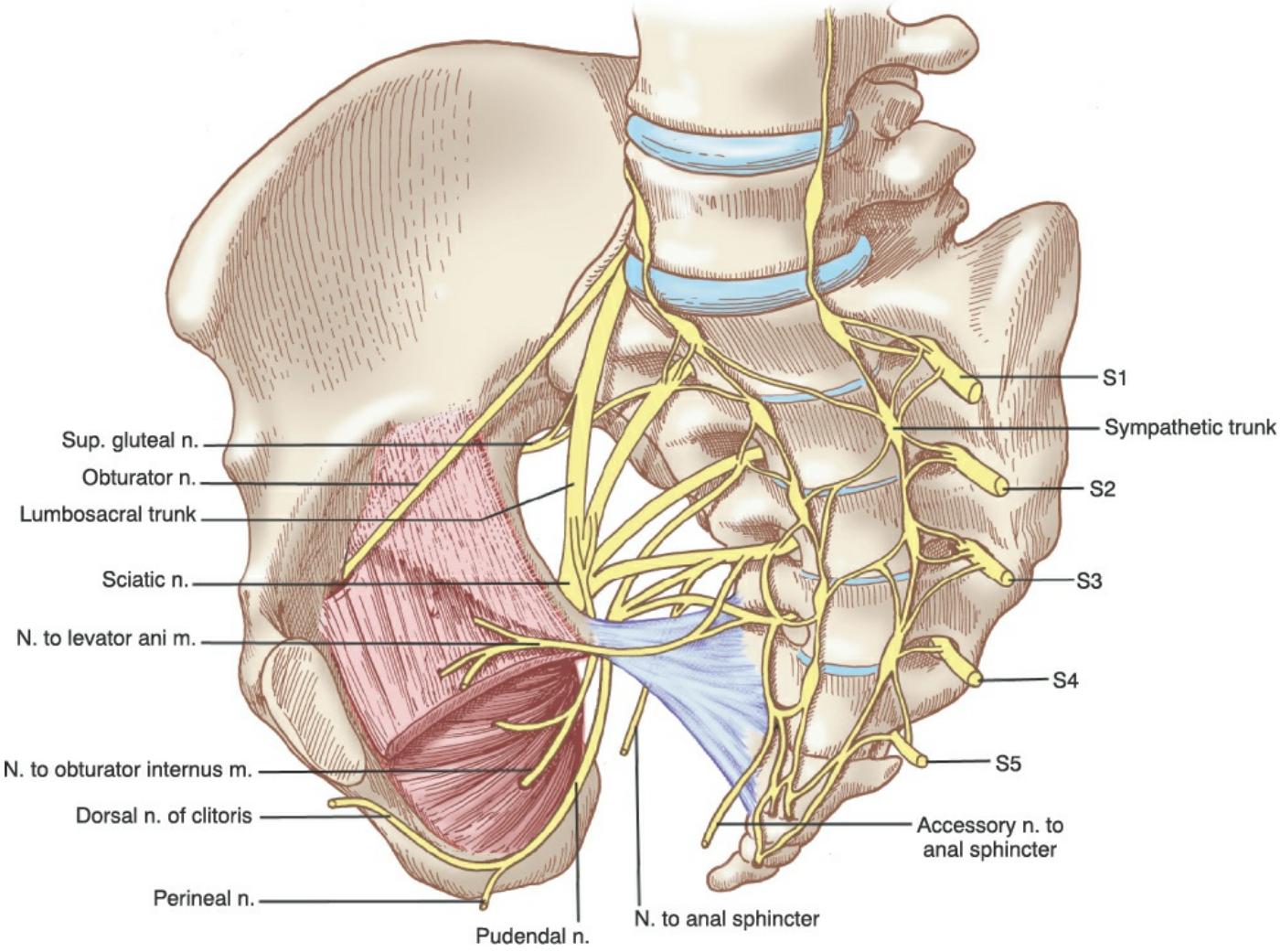


FIGURE 5-12 The sacral plexus. (Modified from **Kamina P**. *Anatomie Gynécologique et Obstétricale*. Paris, France: Maloine Sa Éditeur; 1984:90.)

Table 5-6 Lumbosacral Plexus

Nerve	Spinal Segment	Innervation
Iliohypogastric	T12, L1	Sensory—skin near iliac crest, just above symphysis pubis
Ilioinguinal	L1	Sensory—upper medial thigh, mons, labia majora
Lateral femoral cutaneous	L2, L3	Sensory—lateral thigh to level of knee
Femoral	L2, L3, L4	Sensory—anterior and medial thigh, medial leg and foot, hip and knee joints Motor—iliacus, anterior thigh muscles
Genitofemoral	L1, L2	Sensory—anterior vulva (genital branch), middle/upper anterior thigh (femoral branch)

Obturator	L2, L3, L4	Sensory—medial thigh and leg, hip and knee joints Motor—adductor muscles of thigh
Superior gluteal	L4, L5, S1	Motor—gluteal muscles
Inferior gluteal	L4, L5, S1, S2	Motor—gluteal muscles
Posterior femoral cutaneous	S1, S2, S3	Sensory—vulva, perineum, posterior thigh
Sciatic	L4, L5, S1, S2, S3	Sensory—much of leg, foot, lower extremity joints Motor—posterior thigh muscle, leg and foot muscles
Pudendal	S2, S3, S4	Sensory—perianal skin, vulva and perineum, clitoris, urethra, vaginal vestibule Motor—external anal sphincter, perineal muscles, urogenital diaphragm

Nerves supplying the cutaneous aspects of the anterior, medial, and lateral lower extremities, and the deep muscles of the anterior thigh, primarily leave the pelvis by passing beneath the inguinal ligament. Nerves supporting the posterior cutaneous and deep structures of the hip, thigh, and leg lie deep in the pelvis and should not be vulnerable to injury during pelvic surgery. [3] **The obturator nerve travels along the lateral pelvic wall to pass through the obturator foramen into the upper thigh, and it may be encountered in more radical dissections involving the lateral pelvic wall, in paravaginal repairs, or in trocar-based incontinence and prolapse procedures. Obturator nerve injury results in pain, sensory loss to the medial thigh, and motor loss to the adductor muscle group.**

The pudendal nerve innervates the striated urethral and anal sphincters and the deep and superficial perineal muscles and provides sensory innervation to the external genitalia. This nerve originates from S2–S4, crosses over the piriformis to travel with the internal pudendal vessels into the ischiorectal fossa through the lesser sciatic foramen, and travels through the pudendal canal (Alcock canal) on the medial aspect of the obturator internus muscles, where it divides into its three terminal branches to provide the primary innervation to the perineum. As the pudendal nerve passes posteriorly to the ischial spine and behind the lateral third of the sacrospinous ligament, pudendal nerve entrapment or injury can occur with suture placement into the sacrospinous ligament or arcus tendineus fasciae causing gluteal, perineal, and vulvar

pain. Other nerves contribute to the cutaneous innervation of the perineum:

1. **The anterior labial nerve branches of the ilioinguinal nerve**—these nerves emerge from within the inguinal canal and through the superficial inguinal ring to the mons and upper labia majora.
2. **The genital branch of the genitofemoral nerve**—this branch enters the inguinal canal with the round ligament and passes through the superficial inguinal ring to the anterior vulva.
3. **The perineal branches of the posterior femoral cutaneous nerve**—after leaving the pelvis through the greater sciatic foramen, these branches run in front of the ischial tuberosity to the lateral perineum and labia majora.
4. **Perforating cutaneous branches of the second and third sacral nerves**—these branches perforate the sacrotuberous ligament to supply the buttocks and contiguous perineum.
5. **The anococcygeal nerves**—these nerves arise from S4 to S5 and also perforate the sacrotuberous ligament to supply the skin overlying the coccyx.

Autonomic Innervation

Functionally, the innervation of the pelvic viscera may be divided into an *efferent* component and an *afferent*, or sensory, component. In reality, afferent and efferent fibers are closely associated in a complex interlacing network and cannot be separated anatomically.

Efferent Innervation

***Efferent* fibers of the autonomic nervous system, unlike motor fibers in the somatic system, involve one synapse outside the central nervous system, with two neurons required to carry each impulse. In the *sympathetic* (*thoracolumbar*) *division*, this synapse is generally at some distance from the organ being innervated; conversely, the synapse is on or near the organ of innervation in the *parasympathetic* (*craniosacral*) *division*. In general, the two systems innervate the same target organs but have opposing effects on them to maintain homeostasis. The parasympathetic division has a calming effect on body functions and can be thought of as the "resting and digesting" state. The sympathetic division prepares the body for physical activity and can be thought of as the "fight or flight" reaction**.

Axons from preganglionic neurons emerge from the spinal cord to make contact with peripheral neurons arranged in aggregates known as *autonomic ganglia*. Some of these ganglia, along with interconnecting nerve fibers, form a pair of longitudinal cords called the *sympathetic trunks*. Located lateral to the spinal column from the base of the cranium to the coccyx, the sympathetic trunks lie along the medial border of the psoas

muscle from T12 to the sacral prominence and then pass behind the common iliac vessels to continue into the pelvis on the anterior surface of the sacrum. On the anterolateral surface of the aorta, the *aortic plexus* forms a lacy network of nerve fibers with interspersed ganglia. Rami arising from or traversing the sympathetic trunks join this plexus and its subsidiaries.

The ovaries, part of the fallopian tubes, and broad ligament are innervated by the *ovarian plexus*, a network of nerve fibers accompanying the ovarian vessels and derived from the aortic and renal plexuses. The *inferior mesenteric plexus* is a subsidiary of the *celiac plexus* and *aortic plexus* and is located along the inferior mesenteric artery and its branches, providing innervation to the left colon, sigmoid, and rectum.

The *superior hypogastric plexus* (*presacral nerve*) is the continuation of the aortic plexus beneath the peritoneum in front of the terminal aorta, the fifth lumbar vertebra, and the sacral promontory, medial to the ureters **(Fig. 5-13)**. Embedded in loose areolar tissue, the plexus overlies the middle sacral vessels and is usually composed of two or three incompletely fused trunks. It contains preganglionic fibers from lumbar nerves, postganglionic fibers from higher sympathetic ganglia and the sacral sympathetic trunks, and visceral afferent fibers. Just below the sacral promontory, the superior hypogastric plexus divides into two loosely arranged nerve trunks, the *hypogastric nerves*. These nerves course inferiorly and laterally to connect with the inferior *hypogastric plexuses* (*pelvic plexuses*), which are a dense network of nerves and ganglia that lie along the lateral pelvic sidewall overlying branches of the internal iliac vessels **(Fig. 5-13)**.

The inferior hypogastric plexus includes efferent sympathetic fibers, afferent (sensory) fibers, and parasympathetic fibers arising from the pelvic splanchnic nerves (*S2 to S4, nervi erigentes*).

This paired plexus is the final common pathway of the pelvic visceral nervous system and is divided into three portions, representing distribution of innervation to the viscera:

1. **Vesical plexus**
   - Innervation: bladder and urethra
   - Course: along vesical vessels
2. **Middle rectal plexus (hemorrhoidal)**
   - Innervation: rectum
   - Course: along middle rectal vessels
3. **Uterovaginal plexus (Frankenhäuser ganglion)**
   - Innervation: uterus, vagina, clitoris, vestibular bulbs
   - Course: along uterine vessels and through cardinal and uterosacral ligaments; sympathetic and sensory fibers derive from T10, L1; parasympathetic fibers derive from S2 to S4

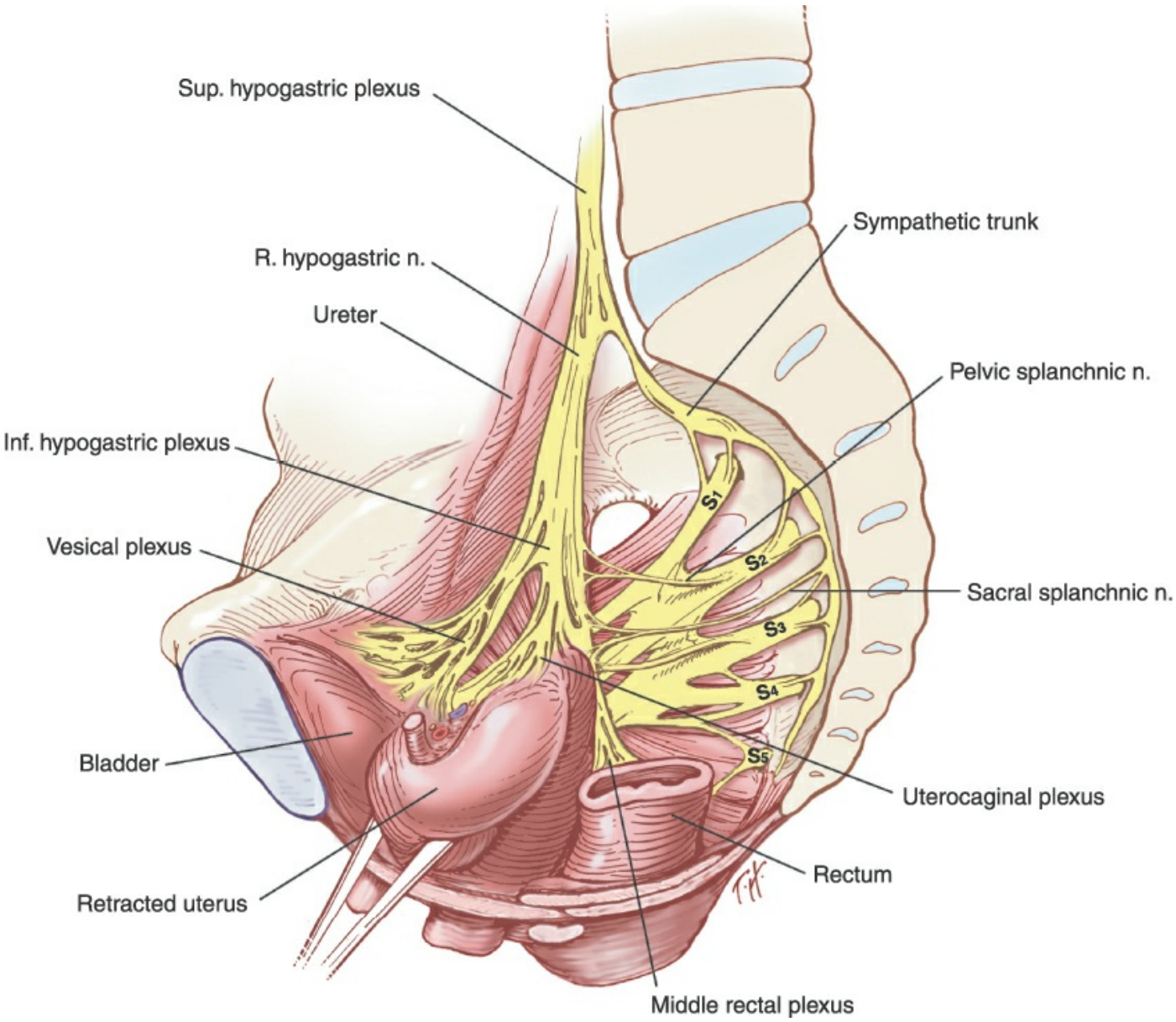


FIGURE 5-13 The presacral nerves.

Disruption of the superior hypogastric plexus or hypogastric nerves can cause de novo bladder, bowel, or sexual dysfunction postoperatively. Radical hysterectomy, where portions of this system are removed, can lead to significant visceral and/or sexual dysfunction (28,29). The sacral hypogastric plexus may be injured during dissection of deep pelvic retroperitoneal spaces for deep infiltrating endometriosis or during exposure of the anterior surface of S1 for mesh fixation during sacrocolpopexy. The hypogastric nerves extend from the superior hypogastric plexus and course through the lateral walls into the peritoneum of the posterior cul-de-sac and uterosacral ligaments. **[3]** Urinary, bowel, and sexual dysfunction have been reported after benign hysterectomy or vaginal apical suspension procedures where the inferior hypogastric nerve is interrupted during transection or securing of the uterosacral ligament (30,31).

Afferent Innervation

Afferent **fibers from the pelvic viscera and blood vessels traverse the same pathways to provide sensory input to the central nervous system**. They are involved in reflex arcs needed for bladder, bowel, and genital tract function. The afferent fibers reach the central nervous system to have their first synapse within the posterior spinal nerve ganglia.

Presacral neurectomy, in which a segment of the superior hypogastric plexus is divided and resected in order to interrupt sensory fibers from the uterus and cervix, is associated with relief of dysmenorrhea secondary to endometriosis in about 50% to 75% of cases in which it was used (32,33). Efferent fibers from the adnexa travel with the ovarian plexus. Pain originating from the ovary or tube is not relieved by resection of the presacral nerve. Disturbance in bowel or bladder function may result because this plexus contains efferent sympathetic and parasympathetic nerve fibers intermixed with afferent fibers. An alternative surgical procedure is resection of the uterosacral ligaments, which is also associated with urinary dysfunction including urinary retention (34).

An anesthetic block of the pudendal nerve is performed most often for pain relief with uncomplicated vaginal deliveries but may provide useful anesthesia for minor perineal surgical procedures. This nerve block may be accomplished transvaginally or through the perineum. A needle is inserted toward the ischial spine with the tip directed slightly posteriorly and through the sacrospinous ligament. As the anesthetic agent is injected, frequent aspiration is required to avoid injection into the pudendal vessels, which travel with the nerve.

PELVIC VISCERA

Genital Structures

Vagina

A sagittal section of the female pelvis is presented in Figure 5-14.

The vagina is a hollow fibromuscular tube extending from the vulvar vestibule to the uterus. In the dorsal lithotomy position, the vagina is directed posteriorly toward the sacrum, but its axis is almost horizontal in the upright position. It is attached at its upper end to the uterus just above the cervix. The spaces between the cervix and vagina are known as the *anterior*, *posterior*, and *lateral vaginal fornices*. **Because the vagina is attached at a higher point posteriorly than anteriorly, the posterior vaginal wall is about 3 cm longer than the anterior wall.**

The posterior vaginal fornix is separated from the posterior cul-de-sac and peritoneal cavity by the vaginal wall and peritoneum. This proximity is clinically

useful, both diagnostically and therapeutically. *Culdocentesis*, a technique in which a needle is inserted just posterior to the cervix through the vaginal wall into the peritoneal cavity, is used to evaluate intraperitoneal hemorrhage (e.g., ruptured ectopic pregnancy, hemorrhagic corpus luteum, other intra-abdominal bleeding), pus (e.g., pelvic inflammatory disease, ruptured intra-abdominal abscess), or other intra-abdominal fluid (e.g., ascites). Incision into the peritoneal cavity from this location in the vagina, known as a *posterior colpotomy*, can be used as an adjunct to laparoscopic excision of adnexal masses, with removal of the mass intact through the posterior vagina.

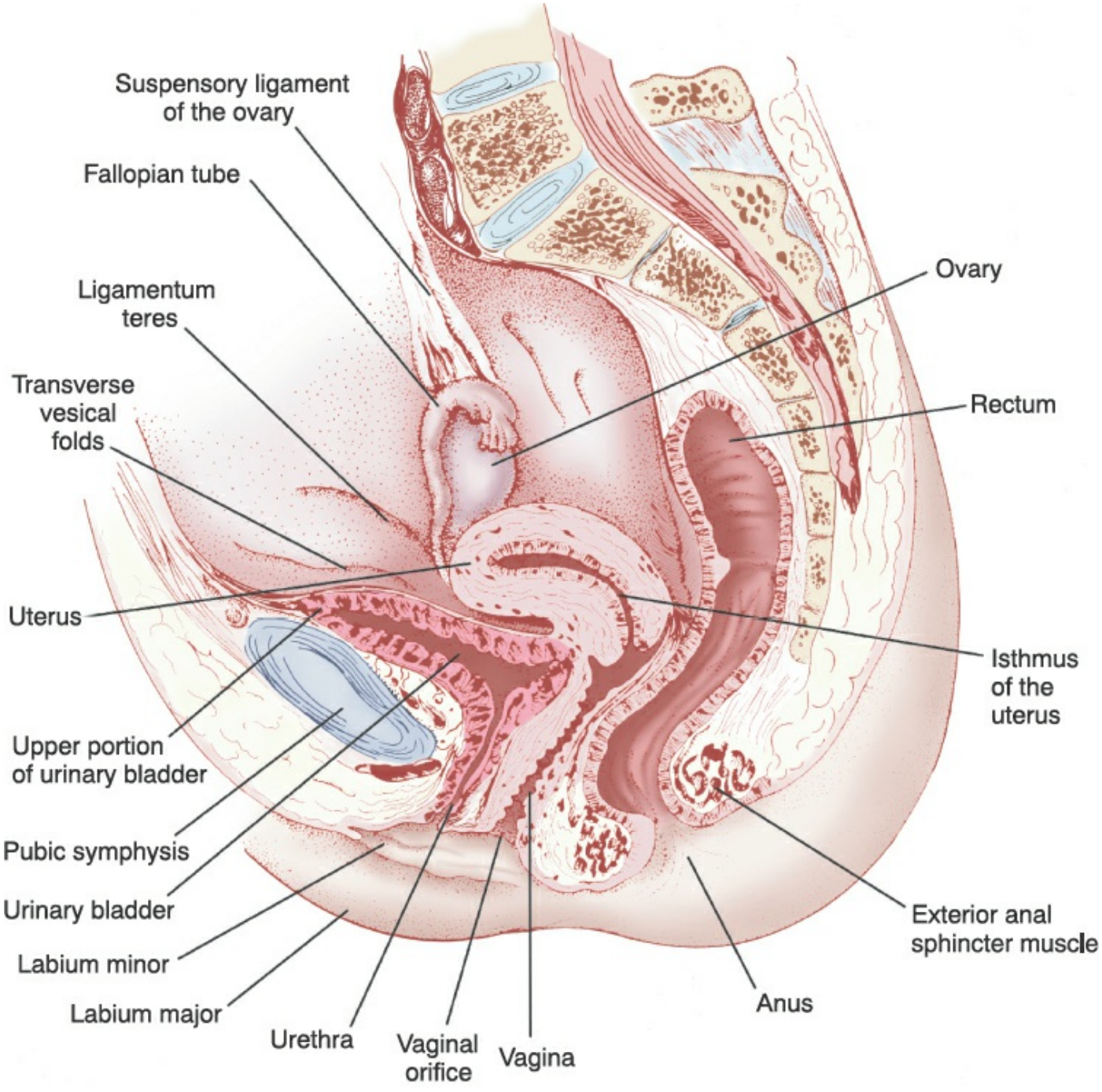


FIGURE 5-14 The pelvic viscera. A sagittal section of the female pelvis with the pelvic viscera and their

relationships.

The vagina is attached to the lateral pelvic wall with endopelvic fascial connections to the *arcus tendineus* (white line), which extends from the pubic bone to the ischial spine. This connection converts the vaginal lumen into a transverse slit with the anterior and posterior walls in apposition; the lateral space where the two walls meet is the *vaginal sulcus*. Lateral detachments of the vagina are recognized in some cystocele formations (lateral cystoceles or paravaginal defects).

The opening of the vagina may be covered by a membrane or surrounded by a fold of connective tissue called the *hymen.* This tissue is usually replaced by irregular tissue tags after sexual activity and childbirth occur. The lower vagina is somewhat constricted as it passes through the urogenital hiatus in the pelvic diaphragm; the upper vagina is more spacious. The entire vagina is characterized by its distensibility, which is most evident during childbirth.

The vagina is closely applied anteriorly to the urethra, bladder neck and trigonal region, and posterior bladder; posteriorly, the vagina lies in association with the perineal body, anal canal, lower rectum, and posterior cul-de-sac. **It is separated from the lower urinary and gastrointestinal tracts by their investing layers of fibromuscular elements known as the *endopelvic fascia.***

The vagina is composed of three layers:

1. **Mucosa**—nonkeratinized stratified squamous epithelium, without glands. Vaginal lubrication occurs primarily by transudation, with contributions from cervical and Bartholin gland secretions. The mucosa has a characteristic pattern of transverse ridges and furrows known as *rugae*. It is hormonally sensitive, responding to stimulation by estrogen with proliferation and maturation. The mucosa is colonized by mixed bacterial flora with *Lactobacillus* predominant; normal pH is 3.5 to 4.5.
2. **Muscularis**—connective tissue and smooth muscle, loosely arranged in inner circular and outer longitudinal layers.
3. **Adventitia**—endopelvic fascia, adherent to the underlying muscularis.

Blood Supply

The blood supply of the vagina includes the vaginal artery and branches from the uterine, middle rectal, and internal pudendal arteries.

Innervation

The innervation of the vagina is as follows: the upper vagina—uterovaginal plexus; the distal vagina—pudendal nerve.

Uterus

The uterus is a fibromuscular organ usually divided into a lower cervix and an

upper corpus or uterine body (Fig. 5-15).

Cervix

The portion of cervix exposed to the vagina is the exocervix or portio vaginalis. It has a convex round surface with a circular or slitlike opening (the external os) into the endocervical canal. **The endocervical canal is about 2 to 3 cm in length and opens proximally into the endometrial cavity at the internal os.**

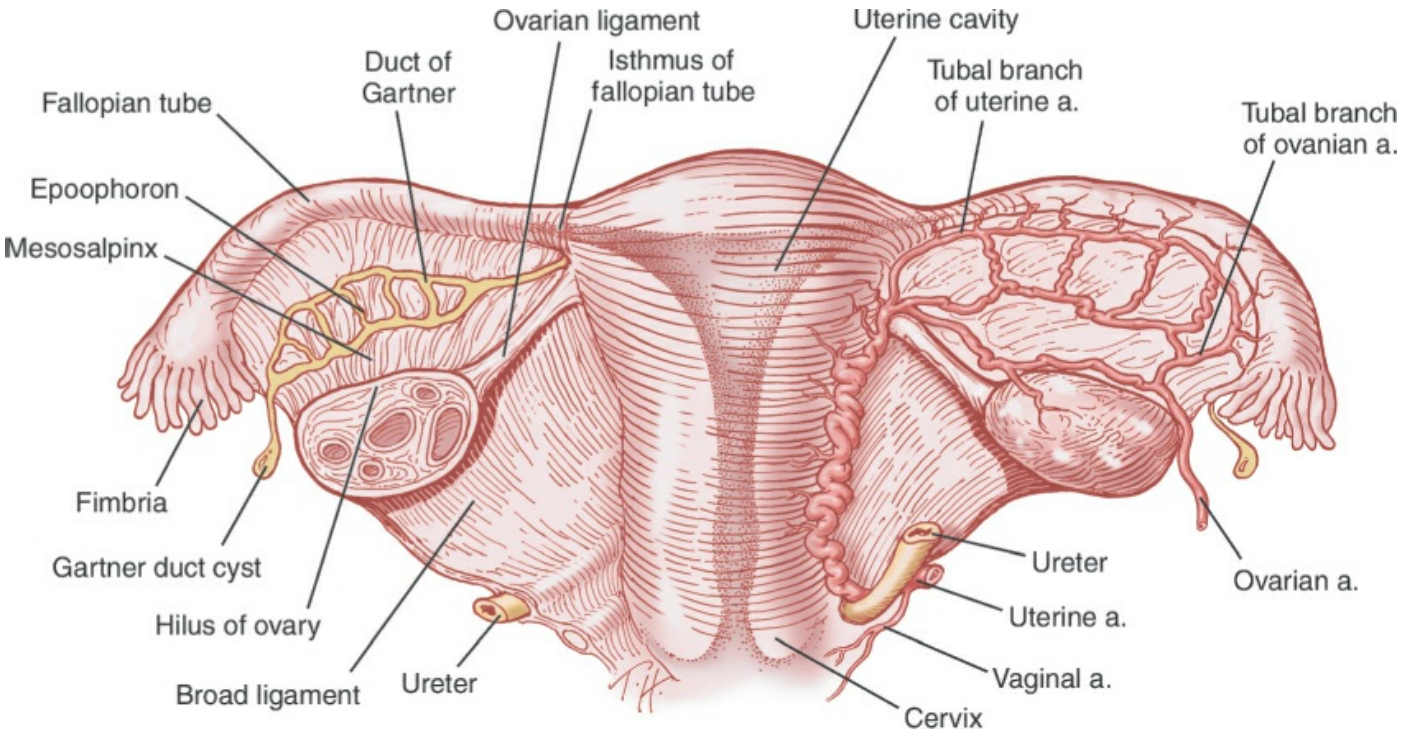


FIGURE 5-15 The uterus, fallopian tubes, and ovaries.

The cervical mucosa contains both stratified squamous epithelium, characteristic of the exocervix, and mucus-secreting columnar epithelium, characteristic of the endocervical canal. The intersection where these two epithelia meet—the squamocolumnar junction—is geographically variable and dependent on hormonal stimulation. It is this dynamic interface, the transformation zone, which is most vulnerable to the development of squamous neoplasia.

In early childhood, during pregnancy, or with oral contraceptive use, columnar epithelium may extend from the endocervical canal onto the exocervix, a condition known as *eversion* or *ectopy.* After menopause, the transformation zone usually recedes entirely into the endocervical canal.

Production of cervical mucus is under hormonal influence. It varies from profuse, clear, and thin mucus around the time of ovulation to scant and thick mucus in the postovulatory phase of the cycle. Deep in the mucosa and submucosa, the cervix is composed of fibrous connective tissue and a small amount of smooth muscle in a

circular arrangement.

Corpus

The body of the uterus varies in size and shape, depending on hormonal and childbearing status. **At birth, the cervix and corpus are about equal in size; in adult women, the corpus has grown to two to three times the size of the cervix**. The position of the uterus in relation to other pelvic structures is variable and is generally described in terms of positioning—anterior, midposition, or posterior; flexion; and version. ***Flexion* is the angle between the long axis of the uterine corpus and the cervix, whereas *version* is the angle of the junction of the uterus with the upper vagina**. Occasionally, abnormal positioning may occur secondary to associated pelvic pathology, such as endometriosis or adhesions.

The uterine corpus is divided into several different regions. The area where the endocervical canal opens into the endometrial cavity is known as the *isthmus or lower uterine segment.* On each side of the upper uterine body, a funnel-shaped area receives the insertion of the fallopian tubes and is called the *uterine cornu*; the uterus above this area is the fundus.

The endometrial cavity is triangular in shape and represents the mucosal surface of the uterine corpus. The epithelium is columnar and gland forming with a specialized stroma. It undergoes cyclic structural and functional change during the reproductive years, with regular shedding of the superficial endometrium and regeneration from the basal layer.

The muscular layer of the uterus, the *myometrium*, consists of interlacing smooth muscle fibers and ranges in thickness from 1.5 to 2.5 cm. Some outer fibers are continuous with those of the tube and round ligament.

Peritoneum covers most of the corpus of the uterus and the posterior cervix and is known as the *serosa.* Laterally, the broad ligament, a double layer of peritoneum covering the neurovascular supply to the uterus, inserts into the cervix and corpus. Anteriorly, the bladder lies over the isthmic and cervical region of the uterus.

Blood Supply

The blood supply to the uterus is the uterine artery, which anastomoses with the ovarian and vaginal arteries. Uterine artery embolization can block the blood supply to the uterine body to treat adenomyosis and control heavy uterine bleeding from fibroids or obstetrical hemorrhage.

Innervation

The nerve supply to the uterus is the uterovaginal plexus.

Fallopian Tubes

The fallopian tubes and ovaries collectively are referred to as the *adnexa.* The

fallopian tubes are paired hollow structures representing the proximal unfused ends of the müllerian duct. They vary in length from 7 to 12 cm, and their function includes ovum pickup, provision of physical environment for conception, and transport and nourishment of the fertilized ovum.

The tubes are divided into several regions:

1. **Interstitial**—narrowest portion of the tube, lies within the uterine wall and forms the tubal ostia at the endometrial cavity.
2. **Isthmus**—narrow segment closest to the uterine wall.
3. **Ampulla**—larger-diameter segment lateral to the isthmus.
4. **Fimbria (infundibulum)**—funnel-shaped abdominal ostia of the tubes, opening into the peritoneal cavity; this opening is fringed with numerous fingerlike projections that provide a wide surface for ovum pickup. The fimbria ovarica is a connection between the end of the tube and ovary, bringing the two closer.

The tubal mucosa is ciliated columnar epithelium, which becomes progressively more architecturally complex as the fimbriated end is approached. The muscularis consists of an inner circular and outer longitudinal layer of smooth muscle. The tube is covered by peritoneum and, through its mesentery (mesosalpinx), which is situated dorsal to the round ligament, is connected to the upper margin of the broad ligament.

Blood Supply

The vascular supply to the fallopian tubes is the uterine and ovarian arteries.

Innervation

The innervation to the fallopian tubes is the uterovaginal plexus and the ovarian plexus.

Ovaries

The ovaries are paired gonadal structures that lie suspended between the pelvic wall and the uterus by the infundibulopelvic ligament laterally and the utero-ovarian ligament medially. Inferiorly, the hilar surface of each ovary is attached to the broad ligament by its mesentery (mesovarium), which is dorsal to the mesosalpinx and fallopian tube. Primary neurovascular structures reach the ovary through the infundibulopelvic ligament and enter through the mesovarium. **The normal ovary varies in size, with measurements up to 5 × 3 × 3 cm.** Variation in dimension results from endogenous hormonal production, which varies with age and with each menstrual cycle. Exogenous substances, including oral contraceptives, gonadotropin-releasing hormone agonists, or ovulation-inducing medication, may either stimulate or suppress ovarian activity and affect size.

Each ovary consists of a cortex and medulla and is covered by a single layer of flattened cuboidal to low columnar epithelium that is continuous with the peritoneum at

the mesovarium. The cortex is composed of a specialized stroma and follicles in various stages of development or attrition. The medulla occupies a small portion of the ovary in its hilar region and is composed primarily of fibromuscular tissue and blood vessels.

Blood Supply

The blood supply to the ovary is the ovarian artery, which anastomoses with the uterine artery.

Innervation

The innervation to the ovary is the ovarian plexus and the uterovaginal plexus.

Urinary Tract

Ureters

The ureter is the urinary conduit leading from the kidney to the bladder; it measures about 25 cm in length and is totally retroperitoneal in location.

The lower half of each ureter traverses the pelvis after crossing the common iliac vessels at their bifurcation, just medial to the ovarian vessels. It descends into the pelvis adherent to the peritoneum of the lateral pelvic wall and the medial leaf of the broad ligament and enters the bladder base anterior to the upper vagina, traveling obliquely through the bladder wall to terminate in the bladder trigone.

The ureteral mucosa is a transitional epithelium. The muscularis consists of an inner longitudinal and outer circular layer of smooth muscle. A protective connective tissue sheath, which is adherent to the peritoneum, encloses the ureter.

Blood Supply

The blood supply is variable, with contributions from the renal, ovarian, common iliac, internal iliac, uterine, and vesical arteries.

Innervation

The innervation is through the ovarian plexus and the vesical plexus.

Bladder and Urethra

Bladder

The bladder is a hollow organ, spherically shaped when full, that stores urine. Its size varies with urine volume, normally reaching a maximum volume of at least 300 mL. The bladder is often divided into two areas, which are of physiologic significance:

1. The **base of the bladder** consists of the urinary trigone posteriorly and a thickened area of detrusor anteriorly. The three corners of the trigone are formed by the two ureteral orifices and the opening of the urethra into the bladder. The bladder base receives α-adrenergic sympathetic innervation and is the area responsible for

maintaining continence.

2. The **dome of the bladder** is the remaining bladder area above the bladder base. It has parasympathetic innervation and is responsible for micturition.

The bladder is positioned posterior to the pubis and lower abdominal wall and anterior to the cervix, upper vagina, and part of the cardinal ligament. Laterally, it is bounded by the pelvic diaphragm and obturator internus muscle.

The bladder wall has four layers—the urothelium, lamina propria, muscularis propria, and serosa. The urothelium is the innermost epithelial lining of the bladder and is composed of transitional cell epithelium. Covering the uroepithelium is a glycosaminoglycan (GAG) layer, which acts as an impermeable protective barrier to prohibit bacterial adherence and prevent urothelial damage from urinary proteases and ions. The lamina propria and muscularis propria (detrusor muscle) are composed of intermeshing muscle fibers, which allow for rapid expansion during bladder filling.

The bladder mucosa is transitional cell epithelium. The muscle wall (detrusor), rather than being arranged in layers, is composed of intermeshing muscle fibers.

Blood Supply

The blood supply to the bladder is from the superior, middle, and inferior vesical arteries, with contribution from the uterine and vaginal vessels.

Innervation

The innervation to the bladder is from the vesical plexus, with contribution from the uterovaginal plexus.

Urethra

The vesical neck is the region of the bladder that receives and incorporates the urethral lumen. The female urethra is about 3 to 4 cm in length and extends from the bladder to the vestibule, traveling just anterior to the vagina.

The urethra is lined by nonkeratinized squamous epithelium that is responsive to estrogen stimulation. Within the submucosa, on the dorsal surface of the urethra, are the paraurethral or Skene glands, which empty through ducts into the urethral lumen. Distally, these glands empty into the vestibule on either side of the external urethral orifice. **Chronic infection of Skene glands, with obstruction of their ducts and cystic dilation, is believed to be an inciting factor in the development of suburethral diverticula. Symptomatic patients can complain of urinary outflow obstruction (e.g., hesitancy, dribbling, lateral spraying, retention, or urinary tract infection).**

The urethra contains an inner longitudinal layer of smooth muscle and outer circularly oriented smooth muscle fibers. The inferior fascia of the urogenital diaphragm or perineal membrane begins at the junction of the middle and distal thirds of the urethra. Proximal to the middle and distal parts of the urethra, voluntary muscle fibers derived

from the urogenital diaphragm intermix with the outer layer of smooth muscle, increasing urethral resistance and contributing to continence. At the level of the urogenital diaphragm, the skeletal muscle fibers leave the wall of the urethra to form the sphincter urethrae and deep transverse perineal muscles. In the coronal plane on MRI studies, the ventral urogenital diaphragm forms an interconnected complex with the compressor urethrae, vestibular bulb, and levator ani. The dorsal part connects the levator ani and vaginal sidewall via a distinct band to the ischiopubic ramus. In the sagittal plane the parallel position of urogenital diaphragm and levator ani can be seen (35).

Blood Supply

The vascular supply to the urethra is from the vesical and vaginal arteries and the internal pudendal branches.

Innervation

The innervation to the urethra is from the vesical plexus and the pudendal nerve.

The lower urinary and genital tracts are intimately connected anatomically and functionally. In the midline, the bladder and proximal urethra can be dissected easily from the underlying lower uterine segment, cervix, and vagina through a loose avascular plane. The distal urethra is essentially inseparable from the vagina. Of surgical significance is the location of the bladder trigone immediately over the middle third of the vagina. Unrecognized injury to the bladder during pelvic surgery may result in development of a vesicovaginal fistula.

Dissection to the level of the trigone is rarely required, and damage to this critical area is unusual.

Lower Gastrointestinal Tract

Sigmoid Colon

The sigmoid colon begins its characteristic S-shaped curve as it enters the pelvis at the left pelvic brim (Fig. 5-16). The columnar mucosa and richly vascularized submucosa are surrounded by an inner circular layer of smooth muscle and three overlying longitudinal bands of muscle called teniae coli. A mesentery of varying length attaches the sigmoid to the posterior abdominal wall.

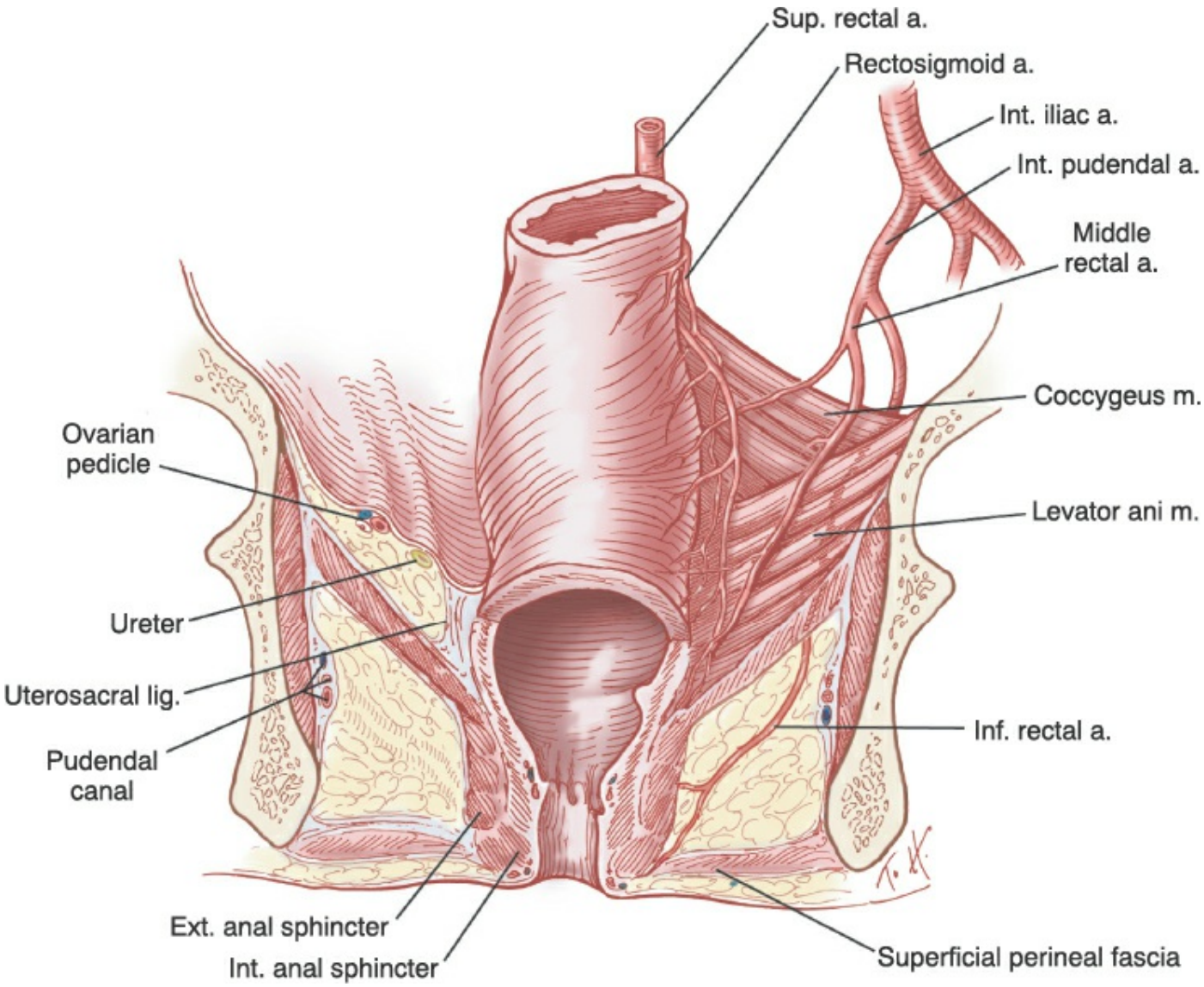


FIGURE 5-16 The rectosigmoid colon, its vascular supply, and muscular support (coronal view: peritoneum removed on right).

Blood Supply

The blood supply to the sigmoid colon is from the sigmoid arteries.

Innervation

The nerves to the sigmoid colon are derived from the inferior mesenteric plexus.

Rectum

The sigmoid colon loses its mesentery in the midsacral region and becomes the rectum about 15 to 20 cm above the anal opening. The rectum follows the curve of the lower sacrum and coccyx and becomes entirely retroperitoneal at the level of the rectouterine pouch or posterior cul-de-sac. It continues along the pelvic curve just posterior to the vagina until the level of the anal hiatus of the pelvic diaphragm, at which point it takes a sharp 90-degree turn posteriorly and becomes the anal canal,

separated from the vagina by the perineal body.

The rectal mucosa is lined by a columnar epithelium and characterized by three transverse folds that contain mucosa, submucosa, and the inner circular layer of smooth muscle. The teniae of the sigmoid wall broaden and fuse over the rectum to form a continuous longitudinal external layer of smooth muscle to the level of the anal canal.

Anal Canal

The anal canal begins at the level of the sharp turn in the direction of the distal colon and is 2 to 3 cm in length. At the anorectal junction, the mucosa changes to stratified squamous epithelium (the pectinate line), which continues until the termination of the anus at the anal verge, where there is a transition to perianal skin with typical skin appendages. It is surrounded by a thickened ring of circular muscle fibers that are a continuation of the circular muscle of the rectum, the internal anal sphincter. Its lower part is surrounded by bundles of striated muscle fibers, the external anal sphincter (36).

The internal anal sphincter maintains a steady state of tonic contraction, transiently relaxes in response to rectal distension, and does not appear to be solely essential for continence. Fecal continence is provided primarily by the puborectalis muscle and internal anal sphincter, which work in conjunction with the external anal sphincter. The puborectalis surrounds the anal hiatus in the pelvic diaphragm and interdigitates posterior to the rectum to form a rectal sling. Its constant tone contributes to the anorectal angle, which prevents stool from entering the anus from the rectum. The external anal sphincter surrounds the terminal anal canal below the level of the levator ani. **[3]** A growing body of literature suggests that both external anal sphincter and levator ani muscles are important for fecal continence and that multiple injuries contribute to pelvic floor dysfunction (37,38). One such MRI study showed that major levator ani muscle injuries were observed in 19.1% women who delivered vaginally with external anal sphincter injuries, 3.5% who delivered vaginally without external anal sphincter injury, and none of the women who delivered by cesarean section before labor. Among women with external anal sphincter injuries, those with major levator ani muscle injuries trended more toward fecal incontinence (37). Patients with chronic fourth-degree lacerations who have absence of the anterior portions of the external anal sphincter and internal anal sphincter can still maintain continence with an intact puborectalis muscle (39). Further studies suggest that thickening of the internal anal sphincter occurs with aging, and that thinning of the external anal sphincter and a corresponding drop in squeeze pressure correlated with fecal incontinence, but not aging (40).

The anatomic proximity of the lower gastrointestinal tract to the lower genital tract is particularly important during surgery of the vulva and vagina. Lack of attention to this proximity during repair of vaginal lacerations or episiotomies can lead to damage of the rectum and fistula formation or injury to the external anal

sphincter, resulting in fecal incontinence. Because of the avascular nature of the rectovaginal space, it is relatively easy to dissect the rectum from the vagina in the midline, which is routinely done in the repair of rectoceles.

Blood Supply

The vascular supply to the rectum and anal canal is from the superior, middle, and inferior rectal arteries. The venous drainage is a complex submucosal plexus of vessels that, under conditions of increased intra-abdominal pressure (pregnancy, pelvic mass, chronic constipation, ascites), may dilate and become symptomatic with rectal bleeding or pain as hemorrhoids.

Innervation

The nerve supply to the anal canal is from the middle rectal plexus, the inferior mesenteric plexus, and the pudendal nerve.

THE GENITAL TRACT AND ITS RELATIONS

The genital tract is situated at the bottom of the intraabdominal cavity and is related to the intraperitoneal cavity and its contents, the retroperitoneal spaces, and the pelvic floor. Accessing it through the abdominal wall or the perineum requires a thorough knowledge of the anatomy of these areas and their relationships.

The Abdominal Wall

The anterior abdominal wall is bounded superiorly by the xiphoid process and the costal cartilage of the 7th to 10th ribs and inferiorly by the iliac crest, anterosuperior iliac spine, inguinal ligament, and pubic bone. It consists of skin, muscle, fascia, nerves, and vessels.

Skin

The lower abdominal skin may exhibit striae, or "stretch marks," and increased pigmentation in the midline in parous women. The subcutaneous tissue contains a variable amount of fat.

Muscles

Five muscles and their aponeuroses contribute to the structure and strength of the anterolateral abdominal wall (Fig. 5-17; Table 5-7).

Fascia

Superficial Fascia

The superficial fascia consists of two layers:

1. **Camper fascia**—the most superficial layer, which contains a variable amount of fat and is continuous with the superficial fatty layer of the perineum
2. **Scarpa fascia**—a deeper membranous layer continuous in the perineum with Colles fascia (superficial perineal fascia) and with the deep fascia of the thigh (fascia lata)

Rectus Sheath

The aponeuroses of the external and internal oblique and the transverse abdominis combine to form a sheath for the rectus abdominis and pyramidalis, fusing medially in the midline at the linea alba and laterally at the semilunar line (Fig. 5-18). Above the arcuate line, the aponeurosis of the internal oblique muscle splits into anterior and posterior lamella (Fig. 5-18A). Below this line, all three layers are anterior to the body of the rectus muscle (Fig. 5-18B). The rectus is covered posteriorly by the transversalis fascia, providing access to the muscle for the inferior epigastric vessels.

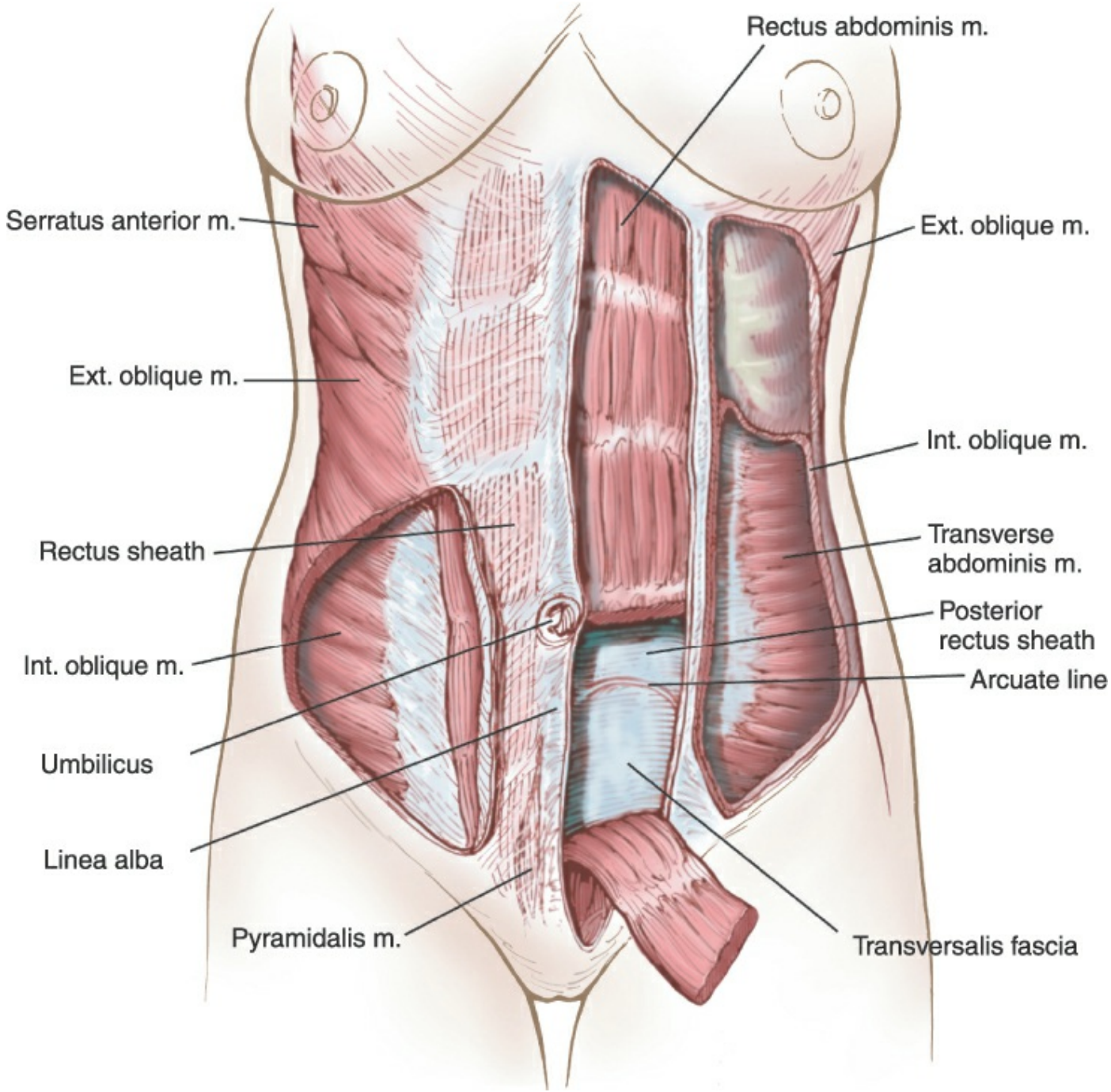


FIGURE 5-17 The abdominal wall muscles.

Table 5-7 Muscles Contributing to the Structure and Strength of the Anterolateral Abdominal Wall

Muscle	Origin	Insertion	Action
External oblique	Fleshy digitations from the outer surfaces of ribs 5–12	Fibers radiate inferiorly, anteriorly, and medially, in most cases ending in the aponeurosis of the external muscle and inserting into the anterior half of the iliac crest, the pubic tubercle, and the linea alba. The superficial inguinal ring is located above and lateral to the pubic tubercle at the end of a triangular cleft in the external oblique muscle, bordered by strong fibrous bands that transmit the round ligament	Compresses and supports abdominal viscera; flexes and rotates vertebral column
Internal oblique	Posterior layer of the thoracolumbar fascia, the anterior two-thirds of the iliac crest, and the lateral two-thirds of the inguinal ligament	Inferior border of ribs 10–12. The superior fibers of the aponeurosis split to enclose the rectus abdominis muscle and join at the linea alba above the arcuate line. The most inferior fibers join with those of the transverse abdominis muscle to insert into the pubic crest and pecten pubis via the conjoint tendon	Compresses and supports abdominal viscera
Transversus abdominis	Inner aspect of the inferior six costal cartilages, the thoracolumbar fascia, the iliac crest, and the lateral one-third of the inguinal ligament	Linea alba with the aponeurosis of the internal oblique, the pubic crest and the pecten pubis through the conjoint tendon	Compresses and supports abdominal viscera
Rectus abdominis	Superior pubic ramus and the ligaments of the symphysis pubis	Anterior surface of the xiphoid process and the cartilage of ribs 5–7	Tenses anterior abdominal wall and flexes trunk
Pyramidalis	Small triangular muscle contained within the rectus sheath, anterior to the lower part of the rectus muscle	On the linea alba, easily recognizable shape, used to locate the midline, particularly in a patient with previous abdominal surgery and scarring of the abdominal wall	Tenses the linea alba, insignificant in terms of function, and is frequently absent

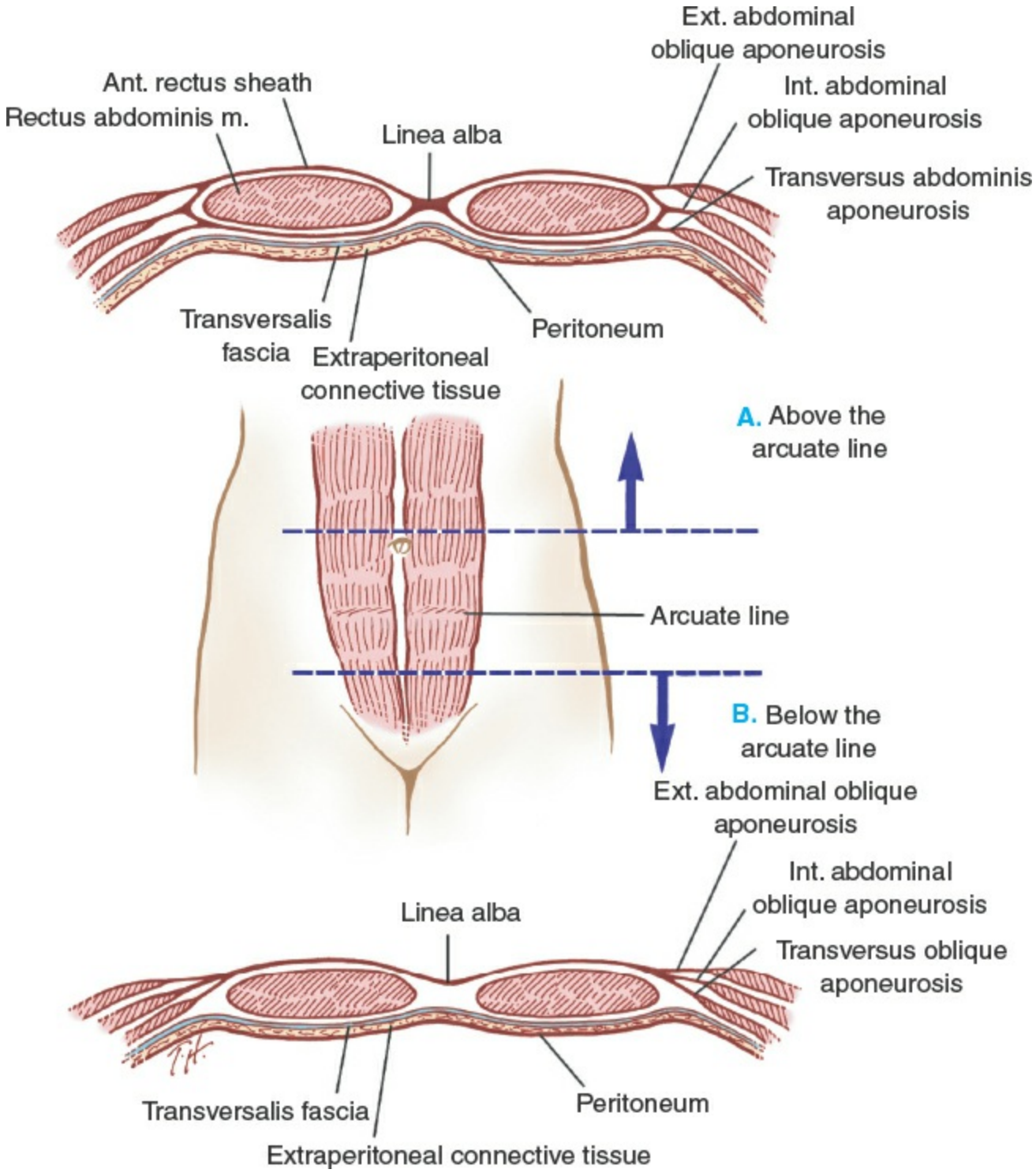


FIGURE 5-18 A transverse section of the rectus abdominis. The aponeurosis of the external and internal oblique and the transversus abdominis from the rectus abdominis. **A:** Above the arcuate line. **B:** Below the arcuate line.

Transversalis Fascia and Endopelvic Fascia

[2] The transversalis fascia is a firm membranous sheet on the internal surface of the transversus abdominis muscle that extends beyond the muscle and forms a fascia lining the entire abdominopelvic cavity. Like the peritoneum, it is divided into a

parietal and a visceral component. It is continuous from side to side across the linea alba and covers the posterior aspect of the rectus abdominis muscle below the arcuate line. Superiorly, it becomes the inferior fascia of the diaphragm. Inferiorly, it is attached to the iliac crest, covers the iliac fascia and the obturator internus fascia, and extends downward and medially to form the superior fascia of the pelvic diaphragm.

[2] Characteristically, the transversalis fascia continues along blood vessels and other structures leaving and entering the abdominopelvic cavity and contributes to the formation of the visceral (*endopelvic*) pelvic fascia (41)**. The pelvic fascia invests the pelvic organs and attaches them to the pelvic sidewalls, thereby playing a critical role in *pelvic support.*** In the inguinal region, the fascial relationships result in the development of the inguinal canal, through which the round ligament exits into the perineum. The fascia is separated from the peritoneum by a layer of preperitoneal fat. Areas of fascial weakness or congenital or posttraumatic and surgical injuries result in herniation of the underlying structures through a defective abdominal wall. The incisions least likely to result in damage to the integrity and innervation of the abdominal wall muscles include a midline incision through the linea alba and a transverse incision through the recti muscle fibers that respects the integrity of its innervation (42).

Nerves and Vessels

The tissues of the abdominal wall are innervated by the continuation of the inferior intercostal nerves T4 to T11 and the subcostal nerve T12. The inferior part of the abdominal wall is supplied by the first lumbar nerve through the iliohypogastric and the ilioinguinal nerves. **Abdominal wall surgical sites below the level of the anterior superior iliac spine have the potential for ilioinguinal or iliohypogastric nerve injury**. Injury to these nerves occurs in approximately 4% of Pfannenstiel incisions (43,44). The primary blood supply to the anterior lateral abdominal wall includes the following:

1. The **inferior epigastric and deep circumflex iliac arteries,** branches of the external iliac artery
2. The **superior epigastric artery,** a terminal branch of the internal thoracic artery

The inferior epigastric artery runs superiorly in the transverse fascia to reach the arcuate line, where it enters the rectus sheath. It is vulnerable to damage by abdominal incisions in which the rectus muscle is completely or partially transected, during placement of lateral laparoscopic ports, or by excessive lateral traction on the rectus. The deep circumflex artery runs on the deep aspect of the anterior abdominal wall parallel to the inguinal ligament and along the iliac crest between the transverse abdominis muscle and the internal oblique muscle. The superior epigastric

vessels enter the rectus sheath superiorly just below the seventh costal cartilage.

The venous system drains into the saphenous vein, and the lymphatics drain to the axillary chain above the umbilicus and to the inguinal nodes below it. The subcutaneous tissues drain to the lumbar chain.

Abdominal Anatomy

Greater Omentum

When the abdomen and peritoneum are opened, the first structure encountered is the greater omentum. The greater omentum is a fold of visceral peritoneum that hangs like an apron over the small and large intestines. It is attached cranially to the greater curvature of the stomach and doubles back to attach to the transverse colon. Lifting the omentum reveals the large intestine on the periphery surrounding coils of small bowel. The blood supply is provided by the right and left gastroepiploic arteries, which anastomose within the anterior greater omentum.

Lesser Omentum

The lesser omentum arises from the lesser curvature of the stomach and extends to the liver. The hepatic artery, the common bile duct, the portal vein, the hepatic plexus of nerves, and lymphatics run in between the two layers of the lesser omentum. An arterial loop formed by the anastomosis of the left gastric artery and right gastric branch of the hepatic artery runs along the attachment to the stomach.

Small Intestine

The small intestine is a convoluted tube measuring approximately 6 m long, which extends from the suspensory ligament of the duodenum (ligament of Treitz) to the ileocecal valve. The small intestine is divided into three portions: the duodenum, jejunum, and the ileum. The shortest portion of the bowel is the duodenum (25 cm), which consists of four parts. The major portion of the small intestine consists of the jejunum and ileum. The jejunum and ileum are attached to the posterior abdominal wall by a mesentery that allows each coil to accommodate itself to changes in form and position. The root of the mesentery is about 15 to 20 cm long and extends obliquely from the duodenojejunal flexure to the right colon.

Blood Supply

The duodenum is supplied by branches originating from the celiac trunk. The jejunum and ileum are supplied by branches of the superior mesenteric artery. Venous drainage occurs via the superior mesenteric vein to the portal vein.

Large Intestine

The large intestine extends from the end of the ileum to the anus and consists of the

cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anus. It is about 1.5 m long and is anchored to the parietal peritoneum along the right and left gutters. The cecum is situated in the right iliac fossa above the lateral half of the inguinal ligament. The vermiform appendix is found off the inferior side of the cecum. The ascending colon passes upward, opposite the colic valve to the undersurface of the right lobe of the liver, on the right side of the gallbladder. It abruptly bends forward and to the left, forming the right colic flexure. The transverse colon is the longest and most moveable part of the colon. It curves sharply on itself beneath the lower end of the spleen, forming the left colic flexure. The descending colon passes downward along the lateral border of the left kidney and then descends to the crest of the ileum where it ends in the iliac colon.

Blood Supply

The blood supply to the large intestine is derived from the colic and sigmoid branches of the mesenteric arteries. The superior mesenteric artery supplies the right colon and transverse colon; the inferior mesenteric artery supplies the left flexure, left sigmoid colon, and the upper two-thirds of rectum; and the internal pudendal artery supplies the anus and lower rectum. The venous drainage mirrors the colonic arterial supply with the inferior mesenteric vein draining into the splenic vein and the superior mesenteric vein joining the splenic vein to form the hepatic portal vein.

Perineum

The perineum is situated at the lower end of the trunk between the buttocks. Its bony boundaries include the lower margin of the pubic symphysis anteriorly, the tip of the coccyx posteriorly, and the ischial tuberosities laterally. These landmarks correspond to the boundaries of the pelvic outlet. The diamond shape of the perineum is customarily divided by an imaginary line joining the ischial tuberosities immediately in front of the anus, at the level of the perineal body, into an anterior urogenital and a posterior anal triangle **(Fig. 5-19)**.

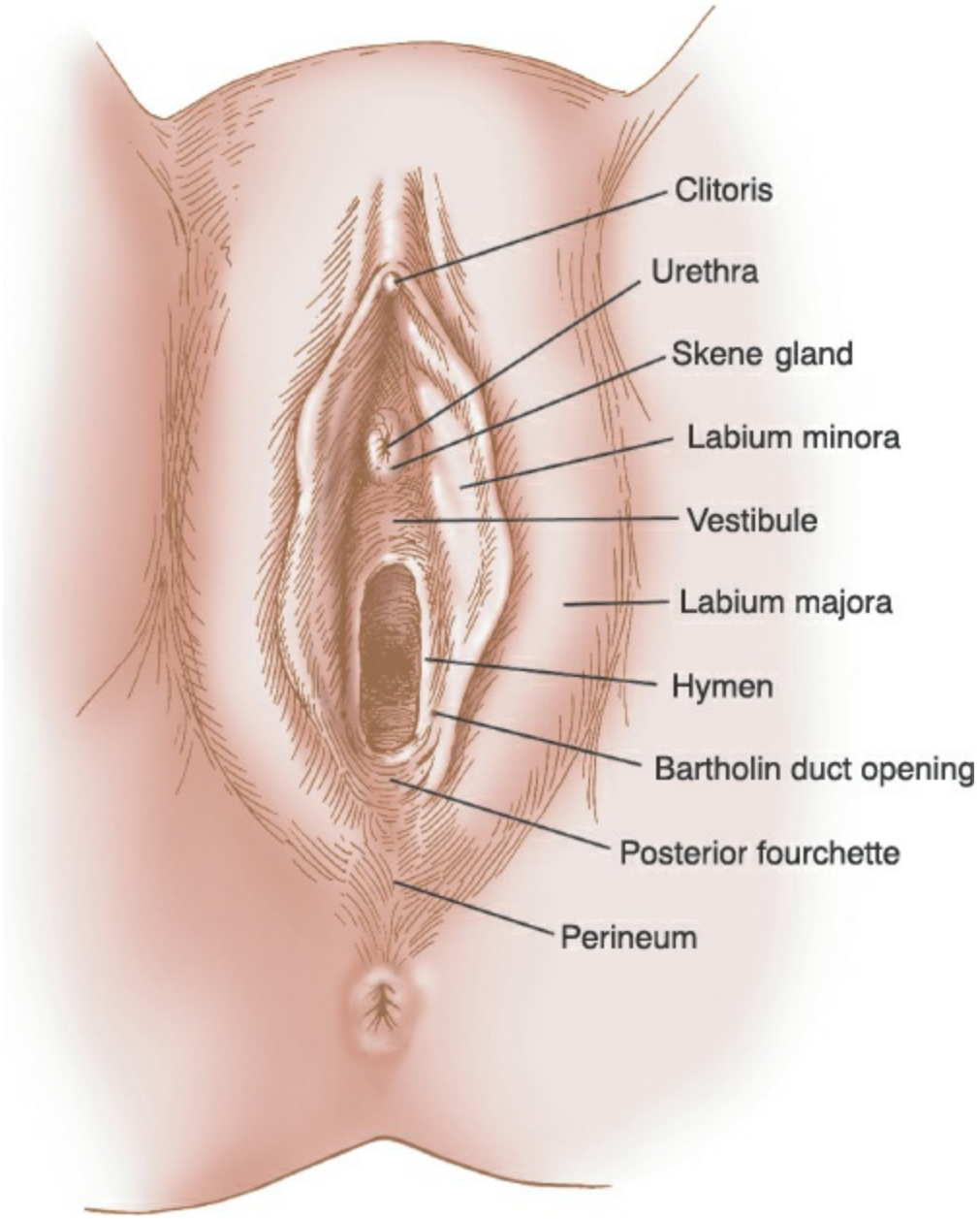


FIGURE 5-19 Vulva and perineum.

Urogenital Triangle

The urogenital triangle includes the external genital structures and the urethral opening (Fig. 5-19). These external structures cover the superficial and deep perineal compartments and are known as the *vulva* (Figs. 5-20 and 5-21).

Vulva

Mons Pubis

The mons pubis is a triangular eminence in front of the pubic bones that consists of adipose tissue covered by hair-bearing skin up to its junction with the abdominal

wall.

Labia Majora

The labia majora are a pair of fibroadipose folds of skin that extend from the mons pubis downward and backward to meet in the midline in front of the anus at the posterior fourchette. They include the terminal extension of the round ligament and occasionally a peritoneal diverticulum, the *canal of Nuck.* They are covered by skin with scattered hairs laterally and are rich in sebaceous, apocrine, and eccrine glands.

Labia Minora

The labia minora lie between the labia majora, with which they merge posteriorly, and are separated into two folds anteriorly as they approach the clitoris. The anterior folds unite to form the prepuce or hood of the clitoris. The posterior folds form the frenulum of the clitoris as they attach to its inferior surface. The labia minora are covered by hairless skin overlying a fibroelastic stroma rich in neural and vascular elements. The area between the posterior labia minora forms the vestibule of the vagina.

Clitoris

The clitoris is an erectile organ that is 2 to 3 cm in length. It consists of two crura and two corpora cavernosa and is covered by a sensitive rounded tubercle (the glans).

Vaginal Orifice

The vaginal orifice is surrounded by the *hymen*, a variable crescentic mucous membrane that is replaced by rounded caruncles after its rupture. The opening of the duct of the *greater vestibular* (*Bartholin*) *glands* is located on each side of the vestibule. Numerous lesser vestibular glands are scattered posteriorly and between the urethral and vaginal orifices.

Urethral Orifice

The urethral orifice is immediately anterior to the vaginal orifice and about 2 to 3 cm beneath the clitoris. The *Skene* (*paraurethral*) *gland* duct presents an opening on its posterior surface.

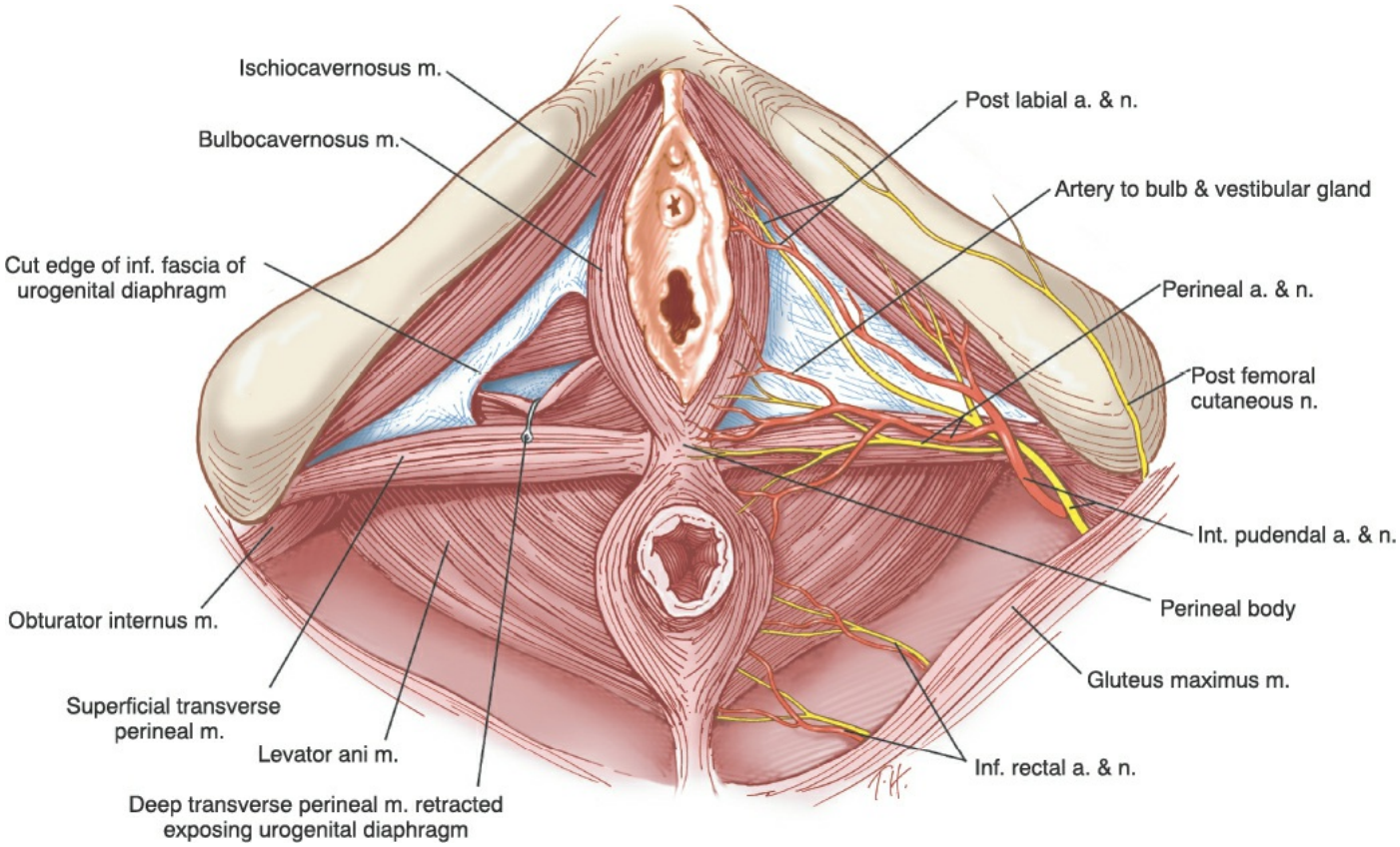


FIGURE 5-20 Superficial perineal compartment.

Superficial Perineal Compartment

The superficial perineal compartment lies between the superficial perineal fascia and the inferior fascia of the urogenital diaphragm (perineal membrane) (Fig. 5-20). The superficial perineal fascia has superficial and deep components. **The superficial layer is relatively thin and fatty and is continuous superiorly with the superficial fatty layer of the lower abdominal wall (*Camper fascia*)**. It continues laterally as the fatty layer of the thighs. The deep layer of the superficial perineal (*Colles*) fascia is continuous superiorly with the deep layer of the superficial abdominal fascia (*Scarpa fascia*), which attaches to the ischiopubic rami and ischial tuberosities. **The superficial perineal compartment is continuous superiorly with the superficial fascial spaces of the anterior abdominal wall, allowing spread of blood or infection along that route**. Such spread is limited laterally by the ischiopubic rami, anteriorly by the transverse ligament of the perineum, and posteriorly by the superficial transverse perineal muscle. The superficial perineal compartment includes the following:

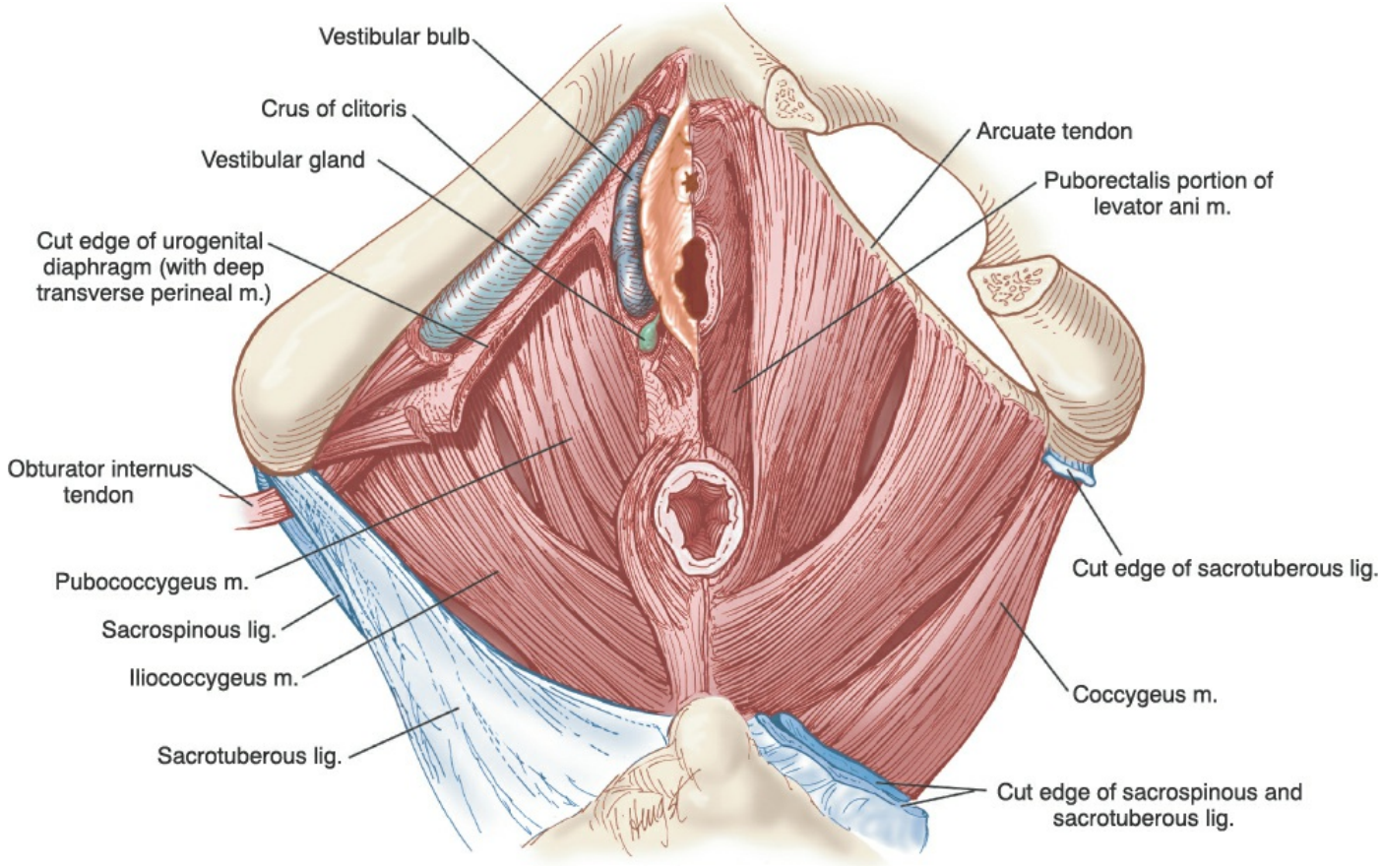


FIGURE 5-21 Deep perineal compartment.

Erectile Bodies

The vestibular bulbs are 3-cm, highly vascular structures surrounding the vestibule and located under the bulbocavernosus muscle. The body of the clitoris is attached by two crura to the internal aspect of the ischiopubic rami. The crura are covered by the ischiocavernosus muscles.

Muscles

The muscles of the vulva are the ischiocavernosus, the bulbocavernosus, and superficial transverse perineal. They are included in the superficial perineal compartment as follows:

Ischiocavernosus

- Origin—ischial tuberosity
- Insertion—ischiopubic bone
- Action—compresses the crura and lowers the clitoris

Bulbocavernosus

- Origin—perineal body

- Insertion—posterior aspect of the clitoris; some fibers pass above the dorsal vein of the clitoris in a sling-like fashion
- Action—compresses the vestibular bulb and dorsal vein of the clitoris

Superficial Transverse Perineal

- Origin—ischial tuberosity
- Insertion—central perineal tendon
- Action—fixes the perineal body

Vestibular Glands

The vestibular glands are situated on either side of the vestibule under the posterior end of the vestibular bulb. They drain between the hymen and the labia minora. Their mucous secretion helps maintain adequate lubrication. Infection in these glands can result in an abscess.

Deep Perineal Compartment

The deep perineal compartment is a fascial space bound inferiorly by the perineal membrane and superiorly by a deep fascial layer that separates the urogenital diaphragm from the anterior recess of the ischiorectal fossa (Fig. 5-21). It is stretched across the anterior half of the pelvic outlet between the ischiopubic rami. The deep compartment may be directly continuous superiorly with the pelvic cavity (45). The posterior pubourethral ligaments, functioning as wing-like elevations of the fascia ascending from the pelvic floor to the posterior aspect of the symphysis pubis, provide a point of fixation to the urethra and support the concept of the continuity of the deep perineal compartment with the pelvic cavity.

The anterior pubourethral ligaments represent a similar elevation of the inferior fascia of the urogenital diaphragm and are joined by the intermediate pubourethral ligament, with the junction between the two fascial structures arcing under the pubic symphysis (46). The urogenital diaphragm includes the *sphincter urethrae* (*urogenital sphincter*) and the *deep transverse perineal* (*transversus vaginae*) muscle.

The urogenital diaphragm (perineal membrane) is composed of two regions: one dorsal and one ventral. The dorsal portion consists of bilateral transverse fibrous sheets that attach the lateral wall of the vagina and perineal body to the ischiopubic ramus. This portion is devoid of striated muscle. The ventral portion is part of a solid three-dimensional tissue mass in which several structures are embedded. It is intimately associated with the compressor urethrae and the urethrovaginal sphincter muscles of the distal uretha. In this region the perineal membrane is continuous with the insertion of the arcus tendineus fasciae pelvis. The levator ani muscles are connected with the cranial surface of the perineal membrane. The vestibular bulb and clitoral crus are fused with

the membrane's caudal surface (47).

The sphincter urethrae **(Fig. 5-22)** is a continuous muscle fanning out as it develops proximally and distally, including the following:

1. **External urethral sphincter**, which surrounds the middle third of the urethra
2. **Compressor urethrae**, arcing across the ventral side of the urethra
3. **Urethrovaginal sphincter**, which surrounds the ventral aspect of the urethra and terminates in the lateral vaginal wall

The deep transverse perineal muscle originates at the internal aspect of the ischial bone, parallels the muscle compressor urethrae, and attaches to the lateral vaginal wall along the perineal membrane. Studies show that a smaller striated urogenital sphincter is associated with stress incontinence and poorer pelvic floor muscle function (48).

The urinary and genital tracts have a common reliance on several interdependent structures for support. **The cardinal and uterosacral ligaments are condensations of endopelvic fascia that support the cervix and upper vagina over the levator plate. Laterally, endopelvic fascial condensations attach the midvagina to the pelvic walls at the arcus tendineus fasciae pelvis anteriorly and the arcus tendineus levator ani posteriorly. The distal anterior vagina and urethra are anchored to the urogenital diaphragm and the distal posterior vagina to the perineal body.**

Anteriorly, the pubourethral ligaments and pubovesical fascia and ligaments provide fixation and stabilization for the urethra and bladder. Posteriorly, they rely on the vagina and lower uterus for support. Partial resection or relaxation of the uterosacral ligaments often leads to relaxation of the genitourinary complex, resulting in the formation of a cystocele. Studies indicate that half of the observed variation in anterior compartment support may be explained by apical support (49). Various types and degrees of genital tract prolapse or relaxation are almost always associated with similar findings in the bladder, urethra, or both.

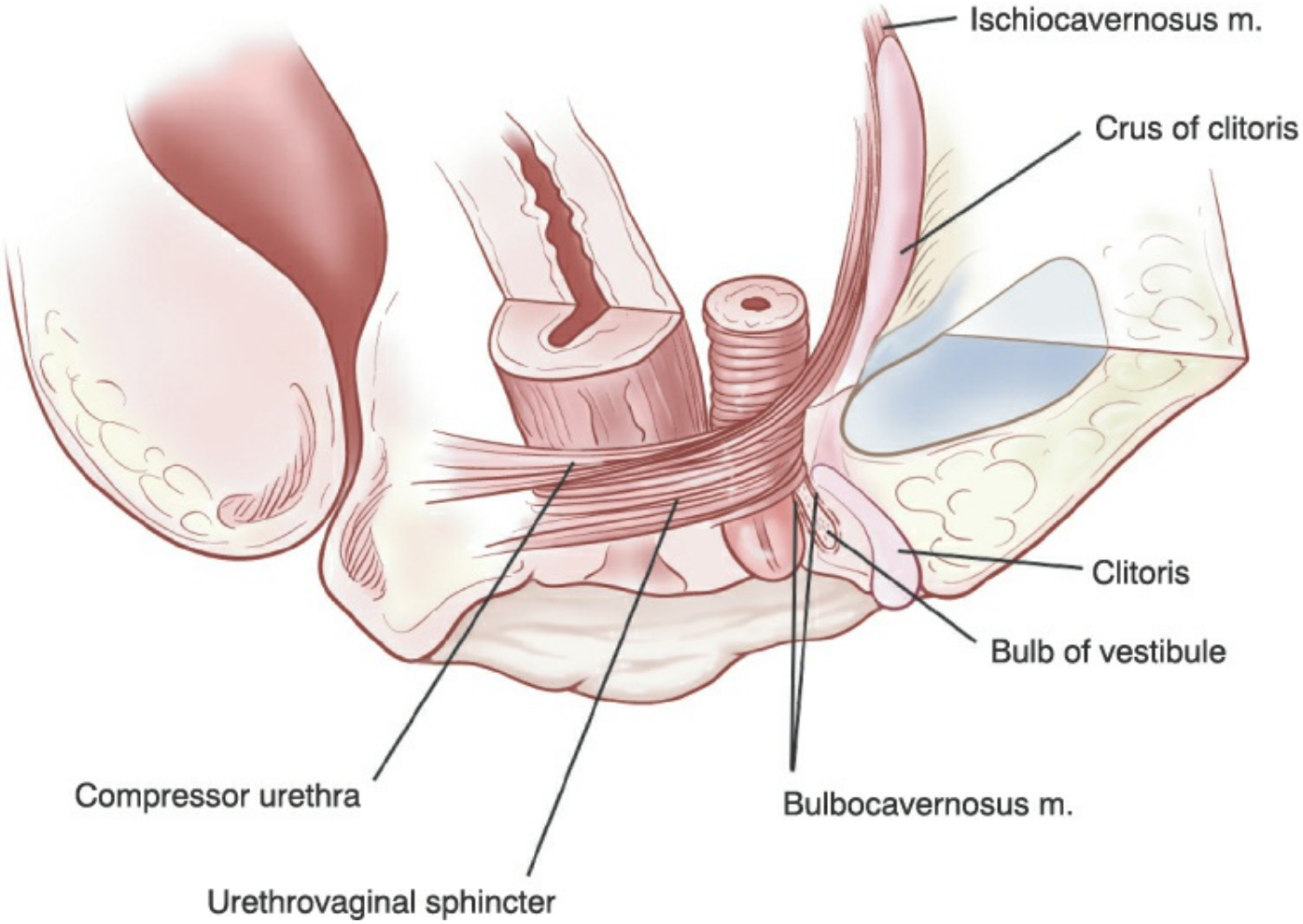


FIGURE 5-22 The complete urogenital sphincter musculature, bladder, and vagina. (Redrawn from **Haderer JM, Pannu HK, Genadry R, et al**. Controversies in female urethral anatomy and their significance for understanding urinary continence: observations and literature review. *Int Urogynecol J Pelvic Floor Dysfunct* 2002;13:236–252, with permission.)

[2] There are three levels of vaginal support as described by DeLancey (Fig. 5-23) (50). Level I support consists of paracolpium that suspends the apical portion of the vagina and is comprised of the cardinal–uterosacral ligament complex. Level II support comprises the paracolpium that is attached to the vagina laterally via the arcus tendineus fasciae pelvis and superior fascia of the levator ani. Level III support consists of the distal vaginal attachments: anteriorly, via fusion of the urethra to the vagina; laterally, to the levators; and posteriorly, with the perineal body.

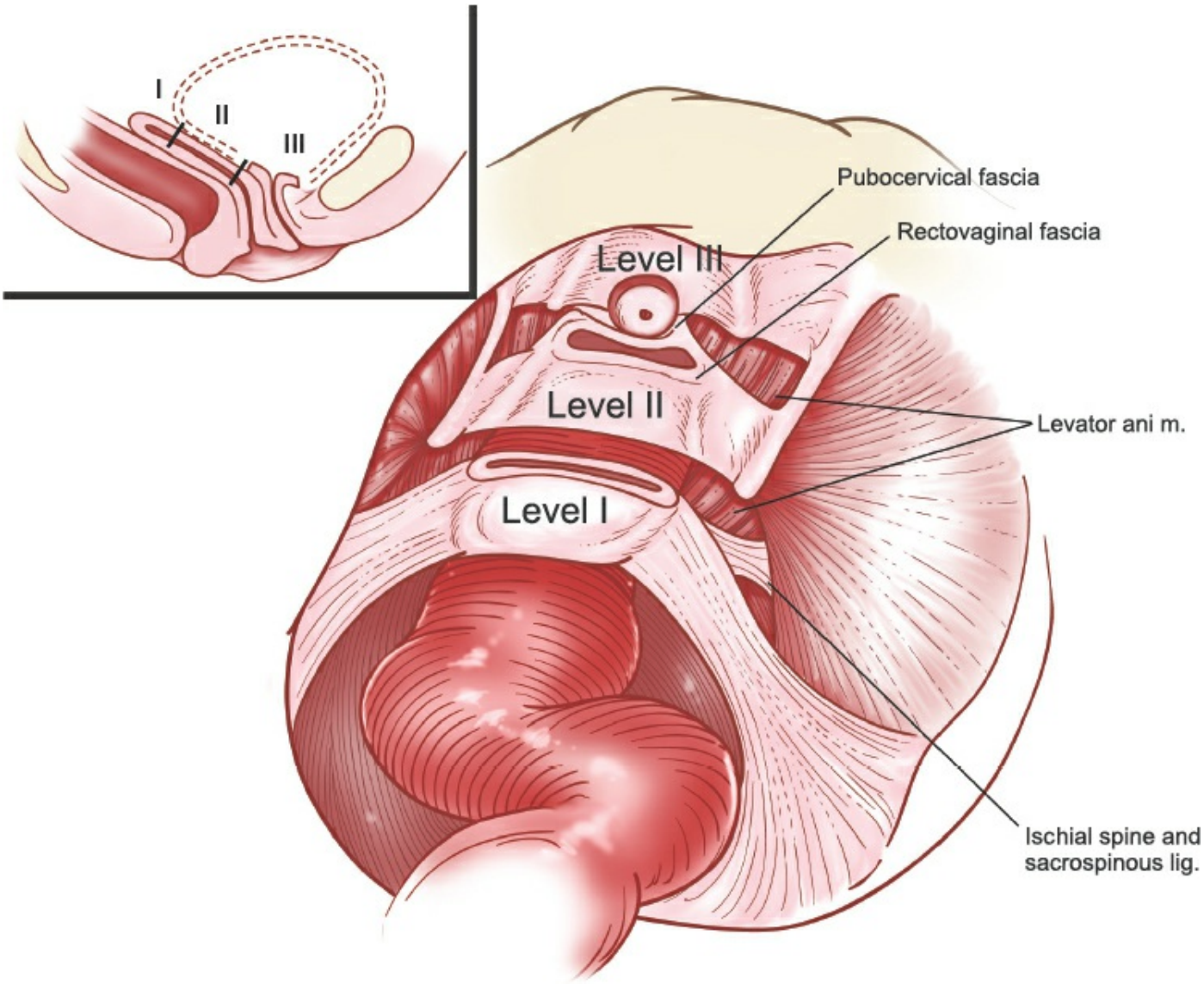


FIGURE 5-23 DeLancey levels of support. (Modified from **DeLancey JO**. Anatomic aspects of vaginal eversion after hysterectomy. *Am J Obstet Gynecol* 1992;166:17–28, with permission.)

Clinical Relevance

[2] Disruption of level I support may lead to prolapse of the uterus or vaginal vault, while damage to level II and III supports predispose to anterior and posterior vaginal prolapse. All levels of defective support should be repaired during reconstructive surgery.

Blood Supply

The blood supply to the vulva is as follows:

1. External pudendal artery (from femoral artery), internal pudendal artery
2. Venous drainage—internal pudendal veins

The blood supply to the superficial and deep perineal compartments is as follows:

1. Internal pudendal artery, dorsal artery of the clitoris
2. Venous drainage—internal pudendal veins, which are richly anastomotic
3. Lymphatic drainage—internal iliac chain

Innervation

The innervation to the vulva is from branches of the following nerves:

1. Ilioinguinal nerve
2. Genitofemoral nerve (genital branch)
3. Lateral femoral cutaneous nerve of the thigh (perineal branch)
4. Perineal nerve (branch of pudendal)
5. Superficial and deep perineal compartments, innervated by the perineal nerve

Perineal Body

The perineal body or central perineal tendon is critical to the posterior support of the lower aspect of the anterior vaginal wall. It is a triangle-shaped structure separating the distal portion of the anal and vaginal canals that is formed by the convergence of the tendinous attachments of the bulbocavernosus, the external anal sphincter, and the superficial transverse perineal muscle. Its superior border represents the point of insertion of the *rectovaginal* (*Denonvilliers*) *fascia*, which extends to the underside of the peritoneum covering the cul-de-sac of Douglas, separating the anorectal from the urogenital compartment (51). The perineal body plays an important anchoring role in the musculofascial support of the pelvic floor. It represents the central connection between the two layers of support of the pelvic floor—the pelvic and urogenital diaphragm. It also provides a posterior connection to the anococcygeal raphe. Thus, it is central to the definition of the bi-level support of the floor of the pelvis.

Anal Triangle

The anal triangle includes the lower end of the anal canal. The external anal sphincter surrounds the anal triangle, and the ischiorectal fossa is on each side. Posteriorly, the *anococcygeal body* lies between the anus and the tip of the coccyx and consists of thick fibromuscular tissue (of levator ani and external anal sphincter origin) giving support to the lower part of the rectum and the anal canal.

The *external anal sphincter* forms a thick band of muscular fibers arranged in three layers running from the perineal body to the anococcygeal ligament. The subcutaneous fibers are thin and surround the anus and, without bony attachment, decussate in front of it. The superficial fibers sweep forward from the anococcygeal ligament and tip of the coccyx, go around the anus, and insert into the perineal body. The deep fibers arise from the perineal body to encircle the lower half of the anal canal to form a true sphincter muscle, which fuses with the puborectalis portion of the levator

ani.

The *ischiorectal fossa* is mainly occupied by fat and separates the ischium laterally from the median structures of the anal triangle. It is a fascia-lined space located inferiorly between the perineal skin and the pelvic diaphragm superiorly; it communicates with the contralateral ischiorectal fossa over the anococcygeal ligament. Superiorly, its apex is at the origin of the levator ani muscle from the obturator fascia. It is bound medially by the levator ani and the external sphincter with their fascial covering, laterally by the obturator internus muscle with its fascia, posteriorly by the sacrotuberous ligament and the lower border of the gluteus maximus muscle, and anteriorly by the base of the urogenital diaphragm. It is widest and deepest posteriorly and weakest medially.

An ischiorectal abscess should be drained without delay, or it will extend into the anal canal. The cavity is filled with fat that cushions the anal canal and is traversed by many fibrous bands, vessels, and nerves, including the pudendal and the inferior rectal nerves. The perforating branch of S2 and S3 and the perineal branch of S4 run through this space.

The *pudendal (Alcock) canal* is a tunnel formed by a splitting of the inferior portion of the obturator fascia running anteromedially from the ischial spine to the posterior edge of the urogenital diaphragm. It contains the pudendal artery, vein, and nerve in their traverse from the *pelvic* cavity to the perineum.

Blood Supply

The blood supply to the anal triangle is from the inferior rectal (hemorrhoidal) artery and vein.

Innervation

The innervation to the anal triangle is from the perineal branch of the fourth sacral nerve and the inferior rectal (hemorrhoidal) nerve.

Retroperitoneum and Retroperitoneal Spaces

The subperitoneal area of the true pelvis is partitioned into potential spaces by the various organs and their respective fascial coverings and by the selective thickenings of the endopelvic fascia into ligaments and septa (Fig. 5-24). It is imperative that surgeons operating in the pelvis be familiar with these spaces, as discussed below.

Prevesical Space

The prevesical (Retzius) space is a fat-filled potential space bound anteriorly by the pubic bone, covered by the transversalis fascia, and extending to the umbilicus between the medial umbilical ligaments (obliterated umbilical arteries); posteriorly,

the space extends to the anterior wall of the bladder. It is separated from the paravesical space by the ascending bladder septum (bladder pillars).

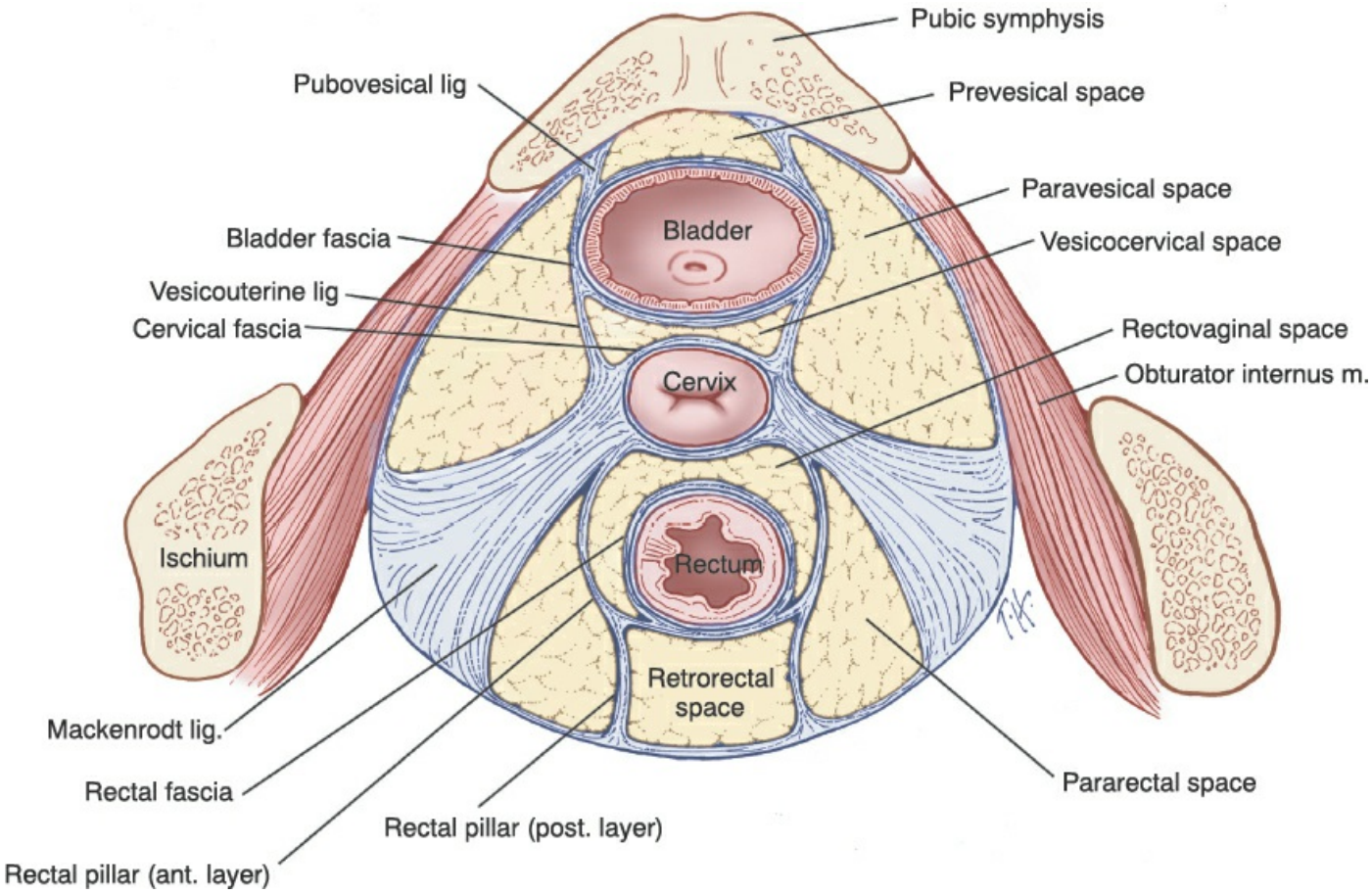


FIGURE 5-24 Schematic sectional drawing of the pelvis shows the firm connective tissue covering. The bladder, cervix, and rectum are surrounded by a connective tissue covering. The Mackenrodt ligament extends from the lateral cervix to the lateral abdominal pelvic wall. The vesicouterine ligament originating from the anterior edge of the Mackenrodt ligament leads to the covering of the bladder on the posterior side. The sagittal rectal column spreads both to the connective tissue of the rectum and the sacral vertebrae closely nestled against the back of the Mackenrodt ligament and lateral pelvic wall. Between the firm connective tissue bundles is loose connective tissue (paraspaces). (From **Von Peham H, Amreich JA.** *Gynaekologische Operationslehre*. Berlin, Germany: S Karger; 1930, with permission.)

[3] Upon entering the prevesical space, the pubourethral ligaments may be seen inserting into the posterior aspect of the symphysis pubis as a thickened prolongation of the arcus tendineus fasciae. With combined abdominal and vaginal bladder neck suspensory procedures, the point of entry is usually the Retzius space between the arcus tendineus and the pubourethral ligaments. During a Burch retropubic colposuspension, the sutures are placed into the iliopectineal line or Cooper ligament. The sutures should be carefully anchored to avoid bleeding from the venous plexus of Santorini, which lies in the space lateral to the bladder neck and urethra.

Paravesical Spaces

The paravesical spaces are fat filled and limited by the fascia of the obturator internus muscle and the pelvic diaphragm laterally, the bladder pillar medially, the endopelvic fascia inferiorly, the lateral umbilical ligament superiorly, the cardinal ligament posteriorly, and the pubic bone anteriorly. The paravesical spaces are developed by blunt dissection during a radical hysterectomy to access the parametria containing the cervical lymphatic system.

Vesicovaginal Space

The vesicovaginal space is separated from the Retzius space by the endopelvic fascia. This space is limited anteriorly by the bladder wall (from the proximal urethra to the upper vagina), posteriorly by the anterior vaginal wall, and laterally by the bladder septa (selective thickenings of the endopelvic fascia inserting laterally into the arcus tendineus). **A tear in these fascial investments and thickenings medially, transversely, or laterally allows herniation and development of a cystocele.**

Rectovaginal Space

The rectovaginal space extends between the vagina and the rectum from the superior border of the perineal body to the underside of the rectouterine Douglas pouch. It is bound anteriorly by the rectovaginal septum (firmly adherent to the posterior aspect of the vagina), posteriorly by the anterior rectal wall, and laterally by the descending rectal septa separating the rectovaginal space from the pararectal space on each side. The rectovaginal septum represents a firm membranous transverse septum dividing the pelvis into rectal and urogenital compartments, allowing the independent function of the vagina and rectum, and providing support for the rectum. It is fixed laterally to the pelvic sidewall by rectovaginal fascia (part of the endopelvic fascia) along a line extending from the posterior fourchette to the arcus tendineus fasciae pelvis, midway between the pubis and the ischial spine (52). An anterior rectocele often results from a defective *septum* or an avulsion of the septum from the perineal body. Reconstruction of the perineum is critical for the restoration of this important compartmental separation and for the support of the anterior vaginal wall (53). **[2] Lateral detachment of the rectovaginal fascia from the pelvic sidewall may constitute a "pararectal" defect analogous to anterior paravaginal defects.**

Pararectal Space

The pararectal space is bound laterally by the levator ani, medially by the rectal pillars, and posteriorly above the ischial spine by the anterolateral aspect of the sacrum. It is separated from the retrorectal space by the posterior extension of the descending rectal septa.

Retrorectal Space

The retrorectal space is limited by the rectum anteriorly and the anterior aspect of the sacrum posteriorly. It communicates with the pararectal spaces laterally above the uterosacral ligaments and extends superiorly into the presacral space.

Presacral Space

The presacral space is the superior extension of the retrorectal space and is limited by the deep parietal peritoneum anteriorly and the anterior aspect of the sacrum posteriorly. It harbors the middle sacral vessels and the hypogastric plexuses between the bifurcation of the aorta invested by loose areolar tissue. Presacral neurectomy requires familiarity with and working knowledge of this space. **[3] Abdominal sacrocolpopexy involves dissection in the presacral space down to the anterior longitudinal ligament, which is the point of fixation for the tail of the Y-shaped mesh graft. The surgical space is bound superiorly by the bifurcation of the great vessels and laterally by the ureter on the right and the mesentery of the sigmoid colon and the left common iliac vein on the left. The presacral venous plexus covers the anterior aspect of the sacrum and can bleed profusely if lacerated during dissection. The middle sacral artery often lies just to the left of the midsacral promontory and is most likely to be injured as the needle exits the tissue. The left iliac vein lies medial to the left iliac artery bounding this space and is more prone to injury during laparoscopic entry or presacral dissection.**

Peritoneal Cavity

The female pelvic organs lie at the bottom of the abdominopelvic cavity covered superiorly and posteriorly by the small and large bowel. Anteriorly, the uterine wall is in contact with the posterosuperior aspect of the bladder. The uterus is held in position by the following structures:

1. The **round ligaments** coursing inferolaterally toward the internal inguinal ring
2. The **uterosacral ligaments**, which provide support to the cervix and upper vagina and interdigitate with fibers from the cardinal ligament near the cervix
3. The **cardinal ligaments**, which provide support to the cervix and upper vagina and contribute to the support of the bladder

Anteriorly, the uterus is separated from the bladder by the vesicouterine pouch and from the rectum posteriorly by the rectouterine pouch or Douglas cul-de-sac. Laterally, the bilateral broad ligaments carry the neurovascular pedicles and their respective fascial coverings, attaching the uterus to the lateral pelvic sidewall.

The broad ligament is in contact inferiorly with the paravesical space, the obturator fossa, the pelvic extension of the iliac fossa to which it provides a

peritoneal covering, and the uterosacral ligament. Superiorly, it extends into the infundibulopelvic ligament.

Ureter

In its pelvic path in the retroperitoneum, several relationships are of significance and identify areas of greatest vulnerability to injury of the ureter (Fig. 5-25):

1. **The ovarian vessels cross over the ureter as it approaches the pelvic brim and lie in lateral proximity to the ureter as it enters the pelvis.**
2. **As the ureter descends into the pelvis, it runs within the broad ligament just lateral to the uterosacral ligament, separating the uterosacral ligament from the mesosalpinx, mesovarium, and ovarian fossa.**
3. **At the approximate level of the ischial spine, the ureter crosses under the uterine artery in its course through the cardinal ligament ("bridge over water" relationship); the ureter divides this area into the supraureteric parametrium surrounding the uterine vessels and the infraureteric paracervix molded around the vaginal vessels and extending posteriorly into the uterosacral ligament. In this location, the ureter lies 2 to 3 cm lateral to the cervix and in proximity to the insertion of the uterosacral ligament at the cervix. This proximity warrants caution when using the uterosacral ligament for vaginal vault suspension** (54,55).
4. **The ureter turns medially here to cross the anterior upper vagina as it traverses the bladder wall.**

[5] About 75% of all iatrogenic injuries to the ureter result from gynecologic procedures (56,57). Laparoscopic hysterectomies have the highest rate of ureteral injuries and vaginal hysterectomies the lowest (58,59). Distortions of pelvic anatomy, including adnexal masses, endometriosis, other pelvic adhesive disease, or fibroids, may increase susceptibility to injury by displacement or alteration of usual anatomy. Ninety-one percent of injuries occur at the level of the pelvic ureter and only 2% and 7% occur at the upper and middle ureteral thirds, respectively (60). **Careful identification of the course of the ureter before securing the infundibulopelvic ligament and uterine artery is the best protection against ureteric injury during hysterectomy or adnexectomy. Even with severe intraperitoneal disease, the ureter can always be identified using a retroperitoneal approach and noting fundamental landmarks and relationships.**

Pelvic Floor

The pelvic floor includes all of the structures closing the pelvic outlet from the skin inferiorly to the peritoneum superiorly. It is commonly divided by the pelvic diaphragm into a pelvic and a perineal portion (61). The pelvic diaphragm is spread transversely in a hammock-like fashion across the true pelvis, with a central hiatus for the urethra, vagina, and rectum. Anatomically and physiologically, the pelvic diaphragm can be divided into two components: the internal and external components.

The *external component* originates from the arcus tendineus, extending from the pubic bone to the ischial spine. It gives rise to fibers of differing directions, including the *pubococcygeus*, the *iliococcygeus*, and the *coccygeus*.

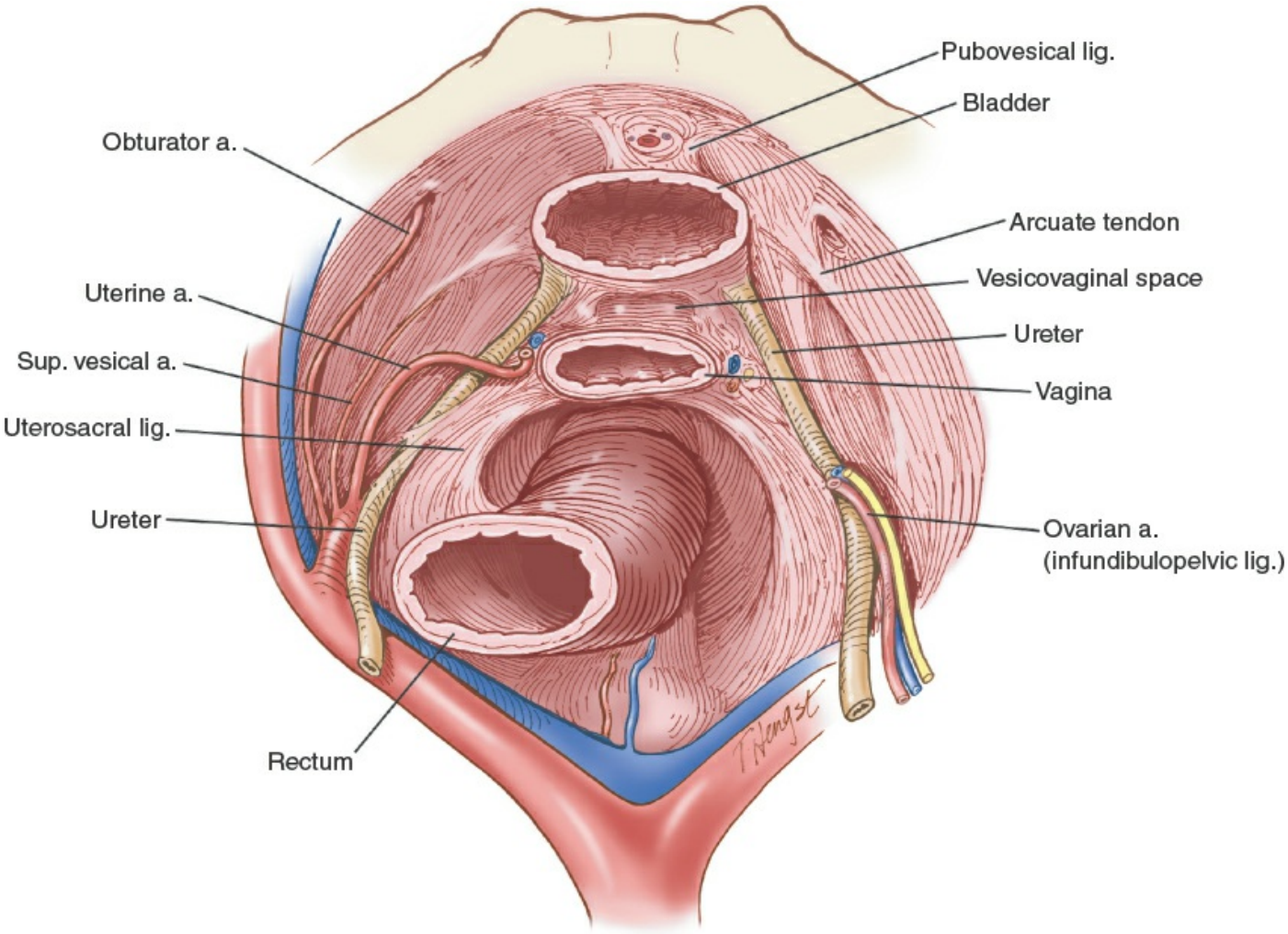


FIGURE 5-25 The course of the ureter and its relationship to the sites of greatest vulnerability.

The *internal component* originates from the pubic bone above and medial to the origin of the pubococcygeus and is smaller but thicker and stronger (61). Its fibers run in a sagittal direction and are divided into the following two portions:

1. *Pubovaginalis* fibers run in a perpendicular direction to the urethra, crossing the lateral vaginal wall at the junction of its lower one-third and upper two-thirds to

insert into the perineal body. The intervening anterior interlevator space is covered by the urogenital diaphragm.
2. *Puborectalis* superior fibers sling around the rectum to the symphysis pubis; its inferior fibers insert into the lateral rectal wall between the internal and external sphincter.

The pelvic diaphragm is covered superiorly by fascia, which includes a parietal and a visceral component and is a continuation of the transversalis fascia (Fig. 5-26). The parietal fascia has areas of thickening (ligaments, septa) that provide reinforcement and fixation for the pelvic floor. **The visceral (*endopelvic*) fascia extends medially to invest the pelvic viscera, resulting in a fascial covering to the bladder, vagina, uterus, and rectum. It becomes attenuated where the peritoneal covering is well defined and continues laterally with the pelvic cellular tissue and neurovascular pedicles**.

Musculofascial elements (the hypogastric sheath) extend along the vessels originating from the internal iliac artery. Following these vessels to their respective organs, the hypogastric sheath extends perivascular investments that contribute to the formation of the endopelvic fascia so critical for the support of the pelvic organs.

Thus, the parietal fascia anchors the visceral fascia, which defines the relationship of the various viscera and provides them with significant fixation (uterosacral and cardinal ligaments), septation (vesicovaginal and rectovaginal), and definition of pelvic spaces (prevesical, vesicovaginal, rectovaginal, paravesical, pararectal, and retrorectal).

For its support, the pelvic floor relies on the complementary role of the pelvic diaphragm and its fascia resting on the perineal fibromuscular complex. It is composed of the perineal membrane (urogenital diaphragm) anteriorly and the perineal body joined to the anococcygeal raphe by the external anal sphincter posteriorly. This double-layered arrangement, when intact, provides optimal support for the pelvic organs and counterbalances the forces pushing them downward with gravity and with any increase in intra-abdominal pressure **(Fig. 5-27)**. Dynamic imaging techniques, such as MRI, CT, and ultrasonography, increasingly are used to provide additional information in the evaluation of pelvic floor problems by visualizing anatomic landmarks during different functional phases.

Endopelvic Fascia

Controversy exists surrounding the use of the term "fascia" as it applies to the pelvis. Histologic studies reveal that the linings of the levator ani, piriformis, and obturator internus are skeletal ligamental connective tissue and genuine examples of pelvic fascia. One example in which the term "fascia" is incorrectly used is in reference to the tissue that is plicated in an anterior colporrhaphy. Histologically, it is the muscular lining of

the vagina that is plicated. There are no discrete capsules of fascia that separate the bladder and vagina from each other.

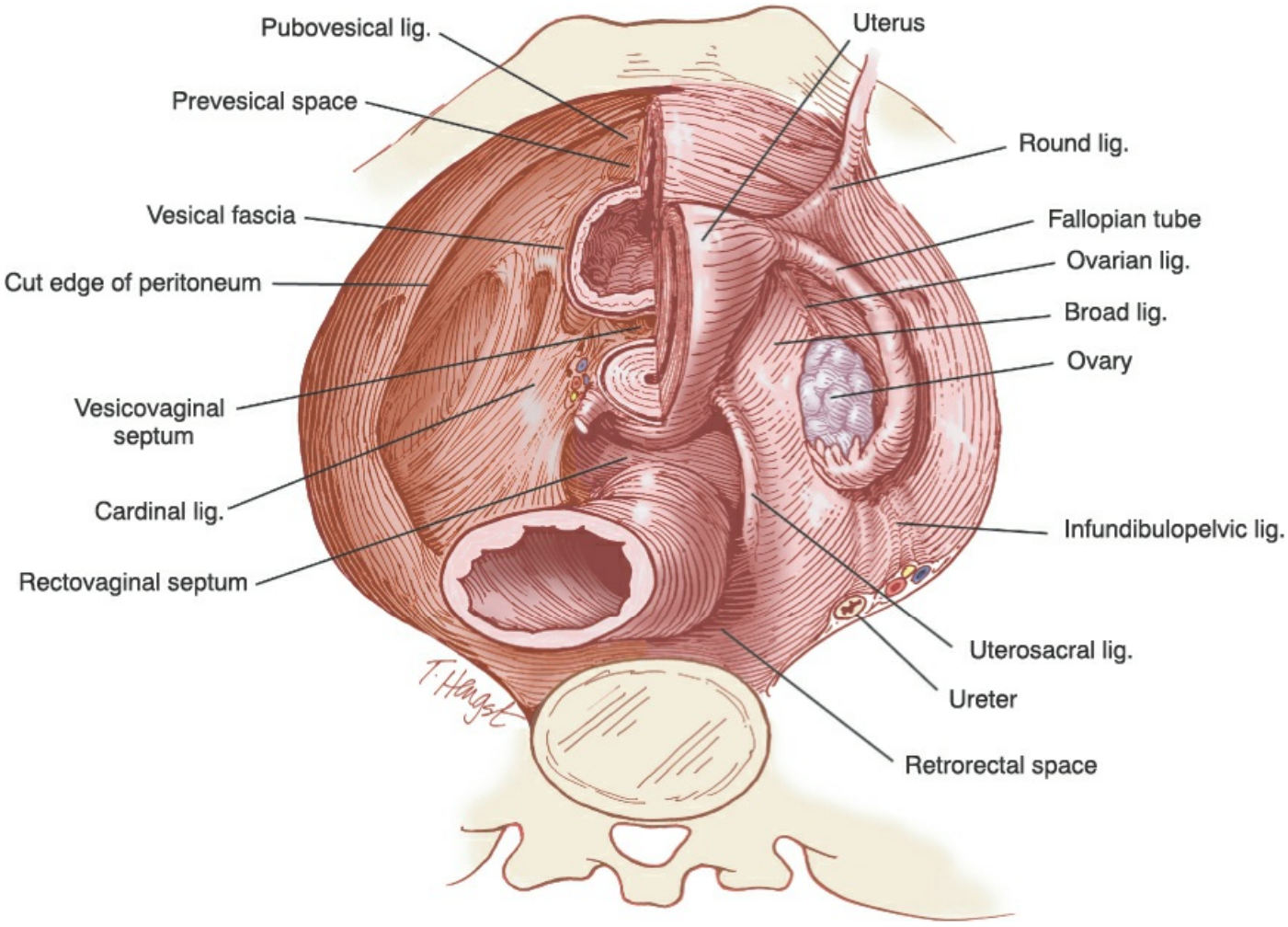


FIGURE 5-26 The fascial components of the pelvic diaphragm.

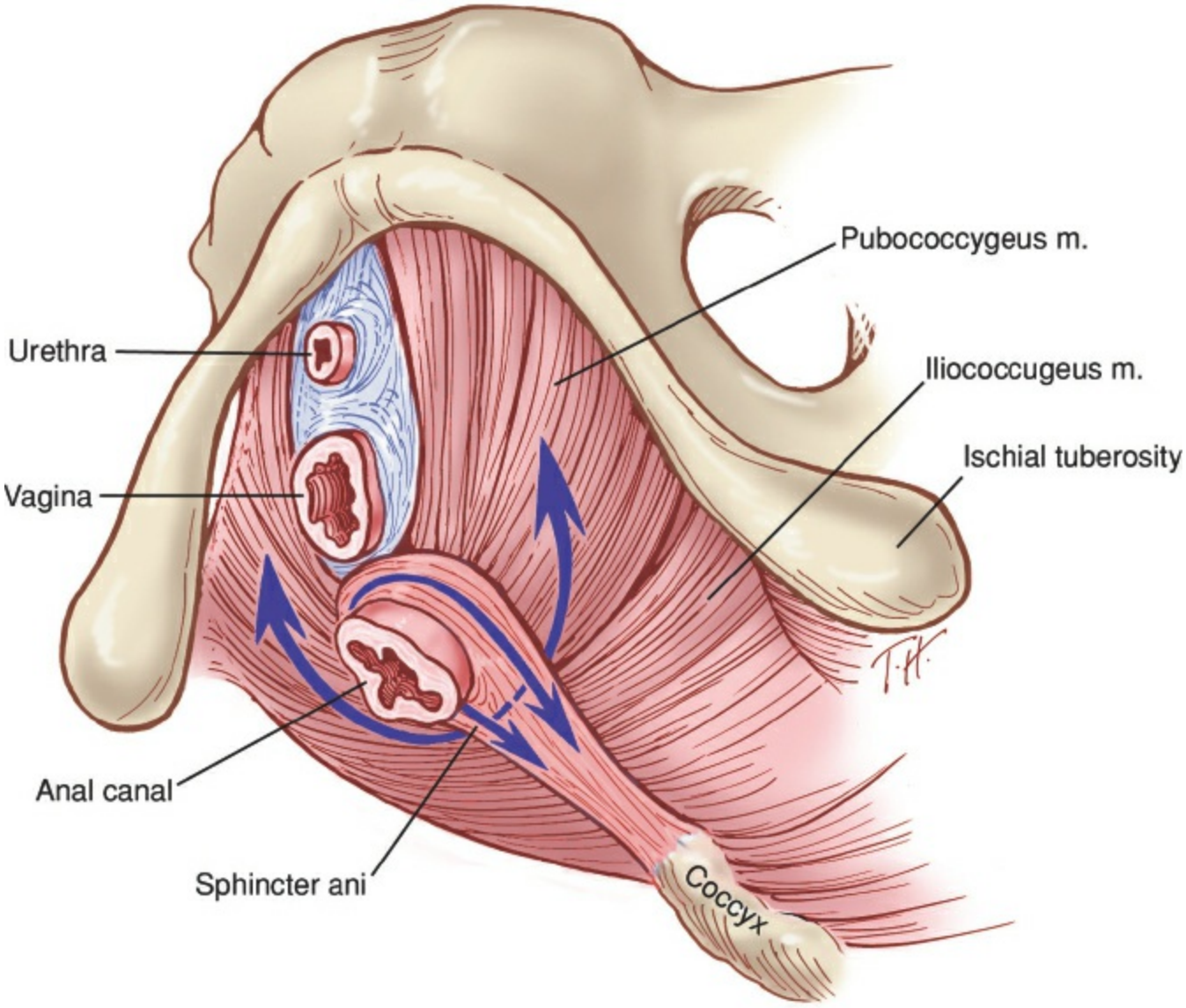


FIGURE 5-27 The double-layered muscular support of the pelvic diaphragm.

The endopelvic fascia is a sheet of fibroareolar tissue following the blood supply to the visceral organs and acts as a retroperitoneal mesentery. The fascia divides the retroperitoneal space into avascular planes. The endopelvic or pubocervical fascia attaches the cervix and vagina to the lateral pelvic sidewall. It is composed of two parts: the parametrium, which is that part connected to the uterus (i.e., the uterosacral and cardinal ligaments), and the paracolpium, which is that part connected to the vagina. The parametrium and cardinal ligaments continue to the vaginal introitus and fuse directly to the supporting tissues associated with the vagina. The uterine and vaginal arteries travel in these structures. The uterosacral ligaments are the posterior components of the cardinal ligaments, extending from the cervix and upper vagina to the lateral sacrum. Lateral pelvic support is provided by linear condensations of obturator and levator ani fascia termed the arcus tendineus fasciae pelvis and the arcus tendineus levator ani, respectively. The arcus tendineus levator ani serves as a point of attachment

for the pubococcygeus and iliococcygeus muscles and lies on the fascia of the obturator internus muscle. It runs from the posterolateral pubic ramus to the ischial spine. The arcus tendineus fasciae pelvis runs from the anterior pubis to the ischial spine as it joins with the arcus tendineus levator ani. It provides lateral (paravaginal) support to the anterior vagina. Detachment of the pubocervical fascia and pubourethral fascia from the arcus tendineus fasciae pelvis may lead to a lateral cystocele.

Obturator Space

The obturator *membrane* is a fibrous sheath that spans the obturator *foramen* through which the obturator neurovascular bundle penetrates via the obturator *canal*. The obturator internus muscle lies on the superior (intrapelvic) side of the obturator membrane. The origin of the obturator internus is on the inferior margin of the superior pubic ramus and the pelvic surface of the obturator membrane. Its tendon passes through the lesser sciatic foramen to insert onto the greater trochanter of the femur to laterally rotate the thigh. The obturator artery and vein originate as branches of the internal iliac vessels. As they emerge from the cranial side of the obturator membrane via the obturator canal and enter the obturator space, they divide into many small branches, supplying blood to the muscles of the adductor compartment of the thigh. Cadaver work contradicted previous reports that the obturator vessels bifurcate into medial and lateral branches (62). Rather, the vessels are predominantly small (<5 mm in diameter) and splinter into variable courses. The muscles of the medial thigh and adductor compartment are (from superficial to deep) the gracilis, adductor longus, adductor brevis, adductor magnus, obturator externus, and obturator internus. In contrast to the vessels, the obturator nerve emerges from the obturator membrane and bifurcates into anterior and posterior divisions, traveling distally down the thigh to supply the muscles of the adductor compartment. With the patient in the dorsal lithotomy position, the nerves and vessels follow the thigh and course laterally away from the ischiopubic ramus. **[3] Transobturator incontinence slings are often placed beneath the adductor longus tendon and just lateral to the descending ischiopubic ramus in order to avoid the obturator neurovascular bundle, which lies lateral and superior to this relatively safe point of entry through the obturator membrane.**

SUMMARY

New surgical approaches are being developed to solve old problems and often require surgeons to revisit familiar anatomy from an unfamiliar perspective or with a different understanding of complex anatomic relationships. Examples of innovative surgical approaches that require renewed understanding of anatomic relationships include laparoscopic or robotic surgery, midurethral incontinence slings that traverse

the obturator or retropubic spaces, and prolapse kits that traverse pararectal and paravesical spaces. Anatomic alterations secondary to disease, congenital variation, or intraoperative complications may make familiar surgical territory suddenly seem foreign. All of these situations require surgeons to be perpetual students of anatomy, regardless of their breadth or depth of experience.

Several strategies for continuing education in anatomy are suggested:

1. **Review relevant anatomy before each surgical procedure.**
2. **Study the gynecologic literature on an ongoing basis—numerous publications document the evolution of newer concepts regarding anatomic issues such as pelvic support.**
3. **Operate with more experienced pelvic surgeons, particularly when incorporating new surgical procedures.**
4. **Periodically dissect fresh or fixed cadaveric specimens; this practice may be arranged through local or regional anatomy boards or medical schools or by special arrangement at the time of autopsy.**
5. **Take advantage of newer computer-generated three-dimensional pelvic models and virtual reality interactive surgical simulators to better understand functional anatomy and to help plan complicated surgical procedures** (63,64).

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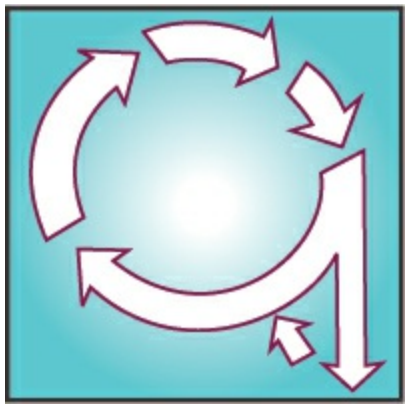
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CHAPTER 6

Molecular Biology and Genetics



Oliver Dorigo, Mana Baskovic, Jonathan S. Berek

Cell Cycle
- Normal Cell Cycle
  - *G_1 Phase*
  - *S Phase*
  - *G_2 Phase*
  - *M Phase*
- Ploidy
- Genetic Control of the Cell Cycle
  - *Cell Division Cycle Genes*
  - *Apoptosis*

Modulation of Cell Growth and Function
- Steroid Hormones
- Growth Factors
- Intracellular Signal Transduction
- Expression of Genes and Proteins
- Cancer Genetics
  - *Gatekeepers and Caretakers*
  - *Hereditary Cancer*
  - *Oncogenes*
  - *Tumor Suppressor Genes*
  - *Stability Genes*
- Genetic Aberrations
  - *Amplification*
  - *Point Mutations*
  - *Deletions and Rearrangements*

The Cancer Genome Atlas Project
- Endometrial Carcinoma
- Ovarian Carcinoma
- Cervical Carcinoma

Immunology
- Immunologic Mechanisms
  - *B Cells, Hormonal Immunity, and Monoclonal Antibodies*
  - *T Lymphocytes and Cellular Immunity*
  - *Monocytes and Macrophages*
  - *Natural Killer Cells*
  - *Cytokines, Lymphokines, and Immune Mediators*
  - *Cytokines in Cancer Therapy*

Factors That Trigger Neoplasia
- Increased Age
- Environmental Factors
- Smoking
- Radiation
- Immune Function

KEY POINTS

1 The regulation and maintenance of normal tissue requires a balance between cell proliferation and programmed cell death, or *apoptosis*.

2 Among the genes that participate in the control of cell growth and function, *proto-oncogenes* and *tumor suppressor genes* are particularly important.

3 Growth factors trigger intracellular biochemical signals by binding to cell membrane receptors. In general, these membrane-bound receptors are *protein kinases* that convert an extracellular signal into an intracellular signal. Many of the proteins that participate in the intracellular signal transduction system are encoded by *proto-oncogenes* that are divided into subgroups based on their cellular location or enzymatic function.

4 Oncogenes comprise a family of genes that result from gain of function mutations of their normal counterparts, proto-oncogenes. The normal function of proto-oncogenes is to stimulate proliferation in a controlled context. Activation of oncogenes can lead to stimulation of cell proliferation and development of a malignant phenotype.

5 Tumor suppressor genes are involved in the development of most cancers and are usually inactivated in a two-step process in which both copies of the tumor suppressor gene are mutated or inactivated by epigenetic mechanisms like methylation. The most commonly mutated tumor suppressor gene in human cancers is *p53.*

2 T lymphocytes have a central role in the generation of immune responses by acting as helper cells in both humoral and cellular immune responses and by acting as effector cells in cellular responses. T cells can be distinguished from other types of lymphocytes by their cell surface phenotype, based on the pattern of expression of various molecules, and by differences in their biologic functions.

2 There are two major subsets of mature T cells that are phenotypically and functionally distinct: *T-helper/inducer cells*, which express the CD4 cell surface marker, and the *T-suppressor/cytotoxic cells*, which express the CD8 marker. T_H1 and T_H2 are two helper T-cell subpopulations that control the nature of an immune response by secreting a characteristic and mutually antagonistic set of cytokines: Clones of T_H1 produce interleukin-2 (IL-2) and interferon-γ (IFN-γ), whereas T_H2 clones produce IL-4, IL-5, IL-6, and IL-10.

Advances in molecular biology and genetics have improved our understanding of basic biologic concepts and disease development. The knowledge acquired with the completion of the human genome project, the data available through The Cancer Genome Atlas (TCGA), the development of novel diagnostic modalities, such as the microarray technology for the analysis of DNA and proteins, and the emergence of treatment strategies that target specific disease mechanisms all have an increasing impact on the specialty of obstetrics and gynecology.

Normal cells are characterized by discrete metabolic, biochemical, and physiologic mechanisms. Specific cell types differ with respect to their mainly genetically determined responses to external influences (Fig. 6-1). An external stimulus is converted to an intracellular signal, for example, via a cell membrane receptor. The intracellular signal is transferred to the nucleus and generates certain genetic responses that lead to changes in cellular function, differentiation, and proliferation. Although specific cell types and tissues exhibit unique functions and responses, many basic aspects of cell biology and genetics are common to all eukaryotic cells.

CELL CYCLE

Normal Cell Cycle

Adult eukaryotic cells possess a well-balanced system of continuous production of DNA (transcription) and proteins (translation). Proteins are constantly degraded and replaced depending on the specific cellular requirements. Cells proceed through a sequence of phases called the cell cycle, during which the DNA is distributed to two daughter cells (*mitosis*) and subsequently duplicated (*synthesis phase*). This process is controlled at key checkpoints that monitor the status of cells, for example, the amount of DNA present in each cell. The cell cycle is regulated by a small number of heterodimeric protein kinases that consist of a regulatory subunit (cyclin) and a catalytic subunit (cyclin-dependent kinase). Association of a cyclin with a cyclin-dependent kinase (CdkC) determines which proteins will be phosphorylated at a specific point during the cell cycle.

The cell cycle is divided into four major phases: M phase (mitosis), G_1 phase (period between mitosis and initiation of DNA replication), S phase (DNA synthesis), and G_2 phase (period between completion of DNA synthesis and mitosis) (Fig. 6-2). Post-mitotic cells can "exit" the cell cycle into the so-called G_0 phase and remain for days, weeks, or even a lifetime without further proliferation. The duration of the cell cycle may be highly variable, although most human cells complete the cell cycle within approximately 24 hours. During a typical cell cycle, mitosis lasts about 30 to 60 minutes, the G_1 phase 7 to 10 hours, S phase 10 hours, and

G_2 phase 5 hours. With respect to the cell cycle, there are three subpopulations of cells:

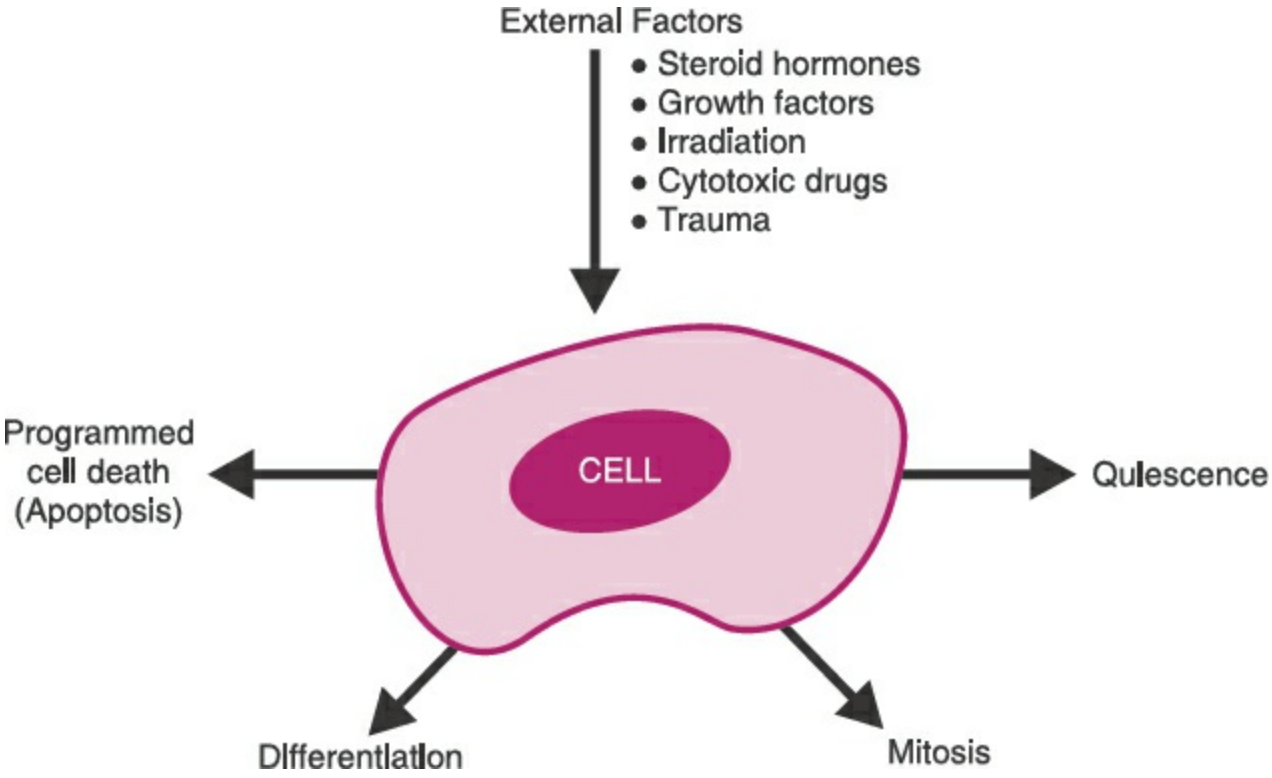


FIGURE 6-1 External stimuli affect the cell, which has a specific coordinated response.

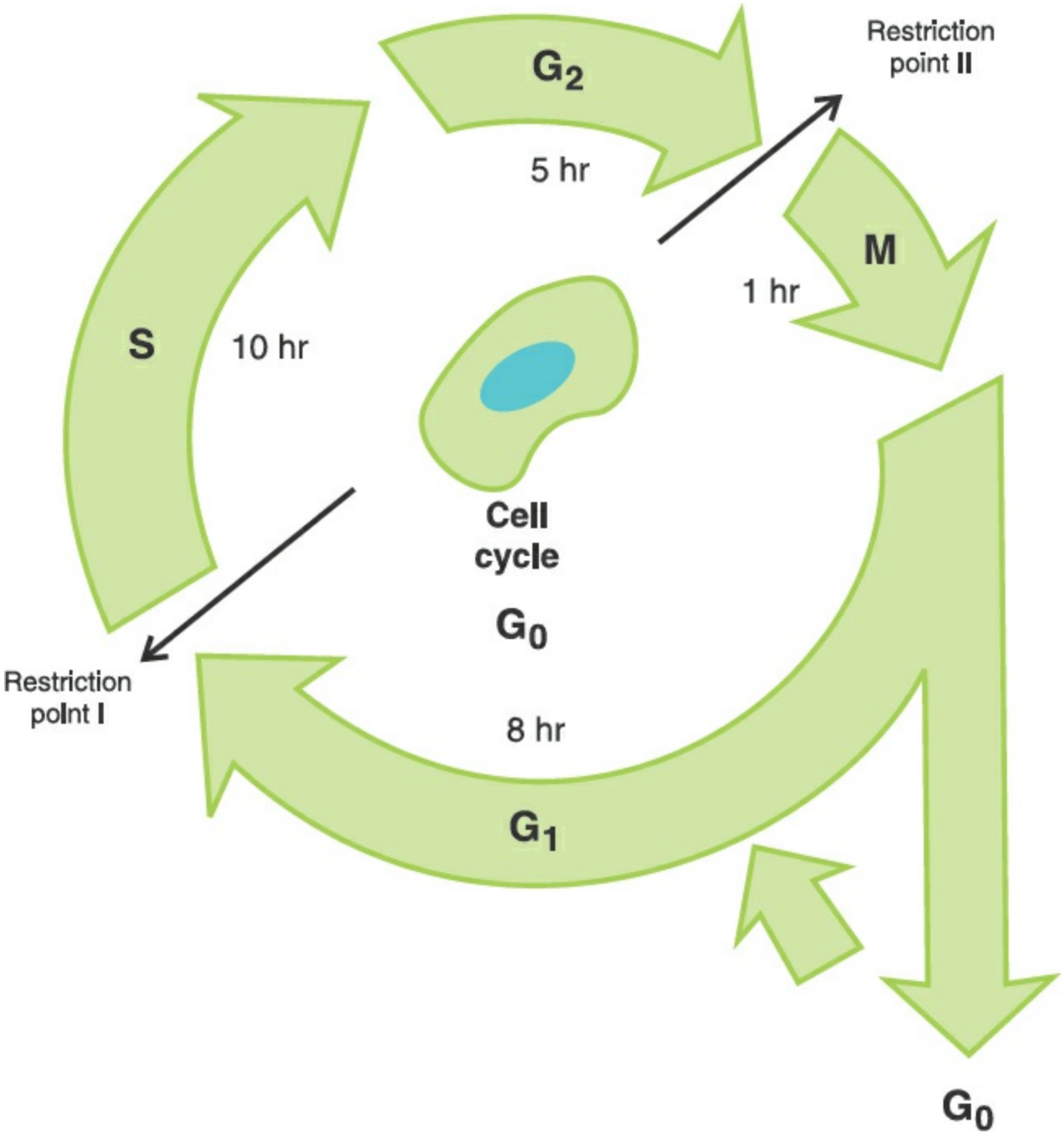


FIGURE 6-2 The cell cycle.

1. ***Terminally differentiated cells*** cannot reenter the cell cycle.
2. ***Quiescent (G0) cells*** can enter the cell cycle if appropriately stimulated.
3. ***Dividing cells*** are currently in the cell cycle.

Red blood cells, striated muscle cells, uterine smooth muscle cells, and nerve cells are terminally differentiated. Other cells, such as fibroblasts, exit from the G_1 phase into the G_0 phase and are considered to be out of the cell cycle. These cells enter the cell

cycle following exposure to specific stimuli, such as growth factors and steroid hormones. Dividing cells are found in the gastrointestinal tract, the skin, and the cervix.

G_1 Phase

In response to specific external stimuli, cells enter the cell cycle by moving from the G_0 phase into the G_1 phase. The processes during G_1 phase lead to the synthesis of enzymes and regulatory proteins necessary for DNA synthesis during S phase and are mainly regulated by G_1 cyclin-dependent kinase–cyclin complexes (G_1CdkC). Complexes of G_1CdkC induce degradation of the S phase inhibitors in late G_1. Release of the S phase CdkC complex subsequently stimulates entry into the S phase. **Variations in the duration of the G_1 phase of the cell cycle, ranging from less than 8 hours to longer than 100 hours, account for the different generation times exhibited by different types of cells.**

S Phase

The nuclear DNA content of the cell is duplicated during the S phase of the cell cycle. The S-phase CdkC complex activates proteins of the DNA prereplication complexes that assemble on DNA replication origins during G_1. The prereplication complex activates initiation of DNA replication and inhibits the assembly of new prereplication complexes. This inhibition ascertains that each chromosome is replicated only once during the S phase.

G_2 Phase

RNA and protein synthesis occurs during the G_2 phase of the cell cycle. The burst of biosynthetic activity provides the substrates and enzymes to meet the metabolic requirements of the two daughter cells. Another important event that occurs during the G_2 phase of the cell cycle is the repair of errors of DNA replication that may have occurred during the S phase. Failure to detect and correct these genetic errors can result in a broad spectrum of adverse consequences for the organism and the individual cell (1). Defects in the DNA repair mechanism are associated with an increased incidence of cancer. Mitotic CdkC complexes are synthesized during the S and G_2 phases, but are inactive until DNA synthesis is completed.

M Phase

Nuclear–chromosomal division occurs during the mitosis or M phase. During this phase, the cellular DNA is equally distributed to each of the daughter cells. Mitosis provides a diploid (2n) DNA complement to each somatic daughter cell. Following mitosis, eukaryotic mammalian cells contain diploid DNA, reflecting a karyotype that includes 44 somatic chromosomes and an XX or XY sex chromosome complement.

Exceptions to the diploid cellular content include hepatocytes (4n) and the functional syncytium of the placenta.

Mitosis is divided into prophase, metaphase, anaphase, and telophase. Mitotic CdkC complexes induce chromosome condensation during the prophase, assembly of the mitotic spindle apparatus, and alignment of the chromosomes during the metaphase. Activation of the anaphase promoting complex (APC) leads to inactivation of the protein complexes that connect sister chromatids during metaphase, permitting the onset of anaphase. During anaphase, sister chromatids segregate to opposite spindle poles. The nuclear envelope breaks down into multiple small vesicles early in mitosis and reforms around the segregated chromosomes as they decondense during telophase. Cytokinesis is the process of division of the cytoplasm that segregates the endoplasmic reticulum and the Golgi apparatus during mitosis. After completion of mitosis, cells enter the G_1 phase and either reenter the cell cycle or remain in G_0.

Ploidy

After meiosis, germ cells contain a haploid (1n) genetic complement. After fertilization, a 46,XX or 46,XY diploid DNA complement is restored. Restoration of the normal cellular DNA content is crucial to normal function. Abnormalities of cellular DNA content cause distinct phenotypic abnormalities, as exemplified by a hydatidiform molar pregnancy (see Chapter 39). In a complete hydatidiform mole, an oocyte without any nuclear genetic material (e.g., an empty ovum) is fertilized by one sperm. The haploid genetic content of the fertilized ovum is duplicated, and the diploid cellular DNA content is restored, resulting in a homozygous 46,XX gamete. Less often, a complete hydatidiform mole results from the fertilization of an empty ovum by two sperm, resulting in a heterozygous 46,XX or 46,XY gamete. In complete molar pregnancies, the nuclear DNA is usually paternally derived, embryonic structures do not develop, and trophoblast hyperplasia occurs. Rarely, complete moles are biparental. This karyotype seems to be found in patients with recurrent hydatidiform moles and is associated with a higher risk of persistent trophoblastic disease.

A partial hydatidiform mole follows the fertilization of a haploid ovum by two sperm, resulting in a 69 XXX, 69 XXY, or 69 XYY karyotype. A partial mole contains paternal and maternal DNA, and both embryonic and placental development occur. Both the 69 YYY karyotype and the 46 YY karyotype are incompatible with embryonic and placental development. These observations demonstrate the importance of maternal genetic material, in particular the X chromosome, in normal embryonic and placental development.

In addition to total cellular DNA content, the chromosome number is an important determinant of cellular function. Abnormalities of chromosome number, which often are caused by nondisjunction during meiosis, result in well-characterized

clinical syndromes such as trisomy 21 (Down syndrome), trisomy 18, and trisomy 13.

Genetic Control of the Cell Cycle

Cellular proliferation must occur to balance normal cell loss and maintain tissue and organ integrity. This process requires the coordinated expression of many genes at discrete times during the cell cycle. In the absence of growth factors, cultured mammalian cells are arrested in the G_0 phase. With the addition of growth factors, these quiescent cells pass through the so-called restriction point 14 to 16 hours later and enter the S phase 6 to 8 hours thereafter. **The restriction point or the G_1/S boundary marks the point at which a cell commits to proliferation. A second checkpoint is the G_2/M boundary, which marks the point at which repair of any DNA damage must be completed** (2). To successfully complete the cell cycle, a number of cell division cycle (*cdc*) genes are activated.

Cell Division Cycle Genes

Among the factors that regulate the cell cycle checkpoints, proteins encoded by the *cdc2* family of genes and the cyclin proteins appear to play particularly important roles (3). Growth factor–stimulated mammalian cells express early- or delayed-response genes, depending on the chronologic sequence of the appearance of specific RNAs. The early- and delayed-response genes act as nuclear transcription factors and stimulate the expression of a cascade of other genes. Early-response genes such as *c-Jun* and *c-Fos* enhance the transcription of delayed-response genes such as *E2Fs*. E2F transcription factors are required for the expression of various cell cycle genes and are functionally regulated by the retinoblastoma (*Rb*) protein. Binding of Rb to E2F converts E2F from a transcriptional activator to a repressor of transcription. Phosphorylation of Rb inhibits its repressing function and permits E2F-mediated activation of genes required for entry into the S phase. Cdk4-cyclin D, Cdk6-cyclin D, and Cdk2-cyclin E complexes cause phosphorylation of Rb, which remains phosphorylated throughout the S, G_2, and M phases of the cell cycle. After completion of mitosis, a decline of the level of Cdk-cyclins leads to dephosphorylation of Rb by phosphatases and, consequently, an inhibition of *E2F* in the early G_1 phase.

Cdks are under evaluation as targets for cancer treatments because they are frequently overactive in cancer disease and Cdk-inhibiting proteins are dysfunctional. The Cdk4 inhibitor P1446A-05, for example, specifically inhibits Cdk4-mediated G_1-S phase transition, arresting cell cycling and inhibiting cancer cell growth (4). SNS-032 selectively binds to Cdk2, -7, and -9, preventing their phosphorylation and activation and subsequently preventing cell proliferation.

As cells approach the G_1-S phase transition, synthesis of cyclin A is initiated. The

Cdk2-cyclin A complex can trigger initiation of DNA synthesis by supporting the prereplication complex. The cyclin-dependent kinase 1 (Cdk1) protein, formerly called *p34 cdc2*, and specific cyclins (namely cyclin B1) form a complex heterodimer referred to as *mitosis-promoting factor* (5), which catalyzes protein phosphorylation and drives the cell into mitosis. Cdk1 assembles with cyclin A and cyclin B in the G_2 phase and promotes the activity of the mitosis promoting factor (MPF). **Mitosis is initiated by activation of the *cdc* gene at the G_2-M checkpoint** (6). After the G_2-M checkpoint is passed, the cell undergoes mitosis. In the presence of abnormally replicated chromosomes, progression past the G_2-M checkpoint does not occur.

The *p53* tumor suppressor gene participates in cell cycle control. Cells exposed to radiation therapy exhibit an S-phase arrest that is accompanied by increased expression of p53. This delay permits the repair of radiation-induced DNA damage. In the presence of *p53* mutations, the S-phase arrest that normally follows radiation therapy does not occur (7). The wild type *p53* gene can be inactivated by the human papillomavirus (HPV) E6 protein, preventing S-phase arrest in response to DNA damage.

Apoptosis

[1] The regulation and maintenance of normal tissue requires a balance between cell proliferation and programmed cell death, or *apoptosis.* When proliferation exceeds programmed cell death, the result is hyperplasia. When programmed cell death exceeds proliferation, the result is atrophy. Programmed cell death is a crucial concomitant of normal embryologic development. This mechanism accounts for deletion of the interdigital webs, palatal fusion, and development of the intestinal mucosa (8). Programmed cell death is an important phenomenon in normal physiology. The reduction in the number of endometrial cells following alterations in steroid hormone levels during the menstrual cycle is, in part, a consequence of programmed cell death (9). In response to androgens, granulosa cells undergo programmed cell death (e.g., follicular atresia) (10).

Programmed cell death, or apoptosis, is an energy-dependent, active process that is initiated by the expression of specific genes. This process is distinct from cell necrosis, although both mechanisms result in a reduction in the total cell number. In programmed cell death, cells shrink and undergo phagocytosis. Conversely, groups of cells expand and lyse when undergoing cell necrosis. This process is energy independent and results from noxious stimuli. Programmed cell death is triggered by a variety of factors, including intracellular signals and exogenous stimuli such as radiation exposure, chemotherapy, and hormones. Cells undergoing programmed cell death may be identified on the basis of histologic, biochemical, and molecular biologic changes. Histologically, apoptotic cells exhibit cellular condensation and fragmentation of the nucleus. Biochemical correlates of impending programmed cell death include an

increase in transglutaminase expression and fluxes in intracellular calcium concentration (11).

Programmed cell death emerged as an important factor in the growth of neoplasms. Historically, neoplastic growth was characterized by uncontrolled cellular proliferation that resulted in a progressive increase in tumor burden. It is recognized that the **increase in tumor burden associated with progressive disease reflects an imbalance between cell proliferation and cell death**. Cancer cells fail to respond to the normal signals to stop proliferating, and they may fail to recognize the physiologic signals that trigger programmed cell death.

MODULATION OF CELL GROWTH AND FUNCTION

The normal cell exhibits an orchestrated response to the changing extracellular environment. The three groups of substances that signal these extracellular changes are steroid hormones, growth factors, and cytokines. The capability to respond to these stimuli requires a cell surface recognition system, intracellular signal transduction, and nuclear responses for the expression of specific genes in a coordinated fashion. **[2] Among the genes that participate in the control of cell growth and function, *proto-oncogenes and tumor suppressor genes* are particularly important.** More than 100 proto-oncogene products that contribute to growth regulation have been identified (Table 6-1) (12). As a group, proto-oncogenes exert positive effects upon cellular proliferation. In contrast, *tumor suppressor genes* exert inhibitory regulatory effects on cellular proliferation (Table 6-2).

Steroid Hormones

Steroid hormones play a crucial role in reproductive biology and in general physiology. Among the various functions, steroid hormones influence pregnancy, cardiovascular function, bone metabolism, and an individual's sense of well-being. The action of steroid hormones is mediated via extracellular signals to the nucleus to affect a physiologic response.

Estrogens exert a variety of effects on growth and development of different tissues. The effects of estrogens are mediated via estrogen receptors (ER), intracellular proteins that function as ligand-activated transcription factors and belong to the nuclear receptor superfamily (13). **Two mammalian ERs have been identified: ERα and ERβ**. The structure of both receptors is similar and consists of 6 domains named A through F from the N- to C-terminus, encoded by 8 to 9 exons (14). Domains A and B are located at the N-terminus and contain an agonist-independent transcriptional activation domain (activation function 1 [AF-1]). The C domain is a highly conserved central DNA-binding domain composed of two zinc fingers through

which ER interacts with the major groove and the phosphate backbone of the DNA helix. The C-terminus of the protein contains domains E and F and functions as ligand-binding domain (LBD–domain E) and AF-2–domain F **(Fig. 6-3)**.

Table 6-1 Proto-Oncogenes

Proto-Oncogenes	Gene Product/Function
	Growth Factors
	Fibroblast growth factor
fgf-5	
Sis	Platelet-derived growth factor β
hst, int-2	
	Transmembrane Receptors
erbB	Epidermal growth factor (EGF) receptor
HER2/neu	EGF-related receptor
Fms	Colony-stimulating factor (CSF) receptor
Kit	Stem cell receptor
Trk	Nerve growth factor receptor
	Inner-Membrane Receptor
bcl-2	
H-ras, N-ras, K-ras	
fgr, lck, src, yes	
	Cytoplasmic Messengers
Crk	
cot, plm-1, *mos, raf/mil*	
	Nuclear DNA-Binding Proteins
erb-B1	
jun, ets-1, *ets*-2, *fos, gil*-1, *rel, ski, vav*	
lyl-1, *maf, myb, myc,* L-*myc,* N-*myc, evi*-1	

Table 6-2 Tumor Suppressor Genes

p53	Mutated in as many as 50% of solid tumors
Rb	Deletions and mutations predispose to retinoblastoma
PTEN	Dual specificity phosphatase that represses PI3-kinase/Akt pathway activation with negative effect on cell growth
$P16^{INK4a}$	Binds to cyclin-CDK4 complex inhibiting cell cycle progression
FHIT	Fragile histidine triad gene with tumor suppressor function via unknown mechanisms
WT1	Mutations are correlated with the Wilms tumor
NF1	Neurofibromatosis gene
APC	Associated with colon cancer development in patients with familial adenomatous

Activation of transcription via the ER is a multistep process. The initial step requires activation of the ER via various mechanisms (Fig. 6-4). For example, estrogens such as 17β-estradiol can diffuse into the cell and bind to the LBD of the ER. Upon ligand binding, the ER undergoes conformational changes followed by a dissociation of various bound proteins, mainly heat shock proteins 90 and 70 (Hsp90 and Hsp70). Activation of the ER also requires phosphorylation by several protein kinases, including casein kinase II, PKA, and components of the Ras/MAPK (mitogen-activated protein kinase) pathway (14). Four phosphorylation sites of the ER are clustered in the NH_2 terminus with the AF-1 region.

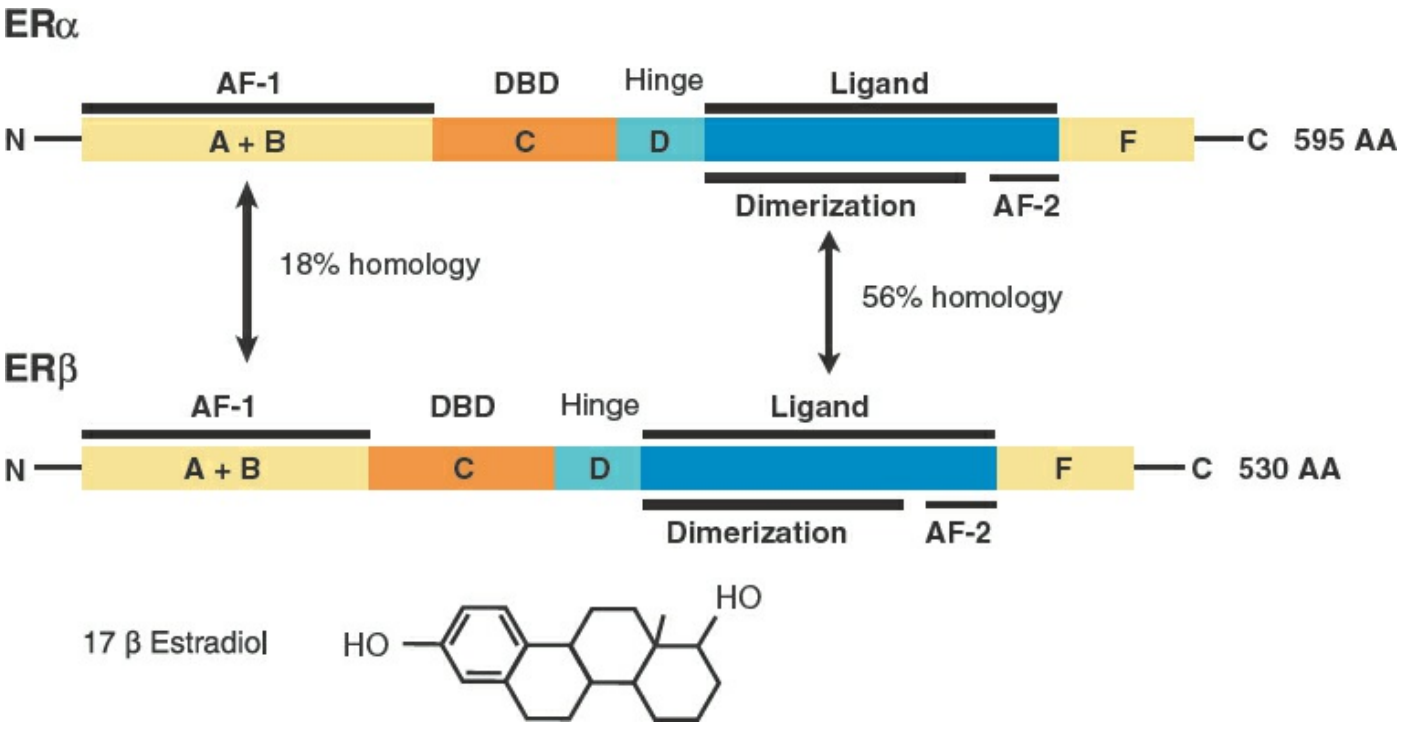


FIGURE 6-3 Structure of the two mammalian estrogen receptors. ERα (595 amino acids) and ERβ (530 amino acids) consist of six domains (A to F from the N- to C-terminus). Domains A and B at the N-terminus

contain an agonist-independent transcriptional activation domain (activation function 1, or AF-1). The C domain is the central DNA-binding sequence (DBD). Domains E and F function as the ligand-binding domain (LBD) and activation function 2 (AF-2). Also shown is the structure of the ER ligand 17β-estradiol.

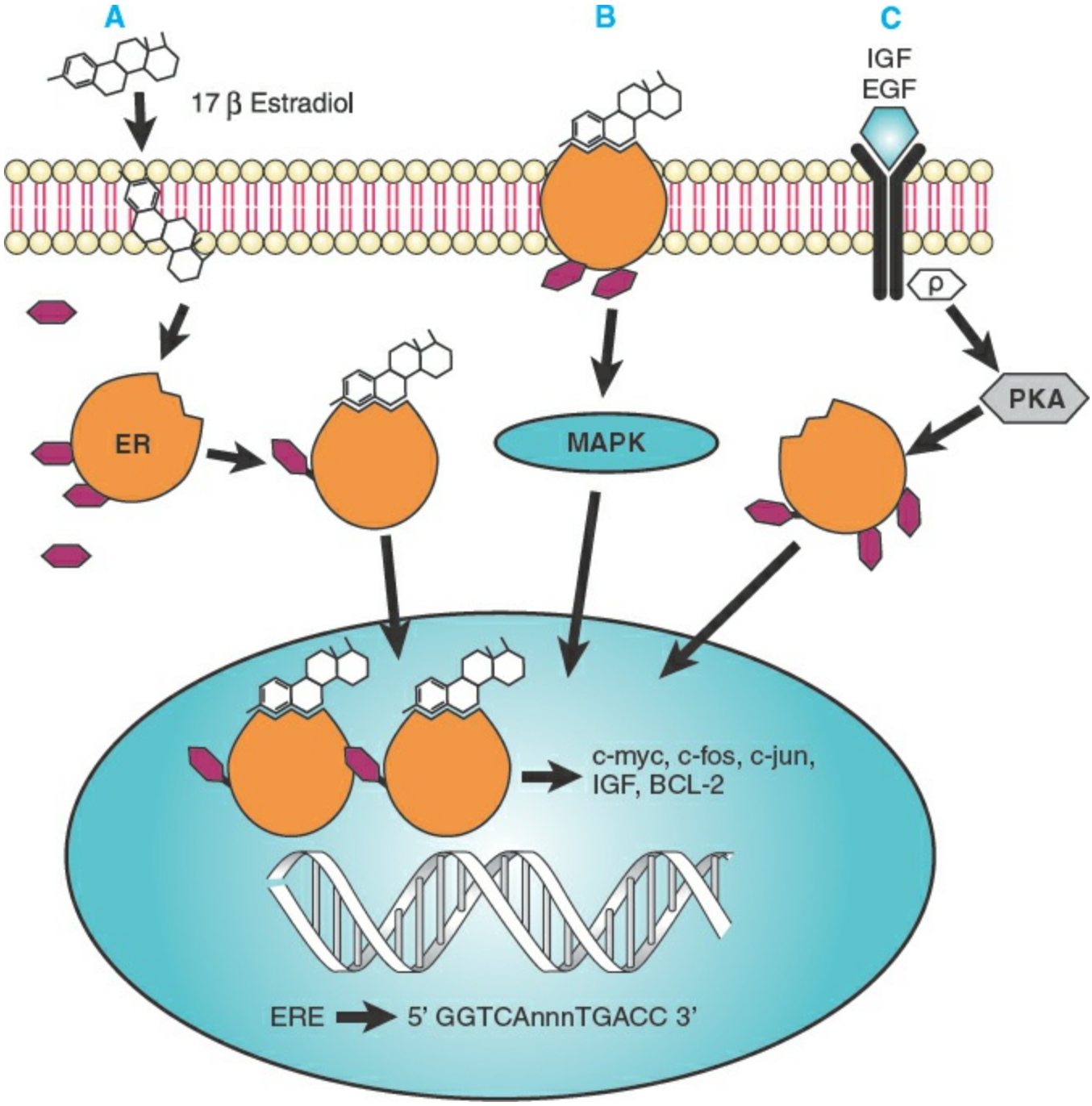


FIGURE 6-4 Activation of estrogen receptor–mediated transcription. Intracellular estrogen receptor signaling is mediated via different pathways. **A:** 17β-Estradiol diffuses through the cell membrane and binds to cytoplasmic ER. The ER is subsequently phosphorylated, undergoes dimerization, and binds to the estrogen response element (ERE) on the promoter of an estrogen responsive gene. **B:** Estrogen ligand binds to membrane-bound ER and activates the mitogen-activated protein kinase (MAPK) pathways that support ER-mediated transcription. **C:** Binding of cytokines such as insulinlike growth factor (IGF) or epidermal growth factor to their membrane receptor can cause activation of protein kinases like PKA, which subsequently activates ER by phosphorylation.

The activated ER elicits a number of different genomic as well as nongenomic effects on intracellular signaling pathways. The classical steroid signaling pathway involves binding of the activated ER to an estrogen responsive element (ERE) on the genome as homodimers and subsequent stimulation of transcription (15). The minimal consensus sequence for the ERE is a 13 bp palindromic inverted repeat (IR) and is defined as 5′-GGTCAnnnTGACC-3′. Genes that are regulated by activated ERs include early gene responses such as *c-myc, c-fos,* and *d-jun,* and genes encoding for growth factors such as insulin growth factor (IGF-1 and IGF-2), epidermal growth factor (EGF), transforming growth factor α (TGF-α), and colony-stimulating factor (CSF-1).

Various ligands with different affinities to the ER were developed and are called *selective estrogen receptor modulators* (*SERMs*). *Tamoxifen,* for example, is a mixed agonist/antagonist for ERα, but it is a pure antagonist for ERβ. The ERβ receptor is ubiquitously expressed in hormone-responsive tissues, whereas the expression of ERα fluctuates in response to the hormonal milieu. The cellular and tissue effects of an estrogenic compound appear to reflect a dynamic interplay between the actions of these ER isoforms. These observations underscore the complexity of estrogen interactions with both normal and neoplastic tissues. Mutations of hormone receptors and their functional consequences illustrate their important contributions to normal physiology.

Growth Factors

Growth factors are polypeptides that are produced by a variety of cell types and exhibit a wide range of overlapping biochemical actions. Growth factors bind to high-affinity cell membrane receptors and trigger complex positive and negative signaling pathways that regulate cell proliferation and differentiation (16). **In general, growth factors exert positive or negative effects upon the cell cycle by influencing gene expression related to events that occur at the G_1-S cell cycle boundary**.

Because of their short half-life in the extracellular space, growth factors act over limited distances through autocrine or paracrine mechanisms. In the autocrine loop, the growth factor acts on the cell that produced it. The paracrine mechanism of growth control involves the effect of growth factors on another cell in proximity. Growth factors that play an important role in female reproductive physiology are listed in Table 6-3. The biologic response of a cell to a specific growth factor depends on a variety of factors, including the cell type, the cellular microenvironment, and the cell cycle status.

The regulation of ovarian function occurs through *autocrine, paracrine,* and *endocrine* mechanisms. The growth and differentiation of ovarian cells are particularly influenced by the insulinlike growth factors (IGF) **(Fig. 6-5)**. IGFs amplify the actions

of gonadotropin hormones on autocrine and paracrine growth factors found in the ovary. IGF-1 acts on granulosa cells to cause an increase in cAMP, progesterone, oxytocin, proteoglycans, and inhibin. On theca cells, IGF-1 causes an increase in androgen production. Theca cells produce tumor necrosis factor α (TNF-α) and EGF, which are regulated by follicle-stimulating hormone (FSH). EGF acts on granulosa cells to stimulate mitogenesis. Follicular fluid contains IGF-1, IGF-2, TNF-α, TNF-β, and EGF. **Disruption of these autocrine and paracrine intraovarian pathways may be the basis of polycystic ovarian disease, disorders of ovulation, and ovarian neoplastic disease**.

TGF-β activates intracytoplasmic serine threonine kinases and inhibits cells in the late G_1 phase of the cell cycle (17). It appears to play an important role in embryonic remodeling. Mullerian-inhibiting substance (MIS), which is responsible for regression of the mullerian duct, is structurally and functionally related to TGF-β (18). TGF-α is an EGF homologue that binds to the EGF receptor and acts as an autocrine factor in normal cells. As with EGF, TGF-α promotes the entry of G_0 cells into the G_1 phase of the cell cycle. The role of growth factors in endometrial growth and function was the subject of several reviews (17,19). Similar to the ovary, autocrine, paracrine, and endocrine mechanisms of control also occur in the endometrial tissue.

Table 6-3 Growth Factors That Play Important Roles in Female Reproductive Physiology

Growth Factor	Sources	Targets	Actions
Platelet-derived growth factor (PDGF)	Placenta, platelets, preimplantation embryo, endothelial cells	Endothelial cells Trophoblasts	Mitogen
Epidermal growth factor (EGF)	Submaxillary gland, theca cells Granulosa cells Endometrium	Mitogen	
Transforming growth factor α (TGF-α)	Embryo, placenta, theca cell, ovarian stromal cell	Placenta Granulosa cells	Mitogen
Transforming growth factor β (TGF-β)	Embryo, theca cells Endometrium Granulosa cells Theca cells	Mitogen	
Insulinlike growth factor 1 (IGF-1)	Granulosa cells	Theca cells Granulosa cells	Mediates growth hormone activity
Insulinlike growth factor 2 (IGF-2)	Theca cells	Theca cells	Insulinlike
Fibroblast growth factor (FGF)	Granulosa cells	Granulosa cells Angiogenic Mitogen	

Intracellular Signal Transduction

[3] Growth factors trigger intracellular biochemical signals by binding to cell membrane receptors. In general, these membrane-bound receptors are *protein kinases* that convert an extracellular signal into an intracellular signal. The interaction between growth factor ligand and its receptor results in receptor dimerization, autophosphorylation, and tyrosine kinase activation. Activated receptors in turn phosphorylate substrates in the cytoplasm and trigger the intracellular signal transduction system **(Fig. 6-6)**. The intracellular signal transduction system relies on serine threonine kinases, *src*-related kinases, and G proteins. Intracellular signals activate nuclear factors that regulate gene expression. **Many of the proteins that participate in the intracellular signal transduction system are encoded by *proto-oncogenes* that are divided into subgroups based on their cellular location or enzymatic function (Fig. 6-7)** (20).

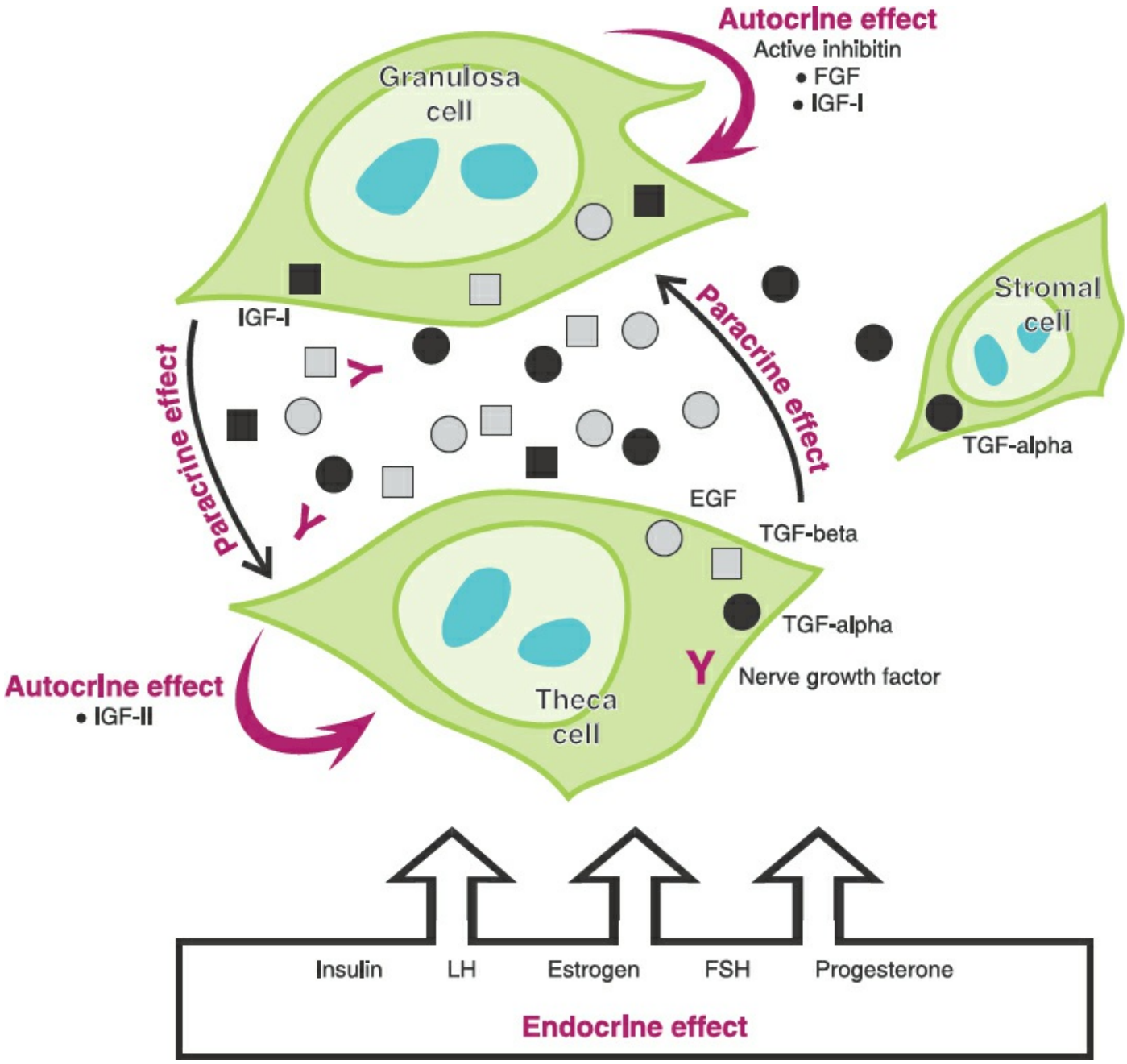


FIGURE 6-5 The regulation of ovarian function occurs through autocrine, paracrine, and endocrine mechanisms.

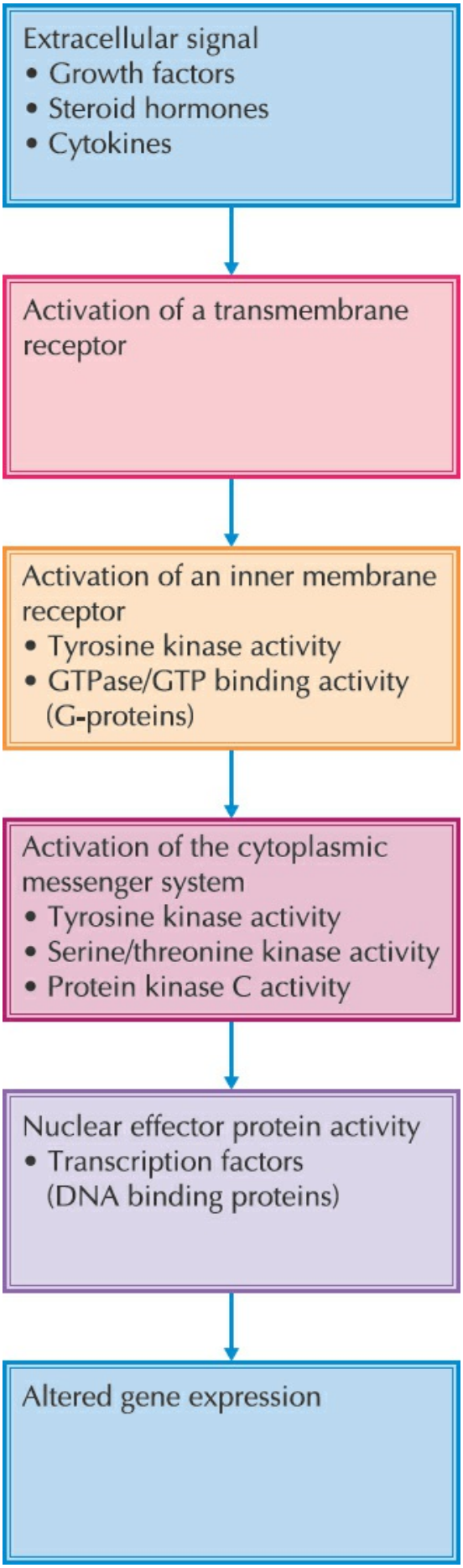

Extracellular signal
• Growth factors
• Steroid hormones
• Cytokines
Activation of a transmembrane receptor
Activation of an inner membrane receptor
• Tyrosine kinase activity
• GTPase/GTP binding activity (G-proteins)
Activation of the cytoplasmic messenger system
• Tyrosine kinase activity
• Serine/threonine kinase activity
• Protein kinase C activity
Nuclear effector protein activity
• Transcription factors (DNA binding proteins)
Altered gene expression

FIGURE 6-6 Pathways of intracellular signal transduction.

The *raf* and *mos* proto-oncogenes encode proteins with serine threonine kinase activity. These kinases integrate signals originating at the cell membrane with those that are forwarded to the nucleus (21). Protein kinase C (PKC) is an important component of a second messenger system that exhibits serine threonine kinase activity. This enzyme plays a central role in phosphorylation, which is a general mechanism for activating and deactivating proteins. It also plays an important role in cell metabolism and division (22).

The *Src* family of tyrosine kinases is related to PKC and includes protein products encoded by the *src*, *yes*, *fgr*, *hck*, *lyn*, *fyn*, *lck*, *alt*, and *fps/fes* proto-oncogenes. These proteins bind to the inner cell membrane surface.

The *G proteins* are guanyl nucleotide-binding proteins. The heterotrimeric, or large G proteins, link receptor activation with effector proteins such as adenyl cyclase, which activates the cAMP-dependent, kinase-signaling cascade (23). The monomeric or small G proteins, encoded by the *Ras* proto-oncogene family, are designated *p21* and are particularly important regulators of mitogenic signals. The *p21 Ras* protein exhibits guanyl triphosphate (GTP) binding and GTPase activity. Hydrolysis of GTP to guanyl diphosphate (GDP) terminates *p21 Ras* activity. The *p21 Ras* protein influences the production of deoxyguanosine and inositol phosphate (IP) 3, arachidonic acid production, and IP turnover.

The phosphoinositide 3 (PI3) kinase can be activated by various growth factors like platelet-derived growth factor (PDGF) or IGF results. Activation of PI3 kinase results in an increase of intracellular, membrane-bound lipids, phosphatidylinositol-(3),(4)-diphosphate (PIP2), and phosphatidylinositol-(3),(4),(5)-triphosphate (PIP3). The *Akt* protein is subsequently phosphorylated by PIP3-dependent kinases (PDK) for full activation. Activated *Akt* is released from the membrane and elicits downstream effects that lead to an increase in cell proliferation, prevention of apoptosis, invasiveness, drug resistance, and neoangiogenesis (24). The *PTEN* (phosphatase and chicken tensin homologue deleted on chromosome 10) protein is an important factor in the PI3 kinase pathway, because it counteracts the activation of *Akt* by dephosphorylating PIP3. Cells with mutated tumor suppressor gene *PTEN* and lack of functional *PTEN* expression display an increased proliferation rate and decreased apoptosis, possibly supporting the development of a malignant phenotype. *PTEN* frequently is mutated in endometrioid adenocarcinoma. Furthermore, lack of functional *PTEN* expression was described in endometriosis.

The mammalian target of rapamycin (mTOR) is regulated by the PI3 kinase pathway. mTOR is a serine/threonine protein kinase that regulates a variety of cellular processes, including proliferation, motility, and translation (25). mTOR integrates the input from various upstream pathways, including insulin and growth factors like IGF proteins. The

mTOR pathway provides important survival signals for cancer cells and therefore was one focus of targeted drug development (26). For example, *rapamycin* inhibits mTOR by associating with its intracellular receptor FKBP12. Derivatives of *rapamycin* like *everolimus* (RAD001) and *temsirolimus* (CCI779) showed promising results in clinical trials (27).

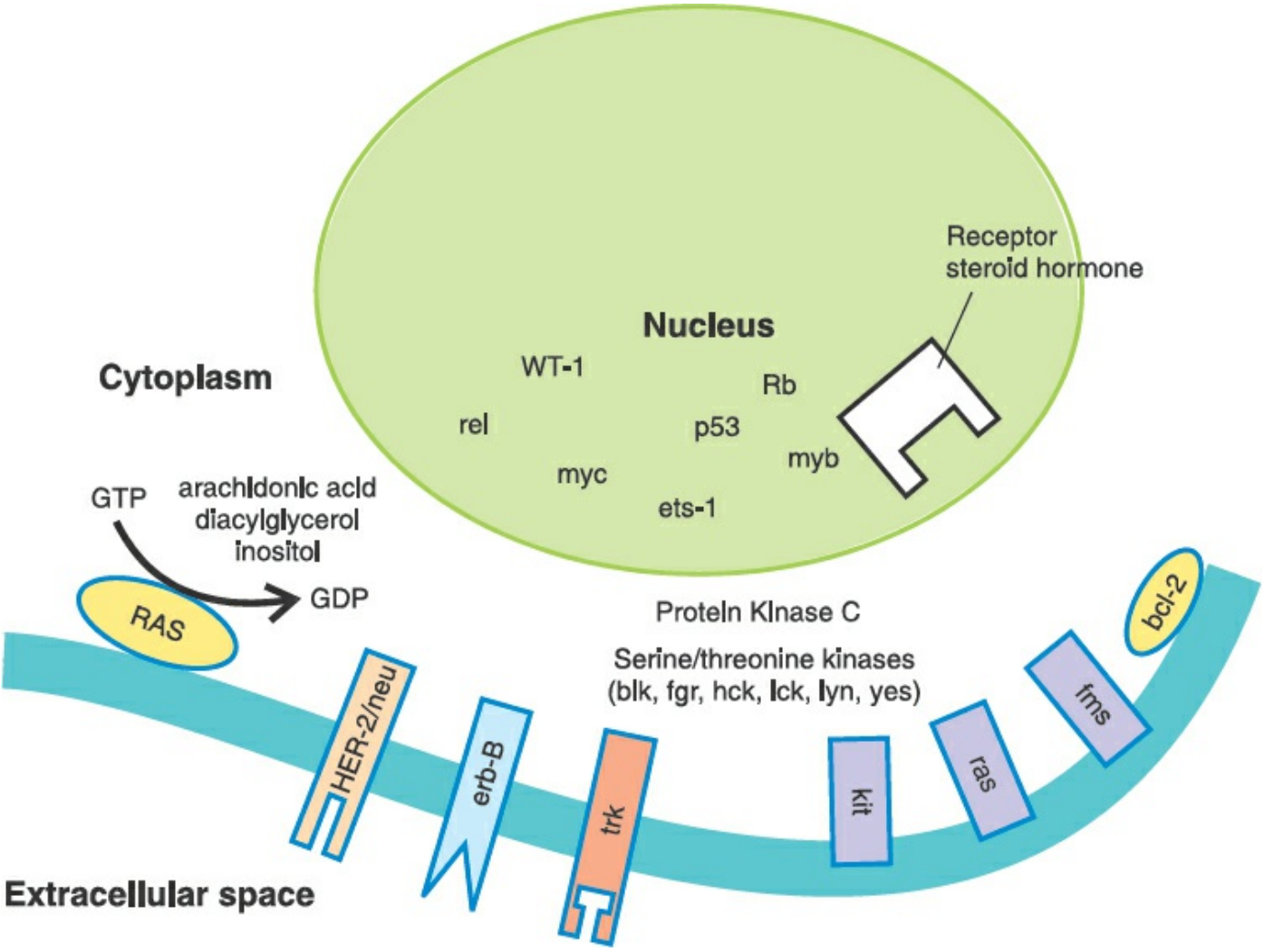


FIGURE 6-7 Proto-oncogenes are divided into subgroups based on their cellular location or enzymatic function.

mTOR functions as the catalytic subunit of two different protein complexes. Among the proteins associated with mTOR complex 1 (mTORC1) is mTOR, the regulatory associated protein of mTOR (Raptor), and PRAS40. This complex functions as a nutrient and energy sensor and controls protein synthesis (28). mTORC1 is activated by insulin, growth factors, amino acids and oxidative stress, low nutrient levels, reductive stress, and growth factor deprivation inhibit its activity. In contrast, the mTOR complex 2 (mTORC2) contains, among others, mTOR, the rapamycin-insensitive protein Rictor, and mammalian stress-activated protein kinase interacting protein 1 (mSIN1). mTORC2

regulates the cytoskeleton and phosphorylates Akt (29). Its regulation is complex, but involves insulin, growth factors, serum, and nutrient levels.

Expression of Genes and Proteins

Ovarian, endometrial, and cervical cancers have distinct molecular and genomic profiles. Ovarian carcinomas, in particular the high-grade serous histologic subtypes, are characterized by genomic instability with low frequencies of conserved mutations (30). Despite substantial differences between the gynecologic cancers, activation of the PI3K pathway is common.

Endometrial cancers demonstrate the highest frequency of PI3K pathway alterations (31). The rate of alterations in PIK3CA range from 25% to 40% and in the PIK3R1 from 15% to 25% (32). In addition to PI3K alterations, 30% to 90% of endometrial cancers have impaired PTEN function, most often identified in endometrioid histologies (33). PI3K inhibition may impair proliferation of endometrial cancer cells. In addition, loss of PTEN or PIK3CA mutation may serve as biomarkers associated with response to novel targeted agents that antagonize PI3K (34). Studies utilizing patient-derived xenograft (PDX) models of endometrial carcinomas, with and without alterations in PIK3CA, have suggested that pan-PI3K inhibition may produce significant anti-tumor responses. Most of the published data regarding PI3K pathway inhibitors in endometrial cancer have been based on mTOR inhibition. Rapalog inhibitors (everolimus, ridaforolimus, and temsirolimus) have been demonstrated to inhibit mTORC1 complex kinase activity. However, in clinical application, the response rates to monotherapy have been low, ranging from 4% to 25%; the higher response rates correlating with patients extensively pretreated with cytotoxic chemotherapy (35). Combination treatment of everolimus and letrozole showed a 32% response rate (11 of 35 patients) (36). These response rates and duration are similar to treatment with alternating courses of megestrol acetate and tamoxifen, with an overall RR of 27%. Based on these comparable response findings, a randomized study is underway comparing these two treatment strategies (GOG-3007) (36).

Genetic alterations of the PI3K pathway have been identified in up to 70% of ovarian cancers (37). Gain of function mutations in PIK3CA have been observed in 4% to 12% of ovarian cancers (38). Ovarian clear cell and endometrioid adenocarcinomas demonstrate a higher frequency of mutations with 33% to 40% activating mutations in PIK3CA in clear cell carcinomas, and 12% to 20% of endometrioid carcinomas (39).

In cervical cancer, amplifications and activating mutations of the PIK3CA gene have been demonstrated in 23% to 36% of cases, with the highest mutation rate found in PIK3CA gene (40). The HPV oncogenic proteins, namely E6, and E7 enhance PI3K pathway signaling via direct activation of PI3K, as well as downstream AKT and rpS6K. These proteins induce ligand-dependent signaling indirectly through epidermal

growth factor receptor (EGFR). Similar to ovarian cancer, data pertaining to the use of targeted PI3K pathway therapy in cervical carcinoma is limited, with studies underway.

Regulation of genetic transcription and replication is crucial to the normal function of the daughter cells, the tissues, and ultimately the organism. Transmission of external signals to the nucleus by way of the intracellular signal transduction cascade culminates in the transcription of specific genes and translation of the mRNA into proteins that ultimately affect the structure, function, and proliferation of the cell.

The human genome project resulted in the determination of the sequence of DNA of the entire human genome (41). **With the completion of this project, it appears that the human haploid genome contains 23,000 protein coding genes**. Sequencing the human genome is a major scientific achievement that has opened the door for more detailed studies of structural and functional genomics. **Structural genomics involves the study of three-dimensional structures of proteins based on their amino acid sequences. Functional genomics provides a way to correlate the structure and function. Proteomics involves the identification and cataloging of all proteins used by a cell, and cytomics involves the study of cellular dynamics, including intracellular system regulation and response to external stimuli**. The **transcriptome** is the set of all RNA molecules, including mRNA, rRNA, tRNA, and other noncoding RNA produced in one or a population of cells. The transcriptome varies with external environmental conditions and reflects the actively expressed genes. **The *metabolome* describes a set of small-molecule metabolites, including hormones and signaling molecules, that are found in a single organism. Similar to the transcriptome and proteome, the metabolome is subject to rapid changes** (42). **The *kinome* of an organism describes a set of protein kinases, enzymes that are crucial for phosphorylation reactions**.

Cancer Genetics

Cancer is a genetic disease that results from a series of mutations in various cancer genes. Uncontrolled cell growth occurs because of accumulation of somatic mutations or the inheritance of one or more mutations through the germline, followed by additional somatic mutations. The mutation in genes that are directly involved in normal cellular growth and proliferation can lead to the development of uncontrolled growth, invasion, and metastasis.

According to the Knudson hypothesis, which was first described in children with hereditary retinoblastoma, two hits or mutations within the genome of a cell are required for a malignant phenotype to develop (43). **In hereditary cancers, the first hit is present in the genome of every cell. Only one additional hit is necessary,**

therefore, to disrupt the correct function of the second cancer gene allele. In contrast, sporadic cancers develop in cells without hereditary mutations in the cancer predisposing alleles. In this case, both hits must occur in a single somatic cell to disrupt both cancer gene alleles (Fig. 6-8).

Most adult solid tumors require 5 to 10 rate-limiting mutations to acquire the malignant phenotype. Among these mutations, some are responsible for causing the cancer phenotype, whereas others might be considered bystander mutations, as with, for example, the amplification of genes that are adjacent to an oncogene. The most compelling evidence for the mutagenic tumor development process is that the age-specific incidence rates for most human epithelial tumors increase at roughly the fourth to eighth power of elapsed time.

Gatekeepers and Caretakers

[4] Cancer susceptibility genes are divided into "gatekeepers" and "caretakers" (44). Gatekeeper genes control cellular proliferation and are divided into oncogenes and tumor suppressor genes. In general, oncogenes stimulate cell growth and proliferation, and tumor suppressor genes reduce the rate of cell proliferation or induce apoptosis. Gatekeepers prevent the development of tumors by inhibiting growth or promoting cell death. Examples of gatekeeper genes include the tumor suppressor gene *p53* and the retinoblastoma gene.

Caretaker genes preserve the integrity of the genome and are involved in DNA repair (stability genes). The inactivation of caretakers increases the likelihood of persistent mutations in gatekeeper genes and other cancer-related genes. The DNA mismatch repair (MMR) genes, MLH1, MSH2, and MSH6, are examples of caretaker genes.

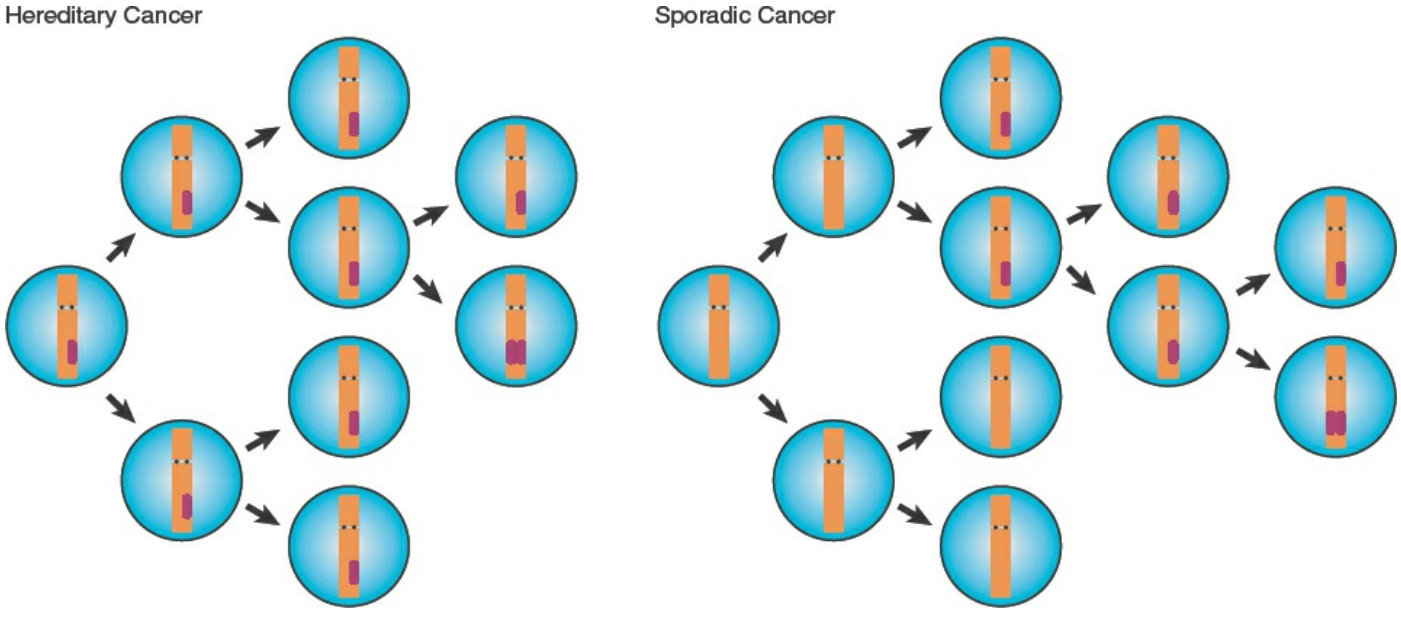


FIGURE 6-8 Hereditary and sporadic cancer development based on the Knudson "two-hit" genetic model.

All cells harbor one mutant tumor suppressor gene allele in hereditary cancer. The loss of the second allele results in the malignant phenotype. Sporadic cancers develop in cells with normal genome, therefore requiring both alleles to be inactivated (two hits).

Hereditary Cancer

Most cancers are caused by spontaneous somatic mutations. However, a small percentage of cancers arise on a heritable genomic background. About 12% of all ovarian cancers and about 5% of endometrial cancers are considered to be hereditary (45,46). Germline mutations require additional mutations at one or more loci for tumorigenesis to occur. These mutations occur via different mechanisms, for example, via environmental factors such as ionizing radiation or mutations of stability genes. **Characteristics of hereditary cancers include diagnosis at a relatively early age and a family history of cancer, usually of a specific cancer syndrome, in two or more relatives**. Hereditary cancer syndromes associated with gynecologic tumors are summarized in Table 6-4.

[4] Various cancer-causing genetic and epigenetic mechanisms are described. On the genomic level, gain of function gene mutations can lead to a conversion of proto-oncogenes into oncogenes, and loss of function gene mutations can inactivate tumor suppressor genes. Epigenetic changes include DNA methylation, which can cause inactivation of tumor suppressor gene expression by preventing the correct function of the associated promoter sequence. Collectively, these genetic and epigenetic changes are responsible for the development of cancer characterized by the ability of cells to invade and metastasize, grow independently of growth factor support, and escape from antitumor immune responses.

Oncogenes

Oncogenes comprise a family of genes that result from the gain of function mutations of their normal counterparts, proto-oncogenes. The normal function of proto-oncogenes is to stimulate proliferation in a controlled context. Activation of oncogenes can lead to stimulation of cell proliferation and development of a malignant phenotype. Oncogenes were initially discovered through retroviral tumorigenesis. Viral infection of mammalian cells can result in integration of the viral sequences into the proto-oncogene sequence of the host cell. The integrated viral promoter activates transcription from the surrounding DNA sequences, including the proto-oncogene. Enhanced transcription of the proto-oncogene sequences results in the overexpression of growth factors, growth factor receptors, and signal transduction proteins, which result in stimulation of cell proliferation. One of the most important group of viral oncogenes is the family of *ras* genes, which include *c-H*(*Harvey*)*-ras*, *c-K*(*Kirsten*)*-ras*, and *N*(*Neuroblastoma*)*-ras*.

Tumor Suppressor Genes

[5] Tumor suppressor genes are involved in the development of most cancers and are usually inactivated in a two-step process in which both copies of the tumor suppressor gene are mutated or inactivated by epigenetic mechanisms like methylation (47). **The most commonly mutated tumor suppressor gene in human cancers is *p53*** (48). The p53 protein regulates transcription of other genes involved in cell cycle arrest such as *p21*. Upregulation of p53 expression is induced by DNA damage and contributes to cell cycle arrest, allowing DNA repair to occur. p53 also plays an important role in the initiation of apoptosis. The most common mechanism of inactivation of p53 differs from the classic two-hit model. In most cases, missense mutations that change a single amino acid in the DNA-binding domain of p53 result in overexpression of nonfunctional p53 protein in the nucleus of the cell.

The identification of tumor suppressor genes was facilitated by positional cloning strategies. The main approaches are cytogenetic studies to identify chromosomal alterations in tumor specimens, DNA linkage techniques to localize genes involved in inherited predisposition to cancer, and examination for loss of heterozygosity (LOH) or allelic alterations among studies in sporadic tumors. Comparative genomic hybridization (CGH) allows fluorescence identification of chromosome gain and loss in human cancers within a similar experiment.

Table 6-4 Hereditary Cancer Syndromes Associated With Gynecologic Tumors

Hereditary Syndrome	Gene Mutation	Tumor Phenotype
Li–Fraumeni syndrome	TP53, CHEK2	Breast cancer, soft tissue sarcoma, adrenal cortical carcinoma, brain tumors
Cowden syndrome, Bannayan–Zonana syndrome	PTEN	Breast cancer, hamartoma, glioma, endometrial cancer
Hereditary breast and ovarian cancer	BRCA1, BRCA2	Cancer of breast, ovary, fallopian tube
Hereditary nonpolyposis colorectal cancer (HNPCC)	MLH1, MSH2, MSH3, MSH6, PMS2	Cancer of colon, endometrium, ovary, stomach, small bowel, urinary tract
Multiple endocrine neoplasia type I	Menin	Cancer of thyroid, pancreas, and pituitary, ovarian carcinoid
Multiple endocrine neoplasia type II	RET	Cancer of thyroid and parathyroid, pheochromocytoma, ovarian carcinoid
Peutz–Jeghers syndrome	STK11	Gastrointestinal hamartomatous polyps, tumors of the stomach, duodenum, colon, ovarian sex cord tumor with

		annular tubules (SCTAT)

Stability Genes

The third class of cancer genes is "stability genes," which promotes tumorigenesis in a different way from tumor suppressor genes or amplified oncogenes. The main function of stability genes is the preservation of the correct DNA sequence during DNA replication (caretaker function) (49). Mistakes that are made during normal DNA replication or induced by exposure to mutagens can be repaired by a variety of mechanisms that involve MMR genes, nuclear-type excision repair genes, and base excision repair genes. The inactivation of stability genes potentially leads to a higher mutation rate in all genes. However, only mutations in oncogenes and tumor suppressor genes influence cell proliferation and confer a selective growth advantage to the mutant cell. Similar to tumor suppressor genes, both alleles of stability genes must be activated to cause loss of function.

Genetic Aberrations

Gene replication, transcription, and translation are imperfect processes, and the fidelity is less than 100%. Genetic errors may result in abnormal structure and function of genes and proteins. Genomic alterations such as gene amplification, point mutations, and deletions or rearrangements were identified in premalignant, malignant, and benign neoplasms of the female genital tract **(Fig. 6-9)**.

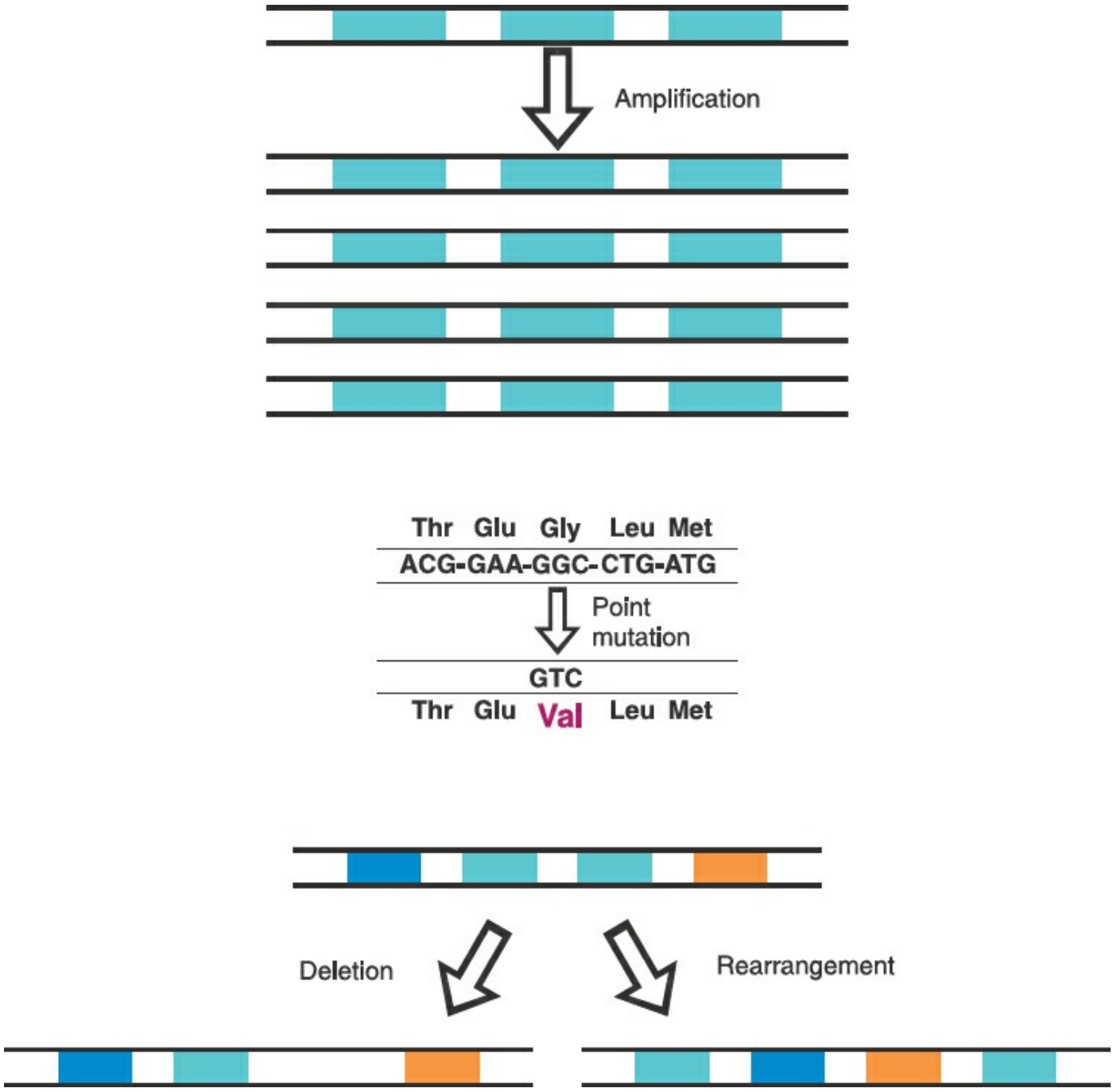


FIGURE 6-9 Genes can be amplified or undergo mutation, deletion, or rearrangement.

Amplification

Amplification refers to an increase in the copy number of a gene. Amplification results in enhanced gene expression by increasing the amount of template DNA that is available for transcription. Proto-oncogene amplification is a relatively common event in malignancies of the female genital tract. The *HER2/neu* proto-oncogene, also known as *c-erbB-2* and HER2, encodes a 185 *kDa* transmembrane glycoprotein with intrinsic tyrosine kinase activity. It belongs to a family of transmembrane receptor genes that includes the EGF receptors *erbB-1*, *erbB-3*, and *erbB-4*. *HER2/neu* interacts with a

variety of different cellular proteins that increase cell proliferation. Overexpression of *HER2/neu* was demonstrated in about 30% of breast cancers, 20% of advanced ovarian cancers, and as many as 50% of endometrial cancers (50). The GOG-177 study (a randomized prospective phase III study including patients with measurable stages III to IV, or recurrent endometrial carcinoma and randomly assigned treatment with either *doxorubicin* and *cisplatin* or *doxorubicin*, *cisplatin*, and *paclitaxel* with G-CSF) also included tumor collection within the study parameters. A review of the tumor specimens showed a 44% rate of HER2 overexpression (2+ or 3+ by immunohistochemical [IHC] staining) and 12% HER2 amplification by fluorescence in situ hybridization (FISH) (51). Morrison et al. investigated HER2 expression and amplification in women with endometrial cancer, including a wide variety of histologies. The investigation showed a correlation between HER2 expression and amplification and tumors of higher grade/stage, lymph node positivity, and survival outcomes. Overall survival was significantly shorter in patients with HER2 expression (median 5.2 years) and/or showed amplification (median 3.5 years) versus those that did not (median 13 years) (52). The clinical significance of HER2 overexpression or gene amplification continues to be debated.

Point Mutations

Point mutations of a gene may remain without any consequence for the expression and function of the protein (gene polymorphism). However, point mutations can alter a codon sequence and subsequently disrupt the normal function of a gene product. The *ras* gene family is an example of oncogene-encoded proteins that disrupt the intracellular signal transduction system following point mutations. Transforming Ras proteins contain point mutations in critical codons (i.e., codons [11, 12], [59], [61]) with decrease of GTPase activity and subsequent expression of constitutively active Ras. Point mutations of the *p53* gene are the most common genetic mutations described in solid tumors. These mutations occur at preferential "hot spots" that coincide with the most highly conserved regions of the gene. The *p53* tumor suppressor gene encodes for a phosphoprotein that is detectable in the nucleus of normal cells. When DNA damage occurs, *p53* can arrest cell cycle progression to allow the DNA to be repaired or undergo apoptosis. The lack of function of normal *p53* within a cancer cell results in a loss of control of cell proliferation with inefficient DNA repair and genetic instability. Somatic mutations of the *p53* gene occur in approximately 50% of advanced ovarian cancers and 30% to 40% of endometrial cancers (predominantly serous histology) but are uncommon in cervical cancer (53,54).

BRCA

Point mutations in the BRCA1 and BRCA2 genes can alter the activity of these genes and predispose to the development of breast and ovarian cancer(s) (55). The

frequency of BRCA1 and BRCA2 mutations in the general population in the United States is estimated at 1:250. Specific founder mutations were reported for various ethnic groups. For example, two BRCA1 mutations (185delAG and 5382insC) and one BRCA2 mutation (6174delT) are found in 2.5% of Ashkenazi Jews of Central and Eastern European descent. Additional founder mutations were described in other ethnic groups, including from the Netherlands (BRCA1, 2804delAA and several large deletion mutations), Iceland (BRCA2, 995del5), and Sweden (BRCA1, 3171ins5).

The BRCA proteins are involved in DNA repair. If DNA is damaged, for example, by ionizing radiation or chemotherapy, the BRCA2 protein binds to the RAD51 protein, which is central for the repair of double-stranded breaks via homologous recombination. BRCA2 regulates the availability and activity of RAD51 in this key reaction. Phosphorylation of the BRCA2/RAD51 complex allows RAD51 to bind to the site of DNA damage and, in conjunction with several other proteins, mediates repair of DNA by homologous recombination. BRCA1 functions within a complex network of protein–protein interactions, mediating DNA repair by homologous recombination and regulating transcription via the BRCA1-associated surveillance complex (BASC).

Deletions and Rearrangements

Individuals carrying a germline BRCA1 or BRCA2 pathogenic mutation have an elevated lifetime risk of developing breast and ovarian cancer(s). Based on a meta-analysis by Chen et al., the 70-year risk of developing ovarian cancer is 40% and 18% for BRCA1 and BRCA2, respectively, and breast cancer is 57% and 49% for BRCA1 and BRCA2, respectively (56). These germline mutations are inherited in an autosomal-dominant fashion. Approximately 5% of breast and 20% of ovarian cancers arise in women carrying heterozygous germline mutations in BRCA1 or BRCA2 (57). BRCA1 and BRCA2 are tumor suppressor genes. Loss of nonmutated (wild-type) allele at either BRCA1 or BRCA2 locus, termed locus-specific LOH, can be observed in tumors. Cells with loss of BRCA function and resultant homologous recombination (HR)–based DNA repair deficiency have enhanced sensitivity to DNA-damaging agents, namely cytotoxic platinum-based chemotherapies and targeted therapies (specifically inhibition of poly [ADP-ribose] polymerases [PARPs]) (58). Although much research has demonstrated that germline pathogenic mutations in BRCA1 or BRCA2 in ovarian cancer can downregulate HR, and thereby increase a patient's sensitivity and response to platinum-based chemotherapy and PARP inhibition, there is less evidence to support the potential impact of somatic sequence variants of BRCA function. Published studies have demonstrated that germline and somatic pathogenic mutations in HR genes (BRCA1, BRCA2, *ATM, BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C,* and *RAD51D*) occur in 31% of patients with serous or nonserous ovarian cancer (59). Of these, 75% of germline HR mutations and 71% of somatic HR mutations were in BRCA (60). The role of somatic pathogenic BRCA mutations in platinum-based

chemotherapy and PARP inhibitor sensitivity indicates that the number of individuals with ovarian cancer who may benefit from such treatments are greater than predicted by the frequency of germline pathogenic mutations alone.

Poly (ADP-Ribose) Polymerases

PARPs are vital components of DNA damage and repair pathways. The concept of synthetic lethality is based on the idea that simultaneous loss of function of two or more gene products can cause cell death, even if a deficiency in one is not lethal (61). For example, a tumor cell without a lethal inactivating mutation of BRCA DNA repair genes, might still be destroyed if also exposed to effects of PARP inhibition. Given that HGSCs are associated with germline BRCA1 or BRCA2 mutations, they remain the most suitable candidates for PARP inhibition. DNA repair function is inherently decreased in tumor cells, compared with normal cells. This discrepancy contributes to the high selectivity of PARP inhibitors (61).

Three different PARP inhibitors have been approved by the FDA for the treatment of ovarian cancer patients, each with a different clinical indication. *Olaparib* and *niraparib* are indicated in patients with platinum-sensitive ovarian cancer as maintenance therapy following response to platinum-based chemotherapy for recurrent disease. Neither drug requires the presence of germline or somatic mutations in BRCA1 or BRCA2 genes for this indication. For the treatment of recurrent ovarian cancer with *olaparib*, patients must have had three or more lines of chemotherapy and have a germline mutation in BRCA1 or BRCA2. Response rates in this patient population is about 30% based on clinical trial data (62). *Rucaparib* is likewise approved for maintenance therapy in patients with recurrent, platinum-sensitive ovarian cancer but requires the presence of a germline or somatic BRCA1 or BRCA2 mutation (63). The most common side effects with PARP inhibitors include hematologic toxicities including thrombocytopenia and anemia, gastrointestinal side effects, in particular nausea and fatigue.

Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer Syndrome, HNPCC)

Lynch syndrome (LS) is an autosomal-dominant inherited disorder caused by germline mutations in DNA MMR genes. Mutations are characterized by predisposition for cancers arising from the colon, rectum, small bowel, endometrium, ovary, stomach, pancreas, renal pelvis, ureter, and brain (64). This syndrome was first identified in patients with familial predisposition to gastrointestinal cancers. Endometrial cancer often precedes colorectal and other LS-associated malignancies. Women with LS have a 15% to 70% lifetime risk of endometrial cancer and a 6% to 8% lifetime risk of ovarian cancer, with this wide range accounting for a variety of histopathologic subtypes (65,66). Such a high incidence has led to increased screening of endometrial carcinoma specimens for abnormalities in the DNA MMR pathway. The most common and convincing method of germline mutation analysis is focused on the four primary MMR

genes associated in LS, including MLH1, MSH2, MSH6, and PMS1. Mutations in MSH2 and/or MLH1 account for 90% of heterozygous mutations, while MSH6 mutations account for most of the remaining cases (67). A smaller subset of patients may carry mutations in the EPCAM gene, which can lead to Lynch phenotype by way of hypermethylation and inactivation of MSH2 promoter. IHC staining for loss of expression serves as the standard screening approach. Microsatellite instability (MSI) testing is available as a substitute or additional modality for abnormalities of the MMR system; however, this testing has been shown to be less sensitive than IHC, primarily because of a failure to detect several MSH6 germline mutation carriers (64).

Deletions and rearrangements reflect gross changes in the DNA template that may result in the synthesis of a markedly altered protein product. Somatic mutations may involve chromosomal translocations that result in chimeric transcripts with juxtaposition of one gene to the regulatory region of another gene. This mutation type is most commonly reported in leukemias, lymphomas, and mesenchymal tumors. The Philadelphia chromosome in chronic myeloid leukemia (CML), for example, is the result of a reciprocal translocation between one chromosome 9 and one chromosome 22. The DNA sequence removed from chromosome 9 contains the proto-oncogene *c-ABL* and inserts into the *BCR* gene sequence on chromosome 22 (Philadelphia chromosome). The resulting chimeric *BCR-ABL* gene product functions as a constitutively active tyrosine kinase and stimulates cellular proliferation by such mechanisms as an increase of growth factors.

Single-nucleotide polymorphism (SNP) describes a variation in the DNA sequence (68). Single nucleotides in the genome differ between paired chromosomes in either one individual or between two individuals. For example, the sequences T**G**ACTA and T**C**ACTA contain one single change in the second nucleotide from guanine (G) to cytosine (C). This results in a G and C allele for this particular gene sequence. SNPs can occur within coding or noncoding sequences of genes or in the intergenic regions. SNPs might not change the amino acid sequence of the protein that is produced (synonymous SNP) or produce a different peptide (nonsynonymous SNPs). If SNPs are located in noncoding regions, various other processes like gene splicing or transcription factor binding might be affected.

The frequency of SNPs in a given population is provided by the minor allele frequency. This frequency differs between ethnic groups and geographic locations. SNPs were associated with various human diseases including cancer. They influence the effect of drug treatment and responses to pathogens and chemicals (69). SNPs are important for the comparison between genomes of different populations, for example, providing information about the susceptibility of a certain population to develop specific cancers (70).

THE CANCER GENOME ATLAS PROJECT

In 2006, the National Cancer Institute and the National Human Genome Research Institute initiated TCGA project. The goal of the project is to provide a comprehensive genomic characterization and sequence analysis of cancer diseases. The initial phase included glioblastoma multiforme, lung, and ovarian cancers (71,72).

TCGA is taking advantage of high-throughput genome analysis techniques, including gene expression profiling, SNP genotyping, copy number variation profiling, genomewide methylation profiling, microRNA profiling, and exon sequencing (73). These data are accessible for researchers via TCGA webpage (https://gdc.cancer.gov). The findings as pertaining to gynecologic malignancies are summarized below.

Endometrial Carcinoma

An integrated genomic, transcriptomic, and proteomic characterization of 373 endometrial carcinomas (tumor samples and corresponding germline DNA) using array- and sequencing-based technologies was performed (74). Uterine serous tumors and 25% of high-grade endometrioid tumors exhibited extensive copy number alterations, few DNA methylation changes, low ER and progesterone receptor levels, and frequent TP53 mutations. The majority of endometrioid tumors were identified as having frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A, and KRAS, novel mutations in SWI/SNF chromatin remodeling complex gene ARID5B, and few copy number alterations or TP53 mutations. In addition, 10% of endometrioid tumors were identified to have markedly increased transversion mutation frequency and a newly identified mutation in POLE. *POLE* is a catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair (75). These new findings classify endometrial carcinomas into four distinct categories: POLE ultramutated, MSI hypermutated, copy-number low, and copy-number high. Somatic copy number alterations (SCNAs) showed that most endometrioid tumors have few SCNAs, most serous and serous-like tumors exhibit extensive SCNAs, and the extent of SCNA roughly correlates with progression-free survival (74).

According to TCGA data, endometrial cancer has higher-frequency mutations in the PI(3)K/AKT pathway than any other tumor type that has been studied. Endometrioid endometrial carcinomas demonstrate parallels with characteristics of colorectal carcinoma, specifically high frequency of MSI (40% and 11%, respectively), *POLE* mutations (7% and 3%, respectively) which lends to ultrahigh mutation rates, and frequent activation of WNT/CTNNB1 signaling. Yet, endometrial carcinomas are unlike those of colorectal carcinomas as they have unique *KRAS* and *CTNNB1* mutations and a distinct means by which pathway activation is achieved. Data pertaining to molecular characterization showed 25% of tumors classified as high-grade endometrioid have a molecular phenotype similar to uterine serous carcinomas, including frequent *TP53*

mutations and extensive SCNA.

Ovarian Carcinoma

TCGA review for ovarian cancer included 489 clinically annotated stages II to IV high-grade serous ovarian cancer (HGSC) samples and corresponding normal DNA. The summary of mutational spectrum includes high prevalence of mutations in TP53 (present in at least 96% of samples), BRCA1, and BRCA2 (including both germline and somatic mutations) in 22% of the tumors (76). HGSC demonstrates a high frequency of mutations in genes involved in homologous recombination, and is hence considered a disease of high genomic instability. The mutation spectrum in HGSC differs from those in other histologic subtypes of ovarian cancer. Clear-cell ovarian cancer tumors have few *TP53* mutations, yet frequent *ARID1A* and *PIK3CA* mutations (39). Endometrioid ovarian cancers carry frequent *CTNNB1*, *ARID1A*, and *PIK3CA* mutations and a lower rate of *TP53*; and mucinous ovarian cancer tumors have prevalent *KRAS* mutations (77). Such differences between ovarian cancer subtypes demonstrate the ongoing need for subtype-specific targeted therapeutic modalities.

Cervical Carcinoma

TCGA study collection included primary frozen cervical cancer tumor tissue and blood samples from patients who had not previously received chemotherapy or radiotherapy. Whole exome sequencing demonstrated the following significantly mutated genes: *ERBB3*, *CASP8*, *HLA-A*, *SHKBP1,* and *TGFBR2* (78). Amplifications and fusion events were reported involving the *BCAR4* gene, a metastasis-promoting lncRNA that enhances cell proliferation in estrogen-resistant breast cancer by activating the HER2/3 pathway, which can be targeted indirectly by *lapatinib* (a dual tyrosine kinase inhibitor that interrupts the HER2 and EGFR pathways) (78,79). Amplifications in *CD274* and *PDCD1LG2* were identified, both of which have been associated with response to *lapatinib*. Another identified novel genomic characteristic that further subclassifies cervical cancers is a group of endometrial-like cervical cancers involved predominantly with HPV-negative tumors and characterized by mutations in *KRAS*, *ARID1A*, and PTEN. These proteins may serve as therapeutic targets.

IMMUNOLOGY

The immune system plays an essential part in host defense mechanisms, in particular the response to infections and neoplastic transformation. Our increased understanding of immune system regulation provides opportunities for the development of novel immunotherapeutic and immunodiagnostic approaches.

Immunologic Mechanisms

The human immune system has the potential to respond to abnormal or tumor cells in various ways. Some of these immune responses occur in an innate or antigen-nonspecific manner, whereas others are adaptive or antigen specific. Adaptive responses are specific to a given antigen. The establishment of a memory response allows a more rapid and vigorous response to the same antigen in future encounters. Various innate and adaptive immune mechanisms are involved in responses to tumors, including cytotoxicity directed to tumor cells mediated by cytotoxic T cells (CTLs), natural killer (NK) cells, macrophages, and antibody-dependent cytotoxicity mediated by complementation activation (80).

Adaptive or specific immune responses include humoral and cellular responses. *Humoral immune responses* refer to the production of antibodies. Antibodies are bifunctional molecules composed of a variable region with specific antigen-binding sites, combined with a constant region that directs the biologic activities of the antibody, such as binding to phagocytic cells or activation of complement. ***Cellular immune responses* are antigen-specific immune responses mediated directly by activated immune cells rather than by the production of antibodies**. The distinction between humoral and cellular responses is historical and originates from the experimental observation that humoral immune function can be transferred by serum, whereas cellular immune function requires the transfer of cells. Most immune responses include both humoral and cellular components. Several types of cells, including cells from both the myeloid and lymphoid lineages, make up the immune system. Specific humoral and cellular immune responses to foreign antigens involve the coordinated action of populations of lymphocytes operating in concert with one another and with phagocytic cells (macrophages). These cellular interactions include direct cognate interactions involving cell-to-cell contact and cellular interactions involving the secretion of and response to cytokines or lymphokines. Lymphoid cells are found in lymphoid tissues, such as lymph nodes or spleen, or in the peripheral circulation. The cells that make up the immune system originate from stem cells in the bone marrow.

B Cells, Hormonal Immunity, and Monoclonal Antibodies

B lymphocytes synthesize and secrete antibodies. Mature, antigen-responsive B cells develop from pre-B cells (committed B-cell progenitors) and differentiate to become plasma cells, which produce large quantities of antibodies. Pre-B cells originate from bone marrow stem cells in adults after rearrangement of immunoglobulin genes from their germ cell configuration. Mature B cells express cell surface immunoglobulin molecules that function as receptors for antigen.

Upon interaction with antigen, mature B cells respond to become antibody-producing cells. The process requires the presence of appropriate cell–cell stimulatory

signals and cytokines. Monoclonal antibodies are directed against a specific antigenic determinant. In contrast, polyclonal antibodies detect multiple epitopes that might be presented by just one or a panel of proteins. The in vitro production of monoclonal antibodies, pioneered by Kohler and Milstein in the 1970s, has become an invaluable diagnostic and therapeutic tool, particularly for the management of malignancies (81). The tumor antigen CA125, for example, was detected in a screen of antibodies generated against ovarian cancer cell lines. A radioimmunoassay is widely used to measure CA125 in the serum of patients with ovarian cancer and guide treatment decisions. Therapeutic approaches utilized immunotoxin-conjugated monoclonal antibodies directed to human ovarian adenocarcinoma antigens. These antibodies induce tumor cell killing and can prolong survival in mice implanted with a human ovarian cancer cell line. However, some obstacles limit the clinical use of monoclonal antibodies, including tumor cell antigenic heterogeneity, modulation of tumor-associated antigens, and cross-reactivity of normal host and tumor-associated antigens. Unique tumor-specific antigens have not been identified. All tumor antigens have to be considered as tumor-related antigens because they are expressed on malignant and nonmalignant tissues. Because most monoclonal antibodies are murine, the host's immune system can recognize and respond to these foreign mouse proteins. The use of the genetically engineered monoclonal antibodies composed of human-constant regions with specific antigen-reactive murine variable regions can result in reduced antigenicity.

T Lymphocytes and Cellular Immunity

[6] T lymphocytes have a central role in the generation of immune responses by acting as helper cells in both humoral and cellular immune responses and by acting as effector cells in cellular responses. T-cell precursors originate in the bone marrow and move to the thymus, where they mature into functional T cells. During their thymic maturation, T cells that can recognize antigens in the context of the *major histocompatibility complex* (MHC) molecules are selected, while self-responding T cells are removed (82).

T cells can be distinguished from other types of lymphocytes by their cell surface phenotype, based on the pattern of expression of various molecules, and by differences in their biologic functions. All mature T cells express certain cell surface molecules, such as the cluster determinant 3 (CD3) molecular complex and the T-cell antigen receptor (TCR), found in close association with the CD3 complex. **T cells recognize antigens through the cell surface T-cell antigen receptor**. The structure and organization of this molecule are similar to those of antibody molecules, which are the B-cell receptors for the antigen. During T-cell development, the T-cell receptor gene undergoes gene arrangements similar to those seen in B cells, but there are important differences between the antigen receptors on B cells and T cells. The T-cell receptor is

not secreted, and its structure is somewhat different from that of antibody molecules. The way in which the B-cell and T-cell receptors interact with antigens is quite different. T cells can respond to antigens only when these antigens are presented in association with MHC molecules on antigen-presenting cells. Effective antigen presentation involves the processing of the antigen into small fragments of peptide within the antigen-presenting cell and the subsequent presentation of these fragments of antigen in association with MHC molecules expressed on the surface of the antigen-presenting cell. T cells can respond to antigens only when presented in this manner, unlike B cells, which can bind antigens directly, without processing and presentation by antigen-presenting cells.

[7] **There are two major subsets of mature T cells that are phenotypically and functionally distinct: *T-helper/inducer cells*, which express the CD4 cell surface marker, and the *CTLs*, which express the CD8 marker.** The expression of these markers is acquired during the passage of T cells through the thymus. CD4 T cells can provide help to B cells, resulting in the production of antibodies by B cells, and interact with antigen presented by antigen-presenting cells in association with MHC class II molecules. CD4 T cells can act as helper cells for other T cells. CD8 T cells include cells that are cytotoxic (cells that can kill target cells bearing appropriate antigens), and they interact with an antigen presented on target cells in association with MHC class I molecules. These T cells can inhibit the biologic functions of B cells or other T cells (80). Although the primary biologic role of *CTLs* seems to be lysis of virus-infected autologous cells, cytotoxic immune T cells can mediate the lysis of tumor cells directly. Presumably, CTLs recognize antigens associated with MHC class I molecules on tumor cells through their antigen-specific T-cell receptor, setting off a series of events that ultimately results in the lysis of the target cell.

Monocytes and Macrophages

Monocytes and macrophages, which are myeloid cells, have important roles in innate and adaptive immune responses; macrophages play a key part in the generation of immune responses. T cells do not respond to foreign antigens unless those antigens are processed and presented by antigen-presenting cells. **Macrophages (and B cells and dendritic cells) express MHC class II molecules and are effective antigen-presenting cells for CD4 T cells.** Helper-inducer (CD4) T cells that bear a T-cell receptor of appropriate antigen and self-specificity are activated by this antigen-presenting cell to provide help (various factors—lymphokines—that induce the activation of other lymphocytes). In addition to their role as antigen-presenting cells, macrophages play an important part in innate responses by ingesting and killing microorganisms. Activated macrophages, besides their many other functional capabilities, can act as cytotoxic, antitumor killer cells.

Natural Killer Cells

NK cells are effector cells in an innate type of immune response: the nonspecific killing of tumor cells and virus-infected cells. Therefore, **NK activity represents an innate form of immunity that does not require an adaptive, memory response for optimal biologic function, but the antitumor activity can be increased by exposure to several agents, particularly cytokines such as interleukin-2 (IL-2).** Characteristically, NK cells have a large granular lymphocyte morphology. NK cells display a pattern of cell surface markers that differs from those characteristic of T or B cells. NK cells can express a receptor for the crystallizable fragment (Fc) portion of antibodies, and other NK-associated markers. NK cells appear to be functionally and phenotypically heterogeneous, when compared with T or B cells. The cells that can carry out antibody-dependent cellular cytotoxicity, or antibody-targeted cytotoxicity, are NK-like cells. Antibody-dependent cellular cytotoxicity by NK-like cells resulted in the lysis of tumor cells in vitro. The mechanisms of this tumor cell killing are not clearly understood, although close cellular contact between the effector cell and the target cell seems to be required.

Cytokines, Lymphokines, and Immune Mediators

Many events in the generation of immune responses (and during the effector phase of immune responses) require or are enhanced by cytokines, which are soluble mediator molecules (Table 6-5) (83,84). Cytokines are pleiotropic in that they have multiple biologic functions that depend on the type of target cell or its maturational state. Cytokines are heterogeneous in the sense that most cytokines share little structural or amino acid homology. ***Cytokines*** **are called** ***monokines*** **if they are derived from monocytes,** ***lymphokines*** **if they are derived from lymphocytes,** ***interleukins*** **if they exert their actions on leukocytes, or** ***interferons*** **(IFNs) if they have antiviral effects.** They are produced by a wide variety of cell types and seem to have important roles in many biologic responses outside the immune response, such as inflammation or hematopoiesis. They may be involved in the pathophysiology of a wide range of diseases and show great potential as therapeutic agents in immunotherapy for cancer. Although cytokines are a heterogeneous group of proteins, they share some characteristics. For instance, most cytokines are low- to intermediate-molecular-weight (10 to 60 kDa) glycosylated-secreted proteins. They are involved in immunity and inflammation, are produced transiently and locally (they act in an autocrine and paracrine rather than an endocrine manner), are extremely potent in small concentrations, and interact with high-affinity cellular receptors that are specific for each cytokine. The cell surface binding of cytokines by specific receptors results in signal transduction followed by changes in gene expression and, ultimately, by changes in cellular proliferation or altered cell behavior, or both. Their biologic actions overlap, and exposure of responsive cells to multiple cytokines can result in synergistic or antagonistic biologic effects.

T-cell subsets characterized by the secretion of distinct patterns of cytokines were identified. **T_H1 and T_H2 are two helper T-cell subpopulations that control the nature of an immune response by secreting a characteristic and mutually antagonistic set of cytokines: clones of T_H1 produce IL-2 and IFN-γ, whereas T_H2 clones produce IL-4, IL-5, and IL-10** (85). A similar dichotomy between T_H1- and T_H2-type responses was reported in humans. Human IL-10 inhibits the production of IFN-γ and other cytokines by human peripheral blood mononuclear cells and by suppressing the release of cytokines (IL-1, IL-6, IL-8, and TNF-α) by activated monocytes (84). IL-10 downregulates class II MHC expression on monocytes, resulting in a strong reduction in the antigen-presenting capacity of these cells. Together, these observations support the concept that IL-10 has an important role as an immune-inhibitory cytokine. Additional T-cell subsets were identified, including Th17 cells and regulatory T cells (Treg). Th17 cells are a distinct, pro-inflammatory T-cell subset, which is functionally characterized by mediating protection against extracellular bacteria and by its pathogenic role in autoimmune disorders (86,87). Th17 cells characteristically produce IL-17, CXCL13 (a B-cell stimulatory chemokine), IL-6, and TNF-α, in contrast to Th2 cells, which characteristically produce IL-4, IL-5, IL-9, and IL-13, or Th1 cells, which produce IFN-γ **(Fig. 6-2)**. Treg cells constitute another subset of CD4-positive T cells that participates in the maintenance of immunologic self-tolerance by actively suppressing the activation and expansion of self-reactive lymphocytes. Treg cells are characterized by the expression of CD25 (the IL-2 receptor chain) and the transcription factor FoxP3 (88,89). Treg cell activity is thought to be important in preventing the development of autoimmune diseases. Removal of Treg may enhance immune responses against infectious agents or cancer. Although much remains to be learned about the role of Treg activity in antitumor immunity, it is clear that such cells may play a role in modulating host responses to cancer. Much of the recent research has been directed at the tumor microenvironment. Specifically, the tumor microenvironment consists of several varieties of cell types that interact with tumor cells to influence tumor initiation, growth, and metastasis (90). The tumor microenvironment plays a key role in allowing tumor cells to evade immune recognition and destruction.

Because epithelial cancers of the ovary usually remain confined to the peritoneal cavity, even in the advanced stages of the disease, it was suggested that the growth of ovarian cancer intraperitoneally could be related to a local deficiency of antitumor immune effector mechanisms (91). Studies showed that ascitic fluid from patients with ovarian cancer contained increased concentrations of IL-10. Various other cytokines are seen in ascitic fluid obtained from women with ovarian cancer, including IL-6, IL-10, TNF-α, *granulocyte colony-stimulating factor* (G-CSF), and *granulocyte-macrophage colony-stimulating factor* (GM-CSF). A similar pattern was seen in serum

samples from women with ovarian cancer with elevations of IL-6 and IL-10.

TNF-α is a cytokine that can be directly cytotoxic for tumor cells, increase immune cell–mediated cellular cytotoxicity, activate macrophages, and induce secretion of monokines. Other biologic activities of TNF-α include the induction of cachexia, inflammation, and fever; it is an important mediator of endotoxic shock.

Cytokines in Cancer Therapy

Cytokines are exceptionally pleiotropic with a wide array of biologic activities, including some outside the immune system (92). Because some cytokines have direct or indirect antitumor and immune-enhancing effects, several of these factors are used in the experimental treatment of cancer.

The precise roles of cytokines in antitumor responses have not been elucidated. Cytokines can exert antitumor effects by many different direct or indirect activities. It is possible that a single cytokine could increase tumor growth directly by acting as a growth factor while at the same time increasing immune responses directed toward the tumor. The potential of cytokines to increase antitumor immune responses was tested in experimental adoptive immunotherapy by exposing the patient's peripheral blood cells or tumor-infiltrating lymphocytes to cytokines such as IL-2 in vitro, thus generating activated cells with antitumor effects that can be given back to the patient (93). Some cytokines can exert direct antitumor effects. TNF can induce cell death in sensitive tumor cells.

The effects of cytokines on patients with cancer might be modulated by soluble receptors or blocking factors. For instance, blocking factors for TNF and for lymphotoxin were found in ascitic fluid from patients with ovarian cancer (93). Such factors could inhibit the cytolytic effects of TNF or lymphotoxin and should be taken into account in the design of clinical trials of intraperitoneal infusion of these cytokines.

Table 6-5 Sources, Target Cells, and Biologic Activities of Cytokines Involved in Immune Responses

Cytokine	Cellular Source	Target Cells	Biologic Effects
IL-1	Monocytes and macrophages	T cells, B cells Neurons	Costimulator Pyrogen
IL-2	Tumor cells	Endothelial cells	
	T cells	T cells	Activation and growth
		B cells	Activation and antibody production
		NK cells	Activation and growth
IL-3	T cells	Immature hemopoietic stem cells	Growth and differentiation
IL-4	T cells (T_H2)	B cells	Activation and growth; isotype switch to IgE; increased MHCII expression
		T cells	Growth
IL-6	Monocytes and macrophages	B cells	Differentiation, antibody production
	T cells (T_H17), B cells	T cells	Costimulator
	Ovarian cancer cells	Hepatocytes	Induction of acute-phase response
	Other tumors	Stem cells	Growth and differentiation
	Tumor cells	Autocrine/paracrine growth and viability-enhancing factor	
IL-10	T cells (Treg, T_H2)	T cells	Inhibition of cytokine synthesis
	Monocytes and macrophages	Monocytes and macrophages	Inhibition of Ag presentation and cytokine production
		B cells	Activation
IL-12	Monocytes	NK cells, T cells	Promotes T_H1 cells
IL-13	T cells (T_H2), mast cells, NK cells	B cells, T_H2 cells, macrophages	Regulates IgE secretion by B cell T_H2 development Macrophage activity
IL-15	Dendritic cells, monocytes, placenta, kidney, lung, heart, T cells	Mast cells	NK cell development and function Mast cell proliferation
IL-17	T cells (T_H17)	T cells, fibroblasts	T-cell activation Induces secretion of cytokines by fibroblasts
IL-23	Monocytes, macrophages	CD4+ T cells	Promotes T_H17 cells
IFN-γ	T cells (T_H1)	Monocytes/macrophages	Activation
	NK cells	NK cells, T cells, B cells	Activation Enhances responses
TNF-α	Monocytes and macrophages	Monocytes/macrophages	
	T cells (T_H17)	T cells, B cells	
		Neurons	
	Monokine production		
	Costimulator		
	Pyrogen		
		Endothelial cells Muscle and fat cells	Activation, inflammation Catabolism/cachexia

IL-1, interleukin-1; Treg, regulatory T cells; T_H1, type 1 T-helper lymphocyte; NK cells, natural killer cells; T_H2, type 2 T-helper lymphocyte; IgE, immunoglobulin E; MHCII, major histocompatibility complex class II; Ag, antigen; IFN, interferon; TNF, tumor necrosis factor.

Modified from **Berek JS, Martinez-Maza O.** *Immunology and immunotherapy.* In: **Lawton FG, Neijt JP, Swenerton KD,** eds. *Epithelial Cancer of the Ovary. London: BMJ; 1995:224,* with permission.

Cytokines have growth-increasing effects on tumor cells in addition to inducing antitumor effects. They can act as autocrine or paracrine growth factors for human tumor cells, including those of nonlymphoid origin. For instance, IL-6 (which is produced by various types of human tumor cells) can act as a growth factor for human myeloma, Kaposi sarcoma, renal carcinoma, and epithelial ovarian cancer cells (94).

Cytokines are of great potential value in the treatment of cancer, but because of their

multiple, even conflicting, biologic effects, a thorough understanding of cytokine biology is essential for their successful use (93).

FACTORS THAT TRIGGER NEOPLASIA

Cell biology is characterized by considerable redundancy and functional overlap, so a defect in one mechanism does not invariably jeopardize the function of the cell. When a sufficient number of abnormalities in structure and function occur, normal cell activity is jeopardized, and uncontrolled cell growth or cell death results. Either end point may result from accumulated genetic mutations. Factors are identified that enhance the likelihood of genetic mutations, jeopardize normal cell biology, and may increase the risk of cancer.

Increased Age

Increasing age is considered the single most important risk factor for the development of cancer (95). Cancer is diagnosed in as much as 50% of the population by 75 years of age. It was suggested that the increasing risk of cancer with age reflects the accumulation of critical genetic mutations over time, which ultimately culminates in neoplastic transformation. The basic premise of the multistep somatic mutation theory of carcinogenesis is that genetic or epigenetic alterations of numerous independent genes result in cancer. Factors that are associated with an increased likelihood of cancer include exposure to exogenous mutagens, altered host immune function, and certain inherited genetic syndromes and disorders.

Environmental Factors

A mutagen is a compound that results in a genetic mutation. A number of environmental pollutants act as mutagens when tested in vitro. Environmental mutagens usually produce specific types of mutations that can be differentiated from spontaneous mutations. A carcinogen is a compound that can produce cancer. It is important to recognize that all carcinogens are not mutagens and that all mutagens are not necessarily carcinogens.

Smoking

Cigarette smoking is perhaps the most well-known example of mutagen exposure that is associated with the development of lung cancer when the exposure is of sufficient duration and quantity in a susceptible individual. An association between cigarette smoking and cervical cancer has been recognized for decades. **It was determined that the mutagens in cigarette smoke are selectively concentrated in**

cervical mucus (96). It was hypothesized that cigarette smoke acted as a mutagen when exposed to the proliferating epithelial cells of the transformation zone, thus increasing the likelihood of DNA damage and subsequent cellular transformation.

Others observed that HPV DNA is frequently inserted into the fragile histidine triad (*FHIT*) gene in cervical cancer specimens. The *FHIT* is an important tumor suppressor gene. Cigarette smoking might facilitate the incorporation of HPV DNA into the *FHIT* gene with subsequent disruption of correct tumor suppressor gene function.

Radiation

Radiation exposure can increase the risk of cancer. The biologic effects of ionization surpass those of x-rays and gamma rays. Ionization of water molecules creates hydroxyl radicals, which cause DNA strand breaks or base damage. Most radiation-induced damage is repaired precipitously. However, misrepair may cause point mutations, chromosome translocations, and gene fusions associated with cancer initiation (97). Normally, radiation damage prompts an S-phase arrest so that DNA damage is repaired. This requires normal *p53* gene function. If DNA repair fails, the damaged DNA is propagated to daughter cells following mitosis. If a sufficient number of critical genes are mutated, cellular transformation may result (98).

Immune Function

Systemic immune dysfunction was recognized for decades as a risk factor for cancer. Patients infected with HIV who have a depressed CD4 cell count are reported to be at increased risk of cervical dysplasia (99). Individuals who underwent high-dose chemotherapy with stem cell support may be at increased risk of developing a variety of solid neoplasms. These examples illustrate the importance of immune function in host surveillance for transformed cells. Another example of altered immune function that may be related to the development of cervical dysplasia is the alteration in mucosal immune function that occurs in women who smoke cigarettes (100). The Langerhans cell population of the cervix is decreased in women who smoke. Langerhans cells are responsible for antigen processing. It is postulated that a reduction in these cells increases the likelihood of successful HPV infection of the cervix.

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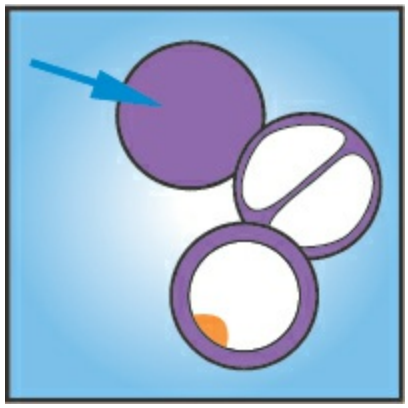
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CHAPTER 7

Reproductive Physiology



David L. Olive, Steven F. Palter, Juan Luis Giraldo Moreno

Neuroendocrinology
Anatomy
Hypothalamus
Pituitary
Reproductive Hormones
Hypothalamus
Gonadotropin-Releasing Hormone
Pituitary Hormone Secretion
Anterior Pituitary
Posterior Pituitary
Menstrual Cycle Physiology
Normal Menstrual Cycle
Hormonal Variations
Uterus
Cyclic Changes of the Endometrium
Ovarian Follicular Development
Meiotic Arrest of Oocyte and Resumption
Follicular Development
Luteal Phase
Summary of Menstrual Cycle Regulation

KEY POINTS

1 The female reproductive process involves the central nervous system (primarily hypothalamus), the pituitary gland, the ovary, and the uterus (endometrium). All must function appropriately for normal reproduction to occur.

2 Hypothalamic gonadotropin-releasing hormone (GnRH) simultaneously regulates the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the pituitary through pulsatile secretions. The pulse frequency determines the relative amounts of LH and FSH secretion.

3 The ovary responds to FSH and LH in a defined, sequential manner to produce follicular growth, ovulation, and corpus luteum formation. The cycle is designed to produce an optimal environment for pregnancy; if pregnancy does not occur, the cycle begins again.

4 In the early menstrual cycle the ovary produces estrogen, which is responsible for endometrial growth. After ovulation, progesterone is produced in significant quantities, which transforms the endometrium into a form ideal for implantation of the embryo. If no pregnancy occurs, the ovary ceases to produce estrogen and progesterone, the endometrium is sloughed, and the cycle repeats.

[1] The reproductive process in women is a complex and highly evolved interaction of many components. The carefully orchestrated series of events that contributes to a normal ovulatory menstrual cycle requires precise timing and regulation of hormonal input from the central nervous system (CNS), pituitary gland, and ovary. This delicately balanced process can be disrupted easily and result in reproductive failure, which is a major clinical issue confronting gynecologists. To manage such conditions effectively, it is critical that gynecologists understand the normal physiology of the menstrual cycle. The anatomic structures, hormonal components, and their interactions, play a vital role in the function of the reproductive system. Fitting together the various pieces of this intricate puzzle creates “the big picture”: an overview of how the reproductive system of women is designed to function.

NEUROENDOCRINOLOGY

Neuroendocrinology represents facets of two traditional fields of medicine: endocrinology, which is the study of hormones (i.e., substances secreted into the bloodstream that have diverse actions at sites remote from the point of secretion); and neuroscience, which is the study of the action of neurons. The discovery of neurons that transmit impulses and secrete their products into the vascular system to function as hormones, a process known as neurosecretion, demonstrates that the two systems are intimately linked. For instance, the menstrual cycle is regulated through the feedback of hormones on the neural tissue of the CNS.

ANATOMY

Hypothalamus

The hypothalamus is a small neural structure situated at the base of the brain above the optic chiasm and below the third ventricle (Fig. 7-1). It is connected

directly to the pituitary gland and is the part of the brain that is the source of many pituitary secretions. Anatomically, the hypothalamus is divided into three zones: *periventricular* (adjacent to the third ventricle); *medial* (primarily cell bodies); and *lateral* (primarily axonal). Each zone is further subdivided into structures known as nuclei, which represent locations of concentrations of similar types of neuronal cell bodies **(Fig. 7-2)**.

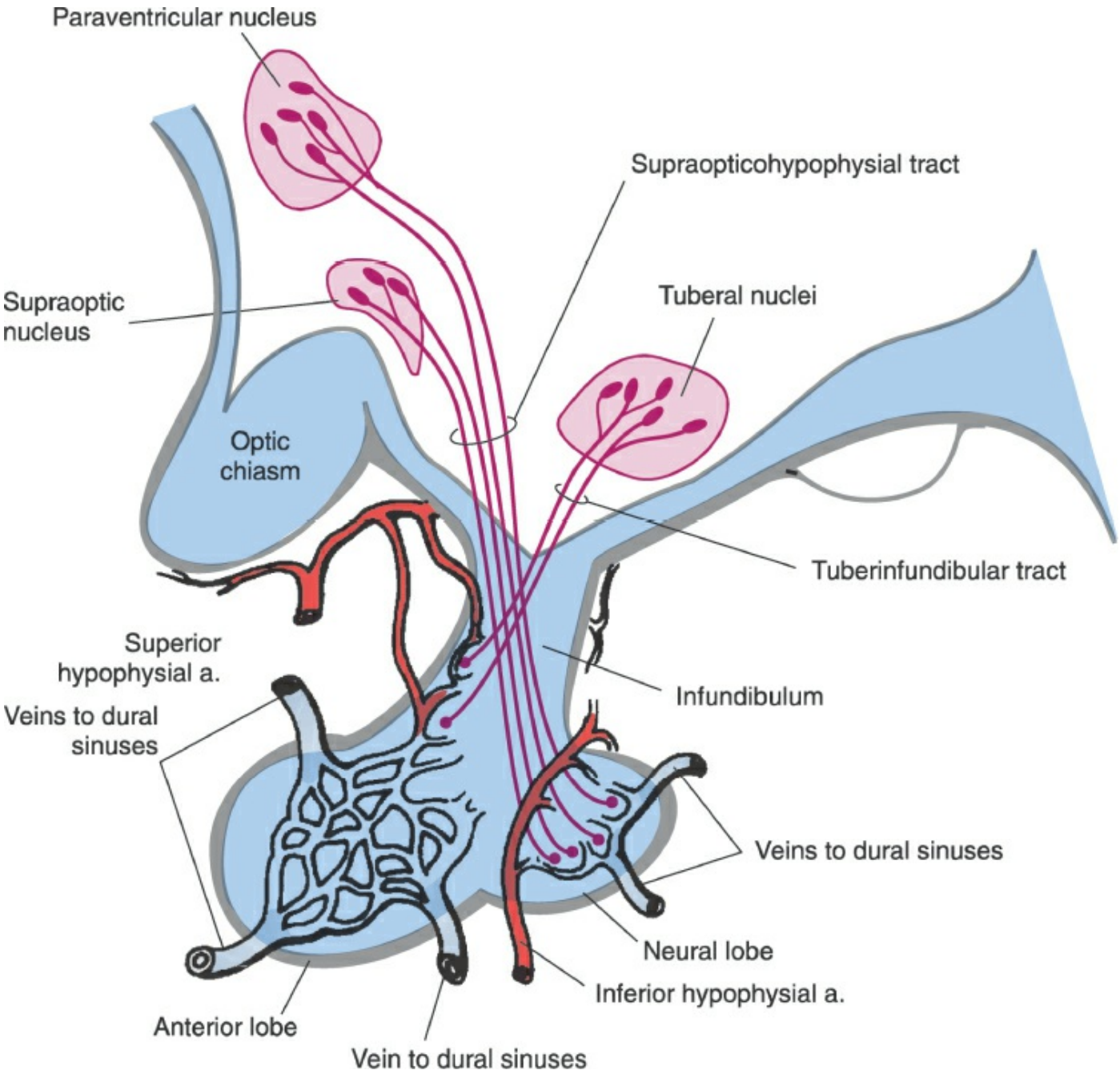


FIGURE 7-1 The hypothalamus and its neurologic connections to the pituitary.

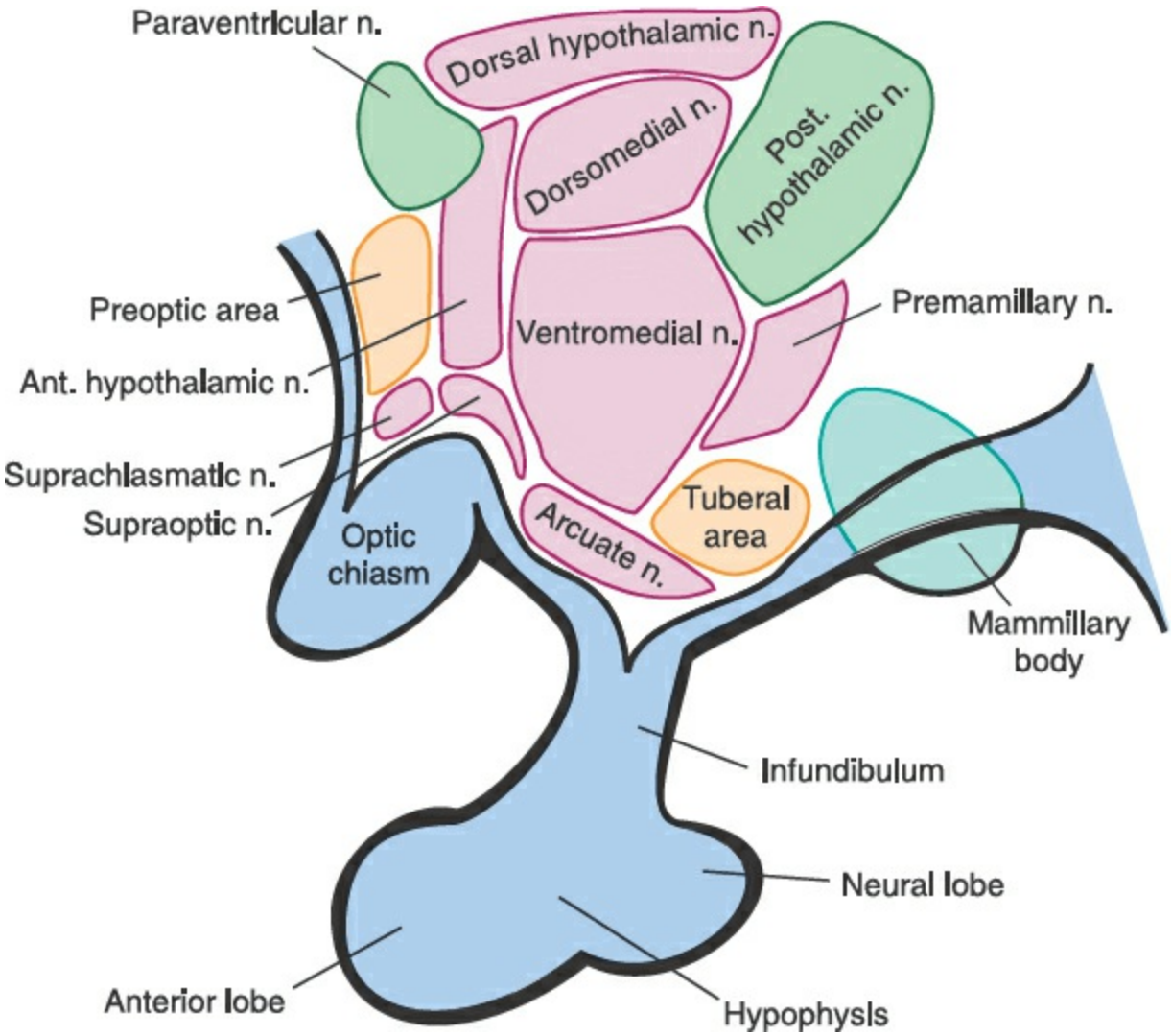


FIGURE 7-2 The neuronal cell bodies of the hypothalamus.

The hypothalamus is not an isolated structure within the CNS; instead, it has multiple interconnections with other regions in the brain. In addition to the well-known pathways of hypothalamic output to the pituitary, there are numerous less well-characterized pathways of output to diverse regions of the brain, including the limbic system (amygdala and hippocampus), the thalamus, and the pons (1). Many of these pathways form feedback loops to areas supplying neural input to the hypothalamus.

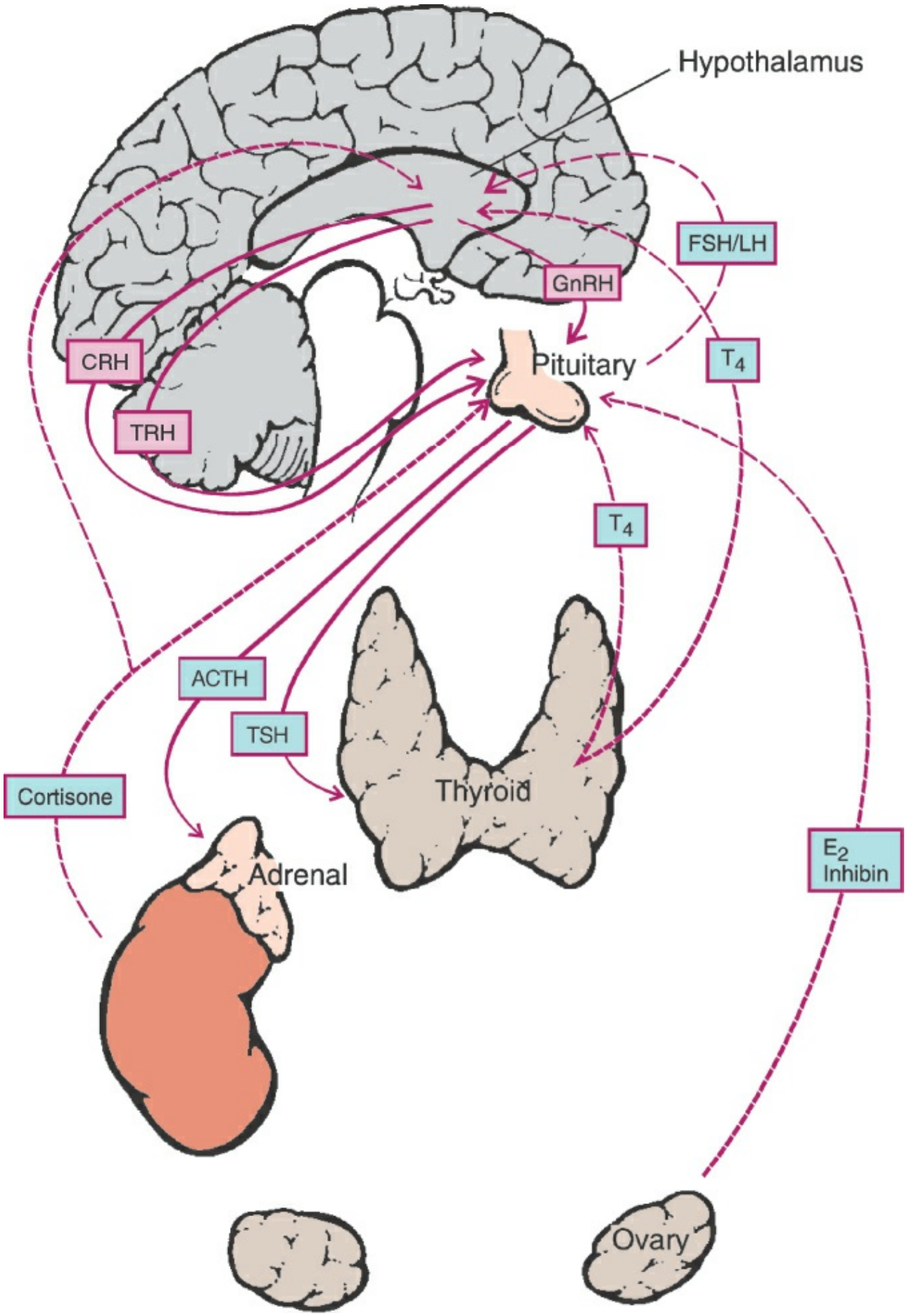

Hypothalamus
FSH/LH
GnRH
CRH
Pituitary
T_4
TRH
T_4
ACTH
TSH
Thyroid
Cortisone
Adrenal
E_2
Inhibin
Ovary

FIGURE 7-3 The hypothalamic secretory products function as pituitary-releasing factors that control the endocrine function of the ovaries, the thyroid, and the adrenal glands. CRH, corticotropin releasing hormone; TRH, thyrotropin releasing hormone; GnRH, gonadotropin releasing hormone; FSH, follicle stimulating hormone; LH, leutinizing hormone; T4, thyroxine; ACTH, adrenocorticotropic hormone; TSH, thyroid stimulating hormone; and E_2, estradiol.

Several levels of feedback to the hypothalamus exist and are known as the long, short, and ultrashort feedback loops. The **long feedback loop** is composed of endocrine input from circulating hormones, just as is the feedback of androgens and estrogens onto steroid receptors in the hypothalamus (2,3). Similarly, pituitary hormones may feed back to the hypothalamus and serve important regulatory functions in **short-loop feedback.** Finally, hypothalamic secretions may directly feed back to the hypothalamus itself in an **ultrashort feedback loop.**

The major secretory products of the hypothalamus are the pituitary-releasing factors (Fig. 7-3):

1. ***Gonadotropin-releasing hormone* (*GnRH*), which controls the secretion of *luteinizing hormone* (*LH*) and *follicle-stimulating hormone* (*FSH*)**
2. ***Corticotropin-releasing hormone* (*CRH*), which controls the release of *adrenocorticotrophic hormone* (*ACTH*)**
3. ***Growth hormone–releasing hormone* (*GHRH*), which regulates the release of *growth hormone* (*GH*)**
4. ***Thyrotropin-releasing hormone* (*TRH*), which regulates the secretion of *thyroid-stimulating hormone* (*TSH*)**

The hypothalamus is the source of all neurohypophyseal hormone production. The neural posterior pituitary can be viewed as a direct extension of the hypothalamus connected by the finger-like infundibular stalk. The capillaries in the median eminence differ from those in other regions of the brain. Unlike the usual tight junctions that exist between adjacent capillary endothelial lining cells, the capillaries in this region are fenestrated in the same manner as capillaries outside the CNS. As a result, there is no blood–brain barrier in the median eminence.

Pituitary

The pituitary is divided into three regions or lobes: *anterior*, *intermediate*, and *posterior*. The *anterior pituitary* (*adenohypophysis*) is quite different structurally from the *posterior neural pituitary* (*neurohypophysis*), which is a direct physical extension of the hypothalamus. The adenohypophysis is derived embryologically from epidermal ectoderm from an infolding of Rathke pouch. Therefore, it is not composed of neural

tissue, as is the posterior pituitary, and does not have direct neural connections to the hypothalamus. Instead, a unique anatomic relationship exists that combines elements of neural production and endocrine secretion.

The adenohypophysis itself has no direct arterial blood supply. Its major source of blood flow is also its source of hypothalamic input—the portal vessels. Blood flow in these portal vessels is primarily from the hypothalamus to the pituitary. Blood is supplied to the posterior pituitary via the superior, middle, and inferior hypophyseal arteries. In contrast, the anterior pituitary has no direct arterial blood supply. Instead, it receives blood via a rich capillary plexus of the portal vessels that originates in the median eminence of the hypothalamus and descends along the pituitary stalk. This pattern is not absolute, however, and retrograde blood flow has occurred (4). This blood flow, combined with the location of the median eminence outside the blood–brain barrier, permits bidirectional feedback control between the two structures.

The specific secretory cells of the anterior pituitary are classified based on their hematoxylin- and eosin-staining patterns. Acidophilic-staining cells primarily secrete GH and prolactin and, to a variable degree, ACTH (5). The gonadotropins are secreted by basophilic cells, and TSH is secreted by the neutral-staining chromophobes.

REPRODUCTIVE HORMONES

Hypothalamus

Gonadotropin-Releasing Hormone

***GnRH* (*also called luteinizing hormone–releasing hormone, or LHRH*) is the controlling factor for gonadotropin secretion** (6). It is a decapeptide produced by neurons with cell bodies primarily in the arcuate nucleus of the hypothalamus (7–9) **(Fig. 7-4)**. Embryologically, these neurons originate in the olfactory pit and migrate to their adult locations (10). These GnRH-secreting neurons project axons that terminate on the portal vessels at the median eminence where GnRH is secreted for delivery to the anterior pituitary. Less clear in function are multiple other secondary projections of GnRH neurons to locations within the CNS.

The gene that encodes GnRH produces a 92-amino-acid precursor protein, which contains the GnRH decapeptide and a 56 amino acid peptide known as GnRH-associated peptide (GAP). The GAP is a potent inhibitor of prolactin secretion and a stimulator of gonadotropin release.

Pulsatile Secretion

[2] GnRH is unique among releasing hormones in that it simultaneously regulates the secretion of two hormones—FSH and LH. It is unique among the body's

hormones because it must be secreted in a pulsatile fashion to be effective, and the pulsatile release of GnRH influences the release of the two gonadotropins (11–13). Using animals that had undergone electrical destruction of the arcuate nucleus and had no detectable levels of gonadotropins, a series of experiments were performed with varying dosages and intervals of GnRH infusion (13,14). Continual infusions did not result in gonadotropin secretion, whereas a pulsatile pattern led to physiologic secretion patterns and follicular growth. Continual exposure of the pituitary gonadotroph to GnRH results in a phenomenon called *downregulation*, through which the number of gonadotroph cell surface GnRH receptors is decreased (15). Similarly, intermittent exposure to GnRH will "upregulate" or "autoprime" the gonadotroph to increase its number of GnRH receptors (16). This allows the cell to have a greater response to subsequent GnRH exposure. Similar to the intrinsic electrical pacemaker cells of the heart, this action most likely represents an intrinsic property of the GnRH-secreting neuron, although it is subject to modulation by various neuronal and hormonal inputs to the hypothalamus.

The continual pulsatile secretion of GnRH is necessary because GnRH has an extremely short half-life (only 2 to 4 minutes) as a result of rapid proteolytic cleavage. The pulsatile secretion of GnRH varies in frequency and amplitude throughout the menstrual cycle and is tightly regulated **(Fig. 7-5)** (17,18).

The **follicular phase** is characterized by frequent, small-amplitude pulses of GnRH secretion. In the late follicular phase, there is an increase in frequency and amplitude of pulses. During **the luteal phase**, however, there is a progressive lengthening of the interval between pulses. The amplitude in the luteal phase is higher than that in the follicular phase, but it declines progressively over the 2 weeks. This variation in pulse frequency allows for variation in LH and FSH throughout the menstrual cycle. For example, decreasing the pulse frequency of GnRH decreases LH secretion but increases FSH, an important aspect of enhancing FSH availability in the late luteal phase. The pulse frequency is not the sole determinant of pituitary response; additional hormonal influences, such as those exerted by ovarian peptides and sex steroids, can modulate the GnRH effect.



FIGURE 7-4 Gonadotropin-releasing hormone is a decapeptide.

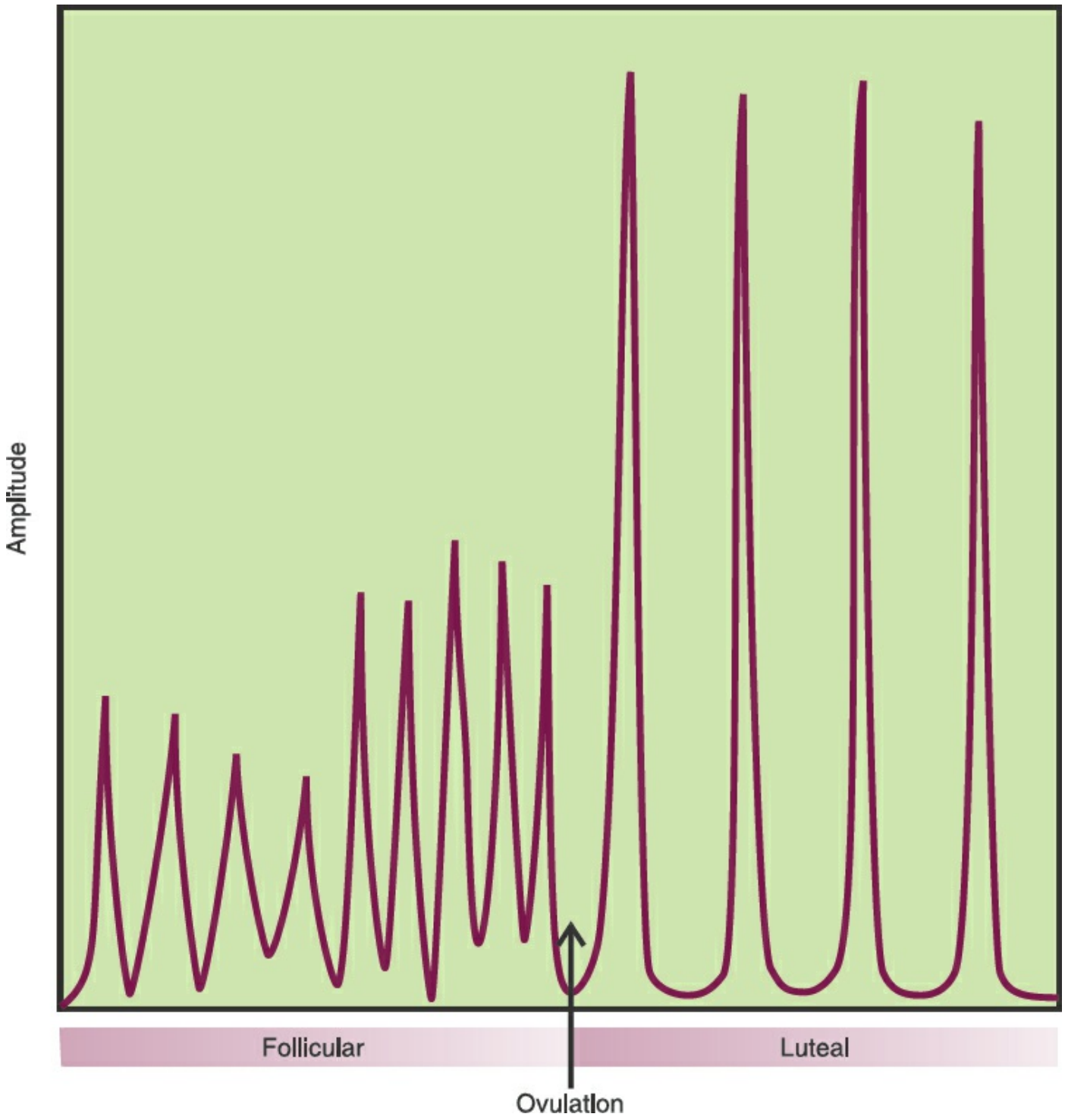


FIGURE 7-5 The pulsatile secretion of gonadotropin-releasing hormone in the follicular and luteal phases of the cycle.

Although GnRH is primarily involved in endocrine regulation of gonadotropin secretion from the pituitary, it is apparent that this molecule has autocrine and paracrine functions throughout the body. The decapeptide is found in neural and nonneural tissues; receptors are present in many extrapituitary structures, including the ovary and placenta. Data suggest that GnRH may be involved in regulating human

chorionic gonadotropin (hCG) secretion and implantation, and in decreasing cell proliferation and mediating apoptosis in tumor cells (19). The role of GnRH in the extrapituitary sites remains to be fully elucidated.

Gonadotropin-Releasing Hormone Agonists

Mechanism of Action

Used clinically, GnRH agonists are modifications of the native molecule to either increase receptor affinity or decrease degradation (20). Their use leads to a persistent activation of GnRH receptors, as if continuous GnRH exposure existed. As would be predicted by the constant GnRH infusion experiments, this leads to suppression of gonadotropin secretion. An initial release of gonadotropins is followed by a profound suppression of secretion. The initial release of gonadotropins represents the secretion of pituitary stores in response to receptor binding and activation. With continued activation of the gonadotroph GnRH receptor, however, there is a downregulation effect and a decrease in the concentration of GnRH receptors. As a result, gonadotropin secretion decreases and sex steroid production falls to castrate levels (21).

Additional modification of the GnRH molecule results in an analogue that has no intrinsic activity but competes with GnRH for the same receptor site (22). **These GnRH antagonists produce a competitive blockade of GnRH receptors, preventing stimulation by endogenous GnRH and causing an immediate fall in gonadotropin and sex steroid secretion** (23). The clinical effect is observed within 24 to 72 hours. Moreover, antagonists may not function solely as competitive inhibitors; evidence suggests they may also produce downregulation of GnRH receptors, further contributing to the loss of gonadotropin activity (24).

Structure—Agonists and Antagonists

As a peptide hormone, GnRH is degraded by enzymatic cleavage of bonds between its amino acids. Pharmacologic alterations of the structure of GnRH led to the creation of agonists and antagonists **(Fig. 7-4)**. The primary sites of enzymatic cleavage are between amino acids 5 and 6, 6 and 7, and 9 and 10. Substitution of the position-6 amino acid glycine with large bulky amino acid analogues makes degradation more difficult and creates a form of GnRH with a relatively long half-life. Substitution at the carboxyl terminus produces a form of GnRH with increased receptor affinity. The resulting high affinity and slow degradation produces a molecule that mimics continuous exposure to native GnRH (20). Thus, as with constant GnRH exposure, downregulation occurs. GnRH agonists are widely used to treat disorders that are dependent on ovarian hormones (21). They are used to control ovulation induction cycles and treat precocious puberty, ovarian hyperandrogenism, leiomyomas, endometriosis, and hormonally dependent cancers. The development of GnRH antagonists proved more difficult because a molecule was needed that maintained the binding and degradation resistance

of agonists but failed to activate the receptor. Early attempts involved modification of amino acids 1 and 2, as well as those previously utilized for agonists. Commercial antagonists have structural modifications at amino acids 1, 2, 3, 6, 8, and 10. The treatment spectrum is expected to be similar to that of GnRH agonists, but with a more rapid onset of action.

Nonpeptide, small molecule structures with high affinity for the GnRH receptor were developed (25). These compounds demonstrated the ability to suppress the reproductive axis in a dose-related manner via oral administration, unlike the parenteral approach required with traditional peptide analogues (26). Investigation may elucidate an expanded therapeutic role for these antagonists.

Endogenous Opioids and Effects on GnRH

The endogenous opioids are three related families of naturally occurring substances produced in the CNS that represent the natural ligands for the opioid receptors (27–29). **There are three major classes of endogenous opioids**, each derived from precursor molecules:

1. ***Endorphins*** are named for their endogenous morphine-like activity. These substances are produced in the hypothalamus from the precursor proopiomelanocortin (POMC) and have diverse activities, including regulation of temperature, appetite, mood, and behavior (30).
2. ***Enkephalins*** are the most widely distributed opioid peptides in the brain, and they function primarily in regulation of the autonomic nervous system. Proenkephalin A is the precursor for the two enkephalins of primary importance: methionine–enkephalin and leucine–enkephalin.
3. ***Dynorphins*** are endogenous opioids produced from the precursor proenkephalin B that serve a function similar to that of the endorphins, producing behavioral effects and exhibiting a high analgesic potency.

The endogenous opioids play a significant role in the regulation of hypothalamic–pituitary function. Endorphins appear to inhibit GnRH release within the hypothalamus, resulting in inhibition of gonadotropin secretion (31). Ovarian sex steroids can increase the secretion of central endorphins, further depressing gonadotropin levels (32).

Endorphin levels vary significantly throughout the menstrual cycle, with peak levels in the luteal phase and a nadir during menses (33). This inherent variability, although helping to regulate gonadotropin levels, may contribute to cycle-specific symptoms experienced by ovulatory women. For example, the dysphoria experienced by some women in the premenstrual phase of the cycle may be related to a withdrawal of endogenous opiates (34). This theory is bolstered by the finding that inhibition of opiate

withdrawal by naltrexone alleviates many premenstrual symptoms (35).

Pituitary Hormone Secretion

Anterior Pituitary

The anterior pituitary is responsible for the secretion of the major hormone-releasing factors—FSH, LH, TSH, and ACTH—and GH and prolactin. Each hormone is released by a specific pituitary cell type.

Gonadotropins

The gonadotropins FSH and LH are produced by the anterior pituitary gonadotroph cells and are responsible for ovarian follicular stimulation. Structurally, there is great similarity between FSH and LH (Fig. 7-6). They are glycoproteins that share identical α subunits and differ only in the structure of their β subunits, which confer receptor specificity (36,37). The synthesis of the β subunits is the rate-regulating step in gonadotropin biosynthesis (38). TSH and placental hCG share identical α subunits with the gonadotropins. There are several forms of each gonadotropin, which differ in carbohydrate content as a result of posttranslation modification. The degree of modification varies with steroid levels and is an important regulator of gonadotropin bioactivity.

Prolactin

***Prolactin,* a 198-amino-acid polypeptide secreted by the anterior pituitary lactotroph, is the primary trophic factor responsible for the synthesis of milk by the breast** (39). Several forms of this hormone, which are named according to their size and bioactivity, are normally secreted (40). Prolactin gene transcription is principally stimulated by estrogen; other hormones promoting transcription are TRH and a variety of growth factors.

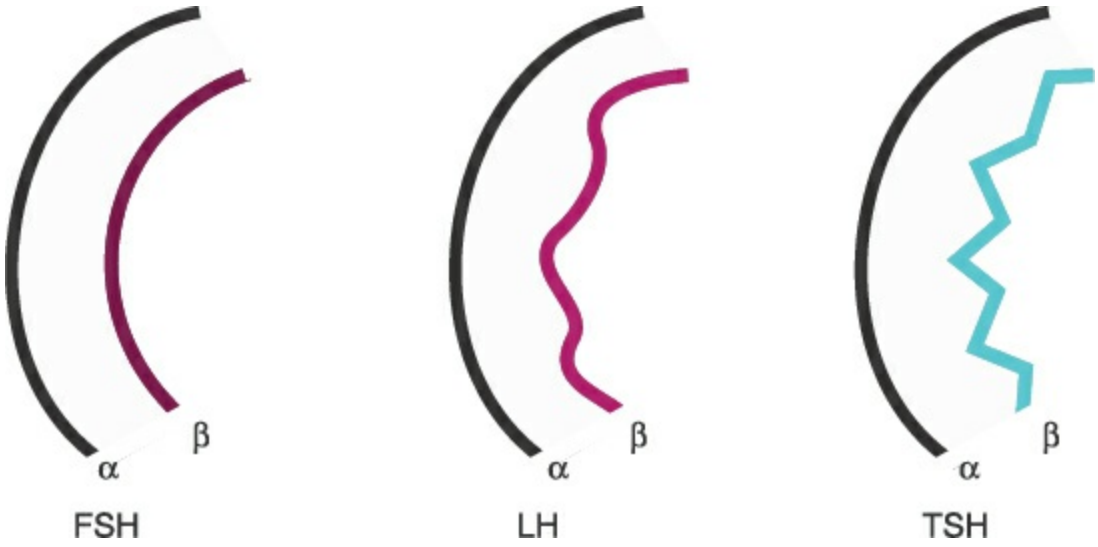


FIGURE 7-6 The structural similarity between follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH). The α subunits are identical, and the β subunits differ.

Prolactin secretion is under tonic inhibitory control by the hypothalamic secretion of dopamine (41). Therefore, disease states characterized by decreased dopamine secretion or any condition that interrupts transport of dopamine down the infundibular stalk to the pituitary gland will result in increased synthesis of prolactin. In this respect, prolactin is unique in comparison with all other pituitary hormones: It is predominantly under tonic inhibition, and release of control produces an increase in secretion. **Clinically, increased prolactin levels are associated with amenorrhea and galactorrhea, and hyperprolactinemia should be suspected in any individual with symptoms of either of these conditions.**

Although prolactin appears to be primarily under inhibitory control, many stimuli can elicit its release, including breast manipulation, drugs, stress, exercise, and certain foods. Hormones that may stimulate prolactin release include TRH, vasopressin, γ-aminobutyric acid (GABA), dopamine, β-endorphin, vasoactive intestinal peptide (VIP), epidermal growth factor (EGF), angiotensin II, estrogens, and possibly GnRH (42–46). The relative contributions of these substances under normal conditions remain to be determined.

Thyroid-Stimulating Hormone, Adrenocorticotropic Hormone, and Growth Hormone

The other hormones produced by the anterior pituitary are TSH, ACTH, and GH. TSH is secreted by the pituitary thyrotrophs in response to TRH. As with GnRH, TRH is synthesized primarily in the arcuate nucleus of the hypothalamus and is secreted into the portal circulation for transport to the pituitary. In addition to stimulating TSH release, TRH is a major stimulus for the release of prolactin. TSH stimulates release of T_3 and T_4 from the thyroid gland, which in turn has a negative feedback effect on pituitary TSH secretion. Abnormalities of thyroid secretion (hyper- and hypothyroidism) are frequently associated with ovulatory dysfunction as a result of diverse actions on the hypothalamic–pituitary–ovarian axis (47).

Adrenocorticotrophic hormone is secreted by the anterior pituitary in response to another hypothalamic-releasing factor, CRH, and stimulates the release of adrenal glucocorticoids. Unlike the other anterior pituitary products, ACTH secretion has a diurnal variation with an early morning peak and a late evening nadir. As with the other pituitary hormones, ACTH secretion is negatively regulated by feedback from its primary end product, which in this case is cortisol.

The anterior pituitary hormone that is secreted in the greatest absolute amount is GH. It is secreted in response to the hypothalamic-releasing factor, GHRH, and by thyroid hormone and glucocorticoids. This hormone is secreted in a pulsatile fashion but with peak release occurring during sleep. In addition to its vital role in the stimulation

of linear growth, GH plays a diverse role in physiologic homeostasis. The hormone plays a role in bone mitogenesis, CNS function (improved memory, cognition, and mood), body composition, breast development, and cardiovascular function. It also affects insulin regulation and acts anabolically. GH appears to have a role in the regulation of ovarian function, although the degree to which it serves this role in normal physiology is unclear (48).

Posterior Pituitary

Structure and Function

The posterior pituitary (neurohypophysis) is composed exclusively of neural tissue and is a direct extension of the hypothalamus. It lies directly adjacent to the adenohypophysis but is embryologically distinct, derived from an invagination of neuroectodermal tissue in the third ventricle. Axons in the posterior pituitary originate from neurons with cell bodies in two distinct regions of the hypothalamus, the supraoptic and paraventricular nuclei, named for their anatomic relationship to the optic chiasm and the third ventricle. Together these two nuclei compose the hypothalamic magnocellular system. These neurons can secrete their synthetic products directly from axonal boutons into the general circulation to act as hormones. This is the mechanism of secretion of the hormones of the posterior pituitary, oxytocin and arginine vasopressin (AVP). Although this is the primary mode of release for these hormones, numerous other secondary pathways were identified, including secretion into the portal circulation, intrahypothalamic secretion, and secretion into other regions of the CNS (49).

In addition to the established functions of oxytocin and vasopressin, several other diverse roles were suggested in animal models. These functions include modulation of sexual activity and appetite, learning and memory consolidation, temperature regulation, and regulation of maternal behaviors (50). In the human, these neuropeptides were linked to social attachment (51–53). Receptor variants for these two molecules were linked to the spectrum of autistic disorders, suggesting that proper function of these two neuropeptides with their receptors is required for positive group interactive behavior. This relationship is strengthened by a strong association between altruistic behavior and the length of the AVP-1a receptor promoter region (52,54). Complex human behaviors may be partially governed by a relatively simple neuropeptide system. Continuing investigation should help elucidate this physiology and potential therapeutic interventions.

Oxytocin

Oxytocin is a 9-amino-acid peptide primarily produced by the paraventricular nucleus of the hypothalamus **(Fig. 7-7)**. The primary function of this hormone in humans is the stimulation of two specific types of muscular contractions **(Fig. 7-8)**. The first type, uterine muscular contraction, occurs during parturition. The second type of

muscular contraction regulated by oxytocin is breast lactiferous duct myoepithelial contractions, which occur during the milk letdown reflex. Oxytocin release may be stimulated by suckling, triggered by a signal from nipple stimulation transmitted via thoracic nerves to the spinal cord and then to the hypothalamus, where oxytocin is released in an episodic fashion (48). Oxytocin release may be triggered by olfactory, auditory, and visual clues, and may play a role in the conditioned reflex in nursing animals. Stimulation of the cervix and vagina can cause significant release of oxytocin, which may trigger reflex ovulation (the Ferguson reflex) in some species.

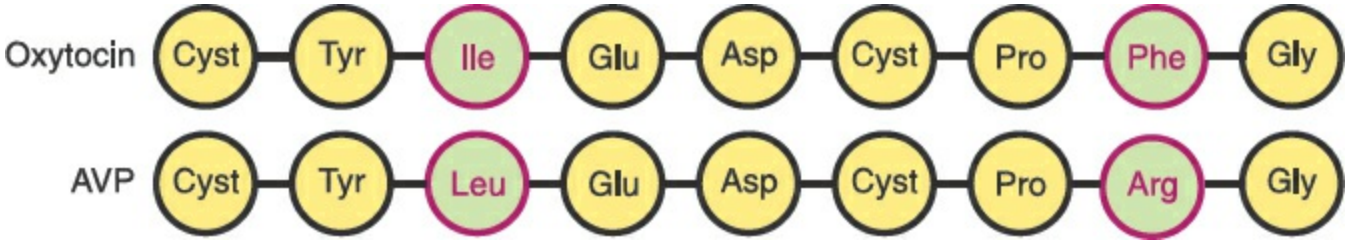


FIGURE 7-7 Oxytocin and arginine vasopressin (AVP) are 9-amino-acid peptides produced by the hypothalamus. They differ in only two amino acids.

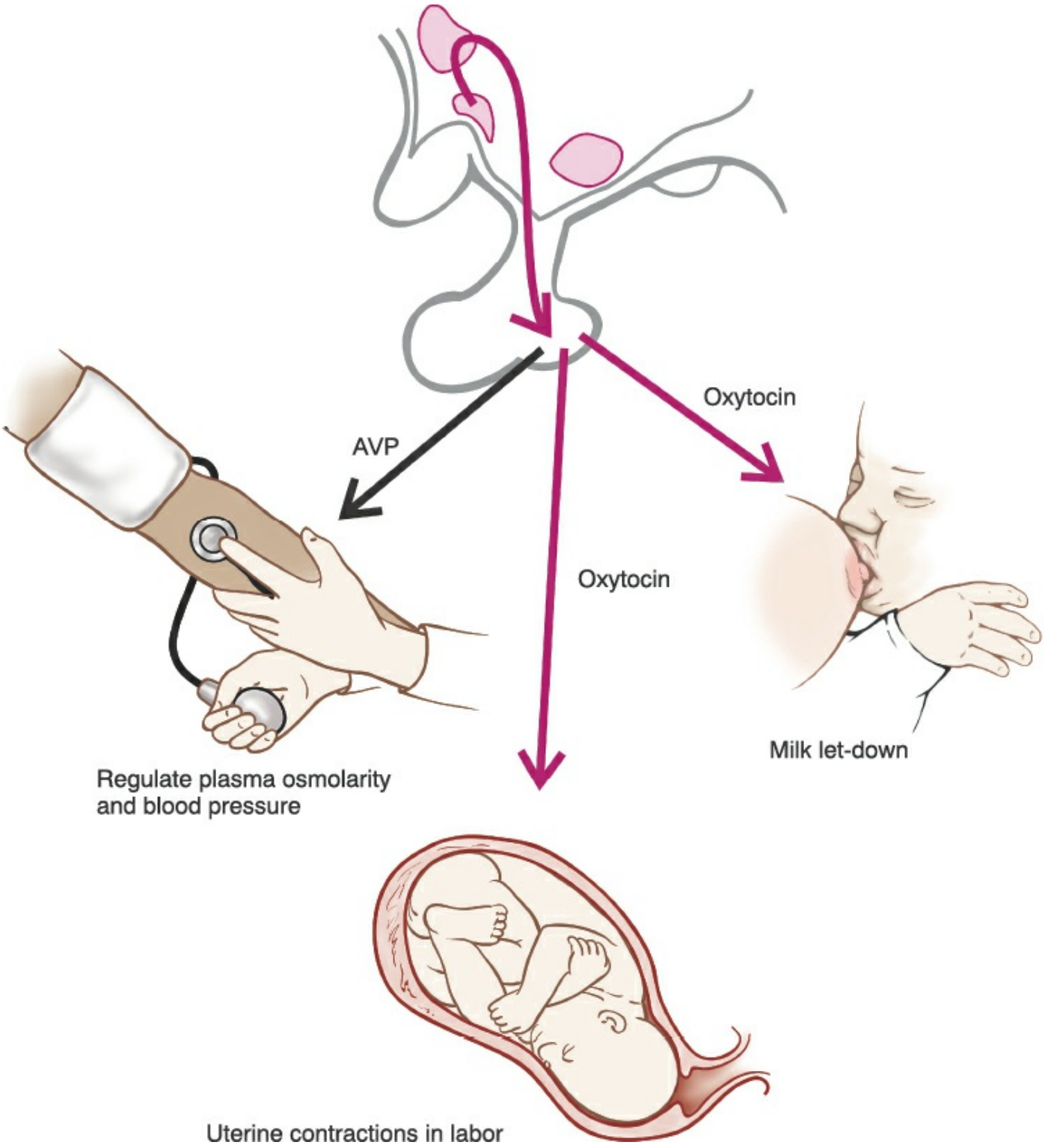


FIGURE 7-8 Oxytocin stimulates muscular contractions of the uterus during parturition and the breast lactiferous duct during the milk letdown reflex. Arginine vasopressin (AVP) regulates circulating blood volume, pressure, and osmolality.

Arginine Vasopressin

Also known as antidiuretic hormone (ADH), AVP is the second major secretory product of the posterior pituitary (Fig. 7-7). It is synthesized primarily by neurons

with cell bodies in the supraoptic nuclei (Fig. 7-8). Its major function is the regulation of circulating blood volume, pressure, and osmolality (55). Specific receptors throughout the body can trigger the release of AVP. Osmoreceptors located in the hypothalamus sense changes in blood osmolality from a mean of 285 mOsm/kg. Baroreceptors sense changes in blood pressure caused by alterations in blood volume and are peripherally located in the walls of the left atrium, carotid sinus, and aortic arch (56). These receptors can respond to changes in blood volume of more than 10%. In response to decreases in blood pressure or volume, AVP is released and causes arteriolar vasoconstriction and renal free–water conservation. This leads to a decrease in blood osmolality and an increase in blood pressure. Activation of the renal renin–angiotensin system can also activate AVP release.

MENSTRUAL CYCLE PHYSIOLOGY

[3] In the normal menstrual cycle, orderly cyclic hormone production and parallel proliferation of the uterine lining prepare for implantation of the embryo. Disorders of the menstrual cycle and, likewise, disorders of menstrual physiology, may lead to various pathologic states, including infertility, recurrent miscarriage, and malignancy.

Normal Menstrual Cycle

The normal human menstrual cycle can be divided into two segments: the ovarian cycle and the uterine cycle, based on the organ under examination. The ovarian cycle may be further divided into follicular and luteal phases, whereas the uterine cycle is divided into corresponding proliferative and secretory phases (Fig. 7-9). The phases of the ovarian cycle are characterized as follows:

1. **Follicular phase—hormonal feedback promotes the orderly development of a single dominant follicle, which should be mature at midcycle and prepared for ovulation. The average length of the human follicular phase ranges from 10 to 14 days, and variability in this length is responsible for most variations in total cycle length.**
2. **Luteal phase—the time from ovulation to the onset of menses has an average length of 14 days.**

A normal menstrual cycle lasts from 21 to 35 days, with 2 to 6 days of flow and an average blood loss of 20 to 60 mL. However, studies of large numbers of women with normal menstrual cycles showed that approximately two-thirds of adult women have cycles lasting 21 to 35 days (57). The extremes of reproductive life

(after menarche and perimenopause) are characterized by a higher percentage of anovulatory or irregularly timed cycles (58,59).

Hormonal Variations

The relative pattern of ovarian, uterine, and hormonal variation along the normal menstrual cycle is shown in Figure 7-9.

1. At the beginning of each monthly menstrual cycle, levels of gonadal steroids are low and have been decreasing since the end of the luteal phase of the previous cycle.
2. With the demise of the corpus luteum, FSH levels begin to rise, and a cohort of growing follicles is recruited. These follicles each secrete increasing levels of estrogen as they grow in the follicular phase. The increase in estrogen is the stimulus for uterine endometrial proliferation.
3. Rising estrogen levels provide negative feedback on pituitary FSH secretion, which begins to wane by the midpoint of the follicular phase. In addition, the growing follicles produce inhibin B, which suppresses FSH secretion by the pituitary. Conversely, LH initially decreases in response to rising estradiol levels, but late in the follicular phase the LH level is increased dramatically (biphasic response).
4. At the end of the follicular phase (just before ovulation), FSH-induced LH receptors are present on granulosa cells and, with LH stimulation, modulate the secretion of progesterone. Progesterone secretion is responsible for the FSH midcycle surge.
5. After a sufficient degree of estrogenic stimulation, the pituitary LH surge is triggered, which is the proximate cause of ovulation that occurs 24 to 36 hours later. Ovulation heralds the transition to the luteal–secretory phase.
6. The estrogen level decreases through the early luteal phase from just before ovulation until the midluteal phase, when it begins to rise again as a result of corpus luteum secretion. Similarly, inhibin A is secreted by the corpus luteum.
7. Progesterone levels rise precipitously after ovulation and can be used as a presumptive sign that ovulation has occurred.
8. Progesterone, estrogen, and inhibin A act centrally to suppress gonadotropin secretion and new follicular growth. These hormones remain elevated through the lifespan of the corpus luteum and wane with its demise, thereby setting the stage for the next cycle.

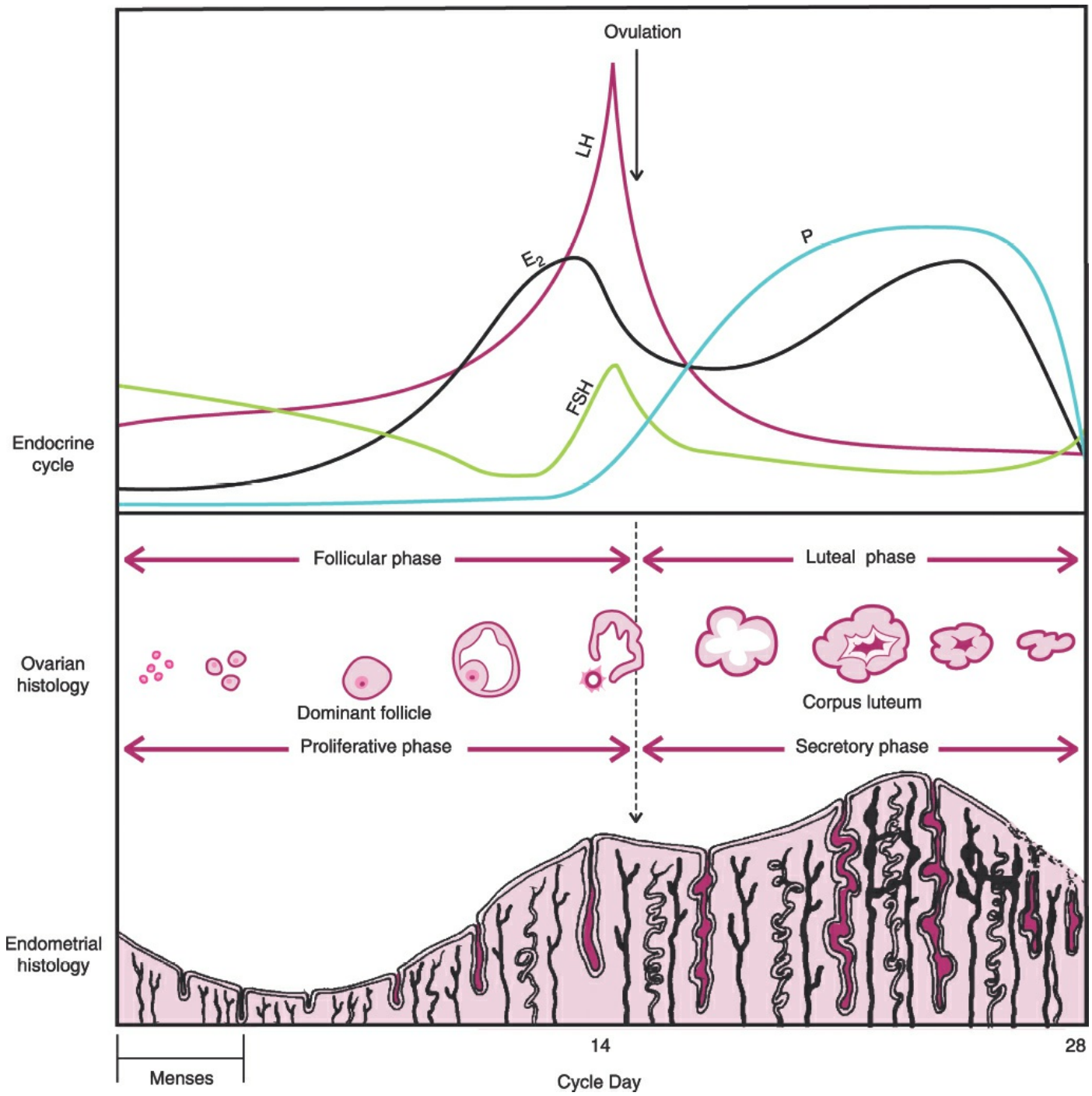


FIGURE 7-9 The menstrual cycle. The ***top panel*** shows the cyclic changes of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), and progesterone (P) relative to the time of ovulation. The ***bottom panel*** correlates the ovarian cycle in the follicular and luteal phases and the endometrial cycle in the proliferative and secretory phases.

Uterus

Cyclic Changes of the Endometrium

In 1950, Noyes, Hertig, and Rock described the cyclic histologic changes in the adult

human endometrium **(Fig. 7-10)** (60). These changes proceed in an orderly fashion in response to cyclic hormonal production by the ovaries **(Fig. 7-9)**. Histologic cycling of the endometrium can best be viewed in two parts: the endometrial glands and the surrounding stroma. **The superficial two-thirds of the endometrium is the zone that proliferates and is ultimately shed with each cycle if pregnancy does not occur. This cycling portion of the endometrium is known as the *decidua functionalis* and is composed of a deeply situated intermediate zone (stratum spongiosum) and a superficial compact zone (stratum compactum). The *decidua basalis* is the deepest region of the endometrium. It does not undergo significant monthly proliferation but, instead, is the source of endometrial regeneration after each menses** (61).

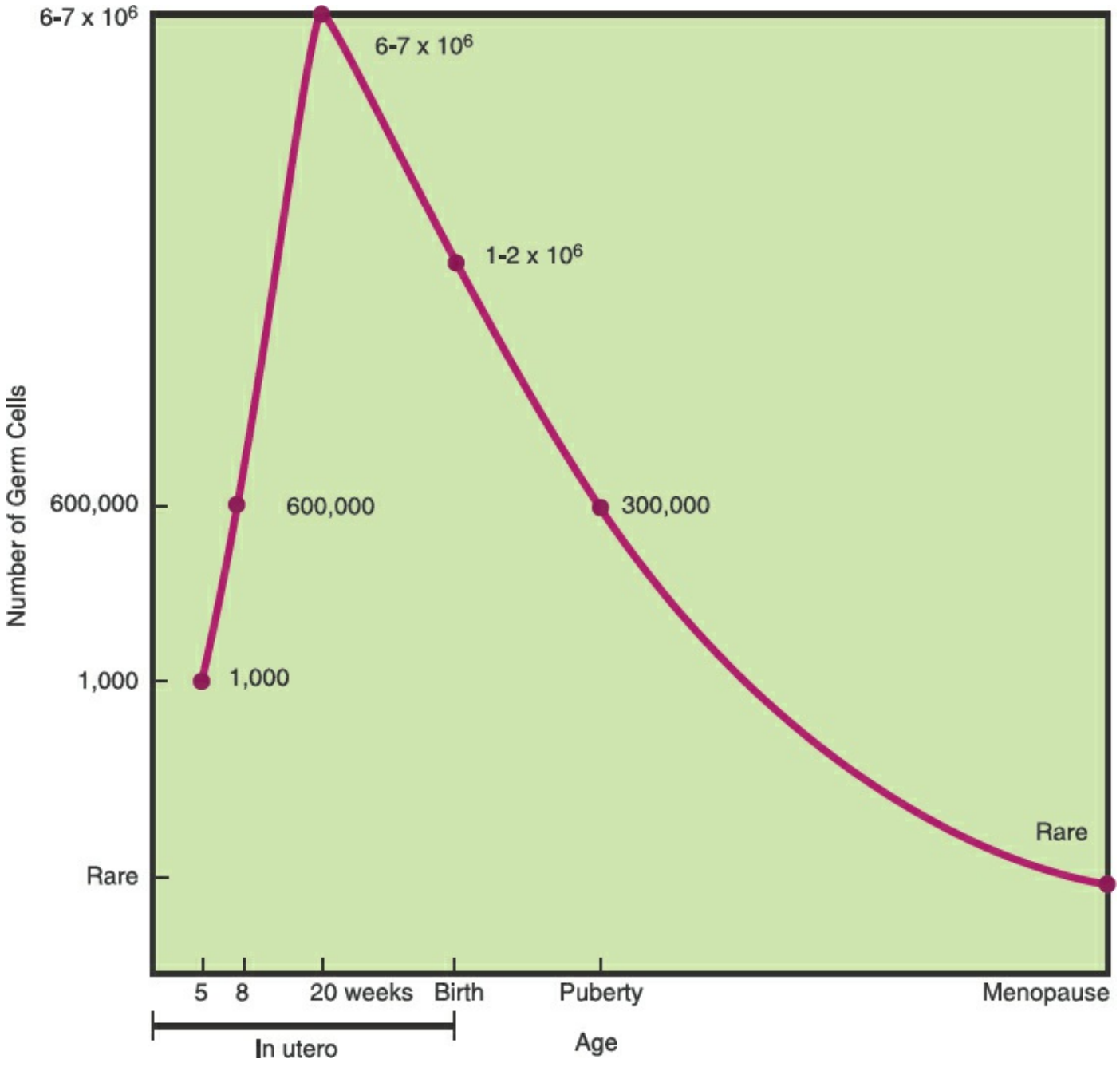


FIGURE 7-10 The number of oocytes in the ovary before and after birth and through menopause.

The existence of endometrial stem cells was assumed but difficult to document. Researchers found a small population of human epithelial and stromal cells that possess clonogenicity, suggesting that they represent the putative endometrial stem cells (62). Further evidence of the existence of such cells, and their source, was provided by another study that showed endometrial glandular epithelial cells, obtained from endometrial biopsies of women undergoing bone marrow transplants, express the HLA type of the donor bone marrow (63). This finding suggests that endometrial stem cells exist, reside in bone marrow, and migrate to the basalis of the endometrium. Furthermore, the timing of the appearance of these cells following the transplant was as long as several years. This experiment has been duplicated using autologous bone marrow–derived stem cells and placing them in the spiral arterioles of patients with intrauterine synechiae (64). Animal models suggest this approach may be of value in regenerating damaged or absent endometrium (65,66). It is likely that this treatment will prove to be of clinical importance in patients with difficult to treat Asherman syndrome.

Proliferative Phase

[4] By convention, the first day of vaginal bleeding is called day 1 of the menstrual cycle. After menses, the decidua basalis is composed of primordial glands and dense scant stroma in its location adjacent to the myometrium. The proliferative phase is characterized by progressive mitotic growth of the decidua functionalis in preparation for implantation of the embryo in response to rising circulating levels of estrogen (67). At the beginning of the proliferative phase, the endometrium is relatively thin (1 to 2 mm). The predominant change seen during this time is evolution of the initially straight, narrow, and short endometrial glands into longer, tortuous structures (68). Histologically, these proliferating glands have multiple mitotic cells, and their organization changes from a low columnar pattern in the early proliferative period to a pseudostratified pattern before ovulation. Throughout this time, the stroma is a dense compact layer, and vascular structures are infrequently seen.

Secretory Phase

In the typical 28-day cycle, ovulation occurs on cycle day 14. Within 48 to 72 hours following ovulation, the onset of progesterone secretion produces a shift in histologic appearance of the endometrium to the secretory phase, so named for the clear presence of eosinophilic protein-rich secretory products in the glandular lumen. In contrast to the proliferative phase, the secretory phase of the menstrual cycle is characterized by the cellular effects of progesterone in addition to estrogen. In general, progesterone's effects are antagonistic to those of estrogen,

and there is a progressive decrease in the endometrial cell's estrogen receptor concentration. As a result, during the latter half of the cycle, estrogen-induced DNA synthesis and cellular mitosis are antagonized (67).

During the secretory phase, the endometrial glands form characteristic periodic acid–Schiff positive–staining, glycogen-containing vacuoles. These vacuoles initially appear subnuclearly and progress toward the glandular lumen (Fig. 7-10) (60). The nuclei can be seen in the midportion of the cells and ultimately undergo apocrine secretion into the glandular lumen, often by cycle day 19 or 20. At postovulatory day 6 or 7, secretory activity of the glands is generally maximal, and the endometrium is optimally prepared for implantation of the blastocyst.

The stroma of the secretory phase remains unchanged histologically until approximately the 7th postovulatory day, when there is a progressive increase in edema. Coincident with maximal stromal edema in the late secretory phase, the spiral arteries become clearly visible and progressively lengthen and coil during the remainder of the secretory phase. By around day 24, an eosinophilic-staining pattern, known as *cuffing*, is visible in the perivascular stroma. Eosinophilia progresses to form islands in the stroma followed by areas of confluence. This staining pattern of the edematous stroma is termed *pseudodecidual* because of its similarity to the pattern that occurs in pregnancy. Approximately 2 days before menses, there is a dramatic increase in the number of polymorphonuclear lymphocytes that migrate from the vascular system. This leukocytic infiltration heralds the collapse of the endometrial stroma and the onset of the menstrual flow.

Menses

In the absence of implantation, glandular secretion ceases and an irregular breakdown of the *decidua functionalis* occurs. The resultant shedding of this layer of the endometrium is termed *menses*. The destruction of the corpus luteum and its production of estrogen and progesterone is the presumed cause of the shedding. With withdrawal of sex steroids, there is a profound spiral artery vascular spasm that ultimately leads to endometrial ischemia. Simultaneously, there is a breakdown of lysosomes and a release of proteolytic enzymes, which further promote local tissue destruction. This layer of endometrium is shed, leaving the decidua basalis as the source of subsequent endometrial growth. Prostaglandins are produced throughout the menstrual cycle and are at their highest concentration during menses (66). Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) is a potent vasoconstrictor, causing further arteriolar vasospasm and endometrial ischemia. $PGF_2\alpha$ produces myometrial contractions that decrease local uterine wall blood flow and may serve to expel physically the sloughing endometrial tissue from the uterus.

Dating the Endometrium

The changes seen in secretory endometrium relative to the LH surge were thought to allow the assessment of the "normalcy" of endometrial development. Since 1950, it was felt that by knowing when a patient ovulated, it was possible to obtain a sample of endometrium by endometrial biopsy and determine whether the state of the endometrium corresponds to the appropriate time of the cycle. Traditional thinking held that any discrepancy of more than 2 days between chronologic and histologic date indicated a pathologic condition termed *luteal phase defect*; this abnormality was linked to infertility (via implantation failure) and early pregnancy loss (69).

Evidence suggests a lack of utility for the endometrial biopsy as a diagnostic test for either infertility or early pregnancy loss (59). In a randomized, observational study of regularly cycling, fertile women, it was found that endometrial dating by hematoxylin and eosin staining is far less accurate and precise than originally claimed and does not provide a valid method for the diagnosis of luteal phase defect (70). Furthermore, a large prospective, multicenter trial sponsored by the National Institutes of Health showed that histologic dating of the endometrium does not discriminate between fertile and infertile women (71). Thus, after half a century of using this test in the evaluation of the subfertile couple, it became clear that the traditional endometrial biopsy has no role in the routine evaluation of infertility or early pregnancy loss.

Given the lack of histologic efficacy in evaluating the receptivity of the endometrium, investigation turned to the use of molecular and genetic markers. Cyclin E and p27 were found to be credible markers to discern endometrial receptivity (72,73). Microarray technology has been utilized to link gene expression to functionally receptive endometrium, with promising results (74,75).

Ovarian Follicular Development

The number of oocytes peaks in the fetus at 6 to 7 million by 20 weeks of gestation **(Fig. 7-10)** (76). Simultaneously (and peaking at the 5th month of gestation), atresia of the oogonia occurs, rapidly followed by follicular atresia. At birth, only 1 to 2 million oocytes remain in the ovaries, and **at puberty, only 300,000 of the original 6 to 7 million oocytes are available for ovulation** (76,77). **Of these, only 400 to 500 will ultimately be released during ovulation.** By the time of menopause, the ovary will be composed primarily of dense stromal tissue with only rare interspersed oocytes remaining.

A central dogma of reproductive biology is that in postnatal mammalian females there is no capacity for oocyte production. Because oocytes enter the diplotene resting stage of meiosis in the fetus and persist in this stage until ovulation, much of the DNA, proteins, and messenger RNA (mRNA) necessary for development of the preimplantation embryo is synthesized by this stage. At the diplotene stage, a single

layer of 8 to 10 granulosa cells surrounds the oogonia to form the primordial follicle. The oogonia that fail to become properly surrounded by granulosa cells undergo atresia (78). The remainder proceeds with follicular development. Thus, most oocytes are lost during fetal development, and the remaining follicles are steadily "used up" throughout the intervening years until menopause.

Evidence has begun to challenge this theory. Studies in the mouse showed that production of oocytes and corresponding folliculogenesis can occur well into adult life (79). The reservoir of germline stem cells responsible for this oocyte development appears to reside in the bone marrow (80). While stem cells have been found in the human adult ovary (81,82), it is not clear if these cells are true ovarian germline stem cells and if they play a physiologic role within the ovary regarding follicular development (82,83).

Meiotic Arrest of Oocyte and Resumption

Meiosis **(the germ cell process of reduction division) is divided into four phases: prophase, metaphase, anaphase, and telophase. The prophase of meiosis I is further divided into five stages: *leptotene, zygotene, pachytene, diplotene,* and *diakinesis.***

Oogonia differ from spermatogonia in that only one final daughter cell (oocyte) forms from each precursor cell, with the excess genetic material discarded in two polar bodies. When the developing oogonia begin to enter meiotic prophase I, they are known as primary oocytes (84). This process begins at roughly 8 weeks of gestation. Only those oogonia that enter meiosis will survive the wave of atresia that sweeps the fetal ovary before birth. The oocytes arrested in prophase (in the late diplotene or "dictyate" stage) will remain thus until the time of ovulation, when the process of meiosis resumes. The mechanism for this mitotic stasis is believed to be an oocyte maturation inhibitor (OMI) produced by granulosa cells (85). Granulosa-derived cAMP seems to be implicated in inhibiting germinal vesicle breakdown and meiosis resumption (86). This inhibitor gains access to the oocyte via gap junctions connecting the oocyte and its surrounding cumulus of granulosa. These intercellular channels are formed by proteins known as connexins. With the midcycle LH surge, the gap junctions are disrupted, granulosa cells are no longer connected to the oocyte, and meiosis I is allowed to resume.

Follicular Development

Follicular development, also known as folliculogenesis, is a dynamic process that continues from menarche until menopause. The process is designed to allow the monthly recruitment of a cohort of primordial follicles and, ultimately, to release a single, mature, dominant follicle during ovulation each month. Therefore, it is highly coordinated with oocyte maturation.

Folliculogenesis has been divided into different steps according to follicular

characteristics regarding the number and appearance of granulosa cells, development of theca cells and formation of a fluid-filled structure known as antrum. **Preantral follicles** include primordial, primary, and secondary follicles. **Antral follicles** include tertiary and preovulatory follicles.

Primordial follicles are 0.03 to 0.05 mm in diameter structures formed by a primary oocyte (arrested in prophase of meiosis I), surrounded by one layer of flattened granulosa cells contained by the basal lamina.

Primary follicles are 0.1 mm follicles formed when granulosa cells are still a one cell layer but acquire a cuboidal form. This is the first sign of follicular recruitment. Protein synthesis and secretion form an extracellular matrix capsule known as the zona pellucida, traversed by intercellular channels (gap unions) that maintain active connections between granulosa cells and the oocyte. Granulosa cells in the primary follicle develop FSH receptors, without endocrine effect as a result of the absence of follicular vascularization and, therefore, nonexistent exposure to circulating FSH.

Secondary follicles are 0.2 mm in size and develop several layers of cuboidal granulosa cells with marked expression of FSH receptors. Stromal cell in contact with the granulosa and basal lamina are differentiated into theca cells with LH receptor expression. In the theca layer neoangiogenesis occurs, vascularizing the follicle and exposing it to circulating FSH and LH.

Tertiary follicles are characterized by the formation of the antral cavity or antrum, as a consequence of granulosa cell secretion intercellular accumulation. **Early tertiary follicles** are 0.2 to 5 mm in size and at this point the theca layer is divided into theca interna and theca externa, which forms a transition with the ovarian stroma. **Late tertiary follicles** are 10 to 20 mm in size. Their large antral cavity divides granulosa in several cell populations, the corona radiata in contact with the oocyte, mural (membranous) granulosa in contact with the follicular wall and the cumulus ophorus that appears as a stalk joining the corona radiata and the mural granulosa.

Preovulatory follicles are the final stage of follicular development and >20 mm in size, structures from which ovulation occurs. Late in this stage and before ovulation, the primary oocyte completes meiosis I, becoming a secondary oocyte arrested in metaphase of meiosis II. Late tertiary/preovulatory follicles are also known as Graafian follicles.

Gonadotropin dependence in folliculogenesis is conditioned by the expression of FSH and LH receptors in granulosa and theca cells, respectively, and by the presence of follicular vascularization. Considerable expression of granulosa FSH receptors and formation of vascularized theca layer occurs in the secondary follicle. Consequently, follicular development is gonadotropin independent up to the formation of secondary follicles or late preantral phase. Early antral follicle development and its maturation process up to a preovulatory follicle is a gonadotropin dependent phase.

Primordial Follicles

The initial recruitment and growth of the primordial follicles is gonadotropin independent and affects a cohort over several months (87). The stimuli responsible for the recruitment of a specific cohort of follicles in each cycle are yet to be understood, but it seems to be under autocrine and paracrine control. Interaction between oocyte and neighboring granulosa cells seems to be fundamental for oocyte growth development, granulosa cell proliferation and the resultant primordial follicle activation.

Maintenance of a population of dormant primordial follicles is the basis for guaranteeing an oocyte supply throughout reproductive life (88). Whether secretion of stimulating or inhibiting factors is involved in recruitment regulation is being studied, although accelerated recruitment in isolated primordial follicles cultured in vitro suggests inhibitory mechanisms can have a more important role (89). Several factors have been implicated with an inhibitory effect over primordial follicle activation, such as anti-mullerian hormone (AMH) (90), phosphate and tensin homolog (PTEN) (91), tuberin/tuberous sclerosis complex (TSC) (92), Forkhead boxL2 (Foxl2) (93), and Forkhead box O3 (FOXO3a) (94). Their expression is responsible for preservation of primordial follicular dormancy and depletion of these factors in knockout mice has been associated with premature activation and early depletion of primordial follicles. On the other hand, phosphotidylinositol-3-kinase signaling mediated by 3-phosphoinositide dependent kinase-1 (PDK1), and mammalian target of rapamycin complex-1 (mTORC1), and S6 kinase-ribosomal protein (S6K1-rpS6), have been related to primordial follicle activation and survival (95–98).

Preantral Follicle

At the secondary follicle stage, after initial recruitment, FSH assumes control of follicular differentiation and growth and allows a cohort of follicles to continue differentiation. This process signals the shift from gonadotropin-independent to gonadotropin-dependent growth. The decline in luteal phase estrogen, progesterone, and inhibin A production by the now fading corpus luteum from the previous cycle allows the increase in FSH that stimulates this follicular growth (99).

Simultaneously, theca cells in the stroma bordering the granulosa cells proliferate. Both cell types function synergistically to produce estrogens that are secreted into the systemic circulation. At this stage of development, each of the seemingly identical cohort members must be either selected for dominance or undergo atresia. It is likely that the follicle destined to ovulate was selected before this point, although the mechanism for selection remains obscure.

Two-Cell, Two-Gonadotropin Theory

The fundamental tenet of follicular development is the two-cell, two-gonadotropin

theory (Fig. 7-11) (87,100,101). **This theory states that there is a subdivision and compartmentalization of steroid hormone synthesis activity in the developing follicle.** Most aromatase activity (for estrogen production) is in the granulosa cells (102). Aromatase activity is enhanced by FSH stimulation of specific receptors on these cells (103,104). Granulosa cells lack several enzymes that occur earlier in the steroidogenic pathway and require androgens as a substrate for aromatization. Androgens, in turn, are synthesized primarily in response to stimulation by LH, and the theca cells possess most of the LH receptors at this stage (103,104). Therefore, a synergistic relationship must exist: LH stimulates the theca cells to produce androgens (primarily androstenedione), which are transferred to the granulosa cells for FSH-stimulated aromatization into estrogens. These locally produced estrogens create a microenvironment within the follicle that is favorable for continued growth and nutrition (105). FSH and local estrogens serve to further stimulate estrogen production, FSH receptor synthesis and expression, and granulosa cell proliferation and differentiation.

Androgens have two positive regulatory roles in follicular development. Within the ovary, androgens promote granulose cell proliferation, aromatase activity, and inhibit programmed death of these cells (106).

As the peripheral estrogen level rises, it negatively feeds back on the pituitary and hypothalamus to decrease circulating FSH levels (107). **Increased ovarian production of inhibin B further decreases FSH production at this point.**

The falling FSH level that occurs with the progression of the follicular phase represents a threat to continued follicular growth. The resulting adverse environment can be withstood only by follicles with a selective advantage for binding the diminishing FSH molecules; that is, those with the greatest number of FSH receptors. The dominant follicle, therefore, can be perceived as the one with a richly estrogenic microenvironment and the most FSH receptors (108). Increase in FSH receptors results from an increase in granulosa cell population, because FSH receptor number is similar and constant in each granulosa cell (109,110). As it grows and develops, the follicle continues to produce estrogen, which results in further lowering of the circulating FSH and creates a more adverse environment for competing follicles. This process continues until all members of the initial cohort, with the exception of the single dominant follicle, have suffered atresia. The stage is set for ovulation.

Chronic elevation of androgens suppresses hypothalamic–pituitary secretion of FSH, a detriment to the development and maturation of a dominant follicle (106). Clinically, androgen excess results in chronic anovulation, as is seen in polycystic ovarian syndrome.

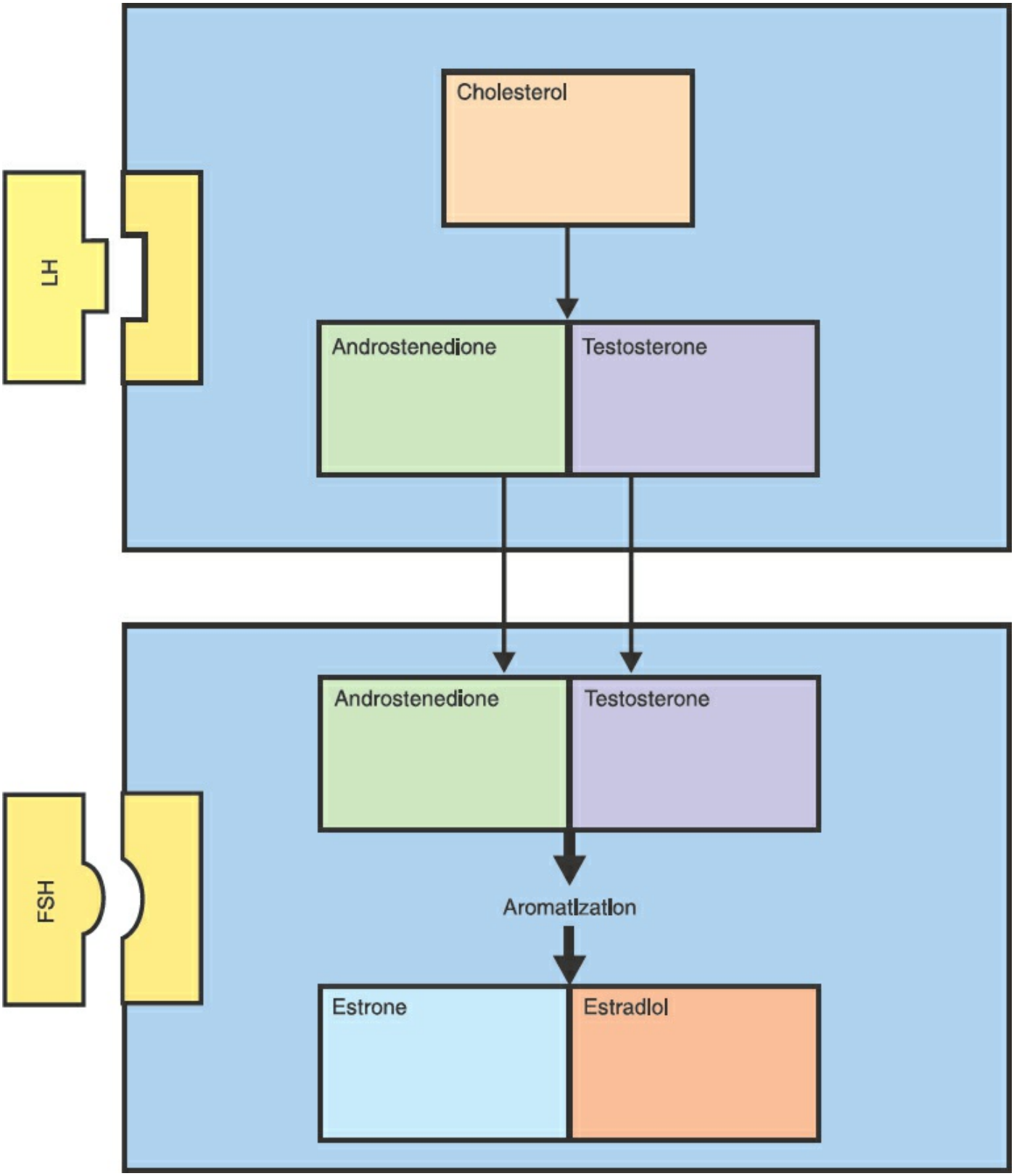


FIGURE 7-11 The two-cell, two-gonadotropin theory of follicular development in which there is compartmentalization of steroid hormone synthesis in the developing follicle. LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Preovulatory Follicle

Preovulatory follicles are characterized by a fluid-filled antrum that is composed of plasma with granulosa cell secretions. The granulosa cells at this point have further differentiated into a heterogeneous population. The oocyte remains connected to the follicle by a stalk of specialized granulosa known as the *cumulus oophorus*.

Rising estrogen levels have a negative feedback effect on FSH secretion. Conversely, LH undergoes biphasic regulation by circulating estrogens. At lower concentrations, estrogens inhibit LH secretion. At higher levels, estrogen enhances LH release. This stimulation requires a sustained high level of estrogen (>200 pg/mL) for more than 48 hours (111). When the rising estrogen level produces positive feedback, a substantial surge in LH secretion occurs.

Concomitant to these events, the local estrogen–FSH interactions in the dominant follicle induce LH receptors on the granulosa cells. Exposure to high levels of LH results in a specific response by the dominant follicle—the result is luteinization of the granulosa cells, production of progesterone, and initiation of ovulation. Late follicular phase progesterone secretion is responsible for the FSH midcycle surge that stimulates plasminogen activator, LH granulosa cell receptor formation, and debilitates oocyte binding to the follicular wall (110). Ovulation will occur in the single mature, or Graafian, follicle 10 to 12 hours after the LH peak or 34 to 36 hours after the initial rise in midcycle LH (112–114).

The sex steroids are not the only gonadotropin regulators of follicular development. Two related granulosa cell–derived peptides were identified that play opposing roles in pituitary feedback (115). **The first of these peptides, inhibin, is secreted in two forms: inhibin A and inhibin B.** Inhibin B is secreted primarily in the follicular phase and is stimulated by FSH, whereas inhibin A is mainly active in the luteal phase (116). **Both forms of inhibin act to inhibit FSH synthesis and release** (117,118). The second peptide, activin, stimulates FSH release from the pituitary gland and potentiates its action in the ovary (119,120). It is likely that there are numerous other intraovarian regulators similar to inhibin and activin, each of which may play a key role in promoting the normal ovulatory process (121). Some of these include follistatin, insulin-like growth factor-1 (ILGF-1), (EGF)/transforming growth factor-α (TGF-α), TGF-β1, growth differentiation factor 9 (GDF-9) (122,123), fibroblast growth factor-β (FGF-β), interleukin-1, tissue necrosis factor-α, OMI, and renin–angiotensin. Anti-mullerian hormone, produced exclusively by granulosa cells of growing primary and preantral follicles, is the most accurate reflection of ovarian reserve and seems to influence the dominant follicle selection by decreasing FSH sensitivity at receptor level, thus inhibiting the initial selection of preantral and small antral follicles (124–126).

Ovulation

The midcycle LH surge is responsible for a dramatic increase in local

concentrations of prostaglandins and proteolytic enzymes in the follicular wall (127). These substances progressively weaken the follicular wall, allowing the formation of a bleb-like superficial follicular protrusion known as the stigma and ultimately the wall's perforation. Ovulation most likely represents a slow extrusion of the oocyte through this opening in the follicle rather than a rupture of the follicular structure (128). Direct measurements of intrafollicular pressures were recorded and failed to demonstrate an explosive event.

Luteal Phase

Structure of Corpus Luteum

After ovulation, the remaining follicular shell is transformed into the primary regulator of the luteal phase: the corpus luteum. Membranous granulosa cells remaining in the follicle begin to take up lipids and the characteristic yellow lutein pigment for which the structure is named. These cells are active secretory structures that produce progesterone, which supports the endometrium of the luteal phase. In addition, estrogen and inhibin A are produced in significant quantities. Unlike the process that occurs in the developing follicle, the basement membrane of the corpus luteum degenerates to allow proliferating blood vessels to invade the granulosa-luteal cells in response to secretion of angiogenic factors such as vascular endothelial growth factor (129). This angiogenic response allows large amounts of luteal hormones to enter the systemic circulation.

Hormonal Function and Regulation

The hormonal changes of the luteal phase are characterized by a series of negative feedback interactions designed to lead to regression of the corpus luteum if pregnancy does not occur. Corpus luteum steroids (estradiol and progesterone) provide negative central feedback and cause a decrease in FSH and LH secretion. Continued secretion of both steroids will decrease the stimuli for subsequent follicular recruitment. Similarly, luteal secretion of inhibin potentiates FSH withdrawal. In the ovary, local production of progesterone inhibits the further development and recruitment of additional follicles.

Continued corpus luteum function depends on continued LH production. In the absence of this stimulation, the corpus luteum will invariably regress after 12 to 16 days and form the scar-like *corpora albicans* (130). The exact mechanism of luteolysis is unclear and most likely involves local paracrine factors. In the absence of pregnancy, the corpus luteum regresses, and estrogen and progesterone levels wane. This removes central inhibition on gonadotropin secretion and allows FSH and LH levels to rise and recruit another cohort of follicles.

If pregnancy does occur, placental hCG will mimic LH action and continually stimulate the corpus luteum to secrete progesterone. Successful implantation results

in hormonal support to allow continued maintenance of the corpus luteum and the endometrium. Evidence from patients undergoing oocyte donation cycles demonstrated that continued luteal function is essential for continuation of the pregnancy until approximately 5 weeks of gestation, when sufficient progesterone is produced by the developing placenta (131). This switch in the source of regulatory progesterone production is referred to as the luteal–placental shift.

Summary of Menstrual Cycle Regulation

Following is a summary of the regulation of the menstrual cycle:

1. **GnRH is produced in the arcuate nucleus of the hypothalamus and secreted in a pulsatile fashion into the portal circulation, where it travels to the anterior pituitary.**
2. **Ovarian follicular development moves from a period of gonadotropin independence to a phase of FSH dependence.**
3. **As the corpus luteum of the previous cycle fades, luteal production of progesterone and inhibin A decreases, allowing FSH levels to rise.**
4. **In response to FSH stimulus, the follicles grow, differentiate, and secrete increasing amounts of estrogen and inhibin B.**
5. **Estrogen stimulates growth and differentiation of the functional layer of the endometrium, which prepares for implantation. Estrogens work with FSH in stimulating follicular development.**
6. **The two-cell, two-gonadotropin theory dictates that with LH stimulation, the ovarian theca cells will produce androgens that are converted by the granulosa cells into estrogens under the stimulus of FSH.**
7. **Rising estrogen and inhibin levels negatively feedback on the pituitary gland and hypothalamus and decrease the secretion of FSH.**
8. **The one follicle destined to ovulate each cycle is called the dominant follicle. It has relatively more FSH receptors and produces a larger concentration of estrogens than the follicles that will undergo atresia. It is able to continue to grow despite falling FSH levels.**
9. **Sustained high estrogen levels cause a surge in pituitary LH secretion that triggers ovulation, progesterone production, and the shift to the secretory, or luteal, phase.**
0. **Luteal function is dependent on the presence of LH. The corpus luteum secretes estrogen, progesterone, and inhibin A, which serve to maintain gonadotropin suppression. Without continued LH secretion, the corpus luteum will regress after 12 to 16 days. The resulting loss of progesterone secretion**

results in menstruation.

1. If pregnancy occurs, the embryo secretes hCG, which mimics the action of LH by sustaining the corpus luteum. The corpus luteum continues to secrete progesterone and supports the secretory endometrium, allowing the pregnancy to continue to develop.

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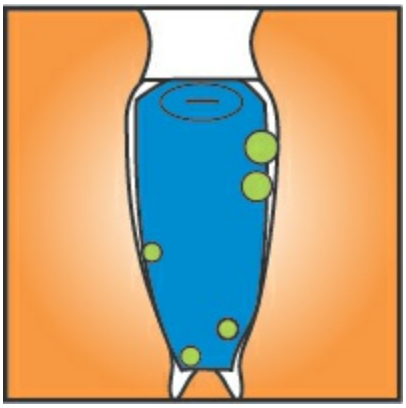
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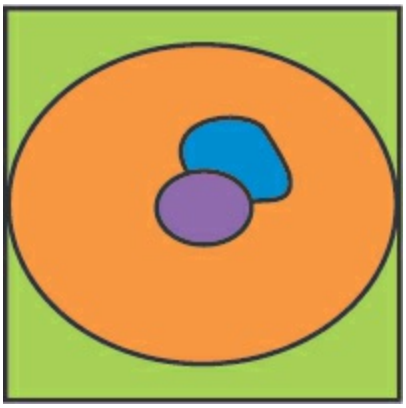
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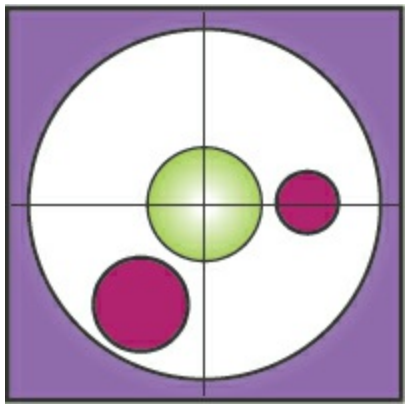
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CHAPTER 8

Puberty



Debra A. Taubel, Robert W. Rebar

Normal Pubertal Development
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KEY POINTS

1 Normal pubertal development occurs in a predictable orderly sequence over a definite time frame.
2 The earliest pubertal changes are detectable in females, on average, at age 10, but the normal age range for the onset of puberty is wide.
3 Delayed puberty is often constitutional but underlying pathology should be investigated.
4 When pubertal development occurs asynchronously with development of breasts in the absence of significant pubic and axillary hair, the diagnosis is usually androgen insensitivity.
5 The most common cause of precocious puberty is constitutional (idiopathic), but more serious causes must be ruled out and therapy focused toward optimizing adult height.
6 The most common cause of heterosexual development at the expected age of puberty is polycystic ovary syndrome.

***Puberty* is the period during which secondary sexual characteristics develop and the capability for sexual reproduction is attained.** The physical changes accompanying pubertal development result directly or indirectly from maturation of the hypothalamus, stimulation of the sex organs, and secretion of sex steroids. Hormonally, puberty in humans is characterized by the resetting of the classic negative gonadal steroid feedback loop, alterations in circadian and ultradian (frequent) gonadotropin rhythms, and the acquisition in the woman of a positive estrogen feedback loop, which controls monthly cycles as an interdependent expression of gonadotropins and ovarian steroids.

The ability to evaluate and treat aberrations of pubertal development, such as amenorrhea and other menstrual abnormalities, requires thorough comprehension of the normal hormonal and physical changes that occur at puberty.

NORMAL PUBERTAL DEVELOPMENT

Factors Affecting Time of Onset

The major determinant of the timing of the onset of puberty is primarily genetic, but a number of other factors appear to influence both the age at onset and the progression of pubertal development. Among these influences are nutritional state, general health, geographic location, exposure to light, and psychological state (1). **The concordance of the age of menarche in mother–daughter pairs and between sisters and in ethnic populations illustrates the importance of genetic factors** (1). Typically, the age of menarche is earlier than average in children with moderate obesity (up to 30% above normal weight for age), whereas delayed menarche is common in those with severe malnutrition. Children who live in urban settings, closer to the equator, and at lower altitudes typically begin puberty earlier than those who live in rural areas, farther from the equator, and at higher elevations. The risk of earlier onset of puberty has been a topic of interest for developmental biologists, associating family discord, lack of a parent, inadequate financial resources, and other domestic stressors with increased risk of early puberty and sexual maturity (2,3). Other risk factors implicated for precocious puberty include

exposure to naturally occurring and synthetic estrogenic endocrine–disrupting chemicals (3). Blind girls apparently undergo menarche earlier than sighted girls, suggesting some influence of light (4).

In Western Europe, the age of menarche declined 4 months each decade between 1850 and 1960 (1). Data suggest that the trend toward earlier pubertal development may be continuing among girls (but not boys) who live in the United States as reported from studies comparing populations of girls from 1940 to 1994 (5). It is presumed that these changes represent improved nutritional status and healthier living conditions.

One of the more controversial hypotheses centers on the role of total body weight and body composition on the age of menarche. It has been suggested that a minimum of 17% body fat must be achieved before the initiation of menarche, and body fat should be at 22% in females older than 16 to maintain regular periods (6). This hypothesis is supported by observations that menarche occurs earliest in overweight girls, followed by normal-weight girls, then underweight girls, and lastly anorectic girls **(Fig. 8-1)**. The importance of other factors is indicated by observations that menarche is often delayed in morbidly obese girls, those with diabetes, and those who exercise intensely but are of normal body weight and body fat percentage. Girls with precocious puberty may undergo menarche even if they have a low body fat percentage, and other girls show no pubertal development with a body fat percentage of 27% (7). Although body fat and weight are factors in determining onset of puberty and maturation, other factors have been the subject of investigation, such as birth weight, accelerated weight gain in infancy, and in utero exposures to toxins or stress (3,8).



FIGURE 8-1 Normal twins at 12 years of age. The heavier twin (weighing 143 lb) is clearly more advanced in puberty than the lighter twin (weighing 87 lb). Anecdotal photographs and data such as these served to provide the basis for the theory that body fat, body mass, and menarche are linked. (From **Wilkins L.** *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*. 3rd ed. Springfield, IL:

Charles C Thomas; 1965:218, with permission.)

Physical Changes During Puberty

[1] The changes associated with puberty occur in an orderly predictable sequence over a definite time frame. Any deviation from this sequence or time frame should be regarded as abnormal. The pubertal changes, their relationship to one another, and the ages at which they occur are distinctly different in girls than in boys. Although this chapter focuses on girls, changes in boys are briefly considered.

Tanner Stage

[2] In girls, pubertal development typically takes place over 4.5 years (Fig. 8-2). The first sign of puberty is accelerated growth, and breast budding is usually the first recognized pubertal change, followed by the appearance of pubic hair, peak growth velocity, and menarche. Pubertal changes begin, on average, in the 11th year of life, but the range of normal is wide. The stages initially described by Marshall and Tanner are often used to describe breast and pubic hair development (9).

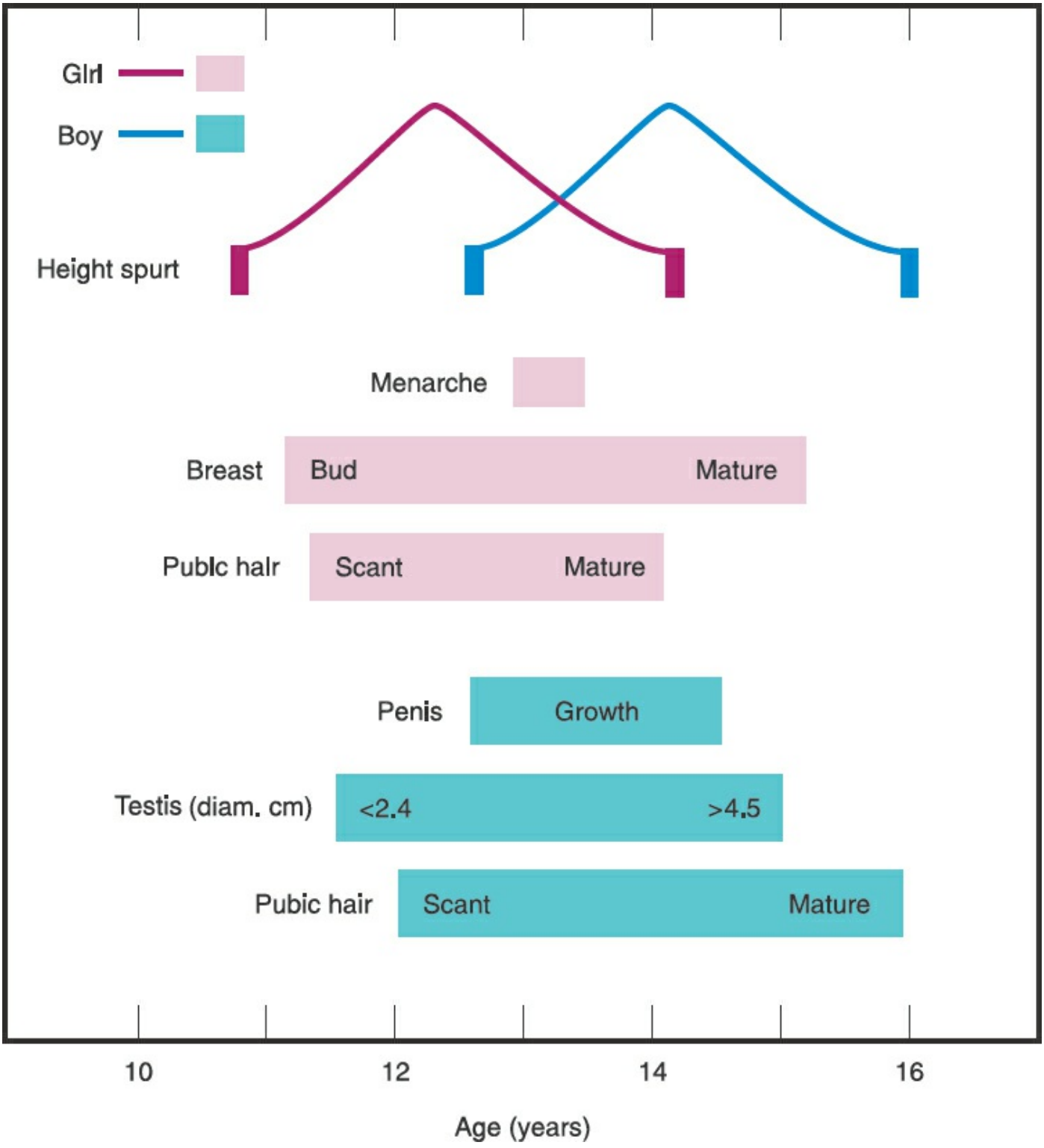


FIGURE 8-2 Schematic sequence of events at puberty. An idealized average girl and an idealized average boy are represented. (From **Rebar RW.** Practical evaluation of hormonal status. In: Yen SSC, Jaffe RB, eds. *Reproductive Endocrinology: Physiology, Pathophysiology and Clinical Management*. 3rd ed. Philadelphia, PA: WB Saunders; 1991:830, with permission; based on data from **Marshall WA, Tanner JM.** Variations in patterns of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303; and **Marshall WA, Tanner JM.** Variation in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13–23, with permission.)

With regard to breast development, *Tanner stage 1* refers to the prepubertal

state and includes no palpable breast tissue, with the areolae generally less than 2 cm in diameter. The nipples may be inverted, flat, or raised. In *Tanner stage 2*, breast budding occurs, with a visible and palpable mound of breast tissue. The areolae begin to enlarge, the skin of the areolae thins, and the nipple develops to varying degrees. *Tanner stage 3* is reflected by further growth and elevation of the entire breast. When the individual is seated and viewed from the side, the nipple is generally at or above the midplane of breast tissue. In most girls, *Tanner stage 4* is defined by projection of the areola and papilla above the general breast contour in a secondary mound. Breast development is incomplete until *Tanner stage 5*, in which the breast is mature in contour and proportion. In most women, the nipple is more pigmented at this stage than earlier in development, and Montgomery glands are visible around the circumference of the areola. The nipple is generally below the midplane of breast tissue when the woman is seated and viewed from the side. Full breast development usually occurs over 3 to 3.5 years, but it may occur in as little as 2 years or not progress beyond stage 4 until the first pregnancy. Breast size is no indication of breast maturity.

Pubic hair staging is related to quantity and distribution (Fig. 8-3). In *Tanner stage 1*, there is no sexually stimulated pubic hair present, but some nonsexual hair may be present in the genital area. *Tanner stage 2* is characterized by the first appearance of coarse, long, crinkly pubic hair along the labia majora. In *Tanner stage 3*, coarse, curly hair extends onto the mons pubis. *Tanner stage 4* is characterized by adult hair in thickness and texture, but the hair is not as widely distributed as in adults and typically does not extend onto the inner aspects of the thighs. Except in certain ethnic groups, including Asians and American Indians, pubic hair extends onto the thighs in *Tanner stage 5*.

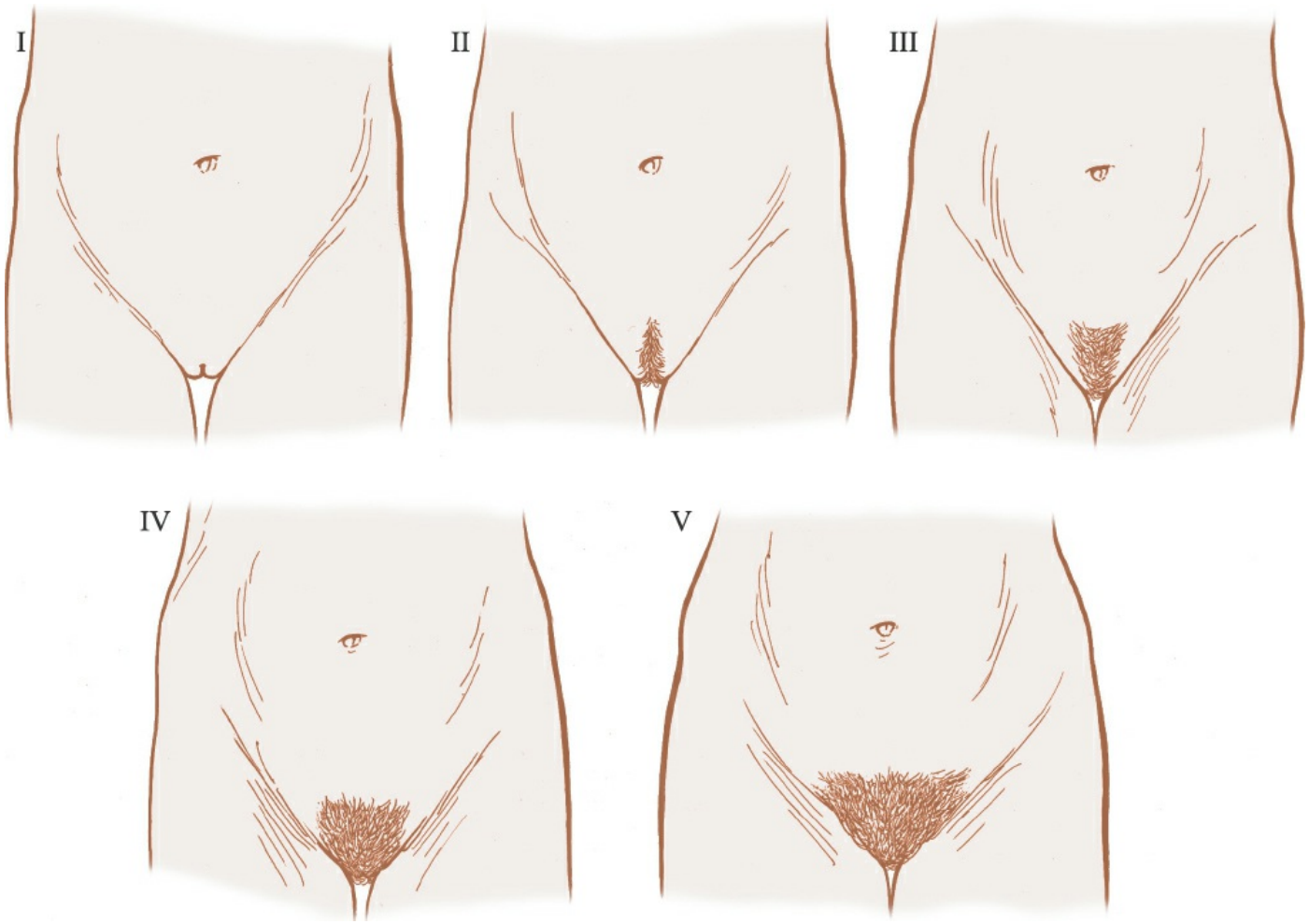


FIGURE 8-3 Diagrammatic depiction of Tanner pubic hair staging in adolescent women. (From **Ross GT, VandeWiele RL, Frantz AG.** The ovaries and the breasts. In: Williams RH, ed. *Textbook of Endocrinology*. 6th ed. Philadelphia, PA: WB Saunders; 1981:355, with permission; adapted from **Marshall WA, Tanner JM.** Variations in patterns of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303.)

The staging of male pubertal sexual maturation is based on genital size and pubic hair development. *Tanner stage 1* is prepubertal. *Tanner stage 2* of genital growth begins when testicular enlargement is first evident. Testis length along the longitudinal axis ranges from 2.5 to 3.2 cm. The size of the penis increases. Pigmented, curly pubic hair is first visible around the base of the penis. In *Tanner stage 3*, there is further growth of the penis in length and diameter, the scrotum develops further, and testis length increases to 3.3 to 4 cm. Thicker, curly hair extends above the penis. *Tanner stage 4* involves further growth of the genitalia, with testis length ranging from 4 to 4.5 cm. Extension of pubic hair over the genital area continues, but the volume is less than in the adult. At this stage, the prostate gland is palpable by rectal examination. In *Tanner stage 5*, the genitalia are within the adult range in size. Average flaccid penile length in adult men ranges between 8.6 and 10.5 cm from tip to base. Pubic hair spreads laterally onto the medial

thighs. Hair may extend from the pubic area toward the umbilicus and anus.

Pigmented pubic hair is often the first recognized sign of male puberty even though it typically occurs 6 months after genital growth begins. Tanner stage 3 puberty is often accompanied by symmetric or asymmetric gynecomastia, and mature sperm first can be identified with microscopic urinalysis.

Height and Growth Rate

Plotting height increments (i.e., growth velocity) against the phases of puberty allows one to see relationships during puberty (Fig. 8-2). Girls reach peak height velocity early in puberty before menarche. As a consequence, they have limited growth potential after menarche. In contrast, boys reach peak height velocity about 2 years later than girls. Boys grow an average of 28 cm during the growth spurt, in comparison to a mean of 25 cm for girls. Adult men eventually are an average of 13 cm taller than adult women because they are taller at the onset of the growth spurt. Hormonal control of the pubertal growth spurt is complex. Growth hormone (GH), insulinlike growth factor 1 (IGF-1), and gonadal steroids play major roles. Adrenal androgens appear to be less important. Mutations limiting conversion of androgens to estrogens in males confirmed that estrogen is a major stimulus to the pubertal growth spurt in boys and girls (10). The transient elevation of gonadotropins and sex steroids observed in the first few months of life has been implicated as an important contributor to subsequent skeletal bone growth and general pubertal development (11).

During the growth spurt associated with puberty, the long bones in the body lengthen and the epiphyses ultimately close. The bone or skeletal age of any individual can be estimated closely by comparing x-rays documenting the development of bones in the nondominant hand (most commonly), knee, or elbow to standards of maturation for the normal population. The Greulich and Pyle atlas is used most often for this purpose (12). Skeletal age is more closely correlated with pubertal stage than with chronologic age during puberty. **With height and chronologic age, an individual's bone age can be used to predict final adult height using the Bayley–Pinneau tables** (13). Bone age determinations can be used to assess the degree of delay, monitor subsequent development, and estimate final adult height.

Another practical clinical approach to predicting adult height uses midparental height. **The adjusted midparental height is calculated by adding 13 cm to the mother's height (for boys) or subtracting 13 cm from the father's height (for girls) and then determining the mean of the heights of the parents, including the adjusted height of the opposite-sex parent. Adding and subtracting 8.5 cm to the calculated predicted height approximates the target range of the 3rd to the 97th percentile for the anticipated adult height of the child.** This quick calculation can be of assistance in evaluating individuals with delayed or precocious pubertal development and those with short stature.

Several changes in body composition occur during pubertal development. **Although lean body mass, skeletal mass, and body fat are equal in prepubertal boys and girls, by maturity, men have 1.5 times the lean body mass and almost 1.5 times the skeletal mass of women, whereas women have twice as much body fat as men** (1). **The changes in body contour in girls, with accumulation of fat at the thighs, hips, and buttocks, occur during the pubertal growth spurt. In this regard, testosterone is a potent anabolic steroid and is responsible for the major changes in boys, whereas estrogen increases total body fat in a characteristic distribution at the thighs, buttocks, and abdomen in girls.**

Other physical changes show sexual dimorphism at puberty. In boys the membranous and cartilaginous portions of the vocal cords lengthen much more than they do in girls, accounting for deepening of the voice. Comedones, acne, and seborrhea of the scalp begin because of increased secretion of adrenal and gonadal steroids at puberty. In general, early-onset acne correlates with the development of severe acne later in puberty. **The appearance of comedones in the nasal creases and behind the pinna may be the first indications of impending pubertal development.**

Hormonal Changes

By 10 weeks of gestation, gonadotropin-releasing hormone (GnRH) is present in the hypothalamus, and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are present in the pituitary gland (14). Gonadotropin levels are elevated in female and male fetuses midgestation; the levels of FSH are higher in females. The levels of gonadotropins and sex steroids are suppressed before birth, but increase in the first few weeks of life, a process named "mini-puberty." This period lasts until approximately 6 months of age in boys and up to age 3 years in girls and is suspected to be the foundation of development of reproductive competency later in life (5). After this early surge, the gonadotropins are suppressed in childhood, and remain low during the prepubertal years. The hypothalamic–pituitary unit appears to be suppressed by the extremely low levels of gonadal steroids present in childhood. Gonadal suppression of gonadotropin secretion is demonstrated by higher gonadotropin levels in children with gonadal dysgenesis and those who undergo gonadectomy before puberty (15).

Several of the hormonal changes associated with pubertal development begin before any of the physical changes are obvious. Early in puberty, there is increased sensitivity of LH to GnRH. Sleep-entrained increases in both LH and FSH can be documented early in puberty (16). In boys, the nocturnal increases in gonadotropin levels are accompanied by simultaneous increases in circulating testosterone levels (17). In contrast, in girls, the nighttime increases in circulating gonadotropin levels are followed by increased secretion of estradiol the next day **(Fig. 8-4)** (18). This delay in estradiol secretion is believed to result from the additional synthetic steps required in

the aromatization of estrogens from androgens. Basal levels of FSH and LH increase through puberty. The patterns differ in boys and girls, with LH levels (measured in mIU/mL) eventually becoming greater than FSH levels **(Fig. 8-5)** (19). Although it appears that gonadotropins are always secreted in an episodic or pulsatile fashion, even before puberty, the pulsatile secretion of gonadotropins is more easily documented as puberty progresses and basal levels increase (20).

Increased adrenal androgen secretion is important in stimulating adrenarche, the appearance of pubic and axillary hair, in boys and girls. Pubarche specifically refers to the appearance of pubic hair. Progressive increases in circulating levels of the major adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), begin as early as 2 years of age, accelerate at 7 to 8 years of age, and continue until 13 to 15 years of age (5). The accelerated increases in adrenal androgens begin about 2 years before the increases in gonadotropin and gonadal sex steroid secretion when the hypothalamic–pituitary–gonadal unit is still functioning at a low prepubertal level. **Pubarche and adrenarche, although often temporally related to gonadarche, should not be used as markers for the onset of puberty** (5).

In girls, mean levels of estradiol, secreted predominantly by the ovaries, increase steadily during puberty (19). Although increases in estradiol first appear during the daytime hours, basal levels eventually increase during the day and night. Estrone, which is secreted in part by the ovaries and arises in part from extraglandular conversion of estradiol and androstenedione, increases early in puberty but plateaus by midpuberty. Thus, **the ratio of estrone to estradiol decreases throughout puberty, indicating that ovarian production of estradiol becomes increasingly important and peripheral conversion of androgens to estrone becomes less important during maturation.**

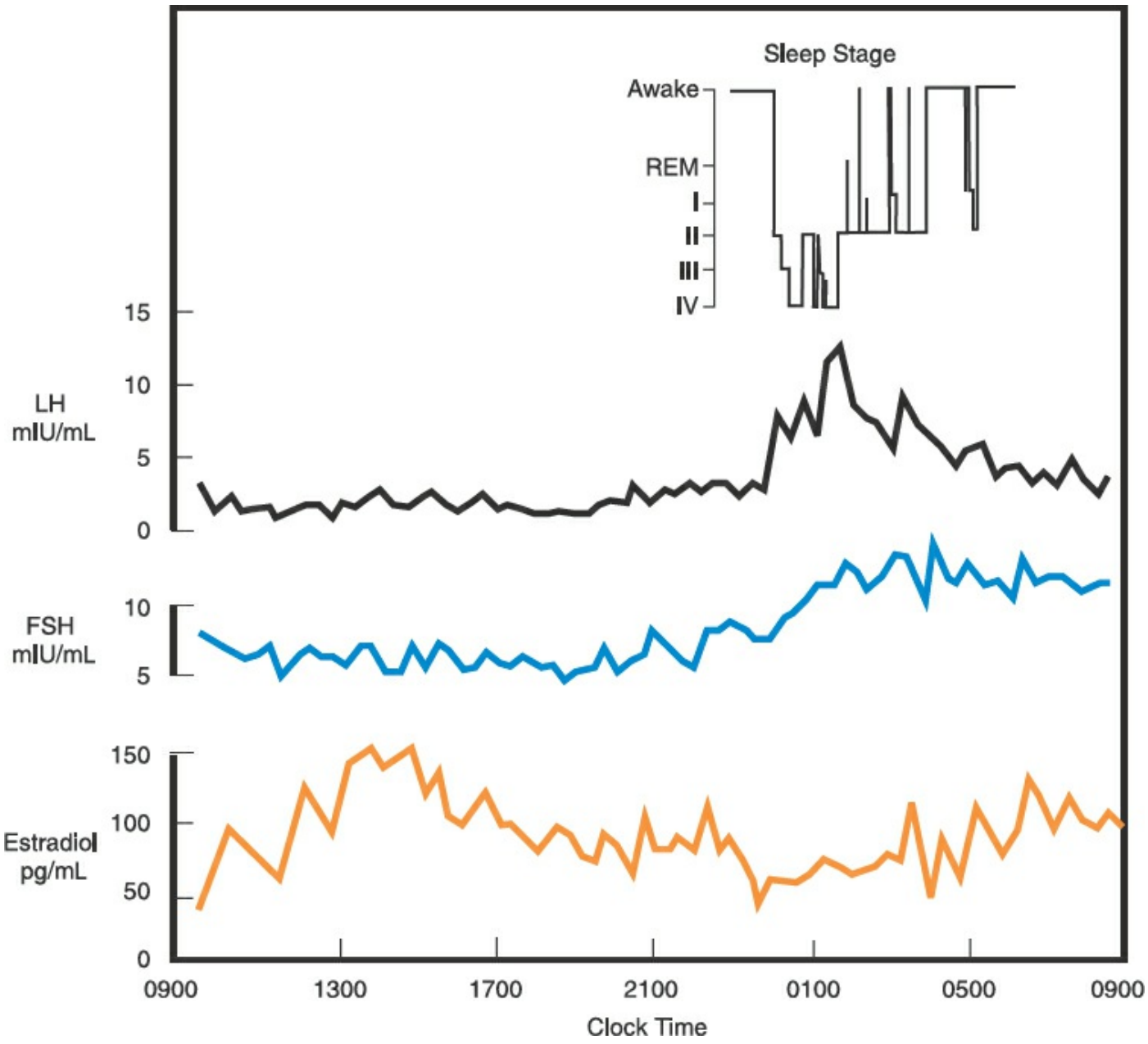


FIGURE 8-4 Patterns of circulating luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol in a stage 3 pubertal girl over a 24-hour period, with the encephalographic stage of sleep indicated. (From **Boyar RM, Wu RHK, Roffwarg H, et al.** Human puberty: 24-hour estradiol patterns in pubertal girls. *J Clin Endocrinol Metab* 1976;43:1418–1421, with permission.)

In boys, most of the testosterone in the circulation arises from direct secretion by the Leydig cells of the testis. Testosterone induces development of a male body habitus and voice change, whereas dihydrotestosterone (DHT), produced following 5α-reduction within target cells, induces enlargement of the penis and prostate gland, beard growth, and temporal hair recession during puberty. Mean plasma testosterone levels rise progressively during puberty, with the greatest increase occurring during Tanner stage 2 (21).

GH secretion increases along with increased gonadotropin secretion at the onset

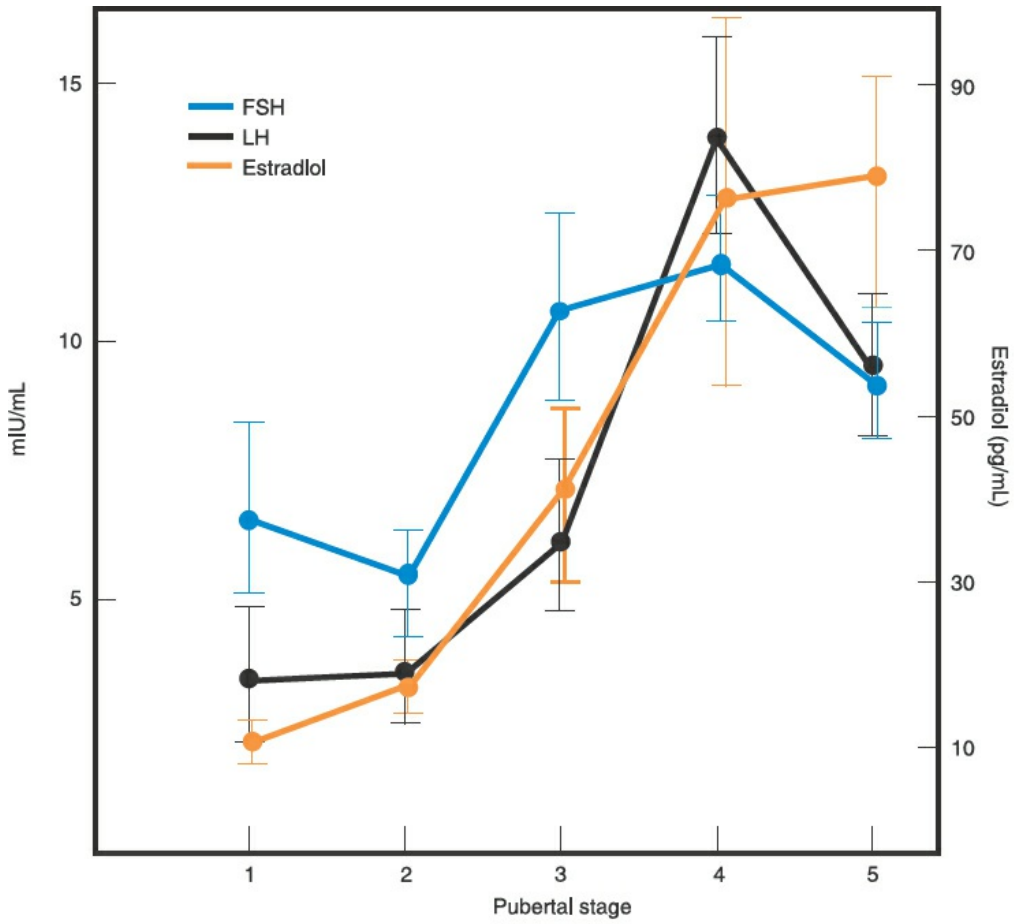
of puberty. It is believed that the increase in GH is mediated by estrogen, which in boys is dependent on aromatization of testosterone to estradiol and reflects increasing sex steroid production at puberty. Nonetheless, there are profound sex differences in GH secretion during puberty. Girls have higher basal levels of GH throughout puberty, reaching maximal levels around the time of menarche and decreasing thereafter. In contrast, basal concentrations of GH remain constant throughout puberty in boys. GH secretion is highly pulsatile, with most pulses occurring during sleep and with sex steroids increasing pulse amplitude rather than altering pulse frequency.

GH stimulates production of IGF-1 in all tissues, with concentrations found in the circulation spilling over from the liver. During puberty the negative feedback effect of IGF-1 on GH secretion must be reduced because IGF-1 and GH levels are high. GH and IGF-1 play significant roles in the changes in body composition that occur at puberty because both hormones are potent anabolic agents.

In the final stages of puberty in both boys and girls, GH secretion begins to diminish, returning to prepubertal levels in adult life, despite continued exposure to high levels of gonadal steroids.

Mechanisms Underlying Puberty

The mechanisms responsible for the numerous hormonal changes that occur during puberty are poorly understood, although it is recognized that a "central nervous system program" must be responsible for initiating puberty. It appears that the hypothalamic–pituitary–gonadal axis in girls develops in two distinct stages during puberty. First, sensitivity to the negative or inhibitory effects of the low levels of circulating sex steroids present in childhood decreases early in puberty. Second, late in puberty, there is maturation of the positive or stimulatory feedback response to estrogen, which is responsible for the ovulatory midcycle surge of LH.


FSH
LH
Estradlol
mIU/mL
Estradiol (pg/mL)
15
10
5
90
70
50
30
10
1
2
3
4
5
Pubertal stage

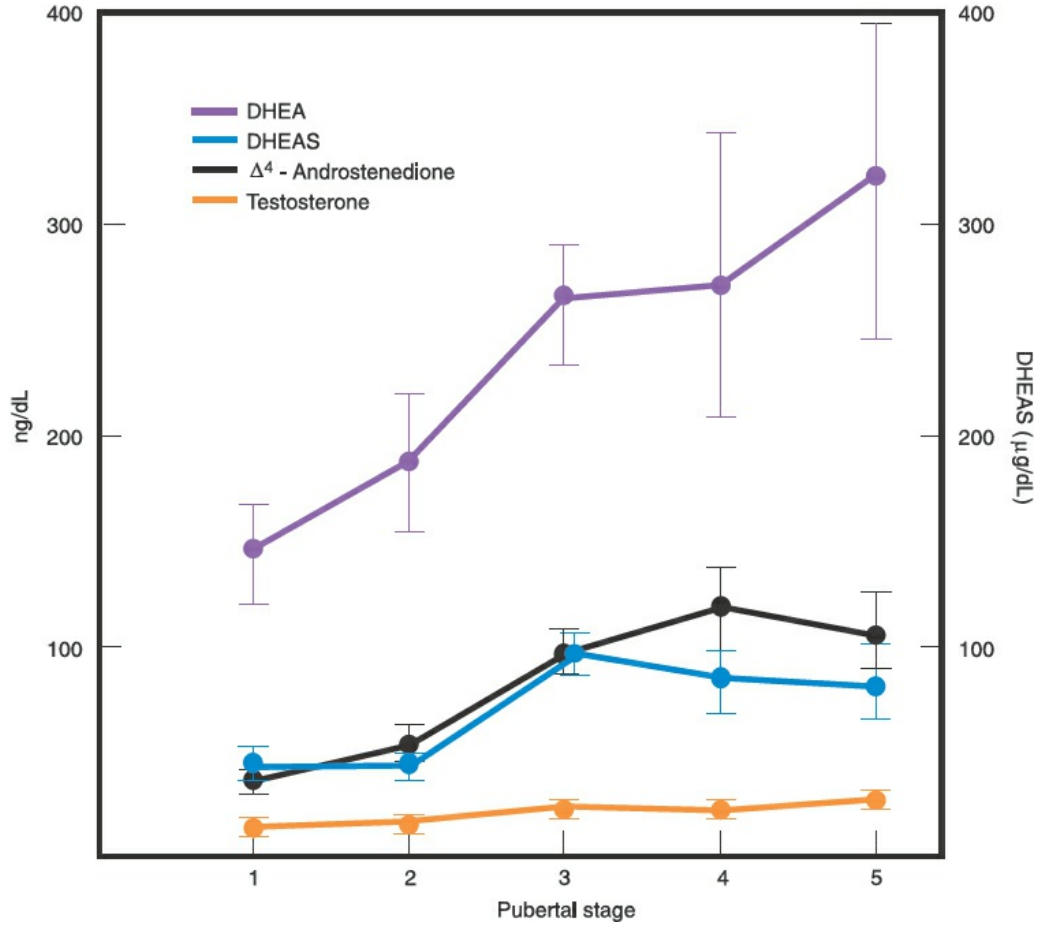

DHEA
DHEAS
Δ4 - Androstenedione
Testosterone
ng/dL
DHEAS (µg/dL)
400
300
200
100
1
2
3
4
5
Pubertal stage

FIGURE 8-5 Increases (± standard error) in circulating levels of gonadotropins and adrenal and gonadal steroids through puberty in girls. DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate. (From **Emans SJH, Goldstein DP.** The physiology of puberty. In: *Pediatric and Adolescent Gynecology*. 3rd ed. Boston, MA: Little, Brown; 1990:95, with permission.)

Evidence suggests that the central nervous system inhibits the onset of puberty until the appropriate time (22). Based on this theory, the neuroendocrine control of puberty is mediated by GnRH-secreting neurons in the medial basal hypothalamus, which act as an endogenous pulse generator. At puberty, the GnRH pulse generator is reactivated (i.e., disinhibited), leading to increased amplitude and frequency of GnRH pulses. The increased GnRH secretion results in increased gonadotropin and then gonadal steroid secretion.

Increasing evidence indicates that there are several influences on the initiation and progression of the GnRH pulse generator, and these include both neuroendocrine signalers and metabolic modifiers. Although the exact details of the pathways are still in the discovery phase, regulators such as *kisspeptin* and *neurokinin B* have been implicated as gatekeepers for the onset of puberty. Metabolic modifiers, such as *leptin* and *nesfatin-1,* can alter the actions of the gatekeepers (23).

Table 8-1 Aberrations of Pubertal Development

I. ***Delayed or interrupted puberty***
A. ***Anatomic abnormalities of the genital outflow tract***
1. Müllerian dysgenesis (Mayer–Rokitansky–Küster–Hauser syndrome)
2. Distal genital tract obstruction
a. Imperforate hymen
b. Transverse vaginal septum
A. ***Hypergonadotropic (follicle-stimulating hormone >30 mIU/mL) hypogonadism (gonadal "failure")***
1. Gonadal dysgenesis with stigmata of Turner syndrome
2. Pure gonadal dysgenesis
a. 46,XX
b. 46,XY
c. Early gonadal "failure" with apparent normal ovarian development
A. ***Hypogonadotropic (luteinizing hormone and follicle-stimulating hormone <10 mIU/mL) hypogonadism***

1. Constitutional delay
2. Isolated gonadotropin deficiency
    a. Associated with midline defects (Kallmann syndrome)
    b. Independent of associated disorders
    c. Prader–Labhart–Willi syndrome
    d. Laurence–Moon–Bardet–Biedl syndrome
    e. Many other rare syndromes
3. Associated with multiple hormone deficiencies
4. Neoplasms of the hypothalamic–pituitary area
    a. Craniopharyngiomas
    b. Pituitary adenomas
    c. Other
5. Infiltrative processes (Langerhans cell–type histiocytosis)
6. After irradiation of the central nervous system
7. Severe chronic illnesses with malnutrition
8. Anorexia nervosa and related disorders
9. Severe hypothalamic amenorrhea (rare)
10. Antidopaminergic and gonadotropin-releasing hormone–inhibiting drugs (especially psychotropic agents, opiates)
11. Primary hypothyroidism
12. Cushing syndrome
13. Use of chemotherapeutic (especially alkylating) agents

II. ***Asynchronous pubertal development***

A. ***Complete androgen insensitivity syndrome (testicular feminization)***

B. ***Incomplete androgen insensitivity syndrome***

III. ***Precocious puberty***

A. ***Central (true) precocious puberty***

1. Constitutional (idiopathic) precocious puberty
2. Hypothalamic neoplasms (most commonly hamartomas)

3. Congenital malformations
4. Infiltrative processes (Langerhans cell–type histiocytosis)
5. After irradiation
6. Trauma
7. Infection

B. ***Precocious puberty of peripheral origin (precocious pseudopuberty)***

1. Autonomous gonadal hypersecretion
    a. Cysts
    b. McCune–Albright syndrome
2. Congenital adrenal hyperplasia
    a. 21-Hydroxylase (P450c21) deficiency
    b. 11β-Hydroxylase (P450c11) deficiency
    c. 3β-Hydroxysteroid dehydrogenase deficiency
3. Iatrogenic ingestion/absorption of estrogens or androgens
4. Hypothyroidism
5. Gonadotropin-secreting neoplasms
    a. Human chorionic gonadotropin secreting
        i. Ectopic germinomas (pinealomas)
        ii. Choriocarcinomas
        iii. Teratomas
        iv. Hepatoblastomas
    b. Luteinizing hormone–secreting (pituitary adenomas)
6. Gonadal neoplasms
    a. Estrogen-secreting
        i. Granulosa–theca cell tumors
        ii. Sex-cord tumors
    b. Androgen-secreting
        i. Sertoli–Leydig cell tumors (arrhenoblastomas)
        ii. Teratomas

7. Adrenal neoplasms
a. Adenomas
b. Carcinomas
D. ***Heterosexual puberty***
A. ***Polycystic ovarian syndrome***
B. ***Nonclassic forms of congenital adrenal hyperplasia***
C. ***Idiopathic hirsutism***
D. ***Mixed gonadal dysgenesis***
E. ***Rare forms of male pseudohermaphroditism (Reifenstein syndrome, 5a-reductase deficiency)***
F. ***Cushing syndrome (rare)***
G. ***Androgen-secreting neoplasms (rare)***

ABERRATIONS OF PUBERTAL DEVELOPMENT

Classification

Several aberrations of pubertal development, as detailed in Table 8-1, can occur in girls. Pubertal aberrations can be classified into four broad categories:

1. ***Delayed or interrupted puberty*** **exists in girls who fail to develop any secondary sex characteristics by age 13, have not had menarche by age 15 (95th percentile is 14.5 years), or have not attained menarche 5 or more years since the onset of pubertal development.**
2. ***Asynchronous pubertal development*** **is characterized by pubertal development that deviates from the normal pattern of puberty.**
3. ***Precocious puberty*** is **defined as pubertal development beginning before the age of 7 years in white girls and before the age of 6 years in African American girls.** This definition has its origin from data collected in the 1960s, using the 95th percentile as the normal designation. However, many pediatric endocrinologists continue to use 8 years as the threshold for initiation of diagnostic testing (24). It is clear that, in most cases, development nearer the mean age of puberty is less likely to have a pathologic basis. Precocious pubertal development is characterized in several ways. In *isosexual* precocious puberty, the early changes are common to the phenotypic sex of the individual. In *heterosexual* precocious puberty, the development is characteristic of the opposite sex. Precocious puberty is sometimes

termed "true" when it is of central origin with activation of the hypothalamic–pituitary unit. In precocious pseudopuberty, also known as *precocious puberty of peripheral origin,* secretion of hormones in the periphery (commonly by neoplasms) stimulates pubertal development.

4. ***Heterosexual puberty*** **is characterized by a pattern of development that is typical of the opposite sex occurring at the expected age of normal puberty.**

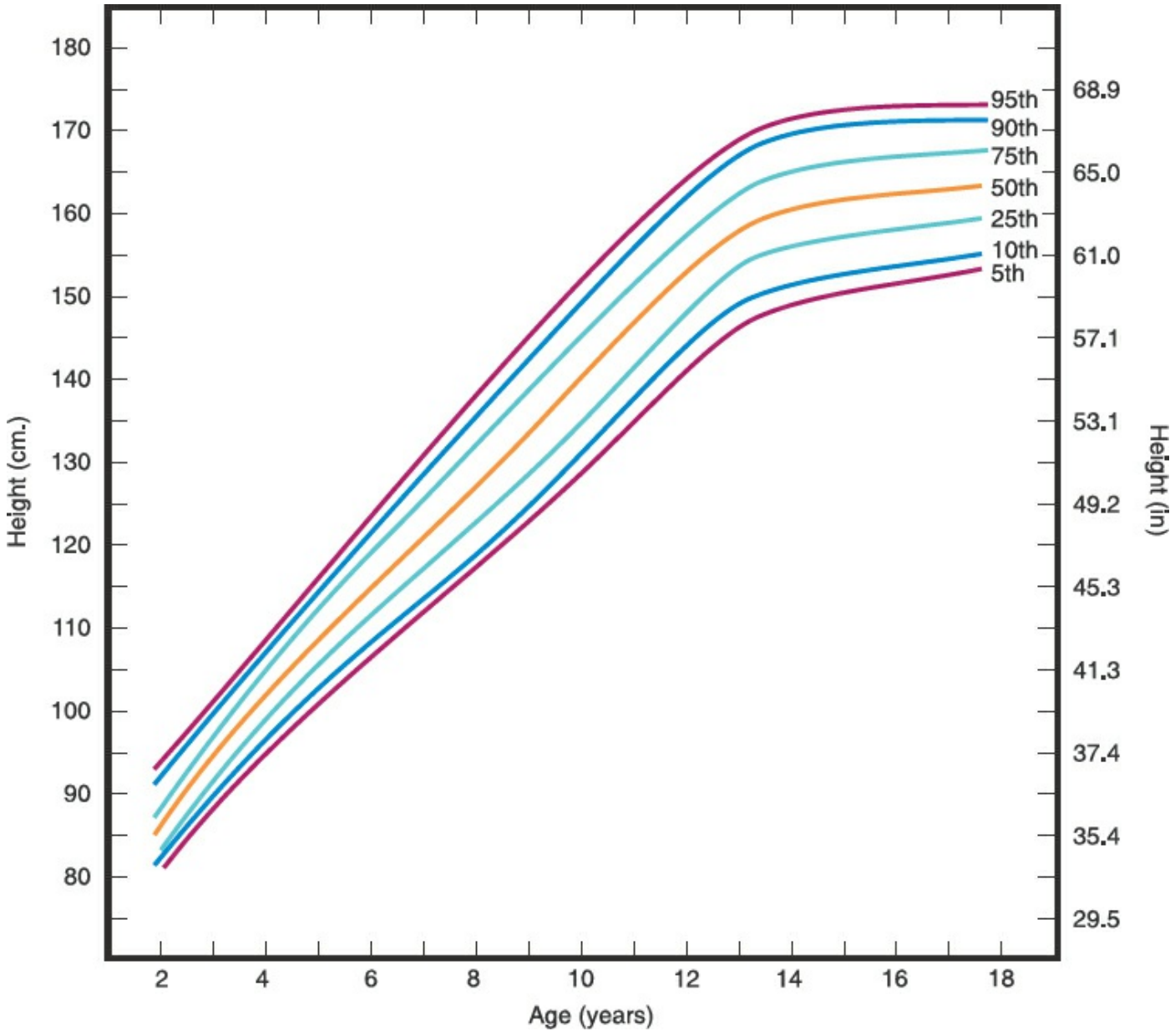


FIGURE 8-6 Growth chart showing stature by age percentiles for girls aged 2 to 18 years. Weight can be plotted in a similar fashion. Several excellent growth charts are available to clinicians, including those from Ross Laboratories (Columbus, OH), Serono Laboratories (Randolph, MA), and Genentech, Inc. (South San Francisco, CA). (From **Hamill PVV, Drizd TA, Johnson CL, et al.** Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr* 1979;32:607–629, with permission; based on data from the National Center for Health Statistics.)

Disorders of sexual development and amenorrhea may be considered in relation to this classification of the aberrations of puberty. It is very helpful to document the growth of the individual and to plot the individual's height and weight on one of several commonly available growth charts **(Fig. 8-6)**.

Delayed or Interrupted Puberty

The history and physical examination, with particular attention to growth, are most important in the evaluation of individuals with delayed puberty. **Pubertal delay is much more common in boys than in girls. [3] The single most common cause of delayed puberty in both sexes is constitutional delay of growth and development (CDGD), which can be assigned when any underlying pathology has not been identified. CDGD has a strong genetic component and it represents an extreme of the normal spectrum of age distribution** (25). **It is important to remember that puberty may be delayed in any child suffering from any severe chronic disease,** including celiac disease, Crohn disease, sickle cell anemia, and cystic fibrosis. Chronic illness should be reviewed during the history and physical examination. One possible approach to evaluation is depicted in **Figure 8-7.**

Anatomic Abnormalities of the Genital Outflow Tract

Those girls who have mature secondary sex characteristics and any of a number of disorders of the outflow tract and uterus, often termed müllerian agenesis and dysgenesis, are most often identified on examination (Fig. 8-8). One of the earlier and more logical proposed classification schemes is shown in Table 8-2 (26). However, this older classification system does not lend itself to describing all possible anomalies and is not entirely based on objective embryologic data. There have been systematic attempts to modify this scheme that are quite complex but may be more effective (27), and other efforts are now underway. The incidence of these anomalies was estimated to be 0.02% of the female population, but the incidence may have increased as a result of the maternal ingestion of diethylstilbestrol (DES) and the resultant increase in anomalies of the lumen of the uterus (class VI) (28). Of the disorders unrelated to drug use, the septate uterus (class V) is most common.

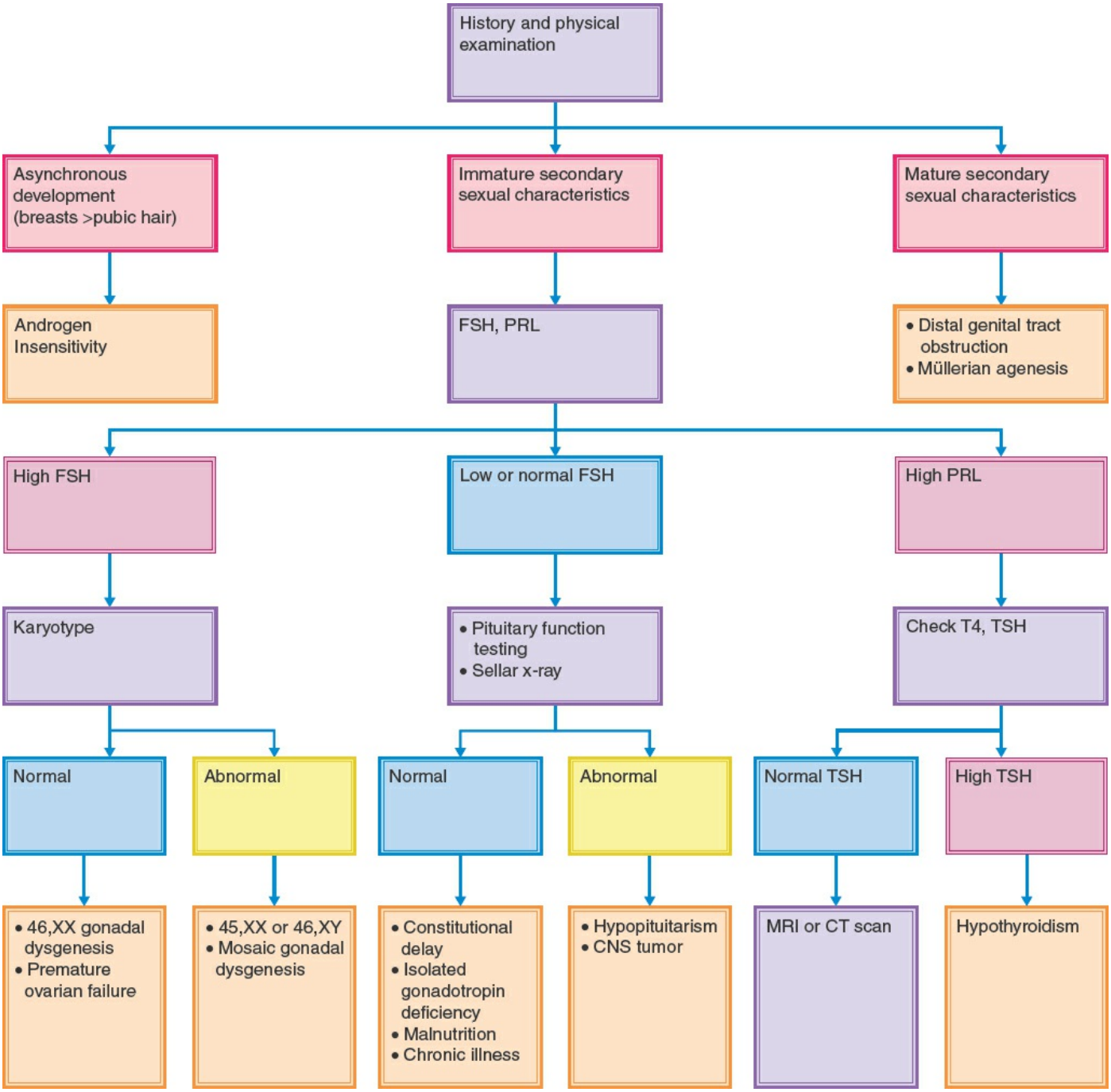


FIGURE 8-7 Flow diagram for the evaluation of delayed or interrupted pubertal development, including primary amenorrhea, in phenotypic girls. Girls with asynchronous development often present because of failure to menstruate. FSH, follicle-stimulating hormone; PRL, prolactin; T4, thyroxine; TSH, thyroid-stimulating hormone; CNS, central nervous system; MRI, magnetic resonance imaging; CT, computed tomography. (From **Rebar RW**. Normal and abnormal sexual differentiation and pubertal development. In: Moore TR, Reiter RC, Rebar RW, et al., eds. *Gynecology and Obstetrics: A Longitudinal Approach*. New York: Churchill Livingstone; 1993:97–133, with permission.)

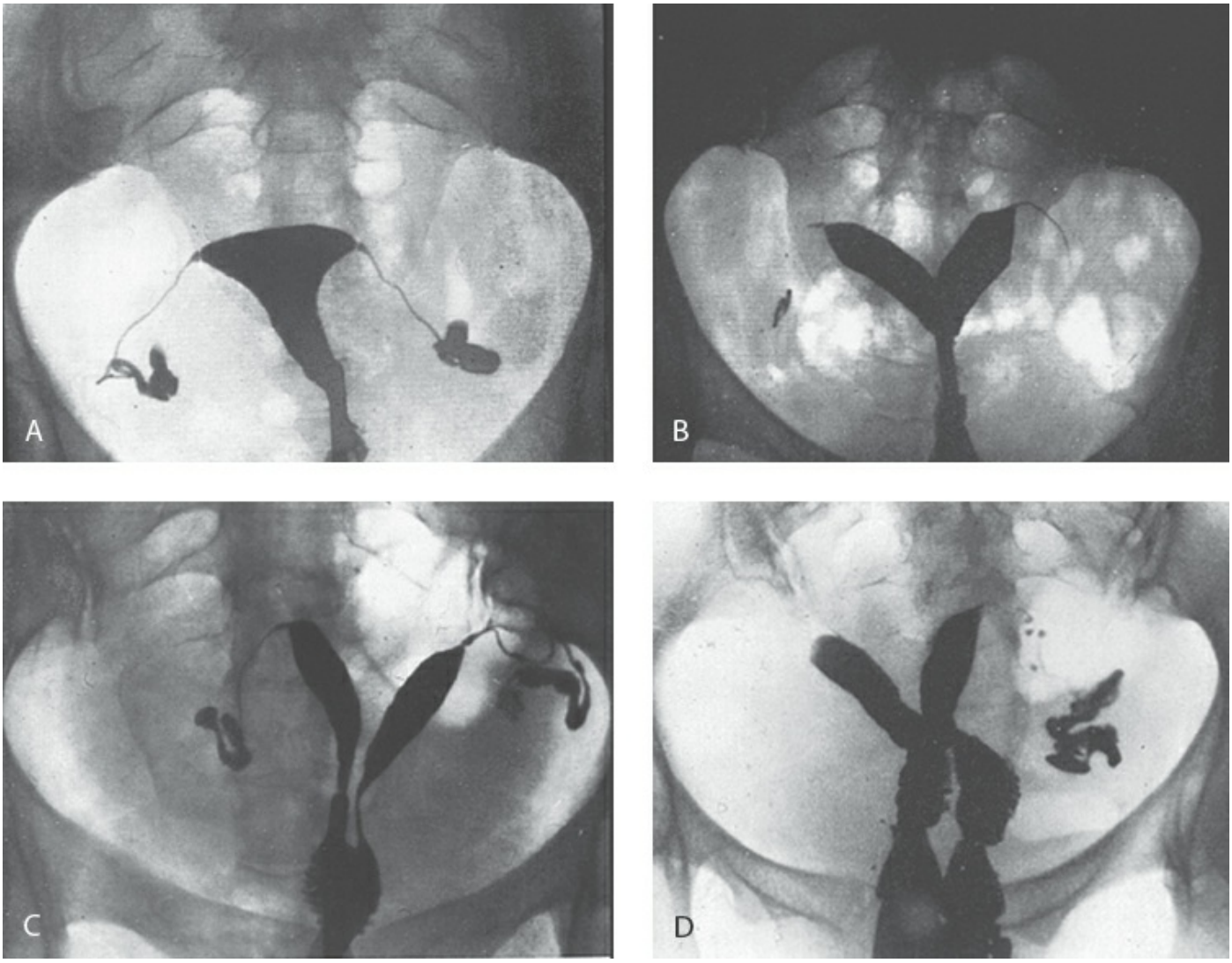


FIGURE 8-8 Hysterosalpingograms of normal and abnormal female genital tracts. The radiographic photographs have been reversed to accentuate the uterine cavities. **A:** Normal study with bilateral spill. **B:** Bicornuate uterus. **C:** Uterus didelphys. **D:** Uterus didelphys with double vagina. (Courtesy of **Dr. A. Gerbie;** from **Spitzer IB, Rebar RW.** Counselling for women with medical problems: ovary and reproductive organs. In: Hollingsworth D, Resnik R, eds. *Medical Counselling Before Pregnancy*. New York: Churchill Livingstone; 1988:213–248, with permission.)

Disorders of the outflow tract and uterus often occur as a part of a syndrome of malformations that include abnormalities of the skeletal and renal systems (***Mayer–Rokitansky–Küster–Hauser syndrome***). Familial aggregates of the most common disorders of müllerian differentiation in girls—müllerian aplasia and incomplete müllerian fusion—are best explained on the basis of polygenic and multifactorial inheritance (29). It is clear that the *HOX* genes, a family of regulatory genes that encode for transcription factors, are essential for proper development of the müllerian tract in the embryonic period, and *HOXA13* is altered in hand–foot–genital syndrome (30). *WNT4* may be involved in uterine development, as a *WNT4* mutation was described in cases involving a Mayer–Rokitansky–Küster–Hauser-like syndrome with

hyperandrogenism (31).

Table 8-2 Classification of Müllerian Anomalies

Class I. Segmented müllerian agenesis or hypoplasia
A. Vaginal
B. Cervical
C. Fundal
D. Tubal
E. Combined
Class II. Unicornuate uterus
A. With a rudimentary horn
1. With a communicating endometrial cavity
2. With a noncommunicating cavity
3. With no cavity
B. Without any rudimentary horn
Class III. Uterus didelphys
Class IV. Bicornuate uterus
A. Complete to the internal os
B. Partial
C. Arcuate
Class V. Septate uterus
A. With a complete septum
B. With an incomplete septum
Class VI. Uterus with internal luminal changes

Adapted from **Buttram VC Jr, Gibbons WE.** Müllerian anomalies: a proposed classification (an analysis of 144 cases). *Fertil Steril* 1979;32:40, with permission.

The most common single anatomic disorder of puberty is the imperforate hymen, which prevents the passage of endometrial tissue and blood. These products can accumulate in the vagina (*hydrocolpos*) or uterus (*hydrometrocolpos*) and result in a bulging hymen that is often bluish in color. The affected individual often has a history of vague abdominal pain with approximately monthly exacerbations. It is sometimes

difficult to distinguish an imperforate hymen from a transverse vaginal septum, and in most situations, examination under anesthesia is required.

Regardless of the cause, uterine anomalies not involving segmental müllerian agenesis or hypoplasia (class I) can be compatible with spontaneous pregnancy. However, increased fetal loss is reported in the presence of these anomalies (32). Uterine malformations are associated with spontaneous abortion, preterm labor, abnormal presentations, and complications of labor (i.e., retained placenta). Many of these uterine anomalies can be identified with hysterosalpingography **(Fig. 8-8)**. Hysterosalpingography, laparoscopy, and hysteroscopy are used to differentiate a septate uterus (class V) from a bicornuate uterus (class IV). Three-dimensional ultrasound has been emerging as the modality of choice in imaging these anomalies and has had a high concordance with results from magnetic resonance imaging (MRI) (33).

Obstruction or malformation of the distal genital tract must be distinguished from androgen insensitivity. Individuals with androgen insensitivity have breast development in the absence of significant pubic and axillary hair development; the vagina may be absent or foreshortened in these women.

Hypergonadotropic and Hypogonadotropic Hypogonadism

Basal levels of FSH and prolactin should be determined in individuals in whom secondary sex characteristics have not developed to maturity (Fig. 8-7). Bone age should be estimated from x-rays of the nondominant hand. If prolactin levels are elevated, thyroid function should be assessed to determine whether the individual has primary hypothyroidism. Paradoxically, primary hypothyroidism can result in precocious puberty. If thyroid function is normal, a hypothalamic or pituitary neoplasm is possible, and careful evaluation of the hypothalamic and pituitary area by MRI or computed tomography (CT) is indicated.

The karyotype should be determined in any individual with delayed puberty and increased basal FSH concentrations. Regardless of the karyotype, the individual with hypergonadotropic hypogonadism has some form of ovarian "failure" (i.e., primary hypogonadism, now known as premature ovarian insufficiency [POI]).

Forms of Gonadal Failure

Turner Syndrome

The diagnosis of Turner syndrome requires the presence of characteristic features in phenotypic females coupled with complete or partial absence of the second sex chromosome, with or without cell line mosaicism. **Most affected individuals have a 45,X karyotype, while others have mosaic karyotypes (i.e., 45,X/46,XX; 45,X/46,XY).** Intrauterine growth restriction is common in infants with a 45,X karyotype. After birth, these patients generally grow slowly, beginning in the 2nd or 3rd

year of life. They typically have many of the associated stigmata, including lymphedema and sometimes large cystic hygromas of the neck at birth; a webbed neck; multiple pigmented nevi; and disorders of the heart, kidneys (most commonly horseshoe), and great vessels (commonly coarctation of the aorta) **(Fig. 8-9)**. Many of the anatomic findings can be detected in prenatal screening. Diabetes mellitus, thyroid disorders, essential hypertension, and other autoimmune disorders are often present in individuals with 45,X karyotypes (32).

Most 45,X patients have normal intelligence, but many affected individuals have an unusual cognitive defect characterized by an inability to appreciate the shapes and relations of objects with respect to one another (i.e., space-form blindness). As they grow older, affected children typically are shorter than normal. Although they do not develop breasts at puberty, some pubic or axillary hair may develop because appropriate adrenarche can occur with failure of thelarche (i.e., breast development).

Although less severe short stature and some adolescent development may occur with chromosomal mosaicism, it is reasonable to assume that any short, slowly growing, sexually infantile girl has Turner syndrome until proved otherwise because this disorder is so prevalent (about 1 in 2,500 newborn phenotypic females). In fact, the 45,X karyotype is the single most frequent chromosomal disorder in humans, but most affected fetuses are aborted spontaneously early in pregnancy.

The short stature commonly associated with the Turner phenotype appears to result from the loss of a homeobox-containing gene, which encodes an osteogenic gene. This gene, which is called *SHOX* (short stature homeobox-containing gene), escapes X inactivation because of its pseudoautosomal location on the short arm of the X (at Xp22). The gene appears to account for the height deficit and other skeletal aberrations commonly associated with Turner syndrome (34).

Even in the presence of typical Turner stigmata, a karyotype is indicated to eliminate the possibility of the presence of any portion of a Y chromosome. Analysis of pooled data suggests that the **presence of Y chromosome material is associated with an increased risk of a gonadoblastoma** (35). **If a Y chromosome is identified, laparoscopic prophylactic gonadectomy is recommended at the time of diagnosis to eliminate the risk of malignancy. Although gonadoblastomas are benign tumors with no metastatic potential that can arise spontaneously in gonads containing a portion of a Y chromosome, they can be precursors to germ cell malignancies, such as dysgerminomas (most commonly), teratomas, embryonal carcinomas, or endodermal sinus tumors** (36). In individuals in whom there is no evidence of neoplastic dissemination, the uterus may be left in situ for donor in vitro fertilization and embryo transfer.

Turner syndrome carries a significantly increased risk of structural and

functional cardiac abnormalities. All individuals with Turner syndrome should have an initial comprehensive cardiac evaluation followed by regular follow-up. **Individuals with Turner syndrome are at increased risk of sudden death from aortic rupture or dissection resulting from cystic medial necrosis during pregnancy, and the risk may be as great as 2% or more** (37). The Practice Committee of the American Society for Reproductive Medicine, in 2012, published guidelines stating that Turner syndrome is a relative contraindication for pregnancy because of this increased risk (38).





FIGURE 8-9 Typical appearance of two individuals with 45,X gonadal dysgenesis. **A:** This 16-year-old individual has obvious short stature, a webbed neck, shortened fourth metatarsals, and a thoracotomy scar from the repair of the coarctation of the aorta that was performed at 13 years of age. **B:** This 11-year-old individual also has obvious short stature and stigmata of Turner syndrome. Note that these two individuals look more like each other than they might look like any genetic siblings.

The evaluation of other commonly involved organ systems should include a careful physical examination, with special attention to the cardiovascular system, and thyroid function tests (including antibody assessment), fasting blood glucose, renal function tests, and intravenous pyelography or a renal ultrasonography.

Treatment of Turner Syndrome

Short stature is the most common finding in females with Turner syndrome. To increase final adult height, commonly accepted treatment strategies include use of exogenous GH. Therapy with GH accelerates growth velocity and improves final adult height. Initiation of therapy as early as 4 years of age maximizes height outcome. GH has had a favorable profile in patients with TS, but unwanted side effects such as scoliosis, benign intracranial hypertension, and others should be screened for on a regular basis (39).

It is not clear if a nonaromatizable anabolic steroid such as *oxandrolone* will provide additional growth. In girls older than 8 years at initiation of therapy or those with extremely short stature, consideration can be given to using high doses of GH and adding *oxandrolone* (39).

Gonadal steroids should be administered to compensate for gonadal failure, typically beginning at ages 12 to 14 years in an emotionally prepared individual, and are required for bone health, breast development, and uterine growth. The dosing of the hormone replacement should be aligned to the physiologic process as much as possible. Transdermal estradiol patches can be used effectively, easily allowing for increasing doses slowly over time. After several months of low-dose estrogen only, or if there is uterine bleeding, a progestogen can be added in phase to mimic natural cycles. The medication regimen should be individualized for each patient based on tolerance of the medication, side effects, and compliance (39).

Long-term use of estrogens and progestogens in women with Turner syndrome necessitates awareness of the increased risk of venous thromboembolism (VTE). In addition to the risk imposed by the medications, there are case reports suggesting a higher rate of VTE in individuals with Turner syndrome (39).

Mosaic Forms of Gonadal Dysgenesis

Individuals with rare mosaic forms of gonadal dysgenesis may develop normally at puberty. The decision to initiate therapy with exogenous estrogen should be based mainly on circulating FSH levels. Levels in the normal range for the patient's age imply

the presence of functional gonads.

Pure Gonadal Dysgenesis

The term *pure gonadal dysgenesis* refers to 46,XX or 46,XY phenotypic females who have streak gonads. This condition may occur sporadically or may be inherited as an autosomal recessive trait or as an X-linked trait in XY gonadal dysgenesis **(Fig. 8-10)**. Affected girls typically are of average height and have none of the stigmata of Turner syndrome, but they have elevated levels of FSH because the streak gonads produce neither steroid hormones nor inhibin. **When gonadal dysgenesis occurs in 46,XY individuals, it is sometimes termed *Swyer syndrome*. Surgical extirpation is warranted in individuals with a 46,XY karyotype to prevent development of germ cell neoplasms.** Both 46,XX and 46,XY forms of gonadal dysgenesis benefit from exogenous estrogen and are potential candidates for donor oocytes.


A


B


D


C

FIGURE 8-10 A: A 16-year-old individual with 46,XX gonadal dysgenesis and primary amenorrhea. Circulating follicle-stimulating hormone (FSH) levels were markedly elevated. The small amount of breast development (Tanner stage 2) is unusual, but some pubertal development may occur in such patients. **B: A 16-year-old individual with 46,XY gonadal dysgenesis who presented with primary amenorrhea and markedly elevated FSH levels.** Most affected individuals do not present with as much pubic and axillary hair development. The right gonad contained a dysgerminoma, but there was no evidence of metastases. **C:** Clitoromegaly noted in the girl with 46,XY gonadal dysgenesis depicted in Figure 8-10B. **D:** The same individual as depicted in Figure 8-10B with 46,XY gonadal dysgenesis 1 year after gonadectomy and replacement with exogenous estrogen. (From **Rebar RW.** Normal and abnormal sexual differentiation and pubertal development. In: Moore TR, Reiter RC, Rebar RW, et al., eds. *Gynecology and Obstetrics: A Longitudinal Approach*. New York: Churchill Livingstone; 1993:97–133, with permission.)

In early gonadal failure, the ovaries apparently develop normally but contain no oocytes by the expected age of puberty. These disorders are considered further in the discussion delineating the evaluation of amenorrhea (see Chapter 34).

Hypogonadotropic Hypogonadism

Hypothalamic–pituitary disturbances are usually associated with low levels of circulating gonadotropins (with both LH and FSH levels less than or equal to 10 mIU/mL) (40). There are sporadic and familial causes of hypogonadotropic hypogonadism, and the differential diagnosis is extensive. **Mutations in several genes cause hypogonadotropic hypogonadism in humans** (41). This condition can arise from abnormalities in hypothalamic GnRH secretion, impaired release of gonadotropins from the pituitary gland, or both.

At least 17 different single-gene mutations are identified as being associated with delayed or absent puberty in humans (42). They are estimated to account for about 30% of individuals with disorders of puberty. These genes include *KAL1* (X-linked Kallmann syndrome), *FGFR1* (autosomal Kallmann syndrome), *DAX1* (the gene for X-linked congenital adrenal hypoplasia), *GNRHR* (the gene for the GnRH receptor), *PC1* (the gene for prohormone convertase 1), and *GPR54* (encoding a G-protein coupled receptor). Delayed puberty may result from mutations in genes affecting gonadotrophs specifically (*GNRHR, LH*b, *FSH*b) or in genes involved more generally in the development and functioning of the pituitary gland (*LHX3, PROP1, HESX1*).

Constitutional Delay

It is important to remember that low levels of LH and FSH are normally present in the prepubertal years; thus, girls with constitutionally delayed puberty may mistakenly be presumed to have hypogonadotropic hypogonadism. **Constitutional delay is the most common cause of delayed puberty.** In a normal population, 2% to 3% of normal children will be classified as having pubertal delay, and this finding may be considered a normal variant.

Kallmann Syndrome

Kallmann syndrome **consists of the triad of anosmia, hypogonadism, and color blindness in men** (43)**. Women may be affected, and other associated defects may include cleft lip and palate, cerebellar ataxia, nerve deafness, and abnormalities of thirst and vasopressin release.** The frequency approximates 1 in 10,000 men and 1 in 50,000 women. Sporadic cases are more common than inherited forms. Inheritance is described as being X-linked recessive, autosomal dominant, and autosomal recessive. Because autopsy studies show partial or complete agenesis of the olfactory bulb, the term *olfactogenital dysplasia* is used to describe the disorder. These anatomic findings coincide with embryologic studies documenting that GnRH neurons originally develop in the epithelium of the olfactory placode and normally migrate into the hypothalamus (44).

Clinically, affected individuals typically present with sexual infantilism and a eunuchoid habitus, but some degree of breast development may occur (Fig. 8-11). Primary amenorrhea is the rule. The ovaries are usually small, with follicles seldom developing beyond the primordial stage. Circulating gonadotropin levels are usually very low but almost invariably measurable. For women not seeking pregnancy, therapy with exogenous estrogen and progestin is indicated.

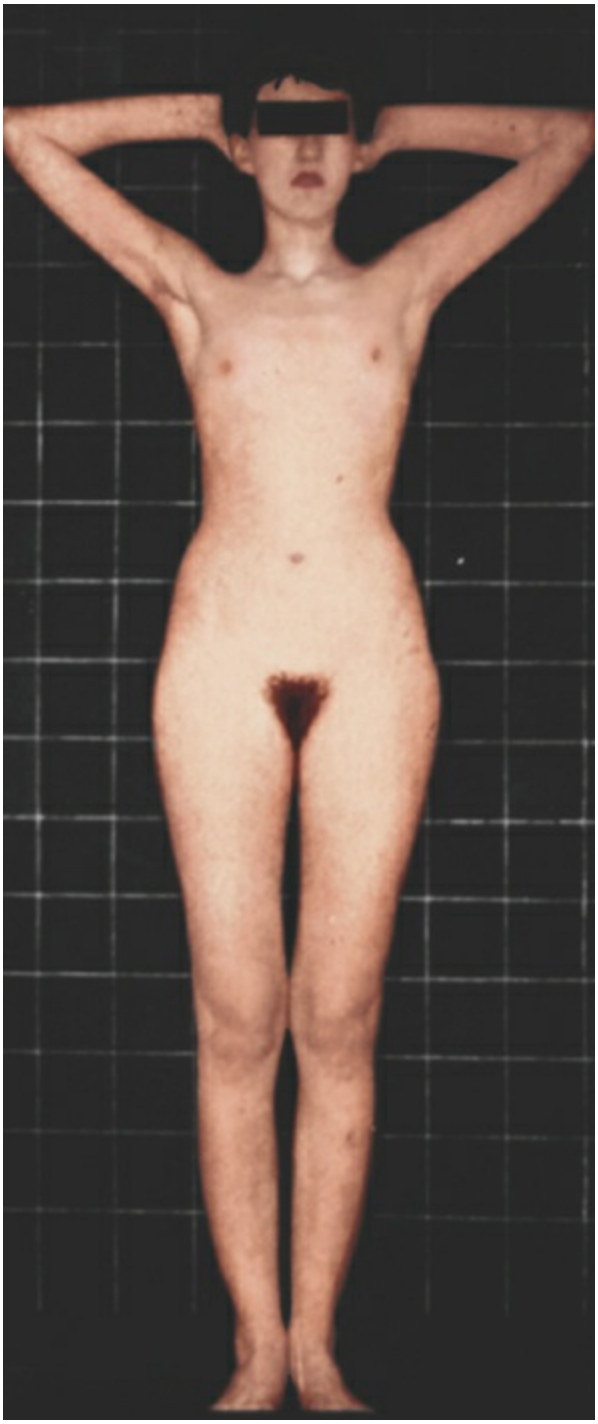


FIGURE 8-11 A 21½-year-old woman with Kallmann syndrome. Note that the patient has some pubic and axillary hair. Bone age was 16 years. It is rare to see affected individuals today who were not given oral contraceptive agents to induce menses (with some consequent breast development). (From **Wilkins L.** *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*. 3rd ed. Springfield, IL: Charles C Thomas; 1965:284, with permission.)

Isolated gonadotropin deficiency can occur in association with the *Prader–Labhart–Willi syndrome,* which is characterized by obesity, short stature, hypogonadism, small hands and feet (acromicria), mental retardation, and infantile hypotonia. When the syndrome occurs in association with the Laurence–Moon–Bardet–

Biedl syndrome, retinitis pigmentosa, postaxial polydactyly, obesity, and hypogonadism may be present. Prader–Labhart–Willi syndrome apparently results from rearrangements of chromosome 15q11 to q13, an imprinted region of the human genome (45). Laurence–Moon–Bardet–Biedl syndrome, inherited in an autosomal recessive manner, is apparently heterogeneous, with at least four involved gene loci having been mapped (46).

Multiple pituitary hormone deficiencies, which are usually hypothalamic in origin, may be congenital and either part of an inherited constellation of findings or sporadic. If GH or thyroid-stimulating hormone (TSH) concentrations are subnormal, growth and pubertal development will be affected. Thus, the condition should be diagnosed before the age of puberty. Because individuals with hypopituitarism have a high mortality rate, predominantly caused by vascular and respiratory disease, it is important to identify affected individuals. Later age at diagnosis, female sex, and above all craniopharyngioma are identified as significant independent risk factors (47). Untreated gonadotropin deficiency is an important risk factor for early mortality.

Tumors of the Hypothalamus and Pituitary

Several different tumors of the hypothalamic and pituitary regions may lead to hypogonadotropic hypogonadism (Fig. 8-12A) (48). **Except for craniopharyngiomas, these tumors are relatively uncommon in children. A craniopharyngioma is a tumor of the Rathke pouch. It is the most common neoplasm associated with delayed puberty, and it accounts for 10% of all childhood central nervous system tumors. Craniopharyngiomas are usually suprasellar in location and may be asymptomatic well into the second decade of life.** Such tumors may present as headache, visual disturbances, short stature or growth failure, delayed puberty, or diabetes insipidus. Visual field defects (including bilateral temporal hemianopsia), optic atrophy, or papilledema may be seen on physical examination. Laboratory evaluation should document hypogonadotropism and may reveal hyperprolactinemia as a result of interruption of hypothalamic dopamine inhibition of prolactin release. Radiographically, the tumor may be either cystic or solid and may show areas of calcification. Appropriate therapy for hypothalamic–pituitary tumors may involve surgical excision or radiotherapy (with adequate pituitary hormone replacement therapy) and are best managed by a team of physicians that includes an endocrinologist, a neurosurgeon, and a radiotherapist.


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FIGURE 8-12 A: A 16-year-old girl with delayed puberty. Breast budding began at 11 years of age, but there was no further development. During the year before presentation, her scholastic performance in school deteriorated, she gained 25 lb, she became increasingly lethargic, and nocturia and polydipsia were noted. Initial evaluation documented low follicle-stimulating hormone, elevated prolactin, and a bone age of 10.5 years. Computed tomography scanning documented a large hypothalamic neoplasm that proved to be an ectopic germinoma. The patient was also documented to be hypothyroid and hypoadrenal and to have diabetes insipidus. Despite the elevated prolactin, she had no galactorrhea because of the minimal breast development. **B: A16-year-old girl (frontal view) with primary amenorrhea who progressed in puberty until about 12 years of age.** Breast budding occurred at about 10 years of age. The patient's short stature is obvious. She proved to have hypopituitarism. Classic radiographic findings established the diagnosis of Langerhans cell–type histiocytosis (Hand–Schüller–Christian disease). **C: Side view of the girl shown in** Figure 8-12B. (From **Rebar RW.** Normal and abnormal sexual differentiation and pubertal development. In: Moore TR, Reiter RC, Rebar RW, et al., eds. *Gynecology and Obstetrics: A Longitudinal Approach*. New York: Churchill Livingstone; 1993:97–133, with permission.)

Other Central Nervous System Disorders

Other central nervous system disorders that may lead to delayed puberty include infiltrative diseases, such as Langerhans cell–type histiocytosis, particularly the form known previously as ***Hand–Schüller–Christian disease*** **(Fig. 8-12B,C)**. Diabetes insipidus is the most common endocrinopathy (because of infiltration of the supraoptic nucleus in the hypothalamus), but short stature resulting from GH deficiency and delayed puberty caused by gonadotropin deficiency are not uncommon in this disorder (49).

Irradiation of the central nervous system for treatment of any neoplasm or leukemia may result in hypothalamic dysfunction. Although GH deficiency is the most frequent finding, partial or complete gonadotropin deficiency may develop in some patients.

Severe chronic illnesses, often accompanied by malnutrition, may lead to slowed growth in childhood and delayed adolescence. Regardless of the cause, weight loss to less than 80% to 85% of ideal body weight often results in hypothalamic GnRH deficiency. If adequate body weight and nutrition are maintained in chronic illnesses such as Crohn disease or chronic pulmonary or renal disease, sufficient gonadotropin secretion usually is present to initiate and maintain pubertal development.

Human Immunodeficiency Virus Infection

Most of the information gathered regarding pubertal development and the presence of HIV are from females who have congenital HIV. Delays in development coincide with treatment status and CD4 count (50).

Anorexia Nervosa and Bulimia

Significant weight loss and endocrine and psychological dysfunction occur simultaneously in anorexia nervosa (51). Although many anorectic girls experience amenorrhea after pubertal development begins, if the disorder begins sufficiently early, pubertal development may be delayed or interrupted **(Fig. 8-13)**. **The following constellation of associated findings confirms anorexia nervosa in most individuals:**

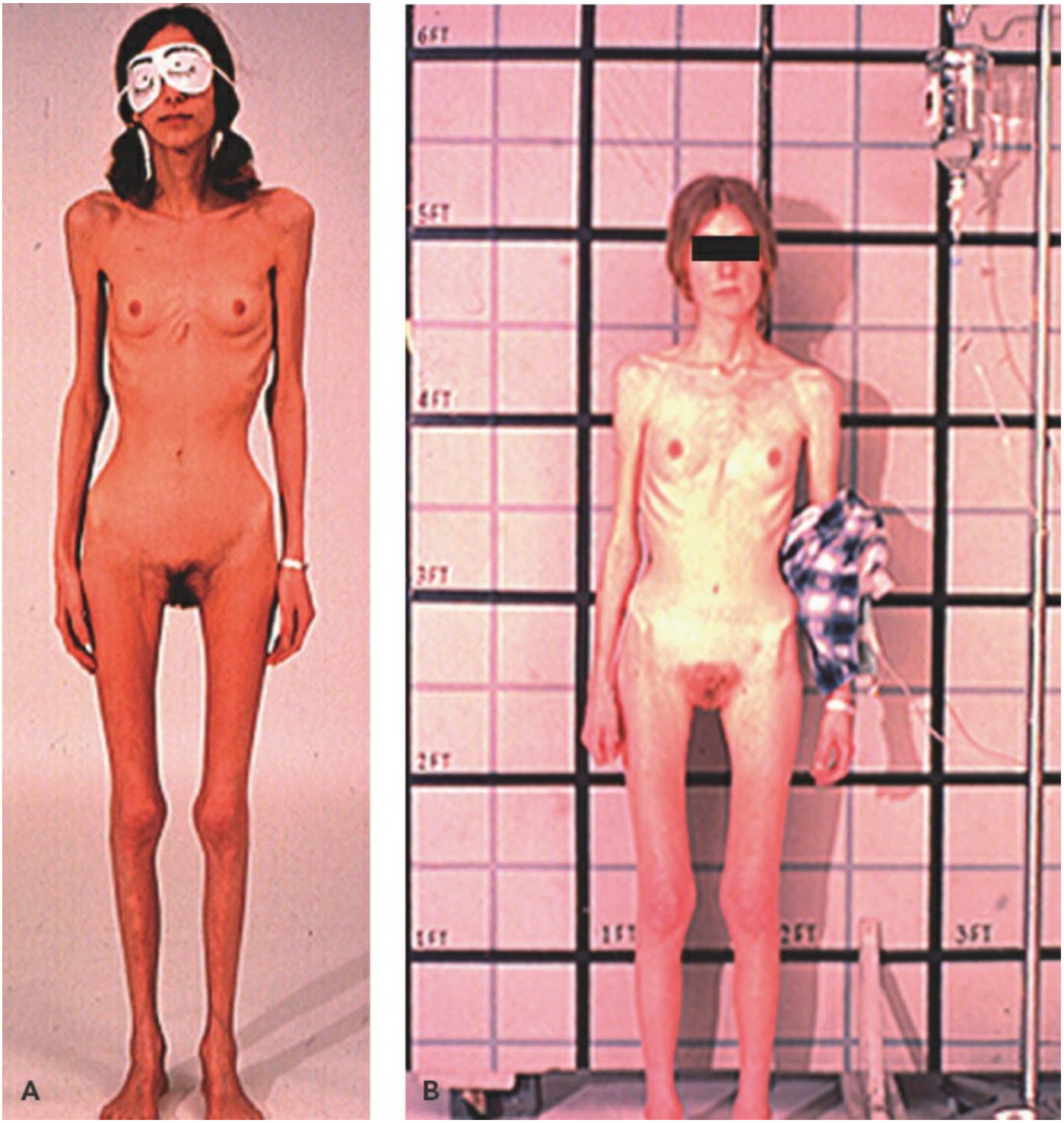


FIGURE 8-13 **A:** A 20-year-old college woman with anorexia nervosa. **B:** A 16-year-old student with anorexia nervosa. In both cases, as is true of most such patients, pubertal development had been completed and menses initiated before anorexia led to marked weight loss.

1. **Relentless pursuit of thinness**
2. **Amenorrhea, sometimes preceding the weight loss**
3. **Extreme inanition**
4. **Obsessive–compulsive personality often characterized by overachievement**

5. **Distorted and bizarre attitude toward eating, food, or weight**
6. **Distorted body image**

Because normal body weight is commonly maintained in bulimia, it is unusual for bulimic patients to experience either delayed development or amenorrhea. Girls with anorexia nervosa may have, in addition to hypogonadotropic hypogonadism, partial diabetes insipidus, abnormal temperature regulation, hypotension, chemical hypothyroidism with low serum triiodothyronine (T_3) and high reverse T_3 levels, and elevated circulating cortisol levels in the absence of evidence of hypercortisolism (51,52). Other common features include hypokalemia, anemia, hypoalbuminemia, high β-carotene levels, and high cholesterol levels. All features of anorexia nervosa are reversible with weight gain, except for amenorrhea (which persists in 30% to 47%) and osteopenia (i.e., it now seems that any bone lost cannot be fully recovered). **Management of patients with anorexia nervosa is notoriously difficult. A team approach involving the primary clinician, psychiatrist, and nutritionist is most effective. In fact, anorexia nervosa has the highest mortality of any psychiatric disorder. Deaths are often sudden and unexpected. Cause of death (often unknown) can include hypoglycemia and electrolyte imbalance.**

Fear of obesity, a syndrome of self-induced malnutrition common among teenage gymnasts and ballet dancers, may slow growth and delay pubertal development (53). These children voluntarily reduce their caloric intake as much as 40%, leading to nutritional growth retardation. An additive role of the energy drain associated with endurance training in the delayed development is possible, but the mechanisms are unclear at this point. These conditions are essentially severe forms of hypothalamic amenorrhea. Inevitably delayed puberty will occur unless adequate caloric intake is provided.

Hyperprolactinemia

Low levels of LH and FSH may be associated with hyperprolactinemia. Galactorrhea cannot occur in the absence of complete breast development. Pituitary prolactinomas are rare during adolescence but must be considered when certain signs and symptoms are present. **Many individuals with prolactinomas have a history of delayed menarche.** The association between the ingestion of certain drugs (most often psychotropic agents and opiates in this age group) is well established. Primary hypothyroidism is associated with hyperprolactinemia because increased levels of thyrotropin-releasing hormone (TRH) stimulate secretion of prolactin. The ***empty sella syndrome***, in which the sella turcica is enlarged but is replaced by cerebrospinal fluid, may be associated with hyperprolactinemia.

Use of Chemotherapeutic Agents

As survival rates following treatment for childhood malignancy improve, the effects of cancer therapy become more important. Radiation therapy to the abdomen and systemic chemotherapeutic agents, particularly alkylating agents, have toxic effects on germ cells. Although prepubertal gonads appear less vulnerable than those of adults, ovarian failure is common. An argument can be made for endocrine assessment as early as 1 year following completion of therapy to identify children who will suffer from hypogonadism. Spontaneous ovarian activity can resume even years after therapy. Counseling regarding preservation of oocytes or ovarian tissue for young women with malignancies prior to treatment is now warranted because of the possibility of future pregnancies with in vitro fertilization using frozen samples.

Asynchronous Puberty

[4] Asynchronous pubertal development is characteristic of androgen insensitivity (i.e., testicular feminization). Affected individuals typically present with breast development (usually only to Tanner stage 3) out of proportion with the amount of pubic and axillary hair present **(Fig. 8-14)**. In this disorder, 46,XY individuals have bilateral testes, female external genitalia, a blind-ending vagina (often foreshortened and sometimes absent), and no müllerian derivatives (i.e., uterus and fallopian tubes) (54). Infrequently, patients may have clitoral enlargement and labioscrotal fusion at puberty, which is referred to as *incomplete androgen insensitivity*.

Asynchronous puberty is heterogeneous but is always related to some abnormality of the androgen receptor or of androgen action (54). In perhaps 60% to 70% of cases, androgen receptors cannot be detected (i.e., the patient is receptor negative). In the remaining cases, androgen receptors are present (i.e., receptor positive), but mutations in the androgen receptor are detected or there is a defect at a more distal step in androgen action (i.e., a postreceptor defect). Receptor-positive individuals are indistinguishable clinically from receptor-negative individuals. Several different mutations in the androgen-receptor gene, most of which occur within the androgen-binding domain of the receptor, are identified in affected individuals who are receptor positive. Severe X-linked androgen-receptor gene mutations cause complete androgen insensitivity, whereas mild mutations impair virilization with or without infertility, and moderate mutations result in a wide phenotypic spectrum of expression among siblings (54).

Because the Sertoli cells of the testes make antimüllerian hormone (AMH), müllerian derivatives are absent in this disorder; thus, müllerian regression occurs normally. The testes are often normal in size and may be located anywhere along the path of embryonic testicular descent—in the abdomen, inguinal canal, or labia. Half of all individuals with androgen insensitivity develop inguinal hernias. It is important to determine the karyotype in prepubertal girls with inguinal hernias, especially if a uterus

cannot be detected with certainty by ultrasound, because a small percentage will have androgen insensitivity.

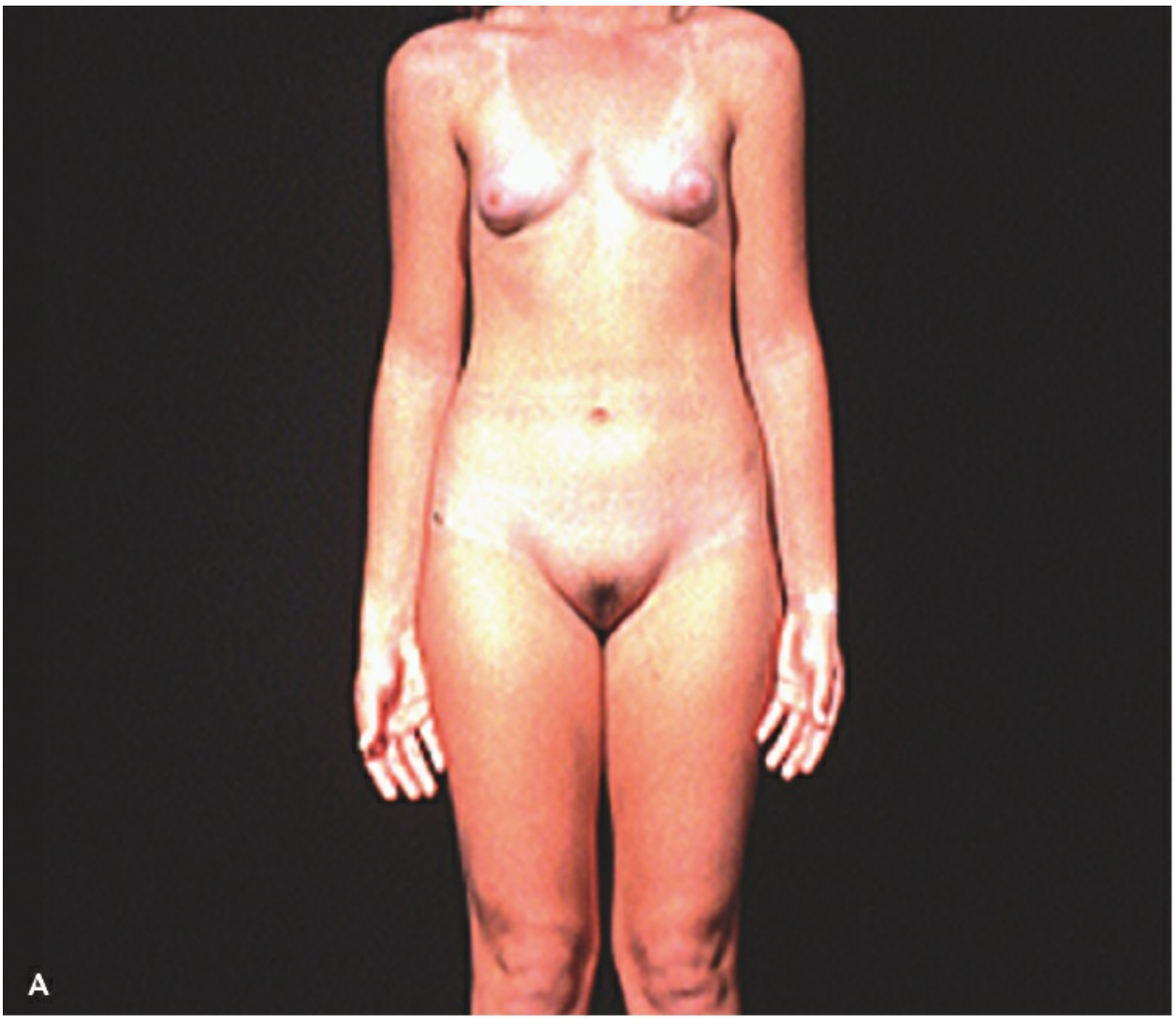
The risk of germ cell malignancy is 2% in complete androgen insensitivity syndrome (54). Most clinicians believe the risk for gonadal neoplasia is low before 25 years of age; thus, the **testes should be left in place until after pubertal feminization, especially because the risk of neoplasia appears to increase with age.** Exogenous estrogen should be provided after gonadectomy.

The diagnosis is often suspected by the typical physical findings and strongly suggested by normal (or even somewhat elevated) male levels of testosterone, normal or somewhat elevated levels of LH, and normal levels of FSH. The diagnosis is confirmed by a 46,XY karyotype.

Interacting with the patient and family requires sensitivity and care. It may be inadvisable to begin by informing the patient of the karyotype; the psychological implications may be devastating because the patient was reared as a girl. Family members should be informed initially that müllerian aplasia occurred and that the risk for neoplasia mandates gonadectomy after puberty. Because the disorder can be inherited in an X-linked recessive fashion, families should undergo appropriate genetic counseling and screening to identify the possible existence of other affected family members.

Precocious Puberty

[5] Although precocious pubertal development may be classified in several ways, it is perhaps simplest to think of the development as gonadotropin dependent (in which case it is almost invariably of central origin) or gonadotropin independent (of peripheral origin). Precocious puberty is 20 times more common in girls than in boys. In 90% of girls, the precocious development is idiopathic, whereas this appears to be true for only 10% of boys. Family history, the rapidity with which secondary sexual characteristics are developing, the rate of growth, and the presence or absence of central nervous system disease should all be considered in deciding whether to pursue evaluation of a girl for precocious puberty. The evaluation of precocious puberty is as follows **(Fig. 8-15)**:


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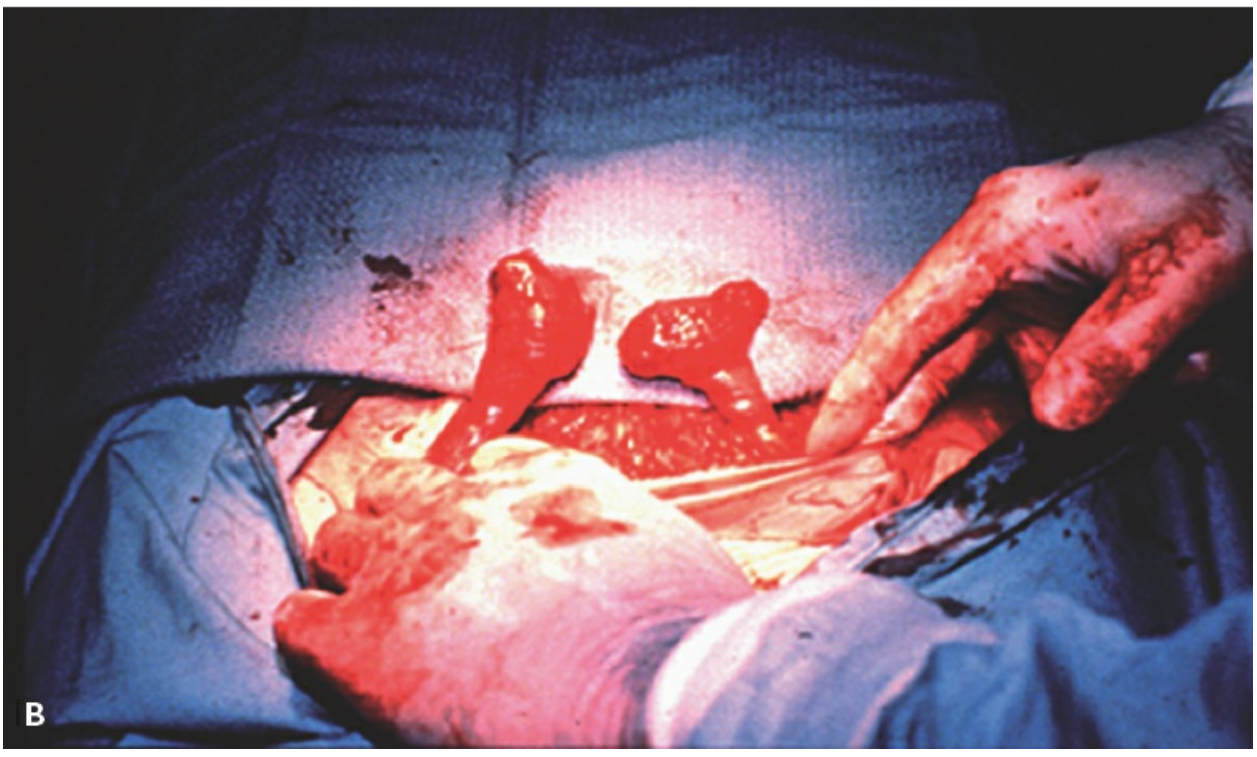

B

FIGURE 8-14 **A:** This 17-year-old individual presented with primary amenorrhea and was found to have a blind-ending vagina and bilateral inguinal masses. Circulating levels of testosterone were at the upper limits of the normal range for men and the karyotype was 46,XY, confirming androgen insensitivity. **B:** Two inguinal testes were found at surgery. (From **Simpson JL, Rebar RW.** Normal and abnormal sexual differentiation and development. In: Becker KL, ed. *Principles and Practice of Endocrinology and Metabolism*. 2nd ed. Philadelphia, PA: JB Lippincott; 1995:788–822, with permission.)

1. Obtain a complete medical, birth, and family history, including details of timing and events of the pubertal development.
2. Specifically determine if there are any signs or symptoms of neurologic disease.
3. Determine the extent of development by examination and assignment of Tanner stage.
4. Carefully determine if signs of other conditions that may be associated with precocious puberty (abdominal mass, skin lesions, etc.) are present.
5. **Determine bone age.**
6. **Initial hormonal evaluation should include measurement of basal gonadotropin levels and assessment of thyroid function.**
7. **Pelvic imaging and imaging of the central nervous system are warranted depending on other findings.**

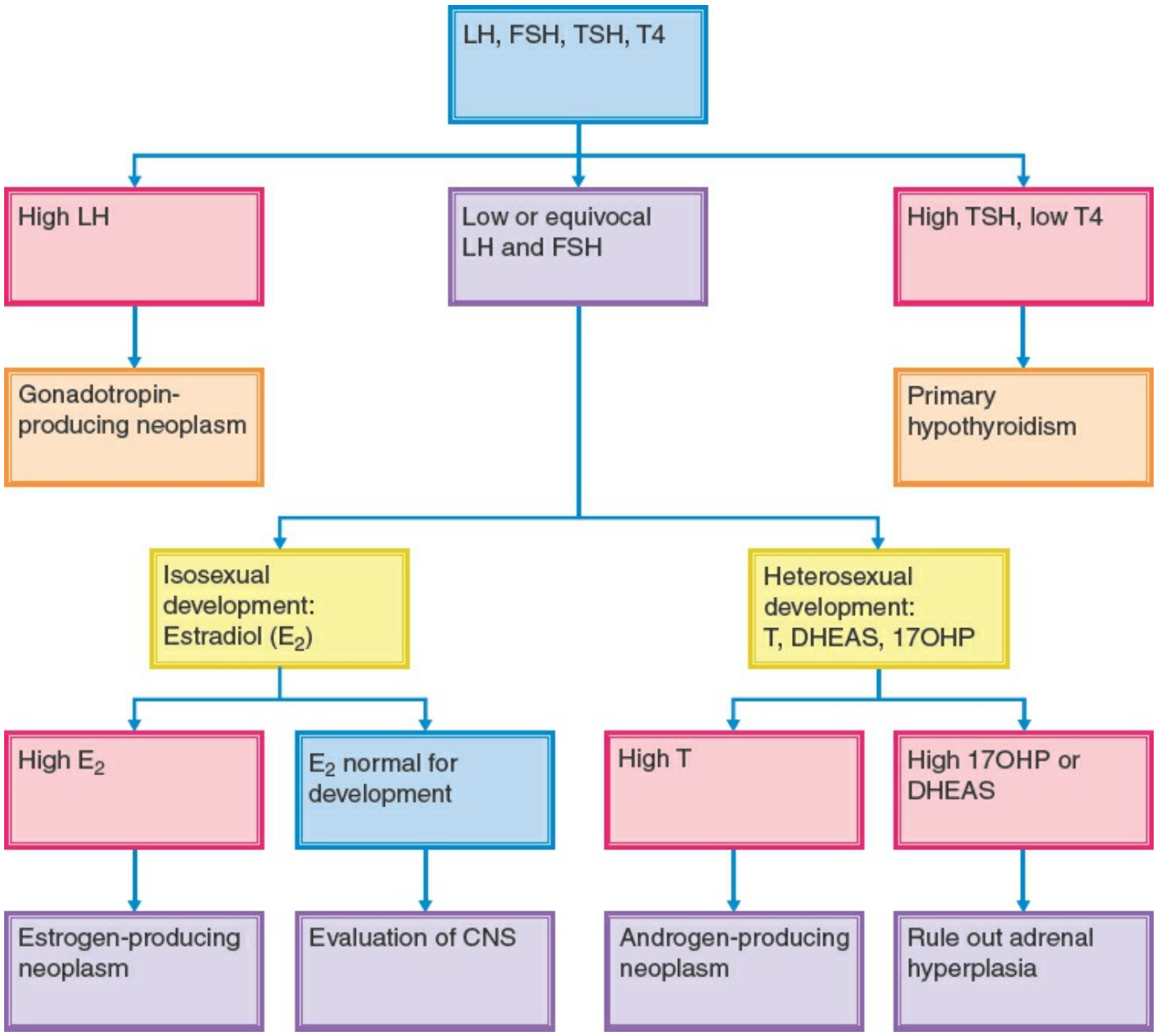


FIGURE 8-15 Flow diagram for the evaluation of precocious puberty in phenotypic females. LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; T4, thyroxine; T, testosterone; DHEAS, dehydroepiandrosterone sulfate; 17OHP, 17-hydroxyprogesterone; CNS, central nervous system. (From **Rebar RW.** Normal and abnormal sexual differentiation and pubertal development. In: Moore TR, Reiter RC, Rebar RW, et al., eds. *Gynecology and Obstetrics: A Longitudinal Approach*. New York: Churchill Livingstone; 1993:97–133, with permission.)

The goal of testing is to determine if the diagnosis of precocious puberty is correct, if the etiology is central or peripheral, and to direct treatment if needed (23).

Perhaps the most difficult decision for the gynecologist is determining how much evaluation is warranted for the young girl brought in by her mother for precocious breast budding only (*precocious thelarche*) or the appearance of pubic or axillary hair alone (*precocious pubarche* or *adrenarche*) (Fig. 8-16). In such cases, it is acceptable to many clinicians to follow the patient at frequent intervals and proceed

with evaluation if there is evidence of pubertal progression. The feasibility of this approach may depend on the concerns of the parents.

Premature Thelarche

Premature thelarche is uni- or bilateral breast enlargement without other signs of sexual maturation. There is no significant nipple or areolar development. It usually occurs by 2 years of age and rarely after age 4. It may be caused by increased sensitivity of the breasts to low levels of estrogen or to increased estradiol secretion by follicular cysts. It is a benign self-limited disorder and thus only reassurance and follow-up are required. In many cases, onset of puberty, adult height, and adult reproductive function are normal. Rarely, premature thelarche can be a harbinger of progressive gonadarche. It has been suggested that measurement of uterine volume (anteroposterior diameter × longitudinal diameter × transverse diameter × 0.523) may be the most sensitive and specific discriminator between premature thelarche and early true precocious puberty (55). If needed, breast ultrasound can help distinguish unilateral premature thelarche from fibroadenomas, cysts, neurofibromas, or other lesions.

Premature Adrenarche

Premature adrenarche or pubarche may be caused by increased sensitivity to low levels of androgens and must be distinguished from late-onset (nonclassic) CAH. If there is no evidence of breast development or of progression, these conditions are virtually always benign.

Girls with premature adrenarche are at increased risk of developing polycystic ovary syndrome (PCOS), hyperinsulinemia, acanthosis nigricans, and dyslipidemia in adolescence and adult life, especially if fetal growth was reduced and birth weight was low (56). Although mean androgen levels are within the normal range, a significant minority have an exaggerated response to corticotropin stimulation. The magnitude of this response is inversely related to insulin sensitivity. Thus, premature adrenarche may be the first sign of insulin resistance or PCOS in some individuals. Treatment of coexisting obesity and long-term follow-up are indicated to address potential complications of PCOS and insulin resistance.


A


B

FIGURE 8-16 A 5-year-old girl with development of pubic hair (**A**) as shown more closely in **B** (precocious adrenarche). Gonadotropin levels were prepubertal, and bone age was appropriate for age. No further development occurred until breast budding at approximately age 9.

Isolated Premature Menarche

Isolated premature menarche is vaginal bleeding at age 1 to 9 years in the absence of other signs of puberty. The bleeding is usually limited to a few days. It can recur for 1 to 6 years and then cease. The etiology is uncertain. Most cases are associated with subsequent normal pubertal development and fertility. The differential diagnosis includes vaginal foreign bodies, trauma, sexual abuse, vaginal infection, or neoplasms such as rhabdomyosarcoma, McCune–Albright syndrome (in which menarche may occur before other manifestations of sexual precocity), and primary hypothyroidism. Ingestion of a large dose of estrogens (such as may be found in several oral contraceptive agents) may also lead to vaginal bleeding.

Central (True) Precocious Puberty

In central precocious puberty, GnRH prematurely stimulates increased gonadotropin secretion. Central precocious puberty may occur in children in whom there is no structural abnormality, in which case it is termed *constitutional* or *idiopathic*. **Constitutional (idiopathic) sexual precocity is the most common cause of precocious puberty.** It is often familial and represents the so-called tail of the Gaussian curve (i.e., the early 2.5% for the age distribution for the onset of puberty). In many of these girls, puberty is slowly progressive, but in a few, development progresses rapidly. The major complication of sexual precocity is limitation of height. Thus, therapy may be warranted to prevent this consequence.

Alternatively, central precocious puberty may result from a tumor, infection, congenital abnormality, or traumatic injury affecting the hypothalamus. A number of congenital malformations, including hydrocephalus, craniostenosis, arachnoid cysts, and septo-optic dysplasia, can be associated with precocious puberty (and with sexual infantilism).

A common etiology (2% to 28%) of central precocious puberty is a hypothalamic hamartoma. It is a congenital malformation composed of a heterotopic mass of nerve tissue containing GnRH neurosecretory neurons, fiber bundles, and glial cells. It is not a true neoplasm and it generally does not change over time based on long-term follow-up studies with periodic CT or MRI scans. Hamartomas appear as isodense, abnormal fullnesses that do not enhance with contrast material. Extreme precocity (usually before 3 years of age) and the absence of tumor markers, such as β-human chorionic gonadotropin and α-fetoprotein, suggest a hamartoma (24). Hamartomas can be associated with laughing (gelastic) seizures, behavioral disturbances, mental retardation, and dysmorphic syndromes. It appears that hamartomas produce GnRH in a

pulsatile manner and thus stimulate gonadotropin secretion **(Fig. 8-17)**. Central precocious pubertal development can be controlled with GnRH-agonist therapy (24).

The efficacy of gonadotropin-releasing hormone analogs (GnRHa) in increasing adult height is undisputed only in early-onset (girls less than 6 years old) central precocious puberty (57). Concerns of weight gain and long-term decrease in bone mineral density with the use of GnRHa do not seem to be warranted. The most important clinical criterion for initiating GnRHa treatment is documented progression of pubertal development over a 3- to 6-month period. This observational period may not be necessary if the child is at or past Tanner stage 3, particularly with advanced skeletal maturation. It appears that discontinuation of GnRHa at a chronologic age of about 11 years and a bone age of about 12 years is associated with maximum adult height (57–60). There are a variety of GnRHa formulations, and the choice of a particular agent depends on patient and physician preference.



FIGURE 8-17 A $7^{1}/_{2}$-year-old girl with Tanner stage 4 pubertal development who began menstruating 1 month earlier. She was 57 in tall (above the 95th percentile). Luteinizing hormone and follicle-stimulating hormone levels were consistent with her development. A large neoplasm that proved to be a hypothalamic hamartoma was present on computed tomography scan. Pubertal development began at about 5 years of age.

Precocious Puberty of Peripheral Origin

In gonadotropin-independent precocious puberty, production of estrogens or

androgens from the ovaries, adrenals, or rare steroid-secreting neoplasms leads to early pubertal development. Small functional ovarian cysts, typically asymptomatic, are common in children and may cause transient sexual precocity (61). **Simple cysts (with a benign ultrasonographic appearance) can be observed and usually resolve over time.** Of the various ovarian neoplasms that can secrete estrogens, granulosa–theca cell tumors occur most frequently but are still rare (24). Although such tumors may grow rapidly, more than two-thirds are benign.

Exposure to exogenous estrogens can mimic gonadotropin-independent precocious puberty. Ingestion of oral contraceptives, other estrogen-containing pharmaceutical agents, and estrogen-contaminated foods and the topical use of estrogens have been implicated in cases of precocious development in infants and children. Ingestion of exogenous steroids over a considerable length of time is required to induce changes typical of complete precocious development.

McCune–Albright Syndrome

The *McCune–Albright syndrome* is characterized by the classic triad of polyostotic fibrous dysplasia of bone, irregular café au lait spots on the skin, and GnRH-independent sexual precocity. The café au lait spots are usually large, do not cross the midline, and have irregular "coast of Maine" margins. They are often located on the same side as the bony lesions. Sexual precocity often begins in the first 2 years and usually presents with menstrual bleeding. Girls develop sexual precocity as a result of functioning ovarian cysts. Serum estradiol is elevated. Other endocrinopathies may be present and include hyperthyroidism, hypercortisolism, hyperprolactinemia, acromegaly, and hyperparathyroidism. Osteomalacia, hepatic abnormalities, and cardiac arrhythmias may occur. Mutations of the G_sa subunit of the G protein, which couple extracellular hormonal signals to the activation of adenylate cyclase, are responsible for the autonomous hyperfunction of the endocrine glands and presumably for other defects present in this disorder (62). Treatment with a GnRH agonist is not effective because the precocious pubertal development is GnRH independent (63). A multicenter trial showed that *tamoxifen* decreases vaginal bleeding, growth rate, and the rate of bone age advancement (64).

Primary Hypothyroidism

Longstanding primary hypothyroidism is associated with sexual precocity. It can present with premature breast development or isolated vaginal bleeding. If serum prolactin is elevated, galactorrhea may be present. On pelvic ultrasound, solitary or multiple ovarian cysts may be found. Primary hypothyroidism is the only cause of precocious puberty that is associated with a delayed bone age. These features return to normal within a few months of initiation of *levothyroxine* therapy.

Congenital Adrenal Hyperplasia

***Heterosexual precocious puberty* is always of peripheral origin and is most often caused by CAH.** In most untreated or poorly treated adolescent girls and in some adolescent boys, spontaneous true isosexual pubertal development does not occur until proper treatment is instituted. In most patients treated satisfactorily from early life, the onset of puberty occurs at the expected chronologic age. Three adrenal enzyme defects —21-hydroxylase deficiency, 11β-hydroxylase deficiency, and 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency—can lead to heterosexual precocity and to virilization of the external genitalia because of increased androgen production beginning in utero (65). The clinical presentation of the various forms of CAH depends on the following factors: (i) the affected enzyme, (ii) the extent of residual enzymatic activity, and (iii) the physiologic consequences of deficiencies in the end products and excesses of precursor steroids.

21-Hydroxylase Deficiency

Most patients with classic CAH have 21-hydroxylase deficiency (Fig. 8-18). All forms of 21-hydroxylase deficiency are caused by homozygous or compound heterozygous mutations in the human *CYP21A2* gene, which encodes the 21-hydroxylase enzyme; in the carrier, heterozygote state, only one allele is mutated. Two *CYP21A2* genes, a *CYP21A2B* gene encoding the functional enzyme and a pseudogene termed *CYP21A2A,* are situated very close to each other within the major histocompatibility locus on the short arm of chromosome 6. At least one-fourth of cases of 21-hydroxylase deficiency result from unequal crossover and genetic recombination between the two genes during meiosis. Severe mutations do not correlate with severe phenotype, and phenotypic variability likely depends on the activity of other interacting genes (66).



FIGURE 8-18 **A:** A $10^{1}/_{2}$-year-old girl with 21-hydroxylase deficiency before treatment. 17-Ketosteroid (KS) excretion was 34 mg per day. **B:** The same patient after 9 months of therapy with cortisone (17-KS excretion: 4.6 mg per day). (From **Wilkins L.** *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*. 3rd ed. Springfield, IL: Charles C Thomas; 1965:439, with permission.)

Neonatal screening suggests an incidence of about 1 in 15,000 births. Because of the location of the gene within the major histocompatibility locus, siblings with 21-hydroxylase deficiency usually have identical human leukocyte antigen (HLA) types.

There are various forms of 21-hydroxylase deficiency, including simple virilizing (typically identified at birth because of genital ambiguity), salt-wasting (in which there is impairment of mineralocorticoid and glucocorticoid secretion), and late-onset or nonclassic (in which heterosexual development occurs at the expected age of puberty). The so-called classic form includes the simple virilizing and salt-wasting forms. The nonclassic form is discussed in the following section on heterosexual pubertal development.

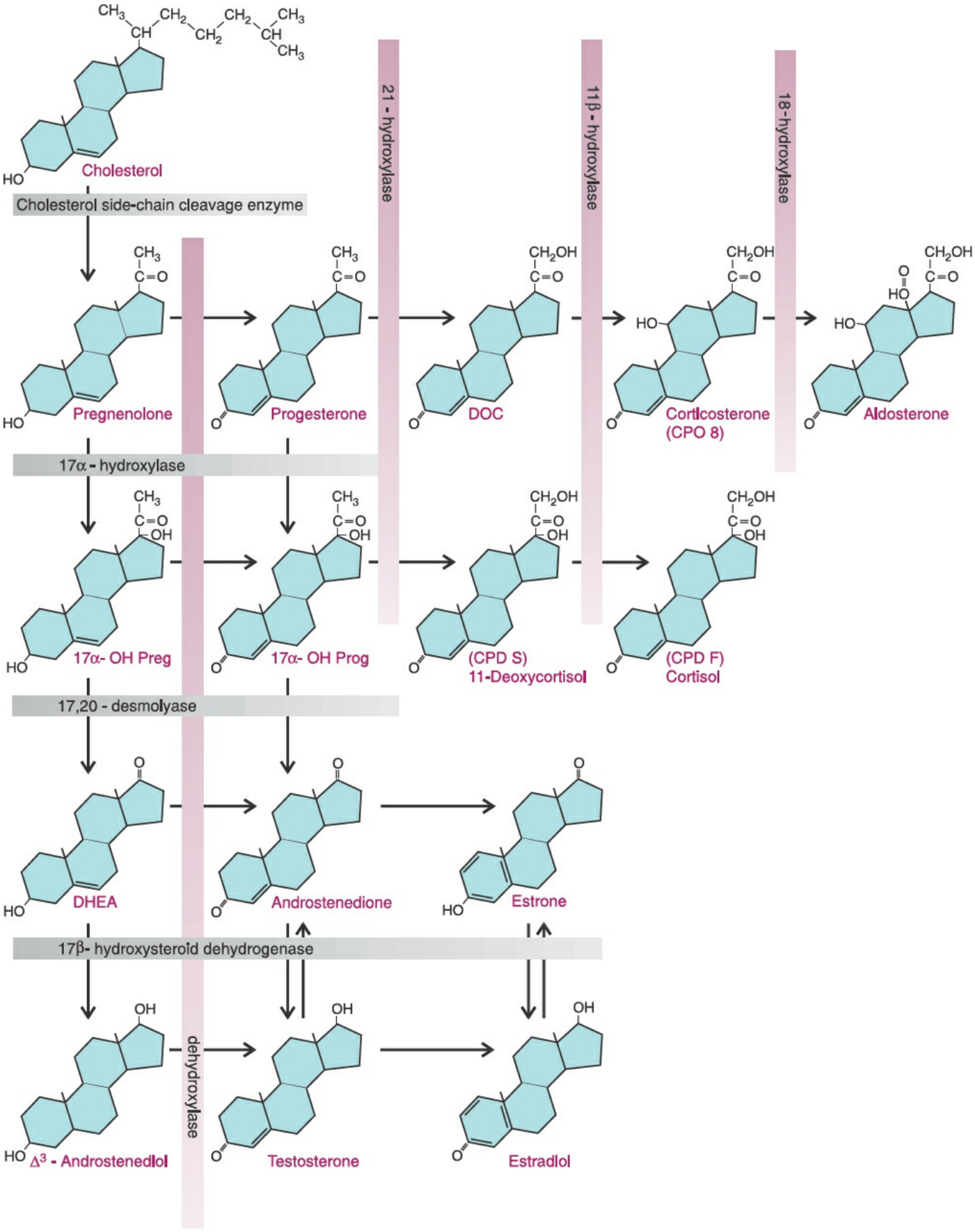


FIGURE 8-19 Gonadal and adrenal steroid pathways and the enzymes required for steroid conversion.

DOC, deoxycorticosterone; 17α-OH Preg, 17α-hydroxypregnenolone; 17α-OH Prog, 17α-hydroxyprogesterone; DHEA, dehydroepiandrosterone sulfate. (From **Rebar RW, Kenigsberg D, Hodgen GD.** The normal menstrual cycle and the control of ovulation. In: Becker KL, ed. *Principles and Practice of Endocrinology and Metabolism*. 2nd ed. Philadelphia, PA: JB Lippincott; 1995:868–880, with permission.)

Deficiency of 21-hydroxylase results in the impairment of the conversion of 17α-hydroxyprogesterone to 11-deoxycortisol and of progesterone to deoxycorticosterone (Fig. 8-19). As a consequence, precursors accumulate, and there is increased conversion to adrenal androgens. Because the development of the external genitalia is controlled by androgens, in the classic form of this disorder, girls are born with ambiguous genitalia, including an enlarged clitoris and fusion of the labioscrotal folds and the urogenital sinus (Fig. 8-20). The internal female organs (including the uterus, fallopian tubes, and ovaries) develop normally because they are not affected by the increased androgen levels. In three-quarters of cases with classic 21-hydroxylase deficiency, salt-wasting occurs, as defined by hyponatremia, hyperkalemia, and hypotension. It is important to recognize that the extent of virilization may be the same in simple virilizing and salt-wasting CAH. Thus, **even a mildly virilized newborn with 21-hydroxylase deficiency should be observed closely for signs of a potentially life-threatening crisis within the first hours, days, and weeks of life.** During childhood, untreated girls with the classic form grow rapidly but have advanced bone ages, enter puberty early, experience early closure of their epiphyses, and ultimately are short in stature as adults. CAH, with appropriate therapy, is the only inherited disorder of sexual differentiation in which normal pregnancy and childbearing are possible. **The classic forms of 21-hydroxylase deficiency are easily diagnosed based on the presence of genital ambiguity and markedly elevated levels of 17α-hydroxyprogesterone.** Some states in the United States have neonatal screening programs to detect 21-hydroxylase deficiency at birth.

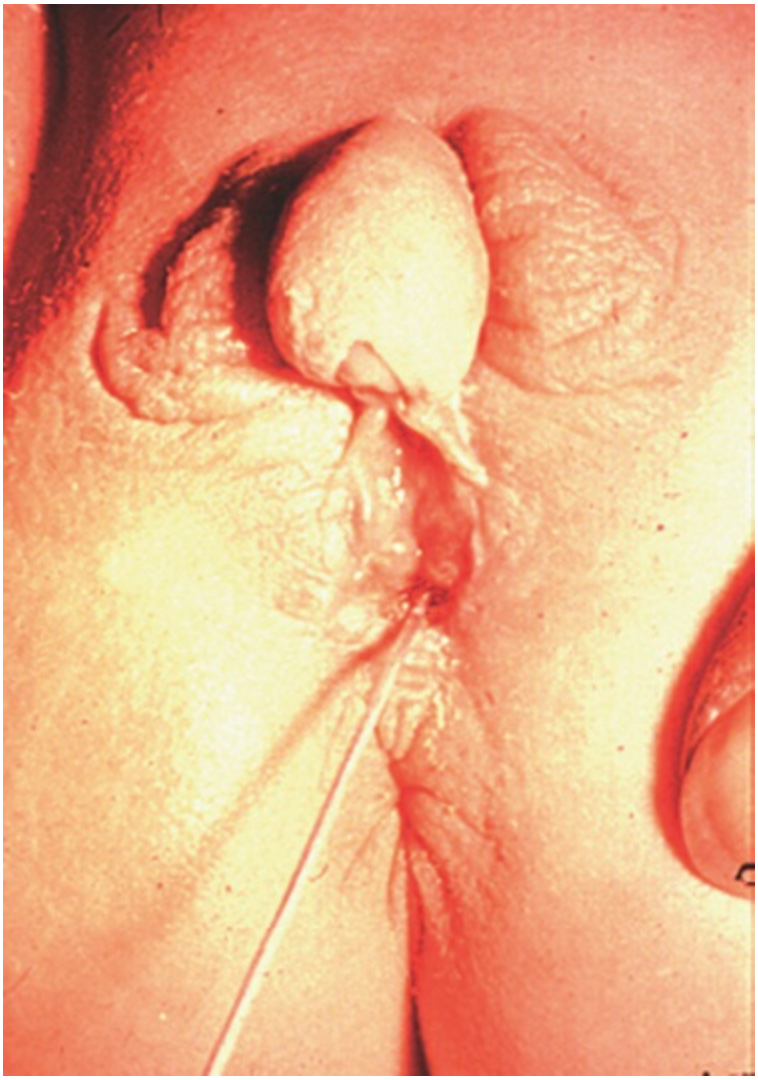


FIGURE 8-20 Newborn girl with 46,XX karyotype and genital ambiguity. There is obvious clitoral hypertrophy, paired frenula, so-called scrotalization of the labia, and a common urogenital sinus (shown by the probe). She had 21-hydroxylase deficiency. (**Rebar RW.** Normal and abnormal sexual differentiation and pubertal development. In: Moore TR, Reiter RC, Rebar RW, et al., eds. *Gynecology and Obstetrics: A Longitudinal Approach.* New York: Churchill Livingstone; 1993:97–133, with permission.)

3b-Hydroxysteroid Dehydrogenase

Deficiency of 3β-HSD, caused by mutations in the *HSD3B2* gene that encodes the 3β-HSDII enzyme, affects the synthesis of glucocorticoids, mineralocorticoids, and sex steroids. Typically, levels of 17-hydroxypregnenolone and DHEA are elevated (Fig. 8-19). The classic form of the disorder, detectable at birth, is quite rare, and affected girls may be only slightly masculinized. In severe cases, salt wasting may be present.

A nonclassic form of this disorder may be associated with heterosexual precocious pubertal development (as is the classic form if untreated), but postpubertal hyperandrogenism occurs more often. The androgen excess in individuals with nonclassic 3β-HSD deficiency appears to result from androgens derived from the peripheral conversion of increased serum concentrations of DHEA.

This disorder is inherited in autosomal recessive fashion, with allelism at the *3*b-*HSD* gene on chromosome 1 believed to be responsible for the varying degrees of enzyme deficiency.

11-Hydroxylase Deficiency

The classic form of 11-hydroxylase deficiency is believed to constitute 5% to 8% of all cases of CAH. Deficiency in 11-hydroxylase, caused by mutations in the *CYP11B1* gene, results in the inability to convert 11-deoxycortisol to cortisol and the consequent accumulation of androgen precursors **(Fig. 8-19)**. Markedly elevated levels of 11-deoxycortisol and deoxycorticosterone are present in the disorder. Because deoxycorticosterone acts as a mineralocorticoid, many individuals with this disorder become hypertensive. A mild nonclassic form of 11-hydroxylase deficiency was reported but apparently is very uncommon (65).

Treatment of Congenital Adrenal Hyperplasia

The treatment of CAH involves providing replacement doses of the deficient steroid hormones. *Hydrocortisone* (10 to 20 mg/m^2 body surface area) or its equivalent is given daily in divided doses to suppress the elevated levels of pituitary corticotropin present and thus suppress the elevated androgen levels. With such treatment, signs of androgen excess should regress. In children, growth velocity, bone age, and hormone levels should be monitored carefully because both overreplacement and underreplacement can result in premature closure of the epiphyses and short stature. Data now indicate that early diagnosis and compliance with therapy lead to adult height within 1 standard deviation of the anticipated target height in girls with 21-hydroxylase deficiency (67).

Mineralocorticoid replacement is generally required in individuals with 21-hydroxylase deficiency whether or not they are salt losing. The intent of glucocorticoid therapy should be to suppress morning 17α-hydroxyprogesterone levels to between 300 and 900 ng/dL. Sufficient *fludrocortisone* should be given daily to suppress plasma renin activity to less than 5 mg/mL per hour.

It is possible to diagnose 21-hydroxylase deficiency prenatally in women known to be at risk of delivering an affected infant (65). The diagnosis is established by documenting elevated levels of 17α-hydroxyprogesterone or 21-deoxycortisol in amniotic fluid. Genetic diagnosis using specific probes and cells obtained by chorionic villus sampling or amniocentesis is also possible. *Dexamethasone*, administered to the pregnant mother, will cross the placenta and can reduce or prevent virilization, but there are maternal risks of induced hypercortisolism and possible neurodevelopmental and physical effects on the infant. Although the risks remain uncertain and not all affected female fetuses appear to benefit, many parents may choose prenatal treatment because of the psychological impact of ambiguous genitalia (68).

Girls with ambiguous genitalia may require reconstructive surgery, including clitoral recession and vaginoplasty. Timing of such surgery is debated, but the girl must be of appropriate size to ensure the surgery is as simple as possible.

Heterosexual Pubertal Development

[6] The most common cause of heterosexual development at the expected age of puberty is PCOS **(Fig. 8-21)**. Because the syndrome is heterogeneous and poorly defined, clinical difficulties affect diagnosis and management (69). For the sake of simplicity, **PCOS may be defined as LH-dependent hyperandrogenism** (70). The Rotterdam criteria are commonly used to identify individuals with PCOS and require the presence of at least two of the following: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries, with exclusion of other etiologies (CAH, androgen-secreting tumors, Cushing syndrome) (71). Polycystic ovaries ultrasonically are defined as the presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL). Most clinical manifestations arise as a consequence of the hyperandrogenism and often include hirsutism beginning at or near puberty and irregular menses from the age of menarche because of oligo- or anovulation. **Clinical manifestations are as follows:**


A


B


C

FIGURE 8-21 Typical facial hirsutism in three women with polycystic ovarian syndrome. **A:** 25-year-old. **B:** 21-year-old. **C:** 17-year-old.

1. **Affected girls may be but are not necessarily somewhat overweight.**
2. **In rare instances, menarche may be delayed, and primary amenorrhea may occur.**
3. **Basal levels of LH tend to be elevated in most affected individuals, and androgen production is invariably increased, even though circulating levels of androgens may be near the upper limits of the normal range in many affected women.**
4. **In anovulatory women, estrone levels are typically greater than estradiol levels.**
5. **Because circulating levels of estrogens are not diminished in PCOS and androgen levels are only mildly elevated, affected girls become both feminized and masculinized at puberty. This is an important feature because girls with classic forms of CAH who do not experience precocious puberty (and even those who do) only become masculinized at puberty (i.e., they do not develop breasts).**
6. **Some degree of insulin resistance may be present, even in the absence of overt glucose intolerance** (72).
7. **Polycystic ovaries are frequently, but not always, present in ultrasound examination.**

Differential Diagnosis and Evaluation

Distinguishing PCOS from the nonclassic forms of CAH can be challenging (70). The evaluation is as follows:

1. **Some clinicians advocate measurement of 17α-hydroxyprogesterone in all women who develop hirsutism.** Although values of 17α-hydroxyprogesterone are commonly elevated more than 100-fold in individuals with classic 21-hydroxylase deficiency, they may or may not be elevated in nonclassic late-onset forms of the disorder.
2. **Measurement of 17α-hydroxyprogesterone can identify women with various forms of 11-hydroxylase deficiency.**
3. **Basal levels of DHEAS and 17α-hydroxyprogesterone may be moderately elevated in patients with PCOS, making the diagnosis even more difficult.**
4. **To screen for CAH, 17α-hydroxyprogesterone should be measured in early morning.**
5. **In women with regular cyclic menses, it is important to measure 17α-hydroxyprogesterone only in the follicular phase because basal levels increase**

at midcycle and in the luteal phase.

Measurements of 17α-hydroxyprogesterone appear to be of value in populations at high risk for nonclassic late-onset 21-hydroxylase deficiency. In the white population, the gene occurs in only about 1 in 1,000 individuals, but it occurs in 1 in 27 Ashkenazi Jews, 1 in 40 Hispanics, 1 in 50 Yugoslavs, and 1 in 300 Italians (66). The incidence is increased among Eskimos and French Canadians. Alternatively, screening might be restricted to hirsute teenagers presenting with the more "typical" features of nonclassic 21-hydroxylase deficiency, including severe hirsutism beginning at puberty, "flattening" of the breasts (i.e., defeminization), shorter stature than other family members, and increased DHEAS levels (between 5,000 and 7,000 ng/mL). Women with a strong family history of hirsutism or hypertension might be screened **(Fig. 8-22)** (40).



FIGURE 8-22 A 19-year-old girl with secondary amenorrhea and severe acne and hirsutism beginning at the normal age of puberty. Stimulatory testing with corticotropin documented nonclassic 21-hydroxylase deficiency. Flattening of the breasts is apparent. She was shorter than her one sister and her mother.

Basal Levels of 17α-Hydroxyprogesterone

Basal levels of 17α-hydroxyprogesterone higher than 800 ng/dL are virtually diagnostic of CAH. Levels between 300 and 800 ng/dL require stimulatory testing with corticotropin to distinguish between PCOS and CAH. To complicate the situation even further, nonclassic 21-hydroxylase deficiency may occur even when basal levels of 17α-hydroxyprogesterone are below 300 ng/dL, thus requiring stimulatory testing in those cases.

Cosyntropin Stimulation Test

The most commonly used stimulatory test involves measurement of 17α-hydroxyprogesterone 30 minutes after administration of a bolus of 0.25 mg of synthetic cosyntropin (*Cortrosyn*) (73). In normal women, this value seldom exceeds 400 ng/dL. Patients with classic 21-hydroxylase deficiency achieve peak levels of 3,000 ng/dL or higher. Patients with nonclassic 21-hydroxylase deficiency commonly achieve levels of 1,500 ng/dL or more. Heterozygous carriers achieve peak levels up to about 1,000 ng/dL. In hirsute women with hypertension, 11-deoxycortisol levels can be determined during the test. If both 11-deoxycortisol and 17α-hydroxyprogesterone levels are increased, the rare 11-hydroxylase deficiency is present. Only measurements of several steroid precursors after corticotropin stimulation can identify individuals with nonclassic forms of 3β-HSD deficiency.

The elevated levels of 17α-hydroxyprogesterone present in all forms of 21-hydroxylase deficiency are rapidly suppressed by administration of exogenous corticoids. Even a single dose of a glucocorticoid such as *dexamethasone* will suppress 17α-hydroxyprogesterone in CAH but not in virilizing ovarian and adrenal neoplasms.

Hirsutism

It has been suggested that androgen-receptor blockade may be preferable to glucocorticoids as primary treatment of nonclassic 21-hydroxylase deficiency (74). Although menses usually (but not always) become regular shortly after beginning therapy with glucocorticoids, the hirsutism in this disorder is remarkably refractory to glucocorticoids. Ovulatory cycles may not occur even with appropriate therapy, and ovulation induction may be required.

Distinguishing nonclassic forms of CAH from idiopathic hirsutism may be problematic. Individuals with idiopathic hirsutism have regular ovulatory menses, thus effectively eliminating PCOS from consideration. Confusion can be created by the fact that some women with nonclassic CAH may continue to ovulate. Basal levels of 17α-hydroxyprogesterone are normal in idiopathic hirsutism, as is the response to adrenocorticotropic hormone stimulation. Idiopathic hirsutism represents enhanced androgen action at the hair follicle (75).

Mixed Gonadal Dysgenesis

The term *mixed gonadal dysgenesis* is used to designate those individuals with asymmetric gonadal development, with a germ cell tumor or a testis on one side and an undifferentiated streak, rudimentary gonad, or no gonad on the other side. Most individuals with this rare disorder have a mosaic karyotype of 45,X/46,XY and are raised as girls who experience virilization at puberty. Gonadectomy is indicated to remove the source of androgens and eliminate any risk for neoplasia.

Rare Forms of Male Pseudohermaphroditism

Individuals who have rare forms of male pseudohermaphroditism, especially 5α-reductase deficiency (the so-called *penis at twelve syndrome*) and the *Reifenstein syndrome,* generally have ambiguous female genitalia with variable virilization at puberty. *Cushing syndrome* may occur rarely during the pubertal years, as may adrenal or ovarian androgen-secreting neoplasms.

GENITAL AMBIGUITY AT BIRTH

Ambiguous external genitalia in a newborn constitutes a major diagnostic challenge. Prompt evaluation is of critical importance to identify a possible life-threatening disorder and to assign the appropriate gender. The prime diagnosis until ruled out is CAH because it is the only condition that is life threatening. Extreme sensitivity is required in interacting with the family, and no attempt should be made to guess the sex of the baby. The incidence of genital ambiguity is 1 in 4,500, although some degree of male undervirilization or female virilization may be present in as many as 2% of live births (76).

Physical Signs

During the 3 to 4 days required for evaluation, it is important to be supportive of the parents. Many clinicians believe that it is important not to attach unusual significance to the genital ambiguity and to treat the abnormality as just another "birth defect." Physicians should emphasize that the child should undergo normal psychosexual development regardless of the sex-of-rearing selected. A name compatible with either sex should be chosen or the naming of the infant should be delayed until the studies are completed.

Although the diagnosis is not usually obvious on examination, there are some helpful distinguishing features **(Fig. 8-20)**. **In normal boys, there is only a single midline frenulum on the ventral side of the phallus; in normal girls, there are two frenula lateral to the midline. A girl with clitoral enlargement still has two frenula, and a boy with hypospadias has a single midline frenulum or several irregular fibrous bands (chordee).** It is important to determine whether any müllerian derivatives are

present. Studies suggest that MRI may be the most effective way of evaluating the infant for the presence of müllerian tissue (77).

The location or consistency of the gonad may be helpful in deducing its composition. A gonad located in the labial or inguinal regions almost always contains testicular tissue. A testis is generally softer than an ovary or a streak gonad and is more apt to be surrounded by blood vessels, imparting a reddish cast. An ovary is more often white, fibrous, and convoluted. A gonad that varies in consistency may be an ovotestis or a testis or a streak gonad that underwent neoplastic transformation. If a well-differentiated fallopian tube is absent on only one side, the side without the tube probably contains a testis or ovotestis.

Diagnosis and Management

Optimal clinical management includes the following (78):

1. **Gender assignment must be avoided before expert evaluation of newborns.**
2. **Evaluation and long-term management should be performed at a center with an experienced multidisciplinary team (pediatric endocrinologist, pediatric urologist, geneticist, clinical psychologist, and reproductive endocrinologist).**
3. **All individuals should receive a gender assignment after appropriate assessment.**
4. **Open communication with patients and families is essential, and participation in decision making should be encouraged.**
5. **Patient and family concerns should be respected and addressed in strict confidence.**

First-line testing in newborns includes:

1. **Karyotyping with X- and Y-specific probe detection (even when prenatal karyotype is available).**
2. **Measurement of serum 17-hydroxyprogesterone, testosterone, gonadotropins, antimüllerian hormone, and electrolytes.**
3. **Abdominopelvic ultrasound (to assess anatomy of the vagina, uterus, or urogenital sinus, exclude renal anomalies, and locate any inguinal gonads).**
4. **Urinalysis (to check for protein as a screen for any associated renal anomaly).**

The results of these investigations are generally available within 48 hours and sufficient to develop a working diagnosis. If needed, additional testing may include (79)**:**

1. **Human chorionic gonadotropin- and adrenocorticotropin-stimulation tests to**

assess testicular and adrenal steroid biosynthesis.

2. **Urinary steroid analysis by gas chromatography mass spectroscopy.**
3. **Further imaging studies.**
4. **Biopsies of gonadal material.**
5. **More detailed genetic testing.**

Although genetic ambiguity is almost always identified at birth, it may not be recognized for several years. Questions about changing the sex-of-rearing may arise. The earlier any necessary sex-of-rearing change may be made, the better. In any case, **surgery for genital ambiguity to make the external genitalia (and development) compatible with the sex-of-rearing of the individual is warranted but is not always completely successful.** Clitoral recession and clitorectomy are the most frequently performed surgical procedures.

Teratogens

It is important to recognize that ambiguous genitalia can result from the maternal ingestion of various teratogens, most of which are synthetic steroids. Exposure to the teratogen must occur early in the pregnancy, during genital organogenesis. Not all exposed fetuses manifest the same anomalies or even the presence of any anomalies. In principle, most synthetic steroids with androgenic properties, including weakly androgenic progestins, can affect female genital differentiation. However, the doses required to produce genital ambiguity are generally so great that the concern is only theoretical. **The one agent that can lead to genital ambiguity when ingested in clinically used quantities is *danazol*. There is no evidence that inadvertent ingestion of oral contraceptives, which contain relatively low doses of steroids, results in virilization** (80).

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CHAPTER 9

Pediatric and Adolescent Gynecology



Paula J. Adams Hillard

Prepubertal Age Group
- Prepubertal Bleeding
  - *Differential Diagnosis of Prepubertal Vaginal Bleeding*
  - *Diagnosis of Prepubertal Bleeding*
  - *Management of Prepubertal Vaginal Bleeding*
- Prepubertal Pelvic Masses
  - *Presentation of Prepubertal Pelvic Masses*
  - *Diagnosis of Prepubertal Pelvic Masses*
  - *Differential Diagnosis*
  - *Management of Prepubertal Pelvic Masses*
- Prepubertal Vulvar Conditions
  - *Neonatal Vulvar Conditions*
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- Prepubertal Vaginal Conditions
  - *Vaginal Discharge in Prepubertal Girls*

Adolescent Age Group
- Adolescent Abnormal Bleeding
  - *Normal Menses in Adolescents*
  - *Differential Diagnosis of Adolescent Abnormal Bleeding*
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  - *Anovulation: Mild Bleeding*
  - *Acute Bleeding*
  - *Long-Term Menstrual Suppression*
- Adolescent Pelvic Masses

Presentation
Diagnosis
Differential Diagnosis of Adolescent Pelvic Masses
Uterine Masses in Adolescents
Inflammatory Masses in Adolescents
Management of Pelvic Masses in Adolescents
Adolescent Vulvar Conditions
Adolescent Vaginal Conditions

KEY POINTS

1 The causes of abnormal bleeding vary by age, with anovulatory bleeding most likely in adolescents and perimenopausal women.
2 Pelvic masses in adolescents are most commonly functional or benign neoplastic ovarian masses, whereas the risks of malignant ovarian tumors increase with age.
3 Although pelvic ultrasonography is an excellent technique for imaging pelvic masses and ultrasonographic characteristics may suggest reassuring characteristics of an ovarian mass, the possibility of malignancy must be kept in mind.
4 Vulvovaginal symptoms of any sort in a young child should prompt the consideration of possible sexual abuse.
5 Preventive services for adolescents should be based on knowledge of the behavioral and medical health risks that can affect their future health, including substance use and abuse, sexual behaviors that invite unintended pregnancy and sexually transmitted diseases (STDs), and the symptoms of impaired mental health.

The gynecologic problems of prepubertal girls and adolescents differ from those of adult women. In the case of prepubertal girls, there are significant differences from adolescents and adult women in the anatomy, bacteriology, physiology, pathophysiology, and epidemiology of gynecologic conditions that are likely to occur. While gynecologists tend to think of menarche as the dividing line between young girls and adolescents, the real differences in the types of gynecologic conditions that occur during adolescence typically begin with the onset of puberty, when steroid hormone production causes changes in breast development **(Fig. 9-1)**, the vaginal epithelium, growth of the uterus, and vulvar changes of hair growth.

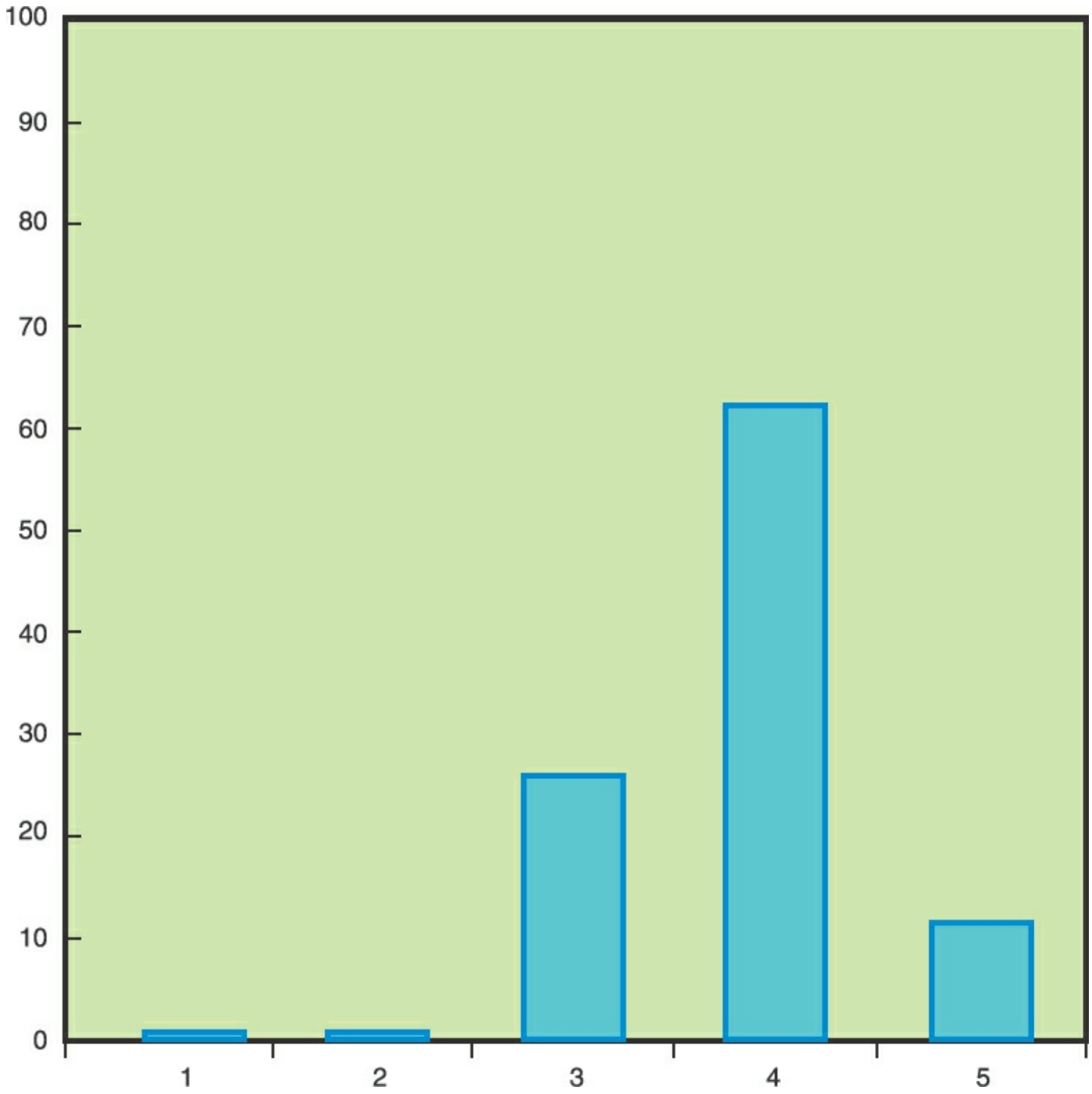


FIGURE 9-1 Tanner breast stage at menarche.

Menarche signals the onset of cyclic ovarian hormone production leading to menstrual bleeding, although many early menstrual cycles are anovulatory. Some conditions, potential developmental genital anomalies, are more likely to be diagnosed during adolescence than in adults. The incidence of ovarian tumors varies by age, with young girls and adolescents more likely to develop germ cell tumors than adults. Some of the gynecologic conditions that occur during adolescence are related to sexual behaviors, including greater risks of sexually transmitted infections and pelvic

inflammatory disease (PID). **The gynecologist's interactions with an adolescent are sometimes more challenging, given that adolescents are developing in a number of spheres: physical maturity, cognitive development, psychosocial development, relationships with family and peers, and sexuality.**

All those spheres do not develop synchronously, and a young adolescent may appear physically more mature than her psychosocial or cognitive development allows her to behave. These are some of the aspects of relating to adolescents with regard to their gynecologic problems that make it challenging. On the other hand, adolescents will often be refreshingly candid if a trusting relationship has been established with their physician. Observing adolescents' growth and development into young adulthood can be immensely rewarding, as they have the capacity to make behavioral changes that adults often find difficult.

The gynecologic examination of prepubertal girls and adolescents is discussed in Chapter 1, as are elements of communication that apply equally to adolescents and to adults. However, **there are some aspects of communication with prepubertal girls and adolescents that are unique to these age groups. It is important to keep in mind that most medical problems in children lead to maternal anxiety, and maternal or parental anxiety may manifest in different ways.** The clinician may occasionally interact with a parent who is not accepting of their parental roles and responsibilities and who is neglectful of the child's health, or who because of their own medical or mental health issues including substance use disorders, is unable to appropriately provide care for their child. These situations are rare, but typically require multidisciplinary interventions, including the services of a social worker or mandatory reporting to local child protective services. Gynecologic conditions for a daughter may be particularly fraught, as they may revive the mother's history of interpersonal violence, sexual abuse, exploitation, reproductive coercion, or adverse interactions with the health care system. **Parents may be concerned that a gynecologic condition will impact their daughter's future fertility or ability to lead a sexually satisfying adult life.** The clinician must recognize that these concerns are quite common, and should address them directly with accurate information.

Communication with toddlers and infants will be primarily with the child's mother. The gynecologic history in a young child will include issues described in Table 9-1.

Adolescents who present for gynecologic consultation are often accompanied by a parent, typically their mother. **ACOG recommends that an adolescent's initial visit to a gynecologist for reproductive health guidance, screening, and provision of preventive services should take place between the ages of 13 and 15 years** (1). **This visit provides an opportunity to directly observe mother–daughter communication during the visit, and to assess whether the relationship appears to be an open and trusting one or whether the mother appears excessively anxious,**

controlling, domineering, authoritarian, or permissive. Adolescents must be afforded confidentiality during a visit in which it is essential to obtain a history of risk-taking behaviors including sexual behaviors, substance use/abuse, and mental health concerns (1,2). Concerns about confidentiality can be a major obstacle to adolescents' willingness to seek health care services.

Table 9-1 Pediatric Gynecology—History

Child's description of symptoms (if child is verbal)
Slang/colloquial terms (explained by mother)
Extent of current symptoms compared to previously
History from mother
Symptoms
Itching
Pain
Burning
Erythema or rash (consider photodocumentation)
Location of symptoms
"Vagina" usually = vulva or vaginal vestibule
Urinary symptoms
External "dysuria"
Dribbling
Urinary leakage
Vaginal discharge
Vaginal bleeding
Constipation
Symptoms
Onset
Frequency
Duration
Exacerbating factors

Alleviating factors
Extent of disruption of activities of daily living including preschool/school
Treatments
Previously prescribed therapies and efficacy
Home remedies
Hygiene
Baths vs. showers and frequency
Bubble baths, soaps, shampoos
Cultural beliefs and previous recommendations about baths
Toileting supervision
Birth history
Past medical history
General health
Chronic medical conditions
Medications
Hospitalizations
Surgeries
Immunizations
Allergies
History of abuse/molestation
Safety discussion with child: “No, Go, Tell”

One structure of an adolescent’s gynecologic consultation visit has been described in which the adolescent and her parent (typically her mother) meet together initially, followed by time in which the physician addresses the mom’s concerns and ascertains her concerns about such issues as risk-taking behaviors **(Table 9-2)** (3). Concepts of confidentiality are explained to the mother at this time, and preventive guidance about adolescent development is provided. The order in which the mother and daughter are seen is intentional, in that the clinician has not yet spoken privately with the adolescent, allowing the clinician to speak in generalities about adolescent behaviors. Subsequently, the adolescent is seen alone, concepts of confidentiality are explained, and psychosocial issues are addressed. Among adolescent medicine clinicians, this assessment is often referred to as the HEEADSSS assessment **(Table 9-3)** (4).

[5] Preventive services for adolescents should be based on knowledge of the behavioral and medical health risks that can affect their future health, including substance use and abuse, sexual behaviors that invite unintended pregnancy and sexually transmitted diseases (STDs), and the symptoms of impaired mental health.

This chapter will address the gynecologic problems of prepubertal girls and adolescents. The gynecologic problems that will be addressed by age group include bleeding, pelvic masses, and vulvovaginal conditions.

PREPUBERTAL AGE GROUP

Prepubertal Bleeding

Prior to menarche, which frequently does not occur before 9 years of age, *any* vaginal bleeding requires evaluation. To appropriately evaluate a young girl with vaginal bleeding, a practitioner should understand the events of puberty (5–7). The hormonal changes that control the cyclic functioning of the hypothalamic–pituitary–ovarian axis are described in Chapter 7. An understanding of the normal sequence and timing of these events is critical to an appropriate assessment of a girl at the onset of bleeding (see Chapter 8). Menarche typically occurs when an adolescent has reached Tanner stage 3 or 4 of breast development **(Fig. 9-1)**. Bleeding in the absence of breast development must be evaluated.

Differential Diagnosis of Prepubertal Vaginal Bleeding

Slight vaginal bleeding can occur within the first few days of life because of withdrawal from exposure to high levels of maternal estrogen. New mothers of female infants should be informed of this possibility to preclude unnecessary anxiety. After the neonatal period, causes of bleeding that should be considered in the prepubertal age group include sexual abuse, precocious puberty, benign and malignant ovarian tumors, as well as vulvar, vaginal, and cervical lesions or tumors **(Table 9-4)**. Menses do not normally occur before breast budding (8,9).

[4] **The causes of bleeding in this age group range from the medically mundane to malignancies that may be life-threatening. The source of bleeding is sometimes difficult to identify, and parents who observe blood in a child's diapers or panties may be unsure of the source—whether from the urinary tract, the vagina, or the rectum. Pediatricians usually look for urinary causes of bleeding, and gastrointestinal factors such as constipation and/or anal fissure, or inflammatory bowel disease should be considered. The possibility of abuse should always be assessed in girls with any vulvovaginal symptoms, particularly if bleeding is present (10). Failure to diagnose sexual abuse may leave a child in significant danger.**

Table 9-2 **Visit Structure for Adolescent Consultation Visit**

Step	Topics Covered	The Clinician in Consultation With
1	Review structure of visit Obtain history of present illness/chief concerns Obtain past medical history and family history	Adolescent and parent(s)
2	Address parental concerns Provide preventive guidance about adolescent development Address confidentiality	Parent(s)
3	Address confidentiality Obtain history, including sexuality and risk-taking behaviors	Adolescent
4	Perform physical examination, as indicated	Adolescent (+/- parent, per adolescent's preference)
5	Summarize findings and recommendations Determine parameters of parental involvement Determine method of notification of laboratory results Provide preventive guidance	Adolescent
6	Summarize findings and recommendations, as appropriate	Adolescent and parent(s)

Vulvar Lesions

Vulvar irritation can lead to pruritus with excoriation, maceration of the vulvar skin, or fissures that can bleed. Other visible external causes of bleeding in this age group include urethral prolapse, condylomas, lichen sclerosus, or molluscum contagiosum. **Urethral prolapse can present acutely with a tender mass that may be friable or bleed slightly; it is most common in African American girls and may be confused with a vaginal mass (Fig. 9-2)**. The classic presentation is a donut-shaped mass symmetrically surrounding the urethra. This condition can typically be managed medically with the topical application of estrogens, although some authors have advocated primary surgical excision (11). The presence of condyloma should prompt questioning about abuse, although it has been suggested that **condyloma that appear during the first several years of life may be acquired perinatally from maternal infection with human papillomavirus (HPV) (Fig. 9-3)** (12). Excoriation and subepithelial hemorrhage ("blood blisters") into the skin can cause external bleeding in the presence of prepubertal lichen sclerosus; this finding may mistakenly be identified as abuse, and the conditions are not mutually exclusive (Fig. 9-4) (13). **Although most gynecologists recognize the appearance of lichen sclerosus in postmenopausal women, the condition can occur in prepubertal girls and may not be recognized by clinicians who are unfamiliar with this condition.** As with adults, the cause of lichen sclerosus remains uncertain; a familial incidence has been identified (14).

Table 9-3 HEEADSSS Psychosocial Assessment for Adolescents

H	Home
E	Education and employment
E	Eating
A	Activities
D	Drugs
S	Sexuality
S	Suicide/depression
S	Safety

Adapted from **Klein DA, Goldenring JM, Adelman WP.** HEEADSSS 3.0: The psychosocial interview for adolescents updated for a new century fueled by media. *Contemp Pediatr* (serial online) 2014. Available online at https://mmcp.dhmh.maryland.gov/epsdt/healthykids/…/sec._4_add_heeadsss.pdf. Accessed September 25, 2017. Available online at https://mmcp.dhmh.maryland.gov/epsdt/healthykids/…/sec._4_add_%20heeadsss.pdf. Accessed September 25, 2017.

Table 9-4 Causes of Vaginal Bleeding in Prepubertal Girls

Vulvar and external
Vulvitis with excoriation
Trauma (e.g., accidental injury [straddle injury] or sexual abuse)
Lichen sclerosus
Condylomas
Molluscum contagiosum
Urethral prolapse
Vaginal
Vaginitis
Vaginal foreign body
Trauma (abuse, penetration)
Vaginal tumor
Uterine
Precocious puberty
Ovarian tumor

Granulosa cell tumor
Germ cell tumor
Exogenous estrogens
Topical
Enteral
Other
McCune–Albright syndrome



FIGURE 9-2 Urethral prolapse in prepubertal girl.



FIGURE 9-3 Perianal condyloma in a prepubertal girl.



FIGURE 9-4 Prepubertal lichen sclerosus.

Foreign Body

A foreign body in the vagina is a common cause of vaginal discharge, which may appear purulent or bloody. Young children explore all orifices and may place all varieties of small objects inside their vaginas **(Fig. 9-5)**. An object, such as a small plastic toy, can sometimes be palpated on rectal examination, and occasionally "milked" toward the vaginal introitus to allow removal. The most common foreign bodies found in the vagina are small pieces of toilet paper (15). Although it has been suggested that the presence of vaginal foreign bodies might be a marker for sexual abuse, this is not always the case; but the possibility of abuse should always be considered.

Precocious Puberty

Vaginal bleeding in the absence of other secondary sexual characteristics may result from precocious puberty (see Chapter 8), although as with normal puberty, the onset of breast budding or pubic hair growth is more likely to occur before vaginal bleeding. A large observational study suggested that the onset of pubertal changes—breast budding and pubic hair—might occur earlier than previously thought (6). Evaluation for precocious puberty was recommended for girls with pubertal development younger than age 8 years. Guidelines proposed evaluation of white girls younger than age 7 years and African American girls younger than age 6 years who have either breast development or pubic hair, rather than the traditional age of 8 (16). An expert panel concluded that **there is reasonable evidence that pubertal milestones are occurring at a younger age in girls** (17).

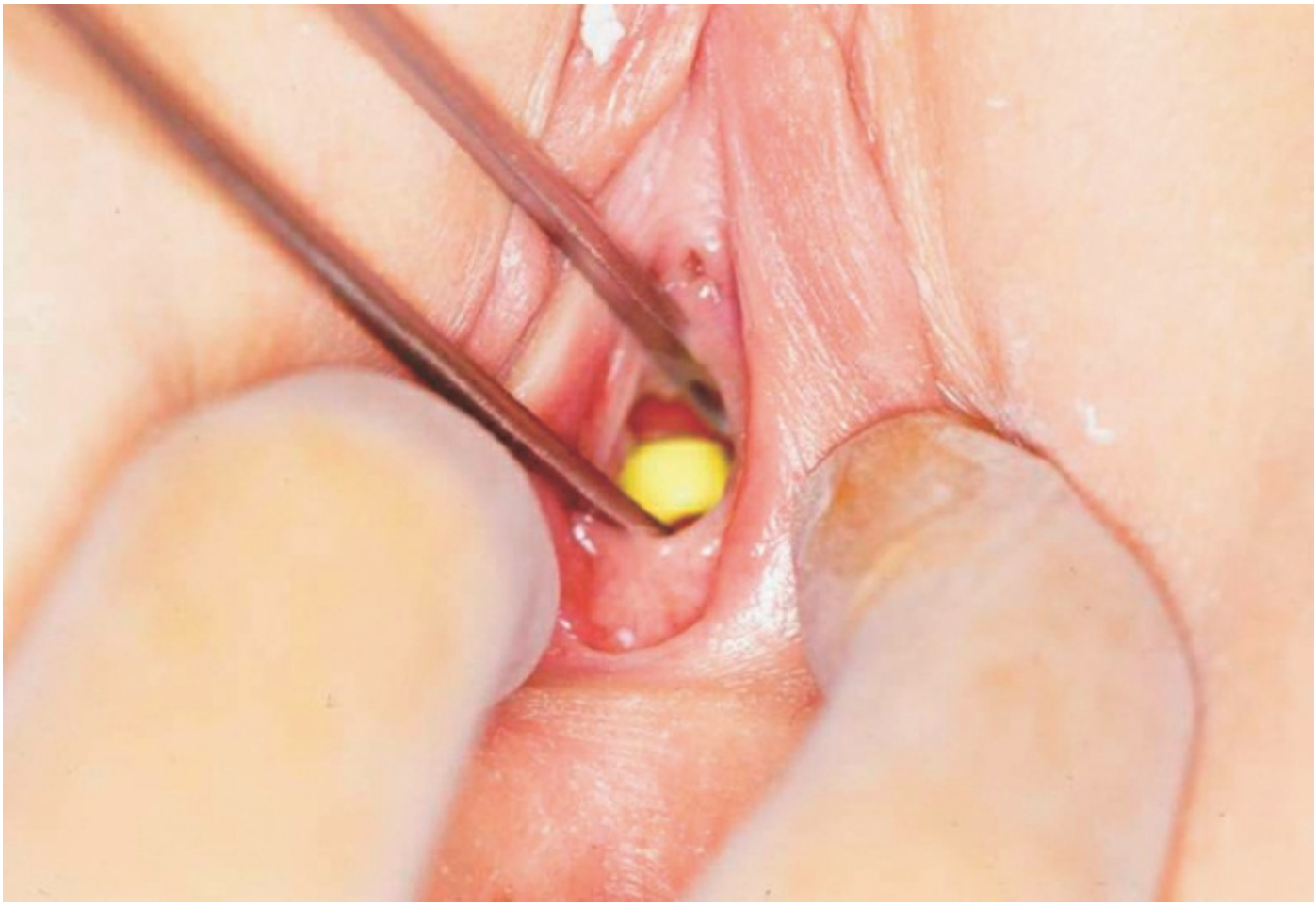


FIGURE 9-5 Foreign body (plastic toy) in the vagina of an 8-year-old girl.

Trauma

Trauma can be a cause of genital bleeding. **A careful history should be obtained from one or both parents or caretakers and the child herself, because trauma caused by sexual abuse often is not recognized. Trauma can be characterized as accidental or nonaccidental, which is described as child abuse.** Physical findings that are inconsistent with the description of the alleged accident should prompt consideration of abuse and appropriate consultation or referral to an experienced social worker or sexual abuse team. **All states impose a mandatory legal obligation to report suspected child physical abuse;** most states specifically require reporting child sexual abuse, but even in those that do not, the laws are broad enough to encompass sexual abuse implicitly (10). Notification is required even with the suspicion of sexual abuse. In general, a straddle injury occurring with accidental trauma affects the anterior and lateral vulvar area, whereas penetrating injuries with lesions of the fourchette or lesions that extend through the hymenal ring are less likely to occur as a result of accidental trauma **(Fig. 9-6)** (18).

Abuse

The medical evaluation of suspected child sexual abuse is best managed by individuals who have experience in assessing the physical findings, laboratory results, and the children's statements and behaviors. Genital findings have been categorized as follows (10):

1. Findings documented in newborns or commonly seen in nonabused children
2. Findings with no expert consensus on interpretation with respect to sexual contact or trauma
3. Findings caused by trauma and/or sexual contact

Most cases of child sexual abuse do not come to light with an acute injury and instead are associated with normal or nonspecific genital findings (10). Forms of abuse such as fondling or digital penetration may not result in visible genital lesions.

Other Causes

Other serious but rare causes of vaginal bleeding include vaginal tumors. The most common tumor in the prepubertal age group is a rhabdomyosarcoma (sarcoma botryoides), which is associated with bleeding and a grapelike clustered mass (see Chapter 38). Other forms of vaginal tumor are rare but should be ruled out with a thorough examination under anesthesia with vaginoscopy if no other obvious external source of bleeding is found.

Hormonally active ovarian tumors can cause endometrial proliferation and bleeding. Likewise, exogenously administered estrogens can result in bleeding. Rarely, bleeding can result from the prolonged use of topical estrogens prescribed as therapy for vulvovaginitis or labial adhesions or from accidental ingestion of prescription estrogens.

Diagnosis of Prepubertal Bleeding

Examination

A careful examination is indicated when a child has genital symptoms. The technique of examining the prepubertal child is described in Chapter 1. **If no obvious cause of bleeding is visible externally or within the distal vagina, an examination can be performed using anesthesia with vaginoscopy to completely visualize the vagina and cervix. This examination should be performed by a clinician who has experience in pediatric and adolescent gynecology.**



FIGURE 9-6 Straddle injury—vulvar hematoma in a 13-year-old girl.

Imaging

If an ovarian or vaginal mass is suspected, a transabdominal pelvic ultrasonographic examination can provide useful information. The appearance of the ovaries (normal prepubertal size and volume, follicular development, cystic, or solid) can be noted, as well as the size and configuration of the uterus. **The prepubertal uterus has a distinctive appearance, with equal proportions of cervix and fundus and a size of approximately 2 to 3.5 cm in length and 0.5 to 1 cm in width (Fig. 9-7)**. The uterine fundus enlarges with estrogen stimulation, resulting in the postmenarchal appearance in which the uterine fundus is larger than the cervix (19). An ultrasonographic examination should be the first imaging study performed; more sophisticated imaging techniques, such as magnetic resonance imaging (MRI) or computed tomography (CT) scanning, are

rarely indicated as initial diagnostic modalities, and they add unnecessary expense and radiation exposure with CT.

Management of Prepubertal Vaginal Bleeding

The management of bleeding in prepubertal-age girls is directed toward the cause of bleeding. If bloody discharge believed to result from nonspecific vulvovaginitis persists despite therapy, further evaluation may be necessary to rule out the presence of a foreign body. Skin lesions (chronic irritation) and lichen sclerosus may be difficult to manage but can be treated with a course of topical steroids; lichen sclerosus often requires the use of ultrahigh-potency topical steroids and ongoing maintenance therapy. **Vaginal and ovarian tumors should be managed in consultation with a gynecologic oncologist.**

Prepubertal Pelvic Masses

Presentation of Prepubertal Pelvic Masses

The probable causes of a pelvic mass found on physical examination or through radiologic studies are vastly different in prepubertal children than they are in adolescents or postmenopausal women (Table 9-5). A pelvic mass may be gynecologic in origin, or it may arise from the urinary tract or bowel. The gynecologic causes of a pelvic mass may be uterine, adnexal, or more specifically ovarian. Because of the small pelvic capacity of a prepubertal child, a pelvic mass very quickly becomes abdominal in location as it enlarges and may be palpable on abdominal examination. Ovarian masses in this age group may be asymptomatic, associated with chronic pressure-related bowel or bladder symptoms, or may present with acute pain caused by rupture or torsion. Abdominal or pelvic pain is one of the most frequent initial symptoms. The diagnosis of ovarian masses in prepubertal girls is difficult because the condition is rare in this age group and, consequently, there is a low index of suspicion. Many symptoms are nonspecific, and acute symptoms are more likely to be attributed to more common entities such as appendicitis. **Abdominal palpation and bimanual rectoabdominal examination are important in any child who has nonspecific abdominal or pelvic symptoms.** An ovarian mass that is abdominal in location can be confused with other abdominal masses occurring in children, such as Wilms tumor or neuroblastoma. Acute pain is often associated with torsion. The ovarian ligament becomes elongated as a result of the abdominal location of ovarian tumors, thus creating a predisposition to torsion. Adnexal torsion is more likely to occur with an ovarian mass than with a normal-size ovary. While torsion of a normal ovary is rare in adolescents and adults, it is more likely to occur in prepubertal girls. **Symptoms of torsion include the acute onset of severe abdominal pain, accompanied by nausea and vomiting.** Recurrent torsion is also a possibility, noted by intermittent episodes of severe pain.

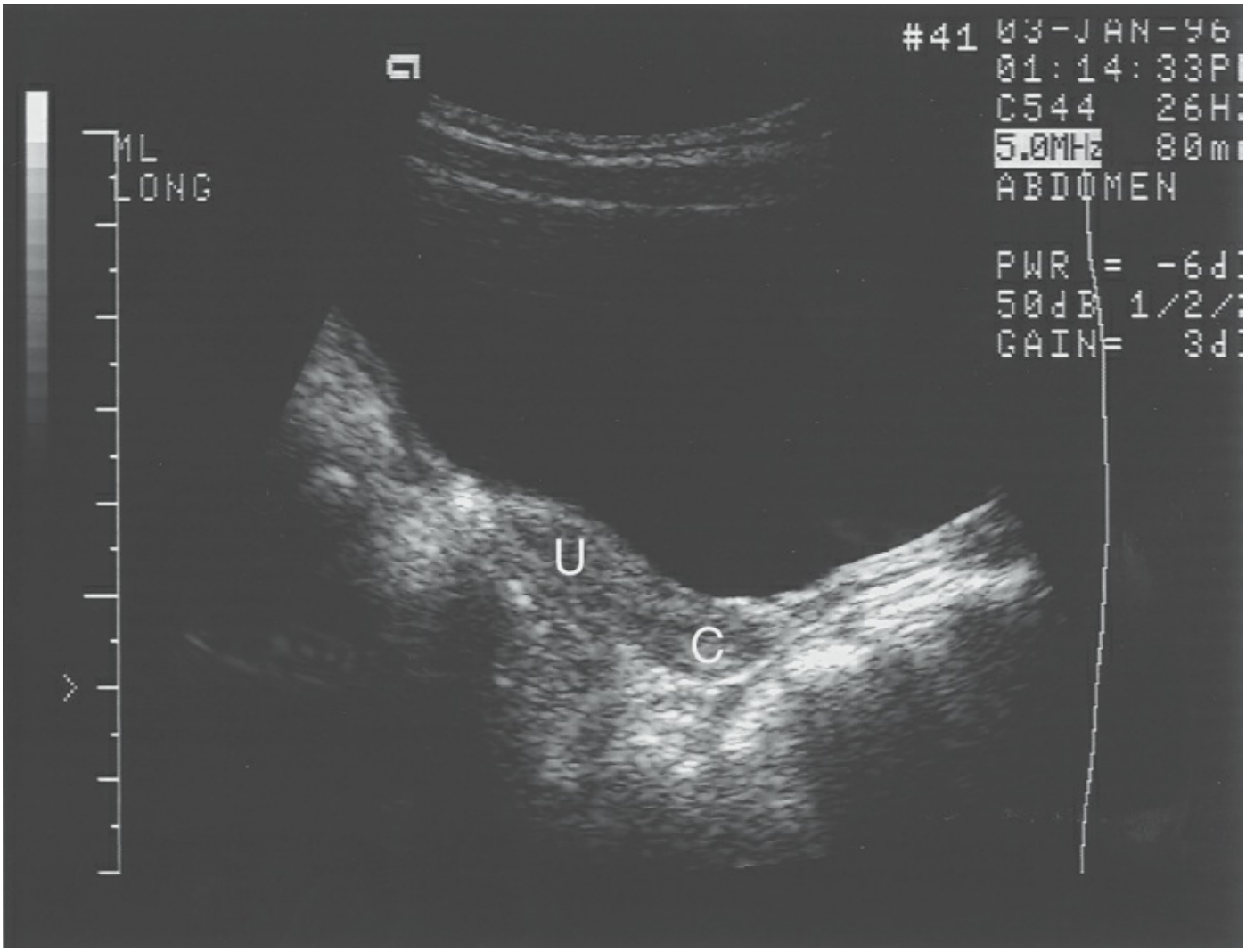


FIGURE 9-7 Pelvic ultrasound (transabdominal) of a premenarchal 10-year-old girl. U, uterine fundus; C, cervix. In prepubertal child, uterine fundus and cervix are similar in size.

Diagnosis of Prepubertal Pelvic Masses

[3] Ultrasonography is the most valuable tool for diagnosing ovarian masses. The characteristics of a pelvic mass can be determined. Whereas both uni- and multilocular cysts frequently resolve with observation, the finding of a solid component mandates surgical assessment because of the high risk of a germ cell tumor (20). Additional imaging studies, such as CT scanning, MRI, or Doppler flow studies, may be helpful in establishing the diagnosis (21).

Table 9-5 Causes of Pelvic Mass by Approximate Frequency and Age

Infancy	Prepubertal	Adolescent	Reproductive	Perimenopausal	Postmenopausal
Functional cyst	Functional cyst	Functional cyst	Functional cyst	Fibroids	Ovarian tumor (malignant or benign)
Germ cell tumor	Germ cell tumor	Pregnancy	Pregnancy	Epithelial ovarian tumor	Functional cyst
		Benign cystic teratoma/other germ cell tumors	Uterine fibroids	Functional cyst	Bowel, malignant tumor or inflammatory
		Obstructing vaginal or uterine anomalies	Epithelial ovarian tumor		Metastases
		Epithelial ovarian tumor			

Differential Diagnosis

Fewer than 2% of ovarian malignancies occur in children and adolescents (22,23). **Ovarian tumors account for approximately 1% of all malignant tumors in these age groups. Germ cell tumors make up one-half to two-thirds of ovarian neoplasms in individuals younger than 20 years of age.** A review of studies conducted from 1940 until 1975 concluded that 35% of all ovarian neoplasms occurring during childhood and adolescence were malignant (24). **In girls younger than 9 years of age, approximately 80% of the ovarian neoplasms were malignant.** Germ cell tumors account for approximately 60% of ovarian neoplasms in children and adolescents compared with 20% of these tumors in adults (24). Epithelial neoplasms are rare in the prepubertal age group; thus, data usually are reported from referral centers. Some reports include only neoplastic masses, whereas others include nonneoplastic masses; some series combine data from prepubertal and adolescent girls. One community survey of ovarian masses revealed that the frequency of malignancy was much lower than previously reported; **of all ovarian masses confirmed surgically in childhood and adolescence, [2]** only 6% of patients with ovarian enlargement had malignant neoplasms, and only 10% of neoplasms were malignant (25). Surgical decision making influences the statistics on incidence; the surgical excision of functional masses that would resolve in time inflates the percentage of benign masses. In one series, nonneoplastic masses in young women and girls younger than 20 years of age constituted two-thirds of the total (26). Even in girls younger than 10 years of age, 60% of the masses were nonneoplastic, and two-thirds of the neoplastic masses were benign. Authors of older case series were less aware of the benign and functional masses that are now found incidentally with routine sonographic images. Functional, follicular cysts can occur in fetuses, newborns, and prepubertal children (27). Rarely, they may be associated with sexual precocity.

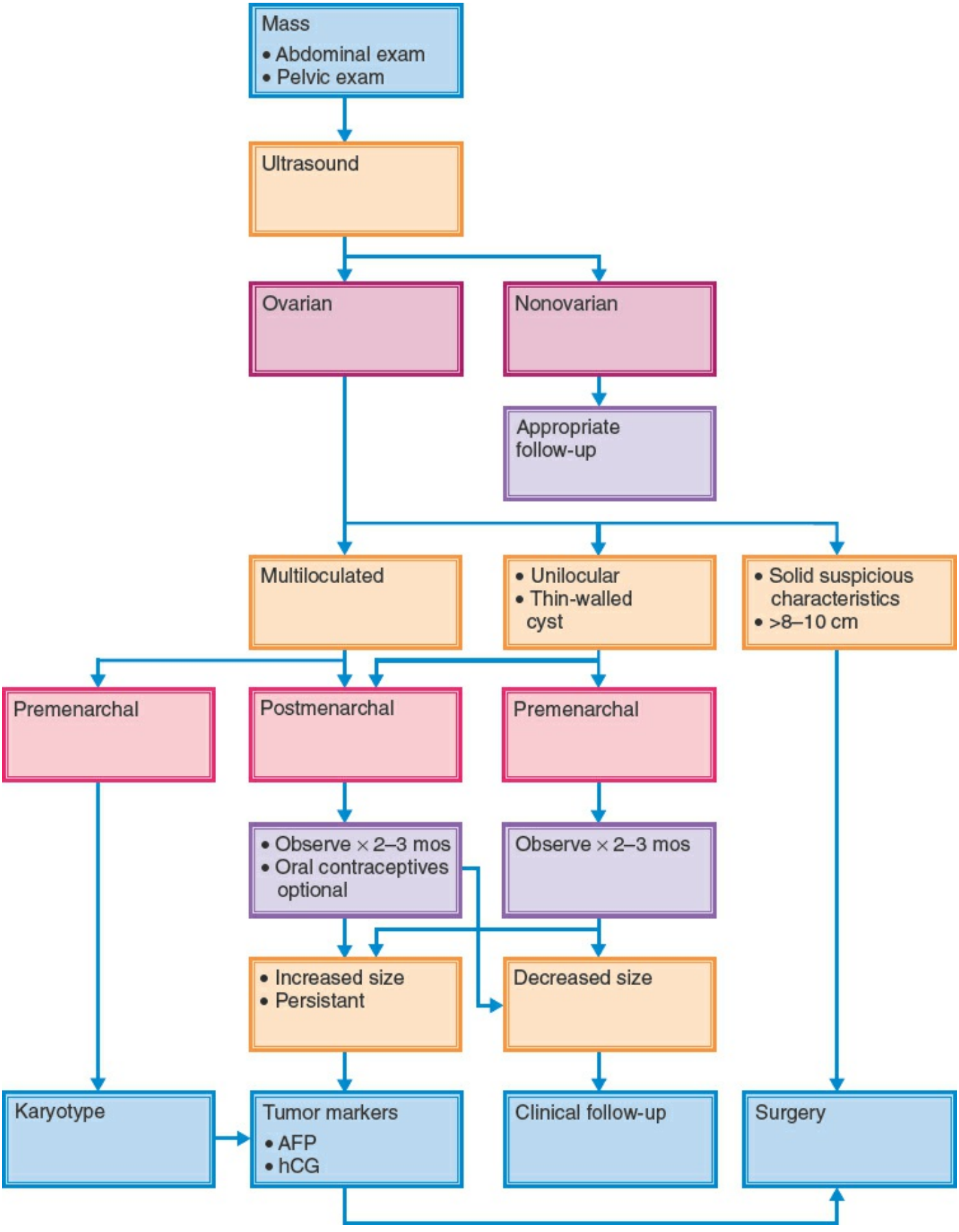


FIGURE 9-8 Management of pelvic masses in premenarchal and adolescent girls.

Management of Prepubertal Pelvic Masses

A plan for the management of pelvic masses in prepubertal-age girls is shown in **Figure 9-8**. **Unilocular cysts are virtually always benign, even in this age group, and will regress in 3 to 6 months; thus, they do not require surgical management with oophorectomy or oophorocystectomy.** Close observation is recommended, and there is a risk of ovarian torsion that must be discussed with the child's parents (28). Recurrence rates after cyst aspiration (either ultrasonographically guided or with laparoscopy) may be as high as 50%. Attention should be directed to long-term effects on endocrine function and future fertility; preservation of ovarian tissue is a priority for patients with benign tumors. Oophorectomy should be avoided if at all possible for benign masses (29–31). **Premature surgical therapy for a functional ovarian mass can result in ovarian and tubal adhesions that can adversely affect future fertility.** Solid masses, those larger than approximately 8 cm, and enlarging masses require surgical intervention, as the likelihood of neoplasm is high.

Prepubertal Vulvar Conditions

Neonatal Vulvar Conditions

Various developmental and congenital vulvovaginal abnormalities are detected in the neonatal age group. Obstetrician-gynecologists will recognize that they must be prepared to deal with the parents and family when an infant is born with ambiguous genitalia. The etiology of these problems and intersex disorders (now termed disorder of sex development [DSD]) that may be discovered in an older child can be complex (32). Chromosomal abnormalities, enzyme deficiencies (including 17- or 21-hydroxylase deficiency as causes of congenital adrenal hyperplasia), or prenatal masculinization of a female fetus resulting from maternal androgen-secreting ovarian tumors or, rarely, drug exposure can all result in genital abnormalities that are noted at birth. These abnormalities are described in Chapter 34.

Ambiguous genitalia represent a social and potential medical urgency that is best handled by a team of specialists, which may include urologists, neonatologists, endocrinologists, and pediatric gynecologists (32). The first question parents ask after a baby is born "is it a boy or a girl?" In the case of ambiguous genitalia, the parents should be informed that the baby's genitals are not fully developed and, therefore, a simple examination of the external genitalia cannot determine the actual sex. The parents should be told that data will be collected but that it may take several days or longer to determine the baby's intended sex. In some situations, it may be best to state simply that the baby has some serious medical complications. The issues of sex assignment and appropriateness or timing of surgical therapy are controversial and should be managed by clinicians with extensive experience in this area (32).

Other genital abnormalities may be noted at birth, although few obstetricians or pediatricians carefully examine the external genitalia of female neonates. It is argued that **careful inspection of the external genitalia of all female infants should be performed, with gentle probing of the introitus and anus to determine the patency of the hymen or a possible imperforate anus.** If patency is in doubt, a rectal thermometer may be used to gently test the patency. It is suggested that this examination should be performed on all female infants in the delivery room (33). Various types of hymenal configurations in the newborn are described, ranging from imperforate to microperforate, to cribriform, to hymenal bands, and to hymens with central anterior, posterior, or eccentric orifices (34). An examination during the neonatal period would prevent the discovery of an imperforate hymen or vaginal septum after a young woman experiences periodic pelvic and abdominal pain with the development of a large hematometra or hematocolpos.

Congenital vulvar tumors may include strawberry hemangiomas, which are relatively superficial vascular lesions, and large cavernous hemangiomas. Treatment is controversial, and many lesions will spontaneously regress.

Childhood Vulvar Conditions

Vulvar and vaginal symptoms, such as burning, dysuria, itching, or a rash, are common initial symptoms among children that are reported to gynecologists. It may be difficult for a young child to describe vulvar sensations. Parents may notice the child crying during urination, scratching herself repeatedly, or complaining of vague symptoms. Often, the child's pediatrician will have evaluated the child for urinary tract infection (UTI). Evaluation for pinworms is warranted, because pinworms can cause severe itching in the vulvar and perianal area. **Vulvovaginitis is the most common gynecologic problem of childhood.** Prepubertally, the vulva, vestibule, and vagina are anatomically and histologically vulnerable to bacterial infection, with the bacteria typically present in the perianal area. The physical proximity of the vagina and vestibule to the anus can result in overgrowth of bacteria that can cause primary vulvitis and secondary vaginitis. Yeast infections are rare in prepubertal children who are toilet trained and out of diapers (35).

The clinician should be familiar with normal prepubertal genital anatomy and hymenal configuration. **The unestrogenized vulvar vestibule is mildly erythematous and can be confused with infection. In addition, smegma in the interlabial sulci and beneath the clitoral prepuce may resemble patches of candida vulvitis. In prepubertal girls, the vulvar area is quite susceptible to chemical irritants.**

Chronic skin conditions such as lichen sclerosus, psoriasis, seborrheic dermatitis, and atopic vulvitis may occur in children (11). Lichen sclerosus, the cause of which is not well-established, has a characteristic "cigarette paper" appearance in a keyhole distribution (around the vulva and anus) **(Fig. 9-4)**. Lichen sclerosus should be treated

in pediatric patients as it is in adults; there is some evidence that the condition may regress as the child progresses through adrenarche and menarche, although this appears to be infrequent. The use of ultrapotent steroids topically has been successful in children and adolescents (36).

Labial agglutination or adhesions may occur as a result of chronic vulvar inflammation from any cause **(Fig. 9-9A)**. The treatment of labial adhesions consists of observation, if they are asymptomatic. With urinary or vulvovaginal symptoms, a brief course (2 to 6 weeks) of externally applied estrogen cream or topical steroid is appropriate (37). The area of agglutination (adhesion) will become thin as a result, and separation can usually be performed in the office with the use of a topical anesthetic (e.g., lidocaine jelly) **(Fig. 9-9B)**. Manual separation in the office without pretreatment and without anesthesia is discouraged, as this practice may be so traumatic to the child that she will not allow subsequent examination. In the absence of a previously traumatic examination, failure of medical therapy, or acute symptoms such as urinary retention, surgical separation is infrequently required (37). Treatment with a topical emollient (such as petrolatum) is indicated after lysis to prevent recurrent adhesions. Urethral prolapse may cause acute pain or bleeding, or the presence of a mass may be noted **(Fig. 9-2)**.

Vulvovaginal symptoms of any sort in a young child should prompt the consideration of possible sexual abuse. Sexually transmitted infections may occur in prepubertal children (38). Although vulvar condyloma presenting before age 2 to 3 years can be transmitted during vaginal delivery from the mother or from warts on caretakers' hands, the possibility of abuse should be considered in all children with genital warts. Condyloma in older girls may be spread in a nonsexual manner, but was classified as "indeterminant" in classification findings that may be associated with sexual abuse (39). Sensitive, but direct, questioning of the parent or caretaker and the child should be a part of the evaluation; if sexual abuse is suspected, the incident must be reported to the appropriate social services agency.

Nonsexually transmitted vulvar ulcers can occur in peripubertal and adolescent girls, often in association with systemic symptoms suggestive of a viral illness (40). Herpes simplex virus, syphilis, and Behçet disease can cause vulvar ulcers, and they may occur as a form of genital aphthosis **(Fig. 9-10)**.

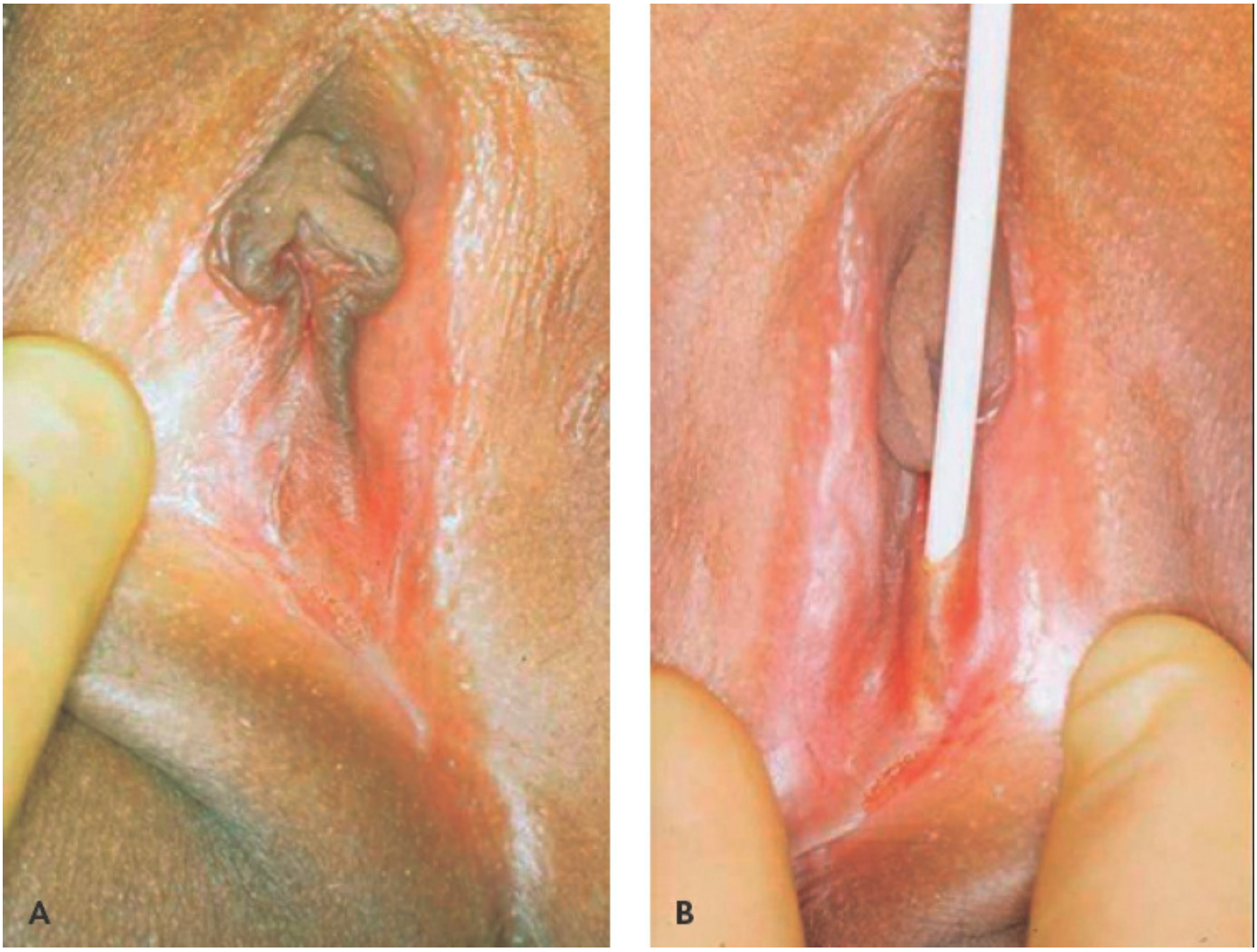


FIGURE 9-9 **A:** Labial adhesions. **B:** Cotton-tipped applicator placed inside the labial adhesions shown in **A**.

Prepubertal Vaginal Conditions

Vaginal Discharge in Prepubertal Girls

The symptom of vaginal discharge in the prepubertal age group is almost always caused by inflammation and irritation. In prepubertal girls, the primary site typically is the vulva with vaginitis following secondarily, whereas in adolescents and adults, vaginitis typically is the primary finding with vulvitis occurring secondarily. **Sexual abuse should always be considered in prepubertal children with vaginal discharge or a foreign body** (41). Although the routine use of cultures to detect STDs in girls with a history of sexual abuse was questioned, vaginal testing for gonorrhea and chlamydia should be performed in girls who have symptoms that include vaginal discharge (10). In prepubertal girls, vulvovaginitis is usually caused by multiple organisms that are present in the perineal area, although a single organism such as *Streptococcus,* or even rarely *Shigella,* may be causative (42). When the cause is related to poor perineal

hygiene, cultures often reveal a mixture of bacterial organisms. In this situation, the typical history is intermittent symptoms of irritation, itching, discharge, and odor over many months to years. Treatment should be initiated with a focus on hygiene and cleansing measures (11). A short-term (less than 4 weeks) course of treatment with topical estrogens and broad-spectrum antibiotics may be necessary. The problem is frequently recurrent. In girls who have a relatively acute onset of vaginal discharge and vulvovaginal symptoms, a single bacterial organism is more likely to be the cause of their symptoms.

Pokorny and Stormer described a technique for obtaining vaginal cultures and for performing vaginal irrigation (43). A catheter within a catheter can be fashioned using the tubing from an intravenous butterfly setup within a sterile urethral catheter. Nonbacteriostatic saline (1 to 3 mL) can be injected, aspirated, and sent for culture **(Fig. 9-11)**. Cultures taken in this manner are almost always better tolerated than cultures obtained using a cotton-tipped applicator. A larger quantity of saline can be used to irrigate the vagina while the catheter is still within the vagina. Small foreign bodies can often be flushed from the vagina in this manner. The most common foreign body is a small piece of toilet paper, although children will place other objects (toys, beans, coins) within their vaginas **(Fig. 9-5)**. **A persistent vaginal discharge after treatment or a discharge that is bloody or brown in color without other obvious external lesions should prompt vaginal irrigation or vaginoscopy to rule out a foreign body** (15).

ADOLESCENT AGE GROUP

The adolescent's experience and expression of illness and pain should be viewed within the context of her life experiences. Most adolescents have limited life experiences with problems such as pain, discomfort, or bleeding. An adolescent may state that she is experiencing the "worst pain of her life" and yet may appear to be reasonably comfortable. She may well be stating the truth about this experience, which the clinician must interpret differently from the symptoms of an adult woman who, for instance, may be in active labor. It should be remembered that an individual's response to illness and pain is to some extent a learned behavior.



FIGURE 9-10 Vulvar aphthosis in a prepubertal girl.

Adolescent Abnormal Bleeding

Normal Menses in Adolescents

[1] To assess vaginal bleeding during adolescence, it is necessary to understand the range of normal menstrual cycles (see Chapter 7). During the first 2 to 5 years after menarche, most cycles are anovulatory. Despite this, they are somewhat regular, within a range of approximately 21 to 45 days, in contrast to adult women, whose cycles typically range between 21 and 38 days (44–46). A pattern of plus or minus 10 days and a cycle length of 21 to approximately 45 days are established within 2 years of menarche **(Table 9-6)**.

The mean duration of menses is 4.7 days; 89% of cycles last 7 days. The average blood loss per cycle is 35 mL, and the major component of menstrual discharge is endometrial tissue (47). An 80 mL/cycle is used as a definition of heavy menstrual bleeding and recurrent bleeding in excess of 80 mL/cycle results in anemia, although the clinical utility of the 80 mL/cycle is question able as neither women nor clinicians can easily estimate this volume (48,49).

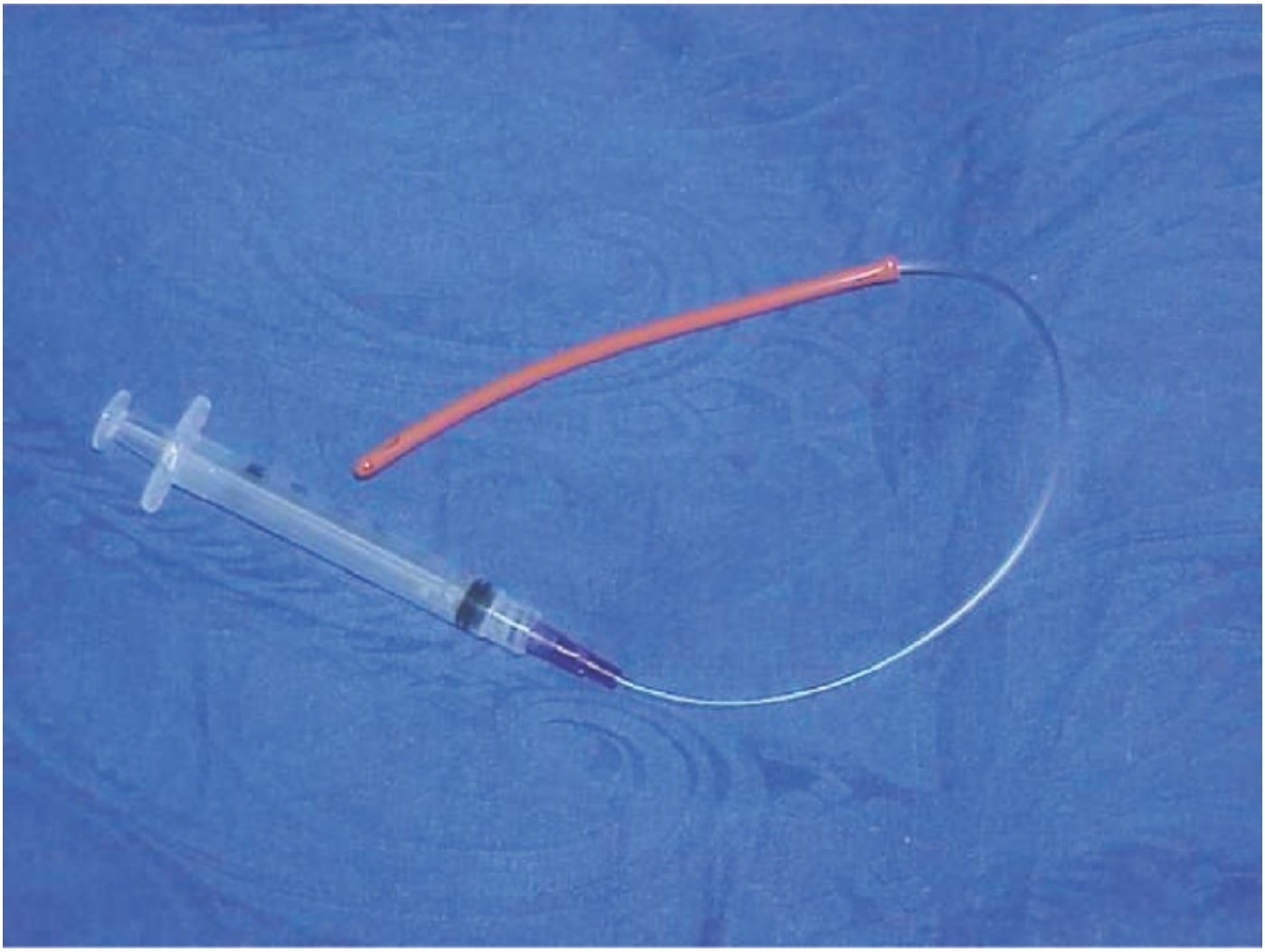


FIGURE 9-11 Catheter technique for obtaining vaginal culture and irrigation.

The common clinical practice of asking how many pads or tampons are soaked on a heavy day or per cycle can give a rough approximation of blood loss (three to five pads per day is typical). Individual variations in fastidiousness, lack of familiarity with the volume of blood loss other than one's own, and errors in estimation or recollection result in inaccuracies in estimations of menstrual volume. One study found that one-third of individuals who estimated their cycles to be moderate or light had bleeding in excess of 80 mL/cycle, whereas nearly one-half of those who described the bleeding as heavy had flow less than 80 mL/cycle (50). In addition, the amount of menstrual blood contained in each tampon or pad may vary both within brands as well as from one brand to another. However, changing a pad hourly, clots larger than "50-pence size," and requiring a change overnight are associated with a measured volume of greater than 80 mL (49).

The transition from anovulatory to ovulatory cycles during adolescence takes place during the first several years after menarche. It results from the so-called *maturation of the hypothalamic–pituitary–ovarian axis,* characterized by positive

feedback mechanisms in which a rising estrogen level triggers a surge of luteinizing hormone and ovulation. **Most adolescents have ovulatory cycles by the end of their second year of menstruation, although most cycles (even anovulatory ones) remain within a rather narrow range of approximately 21 to 42 days.**

Table 9-6 Parameters for Normal Menstrual Cycles in Adolescents

	Normal
Menstrual cycle frequency	21–45 days
Cycle variation from cycle to cycle	Less than in adults
Duration of flow	4–8 days
Volume of flow	4–80 mL

From **Hillard PJ.** Menstruation in young girls: a clinical perspective. *Obstet Gynecol* 2002;99:655–662.

Differential Diagnosis of Adolescent Abnormal Bleeding

Cycles that are longer than 42 days, bleeding that occurs more frequently than 21 days, and bleeding that lasts more than 7 days should be considered abnormal, particularly after the first 2 years from the onset of menarche. Bleeding occurring less frequently than in an interval of 90 days is abnormal, even in the first gynecologic year after menarche (44). The variability in cycle length is greater during adolescence than adulthood; thus, greater irregularity is acceptable if neither significant anemia nor hemorrhage is present. However, consideration should be given to an evaluation of possible causes of abnormal menses (particularly underlying causes of anovulation such as androgen excess syndromes or causes of oligomenorrhea such as eating disorders) for girls whose cycles are consistently outside normal ranges or whose cycles were previously regular and become irregular (45). Conditions that are associated with abnormal bleeding are listed in Table 9-7 and more fully discussed in Chapter 10.

Anovulation

Anovulatory bleeding can be too frequent, prolonged, or heavy, particularly after a long interval of amenorrhea. The physiology of this phenomenon relates to a failure of the feedback mechanism in which rising estrogen levels result in a decline in follicle-stimulating hormone (FSH) with subsequent decline of estrogen levels. In anovulatory cycles, estrogen secretion continues, without opposing progesterone, resulting in endometrial proliferation with subsequent unstable growth and incomplete shedding. The clinical result is irregular, prolonged, and heavy bleeding.

Table 9-7 Conditions Associated With Anovulation and Abnormal Bleeding

Eating disorders
Anorexia nervosa
Bulimia nervosa
Excessive physical exercise
Chronic illness
Primary ovarian insufficiency (POI) (previously termed premature ovarian failure [POF])
Alcohol and other drug abuse
Stress
Thyroid disease
Hypothyroidism
Hyperthyroidism
Diabetes mellitus
Androgen excess syndromes (e.g., polycystic ovary syndrome [PCOS])

Studies of adolescent menses show differences in rates of ovulation based on the number of months or years postmenarche. **The younger the age at menarche, the sooner regular ovulation is established.** In one study, the time from menarche until 50% of the cycles were ovulatory was 1 year for girls whose menarche occurred when they were younger than 12 years of age, 3 years for girls whose menarche occurred between 12 and 12.9 years of age, and 4.5 years for girls whose menarche occurred at 13 years of age or older (51).

Pregnancy-Related Bleeding

The possibility of pregnancy must be considered when an adolescent seeks treatment for abnormal bleeding (Table 9-8). Bleeding in pregnancy can be associated with a spontaneous abortion, ectopic pregnancy, or other pregnancy-related complications, such as a molar pregnancy. In the United States, 11% of 15-year-old adolescent girls have had sexual intercourse, as have 55% of those 18 years old (52). Issues of confidentiality for adolescent health care are critical to an adolescent's willingness to seek appropriate reproductive health care (see Chapter 1).

Table 9-8 Causes of Bleeding by Approximate Frequency and Age Group

Infancy	Prepubertal	Adolescent	Reproductive	Perimenopausal	Postmenopausal
Maternal estrogen withdrawal	Vulvovaginitis	Anovulation	Exogenous	Anovulation	Atrophy
	Vaginal foreign body	Exogenous hormone use	Pregnancy	Fibroids	Endometrial polyps
	Precocious puberty	Pregnancy	Anovulation	Cervical and endometrial polyps	Endometrial cancer
	Tumor	Coagulopathy	Fibroids	Thyroid dysfunction	Hormonal therapy
			Cervical and endometrial polyps		Other tumor—vulvar, vaginal, cervical
			Thyroid dysfunction		

Exogenous Hormones

The cause of abnormal bleeding that is experienced while an individual is taking exogenous hormones usually is very different from bleeding that occurs without hormonal manipulation (53). **Oral contraceptive use is associated with breakthrough bleeding, which occurs in as many as 30% to 40% of individuals during the first cycle of combination pill use. In addition, irregular bleeding can result from missed pills** (54,55). Strict adherence to correct and consistent pill taking is difficult for many individuals who take oral contraceptives; one study reported that only 40% of women took a pill every day (56). Other studies suggest that adolescents have an even more difficult time taking oral contraceptives than do adults. A study of urban teens reported approximately two episodes of three or more consecutive missed pills occurring during each 3-month interval (57). With this many missed pills, it is not surprising that some individuals experience irregular bleeding. The solution is to emphasize consistent pill taking; if the individual is unable to comply with daily pill use, an alternative contraceptive method may be preferable.

All forms of hormonal contraception, from combination and progestin-only minipills, to contraceptive patches, rings, intrauterine devices (IUDs), and injectable and implantable contraception, can be associated with abnormal bleeding, although studies assessing bleeding have not used uniform methodologies and thus comparisons are difficult (58). Irregular bleeding occurs frequently in users of *depomedroxyprogesterone acetate* (*DMPA*), although at the end of 1 year, more than 50% of users will be amenorrheic (59). The mechanism of bleeding associated with these hormonal methods is not well-established; an atrophic endometrium or factors related to angiogenesis may be involved, suggesting options for therapy (60,61). It should not be assumed that any bleeding occurring while an individual is using a hormonal method of contraception is caused by that method. Other local causes of bleeding, such as cervicitis or endometritis, can occur during the use of hormone therapy and may be particularly important to consider in adolescents who are at risk for STDs.



FIGURE 9-12 Uterus didelphys.

Hematologic Abnormalities

In the adolescent age group, the possibility of a hematologic cause of abnormal bleeding must be considered. One classic study reviewed all visits by adolescent patients to an emergency room with the symptom of excessive or abnormal bleeding (62). The most common coagulation abnormality diagnosed was idiopathic thrombocytopenic purpura, followed by von Willebrand disease. Subsequent studies confirmed this association, particularly with excessive bleeding at the time of menarche. Von Willebrand disease occurs in approximately 1% of women in the United States and, in its mildest form, menorrhagia may be the only symptom (63). **Adolescents who have severe menorrhagia, especially at menarche, should be screened for coagulation abnormalities, including von Willebrand disease.**

Infections

Irregular or postcoital bleeding can be associated with chlamydial cervicitis. **Adolescents have the highest rates of chlamydial infections of any age group, and sexually active teens should be screened routinely for chlamydia** (64). **Menorrhagia can be the initial sign in patients infected with sexually transmissible organisms.** Adolescents have the highest rates of PID of any age group of sexually experienced individuals (see Chapter 15).

Other Endocrine or Systemic Problems

Abnormal bleeding can be associated with thyroid dysfunction. Signs and symptoms of thyroid disease can be somewhat subtle in teens (see Chapter 35). Hepatic dysfunction should be considered because it can lead to abnormalities in clotting factor production. Hyperprolactinemia can cause amenorrhea or irregular bleeding.

Polycystic ovary syndrome (PCOS) can occur during adolescence, and manifestations of excess androgen (hirsutism, acne) should prompt evaluation, although the diagnostic criteria for PCOS during adolescence are not well-established (65). **Androgen disorders occur in about 5% to 10% of adult women, making them the most common endocrine disorders in women** (see Chapter 35). **Classic PCOS, functional ovarian hyperandrogenism, or partial late-onset congenital adrenal hyperplasia can occur in adolescence. These disorders often are overlooked, unrecognized, or untreated.** Women with even mild disorders are candidates for intervention, including lifestyle interventions to normalize weight and pharmacologic interventions to manage abnormal bleeding or hirsutism. These disorders may be a harbinger of type 2 diabetes, endometrial cancer, and cerebrovascular disease. **Acne, hirsutism, and menstrual irregularities are often dismissed as normal during adolescence but may be manifestations of hyperandrogenism** (65,66). Androgen abnormality can persist beyond adolescence. Obesity, hirsutism, and acne should be evaluated to minimize the significant psychosocial costs. Androgenic changes are partially reversible if detected early and managed appropriately. Behavioral changes in lifestyle (diet and exercise) should be strongly encouraged but are often difficult to achieve. Signs of insulin resistance (acanthosis nigricans) should be evaluated and managed appropriately (67,68).

Anatomic Causes

Obstructive or partially obstructive genital anomalies typically present during adolescence. Complex müllerian abnormalities, such as an obstructing longitudinal vaginal septum with uterus didelphys, can cause hematocolpos or hematometra **(Fig. 9-12)**. If these obstructing anomalies have or develop a small outlet, persistent dark-brownish discharge (old blood) may appear instead of or in addition to a pelvic mass. Many varieties of uterine and vaginal anomalies exist, and clinicians who have expertise with these anomalies should be involved in their management. **Figure 9-13** illustrates situations in which abnormal bleeding can result from partially obstructing septa.

Diagnosis of Adolescent Abnormal Bleeding

Examination

A careful general physical examination can reveal signs of androgen excess such as acanthosis nigricans or facial, chest or periareolar, or abdominal terminal hair growth. Because body hair is felt by many to be culturally unacceptable in women and girls,

sensitive questioning about specific hair removal techniques (bleaching, waxing, use of depilatories, shaving, plucking, threading) is warranted during an examination. A complete pelvic examination is appropriate in patients who are sexually active, are having severe pain, or may have an anatomic anomaly. Testing for gonorrhea and *Chlamydia trachomatis* infection is appropriate during a speculum examination if the patient is sexually active. Some young teens who have a history that is classic for anovulation, who deny sexual activity, and who agree to return for follow-up evaluation may be managed with a limited gynecologic examination supplemented with pelvic ultrasonography.

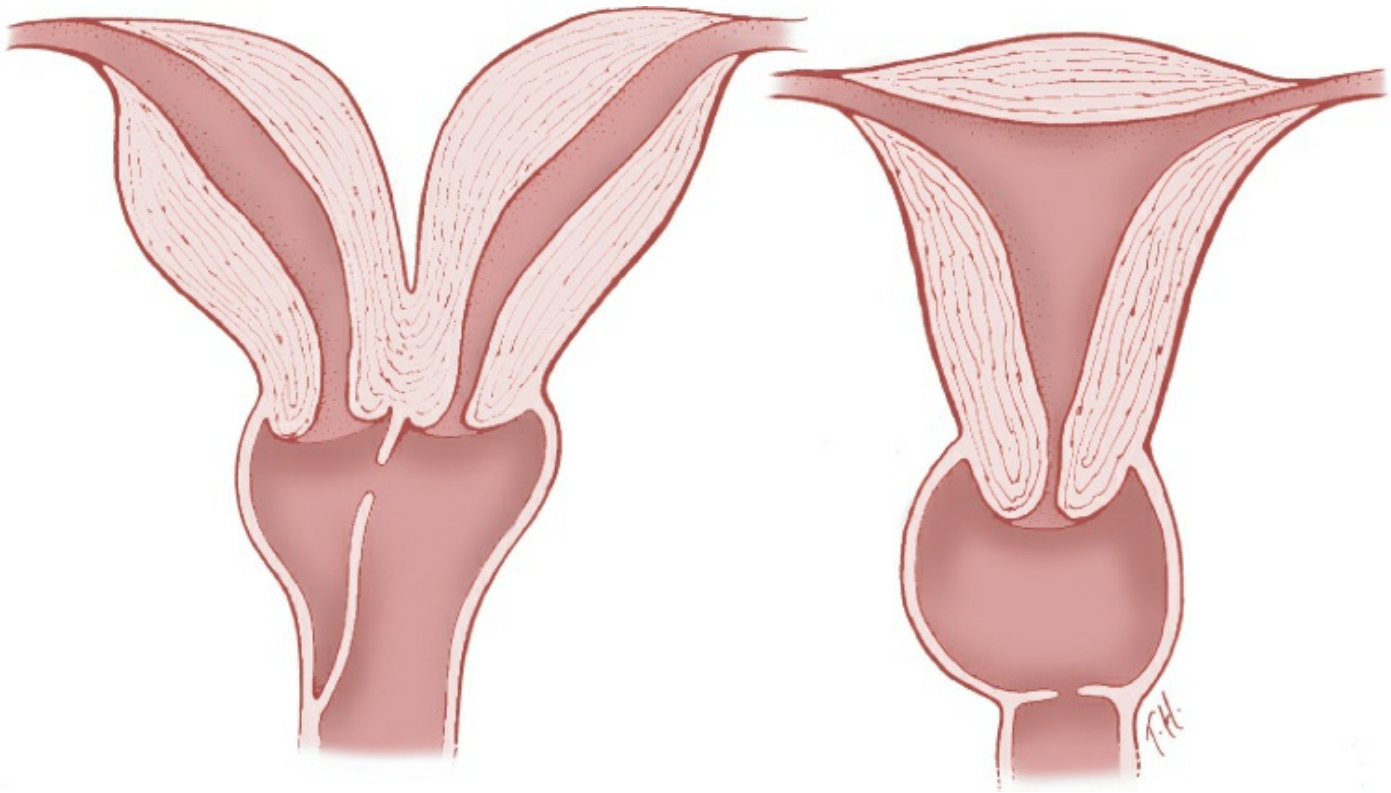


FIGURE 9-13 The types of obstructive or partially obstructive genital anomalies that can occur during adolescence.

Laboratory Testing

Any adolescent with abnormal bleeding should undergo sensitive pregnancy testing, regardless of whether she states that she has had intercourse. The medical consequences of failing to diagnose a pregnancy are too severe to risk missing the diagnosis. Complications of pregnancy should be managed accordingly. In addition to a pregnancy test, laboratory testing should include a complete blood count with platelet count and screening tests for coagulopathies and platelet dysfunction. An international expert panel made recommendations about when a gynecologist should suspect a bleeding disorder and pursue a diagnosis (Table 9-9). The consensus report recommends measurement of complete blood cell count (CBC), platelet count and

function, prothrombin time (PT), activated partial thromboplastin time (aPTT), von Willebrand factor (VWF) (measured with ristocetin cofactor activity and antigen, factor VIII), and fibrinogen to be assessed in collaboration with a hematologist (69).

Thyroid studies may be relevant. Testing for STDs may be performed as warranted on either a cervical or a urine specimen using DNA amplification techniques. Cervical cytology testing is generally not appropriate for adolescents, particularly at an emergency or urgent visit for excessive bleeding (70).

Imaging Studies

If the pregnancy test results are positive, pelvic imaging using ultrasonography may be necessary to confirm a viable intrauterine pregnancy and rule out a spontaneous abortion or ectopic pregnancy. If a pelvic mass is suspected on examination, or if the examination is inadequate (more likely to be the case in an adolescent than an older woman) and additional information is required, pelvic ultrasonography may be helpful. Although transvaginal ultrasonographic examination can be more helpful than transabdominal ultrasonography in ascertaining details of pelvic anatomy, the use of the vaginal probe may not be possible in a young girl or one who has not used tampons or had intercourse. Direct communication between the clinician and the radiologist can be helpful in identifying patients who are appropriate candidates for transvaginal ultrasonographic examination, such as those who are sexually active, rather than a blanket prohibition against transvaginal ultrasound examination in adolescents.

Table 9-9 When Should a Gynecologist Suspect a Bleeding Disorder

Heavy menstrual bleeding since menarche
Family history of bleeding disorder
Personal history of any of the following:
Epistaxis in the last year
Bruising without injury >2 cm diameter
Minor wound bleeding
Oral or gastrointestinal bleeding without anatomic lesion
Prolonged or heavy bleeding after dental extraction
Unexpected postoperative bleeding
Hemorrhage from ovarian cyst
Hemorrhage requiring blood transfusion
Postpartum hemorrhage, especially delayed >24 hrs

Failure to respond to conventional management of menorrhagia

From **James AH, Kouides PA, Abdul-Kadir R, et al.** Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynecol* 2009;201(1):12e11–12e18.

Other imaging studies are not indicated as initial testing but may be helpful in selected instances. **If a pelvic ultrasonographic examination does not lead to clarification of the anatomy when vaginal septa, uterine septa, uterine duplication, or vaginal agenesis is suspected, MRI can be helpful in delineating anatomic abnormalities** (71). This imaging technique is useful in the evaluation of uterine and vaginal developmental anomalies, although laparoscopy can still play a role in the clarification of abnormal anatomy (72). CT scanning may be helpful in detecting nongenital intra-abdominal abnormalities.

Management of Abnormal Bleeding

Management of bleeding abnormalities related to pregnancy, thyroid dysfunction, hepatic abnormalities, hematologic abnormalities, or androgen excess syndromes should be directed to treating the underlying condition. Oral contraceptives can be extremely helpful in managing androgen excess syndromes, inherited bleeding disorders, and anovulation, although an appropriate evaluation should be performed prior to initiation of hormonal contraception (67,73,74).

Treatment with *mefenamic acid* and other nonsteroidal anti-inflammatory agents (NSAIDs) results in decreased menstrual bleeding when compared with placebo (75). *Tranexamic acid,* an antifibrinolytic agent, is more effective in decreasing heavy menstrual bleeding, and was approved by the U.S. Food and Drug Administration (FDA) for this indication in late 2009. After specific diagnoses are ruled out by appropriate laboratory testing, this condition can be managed either expectantly or with hormone therapy, depending on the clinical presentation and other factors, such as the need for contraception.

Anovulation: Mild Bleeding

Adolescents who have mildly abnormal bleeding, as defined by adequate hemoglobin levels and minimal disruption of daily activities, are best managed with prospective menstrual charting, frequent reassurance, close follow-up, and supplemental iron. If the patient is bleeding heavily or for a prolonged interval, an apparent decrease in the bleeding does not necessarily mean that therapy is not required. Intermittent bleeding characterizes anovulatory bleeding and is likely to continue in the absence of therapy.

A patient who is mildly anemic will benefit from hormone therapy. If the patient is not bleeding at the time of evaluation and has no contraindications to the use of estrogen, **a**

combination low-dose oral contraceptive can be prescribed for use in the manner in which it is used for contraception. If the patient is not sexually active, she should be reevaluated after three to six cycles to determine whether she desires to continue this regimen. Parents may sometimes object to the use of oral contraceptives if their daughter is not sexually active (or if they believe her not to be or even if they would like her not to be). These objections are frequently based on misconceptions about the potential risks of the pill and can be overcome by careful explanation of the pill's role as medical therapy. Objections may be based on concerns that hormonal therapy for medical indications is likely to hasten the onset of coitarche or sexual debut, although no data support this fear. If the medication is discontinued when the young woman is not sexually active and she subsequently becomes sexually active and requires contraception, it may be difficult to explain the reinstitution of oral contraceptives to the parents. Oral contraceptives are especially appropriate for the management of abnormal bleeding in adolescents for a number of reasons:

1. **Over 40% of adolescents in the United States are sexually experienced** (52).
2. **Adolescents typically wait many months after initiating sexual activity to seek medical contraception.**
3. **At least 80% of adolescent pregnancies are unintended** (76).
4. **Approximately one-quarter of adolescent pregnancies in the United States end in abortion** (77).
5. **Approximately 11% of adolescent females in the United States give birth before age 20, although these rates vary by race/ethnicity: 8% of white teens, 16% of black teens, and 17% of Hispanic teens** (78).

Consideration should certainly be given to continuing the oral contraception use, and parents should be reassured that the medical risks are small in otherwise healthy adolescents and that there are no significant risks associated with prolonged use. Individuals may choose to continue oral contraceptives for contraception or their noncontraceptive benefits (improvement of acne, decreased dysmenorrhea, and lighter, more regular menstrual flow, protective effect for endometrial and ovarian cancer).

Sometimes, providing parents with accurate information about the safety of oral contraceptives, emphasizing that currently available oral contraceptive preparations contain lower doses of estrogens and progestins than those used in the 1960s and 1970s, and emphasizing the hormonal rather than contraceptive function may not be persuasive. In such cases, cyclic progestins are an alternative. A systematic review of the use of combination hormonal therapy versus progestins alone for the treatment of anovulatory bleeding found a paucity of evidence supporting the efficacy of one management regimen over another (79). ***Medroxyprogesterone acetate,* 5 to 10 mg/day for 10 to 13 days every 1 to 2 months, prevents excessive endometrial buildup and irregular**

shedding caused by unopposed estrogen stimulation. This therapy should be reevaluated regularly and accompanied by oral administration of iron. Eventual maturation of the hypothalamic–pituitary–ovarian axis usually will result in the establishment of regular menses unless there are underlying conditions such as hyperandrogenism.

Acute Bleeding

Moderate

The initial assessment of an adolescent with acute heavy menstrual bleeding requires assessment for hemodynamic instability and signs of hypovolemia.

Consideration should be given to the causes of acute heavy menstrual bleeding, which are the same as the causes of chronic abnormal bleeding, and which have been described by a classification system approved by the International Federation of Gynecology and Obstetrics and ACOG (80). This system describes the causes of abnormal bleeding as related or unrelated to structural abnormalities and categorized by the acronym PALM-COEIN (see Chapter 10) (81). In adolescents, structural abnormalities are much rarer than in women of older reproductive age, and thus the COEIN etiologies: **C**oagulopathy, **O**vulatory dysfunction, **E**ndometrial, **I**atrogenic, and **N**ot otherwise classified are more likely to be causative.

Patients who are bleeding acutely but in a stable condition and do not require hospital admission will typically require hormonal treatment to effectively stop anovulatory bleeding. Limited evidence and expert opinion suggest options for therapy, which in adolescents focus on medical rather than surgical therapies. Options include IV estrogen, combined oral contraceptives, and oral progestins (80). With hormonal therapy, bleeding usually stopped within a few days, and the dosing is typically tapered or stopped to allow shedding of the dyssynchronous endometrium and withdrawal bleeding. With this therapy, the patient and her parents should be given specific written and oral instructions warning them about the potential side effects of high-dose hormone therapy—nausea, breast tenderness, and breakthrough bleeding. The patient should be instructed to call with any concerns rather than discontinue the hormonal treatment, and she must understand that stopping the prescribed regimen may result in a recurrence of heavy bleeding. Both the patient and her mother should be warned to expect heavy withdrawal flow for the first period. Subsequently, the institution of combination low-dose oral contraceptive therapy, given once daily and continued for three to six cycles, allows regular withdrawal flow. If the patient is not sexually active, hormonal therapy may be discontinued after the recommended course of therapy and the menstrual cycles may be reassessed.

Emergency Management

The decision to hospitalize a patient depends on the rate of current bleeding and

the severity of any existing anemia. The actual acute blood loss may not be reflected adequately in the initial blood count but will be revealed with serial hemoglobin assessments. The cause of acute menorrhagia may be a primary coagulation disorder; thus, measurements of coagulation and hemostasis, including screening for coagulopathy, should be performed for any adolescent patient with acute menorrhagia, as noted above in the recommendations of an international panel (63). Von Willebrand disease, platelet disorders, or hematologic malignancies can cause menorrhagia. Depending on the patient's level of hemodynamic stability or compromise, a blood sample can be analyzed for type and screen. The decision to transfuse must be considered carefully, and the benefits and risks should be discussed with the adolescent and her parents. The need for transfusion is determined by hemodynamic stability.

In patients who, by exclusion, are diagnosed as having anovulatory bleeding, hormone therapy usually makes it possible to avoid surgical intervention (dilation and curettage [D&C], operative hysteroscopy, or laparoscopy). A patient who is hospitalized for severe bleeding requires aggressive management as follows:

1. **After stabilization, when appropriate laboratory assessment and an examination establish a working diagnosis of anovulation, hormonal management will usually control bleeding** (80).
2. As noted for moderate bleeding, hormonal therapy is typically effective within 12 to 24 hours.
3. **If this hormonal therapy is not effective, the patient should be reevaluated and the diagnosis should be reassessed.** The failure of hormonal management suggests that a local cause of bleeding is more likely. In this event, consideration should be given to a pelvic ultrasonographic examination to determine any anatomic causes of bleeding (such as uterine leiomyomas, endometrial polyps, or endometrial hyperplasia) and to assess the presence of intrauterine clots that may impair uterine contractility and prolong the bleeding episode. Although anatomic causes of heavy menstrual bleeding are rare in adolescents, they become increasingly common in women of reproductive age (see Chapter 10).
4. **If intrauterine clots are detected, consideration may be given to evacuation of the clots (suction curettage or D&C); alternatively, uterotonics such as misoprostol may be helpful. An intrauterine tamponade with a 26F Foley catheter and 30 mL balloon may be required.** Although a D&C will provide effective immediate control of the bleeding, it is unusual to use this approach in adolescents.

More drastic forms of treatment other than D&C (such as ablation of the

endometrium by laser or cryotherapy) are considered inappropriate for adolescents because of concerns about future fertility.

If intravenous or oral administration of hormonal therapy controls the bleeding, a tapering regimen of hormonal therapy may be given (80). **Subsequent hormonal therapy with combined oral contraceptives, the levonorgestrel intrauterine system (IUS), progestin therapy, and nonhormonal therapies are useful. Nonhormonal antifibrinolytic drugs, such as tranexamic acid, have been shown to reduce chronic abnormal bleeding by 30% to 55%** (80). **Tranexamic acid has been used for the treatment of acute heavy bleeding.**

In general, the prognosis for regular ovulatory cycles and subsequent normal fertility in young women who experience an episode of abnormal bleeding is good, particularly for patients who develop abnormal bleeding as a result of anovulation within the first years after menarche and in whom there are no signs of other specific conditions. Some girls, including those in whom there is an underlying medical cause, such as PCOS, will continue to have abnormal bleeding into middle and late adolescence and adulthood and will benefit from the ongoing use of hormonal therapy including combined oral contraceptives to manage hirsutism, acne, and irregular periods, or menstrual suppression using the levonorgestrel IUS, or IM or oral progestins. Individuals with coagulopathies may benefit from ongoing oral contraceptive use, use of *tranexamic acid,* or intranasal *desmopressin*.

A levonorgestrel-releasing IUD can be effective in managing heavy bleeding, with reductions of heavy bleeding by up to 90%, and can be appropriate for adolescent use (82–84). **Because IUD insertion is viewed as invasive by adolescents, particularly young teens, adjuncts to insertion, such as the use of local anesthesia may be appropriate** (85). The *levonorgestrel* IUD is approved by the FDA for treatment of heavy menstrual bleeding in women requiring contraception and is recommended as first-line medical therapy for this group of women (86).

Long-Term Menstrual Suppression

For patients with underlying medical conditions, such as coagulopathies, a malignancy requiring chemotherapy, or developmental disabilities, long-term therapeutic amenorrhea with menstrual suppression using the following regimens may be necessary or helpful (87,88):

1. Progestins such as oral *norethindrone, norethindrone acetate,* or *medroxyprogesterone acetate* on a continuous daily basis.
2. Continuous (noncyclic) combination regimens of oral estrogen and progestins (birth control pills) or other forms of combination estrogen/progestins (transdermal patch, vaginal ring) that do not include a withdrawal bleeding–placebo week.
3. Depot formulations of progestins (*DMPA*), with or without concurrent estrogens.

4. Gonadotropin-releasing hormone (GnRH) analogs with or without hormonal add-back therapy.
5. *Levonorgestrel* IUS.

The choice of regimen depends on the presence of any contraindications (such as active liver disease precluding the use of estrogens) and the clinician's experience. **Although the goal of these long-term suppressive therapies is amenorrhea, all of these regimens may be accompanied by breakthrough bleeding, especially in the initial months of use** (87). At 1 year, rates of amenorrhea approach 60% with extended cycle combination oral contraceptives, 50% with *DMPA,* and 50% with the *levonorgestrel* IUS (59,88–90). Because *DMPA* and GnRH analogs are associated with disadvantageous effects on bone mineral density, the potential risks must be weighed against their medical benefits. Regular follow-up visits and continued patient encouragement are required with all of these options. Episodes of spotting and breakthrough bleeding that do not result in a lowered hemoglobin level may be managed expectantly. When breakthrough bleeding affects the hemoglobin level, it should be evaluated with respect to the underlying disease. For example, in a patient with underlying platelet dysfunction, breakthrough bleeding may reflect a lowered platelet count. Bleeding in a patient with hepatic disease may reflect worsening hepatic function. The U.S. Selected Practice Recommendations from the Centers for Disease Control summarize the evidence for management of breakthrough bleeding during hormonal contraceptive use (61).

Adolescent Pelvic Masses

Presentation

Adolescents with pelvic masses may be asymptomatic or may have chronic or acute symptoms. An ovarian mass may be discovered incidentally when an ultrasonographic examination is performed to evaluate the urinary system or when imaging is performed to evaluate pelvic pain. The mere presence of a mass on imaging studies does not always indicate that the mass is the cause of pelvic pain. **A "ruptured ovarian cyst" is a classic diagnosis when an adolescent presents with pelvic pain, even if ultrasonography findings suggest only a simple cystic follicle and a physiologic amount of pelvic fluid that are unlikely to cause pain.** An adnexal mass is not always of ovarian origin. The algorithm in **Figure 9-14** illustrates a framework for thinking about adnexal masses in adolescents. Alternatively, ovarian masses can cause severe, acute, or intermittent symptoms caused by torsion, intraperitoneal rupture, or bleeding into the ovarian tissue **(Fig. 9-15)**. These conditions can represent a true surgical emergency or urgency, and their diagnoses can be challenging. The pressure of an enlarging ovarian mass can cause bowel-related symptoms such as constipation, vague

discomfort, and early satiety; urinary frequency; or even ureteral or bladder neck obstruction.

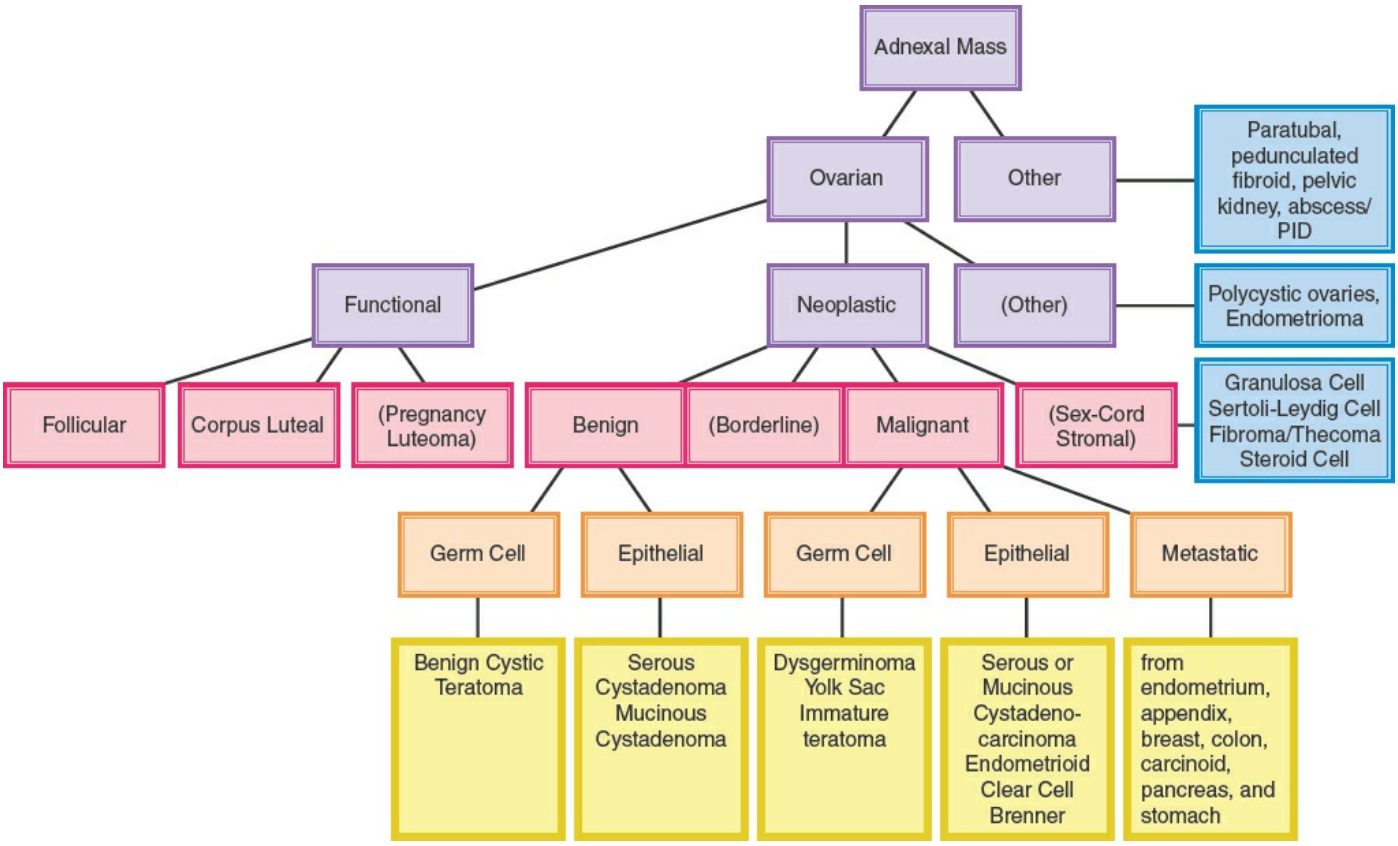


FIGURE 9-14 Algorithm for adnexal masses in adolescents—"dichotomies" of ovarian and other/functional (follicular and corpus luteum cysts) and neoplastic ovarian masses (benign and malignant [germ cell and epithelial]).

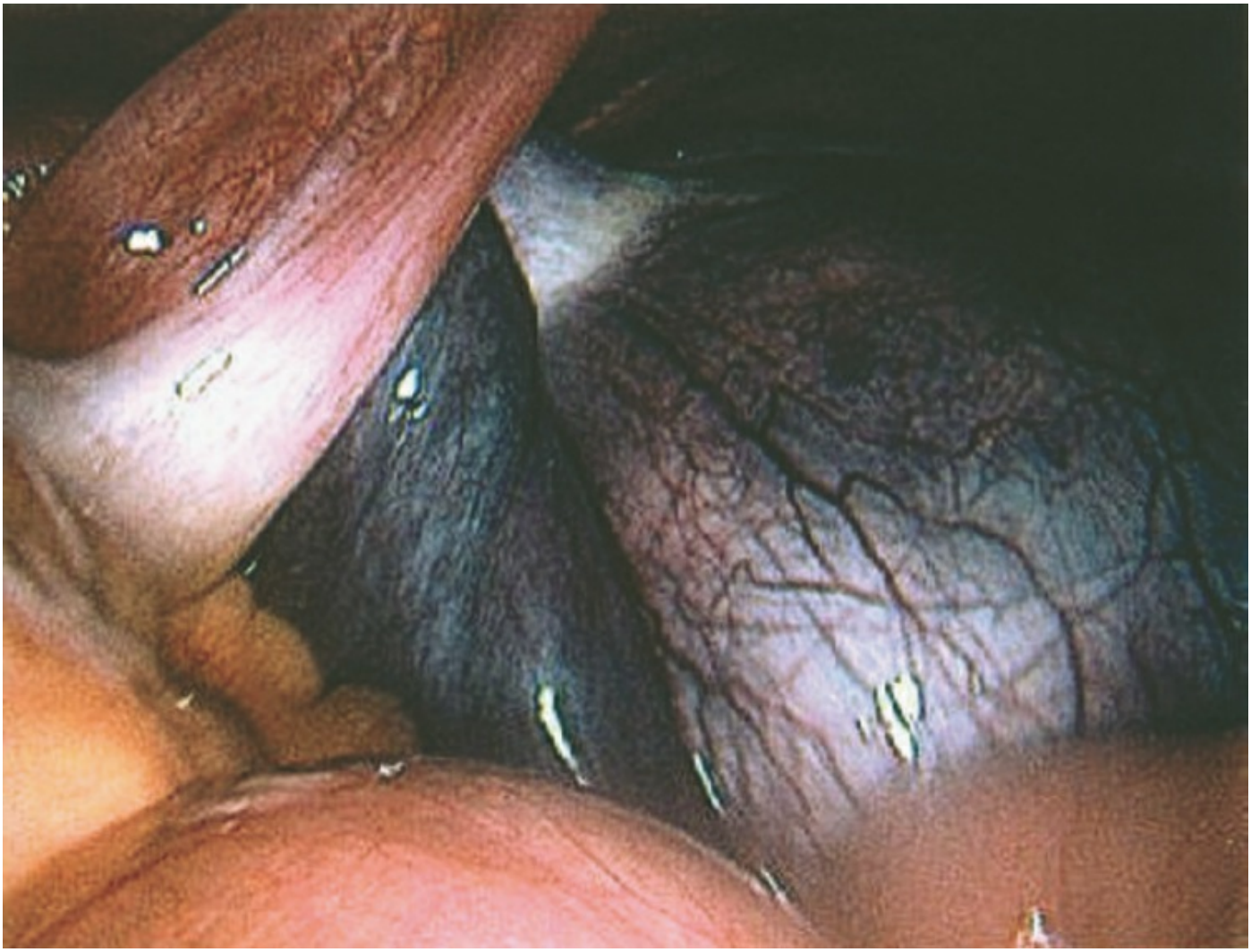


FIGURE 9-15 Adnexal mass with torsion.

Diagnosis

The history and pelvic examination are critical in the diagnosis of a pelvic mass. Considerations in adolescents include the anxiety associated with a first pelvic examination, and issues of confidentiality related to questions about sexual activity. Techniques for history taking and the performance of the first examination are discussed in Chapter 1.

Laboratory studies should always include a pregnancy test (regardless of stated sexual activity), and a complete blood count may be helpful in diagnosing inflammatory masses. Tumor markers, including α-fetoprotein and human chorionic gonadotropin (hCG), may be elaborated by germ cell tumors and can be useful in preoperative diagnosis and follow-up (see Chapter 39).

As in all other age groups, the primary diagnostic technique for evaluating pelvic masses in adolescents is ultrasonography. Although transvaginal ultrasonographic examinations may provide more detail than transabdominal ultrasonography,

particularly with inflammatory masses, a transvaginal examination may not be well-tolerated by adolescents (91,110). Ultrasonography usually is the most helpful imaging technique for assessing ovarian masses. **For cases in which the suspected diagnosis is appendicitis or another nongynecologic condition, or if the results of the ultrasonographic examination are inconclusive, CT or MRI may be helpful.** An accurate preoperative assessment of anatomy is critical, particularly in cases of uterovaginal malformations. MRI can be useful for evaluating this group of rare anomalies (88). Adolescents who present with abdominal pain should be evaluated with some type of imaging procedure because an unexpected finding of a complex uterine or vaginal anomaly requires careful surgical planning and management.

Differential Diagnosis of Adolescent Pelvic Masses

Ovarian Masses in Adolescents

Many studies of ovarian tumors in the pediatric and adolescent age group do not distinguish between prepubertal or premenarchal girls and menarchal adolescents. The findings of some reports are based on the age group, although this is less helpful than a distinction by pubertal development. In evaluating a pelvic or abdominal mass, the clinician must take into consideration the patient's pubertal status because the likelihood of functional masses increases after menarche (Table 9-4). The risk of malignant neoplasms is lower among adolescents than among younger children. Germ cell tumors are the most common tumors of the first decade of life but occur less frequently during adolescence (see Chapter 39). Mature cystic teratoma is the most frequent neoplastic tumor of children and adolescents, accounting for more than one-half of ovarian neoplasms in women younger than 20 years of age (92). Epithelial neoplasms occur with increasing frequency beyond adolescence.

It is well-established that neoplasia can arise in dysgenetic gonads. The risk of malignant tumors in dysgenetic gonads of patients with a Y chromosome depends on the nature of the DSD, the presence of the gonadoblastoma region of the Y chromosome, and other factors—both established and as yet unknown (93). A number of genes involved in gonadal differentiation were described. Recent perspectives suggest that the estimation of individual risk of malignancy should be assessed, and that this may permit a more conservative approach to gonadectomy or its timing (94,95). A multidisciplinary approach to diagnosis of disorders of sex development with attention to biologic, genetic, and psychological factors is advocated (96). **Functional ovarian cysts occur frequently in adolescence.** They may be an incidental finding on examination or may be associated with pain caused by torsion, leakage, or rupture. Paratubal cysts represent embryologic remnants that may be confused with an ovarian mass; they are typically asymptomatic, but can be associated with adnexal torsion **(Fig. 9-15)**. Adnexal or ovarian torsion is a challenging diagnosis to make in prepubertal girls or adolescents; torsion of a mass is more likely to occur than torsion of normal adnexa, although this can

occur. Doppler ultrasound examination may not predict the presence of torsion, although discrepancy in ovarian volume and large volume of the torsed adnexa may be helpful in making the diagnosis (91,97). Management should consist of detorsion rather than oophorectomy, even if the mass appears to have no blood flow, as recovery of ovarian function is likely (98).

Endometriosis is less common during adolescence than in adulthood, although it can occur during adolescence. Of adolescents not responding to conventional medical management of pelvic pain and dysmenorrhea, up to 70% may be found to have endometriosis at the time of laparoscopy (99). Although endometriosis can occur in young women with obstructive genital anomalies (presumably as a result of retrograde menstruation), most adolescents with endometriosis do not have associated obstructive anomalies. In young women, endometriosis may have an atypical appearance characterized by nonpigmented or vesicular lesions, peritoneal windows, and puckering (99).

Uterine Masses in Adolescents

Other causes of pelvic masses, such as uterine abnormalities, are rare in adolescence. Uterine leiomyomas are not often seen in this age group. Obstructive uterovaginal anomalies occur during adolescence, at the time of menarche, or shortly thereafter. Frequently, the correct diagnosis either is not suspected or is delayed (100). A wide range of anomalies can occur, from imperforate hymen to transverse vaginal septa, from vaginal agenesis with a normal uterus and functional endometrium to vaginal duplications with obstructing longitudinal septa, and obstructed uterine horns **(Fig. 9-13)**. Patients may seek treatment for cyclic pain, amenorrhea, vaginal discharge, or an abdominal, pelvic, or vaginal mass. A hematocolpos, hematometra, or both, frequently will be present, and the resulting mass can be quite large (101).

Inflammatory Masses in Adolescents

Adolescents comprise 20% of all diagnoses of PID in the United States (102). An adolescent who has pelvic pain may have an inflammatory mass. Such masses may consist of a tubo-ovarian complex (a mass of matted bowel, tube, and ovary), tubo-ovarian abscess (a mass consisting primarily of an abscess cavity within an anatomically defined structure such as the ovary), pyosalpinx, or, chronically, hydrosalpinx.

The diagnosis of PID is primarily a clinical one based on the presence of lower abdominal, pelvic, and adnexal tenderness; cervical motion tenderness; a mucopurulent discharge; and elevated temperature, white blood cell count, or sedimentation rate (see Chapter 15). The US Centers for Disease Control recommends that clinicians should maintain a low threshold for making this diagnosis, given the potential risks of missing the diagnosis (64). The risk of PID is clearly associated with that of acquiring STDs,

and methods of contraception may either decrease the risk (male latex condoms) or increase it (the IUD in the 3-week interval immediately after insertion) (103,104).

Pregnancy

In adolescents, pregnancy should always be considered as a cause of a pelvic mass. In the United States, more than 40% of adolescent women have experienced sexual intercourse (52). Most pregnancies in adolescents are unintended, and the younger the adolescent, the greater the likelihood that a pregnancy is unintended. Adolescents may be more likely than adults to deny the possibility of pregnancy because of wishful thinking, anxiety about discovery by parents or peers, or unfamiliarity with menstrual cycles and information about fertility. Ectopic pregnancies may cause pelvic pain and an adnexal mass. With the availability of quantitative measurements of β-hCG, more ectopic pregnancies are being discovered before rupture, allowing conservative management with laparoscopic surgery or medical therapy (see Chapter 32). The risk of ectopic pregnancy varies by the method of contraception; users of no contraception have the highest risk, whereas oral contraceptive users have the lowest risk; while levonorgestrel IUSs have a very low risk of failure and pregnancy; if a pregnancy occurs, there is a higher risk of ectopic than if no contraception were used (105). As with older patients, paraovarian cysts and nongynecologic masses can appear as a pelvic or abdominal mass in adolescents **(Fig. 9-16)**.

Management of Pelvic Masses in Adolescents

The management of masses in adolescents depends on the suspected diagnosis and the initial symptom. **Figure 9-8** outlines a plan of management for pelvic masses in adolescents. **Asymptomatic unilocular cystic masses are best managed conservatively because the likelihood of malignancy is low. If surgical management is required based on symptoms or uncertainty of diagnosis, attention should be directed to minimizing the risks of subsequent infertility resulting from pelvic adhesions. Every effort should be made to conserve the ovarian tissue. In the presence of a malignant unilateral ovarian mass, management may include unilateral oophorectomy rather than more radical surgery, even if the ovarian tumor metastasized** (see Chapter 39). **Analysis of frozen sections may not be reliable. In general, conservative surgery is appropriate; further surgery can be performed, if necessary, after an adequate histologic evaluation of the ovarian tumor.**

When symptoms persist in a patient with the clinical diagnosis of PID or tubo-ovarian abscess, laparoscopy should be considered to confirm the diagnosis. A clinical diagnosis may be incorrect in as many as one-third of patients. The surgical management of inflammatory masses is rarely necessary in adolescents, except to treat the rupture of tubo-ovarian abscess or failure of medical management with

broad-spectrum antibiotics (see Chapter 15). Some surgeons advocated laparoscopy to perform irrigation, lysis of adhesions, drainage of unilateral or bilateral pyosalpinx or tubo-ovarian abscess, or extirpation of significant disease. If surgical management is required because of failed medical therapy, conservative, unilateral adnexectomy usually can be performed in these situations, rather than a pelvic clean-out, thereby maintaining reproductive potential. Percutaneous drainage, transvaginal ultrasonographic drainage, and laparoscopic management of tubo-ovarian abscesses are being done more often, although evidence supporting this approach is sparse (106). As with the laparoscopic management of ovarian masses, the clinician's skill and experience with this procedure are critical, and prospective studies on its effectiveness are lacking. Laparoscopic management is associated with a risk of major complications, including bowel obstruction and bowel or vessel injury.

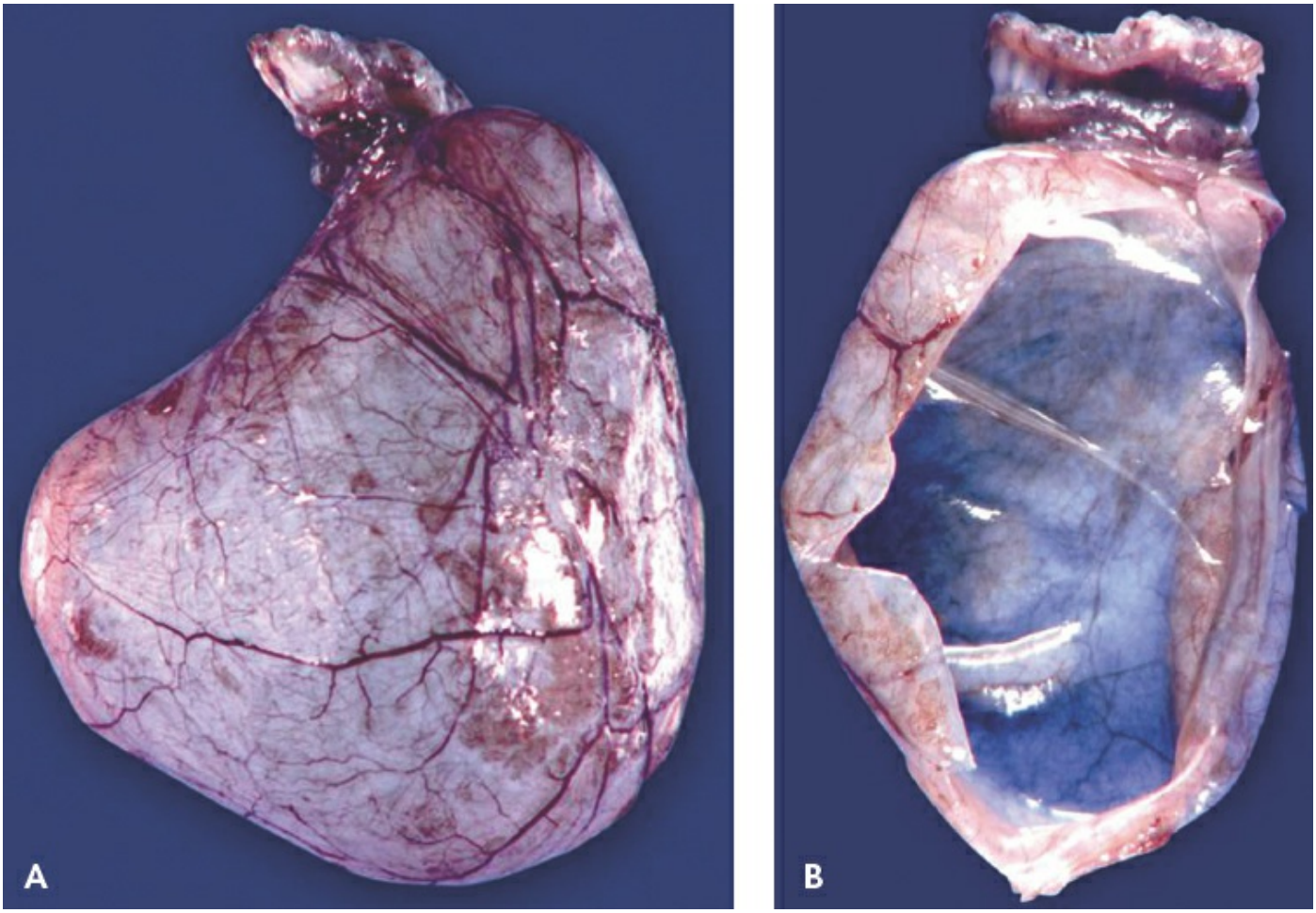


FIGURE 9-16 **A:** Paratubal cyst. **B:** Paratubal cyst, incised.

Adolescent Vulvar Conditions

Disorders of sex development may cause genital ambiguity, typically noted at birth, although virilization may occur at puberty (32). **Adolescents with gonadal**

dysgenesis or androgen insensitivity may have abnormal pubertal development and primary amenorrhea (see Chapters 8, 34, and 35). Various developmental anomalies—vaginal agenesis, imperforate hymen, transverse and longitudinal vaginal septa, vaginal and uterine duplications, hymenal bands, and septa—most frequently are diagnosed in early adolescents with amenorrhea (for the obstructing abnormalities) or with concerns such as inability to use tampons (for hymenal and vaginal bands and septa). These developmental abnormalities must be evaluated carefully to determine both external and internal anatomy.

A tight hymenal ring may be discovered when the patient seeks care because of concerns about the inability to use tampons or have intercourse. Both manual dilation and small relaxing incisions at 6 and 8 o'clock in the hymenal ring can be effective. This procedure can sometimes be done in the office using local anesthesia but may require conduction or general anesthesia in the operating room. Hymenal bands are not rare and lead to difficulty in using tampons; they often can be incised in the office using local anesthetic **(Fig. 9-17)**. "Hypertrophy" of the labia minora may be considered a variant of normal, and reassurance rather than a cosmetic surgical reduction is usually appropriate as the primary therapy (107). Surgical management has been described, although the procedure could be considered to be esthetic rather than medically mandated, and rarely indicated in adolescents (108). Genital ulcerations may occur in girls with leukemia or other cancers requiring chemotherapy. Vulvar ulcerations in the absence of sexual activity or infectious etiology are described as vulvar aphthosis **(Fig. 9-10)** (40). The possibility of sexual abuse, incest, or involuntary intercourse should be considered for young adolescents with vulvovaginal symptoms, STDs, or pregnancy.

The presence of vulvar symptoms such as itching or burning may prompt a patient to seek care; however, this anatomic site is not one that is easily inspected by the patient. Thus, vulvar lesions that were not noticed by the patient may be found on examination. **Vulvar self-examination should be encouraged and could potentially result in the earlier diagnosis of vulvar lesions such as melanoma.** Adolescents presenting with vulvar itching may have lichen sclerosus; this condition can be relatively asymptomatic, even when an examination reveals loss of anatomic structures and scarring **(Fig. 9-4)** (36).

Adolescents and adults often incorrectly self-diagnose vulvovaginal candidiasis; in one study, only one-third of women with self-diagnosed yeast vaginitis were found to have this infection (see Chapter 15) (109). A clinical examination and appropriate testing can be performed even on young adolescents using a clinician or self-obtained cotton swab to obtain vaginal secretions for pH testing and microscopic examination **(Fig. 9-18)**.

Vulvar condyloma is an extremely common cause of vulvar lesions in adolescents (see Chapter 15). Genital warts can affect the vulva, perineum, and perianal skin, and

the vagina, urethra, and anus (Fig. 9-19). Condyloma in adolescents typically is sexually transmitted. They may be asymptomatic or cause symptoms of itching, irritation, or bleeding. Symptomatic, enlarging, or extensive vulvar condyloma can be managed with topical medication applied by the patient or clinician. The choice of treatment should be guided by patient preference, available resources, and the clinician's experience; no one treatment is superior to the others (64). The recent availability of an HPV vaccine that includes HPV types 6 and 11 has had a beneficial impact on the incidence of vulvar condyloma and potentially on HPV-related vulvar intraepithelial neoplasia (VIN).



FIGURE 9-17 Hymenal band.



FIGURE 9-18 Candidal vulvitis.



FIGURE 9-19 Extensive vulvar condyloma.

Adolescent Vaginal Conditions

Vulvovaginal symptoms in adolescents may be caused by a variety of conditions, ranging from vulvar lichen sclerosus to UTI to *C. trachomatis* to non–STD-related vaginitis. Urinary or vaginal symptoms do not differentiate well between UTIs and vaginitis. Adolescent girls who are screened for both *C. trachomatis* and UTI have high rates of concurrent disease (110). Because clinical diagnosis based on symptoms is imprecise, female adolescents with vaginal or urinary symptoms should be tested for *C. trachomatis* and UTI. Testing with DNA-based procedures may be performed on samples obtained from the cervix, from swabs of vaginal secretions (either clinician or patient obtained), and from urine specimens. Testing that does not involve a speculum examination may be particularly helpful for adolescents; a rigorous review concluded that noninvasive chlamydia testing was comparable to cervical or urethral screening, although this was not the case with testing for gonorrhea (111).

Discharge is one of the most common vaginal symptoms. Conditions ranging from

vaginal candidiasis to chlamydia cervicitis to bacterial vaginosis may cause vaginal discharge in adolescents. Infectious vaginal conditions are described in more detail in Chapter 15. The risks of self-diagnosis of vaginal discharge in adolescents may be greater than in adult women, as infection with STDs—including *Neisseria gonorrhoeae, Trichomonas vaginalis, C. trachomatis,* herpes simplex, and *Condyloma accuminata*—are common in adolescents and may be less likely recognized.

Use of tampons is associated with microscopic and macroscopic ulcerations. Healing of the macroscopic ulcerations occurs within several weeks without specific therapy if tampon use is suspended. A follow-up examination to demonstrate healing is appropriate, with biopsy of any persistent ulceration to rule out other lesions.

Toxic shock syndrome (TSS) is associated with tampon use and vaginal exotoxins produced by *Staphylococcus aureus*. This syndrome consists of fever, hypotension, a diffuse erythroderma with desquamation of the palms and soles, plus involvement of at least three major organ systems (112). Vaginal involvement includes mucous membrane inflammation. The frequency of TSS appears to be declining, and an increasing percentage of cases are not associated with menses. Approximately one-half of all cases of TSS are menstrual related (113). Epidemiologic studies suggest that adolescents are at greater risk of menstrual TSS than older women; however, this finding does not appear to be explained by differences in the detection of antibodies to the TSST-1 toxin-producing strain of *S. aureus* or in *S. aureus* vaginal colonization rates (114).

Abscesses of Bartholin and Skene glands are related to both aerobic and anaerobic organisms, with mixed infections accounting for approximately 60% of these and other vulvar and labial abscesses, although the possibility of methicillin-resistant *S. aureus* (MRSA) infections must be considered (115). Therapy consists of surgical drainage, with use of antibiotics as a secondary measure. In younger adolescents, incision and drainage may require general anesthesia.

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CHAPTER 10

Adult Gynecology: Reproductive Years



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Reproductive Age Group
- Abnormal Bleeding
  - *Normal Menses*
  - *Pregnancy-Related Bleeding*
  - *Differential Diagnosis of Abnormal Bleeding*
  - *Adenomyosis, AUB-A*
  - *Leiomyoma, AUB-L*
  - *Malignancy and Hyperplasia, AUB-M*
  - *Coagulopathy, AUB-C*
  - *Ovulatory Dysfunction, AUB-O*
  - *Endometrial, AUB-E*
  - *Iatrogenic, AUB-I*
  - *Not Yet Classified, AUB-N*
- Diagnosis of Abnormal Bleeding
  - *Laboratory Studies*
  - *Imaging Studies*
  - *Endometrial Sampling*
- Management of Abnormal Bleeding
  - *Nonsurgical Management*
  - *Surgical Therapy*
- Pelvic Masses
  - *Differential Diagnosis*
  - *Uterine Masses*
  - *Ovarian Masses*
  - *Other Adnexal Masses*

Diagnosis of Pelvic Masses
Other Studies
Laboratory Studies
Imaging Studies
Management of Pelvic Mass
Leiomyomas
Ovarian Masses
Vulvar Conditions
Vulvar Biopsy
Other Vulvar Conditions
Vulvar Tumors, Cysts, and Masses
Painful Intercourse
Vulvar Ulcers
Vaginal Conditions
Postmenopausal Age Group
Abnormal Bleeding
Differential Diagnosis
Benign Disorders
Neoplasia
Diagnosis of Postmenopausal Abnormal Bleeding
Management of Postmenopausal Abnormal Bleeding
Benign Disorders
Endometrial Hyperplasia
Pelvic Masses
Differential Diagnosis
Diagnosis of Postmenopausal Pelvic Mass
Management of Postmenopausal Pelvic Mass
Vulvar Conditions
Vulvar Dermatoses
Vaginal Conditions

KEY POINTS

1 The causes of abnormal bleeding vary by age, with anovulatory bleeding most likely in adolescents and perimenopausal women.

2 Anatomic causes of abnormal bleeding including endometrial polyps and leiomyoma occur more frequently in women of reproductive age than in women in other age groups

3 Pelvic masses in adolescents and women of reproductive age are most commonly functional or benign neoplastic ovarian masses, whereas the risks of malignant ovarian tumors increase with age.

4 Although pelvic ultrasonography is an excellent technique for imaging pelvic masses and ultrasonographic characteristics may suggest reassuring characteristics of an ovarian mass, the possibility of malignancy must be kept in mind.

5 Most uterine leiomyomas are asymptomatic, although bleeding, pressure symptoms, or pain may necessitate medical or surgical management.

Benign gynecologic conditions can present with signs and symptoms that vary by age. In this chapter, the most likely causes of specific signs and symptoms, diagnosis, and management are described for reproductive age and postmenopausal women. **Common**

gynecologic problems include those that cause pain and bleeding, such as pelvic masses (which may be symptomatic or asymptomatic), and vulvar and vaginal symptoms. Benign conditions of the female genital tract include anatomic lesions of the uterine corpus and cervix, ovaries, fallopian tubes, vagina, and vulva. A classification of benign lesions of the vulva, vagina, and cervix appears in Table 10-1. Leiomyoma, polyps, and hyperplasia are the most common benign conditions of the uterus in adult women. Benign uterine leiomyoma (uterine fibroids) are presented in Chapter 11. Benign tumors of the ovaries are listed in Table 10-2. Malignant diseases are presented in Chapters 37 to 42. Pediatric and adolescent conditions are discussed in Chapter 9.

Table 10-1 Classification of Benign Conditions of the Vulva, Vagina, and Cervix

Vulva
Skin conditions
Pigmented lesions
Tumors and cysts
Ulcers
Nonneoplastic epithelial disorders
Vagina
Embryonic origin
Mesonephric, paramesonephric, and urogenital sinus cysts
Adenosis (related to in utero diethylstilbestrol exposure)
Vaginal septa or duplications
Pelvic organ prolapse/disorders of pelvic support
Anterior vaginal prolapse
Cystourethrocele
Cystocele
Apical vaginal prolapse
Uterovaginal
Vaginal vault
Posterior vaginal prolapse
Enterocele

Rectocele
Other
Condyloma
Urethral diverticula
Fibroepithelial polyp
Vaginal endometriosis
Cervix
Infectious
Condyloma
Herpes simplex virus ulceration
Chlamydial cervicitis
Other cervicitis
Other
Endocervical polyps
Nabothian cysts
Columnar epithelium eversion

Table 10-2 Benign Ovarian Tumors

Functional
Follicular
Corpus luteum
Theca lutein
Inflammatory
Tubo-ovarian abscess or complex
Neoplastic
Germ cell
Benign cystic teratoma
Other and mixed
Epithelial

Serous cystadenoma
Mucinous cystadenoma
Fibroma
Cystadenofibroma
Brenner tumor
Mixed tumor
Other
Endometrioma

REPRODUCTIVE AGE GROUP

Abnormal Bleeding

Normal Menses

After adolescence, menstrual cycles generally conform to a cycle length of 21 to 35 days, with the duration of menstrual flow fewer than 7 days (1). **[1] As a woman approaches menopause, the cycle length becomes more irregular because fewer cycles are ovulatory (1,2). The most frequent cause of irregular bleeding in the reproductive age group is hormonal, although other causes such as pregnancy-related bleeding (spontaneous abortion, ectopic pregnancy) should always be considered (Table 10-3).** A variety of imprecise terms such as menorrhagia or menometrorrhagia have been used to describe abnormal uterine bleeding (AUB); it is strongly recommended that these confusing terms be abandoned in favor of simple designations of menstrual cycles, describing cycle regularity, frequency, duration, and heaviness of flow (Table 10-4) (3,4). The International Federation of Gynecology and Obstetrics (FIGO) and the American College of Obstetricians and Gynecologists (ACOG) have recommended that systematized nomenclature, the PALM-COEIN acronym, be used to describe abnormal menses (Table 10-5). **The term dysfunctional uterine bleeding (DUB) should no longer be used** (3–6).

Prospective charting of bleeding can be helpful in characterizing abnormal bleeding. **The mean duration of menses is 4.7 days; 89% of cycles last 7 days or longer. The average blood loss per cycle is 35 mL** (6). **Menses comprises a suspension of blood- and tissue-derived solids within a mixture of serum and cervicovaginal fluid; the blood content of menses varies over the days of bleeding, but on average is close to 50%** (7). Heavy menstrual bleeding is defined as greater than 80 mL per day, which will result in anemia if recurrent (8).

Pregnancy-Related Bleeding

Pregnancy should always be excluded in women of reproductive age presenting with AUB.

Table 10-3 Causes of Bleeding by Approximate Frequency and Age Group

Infancy	Prepubertal	Adolescent	Reproductive	Perimenopausal	Postmenopausal
Maternal estrogen withdrawal	Vulvovaginitis	Anovulation	Exogenous	Anovulation	Atrophy
	Vaginal foreign body	Exogenous hormone use	Pregnancy	Fibroids	Endometrial polyps
	Precocious puberty	Pregnancy	Anovulation	Cervical and endometrial polyps	Endometrial cancer
	Tumor	Coagulopathy	Fibroids	Thyroid dysfunction	Hormonal therapy
			Cervical and endometrial polyps		Other tumor—vulvar, vaginal, cervical
			Thyroid dysfunction		

Spontaneous abortion can be associated with excessive or prolonged bleeding. A woman may be unaware that she conceived and may seek care because of abnormal bleeding. In the United States, nearly half of pregnancies are unintended. These women may be at particular risk for bleeding related to an unsuspected pregnancy. About one-half of unintended pregnancies result from nonuse of contraception; the other one-half result from contraceptive failures (9). [1] **Unintended pregnancies are most likely to occur among adolescents and women older than 40 years of age** (see Chapter 14). If an ectopic pregnancy is ruled out, the management of spontaneous abortion may include either observation, if the bleeding is not excessive; medical or pharmacologic uterine evacuation (with *misoprostol*); or surgical management with suction curettage or dilation and curettage (D&C), depending on the clinician's judgment and the patient's preference (10).

Differential Diagnosis of Abnormal Bleeding

Structural causes of AUB include the PALM in PALM-COEIN (Polyps, Adenomyosis, Leiomyoma, Malignancy/Hyperplasia). [2] **Anatomic causes of abnormal bleeding occur more frequently in women of reproductive age than in women in other age groups.** [5] **Uterine leiomyomas and endometrial polyps are common conditions that most often are asymptomatic; however, they remain important causes of abnormal bleeding** (11).

Polyps, AUB-P

[2] **Endometrial polyps are a cause of intermenstrual bleeding, heavy menstrual bleeding, irregular bleeding, and postmenopausal bleeding. They are associated with the use of *tamoxifen* and infertility, and can cause dysmenorrhea. As with leiomyomas, most endometrial polyps are asymptomatic.** [2] The incidence of

endometrial polyps increases with age throughout the reproductive years (12). The diagnosis may be suspected on the basis of endometrial thickening on transvaginal pelvic ultrasound, and vascular patterns of feeder blood vessels may aid in distinguishing endometrial polyps from intracavity fibroids and from endometrial malignancy (13–15). Confirmation of a polyp requires visualization with hysteroscopy, sonohysterography, or the microscopic assessment of tissue obtained by a biopsy done in the office or with a D&C. Whether and when to recommend removal is not well established, particularly if a polyp is asymptomatic and is found incidentally. The effect of polyps on fertility is not clear, though there is evidence that removal may improve rates of pregnancy in infertile patients (16). One study of randomly selected Danish women using transvaginal ultrasound and sonohysterography found polyps in 5.8% of asymptomatic premenopausal women and 11.8% of asymptomatic postmenopausal women. In this study, abnormal bleeding was present in 38% of those without polyps versus 13% with polyps (15). Endometrial polyps can regress spontaneously, although it is not clear how frequently this occurs. In one study of asymptomatic women, the 1-year regression rate was 27% (17). Smaller polyps are more likely to resolve, and larger polyps may be more likely to result in abnormal bleeding (18). Whereas polyps may resolve spontaneously over time, a clinically important question is whether they are likely to undergo malignant transformation. Because even asymptomatic polyps are usually removed at the time of identification, this question is difficult to answer. **[2]** The chance of malignancy or premalignant changes in endometrial polyps appears to be quite low in premenopausal women and higher among postmenopausal women, with bleeding reports that range from 0.2% to 24% in premalignant change and 0% to 13% in malignancy (16).

Table 10-4 Menstrual Terminology

Cycle		Normal	
Regularity	Absent	Regular	Irregular
Frequency of menstruation	Infrequent	Normal	Frequent
Duration of menstrual flow	Shortened	Normal	Prolonged
Volume of menstrual flow	Light	Normal	Heavy

Table 10-5 Abnormal Uterine Bleeding Terminology

Structural Causes	PALM
AUB-P	Polyp
AUB-A	Adenomyosis
AUB-L	Leiomyoma
AUB-M	Malignancy + Hyperplasia

Nonstructural	COEIN
AUB-C	Coagulopathy
AUB-O	Ovulatory dysfunction
AUB-E	Endometrial
AUB-I	Iatrogenic
AUB-N	Not yet classified

Adenomyosis, AUB-A

Traditionally adenomyosis has been diagnosed by histology at the time of hysterectomy, making estimates of prevalence and contribution to AUB and pelvic pain unclear. **With improving imaging technology and evolving diagnostic criteria for adenomyosis on ultrasound and MRI, adenomyosis can be diagnosed prior to hysterectomy and is included as a structural cause of abnormal bleeding.** The incidence of incidentally identified adenomyosis on pelvic imaging is not yet known (5).

Leiomyoma, AUB-L

[5] Uterine leiomyomas occur in as many as one-half of all women older than age 35 years and are the most common tumors of the genital tract (12). The incidence varies from 30% to 70%, depending on the criteria for study, whether clinical symptoms, ultrasound, or histologic assessment (11). One study of a randomly selected population estimated a cumulative prevalence of greater than 80% in black women and nearly 70% in white women based on ultrasound (19). Abnormal bleeding is the most common symptom for women with leiomyomas who are symptomatic. **Although the number and size of uterine leiomyomas do not appear to influence the occurrence of abnormal bleeding, submucosal myomas are the most likely to cause bleeding.** The mechanism of abnormal bleeding related to leiomyomas is not well established (see Chapter 11 for further discussion of uterine fibroids).

Malignancy and Hyperplasia, AUB-M

Unopposed estrogen is associated with a variety of abnormalities of the endometrium, from cystic hyperplasia to adenomatous hyperplasia, hyperplasia with cytologic atypia, and invasive carcinoma. **Abnormal bleeding is the most frequent symptom of women with invasive cervical cancer.** A visible cervical lesion should be evaluated by biopsy rather than awaiting the results of cervical cytology testing, because those results may be falsely negative with invasive lesions as caused by tumor necrosis. Although vaginal neoplasia is uncommon, the vagina should be evaluated carefully when abnormal bleeding is present. Attention should be directed to all surfaces of the vagina, including anterior and posterior areas that may be obscured by the vaginal speculum on

examination.

Nonstructural causes of AUB include the COEIN in PALM-COEIN (Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, NOS)

Coagulopathy, AUB-C

As with adolescents, hematologic causes of abnormal bleeding should be considered in women with heavy menstrual bleeding, particularly in those who have had heavy bleeding since menarche. **Of all women with menorrhagia, 5% to 20% have a previously undiagnosed bleeding disorder, primarily the von Willebrand disease** (20). Table 10-6 presents guidelines for a gynecologist's suspicion of a bleeding disorder and pursuit of a diagnosis (21). Abnormal liver function, which can be seen with alcoholism or other chronic liver diseases, results in inadequate production of clotting factors and can lead to excessive menstrual bleeding.

Ovulatory Dysfunction, AUB-O

[1] Most anovulatory bleeding results from what is termed *estrogen breakthrough*. In the absence of ovulation and the production of progesterone, the endometrium responds to estrogen stimulation with proliferation. This endometrial growth without periodic shedding results in eventual breakdown of the fragile endometrial tissue. Healing within the endometrium is irregular and dyssynchronous. Relatively low levels of estrogen stimulation will result in irregular and prolonged bleeding, whereas higher sustained levels result in episodes of amenorrhea followed by acute, heavy bleeding.

Many ovulatory disorders relate to endocrine disturbances. **Both hypothyroidism and hyperthyroidism can be associated with abnormal bleeding. With hypothyroidism, menstrual abnormalities, including menorrhagia, are common (see Chapter 35). The most common cause of thyroid hyperfunctioning in premenopausal women is Graves' disease, which occurs four to five times more often in women than men. Hyperthyroidism can result in oligomenorrhea or amenorrhea, and it can lead to elevated levels of plasma estrogen (22). Other causes of anovulation include hypothalamic dysfunction, hyperprolactinemia, premature ovarian failure (POF), and primary pituitary disease (Table 10-7). These conditions often are considered causes of amenorrhea, but they may be the cause of irregular bleeding (see Chapter 34). The rare and unusual causes of abnormal bleeding should not be overlooked. Women with primary ovarian insufficiency (POI; previously termed POF) frequently see several clinicians with symptoms of oligomenorrhea or amenorrhea prior to receiving a diagnosis; the diagnosis of POI is often delayed during waning ovarian function and insufficiency (23,24).** POI is thought to occur in approximately 1 of 100 women by age 40, 1 of 1,000 women by age 30, and 1 of 10,000 women by age 20. Women should be encouraged to track their menstrual cyclicity and to consider that the menstrual cycle can be a "vital sign" that

reflects the overall health (25).

Table 10-6 When Should a Gynecologist Suspect a Bleeding Disorder

Heavy menstrual bleeding since menarche
Family history of bleeding disorder
Personal history of any of the following:
Epistaxis in the last year
Bruising without injury >2-cm diameter
Minor wound bleeding
Oral or gastrointestinal bleeding without anatomic lesion
Prolonged or heavy bleeding after dental extraction
Unexpected postoperative bleeding
Hemorrhage from ovarian cyst
Hemorrhage requiring blood transfusion
Postpartum hemorrhage, especially delayed >24 h
Failure to respond to conventional management of menorrhagia

From **James AH, Kouides PA, Abdul-Kadir R, et al.** von Willebrand disease and other bleeding disorders in women: Consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynecol* 2009;201:12e1–e8.

Table 10-7 Conditions Associated with Anovulation and Abnormal Bleeding

Eating disorders
Anorexia nervosa
Bulimia nervosa
Excessive physical exercise
Chronic illness
Primary ovarian insufficiency—POI (previously termed premature ovarian failure [POF])
Alcohol and other drug abuse
Stress
Thyroid disease
Hypothyroidism

Hyperthyroidism
Diabetes mellitus
Androgen excess syndromes (e.g., polycystic ovary syndrome [PCOS])

Diabetes mellitus can be associated with anovulation, obesity, insulin resistance, and androgen excess. Androgen disorders are very common among women of reproductive age and should be evaluated and managed accordingly. Polycystic ovary syndrome (PCOS) is present in 5% to 8% of adult women and undiagnosed in many of them (26). Because androgen disorders are associated with significant cardiovascular disease, the condition should be diagnosed promptly and treated. This condition becomes of more immediate concern in women of reproductive age because of concerns related to fertility. Management of bleeding disorders associated with androgen excess consists of an appropriate diagnostic evaluation followed by the use of oral contraceptives (in the absence of significant contraindications or the desire for conception) or the use of insulin-sensitizing agents, coupled with dietary and exercise modification (27,28).

Endometrial, AUB-E

In ovulatory cycles, the endometrium itself may contribute to abnormal or heavy menstrual bleeding (AUB/HMB). There is evidence that deficiencies of vasoconstrictors or excess of vasodilators may lead to heavy bleeding. Local vasoconstrictors include endothelin-1 and prostaglandin F2alpha. Local vasodilators include prostacyclin I2 and prostaglandin E2 (29). Inflammation and infection can affect the endometrium. **Menorrhagia can be the first sign of endometritis in women infected with sexually transmissible organisms. Women with cervicitis, particularly chlamydial cervicitis, can experience irregular bleeding and postcoital spotting** (see Chapter 15). Cervical testing for *Chlamydia trachomatis* should be considered, especially for adolescents, women in their 20s, and women who are not in a monogamous relationship. Endometritis can cause excessive menstrual flow. A woman who seeks treatment for menorrhagia and increased menstrual pain and has a history of light-to-moderate previous menstrual flow may have an upper genital tract infection or pelvic inflammatory disease (PID) (endometritis, salpingitis, oophoritis). Occasionally, chronic endometritis will be diagnosed when an endometrial biopsy is obtained for evaluation of abnormal bleeding in a patient without specific risk factors for PID.

Iatrogenic, AUB-I

Iatrogenic-Exogenous Hormones

Irregular bleeding that occurs while a woman is using contraceptive hormones should be considered in a different context than bleeding that occurs in the absence of exogenous hormone use. Breakthrough bleeding during the first 1 to 3 months of

oral contraceptive use occurs in as many as 30% to 40% of users; it should almost always be managed expectantly with reassurance because the frequency of breakthrough bleeding decreases with each subsequent month of use (30). Irregular bleeding can result from inconsistent use (31,32). Other estrogen–progestin delivery systems, including the contraceptive patch, vaginal ring, and intramuscular regimens, are associated with irregular breakthrough bleeding. These nondaily contraceptive regimens may promote successful use, making irregular bleeding a less important factor for some women in assessing the balance of risks versus benefits (see Chapter 14).

The use of progestin-only methods—including depot medroxyprogesterone acetate (*DMPA),* progestin-only pills, the contraceptive implant, and the *levonorgestrel* intrauterine system (IUS)—is associated with relatively high rates of initial irregular and unpredictable bleeding; rates of amenorrhea vary over time and by method (33). Counseling about the frequent side effects of irregular bleeding is imperative before initially prescribing these methods of contraception. Women who do not believe that they can cope with irregular, unpredictable bleeding may not be good candidates for these methods. Hormonal implants and IUDs releasing progestins do offer significant benefits of high efficacy and ease of use (34,35). **The management of irregular bleeding with hormonal contraceptive use can range from reassurance and initial expectant management to recommendations for a change in the hormonal delivery system or regimen.** The use of additional oral estrogen or combined oral contraceptives for 10 to 20 days improves bleeding with both *DMPA* and the subdermal *levonorgestrel in some studies* (36). The use of a 5- to 7-day course of NSAIDs may result in decreased breakthrough bleeding (36). The development of a better understanding of the mechanisms causing irregular bleeding will likely result in more effective and acceptable management strategies (33).

Not all bleeding that occurs while an individual is using hormonal contraception is a consequence of hormonal factors. In one study, women who experienced irregular bleeding while taking oral contraceptives had a higher frequency of *C. trachomatis* infection (37). Screening for sexually transmitted infections (STIs) should be considered in women presenting with irregular bleeding while using hormonal contraception.

Not Yet Classified, AUB-N

This includes causes of AUB not yet discovered and those rarer and less-understood causes, including myometrial hypertrophy and AV malformations (8).

Diagnosis of Abnormal Bleeding

For all women, the evaluation of excessive and abnormal menses includes a thorough medical and gynecologic history, the exclusion of pregnancy, the consideration of

possible malignancy, and a careful gynecologic examination. **Abnormal bleeding, either intermenstrual or postcoital, can be caused by cervical lesions. Bleeding can result from endocervical polyps and infectious cervical lesions, such as condylomata,** herpes simplex virus ulcerations, chlamydial cervicitis, or cervicitis caused by other organisms. Other benign cervical lesions, such as wide eversion of endocervical columnar epithelium or nabothian cysts, may be detected on examination, but rarely cause bleeding.

For women of normal weight between the ages of approximately 20 and 35 years who do not have clear risk factors for STDs, have no signs of androgen excess, are not using exogenous hormones, and have no other findings on examination, management may be based on a clinical diagnosis. Additional laboratory or imaging studies may be indicated if the diagnosis is not apparent on the basis of examination and history.

Laboratory Studies

In any patient with heavy menstrual bleeding, an objective measurement of hematologic status should be performed with a complete blood count to detect anemia or thrombocytopenia. A pregnancy test should be performed to rule out pregnancy-related problems. A TSH level and chlamydia testing should be considered. Because of the possibility of a primary coagulation problem, screening coagulation studies should be ordered where appropriate (Table 10-6). The consensus report of an international expert panel recommends measurement of CBC, platelet count and function, PT, activated PTT, VWF (measured with ristocetin cofactor activity and antigen, factor VIII), and fibrinogen to be assessed in collaboration with a hematologist (38).

Imaging Studies

Women with abnormal bleeding who have a history consistent with chronic anovulation, are obese, or older than 35 to 40 years of age, require further evaluation. A pelvic ultrasonographic examination may be helpful in delineating anatomic abnormalities if the examination results are suboptimal or if an ovarian mass is suspected. A pelvic ultrasonographic examination is the best initial technique for evaluating the uterine contour, endometrial thickness, and ovarian structure (39,40). The use of a vaginal probe transducer allows assessment of endometrial and ovarian disorders, particularly in women who are obese. **Because of variation in endometrial thickness with the menstrual cycle, measurements of endometrial stripe thickness are significantly less useful in premenopausal than postmenopausal women** (41). Sonohysterography is especially helpful in visualizing intrauterine problems such as polyps or submucosal leiomyoma. Although these sonographic techniques are helpful in visualizing intrauterine pathology, histologic evaluation is required to rule out malignancy. Other techniques, such as CT scanning and MRI, are not as helpful in the

initial evaluation of causes of abnormal bleeding and should be reserved for specific indications, such as exploring the possibility of other intra-abdominal pathology or adenopathy. MRI can be a secondary step in evaluating the location of uterine fibroids with relationship to the endometrial cavity, staging and preoperative evaluation of endometrial cancer, detecting adenomyosis, and delineating adnexal and ovarian pathology (42).

Endometrial Sampling

[1] Endometrial sampling should be performed to evaluate abnormal bleeding in women who are at risk for endometrial pathology, including polyps, hyperplasia, or carcinoma. Such sampling is mandatory in the evaluation of anovulatory bleeding in women older than 45 or in younger women who are obese, in those who do not respond to medical therapy or those with a history of prolonged anovulation (10).

The technique of a D&C, which was previously used extensively for the evaluation of abnormal bleeding, has now been largely replaced by endometrial biopsy in the office. The classic study in which a D&C was performed before hysterectomy with the conclusion that less than one-half of the endometrium was sampled in more than one-half of the patients led to questioning the use of D&C for endometrial diagnosis (43,44). Hysteroscopy, either diagnostic or operative, with endometrial sampling, can be performed either in the office or operating room (45).

A number of devices are designed for endometrial sampling, including a commonly used, inexpensive, disposable, flexible plastic sheath with an internal plunger that allows tissue aspiration; disposable plastic cannulae of varying diameters that attach to a manually locking syringe that allows the establishment of a vacuum; and cannulae (both rigid metal and plastic) with tissue traps that attach to an electric vacuum pump **(Fig. 10-1)**. Several studies comparing the adequacy of sampling using these devices with D&C showed a comparable ability to detect abnormalities. It should be noted that these devices are designed to obtain a tissue sample rather than a cytologic washing. The diagnostic accuracy of endometrial biopsy for endometrial malignancy and hyperplasia is good, although persistent bleeding should prompt further testing (46). Hysteroscopy with targeted biopsies is more sensitive than a D&C in evaluating uterine pathology (29).

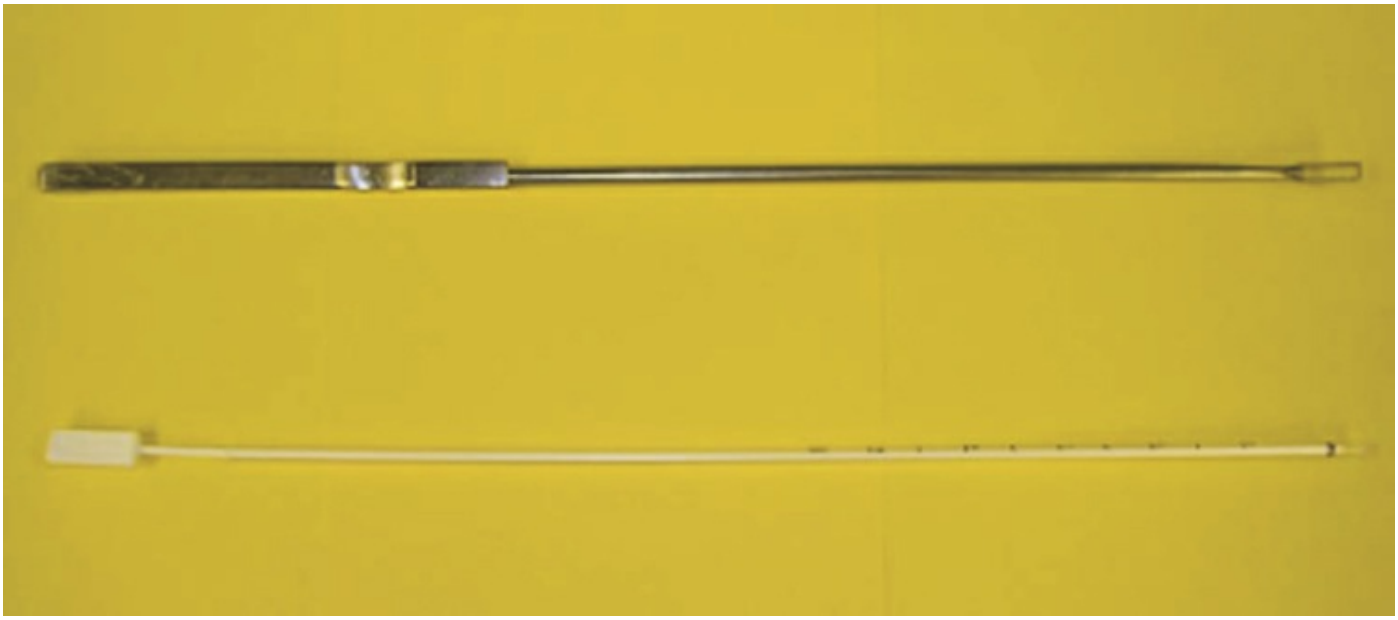


FIGURE 10-1 Devices used for sampling endometrium. **Top:** Kevorkian curette. **Bottom:** Pipelle.

Management of Abnormal Bleeding

Attention should be directed to establishing a cause of abnormal bleeding. In most cases, medical therapy is effective in managing abnormal bleeding and should be attempted before surgical management. [1] Medical management with either combined hormonal contraceptives or progestins is the preferred therapy of anovulatory bleeding in women of reproductive age (8). Progestin-releasing IUDs are effective in treating heavy menstrual bleeding and demonstrate comparable benefits for the quality of life (47). **It is argued that the IUD should be offered prior to consideration of hysterectomy, as there are comparable benefits on heavy menstrual bleeding and clear cost benefits** (48). When medical therapy fails in women with anovulatory uterine bleeding and without the desire for future childbearing, the surgical options of endometrial ablation or hysterectomy can be considered. Endometrial ablation is an efficient and cost-effective alternative to hysterectomy, although this therapy may not be definitive, with increasing rates of repeat ablation and hysterectomy over time (8). In women with leiomyomas, hysterectomy provides a definitive cure. A variety of surgical alternatives to hysterectomy are available to women with symptomatic uterine leiomyomas (see Chapter 11).

Nonsurgical Management

Most bleeding problems, including anovulatory bleeding, can be managed nonsurgically. Treatment with NSAIDs, such as *ibuprofen* and *mefenamic acid,* decreases menstrual flow by 30% to 50%, but is less effective than *tranexamic acid, danazol,* or *levonorgestrel* IUD (49). Antifibrinolytics, such as *tranexamic acid,* are

effective in reducing menstrual blood loss, and this indication was approved by the FDA in late 2008 (50).

Hormonal management of abnormal bleeding can frequently control excessive or irregular bleeding. The treatment of choice for anovulatory bleeding is medical therapy with combined oral contraceptives or progestins including the levonorgestrel IUD (5). Oral contraceptives are used clinically to decrease menstrual flow, although supporting data from prospective clinical trials are sparse (51). Low-dose oral contraceptives may be used by reproductive age women without medical contraindications and during the perimenopausal years in healthy nonsmoking women who have no major cardiovascular risk factors. The benefits of menstrual regulation in such women often override the potential risks. The medical treatment of acute abnormal bleeding in reproductive age women is the same as that described for adolescents (see Chapter 9).

For patients in whom estrogen use is contraindicated, progestins, both oral and parenteral, can be used to control excessive bleeding. Cyclic oral *medroxyprogesterone acetate,* administered from day 15 or 19 to day 26 of the cycle, reduces menstrual flow but offers no advantages over other medical therapies, such as NSAIDs, *tranexamic acid, danazol,* or the *levonorgestrel* IUD; progestin therapy for 21 days of the cycle reduces menstrual flow, although women found the treatment less acceptable than the *levonorgestrel* IUD (52). The benefits of progestins to the patient with oligomenorrhea and anovulation include a regular flow and the prevention of long intervals of amenorrhea, which may end in unpredictable, profuse bleeding. This therapy reduces the risk of hyperplasia resulting from persistent, unopposed estrogen stimulation of the endometrium. Depot formulations of *medroxyprogesterone acetate,* oral progestins, levonorgestrel IUDs, and combined oral contraceptives are used to establish amenorrhea in women at risk of excessive bleeding (53). Oral, parenteral, or intrauterine delivery of progestins is used in selected women with endometrial hyperplasia or early endometrial cancer who wish to maintain their fertility or in whom surgical risks are judged to be prohibitive (29). Continued monitoring with repeated sampling is indicated. *Danazol* is effective in decreasing bleeding and inducing amenorrhea; it is rarely used for ongoing management of abnormal bleeding because of its androgenic side effects, including weight gain, hirsutism, alopecia, and irreversible voice changes. GnRH analogs are used for short-term treatment of abnormal bleeding, either alone or with add-back therapy consisting of combined estrogen/progestogen or progestogen alone (54).

Surgical Therapy

The surgical management of abnormal bleeding should be reserved for situations in which medical therapy is unsuccessful or is contraindicated. Although sometimes appropriate as a diagnostic technique, D&C is questionable as a therapeutic modality. One study reported a measured reduction in menstrual blood loss for the first

menstrual period only (55). Other studies suggest a longer-lasting benefit (56).

The surgical options range from a variety of techniques for endometrial ablation or resection, to hysterectomy or a variety of conservative surgical techniques for the management of uterine leiomyoma, including hysteroscopy with resection of submucous leiomyomas, laparoscopic and robotic techniques of myomectomy, uterine artery embolization, and magnetic resonance–guided focused ultrasonography ablation (see Chapters 26 and 27). The choice of procedure depends on the cause of bleeding, the patient's preferences, the physician's experience and skills, the availability of newer technologies, and a careful assessment of risks versus benefits based on the patient's medical condition, concomitant gynecologic symptoms or conditions, and desire for future fertility. The assessment of the relative advantages, risks, benefits, complications, and indications of these procedures is a subject of ongoing clinical research. Various techniques of endometrial ablation were compared with the gold standard of endometrial resection, and the evidence suggests comparable success rates and complication profiles (57). The advantages of techniques other than hysterectomy include a shorter recovery time and reduced early morbidity. Symptoms can recur or persist and repeat procedures or subsequent hysterectomy may be required if conservative options are chosen. Additional studies that include quality-of-life outcomes will be helpful. Collaborative decision making, taking into account individual patient preferences, should follow a thorough discussion of options, risks, and benefits (58,59). Much is written about the psychological sequelae of hysterectomy, and some of the aforementioned surgical techniques were developed in an effort to provide less drastic management options. **Most well-controlled studies suggest that, in the absence of pre-existing psychopathology, indicated but elective surgical procedures for hysterectomy have few, if any, significant psychological sequelae (including depression)** (see Chapters 23 and 27) (60,61).

Pelvic Masses

[3] Conditions diagnosed as a pelvic mass in women of reproductive age are presented in Table 10-8.

Differential Diagnosis

It is difficult to determine the frequency of diagnoses of pelvic mass in women of reproductive age because many pelvic masses are not treated with surgery. **Nonovarian or nongynecologic conditions may be confused with an ovarian or uterine mass (Table 10-8). The frequency of masses found at laparotomy has been studied, although the percentages are affected by varying indications for surgery, indications for referral, type of practice (gynecologic oncology vs. general gynecology), and patient populations (e.g., a higher percentage of African**

Americans with uterine leiomyomas). Benign masses, such as functional ovarian cysts or asymptomatic uterine leiomyoma, typically do not require or warrant surgery (Table 10-9).

Table 10-8 Conditions Diagnosed as a Pelvic Mass in Women of Reproductive Age

Urinary
Full urinary bladder
Urachal cyst
Uterus
Sharply anteflexed or retroflexed uterus
Intraligamentous leiomyomas
Pregnancy (with or without concomitant leiomyomas)
Intrauterine
Tubal
Abdominal
Ovarian or adnexal masses
Functional cysts Neoplastic tumors Benign Malignant
Inflammatory masses Tubo-ovarian complex Diverticular abscess Appendiceal abscess
Other
Matted bowel and omentum
Peritoneal cyst
Stool in sigmoid
Paraovarian or paratubal cysts
Less common conditions that must be excluded:
Pelvic kidney
Carcinoma of the colon, rectum, appendix
Carcinoma of the fallopian tube

Retroperitoneal tumors (anterior sacral meningocele)
Uterine sarcoma or other malignant tumors

Table 10-9 Causes of Pelvic Mass by Approximate Frequency and Age

Infancy	Prepubertal	Adolescent	Reproductive	Perimenopausal	Postmenopausal
Functional cyst	Functional cyst	Functional cyst	Functional cyst	Fibroids	Ovarian tumor (malignant or benign)
Germ cell tumor	Germ cell tumor	Pregnancy	Pregnancy	Epithelial ovarian tumor	Functional cyst
		Benign cystic teratoma/ other germ cell tumors	Uterine fibroids	Functional cyst	Bowel, malignant tumor, or inflammatory
		Obstructing vaginal or uterine anomalies	Epithelial ovarian tumor		Metastases
		Epithelial ovarian tumor			

Age is an important determinant of the likelihood of malignancy. In one study of women who underwent laparotomy for pelvic mass, malignancy was seen in only 10% of those younger than 30 years of age, and most of these tumors had low malignancy potential (62). **The most common tumors found during laparotomy for pelvic mass are mature cystic teratomas or dermoids (seen in one-third of women younger than 30 years of age) and endometriomas (approximately one-fourth of women 31 to 49 years of age)** (62).

Uterine Masses

Uterine leiomyomas, commonly termed uterine fibroids, are by far the most common benign uterine tumors and are usually asymptomatic. Other benign uterine growths, such as uterine vascular tumors, are rare. See Chapter 11 for discussion of diagnosis, types and locations of fibroids, incidence, symptoms, causes, natural history, pathology, and management.

Ovarian Masses

[3] During the reproductive years, the most common ovarian masses are benign. Ovarian masses can be functional or neoplastic, and neoplastic tumors can be benign or malignant. Functional ovarian masses include follicular and corpus luteal cysts. About two-thirds of ovarian tumors are encountered during the reproductive years. Most ovarian tumors (80% to 85%) are benign, and two-thirds of these occur in women between 20 and 44 years of age. **The chance that a primary ovarian tumor is malignant in a patient younger than 45 years of age is less than 1 in 15.** Most tumors produce few or only mild, nonspecific symptoms. The most common symptoms include abdominal distention, abdominal pain or discomfort, lower abdominal pressure sensation, and urinary or gastrointestinal symptoms. If the tumor is hormonally active,

symptoms of hormonal imbalance, such as vaginal bleeding related to estrogen production, may be present. Acute pain may occur with adnexal torsion, cyst rupture, or bleeding into a cyst. Pelvic findings in patients with benign and malignant tumors may differ. Masses that are unilateral, cystic, mobile, and smooth are most likely to be benign, whereas those that are bilateral, solid, fixed, irregular, and associated with ascites, *cul-de-sac* nodules, and a rapid rate of growth are more likely to be malignant (63).

In assessing ovarian masses, the distribution of primary ovarian neoplasms by a decade of life can be helpful. Ovarian masses in women of reproductive age are most likely benign, but the possibility of malignancy must be considered **(Fig. 10-2)**.

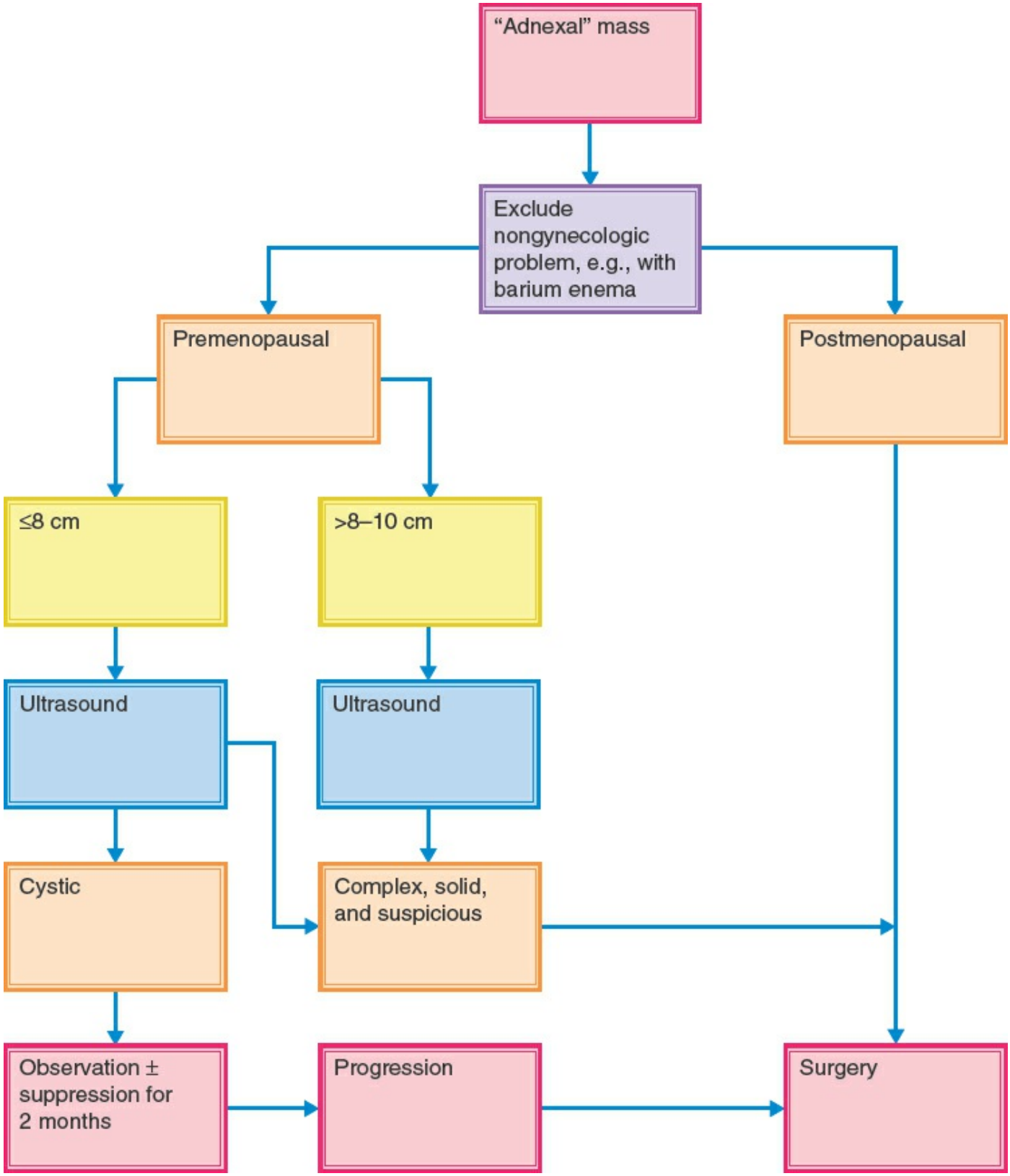


FIGURE 10-2 Preoperative evaluation of the patient with an adnexal mass.

Nonneoplastic Ovarian Masses

[3] Functional ovarian cysts include follicular cysts, corpus luteum cysts, and theca

lutein cysts. All are benign and usually do not cause symptoms or require surgical management. Cigarette and marijuana smoking are associated with an increased risk of functional cysts, although the increased risk may be attenuated in overweight or obese women (64). **Oral contraceptive use is associated with a decreased risk of developing functional ovarian cysts, although low-dose pills may have a smaller benefit. Oral contraceptives do not hasten the resolution of ovarian cysts** (65,66). The annual rate of hospitalization for functional ovarian cysts is estimated to be as high as 500 per 100,000 woman-years in the United States, although little is known about the epidemiology of the condition. **[3] The most common functional cyst is the follicular cyst, which is rarely larger than 8 cm.** A cystic follicle can be defined as a follicular cyst when its diameter is greater than 3 cm. These cysts usually are found incidental to pelvic examination or pelvic imaging, although they may rupture or torse, causing pain and peritoneal signs. They typically resolve in 4 to 8 weeks with expectant management (66).

Corpus luteum cysts are less common than follicular cysts. Corpus luteum cysts may rupture, leading to a hemoperitoneum and requiring surgical management. Patients taking anticoagulant therapy or with bleeding diatheses are at particular risk for hemorrhage and rupture. Rupture of these cysts occurs more often on the right side and may occur during intercourse. **Most ruptures occur on cycle days 20 to 26** (67). Unruptured corpus luteum cysts can cause pain, presumably because of bleeding into the enclosed ovarian cyst cavity. They can produce symptoms and be difficult to discern from adnexal torsion.

Theca lutein cysts are the least common of functional ovarian cysts. They are usually bilateral and occur with pregnancy, including molar pregnancies. They may be associated with multiple gestations, molar pregnancies, choriocarcinoma, diabetes, Rh sensitization, clomiphene citrate use, human menopausal gonadotropin–human chorionic gonadotropin ovulation induction, and the use of GnRH analogs. Up to one-quarter of complete molar pregnancies will have theca lutein cysts which will regress spontaneously (68).

Combination monophasic oral contraceptive therapy is reported to reduce the risk of developing functional ovarian cysts by suppression of both follicular development and ovulation (69). It appears that, in comparison with previously available higher-dose pills, the effect of cyst suppression with low-dose oral contraceptives is attenuated. The use of triphasic oral contraceptives is not associated with an appreciable increased risk of functional ovarian cysts.

Other Benign Masses

Women with endometriosis may develop ovarian endometriomas (“chocolate” cysts), which can enlarge from 6 to 8 cm in size. A mass that does not resolve with observation may be an endometrioma (see Chapter 13). Excision of endometriosis is preferable to

ablative techniques with regard to achievement of spontaneous pregnancy (70). New data suggests that women with or without endometriomas have similar success with conceiving when using ART and do not need removal prior to fertility treatment if asymptomatic and the diagnosis is not in question (71,72).

Although enlarged, polycystic ovaries were originally considered the *sine qua non* of PCOS, and are included among the Rotterdam diagnostic criteria; they are not always present with other features of the syndrome (73,74). An enlarged ovarian volume is suggested as an alternative diagnostic criterion, although what the threshold should be has been debated (75). The 2003 Rotterdam consensus uses a volume greater than 10 mL in either ovary or 12 or more subcentimeter antral follicles in either ovary (74).

The prevalence of PCOS among the general population depends on the diagnostic criteria used. In one study, 257 volunteers were examined with ultrasonography; 22% were found to have polycystic ovaries (76). The finding of generously sized ovaries on examination or polycystic ovaries on ultrasonographic examination should prompt evaluation for the full-blown syndrome, which includes hyperandrogenism, chronic anovulation, and polycystic ovaries (26). Therapy for PCOS is generally medical rather than surgical, with lifestyle modification and weight loss playing a potentially important role (77).

Neoplastic Masses

[3] Most benign cystic teratomas (dermoid cysts) occur during the reproductive years in adolescents and young women, although dermoid cysts have a wider age distribution than other ovarian germ cell tumors; in some case series, up to 25% of dermoids occur in postmenopausal women, and they can occur in newborns (78). **[3]** Histologically, benign cystic teratomas have an admixture of elements **(Fig. 10-3)**. Malignant transformation occurs in less than 2% of dermoid cysts in women of all ages; most cases occur in women older than 40 years of age. The risk of torsion with dermoid cysts is approximately 15%, and occurs more frequently than with other ovarian tumors, perhaps because of the high fat content of most dermoid cysts, allowing them to float within the abdominal and pelvic cavity. As a result of this fat content, on pelvic examination a dermoid cyst frequently is described as anterior in location. They are bilateral in approximately 10% of cases, although many have advanced the argument against bivalving a normal-appearing contralateral ovary because of the risk of adhesions, which may result in infertility. **An ovarian cystectomy is almost always possible, even if it appears that only a small amount of ovarian tissue remains.** Preserving a small amount of ovarian cortex in a young patient with a benign lesion is preferable to the loss of the entire ovary (79). Laparoscopic cystectomy often is possible, and intraoperative spill of tumor contents is rarely a cause of complications, although granulomatous peritonitis has been reported (80). A minimally invasive, fertility-sparing approach is preferred for benign masses (81).

[3] The risk of epithelial tumors increases with age. Although serous cystadenomas are often considered the more common benign neoplasm, in one study, benign cystic teratomas represented 66% of benign tumors in women younger than 50 years of age; serous tumors accounted for only 20% (82). **Serous tumors are generally benign; 5% to 10% have borderline malignant potential, and 20% to 25% are malignant. The major risk factor for ovarian cancer is a family history of ovarian cancer or a familial syndrome, particularly BRCA1 mutation (approx. 40% risk), BRCA2 mutation (15% risk) or the Lynch syndrome (5% risk)** (81).

Serous cystadenomas are often multilocular, sometimes with papillary components **(Fig. 10-4)**. The surface epithelial cells secrete serous fluid, resulting in a watery cyst content. Psammoma bodies, which are areas of fine calcific granulation, may be scattered within the tumor and are visible on the radiograph. A frozen section is necessary to distinguish between benign, borderline, and malignant serous tumors because this distinction cannot be made on gross examination alone. Mucinous ovarian tumors may grow to large dimensions. Benign mucinous tumors typically have a lobulated, smooth surface, are multilocular, and may be bilateral in up to 10% of cases. Mucoid material is present within the cystic loculations. **Five to 10% of mucinous ovarian tumors are malignant (see Chapter 39).** They may be difficult to distinguish histologically from metastatic gastrointestinal malignancies. Other benign ovarian tumors include fibromas (a focus of stromal cells), Brenner tumors (which appear grossly similar to fibromas and are frequently found incidentally), and mixed forms of tumors, such as the cystadenofibroma.

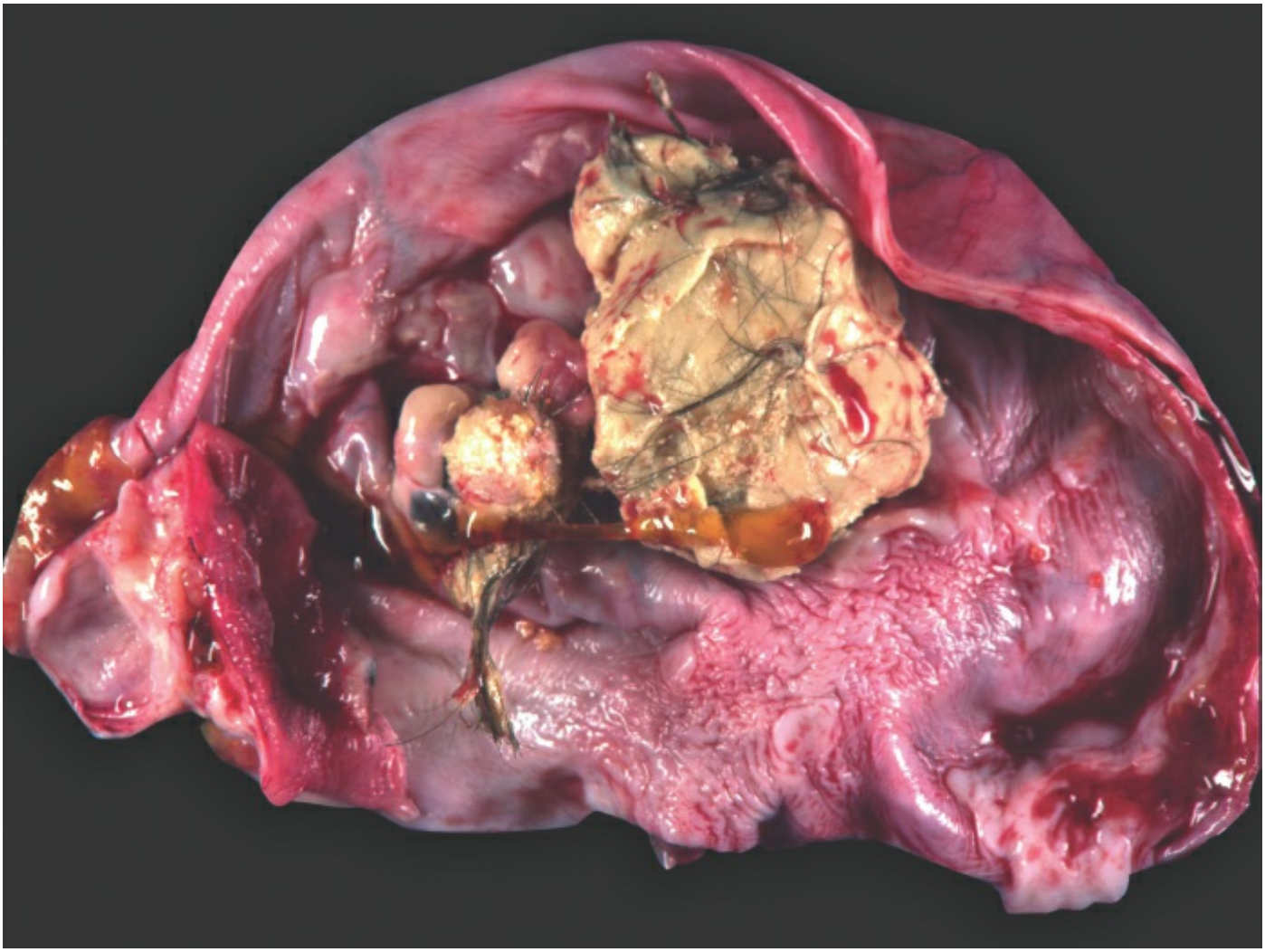


FIGURE 10-3 Mature cystic teratoma (dermoid cyst) of the ovary.

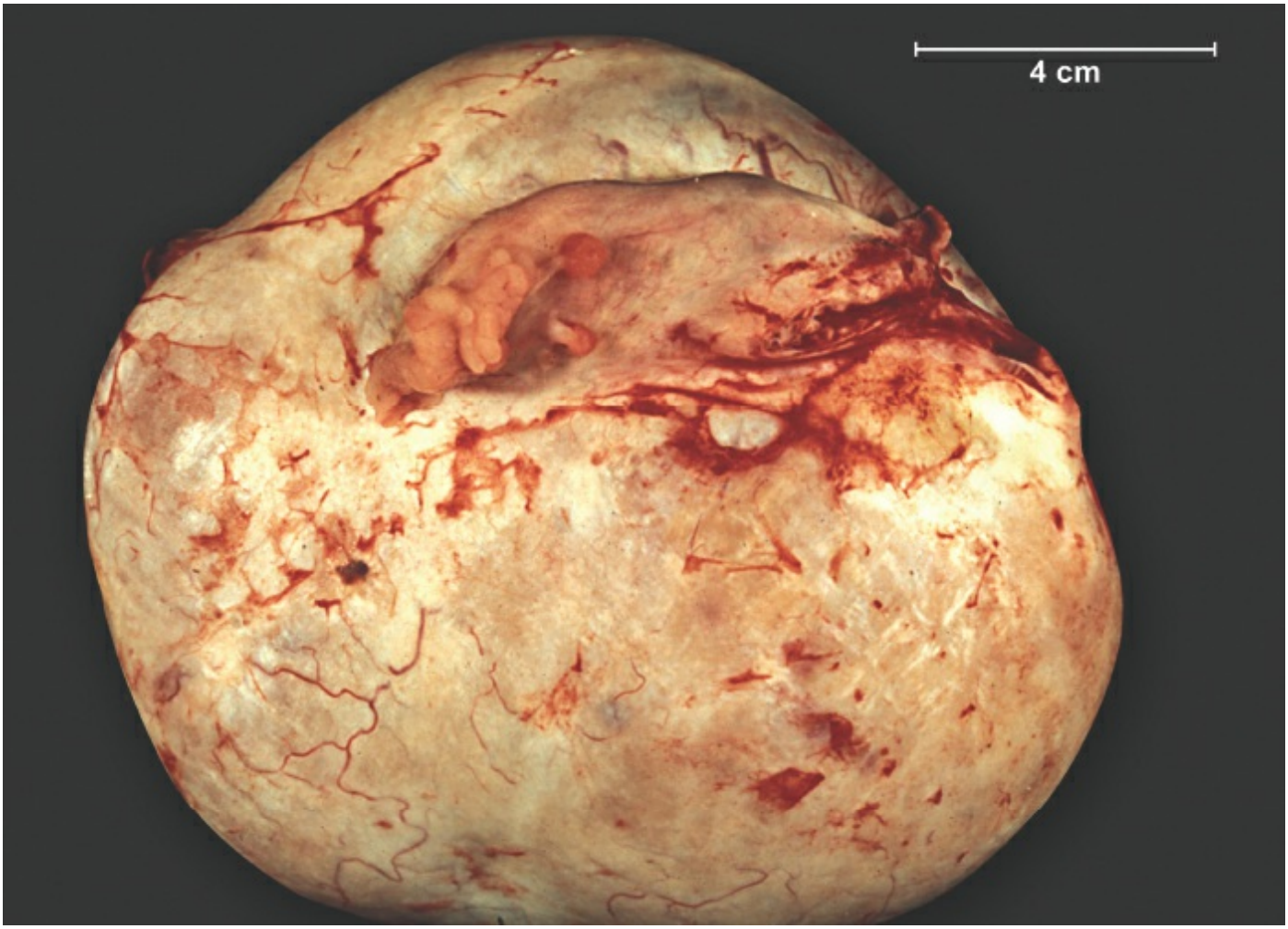


FIGURE 10-4 Serous cystadenoma.

Uterine, gastric, breast, and colorectal malignancies can metastasize to the ovaries and should be considered, although as with many malignancies, these tumors are more common in postmenopausal-aged women.

Other Adnexal Masses

[3] Masses that include the fallopian tube are related primarily to inflammatory causes in the reproductive age group. A tubo-ovarian abscess can be present in association with PID (see Chapter 15). A complex inflammatory mass consisting of the bowel, tube, and ovary may be present without a large abscess cavity. Ectopic pregnancies can occur in the reproductive age group and must be excluded when a patient presents with pain, a positive pregnancy test, and an adnexal mass (see Chapter 32). Paraovarian cysts may be noted on examination or in imaging studies. In many instances, a normal ipsilateral ovary can be visualized using ultrasonography. The frequency of malignancy in paraovarian tumors is quite low and may be more common in paraovarian masses larger than 5 cm (83).

Diagnosis of Pelvic Masses

A complete pelvic examination, including rectovaginal examination and Papanicolaou (Pap) test, should be performed. **Estimations of the size of a mass should be presented in centimeters** rather than in comparison to common objects or fruit (e.g., orange, grapefruit, tennis ball, golf ball). After pregnancy is excluded, one simple office technique that can help determine whether a mass is uterine or adnexal includes sounding and measuring the depth of the uterine cavity. Pelvic imaging can confirm the characteristics of the adnexal mass—whether solid or cystic or mixed echogenicity. Diagnosis of uterine leiomyomas usually is based on the characteristic finding of an irregularly enlarged uterus. The size and location of the usually multiple leiomyomas can be confirmed and documented with pelvic ultrasonography **(Fig. 10-5)**. If the examination is adequate to confirm uterine leiomyoma and symptoms are absent, ultrasonography is not always necessary unless an ovarian mass cannot be excluded. A fixed or nodular pelvic mass should always raise concern for malignancy.

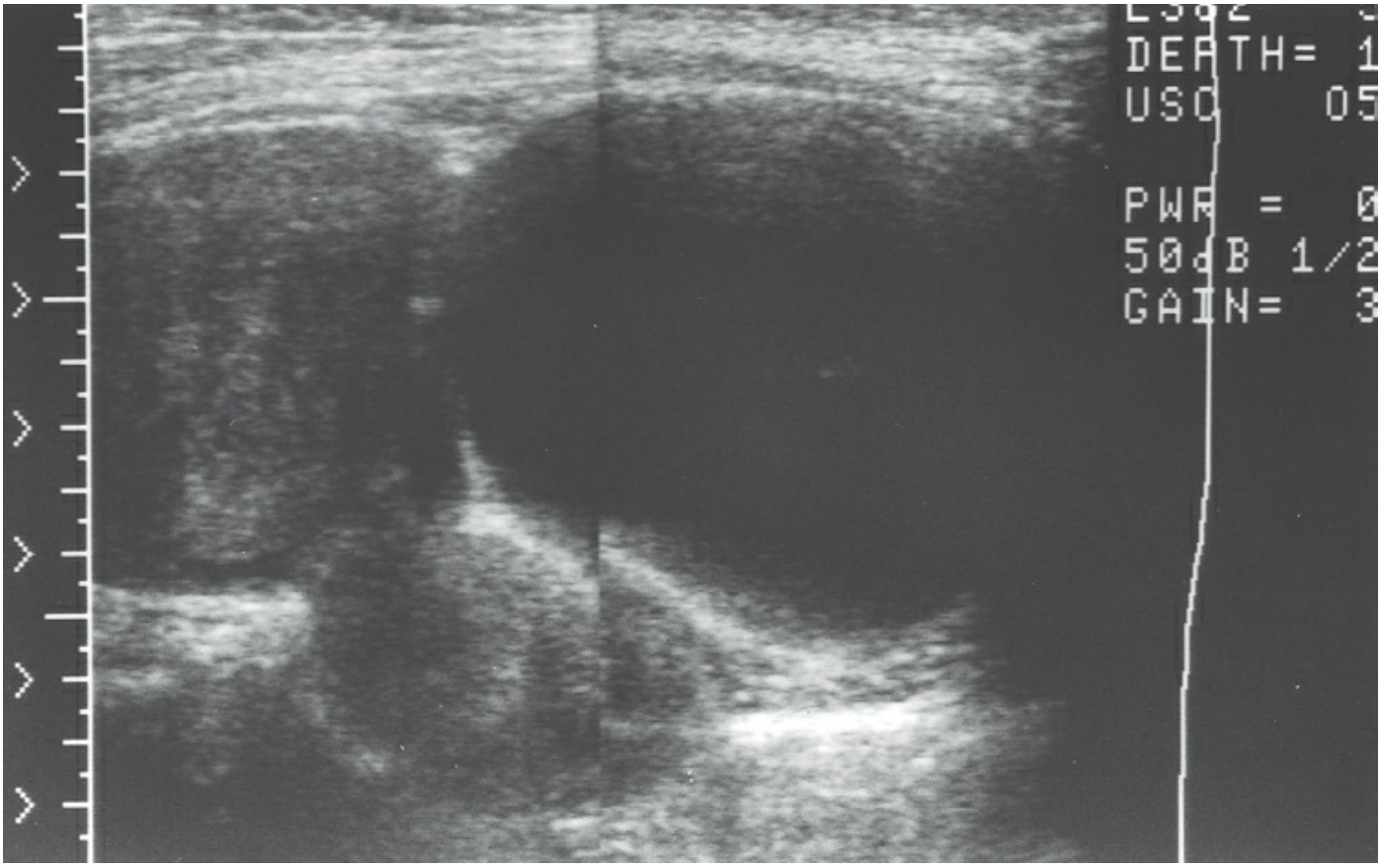


FIGURE 10-5 Transvaginal pelvic ultrasound demonstrating multiple uterine leiomyomas.

Other Studies

Endometrial sampling with an endometrial biopsy or hysteroscopy is mandatory when both pelvic mass and abnormal bleeding are present. An endometrial lesion—

carcinoma or hyperplasia—may coexist with a benign mass such as a leiomyoma. In a woman with leiomyomas, abnormal bleeding cannot be assumed to be caused solely by the fibroids. Clinicians differ in recommendations about the need for endometrial biopsy when the diagnosis is leiomyomas with regular menses.

If urinary symptoms are prominent, studies of the urinary tract may be necessary, including urodynamic testing, if incontinence or symptoms of pelvic pressure are present. Cystoscopy may be necessary or appropriate to rule out intrinsic bladder lesions.

Laboratory Studies

Laboratory studies that are indicated for women of reproductive age with a pelvic mass include pregnancy test, cervical cytology, and complete blood count. The value of tumor markers, such as CA125 in distinguishing malignant from benign adnexal masses in *premenopausal* women with a pelvic mass, is questioned. **A number of benign conditions, including uterine leiomyomas, PID, pregnancy, and endometriosis can cause elevated CA125 levels in premenopausal women; thus, measurement of CA125 levels is not as useful in premenopausal women with adnexal masses. Values greater than 200 in a premenopausal female may warrant gynecologic-oncology comanagement or referral** (81). **Ultrasonographic characteristics are more helpful than CA125 in suggesting risks of malignancy in premenopausal women** (84).

Imaging Studies

Other studies may be necessary or appropriate. **[4]** The most commonly indicated study is pelvic ultrasonography, which will help document the origin of the mass to determine whether it is uterine, adnexal, bowel, or gastrointestinal. The ultrasonographic examination provides information about the size of the mass and its consistency—unilocular cyst, mixed echogenicity, multiloculated cyst, or solid mass—which can help determine management (**Figs. 10-6** and **10-7**). Size greater than 10 cm, solid components, irregularity, papillary excrescences, and ascites increase the suspicion of malignancy (81). A number of different ultrasound scoring systems were developed in an effort to quantify the risks of malignancy.

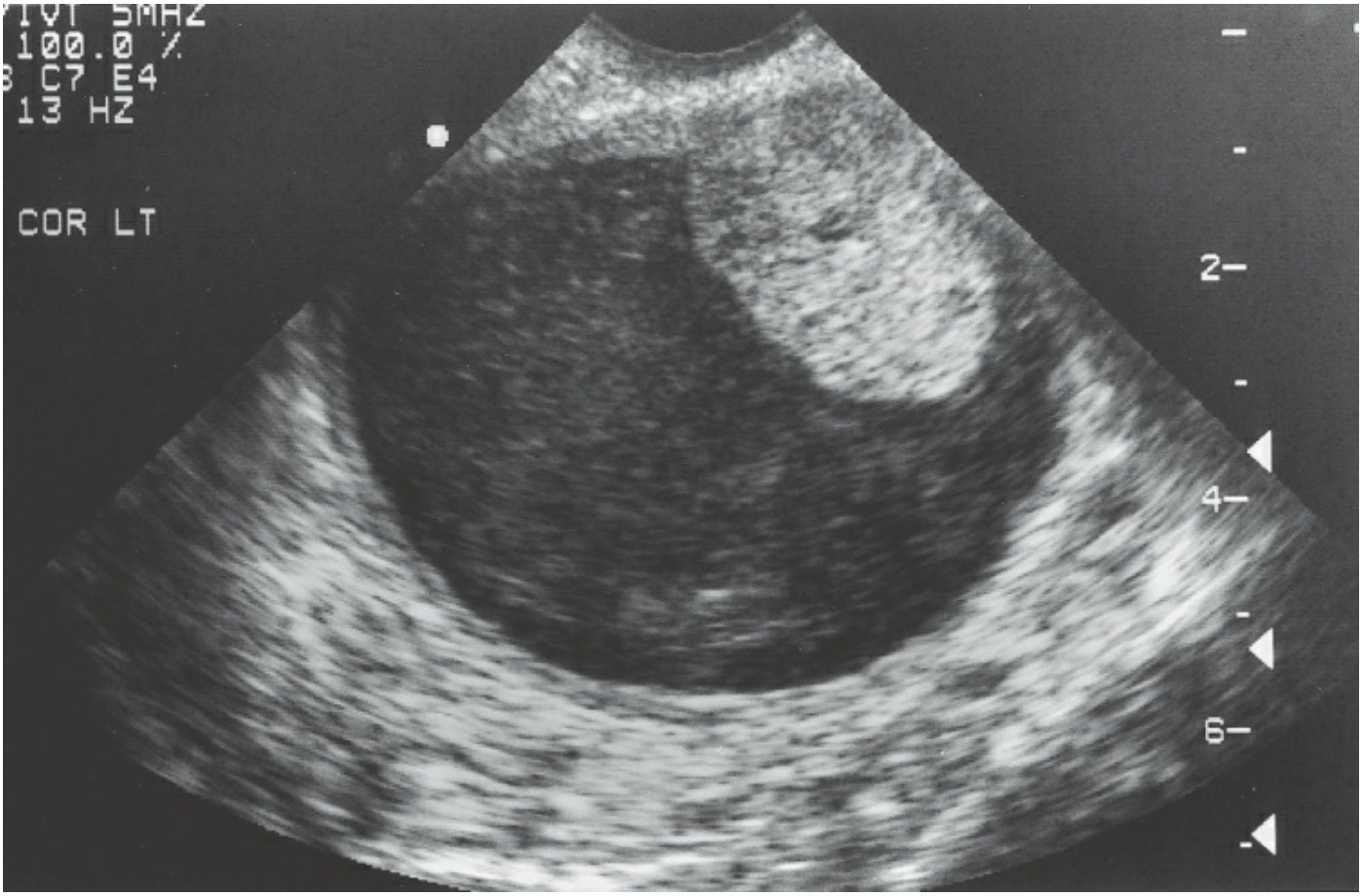


FIGURE 10-6 Transvaginal ultrasound of a unilocular ovarian cyst.

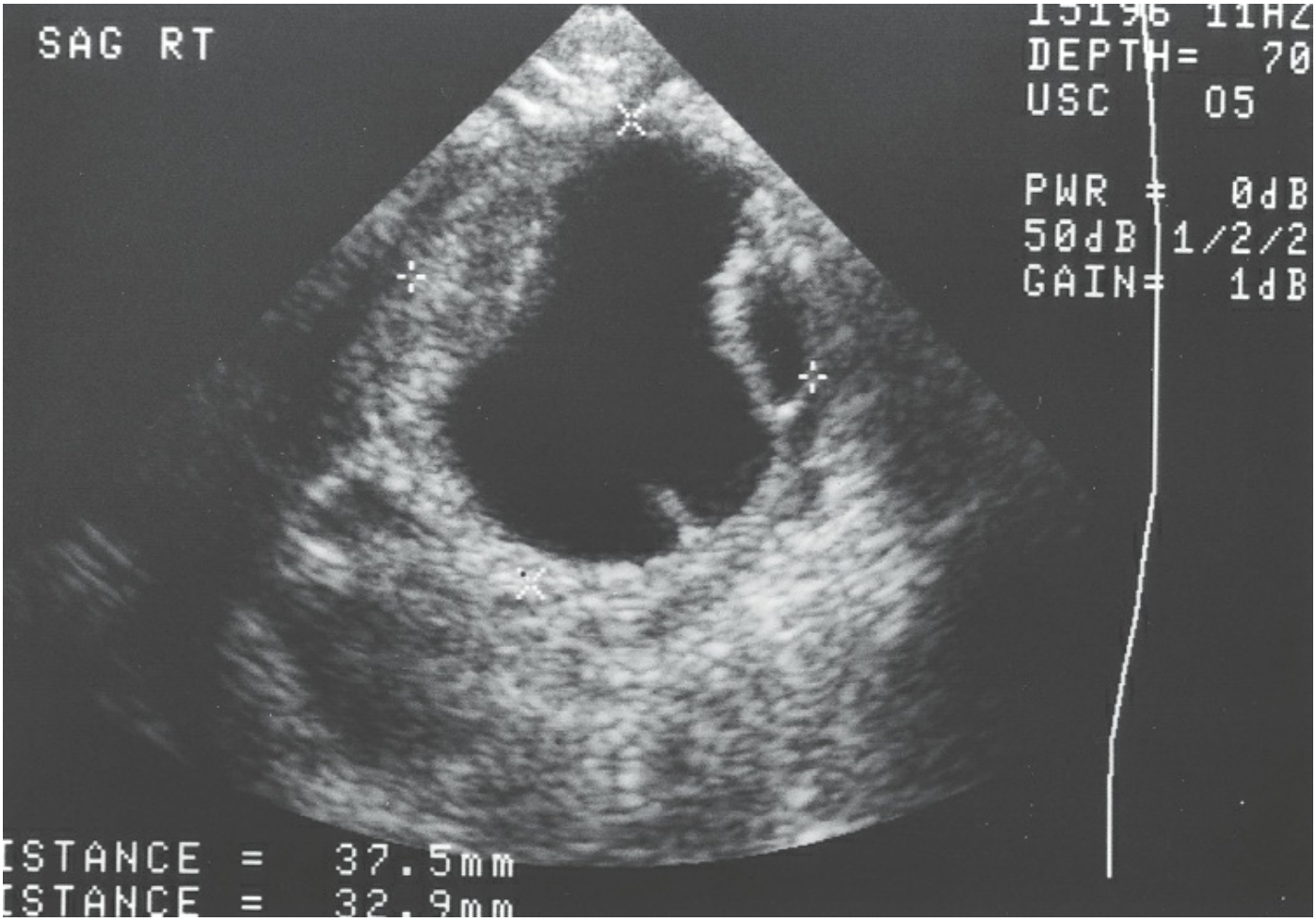


FIGURE 10-7 Transvaginal ultrasonogram of a complex, predominantly solid mass.

[4] Transvaginal and transabdominal ultrasonography are complementary in the diagnosis of pelvic masses, particularly those that have an abdominal component. Transvaginal ultrasonography has the advantage of providing additional information about the internal architecture or anatomy of the mass. Heterogeneous pelvic masses, described as tubo-ovarian abscesses on transabdominal ultrasonography, can be differentiated as pyosalpinx, hydrosalpinx, tubo-ovarian complex, and tubo-ovarian abscess with transvaginal ultrasonography **(Fig. 10-8)**.

The diagnostic accuracy of transvaginal ultrasonography in diagnosing endometrioma can be quite high (Fig. 10-9). Endometriomas can have a variety of ultrasonographic appearances, from purely cystic to varying degrees of complexity with septation or debris to a solid appearance. A variety of scoring systems were developed with the intent of predicting benign versus malignant adnexal masses using ultrasound; the ultrasonographic morphologic characteristics used in many types of scoring systems are listed in Table 10-10 (81). Color flow Doppler was added to other sonographic characteristics to predict the risk of malignancy; ultrasound techniques are comparable to CT and MRI in differentiating benign from malignant masses (81,85). Although an

analysis of such features may be helpful, histologic confirmation of surgically removed persistent masses remains the standard of care.

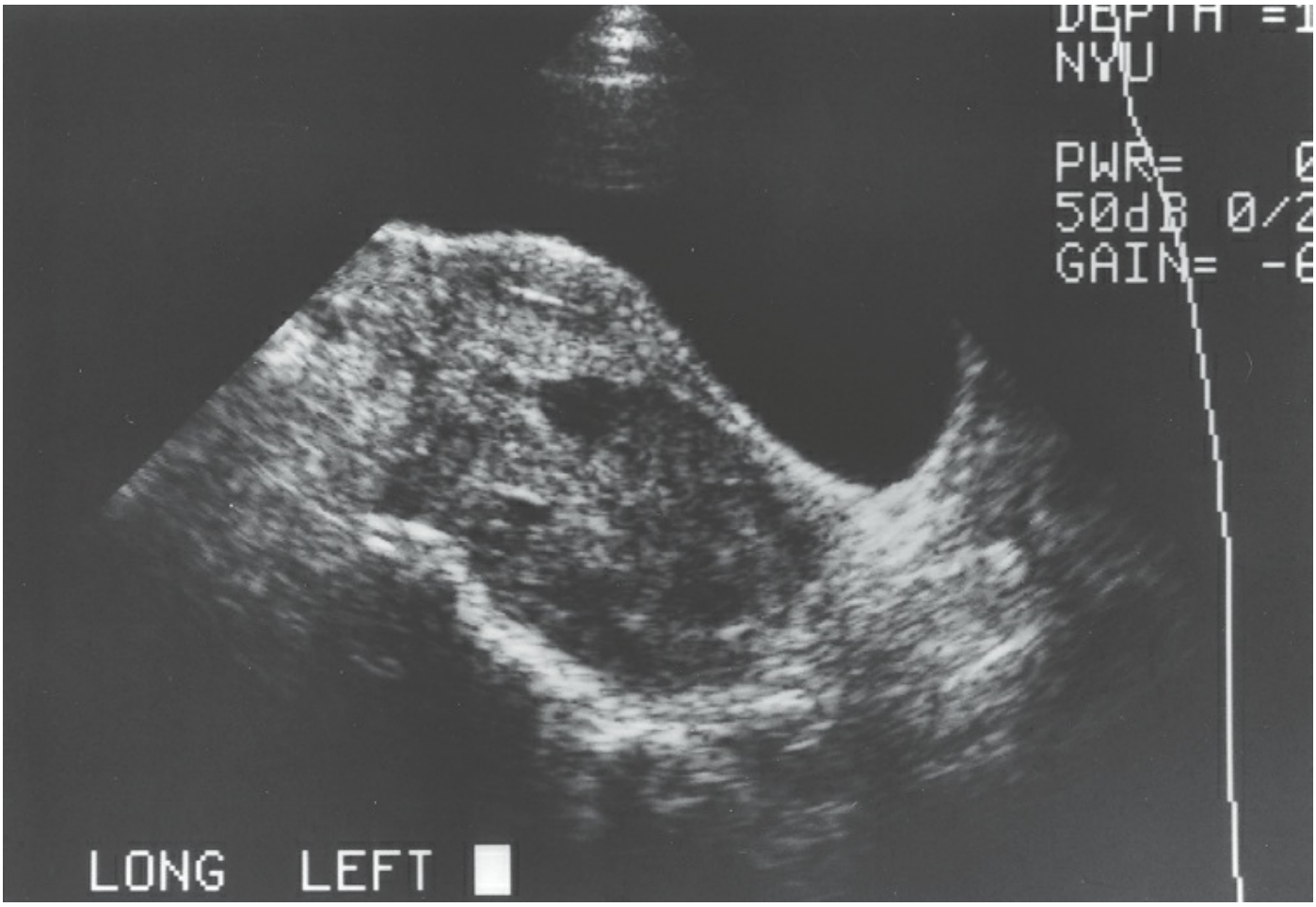


FIGURE 10-8 Transvaginal ultrasonogram of bilateral tubo-ovarian abscesses.

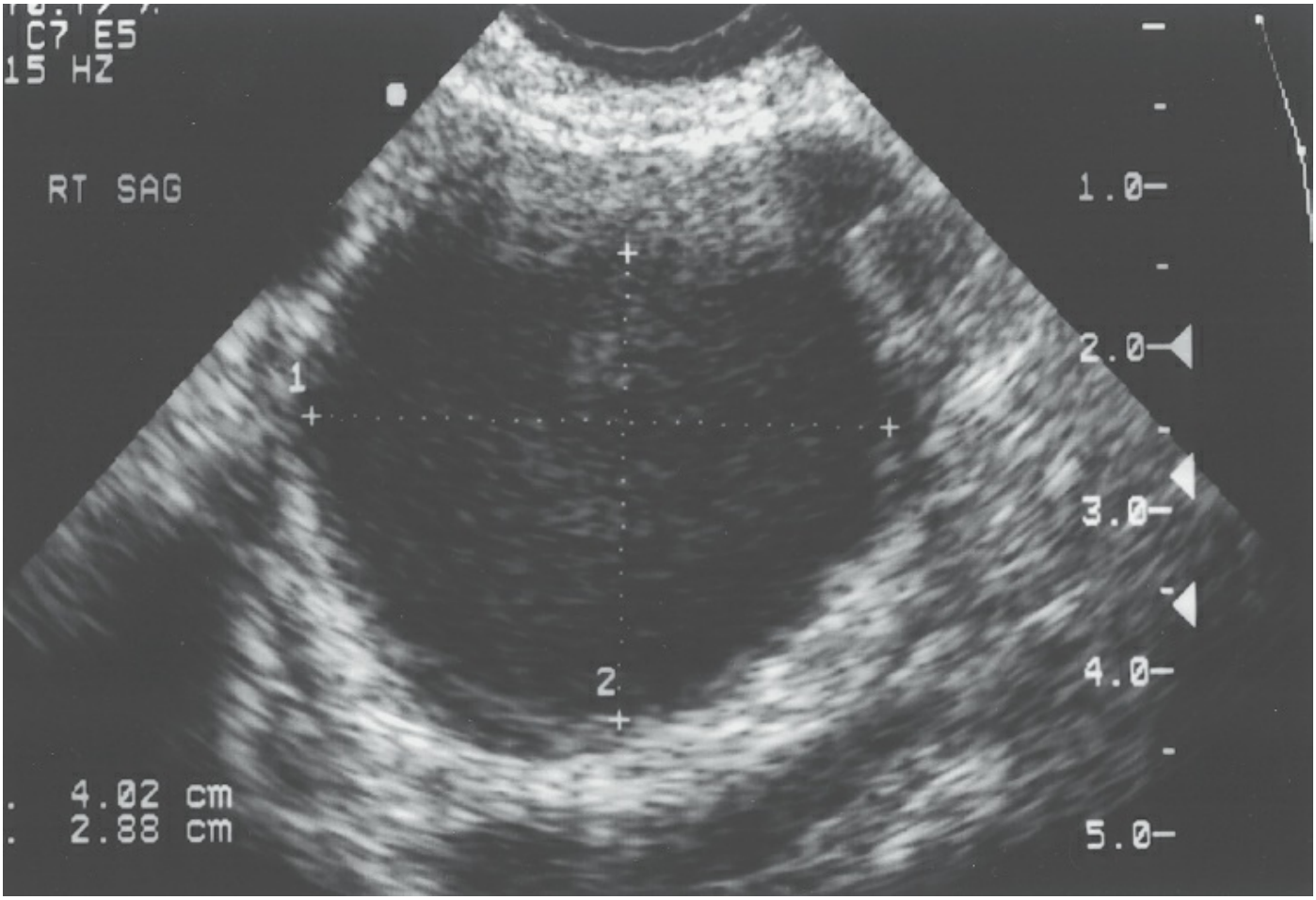


FIGURE 10-9 Transvaginal ultrasonogram of an endometrioma of the ovary.

CT seldom is indicated as a primary diagnostic procedure, although it may be helpful in planning treatment when a malignancy is strongly suspected or when a nongynecologic disorder may be present. Abdominal flat-plate radiography is not a primary diagnostic procedure, although if used for other indications, it may reveal calcifications that can assist in the discovery or diagnosis of a mass. Pelvic calcifications (teeth) consistent with a benign cystic teratoma, a calcified uterine fibroid, or scattered calcifications consistent with psammoma bodies of a papillary serous cystadenoma can be seen with abdominal radiography **(Fig. 10-10)**.



FIGURE 10-10 Benign cystic teratoma (dermoid cyst) of the ovary with teeth seen on abdominal radiograph.

Ultrasonography or CT imaging may be appropriate to demonstrate ureteral deviation, compression, or dilation in the presence of moderately large and laterally located fibroids or other pelvic mass. Such findings rarely provide an indication for surgical intervention for otherwise asymptomatic leiomyomas.

Table 10-10 Ultrasonographic Characteristics of Adnexal Masses That May Be Useful in Predicting Malignancy

Unilocular cyst vs. multilocular vs. solid components
Regular contour vs. irregular border
Smooth walls vs. nodular vs. irregular
Presence or absence of ascites
Unilateral vs. bilateral
Wall thickness

Internal echogenicity and septations (including thickness)
Presence of other intra-abdominal pathology (liver, etc.)
Vascular characteristics and color flow Doppler pattern

Hysteroscopy provides direct evidence of intrauterine pathology or submucous leiomyomas that distort the uterine cavity (see Chapter 26). Hysterosalpingography will demonstrate indirectly the contour of the endometrial cavity and any distortion or obstruction of the uterotubal junction secondary to leiomyomas, an extrinsic mass, or peritubal adhesions. The techniques combining hysterosalpingography, in which fluid is instilled into the uterine cavity, with transvaginal ultrasonography are helpful in the diagnosis of intrauterine pathology. Hysterosalpingography or sonohysterography may be indicated in women with infertility and uterine leiomyoma.

MRI may be most useful in the diagnosis of uterine anomalies, although its value rarely justifies the increased cost of the procedure over ultrasonography for the diagnosis of other pelvic masses (86).

Management of Pelvic Mass

The management of a pelvic mass is based on an accurate diagnosis. An explanation of this diagnosis should be conveyed to the patient, along with a discussion of the likely course of the disease (e.g., growth of uterine leiomyomas, regression of fibroids at menopause, regression of a follicular cyst, the uncertain malignant potential of an ovarian mass). All options for management should be presented and discussed, although it is appropriate for the physician to state a recommended approach with an explanation of the reasons for the recommendation. Management should be based on the primary symptoms and may include observation with close follow-up, temporizing surgical therapies, medical management, or definitive surgical procedures.

Leiomyomas

[5] The management of uterine leiomyomas is dependent on the patient's age and proximity to anticipated menopause, symptoms, patient preference, and the experience and skills of the clinician. Variability in reporting data regarding the severity of symptoms, uterine anatomy, and response to therapy makes it difficult to compare different types of therapies, which include observation, medical, surgical, and radiologic-based techniques (see Chapter 11 for discussion of uterine fibroids).

Ovarian Masses

The now-routine application of ultrasound technology to gynecologic examinations led to the more frequent detection of ovarian cysts, sometimes as an incidental finding. Ultrasonography is a relatively easy diagnostic study to perform, but this ease led to the

labeling of physiologic ovarian morphology and cystic follicles, as pathologic and the subsequent referral of patients for therapies, including surgery, without indications. **Treatment of ovarian masses that are suspected to be functional tumors is expectant (Fig. 10-2). A number of randomized prospective studies showed no acceleration of the resolution of functional ovarian cysts** (some of which were associated with the use of *clomiphene citrate* or human menopausal gonadotropins) **with oral contraceptives compared with observation alone** (66). **Oral contraceptives are effective in reducing the risk of subsequent ovarian cysts and may be appropriate for women who desire both contraception and their noncontraceptive benefits.**

Symptomatic cysts should be evaluated promptly, although mildly symptomatic masses suspected to be functional should be managed with analgesics rather than surgery to avoid the risk of surgical complications, including the development of adhesions that may impair subsequent fertility. Surgical intervention is warranted in the presence of severe pain or the suspicion of malignancy or torsion.

[4] On ultrasonography, ascites, cysts greater than 10 cm and those that have multiloculations are concerning for malignancy (81). **If a malignant mass is suspected at any age, surgical evaluation should be performed promptly.**

Simple cysts up to 10 cm in size are likely benign and can be managed expectantly at any age, if asymptomatic (81).

Ovarian or adnexal torsion is suspected on the basis of peritoneal signs and the acuity of onset, often accompanied by nausea and vomiting. Doppler flow studies suggesting abnormal flow are predictive of torsion, although torsion can be seen with normal flow (87). The absence of internal ovarian flow is not specific to torsion and may be seen with cystic lesions, although in these situations peripheral flow usually can be visualized.

The management of suspected ovarian torsion, which can occur at any age from prepubertal to postmenopausal, is surgical. When torsion is confirmed by laparoscopy, untwisting of the mass and ovarian preservation rather than extirpation are generally indicated (88). The value of oophoropexy in preventing recurrent torsion is not well established.

Ultrasonographic or CT-directed aspiration procedures of ovarian masses should not be used in women in whom there is a suspicion of malignancy. In the past, laparoscopic surgery for ovarian masses was reserved for diagnostic or therapeutic purposes in patients at very low risk for malignancy. With the recent advancements in minimally invasive surgery the current recommendation is for **laparoscopic management of suspected benign adnexal masses (Fig. 10-11)**, even those greater than 10 cm. Rates of intraoperative rupture were found to be similar between the open and laparoscopic approaches in three randomized trials made up of 394 patients. The

benefits of laparoscopy included decreased operative time, hospital stay, postoperative pain, and perioperative morbidity. The conversion rate to laparotomy was less than 2% (81).

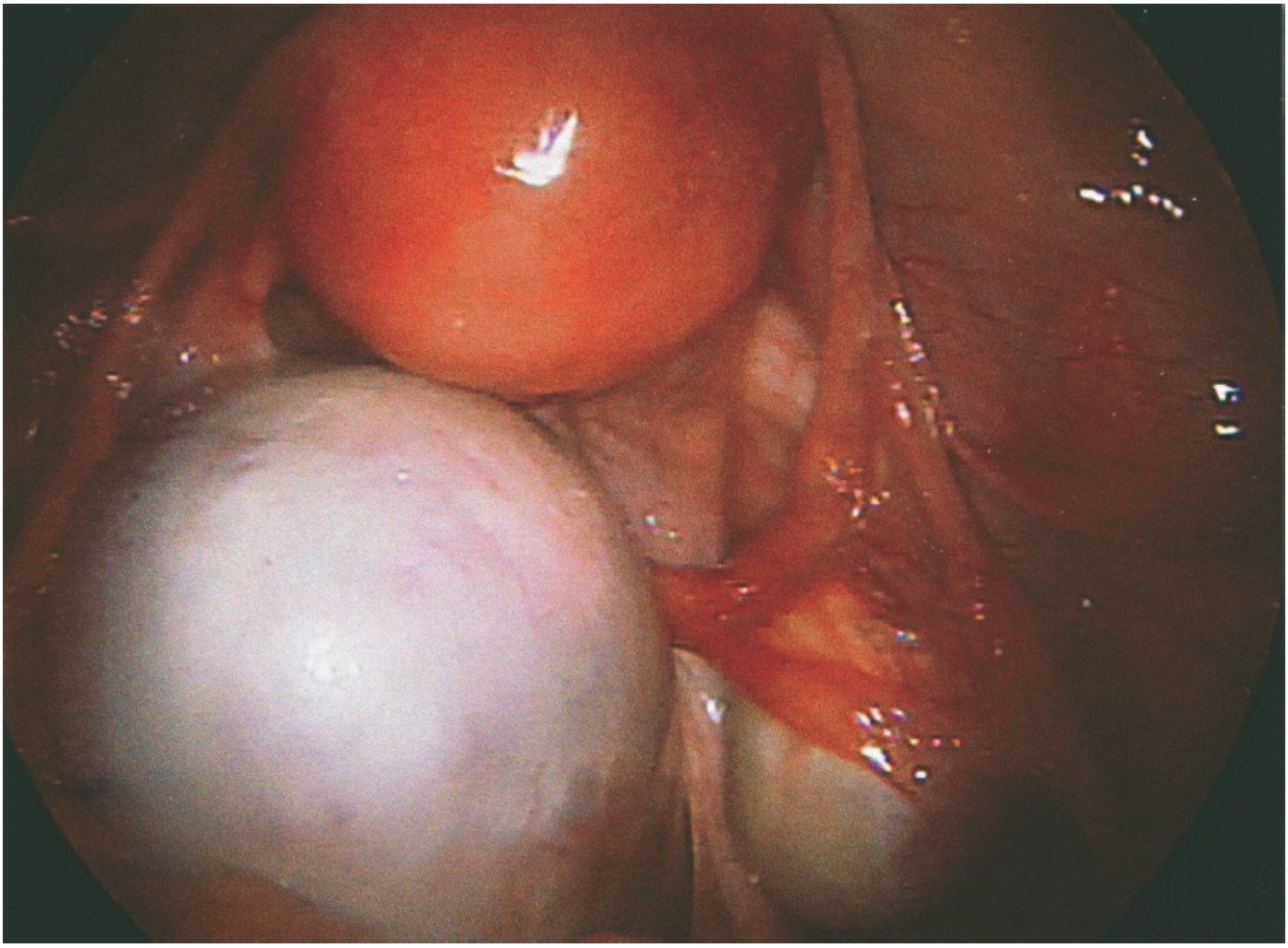


FIGURE 10-11 Laparoscopic appearance of benign ovarian mass (dermoid cyst).

Vulvar Conditions

In postmenarchal individuals, vulvar symptoms are most often related to a primary vaginitis and a secondary vulvitis. The mere presence of vaginal discharge can lead to vulvar irritative symptoms, or candidal vulvitis may be present **(Fig. 10-12)**. The causes of vaginitis and cervicitis are covered in Chapter 15. Adult women describe vulvar symptoms using a variety of terms (itching, pain, discharge, discomfort, burning, external dysuria, soreness, pain with intercourse or sexual activity). **Burning with urination from noninfectious causes may be difficult to distinguish from a urinary tract infection, although some women can distinguish pain when the urine hits the vulvar area (an external dysuria) from burning pain (often suprapubic in location)**

during urination. Itching is a very common vulvar symptom. A variety of vulvar conditions and lesions can present with pruritus. Vulvovaginal symptoms may be caused by STDs, nonsexually transmitted vaginitis, or UTIs. The distinction between symptoms related to a UTI and those of vaginitis is difficult, and consideration should be given to testing for both *C. trachomatis* and obtaining a urine culture, particularly in young reproductive age women (89).



FIGURE 10-12 Candidal vulvitis.

A number of skin conditions that occur on other areas of the body may occur on the vulvar area. Table 10-11 contains a list of these conditions classified by either infectious or noninfectious causes. Whereas the diagnosis of some of these conditions is apparent from inspection alone (e.g., a skin tag), any lesions that appear atypical or in which the diagnosis is not clear should be analyzed by biopsy, because the risks of malignant lesions increases with age (Fig. 10-13).

Pigmented vulvar lesions include benign nevi, lentigines, melanosis, seborrheic keratosis, condyloma, and some vulvar intraepithelial neoplasias (VINs), especially

multifocal VIN-3 **(Fig. 10-14)**. **Suspicious pigmented vulvar lesions in particular should warrant biopsy to rule out VIN or malignant melanoma** (90). Approximately 10% of white women have a pigmented vulvar lesion; some of these lesions may be malignant (see Chapter 40) or have the potential for progression (VIN) (see Chapter 16). There is an increase in rates of VIN in women younger than age 50, along with increasing rates of vulvar squamous cell carcinoma *in situ,* possibly related to increasing rates of human papillomavirus (HPV) infection. Heightened awareness among clinicians may play a role in the increasing frequency of diagnosis; suspicious lesions warrant vulvar biopsy. Pigmented lesions include common nevi, lentigines, melanomas, dysplastic nevi, blue nevi, and a lesion termed atypical melanocytic nevi of the genital type (AMNGT) (91). AMNGTs have some histologic features that may overlap with those of melanoma, but with a benign prognosis.

Table 10-11 Subacute and Chronic Skin Recurrent Conditions of the Vulva

Noninfectious	Infectious
Acanthosis nigricans	Cellulitis
Atopic dermatitis	Folliculitis
Behçet disease	Furuncle/carbuncle
Contact dermatitis	Insect bites (e.g., chiggers, fleas)
Crohn disease	Necrotizing fasciitis
Diabetic vulvitis[a]	Pubic lice
Hidradenitis suppurativa[a]	Scabies
	Tinea
Lichen sclerosus	Condyloma
Paget disease	Vulvar candidiasis
“Razor bumps”—folliculitis or pseudofolliculitis	HSV
Psoriasis	
Seborrheic dermatitis	
Vulvar aphthous ulcer	
Vulvar intraepithelial neoplasia	

[a]Etiology unknown, often secondarily infected.



FIGURE 10-13 Large benign skin tag from left labium majus.



FIGURE 10-14 Pigmented vulvar lesion.

Vulvar Biopsy

A vulvar biopsy is essential for distinguishing benign from premalignant or malignant vulvar lesions, especially because many types of lesions may have a somewhat similar appearance. Vulvar biopsies should be performed liberally in women of reproductive age to ensure that these lesions are diagnosed and treated appropriately. A prospective study of vulvar lesions evaluated by biopsy in a gynecologic clinic found lesions occurring in the following order of frequency: epidermal inclusion cyst, lentigo, Bartholin duct obstruction, carcinoma *in situ,* melanocytic nevi, acrochordon, mucous cyst, hemangiomas, postinflammatory hyperpigmentation, seborrheic keratoses, varicosities, hidradenomas, verruca, basal cell carcinoma, and unusual tumors such as neurofibromas, ectopic tissue, syringomas, and abscesses (92). The frequency with which a lesion would be reported after a tissue biopsy is related to the frequency with which all lesions of a given pathology are evaluated in this manner. This listing probably underrepresents such common lesions as condylomata **(Fig. 10-15)**.



FIGURE 10-15 Extensive vulvar condyloma.

Biopsy is easily performed in the office using a local anesthetic. Typically, 1% *lidocaine* is infiltrated beneath the lesion using a small (25- to 27-gauge) needle. Disposable punch biopsy instruments come in a variety of sizes from 2 to 6 mm in diameter. These skin biopsy instruments, along with fine forceps, scissors, and a scalpel, should be available in all outpatient gynecologic settings. For smaller biopsies, it is usually not necessary to place a suture. Topical *silver nitrate* can be used for hemostasis. Multiple tissue samples may be appropriate to obtain representative areas of a lesion if the lesion has a variable appearance or is multifocal. Although the vulvar biopsy procedure involves minimal discomfort during the procedure, the biopsy sites will be painful for several days after the procedure. The prescription of a topical anesthetic such as 2% *lidocaine* jelly, to be applied periodically and before urinating, is appreciated by patients who require this procedure. Infection of the site can occur, and patients should be cautioned to report excessive erythema or purulent drainage.

Other Vulvar Conditions

Classification and description of intraepithelial lesions of the vulva are presented in Chapter 16.

Pseudofolliculitis or Mechanical Folliculitis

This is similar to what is described as pseudofolliculitis barbae (razor bumps) and may occur in women who follow the popular practice of shaving pubic hair (93). **Pseudofolliculitis consists of an inflammatory reaction surrounding an ingrown hair and occurs most commonly among individuals with curly hair, particularly African Americans.**

Infectious Folliculitis

Shaving may be associated with an infectious folliculitis, commonly caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. Shaving and other methods of pubic hair removal are associated with razor burn, contact dermatitis, and the transmission of other infectious agents such as *Molluscum contagiosum,* HPV, and herpes simplex along with other bacteria including *Pseudomonas aeruginosa* (93).

Fox–Fordyce Disease

This condition is characterized by a chronic, pruritic eruption of small papules or cysts formed by keratin-plugged apocrine glands. It is commonly present over the lower abdomen, mons pubis, labia majora, and inner portions of the thighs. **Hidradenitis suppurativa is a chronic condition involving the apocrine glands with the formation of multiple deep nodules, scars, pits, and sinuses that occur in the axilla, vulva, and perineum.** Hyperpigmentation and secondary infection are often seen. Hidradenitis suppurativa can be extremely painful and debilitating. It has been treated with antibiotics, isotretinoin, or steroids; surgical therapy with wide local excision may be necessary (94).

Acanthosis Nigricans

This disease involves widespread velvety pigmentation in skin folds, particularly the axillae, neck, thighs, submammary area, and vulva and surrounding skin **(Fig. 10-16)**. It is of particular interest to gynecologists because of its association with hyperandrogenism and PCOS; as such, it is associated with obesity, chronic anovulation, acne, glucose intolerance, insulin resistance, and cardiovascular disease (95). Topical and oral retinoids are used to treat the acanthosis nigricans, along with management of the underlying conditions including obesity and insulin resistance or diabetes.



FIGURE 10-16 Acanthosis nigricans of the neck.

Extramammary Paget Disease

This is an intraepithelial neoplasia containing vacuolated Paget cells (see Chapter 16). Clinically, the appearance of Paget disease is variable, and it may have an appearance varying from moist, oozing ulcerations to an eczematoid lesion with scaling and crusting to a grayish lesion (96). It may be confused with candidiasis, psoriasis, seborrheic dermatitis, contact dermatitis, and VIN. A biopsy to confirm the diagnosis is mandatory. Treatment has traditionally been surgery, although recurrences are very common; topical therapies including imiquimod are being used (97).

Vulvar Intraepithelial Neoplasia

VIN is associated with HPV infection and is increasing in frequency, particularly among young women (see Chapter 16). Diagnosis requires biopsy of any suspicious vulvar lesions, particularly those that are pigmented or discolored. The increasing frequency of this entity dictates a careful vulvar inspection during annual gynecologic examinations.

Vulvar Tumors, Cysts, and Masses

Condylomata Acuminata

These are very common vulvar lesions and are usually easily recognized. They may resolve spontaneously; treatment is guided by wart number, size, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience (98). **Treatments may be patient-applied or provider-administered. Other sexually transmitted organisms, such as the virus responsible for *M. contagiosum* and the lesions of syphilis and condylomata lata, may occasionally be mistaken for vulvar condylomata acuminata caused by HPV** (see Chapter 15). A summary of benign vulvar tumors is listed in **Table 10-12**. There is an argument regarding whether sebaceous cysts exist on the vulva or whether these lesions are histopathologically epidermal or epidermal inclusion cysts (99). The so-called sebaceous cysts are clinically indistinguishable from epidermal inclusion cysts that may result from the burial of fragments of skin after the trauma of childbirth or episiotomy or that arise from occluded pilosebaceous ducts. These cysts are seldom symptomatic, although if infection develops, incision and drainage may be required acutely, and ultimately complete excision is indicated.

Table 10-12 Types of Vulvar Tumors

1. *Cystic lesions*
Bartholin duct cyst
Cyst in the canal of Nuck (hydrocele)
Epithelial inclusion cyst
Skene duct cyst
2. *Solid tumors*
Acrochordon (skin tag)
Angiokeratoma
Bartholin gland adenoma
Cherry angioma
Fibroma
Hemangioma
Hidradenoma
Lipoma

Granular cell myoblastoma
Neurofibroma
Papillomatosis
3. *Anatomic*
Hernia
Urethral diverticulum
Varicosities
4. *Infections*
Abscess—Bartholin, Skene, periclitoral, other
Condyloma lata
Molluscum contagiosum
Pyogenic granuloma
5. *Ectopic*
Endometriosis
Ectopic breast tissue

Bartholin Duct Cysts

These are common vulvar lesions in reproductive age women. They result from occlusion of the duct with accumulation of mucus and may be asymptomatic. Infection of the gland can result in the accumulation of purulent material, with the formation of a rapidly enlarging, painful, inflammatory mass (a Bartholin abscess). An inflatable bulb-tipped catheter was described by Word and is quite easy to use (100). The small catheter is inserted through a small stab wound into the abscess after infiltration of the skin with local anesthesia; the balloon of the catheter is inflated with 2 to 3 mL of saline and the catheter remains in place for 4 to 6 weeks, allowing epithelialization of a tract and the creation of a permanent gland opening.

Skene Duct Cysts

These are cystic dilations of the Skene glands, typically located adjacent to the urethral meatus within the vulvar vestibule. Although most are small and often asymptomatic, they may enlarge and cause urinary obstruction, requiring excision **(Fig. 10-17)**.



FIGURE 10-17 The Skene gland cyst.

Painful Intercourse

Painful intercourse (dyspareunia) may be caused by many different vulvovaginal conditions, including common vaginal infections and vaginismus (see Chapters 15 and 17). A careful sexual history is essential, as is a careful examination of the vulvar area and vagina. *Vulvodynia* is the term used to describe unexplained vulvar pain, sexual dysfunction, and the resultant psychological disability (101,102). **The term *vulvar vestibulitis* was previously used to describe a situation in which there is pain during intercourse or when attempting to insert an object into the vagina; pain on pressure to the vestibule on examination and vestibular erythema (known as the Friedrich triad); this entity is now described as localized vulvodynia, which may be provoked or spontaneous, primary or secondary, and intermittent, persistent, constant, immediate, or delayed** (see Chapter 12) (102,103). A number of studies failed to demonstrate a consistent relationship with any genital infectious organism, including *C. trachomatis*, gonorrhea, *Trichomonas*, mycoplasma, *Ureaplasma*,

Gardnerella, candida, or HPV, and the condition has been characterized as multifactorial, with inflammatory, neuropathic, and functional components (104). Although the symptoms of dyspareunia with insertion can be disabling, no curative therapies were found. Medical and behavioral therapies are of some benefit, and some authors encourage surgery, but the role of this treatment and newer therapies such as the injection of botulinum toxin A is not well established (104).

Vulvar Ulcers

A number of STDs can cause vulvar ulcers, including herpes simplex virus, syphilis, lymphogranuloma venereum, and granuloma inguinale (see Chapter 15). *Crohn disease* can include vulvar involvement with abscesses, fistulae, sinus tracts, fenestrations, and other scarring. Medical treatment with systemic steroids and other systemic agents is the standard therapy; surgical therapy for intestinal and vulvar disease may be required.

The Behçet Disease

This systemic condition is characterized by genital and oral ulcerations with ocular inflammation and many other manifestations (105). The cause and the most effective therapy are not well established, although anti-inflammatory, immunomodular, and immunosuppressive therapies may be effective (106).

Lichen Planus

This condition causes oral and genital ulcerations. Typically, there is desquamative vaginitis with erosion of the vestibule. Treatment is based on the use of topical and systemic steroids. Plasma cell mucositis appears as erosions in the vulvar area, particularly the vestibule. Biopsy is essential in establishing the diagnosis.

Vaginal Conditions

Vaginal discharge is one of the most common vaginal symptoms. Conditions ranging from vaginal candidiasis to chlamydia cervicitis to bacterial vaginosis to cervical carcinoma may cause vaginal discharge. Infectious vaginal conditions are addressed more completely in Chapter 15. Vaginal lesions may occasionally be palpable to a woman. More commonly, vaginal lesions are discovered on examination by a clinician. They may contribute to symptoms (such as bleeding or discharge) or they may be entirely asymptomatic. Vaginitis, cervicitis, and vaginal or cervical lesions (including malignancies) can be causes of vaginal discharge. Other noninfectious causes of discharge are as follows:

1. **Retained foreign body—tampon, pessary**
2. **Ulcerations—tampon-induced, lichen planus, herpes simplex infection**
3. **Malignancy—cervical, vaginal**

Some vaginal lesions are asymptomatic and are noted incidentally on examination. Fibroepithelial polyps consist of polypoid folds of connective tissue, capillaries, and stroma covered by vaginal epithelium. Although they can be excised easily in the office, their vascularity can be troublesome, and excision is not necessary unless the diagnosis is in question. **Cysts of embryonic origin can arise from mesonephric, paramesonephric, and urogenital sinus epithelium. Gartner duct cysts are of mesonephric origin and are usually present on the lateral vaginal wall.** They rarely cause symptoms and do not require treatment. Other embryonic cysts can arise anterior to the vagina and beneath the bladder. Cysts that arise from the urogenital sinus epithelium are located in the area of the vulvar vestibule. Vaginal adenosis, the presence of epithelial-lined glands within the vagina, is associated with *in utero* exposure to *diethylstilbestrol*. No therapy is necessary other than close observation and periodic palpation to detect nodules that may need to be evaluated by biopsy to rule out vaginal clear cell adenocarcinoma (see Chapter 38).

Women will sometimes describe a bulging lesion of the vagina and vulvar area, variably associated with symptoms of pressure or discomfort. The most common cause of such a lesion is one of the disorders of vaginal support. Management of these conditions is discussed in Chapter 30. Other genital lesions, such as urethral diverticula or embryonic cysts, may cause similar symptoms.

POSTMENOPAUSAL AGE GROUP

Abnormal Bleeding

Differential Diagnosis

[1] The causes of postmenopausal bleeding and the percentage of patients who seek treatment for different conditions are presented in Table 10-13.

Table 10-13 Etiology of Postmenopausal Bleeding

Factor	Approximate Percentage
Exogenous estrogens	30
Atrophic endometritis/vaginitis	30
Endometrial cancer	15
Endometrial or cervical polyps	10
Endometrial hyperplasia	5
Miscellaneous (e.g., cervical cancer, uterine sarcoma, urethral caruncle, trauma)	10

From **Hacker NF, Moore JG.** *Essentials of Obstetrics and Gynecology*. 3rd ed. Philadelphia, PA: WB Saunders; 1998:635, with permission.

Benign Disorders

Hormone therapy (HT) may be used to manage troublesome menopausal symptoms including vasomotor and genitourinary symptoms. The North American Menopause Society has issued a statement noting that HT is the most effective treatment for these symptoms, and has been shown to prevent bone loss and fracture; the society noted that the risks of HT depend on the type, dose, duration, route of administration, timing of initiation, and concurrent use of a progestogen, thus requiring individualization of use, with periodic revaluation of the benefits versus the risks (107). Long-term combined HT has been associated with increased risks of venous thromboembolism, stroke, breast cancer, coronary events, gallbladder disease, and death from lung cancer (108). Women who are taking HT during menopause may be using a variety of hormonal regimens that can result in bleeding. Because unopposed estrogen therapy can result in endometrial hyperplasia, various regimens of progestins are typically added to the estrogen regimen; they are given in a continuous fashion, although they may be given in a sequential fashion for women within 1 year of menopause. Endometrial sampling is indicated for any unexpected bleeding that occurs with hormonal therapy. **A significant change in withdrawal bleeding or breakthrough bleeding (e.g., absence of withdrawal bleeding for several months followed by resumption of bleeding or a marked increase in the amount of bleeding) should prompt endometrial sampling.**

Patient adherence to hormonal regimens is a significant issue with HT, with the challenges of oral therapy mitigated by nonoral routes of administration (109). Missed doses of oral medication and failure to take the medication in the prescribed fashion can lead to irregular bleeding or spotting that is benign in origin but that can result in patient dissatisfaction.

The problems that women most often report with HT include vaginal bleeding and weight gain. The use of a continuous low-dose combined regimen has the advantage that for many women, bleeding will ultimately cease after several months, during which irregular and unpredictable bleeding may occur (110). Some women are unable to tolerate these initial months of irregular bleeding. The risk of endometrial hyperplasia or neoplasia with this regimen is low.

Other benign causes of bleeding include atrophic vaginitis and endometrial and cervical polyps, which may become apparent as postcoital bleeding or spotting. Women who experience bleeding after menopause may attempt to minimize the extent of the problem; they may describe it as “spotting” or “pink or brownish discharge.” However, any indication of bleeding or spotting should be evaluated. **[1] In the absence of HT, any bleeding after menopause (classically defined as absence of menses for 1 year) should prompt evaluation with endometrial sampling.** Studies of transvaginal

ultrasonography revealing an endometrial thickness 4 mm or less correlate with a low risk of endometrial malignancy, and thus endometrial sampling is not required (111). Endometrial polyps and other abnormalities can be seen in women who are taking *tamoxifen.* These polyps are more likely to involve cystic dilation of glands, stromal condensation around the glands, and squamous metaplasia of the overlying epithelium. These polyps can be benign, although they must be distinguished from endometrial malignancies, which may occur when taking *tamoxifen.* **[2]** The incidence of endometrial polyps not associated with *tamoxifen* increases with age during the reproductive years; it is not clear whether the incidence subsequently peaks or decreases during the postmenopausal years (12). Endometrial polyps are more likely to be malignant in postmenopausal women, and hypertension is associated with an increased risk of malignancy (112).

Neoplasia

Endometrial, cervical, and ovarian malignancies must be ruled out in the presence of postmenopausal bleeding. One series found a malignancy (endometrial or cervical) in approximately 10% of women with postmenopausal bleeding (113). **Cervical cytology testing is essential when postmenopausal bleeding is noted, although cytologic testing is an insensitive diagnostic tool for detecting endometrial cancer.** The cytology test results are negative in some cases of invasive cervical carcinoma because of tumor necrosis.

Cervical malignancy is diagnosed by cervical biopsy of grossly visible lesions and colposcopically directed biopsy for women with abnormal Pap test results (see Chapter 16). **Functional ovarian tumors may produce estrogen and lead to endometrial hyperplasia or carcinoma, which may cause bleeding.**

Diagnosis of Postmenopausal Abnormal Bleeding

Pelvic examination to detect local lesions and a Pap test to assess the cytology are essential first steps in finding the cause of postmenopausal bleeding. Pelvic ultrasonographic examination and, in particular, transvaginal ultrasonography or sonohysterography can suggest the cause of bleeding (111,114). **Endometrial sampling, through office biopsy, hysteroscopy, or D&C, is usually considered essential.** An endometrial thickness of less than 5 mm measured by transvaginal ultrasonography is unlikely to indicate endometrial cancer, and some authors suggest that the diagnostic accuracy is overestimated and recommend a cutoff of 3 mm (115).

Management of Postmenopausal Abnormal Bleeding

Benign Disorders

The management of bleeding caused by atrophic vaginitis includes topical (vaginal) or systemic use of estrogens after other causes of abnormal bleeding are excluded. Such therapy can provide significant benefits in terms of the quality of life, but must be weighed with each individual, considering contraindications and patient preferences (107). Serum levels appear to be lower with vaginal administration using creams, tablets, or rings (116). Cervical polyps can easily be removed in the office.

Endometrial Hyperplasia

The terminology used to describe endometrial hyperplasia is confusing, and the clinician must consult with the pathologist to ensure an understanding of the diagnosis to dictate correct management. In 2015, the ACOG and the Society of Gynecologic Oncology recommended that the **World Health Organization (WHO) system be replaced with the endometrial intraepithelial neoplasia (EIN) schema as described in Table 10-14 to distinguish benign lesions from those that are premalignant and should be managed more conservatively.**

Table 10-14 Nomenclature for Endometrial Hyperplasia

Class	Nomenclature	Treatment
Benign	Benign endometrial hyperplasia	Medical
Premalignant	Endometrial intraepithelial neoplasia (EIN), replaces atypical hyperplasia	Surgical vs. medical (desires fertility or poor surgical candidate)
Malignant	Endometrial adenocarcinoma, endometrioid type, well differentiated	Surgical +/– staging

The new nomenclature has three categories:

1. **Benign = Benign endometrial hyperplasia**
2. **Premalignant = EIN, replaces atypical hyperplasia**
3. **Malignant = Endometrial adenocarcinoma, endometrioid type, well differentiated**

Many pathologists still use the WHO system, which classifies endometrial hyperplasia as simple hyperplasia, complex hyperplasia, simple atypical hyperplasia, and complex atypical hyperplasia (117). Approximately 40% to 50% of women with atypical hyperplasia or EIN have concurrent carcinoma. **The management of endometrial hyperplasia is based on an understanding of the natural history of the lesion involved.** The risk of progression of hyperplasia without atypia is low but is approximately 30% among those with atypical hyperplasia (117). Hysterectomy is recommended as definitive treatment of EIN in postmenopausal women, and rules out

possible concurrent carcinoma. Management of endometrial cancer with surgical staging and multidisciplinary review of pathology and treatment planning is addressed in Chapter 37.

Progestin therapy (oral, parenteral, or intrauterine device delivery) has been used in women with EIN or endometrial cancer who are poor operative candidates (29,118). These women should have an endometrial biopsy every 3 months to check for recurrence, with recurrence risks approaching 50% (118). A suggested scheme of management is outlined in **Figure 10-18**. This treatment is discussed in more detail in Chapter 37.

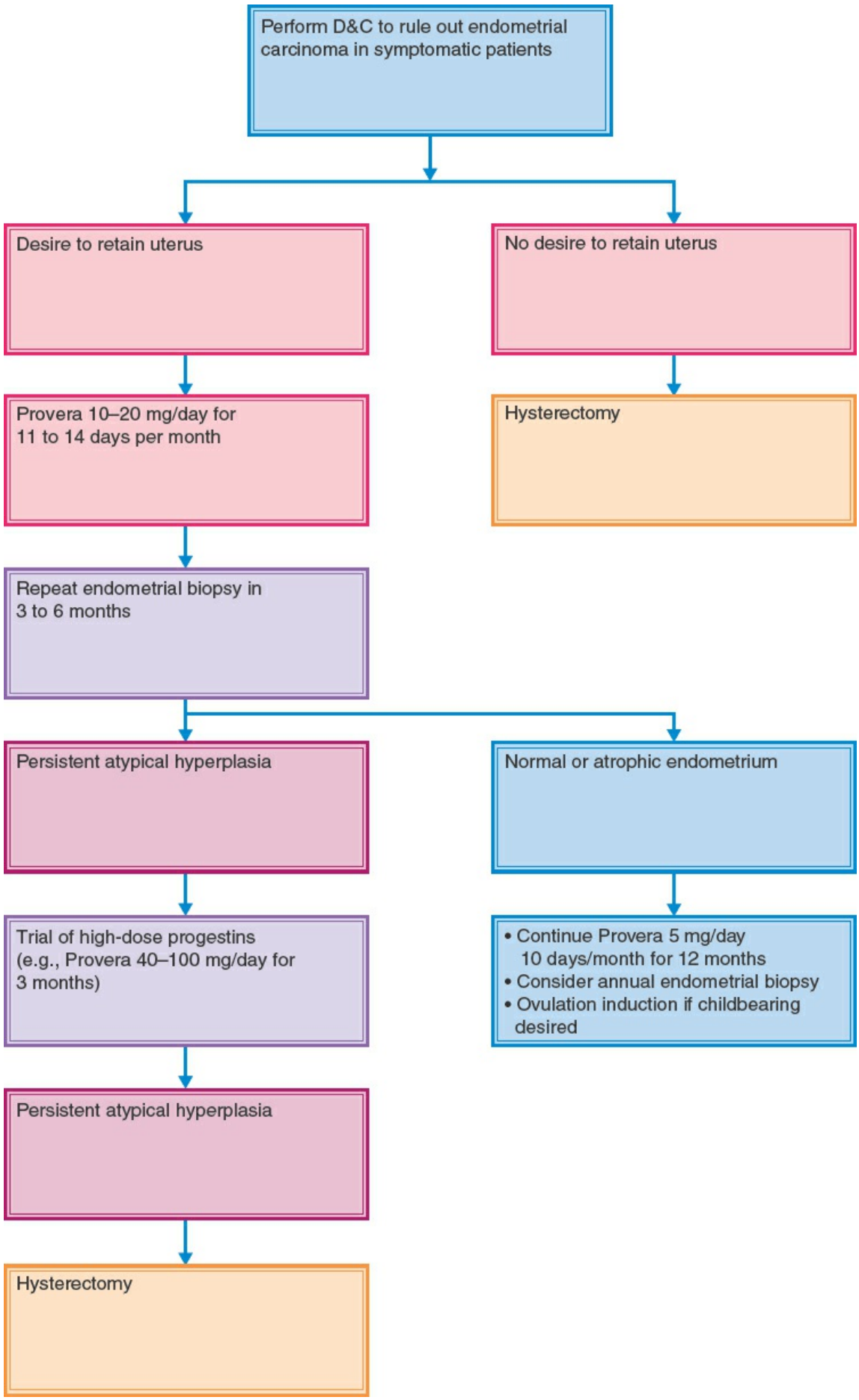

Perform D&C to rule out endometrial carcinoma in symptomatic patients
Desire to retain uterus
No desire to retain uterus
Provera 10–20 mg/day for 11 to 14 days per month
Hysterectomy
Repeat endometrial biopsy in 3 to 6 months
Persistent atypical hyperplasia
Normal or atrophic endometrium
Trial of high-dose progestins (e.g., Provera 40–100 mg/day for 3 months)
• Continue Provera 5 mg/day 10 days/month for 12 months
• Consider annual endometrial biopsy
• Ovulation induction if childbearing desired
Persistent atypical hyperplasia
Hysterectomy

FIGURE 10-18 Management of endometrial hyperplasia. (From **Hacker NF, Friedlander ML**. Uterine cancer. In: Berek JS, Hacker NF. *Berek & Hacker's Gynecologic Oncology*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2014: 404.)

Pelvic Masses

Differential Diagnosis

Ovarian Masses

During the postmenopausal years, the ovaries become smaller. Ovarian volume is related to age, menopausal status, weight, height, and the use of exogenous hormones (119). A large body habitus and uterine size make it more difficult to palpate and assess the ovarian size, particularly among postmenopausal women, and transvaginal ultrasonography is significantly more accurate than clinical examination. Transvaginal ultrasonography is suggested in addition to annual pelvic examination among overweight postmenopausal women (120). **[3]** Although ovarian cancer is notoriously difficult to diagnose at any early stage, the concept that it is frequently asymptomatic has been challenged. Symptoms may include back pain, fatigue, bloating, constipation, abdominal pain, and urinary symptoms; these symptoms are of greater severity and more recent onset in women with ovarian malignancy (121). It is argued that among primary clinicians, the possibility of an ovarian mass (either benign or malignant) in women with these symptoms warrants further diagnostic investigation. The positive predictive value of these symptoms is not high for the prediction of early-stage disease, and the use of symptoms to trigger an evaluation for ovarian cancer is noted to result in diagnosis of the disease in only 1 in 100 women in the general population with such symptoms (122). **[3]** Ovarian cancer is predominantly a disease of postmenopausal women; the incidence increases with age, and the average patient age is about 56 to 60 years (see Chapter 39).

With increased use of pelvic ultrasonographic evaluation, a new problem arose in postmenopausal women: the discovery of a small ovarian cyst. This is particularly troublesome in a woman who is entirely asymptomatic and whose ultrasonographic examination was performed for indications unrelated to pelvic pathology. It is suggested that **when the cyst is asymptomatic, small (<10 cm in diameter), unilocular, and thin walled, with a normal CA125 level, the risk of malignancy is extremely low and these masses can be followed conservatively, without surgery** (81,123,124). Surgery may be indicated in some women with a strong family history of ovarian, breast, endometrial, or colon cancer, or with a mass that appears to be enlarging (see Chapter 39). The addition of color flow Doppler examination and other ultrasonographic characteristics may be helpful in distinguishing benign from malignant masses, although the role of Doppler ultrasonography remains somewhat controversial **(Table 10-10)** (81).

[5] Many postmenopausal women have not had regular gynecologic care, and the discovery of a pelvic mass may reflect the persistence of a uterine leiomyoma that previously was not discovered. The possibility of transient ovarian cysts is noted above, and it may be difficult to distinguish an ovarian from a uterine mass. Some women may not remember having been told they had a pelvic mass. Thus, **a review of medical records may be helpful in determining the pre-existence of a benign pelvic mass.** Uterine leiomyomas are hormonally responsive and typically decrease in size or resolve after menopause (see Chapter 11).

Diagnosis of Postmenopausal Pelvic Mass

A personal and family medical history is helpful in detecting individuals at increased risk for the development of ovarian cancer. Several hereditary family cancer syndromes involve ovarian neoplasms (see Chapter 39). **Patients with hereditary forms of epithelial ovarian cancer account for only a small percentage of all cases; 90% to 95% of cases of ovarian cancer are sporadic and without identifiable heritable risk.**

In postmenopausal women with a pelvic mass, a CA125 measurement may be helpful in predicting a higher likelihood of a malignancy, which may guide decisions regarding management, consultation, or referral. A high index of suspicion by women and their clinicians represents the best way to detect early ovarian cancer. Persistent symptoms such as an increase in abdominal size, bloating, fatigue, abdominal pain, indigestion, inability to eat normally, urinary frequency, pelvic pain, constipation, back pain, new onset of urinary incontinence, or unexplained weight loss require evaluation and consideration of the possibility of ovarian cancer. **A normal CA125 level does not rule out ovarian cancer; up to 50% of early-stage ovarian malignancies and 20% to 25% of advanced cancers have normal values of CA125** (125).

Management of Postmenopausal Pelvic Mass

The use of improved imaging techniques may allow the nonoperative management of ovarian masses that are probably benign **(Table 10-10)**. **A suspicious or persistent complex mass requires surgical evaluation. Patients with masses that are clinically suspicious for cancer should be offered the opportunity of a preoperative consultation with a gynecologic** oncologist, a physician trained to appropriately stage and debulk ovarian cancer to optimize the patient's outcome (126). Comprehensive surgical staging facilitates appropriate therapy and optimizes prognosis.

Vulvar Conditions

Anatomic changes that occur in postmenopausal women include atrophy of the labia majora and increasing prominence of the labia minora. The epithelium of the hymen and vestibule become thin; there is a shift in vaginal cellular maturation in response to estrogen deprivation, with resultant thinning. Although these changes lead to minimal symptoms in most women, external dysuria, pruritus, tenderness, dyspareunia, and bleeding can result from fissuring and excoriations. **Because of the risk of VIN and malignancy, suspicious lesions require vulvar biopsy.**

Vulvar Dermatoses

Several vulvar conditions occur most commonly in postmenopausal women. Symptoms are primarily itching and vulvar soreness, in addition to dyspareunia.

In the past, numerous terms were used to describe disorders of vulvar epithelial growth that produce a number of nonspecific gross changes. These terms included *leukoplakia, lichen sclerosus,* and *atrophicus, atrophic* and *hyperplastic vulvitis,* and *kraurosis vulvae.* The ISSVD in 2006 recommended a classification of vulvar dermatoses based on histologic patterns, listed with the likely clinical diagnoses, rather than on the basis of clinical morphology as in the previous categorization (see Chapter 12) (127). This classification system excludes neoplastic and infectious conditions. Vulvar conditions that are described in this classification system include atopic, allergic, and irritant contact dermatitis, psoriasis, lichen simplex chronicus, lichen sclerosus, lichen planus, pemphigoid, aphthous ulcers, Behçet disease, and Crohn disease.

Lichen Sclerosus

Lichen sclerosus is the most common white lesion of the vulva. Lichen sclerosus can occur at any age, although it is most common among postmenopausal women and prepubertal girls (Fig. 10-19). The symptoms are pruritus, dyspareunia, and burning. Lichen sclerosus characteristically is associated with decreased subcutaneous fat to the extent that the vulva is atrophic, with small or absent labia minora, obliteration of the anatomic landmarks, thin labia majora, and sometimes phimosis of the prepuce. The surface is pale with a shiny, crinkled pattern (described as having characteristics like “cigarette paper”), often with fissures and excoriation. The lesion tends to be symmetric and often extends to the perineal and perianal areas. The diagnosis is confirmed by biopsy. Invasive cancer is associated with lichen sclerosus, although the significance of this association is unclear in terms of causation (128).



FIGURE 10-19 Prepubertal lichen sclerosus.

Treatment is with an ultrapotent topical steroid such as 0.05% *clobetasol.* Approximately 96% of patients respond satisfactorily (129). Maintenance therapy is frequently required, and a graduated reduction from ultrapotent to medium- and low-potency topical steroids can help to maintain remission of symptoms (130). The topical calcineurin inhibitors *pimecrolimus* and *tacrolimus* were effective in individuals not responding to topical steroids, although the FDA approved a warning suggesting possible risk of cancer from this class of drugs and caution is advised with long-term use avoided (131).

Premalignant Vulvar Lesions

Squamous VIN is seen most often in postmenopausal women but may occur during the reproductive years. Pruritus is the most common symptom, although "lumps" may be described and are sometimes confused with condyloma (132). Current terminology describes two types of VINs: VIN, usual type, that is typically HPV-related and encompassing former VIN-2 and -3 with warty, basaloid, and mixed types; and VIN, differentiated type (133). The lesion appears thickened and hyperkeratotic, and there may be excoriation. Lesions may be discrete but may be symmetric and multiple. About one-third of women will have a history of HPV-related cervical disease or condyloma (132). Most women with VIN are smokers. Biopsy is necessary to confirm the diagnosis and to exclude malignancy. See Chapter 16 for management of VIN.

Urethral Lesions

The urethra and vagina have a common embryonic origin and are steroid-dependent tissues. Urethral caruncles and prolapse of the urethral mucosa are examples of vulvar lesions that may be seen in other age groups but that occur more commonly among older women. Both conditions can be treated with topical or systemic estrogen preparations. Various vulvar skin lesions, including seborrheic keratoses and cherry hemangiomas (senile hemangiomas), occur more commonly on aging skin.

Vaginal Conditions

Up to half of postmenopausal women have symptoms of atrophic vaginitis, although many do not seek therapy. Symptoms include an external dysuria, pruritus, tenderness, dyspareunia, and bleeding from fissuring or ulcerations. In addition to the clinical findings of a shiny, flat, thin-appearing vaginal mucosa without rugae, microscopic examination of vaginal secretions reveals an increased number of white blood cells. **Treatment with local or systemic estrogens effectively manages the symptoms and restores normal pH levels with ongoing therapy** (134). Systemic absorption does occur with topical estrogen therapy, and rates of absorption differ depending on the

degree of atrophy. Topical emollients may be helpful if estrogens are not desired or are contraindicated. Vaginal lubricants are universally useful in minimizing symptoms of dyspareunia for postmenopausal women (135).

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CHAPTER 11

Uterine Fibroids



William H. Parker

Origins of Uterine Fibroids
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- Etiology
- Genetics
- Hormones
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- Risk Factors

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Endometrial Ablation for Abnormal Bleeding Associated With Fibroids
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Clinical Follow-Up
Prognostic Factors Related to New Appearance of Fibroids
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Uterine Artery Embolization Technique
Uterine Artery Embolization Outcomes
Uterine Artery Occlusion
Magnetic Resonance–Guided Focused Ultrasound
Management Summary

KEY POINTS

1 Fibroids are very common; most are asymptomatic and can be managed expectantly.

2 There is no definite relationship between oral contraceptives and the presence of fibroids.

3 First-degree relatives of women with fibroids have a 2.5 times increased risk of developing fibroids.

4 The risk of having fibroids is 2.9 times greater in African American women than in white women.

5 Women with fibroids are only slightly more likely to experience pelvic pain than women without fibroids.

6 Rapid uterine growth is not well defined, and almost never indicates sarcoma in premenopausal women; sarcomas are rare and more likely occur in postmenopausal women with symptoms of pain and bleeding.

7 Sonography is the most readily available and least costly imaging technique to differentiate fibroids from other pelvic pathology; however, MRI permits more precise evaluation of the number, size, and position of fibroids, including the proximity to the endometrial cavity.

8 The presence of submucosal fibroids decreases fertility and removing them can increase fertility; subserosal fibroids do not affect fertility and removing them does not increase fertility; intramural fibroids may slightly decrease fertility, but removal does not increase fertility.

9 Most fibroids do not increase in size during pregnancy.

10 For women who are mildly or moderately symptomatic with fibroids, watchful waiting may allow treatment to be deferred, perhaps indefinitely.

11 As women approach menopause, watchful waiting may be considered because there is limited time to develop new symptoms, and after menopause bleeding stops and fibroids decrease in size.

12 Surgical treatment options include abdominal myomectomy, laparoscopic myomectomy, laparoscopic radiofrequency ablation, hysteroscopic myomectomy, endometrial ablation, and abdominal, vaginal, or laparoscopic hysterectomy.

13 An inability to evaluate the ovaries on pelvic examination is not an indication for surgery.

14 Myomectomy should be considered as a safe alternative to hysterectomy, even for those women

who have large uterine fibroids and wish to retain their uterus.

15 Submucous fibroids, sometimes associated with increased menstrual bleeding or infertility, often can be removed hysteroscopically.

16 Routine ultrasound follow-up is sensitive, and may detect many clinically insignificant fibroids.

17 Uterine artery embolization (UAE) is an effective treatment for selected women with uterine fibroids. The effects of UAE on early ovarian failure, fertility, and pregnancy are unclear.

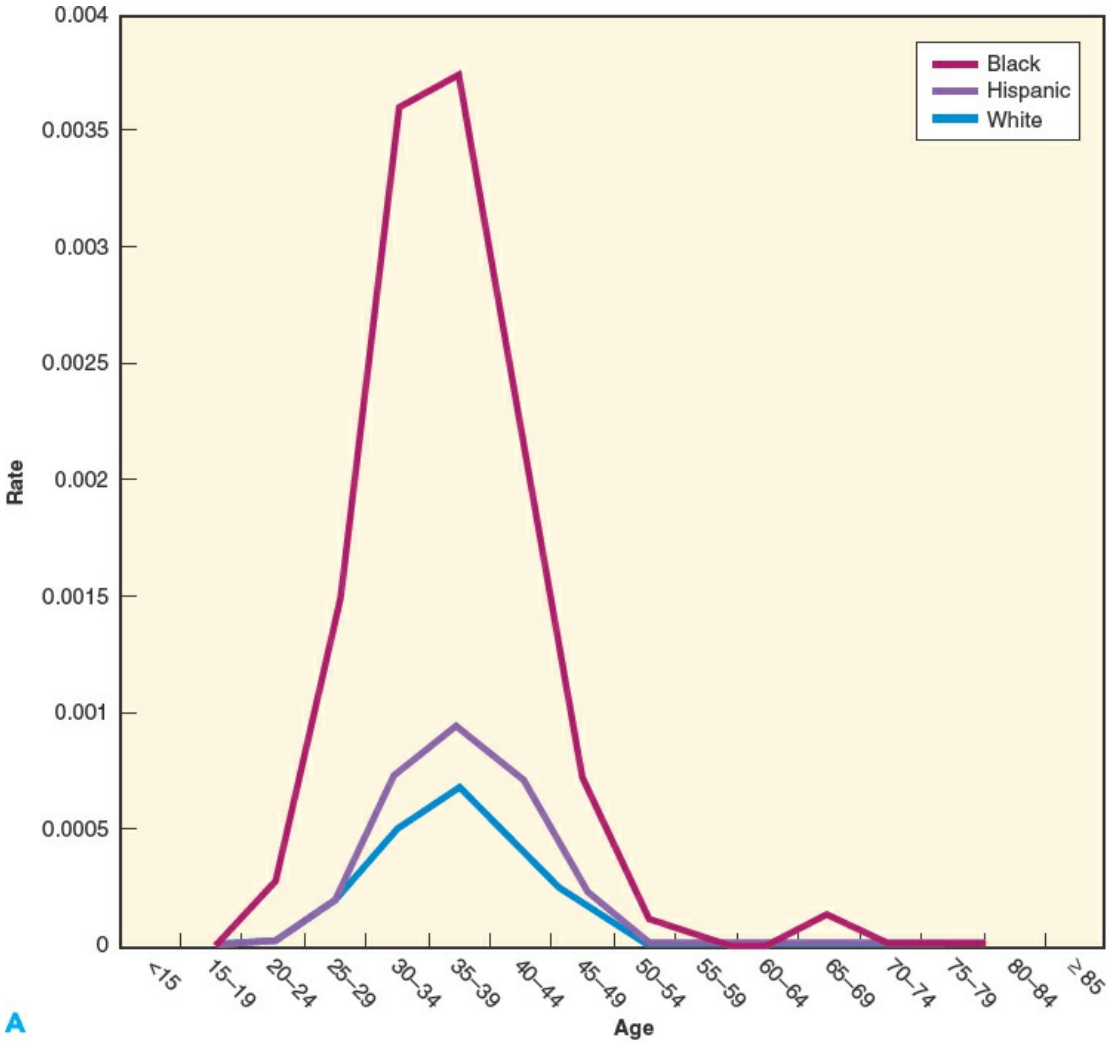
Fibroids (leiomyomas, myomas) are an important health care concern because they are the most frequent indication for the performance of hysterectomy, accounting for nearly 240,000 such procedures in the United States (1). In comparison, approximately 30,000 myomectomies are performed every year. Inpatient surgery for fibroids costs $2.1 billion per year in the United States, and the cost of outpatient surgeries, medical and nonmedical costs, and time away from work or family add significantly to these expenditures (2).

ORIGINS OF UTERINE FIBROIDS

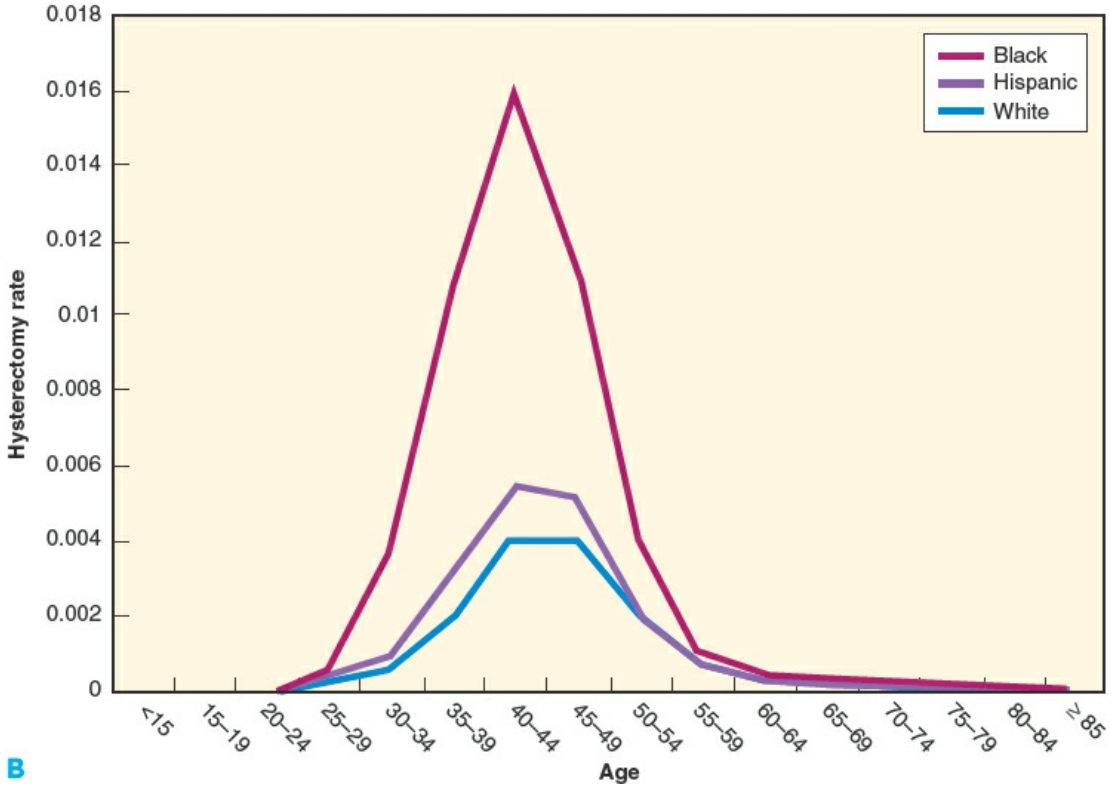
Fibroids **are benign, monoclonal tumors of the smooth muscle cells of the myometrium** and contain large aggregations of extracellular matrix composed of collagen, elastin, fibronectin, and proteoglycan (3).

Incidence

[1] Fibroids are remarkably common. Fine serial sectioning of uteri from 100 consecutive women subjected to hysterectomy discovered fibroids in 77%, some as small as 2 mm (4). A random sampling of women aged 35 to 49, screened by self-report, medical record review, and sonography, found that among African American women by age 35 the incidence of fibroids was 60%, and it was over 80% by age 50 **(Fig. 11-1)**. White women have an incidence of 40% at age 35 and almost 70% by age 50 (5).


0.004
0.0035
0.003
0.0025
0.002
0.0015
0.001
0.0005
0
Rate
Black
Hispanic
White
<15
15–19
20–24
25–29
30–34
35–39
40–44
45–49
50–54
55–59
60–64
65–69
70–74
75–79
80–84
≥85
Age

A


0.018
0.016
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
Hysterectomy rate
Black
Hispanic
White
<15
15–19
20–24
25–29
30–34
35–39
40–44
45–49
50–54
55–59
60–64
65–69
70–74
75–79
80–84
≥85
Age

B

FIGURE 11-1 **A:** Age- and race-specific incidence of myomectomy, 1997, based on NIS and U.S. Census Bureau estimates. **B:** Age- and race-specific incidence of hysterectomy for fibroids, 1997, based on NIS and U.S. Census Bureau estimates. (From Health Services/Technology Assessment Tests [HSTAT]. Available online at http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.section.48317.)

Etiology

Although the precise causes of fibroids are unknown, advances have been made in understanding the molecular biology of these benign tumors and their hormonal, genetic, and growth factors (6).

Genetics

Fibroids are monoclonal and are made up of concentric smooth muscle fibers and fibrous connective tissue surrounded by a vascular pseudocapsule. Some authors postulate that hypoxic conditions, perhaps associated with menstruation, induce mutations in a single myometrial smooth muscle stem cell. Approximately 40% to 50% of fibroids display nonrandom and tumor-specific chromosome rearrangements involving mostly deletions, duplications, and translocations of chromosomes 6, 7, 12, and 14. These complex molecular changes affect energy metabolism, extracellular matrix remodeling, and estrogen and progesterone receptor status.

Growth factors, small proteins that act as signaling molecules, interact with specific receptors on the cell surface and are important for the development of fibroids. Transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and insulinlike growth factor (IGF) modulate cellular growth, proliferation, and differentiation. The TGF-β family upregulates the synthesis of many extracellular matrix components that increase the fibrous component of fibroids. Proliferation of smooth muscle cells are induced by bFGF, which promotes angiogenesis. Estrogen and progesterone influence fibroid development by regulating growth factors and their signaling pathways. Fibroids may be affected by environmental chemicals, which can increase or decrease estrogen and/or progesterone receptors.

Genetic differences between fibroids and leiomyosarcomas (LMSs) indicate that LMSs do not result from the malignant degeneration of fibroids. Cluster analysis of 146 genes found that the majority are downregulated in LMSs but not in fibroids or myometrium. Comparative genomic hybridization did not find specific anomalies shared by fibroids and LMSs (7).

Hormones

Estrogen and progesterone appear to promote the development of fibroids.

Fibroids are rarely observed before puberty, are most prevalent during the reproductive years, and regress after menopause. Factors that increase overall lifetime exposure to estrogen, such as obesity and early menarche, increase the incidence. Decreased exposure to estrogen found with smoking, exercise, and increased parity is protective (8).

Serum levels of estrogen and progesterone are similar in women with and without clinically detectable fibroids. As a result of increased levels of aromatase within fibroids, *de novo* production of estradiol is higher than in normal myometrium (8). Progesterone is important in the pathogenesis of fibroids, which have increased concentrations of progesterone receptors A and B compared with normal myometrium (9,10). The highest mitotic counts are found in fibroids at the peak of progesterone production (11). Gonadotropin-releasing hormone (GnRH) agonists decrease the size of fibroids, but progestin given concurrently with GnRH prevents a decrease in size (12).

Human fibroid tissue, grafted to immunodeficient mice, increased in size in response to estradiol plus progesterone, but the growth was blocked by the antiprogestin *RU486* (12). The volume of grafted fibroid tissue decreased after progesterone withdrawal. Treatment with estradiol alone did not increase the graft size, but did induce expression of progesterone receptors and supported the action of progesterone on the grafts (12).

Growth Factors

Growth factors, proteins, or polypeptides, produced locally by smooth muscle cells and fibroblasts, appear to stimulate fibroid growth primarily by increasing extracellular matrix (6). Many of these growth factors are overexpressed in fibroids and either increase smooth muscle proliferation (TGF-β, bFGF), increase DNA synthesis (epidermal growth factor [EGF], PDGF), stimulate synthesis of extracellular matrix (TGF-β), promote mitogenesis (TGF-β, EGF, IGF, prolactin [PRL]), or promote angiogenesis (bFGF, VEGF).

Risk Factors

Prospective, longitudinal studies characterize the factors that influence the development of uterine fibroids (4,13,14). Although selection bias may limit epidemiologic studies, risk factors are considered.

Age

The incidence of fibroids increases with age, 4.3 per 1,000 woman-years for 25 to 29 year olds and 22.5 for 40 to 44 year olds. African American women develop fibroids at an earlier age than white women (13).

Endogenous Hormonal Factors

Greater exposure to endogenous hormones, as found with early menarche (younger than 10 years of age), increases and late menarche decreases the likelihood of having uterine fibroids (14). Fibroids are smaller, less numerous, and have smaller cells in hysterectomy specimens from postmenopausal women, when endogenous estrogen levels are low (4,15).

Family History

[3] First-degree relatives of women with fibroids have a 2.5 times increased risk of developing fibroids (26). Monozygous twins are reportedly hospitalized for treatment of fibroids more often than heterozygous twins, but these findings may be the result of reporting bias (27).

Ethnicity

[4] African American women have a 2.9 times greater risk of having fibroids than white women, unrelated to other known risk factors (28). African American women have fibroids develop at a younger age and have more numerous, larger, and more symptomatic fibroids (29). It is unclear whether these differences are genetic or result from known differences in circulating estrogen levels, estrogen metabolism, diet, or environmental factors.

Weight

A prospective study found that the risk of fibroids increased 21% with each 10 kg increase in body weight, and with increasing body mass index (BMI) (20). Similar findings were reported in women with greater than 30% body fat (21). Obesity increases conversion of adrenal androgens to estrone and decreases the sex hormone–binding globulin (SHBG). The result is an increase in biologically available estrogen, which may explain the increase in fibroid prevalence and/or growth.

Diet

Few studies examined the association between diet and the presence or growth of fibroids (22). A diet rich in beef, other red meat, and ham increased the incidence of fibroids, while a diet rich in green vegetables decreased this risk. These findings are difficult to interpret because calorie and fat intake were not measured.

Exercise

Women in the highest category of physical activity (approximately 7 hours per week) were significantly less likely to have fibroids than women in the lowest category (less than 2 hours per week) (23).

Oral Contraceptives

[2] There is no definite relationship between oral contraceptives and the presence

of fibroids. An increased risk of fibroids with oral contraceptive use was reported, but a subsequent study found no increased risk with the use or duration of use (24,25). Studies in women with known fibroids who were prescribed oral contraceptives showed no increase in fibroid growth (20,26). The formation of new fibroids does not appear to be influenced by oral contraceptive use (27).

Menopausal Hormone Therapy

For the majority of postmenopausal women with fibroids, hormone therapy will not stimulate fibroid growth. If fibroids do grow, progesterone is likely to be the cause (28). One study evaluated postmenopausal women with fibroids who were given 2 mg of oral *estradiol* daily and randomized to 2.5 or 5 mg of *medroxyprogesterone acetate* (*MPA*) per day (28). One year after starting treatment, 77% of women taking 2.5-mg *MPA* had either no change or a decrease in fibroids diameters and 23% had a slight increase. However, 50% of women taking 5-mg *MPA* had an increase in fibroid size (mean diameter increase of 3.2 cm).

Postmenopausal women with fibroids treated with 0.625 of *conjugated equine estrogen* (*CEE*) and 5-mg *MPA* were compared over 3 years to a similar group of women not taking hormone therapy (29). By the end of the third year, only 3 of 34 (8%) treated and 1 of 34 (3%) untreated women had any increase in fibroid volume over baseline (28). Postmenopausal women with known fibroids, followed with sonography, were noted to have an average 0.5-cm increase in the diameter of fibroid after using transdermal *estrogen* patches plus oral *progesterone* for 12 months (29). Women taking oral *estrogen* and *progesterone* had no increase in fibroid size (34).

Pregnancy

Increasing parity decreases the incidence and number of clinically apparent fibroids (31–33). The remodeling process of the postpartum myometrium, a result of apoptosis and dedifferentiation, may be responsible for the involution of fibroids (34). Another theory postulates that the vessels supplying fibroids regress during involution of the uterus, depriving fibroids of their source of nutrition (35).

Smoking

Smoking reduces the incidence of fibroids. Reduced conversion of androgens to estrone, caused by inhibition of aromatase by nicotine, increased 2-hydroxylation of estradiol, and stimulation of higher levels of SHBG decrease bioavailability of estrogen (36–38).

Tissue Injury

Cellular injury or inflammation resulting from an environmental agent, infection, or hypoxia was proposed as a mechanism for initiation of fibroid formation (39). Repetitive tissue injury to the endometrium and endothelium might promote the development of monoclonal smooth muscle proliferations in the muscular wall.

Frequent mucosal injury with stromal repair (menstruation) may release growth factors that promote the high frequency of uterine fibroids (39).

No increased incidence was found in women with prior sexually transmitted infections, prior intrauterine device (IUD) use, or prior talc exposure (31). Herpes simplex virus (HSV) I or II, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and chlamydia were not found in fibroids.

SYMPTOMS

Fibroids are almost never associated with mortality, but they may cause morbidity and significantly affect the quality of life (40). **Women who have hysterectomies because of fibroid-related symptoms have significantly worse scores on SF-36 quality-of-life questionnaires than women diagnosed with hypertension, heart disease, chronic lung disease, or arthritis** (40).

Of 116 women with fibroids larger than 5 cm on sonographic examination and uterine size greater than 12 cm on pelvic examination, 42% were satisfied with their initial level of symptoms, including stress, bleeding, and pain (41). Most of the 48 women who chose to have treatment within 1 year were more likely to have higher scores on bleeding and pain scales and be more concerned about their symptoms. Most women chose myomectomy ($n = 20$), hysterectomy ($n = 15$), or hysteroscopic myomectomy ($n = 4$), and symptom scores improved markedly during the 7.5 months (mean) of follow-up.

Abnormal Bleeding

The association of fibroids with heavy menstrual bleeding is not clearly established. Therefore, other possible etiologies, including coagulopathies such as the von Willebrand disease, should be considered in a woman with heavy menstrual bleeding (42).

Type 0 and 1 fibroids have been associated with anemia. Of 1,665 women having office hysteroscopic evaluation for heavy menstrual bleeding, 259 women had a submucous fibroid diagnosed; 63 were type 0, 110 type 1, and 52 were type 2 (25 were not documented). Hemoglobin concentrations below 12 were significantly associated with submucous fibroids and most strongly correlated with type 0 fibroids (43).

Another study found that women with fibroids used 7.5 pads or tampons on the heaviest day of bleeding compared with 6.1 pads or tampons used by women without fibroids (44). Women with fibroids larger than 5 cm had slightly more gushing and used about 3 more pads or tampons on the heaviest day of bleeding than women with smaller fibroids.

Pain

[5] Women with fibroids are only slightly more likely to experience pelvic pain than women without fibroids. Transvaginal sonography (TVS) was performed on a population-based cohort of 635 non–care-seeking women with an intact uterus to determine the presence of uterine fibroids (45). Dyspareunia, dysmenorrhea, or noncyclic pelvic pain was measured by visual analog scales. The 96 women found to have fibroids were only slightly more likely to report moderate or severe dyspareunia or noncyclic pelvic pain and had no higher incidence of moderate or severe dysmenorrhea than women without fibroids. Neither the number nor the total volume of fibroids was related to pain. However, women who present for clinical evaluation for fibroid-associated pain may be different from those in the general population (45).

Fibroid degeneration may cause pelvic pain. As fibroids enlarge, they may outgrow their blood supply, with resulting cell death (46). Types of degeneration determined both grossly and microscopically include hyaline degeneration, calcification, cystic degeneration, and hemorrhagic degeneration. The type of degeneration appears to be unrelated to the clinical symptoms (46). Pain from fibroid degeneration is often successfully treated with analgesics and observation. Torsion of a pedunculated subserosal fibroid may produce acute pelvic pain that requires surgical intervention (47).

Urinary Symptoms

Fibroids may cause urinary symptoms, although few studies examined this association. Following uterine artery embolization (UAE) with a 35% reduction in the mean uterine volume, frequency and urgency were greatly or moderately improved in 68% of women, slightly improved in 18%, and unchanged or worse in only 14% (48). This finding suggests that **increased uterine volume associated with fibroids is related to urinary symptoms.**

Fourteen women with large fibroids and urinary symptoms were given six monthly injections of GnRH agonist (GnRH-a) with a resulting 55% decrease in uterine volume (49). Following therapy, urinary frequency, nocturia, and urgency decreased. There were no changes in urge or stress incontinence as measured by symptoms or urodynamic studies. It is not clear whether these findings are related to a decrease in uterine volume or to other effects of GnRH treatment.

NATURAL HISTORY OF FIBROIDS

Most fibroids grow slowly. A prospective, longitudinal study of 72 premenopausal women (38 African American, 34 white) using computer analysis of serial MRI found that the median growth rate was 9% over 12 months (13). Multiple fibroids in the same individual were found to have highly variable growth rates, suggesting that growth

results from factors other than hormone levels. After age 35, growth rates declined with age for white women but not for African American women, which likely explains the increased fibroid-related symptoms noted in African American women. Seven percent of fibroids regressed over the study period. Continued follow-up of these women is planned and may provide a better understanding of this issue.

Rapid Fibroid Growth

[6] In premenopausal women, "rapid uterine growth" almost never indicates the presence of uterine sarcoma. One study found only 1 sarcoma among 371 (0.26%) women operated on for rapid growth of presumed fibroids (50). No sarcomas were found in the 198 women who had a 6-week increase in uterine size over 1 year, which is the definition of rapid growth that was used in the past.

Uterine Sarcoma

Women found to have uterine sarcoma are often clinically suspected of having a pelvic malignancy (50,51). **Women with pain and bleeding and who are closer to menopause or postmenopausal may have a rare sarcoma. Of nine women found to have uterine sarcomas, all were postmenopausal and eight were admitted with abdominal pain and vaginal bleeding** (51). All eight had presumed gynecologic malignancies: uterine sarcoma in four, endometrial carcinoma in three, and ovarian cancer in one. One additional woman had surgery for prolapse and a sarcoma was found incidentally (51).

The Surveillance, Epidemiology, and End Results (SEER) database identified 13,089 patients diagnosed with uterine sarcoma in the period from 2000 to 2012. The mean age of patients with sarcomas was 68 for carcinosarcoma; 55 for LMS; 54 for stromal sarcoma; and 59 for adenosarcoma (52). A literature review found a mean age of 36 years in women subjected to myomectomy (50).

DIAGNOSIS

Pelvic Examination

Clinically significant subserosal and intramural fibroids can usually be diagnosed by pelvic examination based on findings of an enlarged, irregularly shaped, firm, and nontender uterus. Uterine size assessed by bimanual examination, even for most women with BMI greater than 30, correlates well with uterine size and weight at pathologic examination (53). Routine sonographic examination is not necessary when the diagnosis is almost certain. A definite diagnosis of submucous fibroids often requires saline-infusion sonography (SIS), hysteroscopy, or magnetic resonance imaging

(MRI) (54).

Fibroid Location

The FIGO fibroid classification system categorizes submucous, intramural, subserosal, and transmural fibroids.

***Type 0*—intracavitary (e.g., a pedunculated submucosal fibroid entirely within the cavity)**

***Type 1*—less than 50% of the fibroid diameter within the myometrium**

***Type 2*—50% or more of the fibroid diameter within the myometrium**

***Type 3*—abut the endometrium without any intracavitary component**

***Type 4*—intramural and entirely within the myometrium, without extension to either the endometrial surface or to the serosa**

***Type 5*—subserosal at least 50% intramural**

***Type 6*—subserosal less than 50% intramural**

***Type 7*—subserosal attached to the serosa by a stalk**

***Type 8*—no involvement of the myometrium; includes cervical lesions, those in the round or broad ligaments without direct attachment to the uterus, and "parasitic" fibroids**

Transmural fibroids are categorized by their relationship to both the endometrial and the serosal surfaces, with the endometrial relationship noted first, for example, types 2 to 3 (Table 11-1; Fig. 11-2) (55).

Table 11-1 FIGO Leiomyoma Classification System

SM—submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O—other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify, e.g., cervical, parasitic)
Hybrid leiomyomas		Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers

(impact both endometrium and serosa)		to the relationship to the serosa. One example is given below.
	2–5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

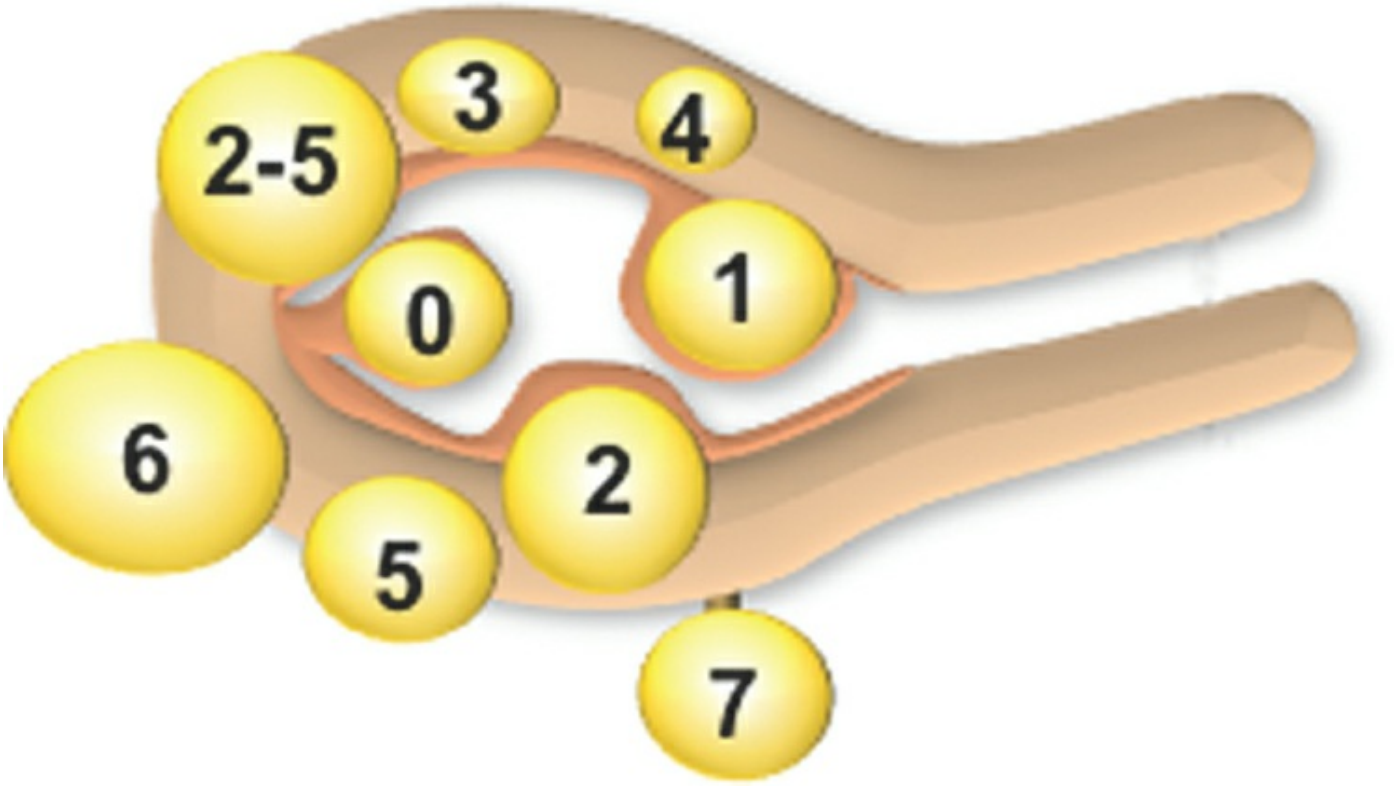


FIGURE 11-2 FIGO leiomyoma classification system.

Fibroid Variants

A number of benign uterine smooth muscle tumors have been defined according to histologic criteria issued by the World Health Organization. Mitotically active leiomyoma is defined by the presence of 10 to 15 mitoses/10 high-power fields (hpf) and may be seen in patients who are pregnant or are using exogenous hormones.

Increased cellularity, higher than that of nearby myometrium, is defined as a cellular leiomyoma. Taran et al. reported a series of women treated for cellular leiomyomas and 2 of 99 patients (2%) had recurrent disease (56). One study suggested that cellular leiomyomas exhibiting chromosome 1p deletions, a genetic alteration found in LMS, may be clinically more aggressive and require more intense surveillance (57).

Leiomyoma with bizarre nuclei (also called atypical or symplastic) shows scattered large atypical cells. Ly et al. described 34 patients with atypical leiomyomas undergoing hysterectomy and 4 had recurrent disease (12%) (58).

Smooth muscle tumors of uncertain malignant potential (STUMP) show atypical histologic features that range between leiomyoma and LMS, uncertain types of necrosis,

the presence of focal or diffuse cytologic atypia but the mitotic count is less than 10/10 hpf, the presence of coagulative tumor necrosis but mitosis is less than 10/10 hpf, and cellular tumors with more than 15 mitoses/10 hpf. Rarely STUMPs, mostly those that are p53 and p16 positive, have been found to exhibit malignant potential to develop a low-grade LMS (not high-grade). Guntupalli et al. reported a series of 41 patients with STUMPs: three (7.3%) had recurrence (all local and distant) after undergoing a total abdominal hysterectomy, and one of the recurrences was an LMS (59).

LMSs exhibit hypercellularity, diffuse moderate-to-marked nuclear atypia, a high mitotic rate (≥10/hpf), and tumor cell necrosis. LMS is an aggressive cancer and has a poor prognosis caused by early hematogenous spread, even in early-stage disease. The 5-year survival for stage I LMS is 61% and for stages III and IV is about 30%. Pritts et al. published a rigorous meta-analysis of 133 studies of women having surgery for presumed fibroids and determined that the prevalence of LMS was 1 in 1,960, or 0.051% (60). The Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services updated the analysis, added 91,294 more surgeries, and calculated a prevalence of LMS of 1 in 1,429 (0.07%) cases of surgery for presumed fibroids (61).

There is no reliable method of preoperative diagnosis of LMS available and it is difficult to differentiate this disease from benign fibroids.

Imaging

For symptomatic women, consideration of medical therapy, noninvasive procedures, or surgery often depends on an accurate assessment of the size, number, and position of fibroids. TVS, SIS, hysteroscopy, and MRI were all performed on 106 women scheduled for hysterectomy and the findings were compared to pathologic examination (54). **[7]** Submucous fibroids were best identified with MRI (sensitivity 100%, specificity 91%). Identification was about equal with TVS (sensitivity 83%, specificity 90%), SIS (sensitivity 90%, specificity 89%), and hysteroscopy (sensitivity 82%, specificity 87%). MRI is not technique dependent and has low interobserver variability for diagnosis of submucous fibroids, intramural fibroids, and adenomyosis when compared with TVS, SIS, and hysteroscopy (62,63).

The presence of adenomyosis is associated with junctional zone thickness of more than 15 mm (or 12 mm in a nonuniform junctional zone). Focal, not well-demarcated, and high- or low-intensity areas in the myometrium correlate with adenomyosis (65).

MRI allows evaluation of the number, size, and position of submucous, intramural, and subserosal fibroids and can evaluate their proximity to the bladder, rectum, and endometrial cavity. MRI helps define what can be expected at surgery and may help the surgeon avoid missing fibroids during surgery (66). For women who wish to preserve fertility, MRI to document location and position relative to the endometrium may be

helpful prior to hysteroscopic, laparoscopic, or abdominal myomectomy.

[7] Sonography is the most readily available and least costly imaging technique to differentiate fibroids from other pelvic pathology. It is reasonably reliable for evaluation of uterine volume less than 375 cc and containing four or fewer fibroids (62). Sonographic appearance of fibroids can be variable, but often they appear as symmetrical, well-defined, hypoechoic, and heterogeneous masses. Areas of calcification or hemorrhage may appear hyperechoic, while cystic degeneration may appear anechoic. SIS utilizes saline inserted into the uterine cavity to provide contrast and better defines submucous fibroids (62).

Imaging of Uterine Sarcomas

The preoperative diagnosis of LMS may be possible. Diagnosis with total serum lactate dehydrogenase (LDH) and LDH isoenzyme 3 measurements along with gadolinium-enhanced diethylenetriamine pentaacetic acid (Gd-DTPA) dynamic MRI was reported to be highly accurate (66). MRI images are taken during the arterial phase, between 40 and 60 seconds after infusion of gadolinium. Sarcomas have increased vascularity and show increased enhancement with gadolinium, while degenerating fibroids have decreased perfusion and exhibit decreased enhancement. Using LDH measurements and Gd-DTPA, a study of 87 women with uterine fibroids, 10 women with LMSs, and 130 women with degenerating fibroids reported 100% specificity, 100% positive predictive value, 100% negative predictive value, and 100% diagnostic accuracy for LMS **(Fig. 11-3)**.

A form of MRI functional imaging called diffusion-weighted imaging (DWI) has been used to distinguish between malignant and benign tumors. Malignant lesions have higher cellularity and nuclear area, which restrict water diffusion as measured by the apparent diffusion coefficient (ADC). Sixteen patients with uterine LMSs and 26 patients with degenerating fibroids confirmed by surgery and pathology underwent MRI and DWI. The mean ADC in LMSs was significantly lower than that in degenerating fibroids. The sensitivity and specificity were 100% and 90%. Other studies show conflicting results and DWI needs further investigation (67).

FERTILITY

[8] The presence of submucous fibroids decreases fertility rates and removing them increases fertility rates. Subserosal fibroids do not affect fertility rates but removing them does increase fertility. Intramural fibroids may slightly decrease fertility, but removal does not increase fertility (68). A meta-analysis of the effect of fibroids on fertility and the effect of myomectomy on fertility found that submucous fibroids that distort the uterine cavity appear to decrease fertility, with ongoing

pregnancy/live birth rates decreased by about 70% (relative risk [RR] 0.32; 95% confidence interval [CI], 0.12–0.85) (68). Resection of submucous fibroids slightly increased fertility relative to infertile controls without fibroids (ongoing pregnancy/live birth rate, RR 1.13; 95% CI, 0.96–1.33).

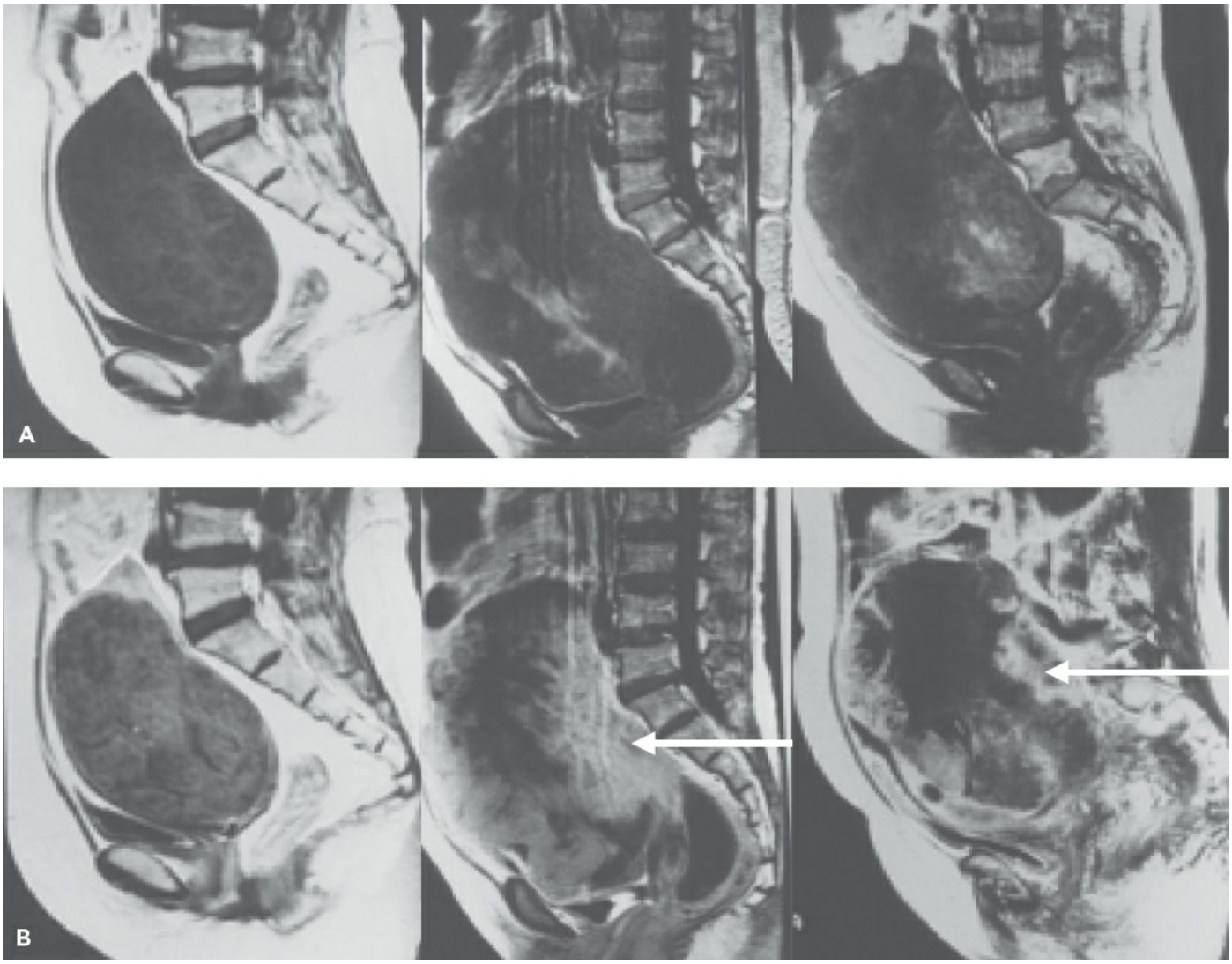


FIGURE 11-3 MR images. **A:** Degenerating fibroid. **Left to right.** Pre-enhanced T1 image, T2 image, and no enhancement on T1 Gd-DTPA at 60 seconds. **B:** Leiomyosarcoma. **Left to right.** Pre-enhanced T1 image, T2 image (*arrow* to dorsal part of tumor), and enhancement of dorsal part of tumor (*arrow*) on T1 Gd-DTPA at 60 seconds. (From **Goto A, Takeuchi S, Sugimura K, et al.** Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. Int J Gynecol Cancer 2002;12:354–361.)

Several studies have described the role of HOXA10 and HOXA11 transcription factors on uterine factor infertility associated with endometrial receptivity. In normal endometrium, BMP-2 upregulates HOXA10 expression. This process is absent in endometrial cells of women with submucous fibroids. The result is altered decidualization and inhibition of embryo implantation and decreased uterine factor

fertility (69).

Analysis of studies that routinely used hysteroscopy to confirm clear nondistortion of the cavity by intramural fibroids found ongoing pregnancy/live birth rates were not significantly different compared to controls (RR 0.73; 95% CI, 0.38–1.40) (66). Removal of intramural or subserosal fibroids did not improve ongoing pregnancy/live birth rates (RR 1.67; 95% CI, 0.75–3.72). Another study evaluated pregnancy rates for 102 women undergoing ovarian stimulation—intra-uterine insemination (OS-IUI) for unexplained infertility and who had at least one documented fibroid and a normal uterine cavity determined by hysterosonography or hysterosalpingogram. No differences were observed in conception and live birth rates in women with non–cavity-distorting fibroids and those without fibroids (70).

Myomectomy may involve operative and anesthetic risks, risks of infection or postoperative adhesions, a slight risk of uterine rupture during pregnancy, an increased likelihood that a cesarean section will be recommended for delivery, plus the expense of surgery and time for recovery. Therefore, until intramural fibroids are shown to decrease and myomectomy to increase fertility rates, surgery should be undertaken with reluctance (68). Randomized studies are needed to clarify the RRs and benefits of surgical intervention.

FIBROIDS AND PREGNANCY

Incidence of Fibroids During Pregnancy

The prevalence of fibroids among pregnant women is 18% in African American women, 10% in Hispanic women, and 8% in white women, based on first trimester sonography (71). Mean size of the fibroids was 2.5 cm. Clinical examination detects 42% of fibroids greater than 5 cm during pregnancy, but only 12.5% when they are less than 5 cm (72).

Effect of Pregnancy on Fibroids

[9] Most fibroids do not increase in size during pregnancy. Pregnancy has a variable, and unpredictable, effect on fibroid growth, likely dependent on individual differences in fibroid gene expression, circulating growth factors, and fibroid-localized receptors (72,73). A prospective study of 36 pregnant women with a single fibroid discovered during routine first trimester sonographic screening and examined by sonography at 2- to 4-week intervals found that 69% of the women had no increase in fibroid volume throughout pregnancy (73). In the 31% of women noted to have an increase in volume, the greatest increase occurred before the 10th week of gestation. There was no relationship between initial fibroid volume and fibroid growth during gestational periods. A reduction in fibroid size toward baseline measurements was observed 4

weeks after delivery.

Fibroid Degeneration During Pregnancy

In women noted to have fibroids during pregnancy, clinical symptoms and sonographic evidence of fibroid degeneration occur in about 5% (74). Among 113 women followed during pregnancy with serial sonography, 10 (9%) developed anechoic spaces or coarse heterogeneous patterns consistent with fibroid degeneration. Seven of 10 women had severe abdominal pain requiring hospitalization, consistent with clinical symptoms of degeneration. No sonographic changes were noted in the other 103 women, and only 11.7% had similar abdominal pain. A small study of women with fibroid-associated pain during pregnancy found use of *ibuprofen* shortened the hospital stay and decreased the rate of readmission (75).

Influence of Fibroids on Pregnancy

Very rarely does the presence of a fibroid during pregnancy lead to an unfavorable outcome. Research was conducted on large populations of pregnant women examined with routine second trimester sonography with follow-up care and delivery at the same institution (76,77). In a study of 12,600 pregnant women, the outcomes of 167 women with fibroids were no different with regard to the incidence of preterm delivery, premature rupture of membranes, fetal growth restriction, placenta previa, placental abruption, postpartum hemorrhage, or retained placenta (76). Cesarean section was more common among women with fibroids (23% vs. 12%).

The other study of 15,104 pregnancies, including 401 women with fibroids, found no increased risk of premature rupture of membranes, operative vaginal delivery, chorioamnionitis, or endometritis (77). However, there were increased risks of preterm delivery (19.2% vs. 12.7%), placenta previa (3.5% vs. 1.8%), and postpartum hemorrhage (8.3% vs. 2.9%). Cesarean section was again more common (49.1% vs. 21.4%). A small retrospective study found an association between retroplacental fibroids and placental abruption; 8 of 14 women with retroplacental fibroids developed abruption compared with 2 of 79 women without retroplacental fibroids (78).

Fetal injury attributed to mechanical compression by fibroids is uncommon. A search of the PubMed database from 1980 to 2010 revealed one case of fetal head anomalies with fetal growth restriction, one case of a postural deformity, one case of a limb reduction, and one case of fetal head deformation with torticollis (79–82).

Any decision to perform a myomectomy in order to prevent problems during pregnancy should take into account the risks of surgery, anesthesia, postoperative adhesions, and an increased likelihood of subsequent cesarean delivery, along with concerns about discomfort, expense, and time away from work or family.

Rupture of Myomectomy Scar During Pregnancy

Following abdominal myomectomy, uterine rupture during pregnancy appears to be a rare event.

Trial of labor after myomectomy is associated with a 0.47% risk of uterine rupture. Eleven studies that included 1,034 pregnancies and 756 viable (≥24 weeks) deliveries found 7 uterine ruptures after myomectomy (0.93%); the rate was 0.47% (2/426) in women undergoing trial of labor after myomectomy and 1.52% (5/330) in women before the onset of labor. Five of the seven uterine ruptures occurred before 36 weeks. Size, number, and positions of removed fibroids or the type of myometrial closure was not available to determine specific risk factors for rupture. The 0.47% rate of rupture for women with a trial of labor after myomectomy is similar to the 0.5% to 1% risk of rupture for trial of labor after previous cesarean delivery (83).

Operative techniques, instruments, and energy sources used during laparoscopic myomectomy may differ from those employed during laparotomy. A study of 19 published and unpublished cases of uterine rupture during pregnancy following laparoscopic myomectomy found that almost all cases involved deviations from standard surgical technique as described for abdominal myomectomy (84). In 7 cases, the uterine defect was not repaired; in 3 cases it was repaired with a single suture; in 4 cases it was repaired with only one layer of suture; and in 1 case only the serosa was closed. In only 3 cases was a multilayered closure employed. In 16 of the cases, monopolar or bipolar energy was used for hemostasis.

Although definite conclusions and recommendations regarding appropriate technique for laparoscopic myomectomy must await proper study of myometrial wound healing, it appears prudent for surgeons to adhere to time-tested techniques developed for abdominal myomectomy, including multilayered closure of myometrium (for other than superficial uterine defects) and limited use of electrosurgery for hemostasis. Even with ideal surgical technique, individual wound-healing characteristics may predispose to uterine rupture.

TREATMENT

The development of new treatments for fibroids is slow, perhaps because many women with fibroids are asymptomatic, fibroids are benign, and mortality is very low (84). **If offered hysterectomy as a first, and sometimes only, treatment option, some women choose to accommodate to symptoms and stop seeking treatment.** This may lead physicians to underestimate the true impact of the condition, despite the fact that women who have hysterectomies as a result of fibroid-related symptoms have significantly worse scores on SF-36 quality-of-life questionnaires than women diagnosed with hypertension, heart disease, chronic lung disease, or arthritis (40).

After an exhaustive review of the medical literature published between 1975 and

2000, with evaluation of 637 relevant articles and careful study of 200 articles, the authors found no satisfactory answers to fundamental questions about fibroid treatments (86). Women and their physicians need information on which to base decisions regarding possible treatments.

This section summarizes the literature regarding the management of fibroids. Treatment options include observation, medical therapy, hysteroscopic myomectomy, laparoscopic myomectomy, hysterectomy, UAE, and focused ultrasound.

Watchful Waiting

Not having treatment for fibroids rarely results in harm, except for women with severe anemia from fibroid-related heavy menstrual bleeding or hydronephrosis from ureteric obstruction from a massively enlarged fibroid uterus. Predicting future fibroid growth or onset of new symptoms is not possible (84). During observation, the average fibroid volume increases 9% per year with a range of −25% to +138% (87). A nonrandomized study of women with uterine size 8 weeks or greater who chose watchful waiting found that 77% of women had no significant changes in the self-reported amount of bleeding, pain, or degree of bothersome symptoms at the end of 1 year (88). Furthermore, mental health, general health, and activity indexes were also unchanged. Of the 106 women who initially chose watchful waiting, 23% opted for hysterectomy during the course of the year.

[10] Therefore, for women who are mildly or moderately symptomatic with fibroids, watchful waiting may allow treatment to be deferred, perhaps indefinitely.

[11] As women approach menopause, watchful waiting may be considered, because there is limited time to develop new symptoms and after menopause, bleeding stops and fibroids decrease in size (15). Although not specifically studied, the incidence of hysterectomy for fibroids declines considerably after menopause, suggesting that there is a significant decline in symptoms.

Medical Therapy

Nonsteroidal Anti-Inflammatory Medication

Nonsteroidal anti-inflammatory drugs (NSAIDs) were not shown to be effective for the treatment of heavy menstrual bleeding in women with fibroids. A placebo-controlled, double-blind study of 25 women with menorrhagia, 11 of whom had fibroids, found a 36% decrease in blood loss among women with idiopathic heavy menstrual bleeding, but no decrease in women with fibroids. No other studies examined this treatment (89).

Tranexamic Acid

Tranexamic acid is a synthetic antifibrinolytic medication which can be used for the management of menorrhagia at a dosage of 1.3 g, three times a day for 3 to 5 days during menstrual bleeds. A pooled analysis of two randomized, double-blind, placebo-controlled, parallel-group studies of women with heavy menstrual bleeding and fibroids found mean menstrual blood loss was significantly (p <0.001) reduced compared with placebo maintained across three treatment cycles (90). Adverse events included headache (55%) and nausea (15%). The results of this analysis may not be generalizable to women with markedly enlarged fibroids that require surgical management.

Gonadotropin-Releasing Hormone Agonists

Treatment with GnRH-a decreases uterine volume, fibroid volume, and bleeding. The benefits of GnRH-a are limited by side effects and risks associated with long-term use (91,92). Monthly GnRH-a given for 6 months reduced fibroid volume by 30% and total uterine volume by 35% (91). Reduction in the uterine size occurs mostly within the first 3 months of treatment (92). Heavy menstrual bleeding responds well to GnRH-a; 37 of 38 women had resolution by 6 months. Following discontinuation of GnRH-a, menses returns in 4 to 8 weeks and uterine size returns to pretreatment levels within 4 to 6 months (93). In this study 64% of women remained asymptomatic 8 to 12 months after treatment.

Side effects occur in 95% of women treated with GnRH-a (89). Seventy-eight percent experience hot flushes, 32% vaginal dryness, and 55% have transient frontal headaches. During 6 months of treatment only 8% of women discontinued GnRH-a because of the side effects. Arthralgia, myalgia, insomnia, edema, emotional lability, depression, and decreased libido are reported. **The hypoestrogenic state induced by GnRH-a causes significant bone loss after 6 months of therapy** (94).

In an effort to reduce side effects, inhibit bone loss, and allow long-term use of GnRH-a, low doses of *estrogen* and *progestins* may be added while continuing GnRH-a. A study of long-term use of GnRH-a over 6 years found a wide range of reduction in bone density among women and no difference in bone loss between groups given *estrogen* and *progestin* versus those treated with GnRH-a alone (95).

Gonadotropin-Releasing Hormone Agonist as Temporary Treatment for Perimenopausal Women

Women in late perimenopause who are symptomatic from uterine fibroids may consider short-term use of GnRH-a. Thirty-four perimenopausal women with symptomatic fibroids were treated with GnRH-a for 6 months, 12 of whom required repeat treatment 6 months after discontinuation of the medication (96); 31 women avoided surgery; 15 women went into natural menopause. Although not specifically studied, add-back therapy might be considered in this setting.

Gonadotropin-Releasing Hormone Antagonist

The immediate suppression of endogenous GnRH by daily subcutaneous injection of the GnRH antagonist *ganirelix* results in a 29% reduction in fibroid volume within 3 weeks (97). Treatment is accompanied by hypoestrogenic symptoms. When long-acting compounds are available, a GnRH antagonist might be considered for medical treatment prior to surgery.

Progesterone-Mediated Medical Treatment

The reduction in uterine size following treatment with the progesterone-blocking drug *mifepristone* is similar to that found with GnRH-a (98). A prospective, randomized controlled trial of *mifepristone* treatment found a 48% decrease in the mean uterine volume after 6 months (99). *Mifepristone* blocks progesterone, and the unopposed exposure of the endometrium to estrogen may lead to endometrial hyperplasia. A systematic review found endometrial hyperplasia in 10 of 36 (28%) women screened with endometrial biopsies (100).

Ulipristal Acetate

Ulipristal acetate (UPA) is a selective progesterone receptor modulator with pure antagonist activity. UPA modulates the progesterone signaling pathway and promotes remodeling of the extracellular matrix and reduction of collagen synthesis. UPA is effective for controlling bleeding and reducing the size of fibroids, while increasing the quality of life. The largest study included 451 women with symptomatic uterine fibroids, uterine size less than 16 weeks, and heavy menstrual bleeding (101). Women received four repeated 12-week treatment courses of daily UPA, 5 or 10 mg, given orally. Both doses led to amenorrhea, usually within 1 week, in ≥70% of women and bleeding was controlled in ≥73%. Hemoglobin levels increased over the first two treatment courses and were maintained during follow-up.

By the fourth treatment course, approximately 80% of women had more than 25% reduction in the volume of the three largest fibroids. Patients had significant improvement in pain and quality of life and reached scores reported for healthy individuals. Six cases of hyperplasia were observed, all of which returned to normal endometrium during the study.

Adverse events included headache and hot flushes in 11% of women, almost all of which were mild or moderate. Levels of E2 remained well above postmenopausal levels, suggesting that bone mineral density will not be adversely affected by ulipristal.

Progesterone-Releasing Intrauterine Device

The *levonorgestrel*-releasing intrauterine system (LNG-IUS) may be a reasonable treatment for selected women with fibroid-associated heavy menstrual bleeding.

Evidence from a systematic review of 11 studies of premenopausal women with uterine fibroids using LNG-IUS concluded that they significantly reduced menstrual blood loss and increased hemoglobin and ferritin levels, but did not decrease the

fibroid volume. Device expulsion rates were 15.4% with fibroids larger than 3 cm, but only 6.3% with fibroids smaller than 3 cm and unrelated to fibroid location (102).

Alternative Medicine Treatment

A nonrandomized, nonblinded study compared fibroid growth in 37 women treated with Chinese medicine, body therapy, and guided imagery to 37 controls treated with NSAIDs, progestins, or oral contraceptive pills (103). After 6 months, sonographic evaluation demonstrated that fibroids stopped growing or shrank in 22 of 37 (59%) women treated with Chinese medicine compared to 3 of 37 (8%) controls. Although symptoms responded equally well in both groups, satisfaction was higher in the Chinese medicine group. Participants actively sought alternative therapy and assessment of satisfaction may reflect selection bias.

An uncontrolled study reported treatment of 110 women with fibroids smaller than 10 cm with the Chinese herbal medicine kuei-chih-fu-ling-wan for at least 12 weeks (104). Clinical and sonographic evaluation found complete resolution of fibroids in 19% of women, a decrease in size in 43%, no change in 34%, and an increase in 4%. Heavy menstrual bleeding improved in 60 of 63 (95%) women and dysmenorrhea improved in 48 of 51 (94%). Fifteen of the 110 (14%) women chose to have a hysterectomy during the 4 years of the study.

SURGICAL TREATMENT OPTIONS

[12] Surgical treatment options include abdominal myomectomy, laparoscopic myomectomy, laparoscopic radiofrequency ablation, hysteroscopic myomectomy, endometrial ablation, and abdominal, vaginal, or laparoscopic hysterectomy.

Serious medical conditions, such as severe anemia or ureteral obstruction, often need to be addressed surgically. Pain from fibroid degeneration is usually successfully treated with analgesics until symptoms resolve, but if severe the patient may opt for surgery. Torsion of a pedunculated subserosal fibroid may produce acute pain that requires surgical intervention. Surgical intervention may be indicated in women with fibroids associated with heavy menstrual bleeding, pelvic pain or pressure, urinary frequency, or incontinence that compromises the quality of life (105).

Abdominal myomectomy was long employed as a conservative treatment for uterine fibroids, and much of the literature predates the use of prospective, randomized controlled trials. Although myomectomy is stated to relieve symptoms in 80% of women, there is scant literature documenting its efficacy and many large series have not reported data for relief of symptoms following surgery (105–107). A prospective, nonrandomized study comparing myomectomy with UAE did report that 75% of women in the myomectomy group had a significant decrease in symptom scores after 6 months (108).

Back pain may, on occasion, be related to the presence of fibroids, but other possible causes should be considered. **[13] Inability to evaluate the ovaries on pelvic examination is not an indication for surgery** (109). There is no evidence that pelvic examination increases early detection or decreases the mortality related to ovarian cancer, and sonography can be used to evaluate the adnexa should symptoms develop. Recent evidence that most serous "ovarian" cancers have a tubal origin makes early sonographic diagnosis particularly unlikely.

Treating Preoperative Anemia

In women with significant preoperative anemia, intravenous iron infusions, epoetin, and GnRH agonists have been used to increase hemoglobin levels. A randomized study of women with heavy menstrual bleeding and Hb levels <9.0 g/dL who were scheduled to have surgery received iron either intravenously (based on the calculated total iron deficit, 3 times a week for 3 weeks) or orally (80 mg/day of oral iron protein succinylate daily). The mean increase in hemoglobin was higher in the intravenous iron group than the oral group (3.0 vs. 0.8 g/dL) and there were no severe adverse events in either group (110). A randomized study showed that the use of epoetin, a recombinant form of erythropoietin, 250 IU/kg (approximately 15,000 U) per week for 3 weeks prior to elective surgery increased hemoglobin concentrations by 1.6 g/dL and significantly reduced transfusion rates when compared to controls (111). GnRH-a may be used preoperatively to stop abnormal bleeding, with a resultant increase of hemoglobin concentration. One study of women with fibroids and mean hemoglobin concentrations of 10.2 g who were randomized to GnRH-a plus oral iron or placebo plus oral iron found that after 12 weeks, 74% of the women treated with GnRH-a and iron had hemoglobin greater than 12 g compared with 46% of the women treated with only iron (112).

Abdominal Myomectomy

[14] Myomectomy should be considered a safe alternative to hysterectomy. Victor Bonney, an early advocate of abdominal myomectomy, stated in 1931 that "The restoration and maintenance of physiologic function is, or should be, the ultimate goal of surgical treatment."

Case-controlled studies suggest that there may be less risk of intraoperative injury with myomectomy when compared with hysterectomy (113). A retrospective review of 197 women who had myomectomies and 197 women who underwent hysterectomies with similar uterine size (14 vs. 15 weeks) found operating times were longer in the myomectomy group (200 vs. 175 minutes), but estimated blood loss was greater in the hysterectomy group (227 vs. 484 mL) (113). The risks of hemorrhage, febrile morbidity, unintended surgical procedure, life-threatening events, and rehospitalization were no

different between groups. However, 26 (13%) women in the hysterectomy group suffered complications, including 1 woman with bladder injury, 1 with ureteral injury, 3 bowel injuries, 8 with ileus, and 6 with pelvic abscesses. In contrast, complications occurred in 11 (5%) of the myomectomy patients, including 1 woman with bladder injury, 2 with reoperation for small bowel obstruction, and 6 with ileus.

Hysterectomy, without oophorectomy, may have a more lasting adverse effect on ovarian reserve than myomectomy. Serum AMH was significantly lower 3 months following hysterectomy compared with the preoperative level. Following myomectomy, serum AMH was similar to the preoperative level 3 months after surgery (114).

Myomectomy may be considered even for those women who have large uterine fibroids and wish to retain their uterus. A study of 91 women with uterine size larger than 16 cm (range 16 to 36 cm) reported 1 bowel injury, 1 bladder injury, and 1 reoperation for bowel obstruction, but no women had conversion to hysterectomy (115). The cell saver, which is a device used to collect blood intraoperatively and reinfuse, was used in 70 women, and only 7 required homologous blood transfusion. A retrospective cohort study by Iverson et al. compared 89 women having abdominal hysterectomy for fibroids (mean uterine size 15 cm) to abdominal myomectomy in 103 women (mean uterine size 12 cm) (116). Although selection bias was likely, the hysterectomy group suffered two ureteral, one bladder, one bowel, and one nerve injury and two reoperations for bowel obstruction, while there were no visceral injuries in the myomectomy group. A review of 6 observational studies, which included the patients from the Iverson study, found that among the 1,520 women with uterine size up to 18 weeks, there was no difference in morbidity between those having an abdominal myomectomy compared with those having an abdominal hysterectomy (117).

Cesarean Section and Concurrent Myomectomy

In carefully selected women, myomectomy may be safely accomplished at the time of cesarean section by experienced surgeons. One series reported 25 women with removal of 84 fibroids (2 to 10 cm) at the time of cesarean section without the need for cesarean hysterectomy (118). Estimated blood loss was 876 mL (range 400 to 1,700 mL) and 5 women required blood transfusion. Another study compared 111 women who had myomectomy at the time of cesarean section with 257 women with fibroids who were not subjected to myomectomy during cesarean section (119). Only one of the women in the myomectomy group required transfusion and none required hysterectomy or embolization. There were no differences in mean operative times, incidence of fever, or length of hospital stay between the two groups. Although the cases were likely selected carefully, the authors concluded that, in experienced hands, myomectomy might be safely performed in selected women during cesarean section.

Surgical Technique for Abdominal Myomectomy

Managing Blood Loss

Available surgical techniques allow safe removal of even large fibroids. Tourniquets or vasoconstrictive agents may be used to limit blood loss. *Vasopressin,* an antidiuretic hormone, causes constriction of smooth muscle in the walls of capillaries, small arterioles, and venules.

Significant reductions in blood loss during myomectomy have been found in several interventions: vaginal misoprostol (−98 mL); intramyometrial vasopressin (−246 mL); intravenous tranexamic acid (−243 mL); a Foley catheter secured around the cervix (−240 mL), and a polyglactin suture placed around both the cervix and infundibulopelvic ligaments (−1,870 mL) (120). A significant reduction in the need for blood transfusion has been shown while using vasopressin and tourniquets, but not for misoprostol or tranexamic acid. There are no data regarding whether the combined use of any of these measures decreases blood loss more effectively than individual measures.

Care should be taken to avoid intravascular injection of vasopressin and resultant cardiovascular collapse. Nonetheless, cardiovascular complications have been reported following intramyometrial injection. The maximal safe dose of vasopressin is not well established, but less than 5 units in total is suggested. The half-life of intramuscular vasopressin is 10 to 20 minutes, with a duration of action of 2 to 8 hours. Loss of peripheral pulses and nonmeasurable arterial blood pressure following vasopressin injection have been attributed to cardiovascular collapse or hypotension. Severe peripheral arterial vasospasm and elevated proximal blood pressure may occasionally occur with high-dose vasopressin and should be considered before administering additional vasopressors (121). The use of *vasopressin* to decrease blood loss during

myomectomy is an off-label use of this drug.

Cell savers may be considered for use during myomectomy. Use of the cell saver avoids the risks of infection and transfusion reaction, the oxygen transport capacity of salvaged red blood cells is equal to or better than stored allogeneic red cells, and the survival of red blood cells appears to be at least as good as transfused allogeneic red cells (122). The device suctions blood from the operative field, mixes it with heparinized saline, and stores the blood in a canister. If the patient requires blood reinfusion, the stored blood is washed with saline, filtered, centrifuged to a hematocrit of approximately 50%, and given back to the patient intravenously. Consequently, the need for preoperative autologous blood donation or heterologous blood transfusion often can be avoided (123). In a study of 92 women who had myomectomy for uterine size greater than 16 cm the cell saver was used for 70 women with a mean volume of reinfused packed red blood cells of 355 mL (124).

The cost of using a cell saver compared with donation of autologous blood was not studied for abdominal myomectomy. However, economic models suggest it is cost effective (124). Most hospitals charge a minimal fee for having the cell saver available "on-call" and charge an additional fee if it is used. Assuming that most women who donate autologous blood prior to myomectomy do not require blood transfusion, availability of the cell saver should spare many women the time and expense of donating, storing, and processing autologous blood. For a cohort of women, the cost of using the cell saver should, therefore, be significantly lower than the cost of autologous blood.

When heavy bleeding is anticipated or if copious bleeding is encountered, ligation of both uterine arteries can be performed (125). UAE was used successfully to control bleeding at the time of, or following, myomectomy (126). Because the uterine arteries recannulate, future fertility should not be compromised. These techniques often obviate the need for hysterectomy.

Uterine incisions can be made either vertically or transversely, because fibroids distort normal vascular architecture, making attempts to avoid the arcuate vessels impossible (127). **Careful planning and placement of uterine incisions can avoid inadvertent extension of the incision to the uterine cornua or ascending uterine vessels.**

Based on vascular corrosion casting and examination by electron microscopy, fibroids are completely surrounded by a dense blood supply and no distinct vascular pedicle exists at the base of the fibroid **(Fig. 11-4)** (128). Extending the uterine incisions through the myometrium and entire pseudocapsule until the fibroid is clearly distinguished identifies a less vascular surgical plane, which is deeper than commonly recognized.

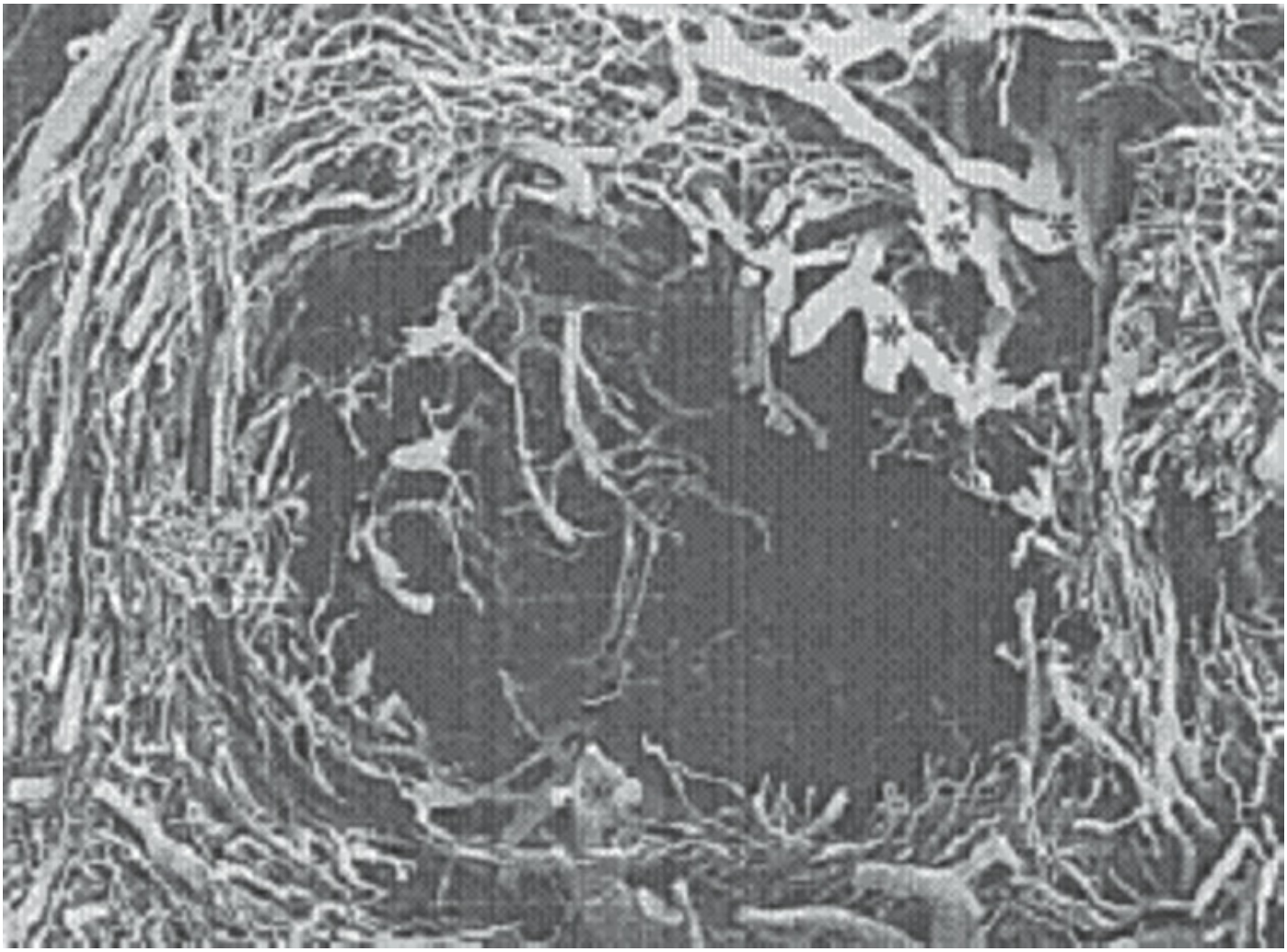


FIGURE 11-4 Corrosion casting of fibroid vessels.

Limiting the number of uterine incisions has been suggested in order to reduce the risk of adhesions to the uterine serosa (129). However, in this manner tunnels must be created within the myometrium in order to extract distant fibroids, making hemostasis more difficult within these defects. Hemostasis is important in order to avoid adhesion formation, and fibrin, leucocytes, and platelets in the presence of erythrocytes leads to adhesion formation. If tunneling incisions are avoided and hemostasis secured immediately, the risk of adhesion formation should be lessened. Therefore, if incisions are made directly over the fibroids and only those fibroids that are easily accessed are removed, the defects can be promptly closed and hemostasis can be secured immediately (115). Multiple uterine incisions may be needed, but adhesion barriers may help limit adhesion formation (130).

Laparoscopic Myomectomy

Available instruments make laparoscopic myomectomy feasible, although the size and number of fibroids reasonably removed limits the wide application of this approach

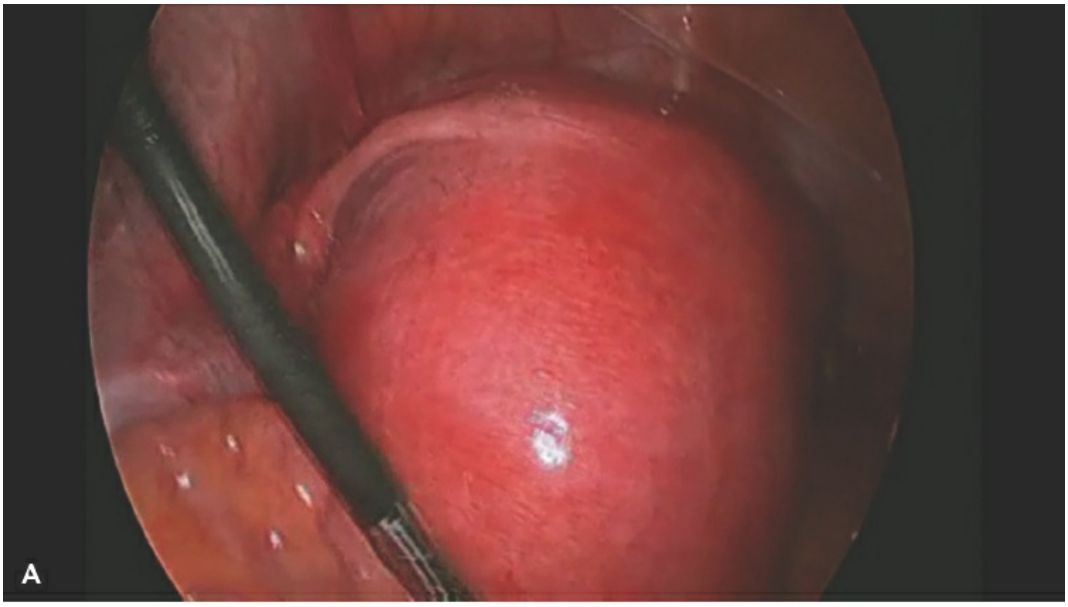
because of the technical difficulty of the procedure and laparoscopic suturing (131). Although microprocessor-assisted myomectomy (robotic) may obviate some of these technical problems, the added cost and longer operating times associated with this approach must be considered (see Chapter 28).

A systematic review of randomized controlled trials of laparoscopic versus open myomectomy included six studies with a total of 576 patients (132). Laparoscopic myomectomy was associated with longer operating times but reduced operative blood loss, less postoperative decline in hemoglobin levels, reduced postoperative pain, more patients fully recuperated at day 15, and fewer overall complications. Major complications, pregnancy rates, and new appearance of fibroids were comparable in the two groups.

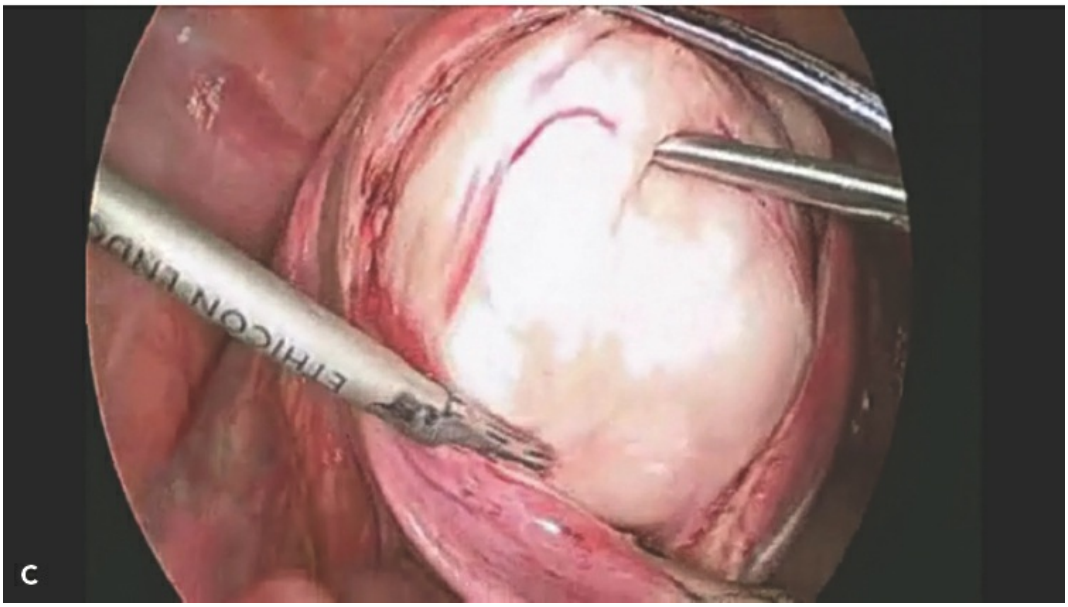
Case series without controls show the feasibility of laparoscopic surgery in women with large fibroids. In a series of 144 women with mean fibroid diameter of 7.8 cm (range, 5 to 18 cm), only 2 women required conversion to laparotomy (133). In another series of 332 consecutive women undergoing laparoscopic myomectomy for symptomatic fibroids as large as 15 cm, only 3 women required conversion to laparotomy (134).

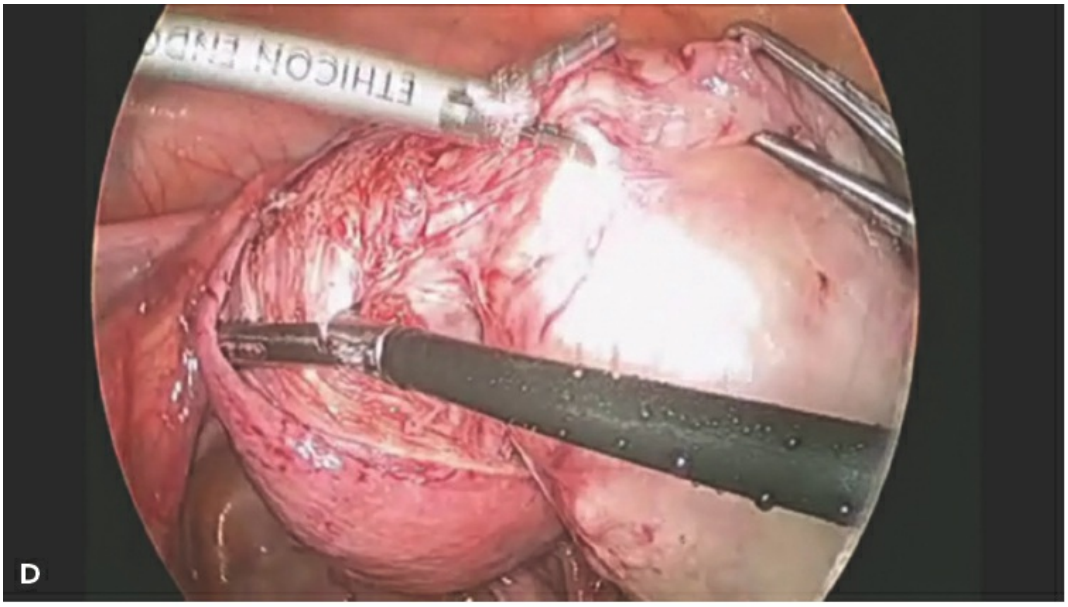
Surgical Technique for Laparoscopic Myomectomy

Port placement should be based on the position and size of the fibroids to be removed **(Fig. 11-5)**. Laparoscopic suturing may be more ergonomic if there are two ports on either the patient's right side for right-handed surgeons or left side for left-handed surgeons; a 12-mm port about 2 cm medial to the iliac crest for suture access, and another 5-mm lateral port near the level of the umbilicus (135). A left upper quadrant approach may be used for initial access when the uterine size is near or above the umbilicus (136).

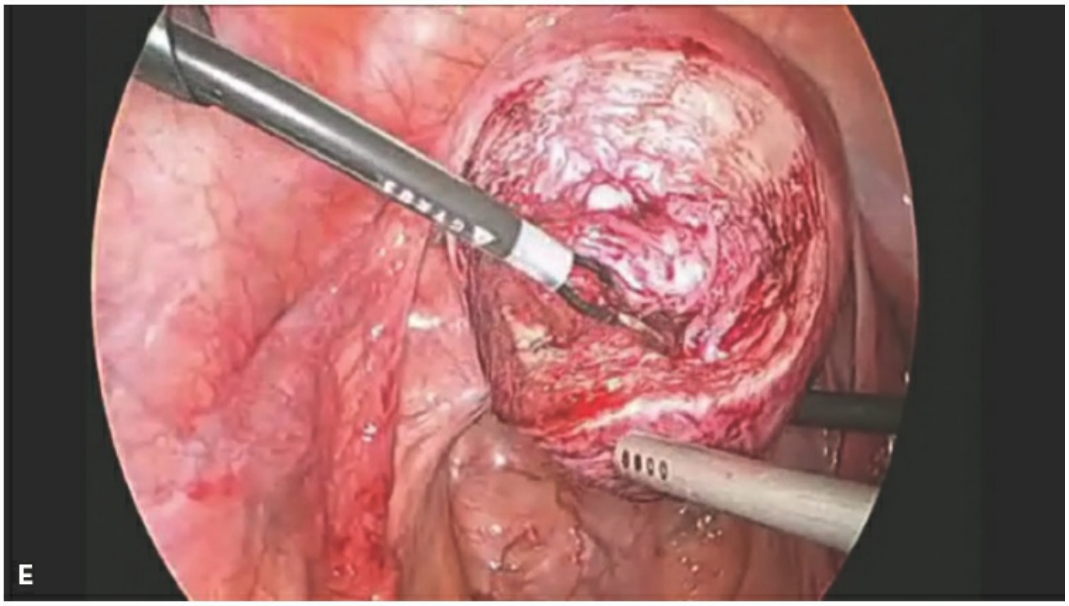

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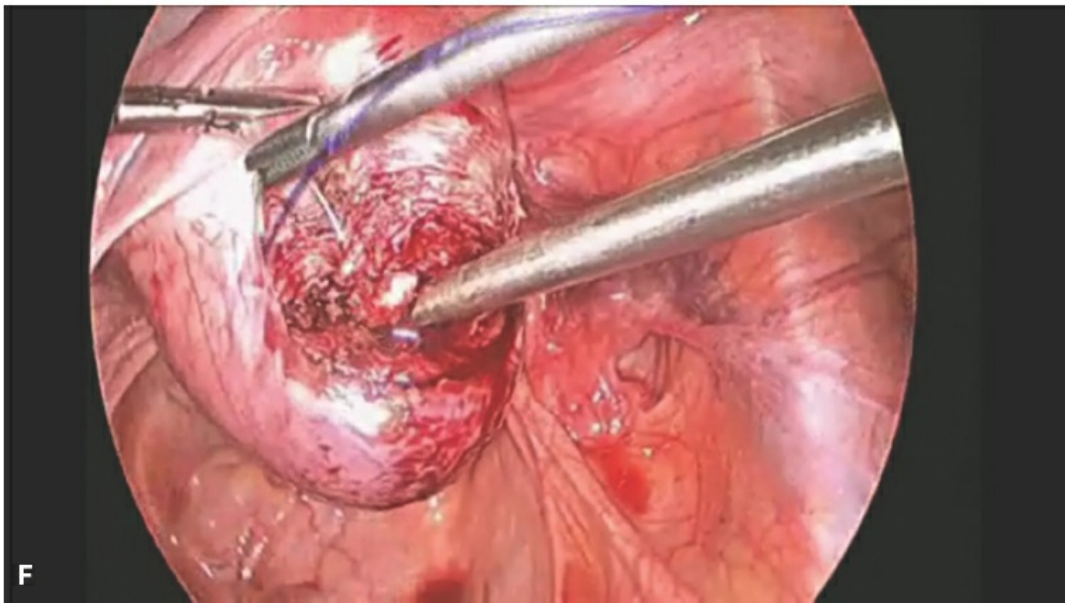

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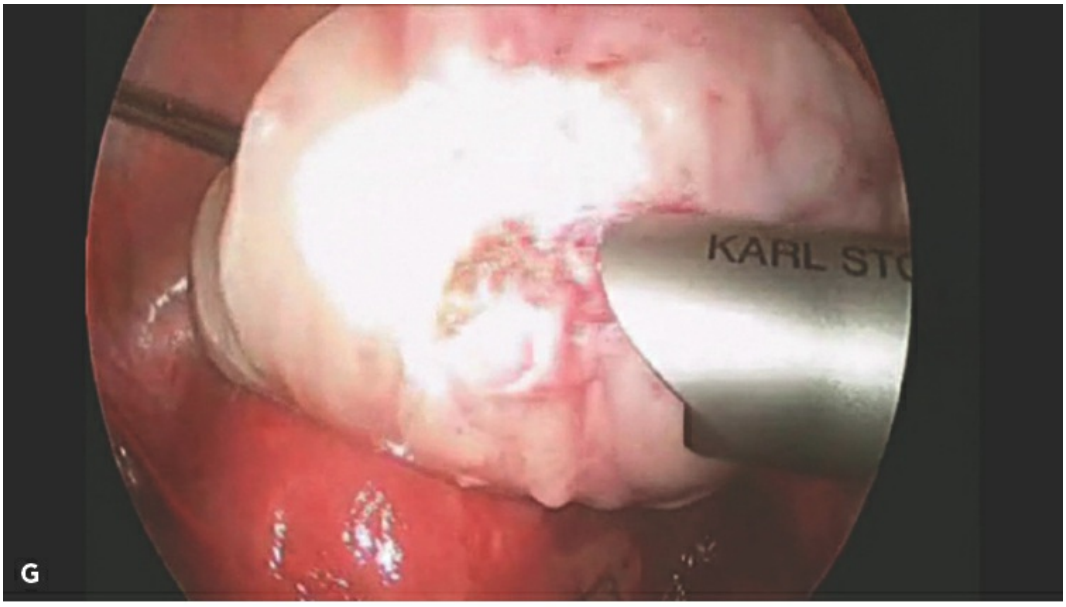

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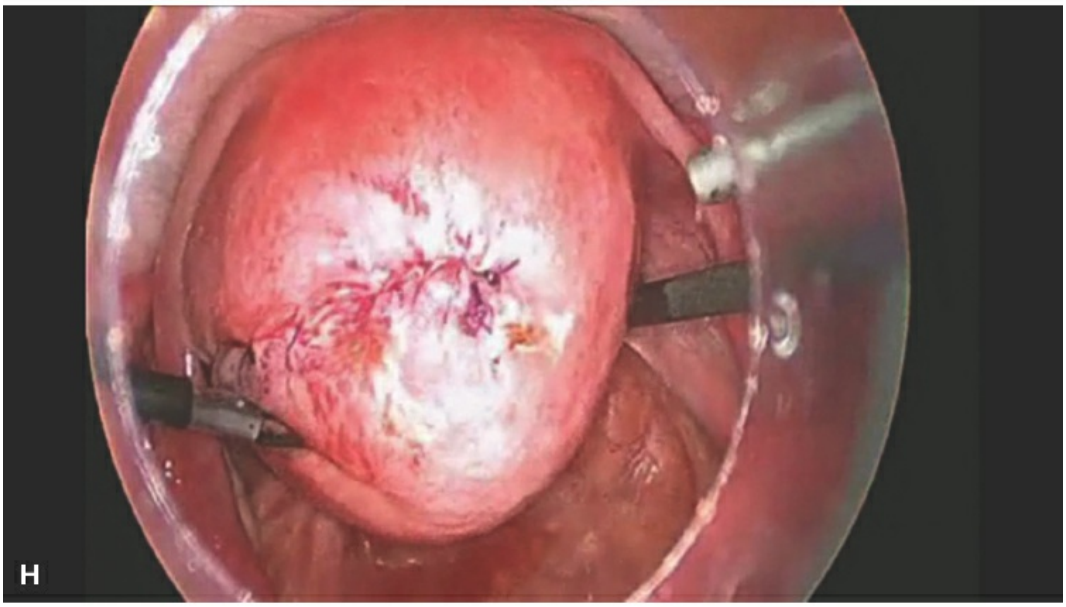
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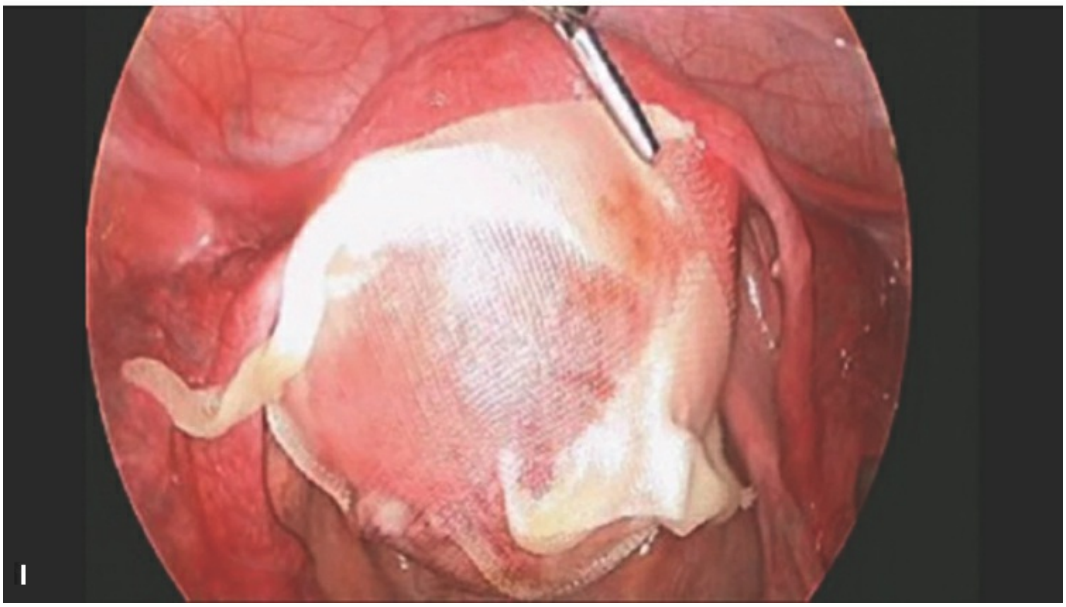

I

FIGURE 11-5 Laparoscopic myomectomy. **A:** A 7-cm, posterior intramural fibroid. **B:** Transverse incision through myometrium until fibroid reached. **C:** Traction on fibroid and countertraction on myometrium to tease fibroid away from myometrium. **D:** Adherent attachments to myometrium are cut. **E:** Minimal use of bipolar electrosurgery to control larger vessels. **F:** Three-layer suture closure of myometrium. **G:** Morcellator used to remove fibroid from abdominal cavity. **H:** Pelvis irrigated and suctioned. **I:** Adhesion barrier placed over uterine incision.

Vasopressin is injected into the fibroid. An incision is made directly over the fibroid and carried deeply until definite fibroid tissue and the avascular surgical plane is noted. Transverse incisions permit more ergonomic suturing. The fibroid is grasped with a tenaculum for traction and the plane between the myometrium and fibroid is dissected until the fibroid is free. Bleeding vessels in the myometrial defect are desiccated sparingly with bipolar electrosurgical paddles, taking care not to devascularize the myometrium and interfere with wound healing. Delayed absorbable sutures are placed in one, two, or three layers, as needed, adhering to accepted surgical technique at laparotomy. Morcellation of the fibroid with an electromechanical device is accomplished under direct vision. The pelvis and abdomen are irrigated, the fluid suctioned, and an adhesion barrier may be placed.

Tissue Morcellation

Morcellation describes a surgical method of dividing tissue into small sections in order to allow the tissue to be removed from the abdomen or vagina. With laparoscopic myomectomy, morcellation is usually necessary through the vagina, a Mini-laparotomy incision or electromechanical morcellation passed through a laparoscopic port incision. Morcellation allows many women the benefits of minimally invasive surgery: lower mortality rates, fewer intraoperative and postoperative complications, less postoperative pain with less need for narcotic pain medication, shorter hospital stays, and faster return to work and family.

Morcellation should not be performed in the presence of known or suspected uterine or cervical malignancy. Ultrasound or MRI findings of a large irregular vascular mass, often with irregular anechoic (cystic) areas reflecting necrosis or enhancement of uterine masses on MRI with gadolinium imaged in the arterial phase, should raise suspicion of LMS.

There is no evidence that the type of morcellation, electromechanical or scalpel, alters survival for women with LMS. Analysis of 16 studies that included 196 women with sarcomas reported no significant difference in 5-year survival rates between women having electromechanical morcellation, scalpel morcellation, or no tissue morcellation (137). Importantly, laparoscopic-aided morcellation allows the surgeon to inspect the pelvic and abdominal cavities, remove tissue fragments, and copiously irrigate and suction under visual control. In contrast, the possibility of retained tissue

fragments is greater with vaginal or mini-laparotomy morcellation procedures because the surgeon cannot visually inspect the peritoneal cavity.

Laparoscopic Radiofrequency Thermal Ablation

Laparoscopic ultrasound–guided radiofrequency ablation of uterine fibroids can be accomplished via a hand piece coupled to a radiofrequency generator. Health-Related Quality of Life (HRQL) scores showed improvement at 3 months, which was maintained at 36 months. Fourteen of 135 (11%) women required another treatment intervention for fibroid-related symptoms over 3 years of follow-up (138). Larger studies will be needed to assess the effectiveness of this treatment.

Adhesions Following Myomectomy

Adhesion formation after myomectomy is well documented (139). A Cochrane review found that *Interceed* reduced the incidence of adhesion formation, both de novo and reformation, at laparoscopy and laparotomy (140). Data were insufficient to support its use to improve pregnancy rates. There was limited evidence of effectiveness of *Seprafilm* (Genzyme, Cambridge, MA) in preventing adhesion formation in a prospective study that randomized 127 women undergoing abdominal myomectomy to treatment or no treatment with *Seprafilm* (130). During second-look laparoscopy, women treated with *Seprafilm* had significantly fewer adhesions and lower adhesion severity scores than untreated women. This study and others found an increased incidence of adhesions with posterior uterine incisions compared to anterior incisions (141).

Hysteroscopic Myomectomy

[15] Submucous fibroids, sometimes associated with increased menstrual bleeding or infertility, often can be removed hysteroscopically. Classification of submucous fibroids is based on the degree of the fibroid within the cavity; class 0 fibroids are intracavitary; class I have 50% or more of the fibroid within the cavity; and class II have less than 50% of the fibroid within the cavity **(Fig. 11-6)** (55). A meta-analysis of the effect of fibroids on fertility found that submucous fibroids with distortion of the uterine cavity decreased ongoing pregnancy/live birth rates by 70% (RR 0.32; 95% CI, 0.12–0.850) and resection increased ongoing pregnancy/live birth rates (RR 1.13; 95% CI, 0.96–1.33) (68).

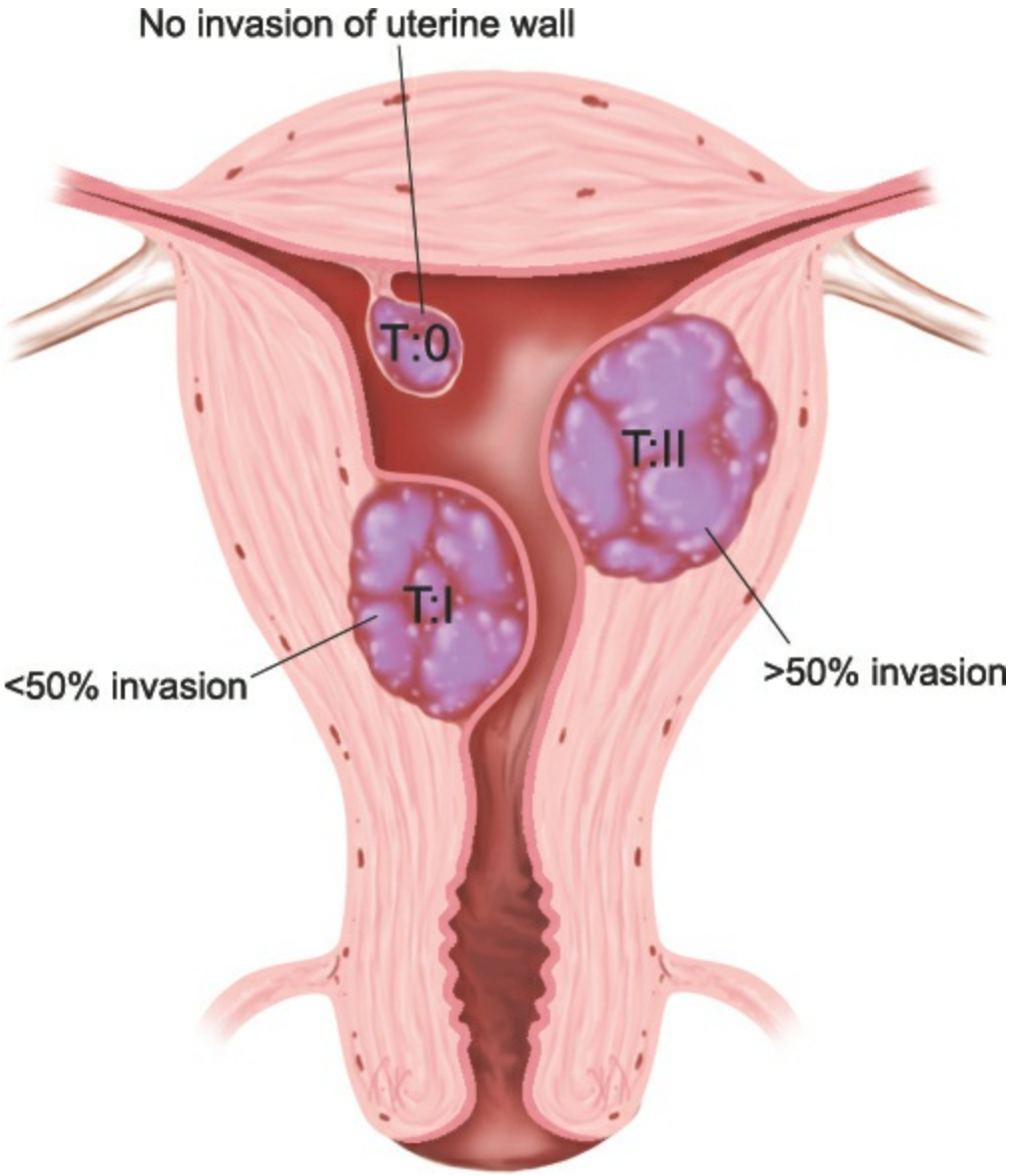


FIGURE 11-6 Fibroid classification. (From **Munro MG, Critchley HO, Broder MS, et al;** FIGO Working Group on Menstrual Disorders. FIGO classification system [PALM-COEIN] for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011;113:3–13.)

No meta-analysis of the association of submucous fibroids and abnormal uterine bleeding was performed. However, most studies show a reduction in bleeding following resection. Using pictorial assessment to estimate menstrual blood loss prior to and for 41 months following hysteroscopic resection of submucous fibroids, a significant decrease in bleeding was reported in 42 of 51 (82%) women with submucous pedunculated (type 0), 24 of 28 (86%) with sessile (type 1), and 15 of 22 (68%) with intramural fibroids (type 2) (143). A study of 285 consecutive women with heavy menstrual bleeding or irregular menstrual bleeding who had hysteroscopic resection of submucous fibroid(s) found that additional surgery was required for 9.5% at 2 years, 10.8% at 5 years, and 26.7% at 8 years (144).

Surgical Technique for Hysteroscopic Myomectomy

Hysteroscopic resection of a submucous fibroid can be accomplished under visual control using a telescope and continuous flow of distension fluid through the uterine cavity. The electrosurgical working element uses monopolar or bipolar electrodes. Monopolar electrodes require nonconducting distending solution (sorbitol 5%, sorbitol 3% with mannitol 0.5%, or glycine 1.5%), while bipolar electrodes can be used with saline.

Cervical dilation is usually required prior to insertion of the hysteroscope. *Cytotec* may facilitate easier dilation (145). The cutting loop is passed beyond the fibroid and cutting activated only when the loop is moving toward the surgeon and in direct view. Fibroids should be resected down to the level of the surrounding myometrium and, if fertility is desired, care should be taken to avoid excessive thermal damage to normal myometrium. Often, the remaining portion of the fibroid will be expressed into the uterine cavity by uterine contractions, allowing further resection. Fragments of fibroid are removed from the cavity with a grasping forceps or by capturing the fragments with the loop and extracting the telescope. G0 and G1 fibroids as large as 5 cm may be resected hysteroscopically.

G2 fibroids require careful preoperative evaluation with SIS or MRI to gauge the thickness of normal myometrium between the fibroid and the serosa in order to assess the potential risk of uterine perforation with the loop electrode. The risk of perforation increases with deeper myometrial involvement of the fibroid (146). In some cases, repeat resection may be required after a few weeks, as the remaining portion of the fibroid is expressed into the uterine cavity by uterine contractions.

Hysteroscopic Tissue Removal systems (HTRs) using intrauterine morcellation in physiologic saline solution for distension and irrigation, have been developed for the management of polyps and submucous fibroids. A systematic review of 8 studies included 283 women who underwent intrauterine morcellation of submucous fibroids (147). A deficit of 2,500 mL of isotonic solution is well tolerated by healthy women and no significant intra- or postoperative complications were reported. Complete resection rates were comparable to resectoscopic surgery. There was no significant difference in postoperative hemoglobin levels or patient satisfaction between the resection group compared with HTRs at 3-month follow-up. Uterine Fibroid Symptom-Quality of Life and Health-Related Quality of Life scores improved significantly 12 months after myomectomy using HTRs. As is true with resectoscopic surgery, type 0 and 1 submucous fibroids were found to be easier to manage than type 2.

Procedure-Specific Risks

Cervical dilatation or insertion of the hysteroscope can cause uterine perforation, as can deep myometrial resection. Often the first sign of perforation is a rapid increase in the fluid deficit. Careful inspection of the uterine cavity should be undertaken to look for

brisk bleeding or bowel injury. If no injury is apparent, the procedure should be terminated and the patient should be observed and may be discharged if stable (148). If a perforation occurs during activation of the electrode, then laparoscopy should be performed to carefully inspect for bowel or bladder injury.

Fluid Absorption and Electrolyte Imbalance

Intravascular absorption of distending media is a potentially dangerous complication that can result in pulmonary edema, hyponatremia, heart failure, cerebral edema, and death (149). Careful monitoring of the fluid deficit is important and a fluid deficit of 750 mL during surgery should serve as a warning sign, with planned termination of the procedure. **Many authors suggest termination of the procedure when the fluid deficit exceeds 1,000 mL, although other guidelines suggest termination after introduction of 1,500 mL of a nonelectrolyte solution or 2,500 mL of an electrolyte solution** (149). Electrolytes should be assessed and corrected if necessary and diuretics considered. Risk factors for fluid overload include resection of fibroids with deep intramural extension or prolonged operating time. The use of normal saline combined with bipolar energy reduces the risk of hyponatremia, but a fluid deficit over 1,500 mL can lead to cardiac overload (150).

Endometrial Ablation for Abnormal Bleeding Associated With Fibroids

In selected women not desiring future childbearing, endometrial ablation with or without hysteroscopic myomectomy may be efficacious. Pad counts following ablation with or without fibroid resection found that 48 of 51 (94%) women had resolution of abnormal bleeding after a mean follow-up of 2 years (range, 1 to 5 years) (151). A study of 62 women followed for an average of 29 months (range, 12 to 60 months) found that 74% of the women had hypomenorrhea or amenorrhea, and only 12% required a hysterectomy (152).

Hydrothermal ablation was used to treat 22 women with known submucous fibroids up to 4 cm, with 91% reporting amenorrhea, hypomenorrhea, or eumenorrhea after a minimum of 12 months' follow-up (153). In a study of 65 women with menometrorrhagia and type 1 or 2 submucous myomas up to 3 cm, after treatment with *NovaSure* endometrial ablation device (Hologic, Bedford, MA), normal bleeding or amenorrhea was observed in most women at 1 year (154).

NEW APPEARANCE OF FIBROIDS

Although new fibroids may sometimes develop following myomectomy, most women will not require additional treatment. If the first surgery is performed in the presence of a single fibroid, only 11% of women will need subsequent surgery (155). If multiple fibroids are removed during the initial surgery, only 26% will need subsequent surgery

(mean follow-up 7.6 years). Individual fibroids, once removed, do not grow back. Fibroids detected after myomectomy, often referred to as "recurrence," result either from failure to remove fibroids at the time of surgery or are newly developed fibroids. Perhaps this circumstance is best designated "new appearance" of fibroids (156).

Sonography found that 29% of women had persistent fibroids 6 months after myomectomy (157). In addition, the background formation of new fibroids in the general population should be considered. A hysterectomy study found fibroids in 77% of specimens from women who did not have a preoperative diagnosis of fibroids (4).

Incomplete follow-up, insufficient length of follow-up, the use of either transabdominal or transvaginal sonography (with different sensitivity), detection of very small clinically insignificant fibroids, or use of calculations other than life-table analysis confound many studies of new fibroid appearance (158).

Clinical Follow-Up

Self-reported diagnosis based on symptom questionnaires has reasonably good correlation with sonographic or pathologic confirmation of significant fibroids and may be the most appropriate method of gauging clinical evidence of new appearance (18). One study of 622 patients aged 22 to 44 at the time of surgery and followed over 14 years found the cumulative new appearance rate based on clinical examination and confirmed by ultrasound was 27% **(Fig. 11-7)** (159). An excellent review of life-table analysis studies found a cumulative risk of clinically significant new appearance of 10% 5 years after abdominal myomectomy (160).

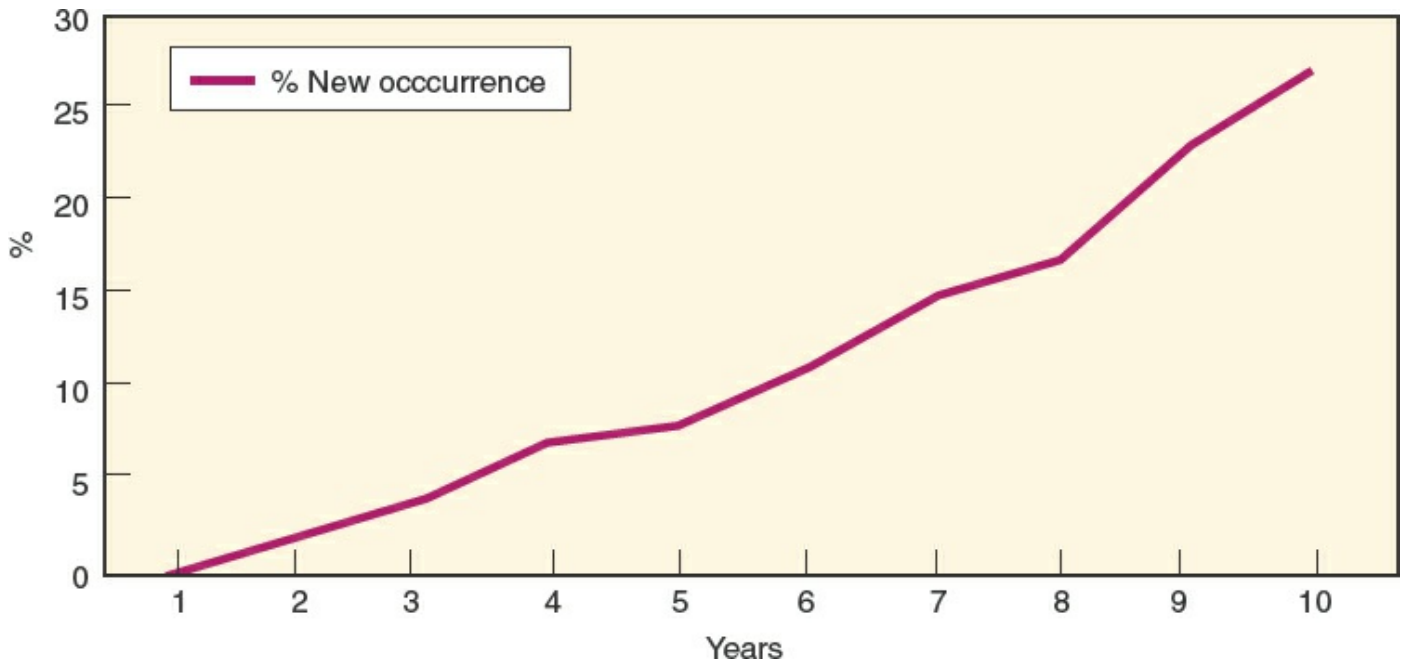


FIGURE 11-7 Overall 10-year new appearance after initial myomectomy. (From **Candiani G, Fedele L, Parazzini F, et al.** Risk of recurrence after myomectomy. Br J Obstet Gynecol 1991;98:385–389.)

Sonographic Follow-Up

[16] Routine ultrasound follow-up is sensitive but detects many clinically insignificant fibroids. One hundred forty-five women, with mean age 38 (ranging from 21 to 52), were followed after abdominal myomectomy with clinical evaluation every 12 months and TVS at 24 and 60 months (sooner, with clinical suspicion of new fibroids) (157). No lower size limit was used for the sonographic diagnosis of fibroids and, thus, the cumulative probability of new appearance was 51% at 5 years. A study of 40 women who had a normal sonogram 2 weeks following abdominal myomectomy found that the cumulative risk of sonographically detected new fibroids larger than 2 cm was 15% over 3 years (161).

Need for Subsequent Surgery

Meaningful information for a woman considering treatment for her fibroids is the approximate risk of developing symptoms that would require yet additional treatment. A study of 125 women followed by symptoms and clinical examination after a first abdominal myomectomy found that a second surgery was required during the follow-up period (average 7.6 years) for 11% of women who had one fibroid removed initially and for 26% of women who had multiple fibroids removed (155). Crude rates of hysterectomy after myomectomy vary from 4% to 16% over 5 years (162,163).

Prognostic Factors Related to New Appearance of Fibroids

Age

Given that the incidence of fibroids increases with increasing age, 4 per 1,000 woman-years for 25 to 29 year olds and 22 per 1,000 for 40 to 44 year olds, new fibroids would be expected to form as age increases, even following myomectomy (13).

Subsequent Childbearing

The 10-year clinical new appearance rate for women who subsequently gave birth was 16%, but for those women who did not the rate was 28% (159).

Number of Fibroids Initially Removed

After at least 5 years of follow-up, 27% of women who initially had a single fibroid removed had clinically detected new fibroids and 59% of women with multiple fibroids initially removed had new fibroids (151).

Gonadotropin-Releasing Hormone Agonists

Preoperative treatment with GnRH-a decreases fibroid volume and may make smaller fibroids harder to identify during surgery. A randomized study found that 3 months following abdominal myomectomy, 5 (63%) of 8 women in the GnRH group had fibroids less than 1.5 cm detected sonographically, while only 2 of 16 (13%) untreated

women had small fibroids detected (157).

Laparoscopic Myomectomy

New appearance of fibroids is not more common following laparoscopic myomectomy when compared with abdominal myomectomy. Eighty-one women randomized to either laparoscopic or abdominal myomectomy were followed with TVS every 6 months for at least 40 months (164). Fibroids larger than 1 cm were detected in 27% of women following laparoscopic myomectomy compared to 23% in the abdominal myomectomy group, and no woman in either group required any further intervention.

UTERINE ARTERY EMBOLIZATION

[17] Uterine artery embolization (UAE) is an effective treatment for selected women with uterine fibroids. The effects of UAE on early ovarian failure, fertility, and pregnancy are unclear. Therefore, many interventional radiologists advise against the procedure for women considering future fertility. Appropriate candidates for UAE include women who have sufficiently bothersome symptoms to warrant hysterectomy or myomectomy. Although extremely rare, complications of UAE may necessitate life-saving hysterectomy, and women who would not accept hysterectomy, even for life-threatening complications, should not undergo UAE. Contraindications to treatment of fibroids with UAE include women with active genital infection, genital tract malignancy, diminished immune status, severe vascular disease limiting access to the uterine arteries, contrast allergy, or impaired renal function (165). UAE outcomes are well studied and documented.

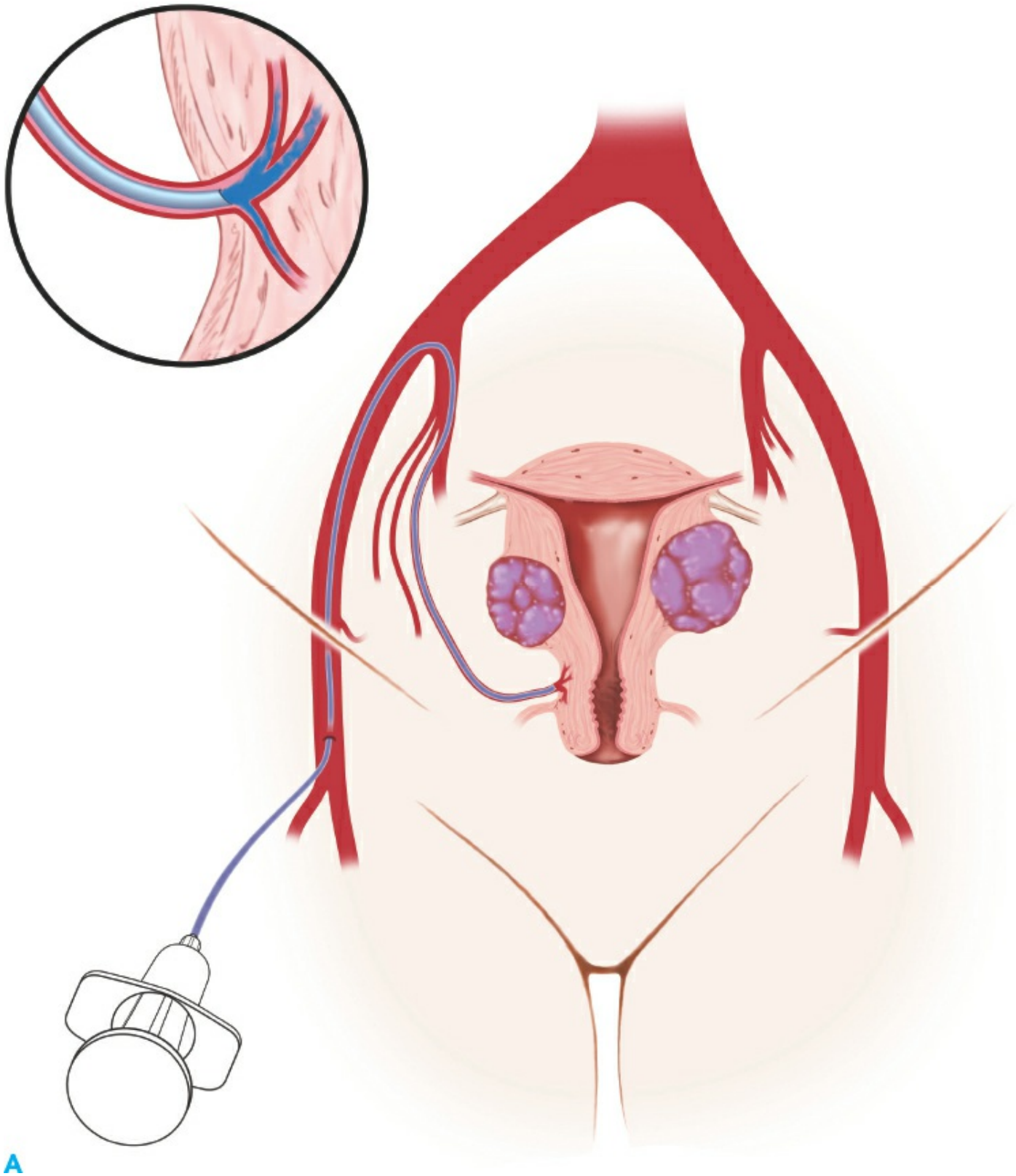
Fibroid and uterine volume decreased significantly and consistently following UAE and reports from the EMMY trial confirmed that fibroid and uterine volume reductions persisted up to 5 years after UAE (61). However, 28% of women underwent subsequent hysterectomy. Other studies, with length of follow-up ranging from 6 to 60 months, reported the need for subsequent treatment: hysterectomy in 17.5%, myomectomy in 8.8%, repeat embolization in 6.3%, IUD placement in 8%, medical therapy in 6.7%, and endometrial ablation in 1.2%. Decline in bleeding and/or pain were reported in most RCTs. Major procedure-related complication rates ranged from 1.2% to 6.9%.

A Cochrane review found no difference between UAE and myomectomy or hysterectomy in the risk of major complications, but UAE was associated with a higher rate of minor complications (166). UAE had an increased likelihood of requiring surgical intervention within 2 to 5 years of the initial procedure. One small study found that myomectomy was associated with better fertility outcomes than UAE. Patient satisfaction rates at up to 5 years following UAE versus myomectomy or hysterectomy found no difference between the interventions.

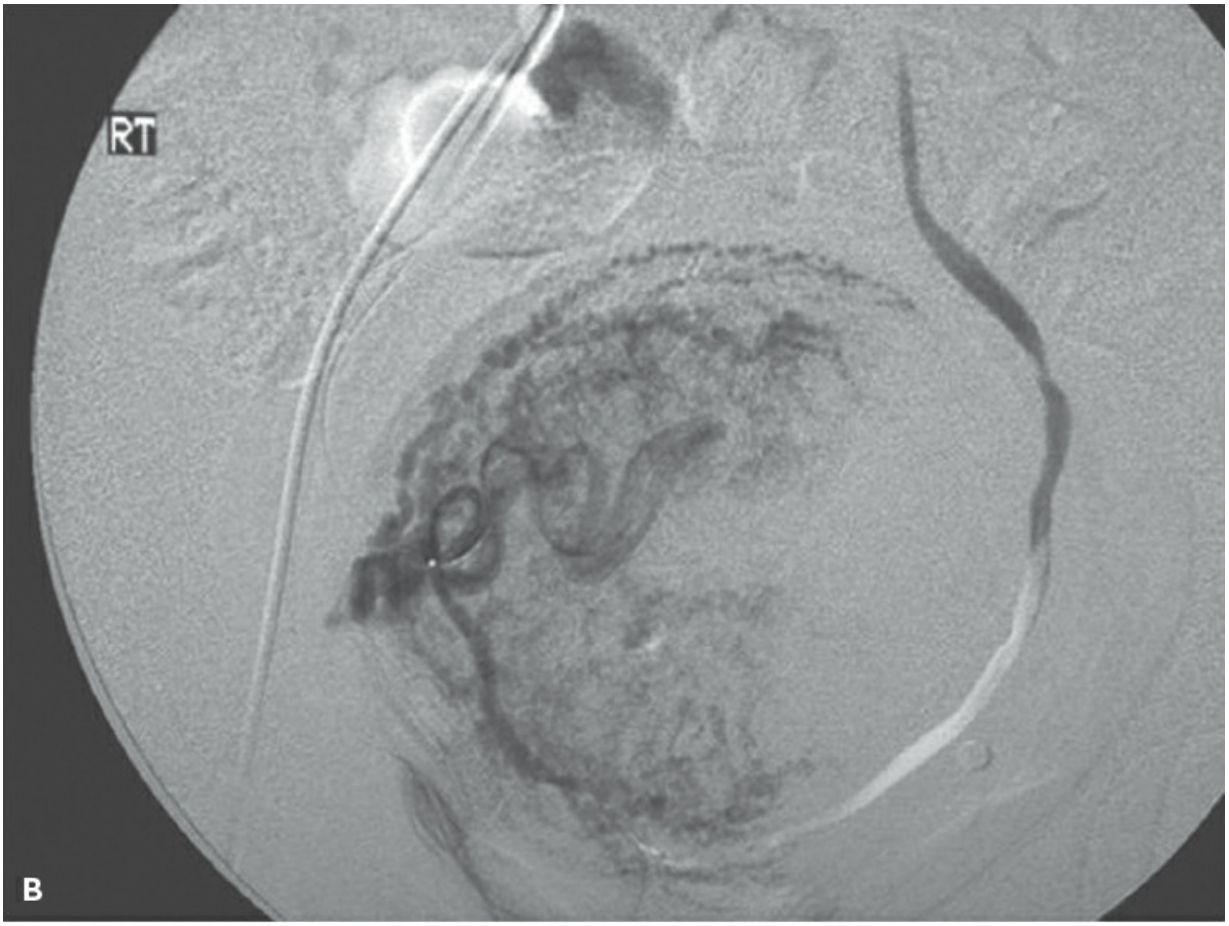
The American College of Obstetricians and Gynecologists recommends that women considering UAE have a thorough evaluation with a gynecologist to help facilitate collaboration with the interventional radiologist and that responsibility of caring for the patient be clear (168).

Uterine Artery Embolization Technique

Percutaneous cannulation of the femoral artery is performed by a properly trained and experienced interventional radiologist **(Fig. 11-8)** (169). Embolization of the uterine artery and its branches is accomplished by injecting gelatin sponges, polyvinyl alcohol particles (PVA), or tris-acryl gelatin microspheres via the catheter until occlusion, or slow flow, is documented. Total radiation exposure (approximately 15 cGy) is comparable to one or two computed tomography scans or barium enemas (170).



A


RT
B


RT
POST
C

FIGURE 11-8 A–C: UAE techniques. **A:** A catheter is threaded to the uterine arteries and embolic material injected to block off blood flow to the uterus. **B:** Contrast dye shows the vessels supplying the fibroid prior to UAE. **C:** Following UAE, embolic material blocks blood flow to the fibroid.

Tissue hypoxia secondary to UAE causes postprocedural pain that usually requires pain management in the hospital for 1 day. NSAID medications are usually taken for 1 to 2 weeks, and many women return to normal activity within 1 to 3 weeks. Approximately 5% to 10% of women have pain for longer than 2 weeks (170). Ten percent of women require readmission to the hospital for postembolization syndrome, characterized by diffuse abdominal pain, nausea, vomiting, low-grade fever, malaise, anorexia, and leukocytosis. Treatment with intravenous fluids, NSAID medications, and pain management usually leads to resolution of symptoms within 2 to 3 days (170). **Persistent fever should be managed with antibiotics. Failure to respond to antibiotics may indicate sepsis, which needs to be aggressively managed with hysterectomy.**

Uterine Artery Embolization Outcomes

The largest prospective study reported to date includes 555 women aged 18 to 59 (mean, 43), 80% of whom had heavy bleeding, 75% had pelvic pain, 73% had urinary frequency or urgency, and 40% of women had required time off work due to fibroid-related symptoms (171). Telephone interviews 3 months after UAE found that heavy menstrual bleeding improved in 83% of women, dysmenorrhea improved in 77%, and urinary frequency in 86%. Mean fibroid volume reduction of the dominant fibroid was 33% at 3 months, but improvement in heavy menstrual bleeding was not related to preprocedural uterine volume (even >1,000 cm^3) or to the degree of volume reduction obtained. Of note, two women (0.4%) had continued uterine growth and worsening pain and were found to have sarcomas. The hysterectomy rate caused by complications was 1.5%. Within the follow-up period, 3% of women under 40, but 41% of women over 50, had amenorrhea.

A prospective, randomized trial comparing hysterectomy and UAE in 177 women with symptomatic fibroids found that major complications were rare. Hospital stay was significantly shorter for UAE (2 vs. 5 days), but UAE was associated with more readmissions (9 vs. 0) for pain and/or fever in the 6-week postoperative period. Significant complications included one woman who required resection of a submucous fibroid, one who had sepsis in the UAE group, and one woman who had a vesicovaginal fistula following hysterectomy.

Early Ovarian Failure

The risk of premature ovarian failure following UAE needs further study. Transient amenorrhea was reported in as many as 15% of women. Ovarian arterial perfusion as

measured by Doppler sonography immediately following UAE shows that 35% of women had decreased ovarian perfusion and 54% had complete loss of perfusion (173). However, basal follicle-stimulating hormone (FSH) and anti-müllerian hormone (AMH) levels indicated decreased ovarian reserve in all women in one study (174).

Kim et al. reported a significant decrease of AMH and antral follicle counts (AFC) at 3 and 12 months after UAE (175). A significant recovery of AMH at the 12-month measurement was seen, but only in patients <40 years of age. These results suggest that ovaries may be damaged following UAE, but they may recover in younger women. A study comparing women who underwent UAE with women having laparoscopic myomectomies found significantly lower AMH levels and AFC in the UAE group (176). Although normal FSH, estradiol, ovarian volume, and AFC were documented in most women following UAE, these tests cannot predict earlier onset of menopause (177). Younger women, whose ovaries contain a large number of follicles, are likely to maintain a normal FSH despite destruction of a significant number of follicles, but it is not clear if future fertility will be impaired. Loss of follicles might cause menopause at an age earlier than would otherwise be expected. Long-term follow-up of women having UAE will be necessary to answer this important question.

Fertility and Pregnancy Following Uterine Artery Embolization

Because of the possibility of decreased ovarian function, and the potential for increased pregnancy complications, women who wish to conceive should not be treated with UAE (178). Although the risk appears to be low for women younger than 40 years old, premature ovarian failure would be devastating in this setting. Potential fertility following UAE is uncertain. A prospective trial of women with intramural fibroids larger than 4 cm, randomly selected for either UAE or myomectomy, reported more pregnancies and fewer spontaneous abortions after surgery than after UAE (176). Obstetrical and perinatal results were similar.

Two hundred twenty-seven completed pregnancies after UAE were compared with pregnancies in untreated women matched for age and fibroid location (controls) (179). Miscarriage rates (35% vs. 17%) and postpartum hemorrhage rates (14% vs. 3%) were higher in UAE pregnancies compared with controls. Rates of preterm delivery, IUGR, and malpresentation were similar in UAE pregnancies and in control pregnancies with fibroids. One small randomized study compared fertility outcomes of UAE with laparoscopic myomectomy (176). Twenty-six patients after UAE and 40 after myomectomy tried to conceive, with a pregnancy rate of 50% vs. 78% (p <0.05) and miscarriage rate of 53% vs. 19% (p <0.05) for UAE and myomectomy, respectively. A Cochrane database review stated that UAE may be associated with less favorable fertility outcomes than myomectomy, but the data is low quality and should be regarded with extreme caution (166).

Another study reported eight term and six preterm deliveries, but two women had

placenta previa and one woman had a membranous placenta. It is not clear whether this high incidence of abnormalities is related to an effect of UAE on the endometrium or a placental problem inherent to women with uterine fibroids. As a result, some authors recommend early-pregnancy sonography to look for placenta accreta (180). Uterine wall defects, necrosis, and fistula have been reported following UAE, and the integrity of the uterine wall during pregnancy and childbirth remains unknown (181).

Uterine Artery Occlusion

Alternative methods of uterine artery occlusion include laparoscopic uterine artery occlusion. Fifty-eight patients were randomized to UAE or laparoscopic uterine artery occlusion (182). After a median follow-up of 48 months, clinical failures and symptom recurrence occurred in 14 women after laparoscopy (48%) and in five women after UAE (17%). Laparoscopic occlusion requires general anesthesia, is invasive, and requires a skilled laparoscopic surgeon.

Magnetic Resonance–Guided Focused Ultrasound

Ultrasound energy can be focused to create sufficient heat at a specific point so that protein is denatured and cell death occurs. Concurrent MRI allows precise targeting of tissue and monitoring of therapy by assessing the temperature of treated tissue (183). The advantages of this procedure are a very low morbidity and a very rapid recovery, with return to normal activity in one day. The procedure is not recommended for women wishing future fertility (183). Initial studies had treatment limited by the U.S. Food and Drug Administration to approximately 10% of fibroid volume, and while a 15% reduction in fibroid size was reported 6 months following treatment, only an additional 4% reduction was noted at 24 months (184). More recent studies with larger treatment areas reported better results; 6 months after treatment, the average volume reduction was 31% (+/−28%) (185).

An evidence-based review found cohort studies involving 1,594 patients with short-term follow-up (<1 year) (186). Twenty-six major complications (1.6%) were reported. MRgHIFU resulted in statistically and clinically significant reductions in fibroid-related symptoms. For women failing medical therapy and seeking alternatives to hysterectomy for symptomatic uterine fibroids, the author concluded that MRgHIFU provides a safe and effective, noninvasive, uterine-preserving treatment with a rapid recovery. Disadvantages of MRgHIFU include restricted eligibility, lengthy procedure time, and availability of an MR device.

A nonrandomized comparative study of 166 patients with uterine fibroids who underwent MRgHIFU (n = 99) and laparoscopic myomectomy (n = 67) reported the laparoscopic myomectomy group showed substantial symptom improvement in 52 patients and partial symptom improvement in 13 (187). In the MRgHIFU group, 6

months after treatment, 62 patients showed complete symptom relief and 36 patients showed partial relief. MRgHIFU requires no general anesthesia or blood loss and leads to quick postoperative recovery. This study had no description of patient or fibroid characteristics and both patient and physician selection bias were likely. The lack of high-quality comparative evidence between MRgHIFU and other, more established uterine-preserving treatments, limits informed decision making among treatment options.

MANAGEMENT SUMMARY

A woman's individual circumstance, including fibroid-related symptoms and their effect on the quality of life, desire (or not) to preserve fertility, and her wishes regarding treatment options should be considered when discussing possible treatments. Multiple treatment options usually exist and the following points should be considered.

For an asymptomatic woman diagnosed with fibroids who desires fertility in the near future, evaluation of the uterine cavity with SIS, hysteroscopy, or MRI provides useful information regarding the presence of submucous fibroids and their potential impact on fertility. If the cavity is not deformed, fibroids need not be treated and conception may be attempted. If the cavity is deformed, myomectomy (hysteroscopic or abdominal) can be considered. An experienced laparoscopic surgeon may offer laparoscopic myomectomy, with a multilayered myometrial closure.

For an asymptomatic woman who does not desire future fertility, observation (watchful waiting) should be considered. A periodic review of the patient's symptoms and a pelvic examination to evaluate the uterine size should be accomplished. In the presence of very large fibroids, renal ultrasound or computed tomography urogram can be considered to rule out significant hydronephrosis.

For a symptomatic woman who desires future fertility and her primary symptom is abnormal bleeding, baseline hemoglobin measurement should be considered because accommodation to anemia can occur. If indicated, further evaluation of the endometrium with endometrial biopsy can be performed. Evaluation of the uterine cavity with SIS, hysteroscopy, or MRI can help determine the appropriate treatment options.

If the cavity is deformed, myomectomy (hysteroscopic or abdominal) should be considered. An experienced laparoscopic surgeon may offer laparoscopic myomectomy. If the symptoms of pain or pressure (bulk symptoms) are present, and if the uterine cavity is not deformed, myomectomy (abdominal or laparoscopic) can be considered.

For a symptomatic woman who does not desire future fertility, observation (watchful waiting) can be considered if no treatment is desired at that time. A

symptomatic perimenopausal woman may desire observation until she enters menopause, when symptoms often diminish. Baseline hemoglobin measurements should be obtained and if a significant anemia exists, treatment should be considered. If irregular menstrual bleeding is present, evaluation of the endometrium with sonography or endometrial biopsy should be considered. If the endometrium is normal, a *levonorgestrel*-IUS or endometrial ablation may be appropriate treatment. Myomectomy (hysteroscopic, abdominal, or laparoscopic), hysterectomy (vaginal, laparoscopic, or abdominal), or UAE can be considered.

For a woman with primarily fibroid-related pain or pressure symptoms (bulk symptoms), myomectomy, hysterectomy, and UAE or focused ultrasound (limited by size and number of fibroids) may be considered.

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CHAPTER 12

Pelvic Pain and Dysmenorrhea



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Definitions
Acute Pain
- Evaluation of Acute Pelvic Pain
- Reproductive Tract Causes of Acute Pelvic Pain
  - *Ectopic Pregnancy*
  - *Leaking or Rupture of an Ovarian Cyst*
  - *Adnexal Torsion*
  - *Acute Salpingo-Oophoritis and Pelvic Inflammatory Disease*
  - *Tubo-Ovarian Abscess*
  - *Uterine Leiomyomas*
  - *Endometriosis-Related Acute Pain*
- Gastrointestinal Tract Causes of Acute Pelvic Pain
  - *Appendicitis*
  - *Acute Diverticulitis*
  - *Intestinal Obstruction*
- Urinary Tract Causes of Acute Pelvic Pain
- Acute Pelvic Pain: Summary

Cyclic Pain: Primary and Secondary Dysmenorrhea
- Primary Dysmenorrhea
- Secondary Dysmenorrhea
  - *Endometriosis*
  - *Adenomyosis*

Chronic Pelvic Pain
- Evaluation of Chronic Pelvic Pain
- Reproductive Tract

Endometriosis
Adhesions
Pelvic Congestion
Subacute Salpingo-Oophoritis
Ovarian Remnant and Residual Ovary Syndromes
Gastroenterologic Etiology
Irritable Bowel Syndrome
Urologic Etiology
Urethral Syndrome
Interstitial Cystitis/Bladder Pain Syndrome or Painful Bladder Syndrome
Neurologic and Musculoskeletal Causes
Nerve Entrapment
Myofascial Pain
Fibromyalgia
Low-Back Pain Syndrome
Vulvodynia
Psychological Factors
Management of Chronic Pelvic Pain
Multidisciplinary Approach
Pharmacologic Interventions
Physical Therapy
Laparoscopy
Hysterectomy

KEY POINTS

1 Acute pelvic pain is rapid in onset, often associated with unstable vital signs and obvious abnormalities on physical examination and laboratory assessment. Improper diagnosis can result in significant morbidity and even mortality.

2 Timely and thorough assessment, guided by organ system (reproductive, gastrointestinal, urinary) and category of pathology, will ensure effective diagnosis and management of infection, obstruction, ischemia (torsion), leakage of irritating substance (viscus or cyst rupture), or pregnancy-related pain.

3 Chronic pelvic pain (CPP) is a multifaceted disorder characterized by changes in the processing of afferent signaling in the pelvic organs, the surrounding somatic tissues, the spinal cord, and the brain. The shared thoracolumbar and sacral innervations of the pelvic structures and the upregulation processing of neural input in the central nervous system account for the multiplicity of somatic and psychological symptoms experienced by women with CPP.

4 A thorough history and physical examination are important for successful management of acute and chronic pain. The ancillary laboratory and diagnostic procedures performed to assess acute, life-threatening processes differ from those focused on chronic pain conditions. CPP requires a multidisciplinary approach for diagnosis and management.

DEFINITIONS

[1] *Acute pain* is intense and characterized by sudden onset, sharp rise, and short course. *Cyclic pain* refers to pain that occurs with a definite association to the menstrual period. *Dysmenorrhea*, or painful menstruation, is the most common

cyclic pain phenomenon and is classified as *primary* or *secondary* on the basis of associated anatomic pathology (1). ***Chronic* pelvic pain (*CPP*) is defined as pain of greater than 3 months in duration, localized to the anatomic pelvis, and sufficiently severe to cause functional disability or necessitate medical care** (2).

Whereas acute pain is generally associated with autonomic reflex responses, such as nausea, emesis, diaphoresis, and apprehension, these autonomic reflex responses are not present in women with CPP. Acute pain is often affiliated with signs of inflammation or infection, such as fever and leukocytosis, which are absent in chronic pain states. The pathophysiology of acute pelvic pain involves mediators of inflammation present in high concentration as a result of infection, ischemia, or chemical irritation.

By contrast, the etiology of CPP often involves changes in modulation or "upregulation" of normally nonpainful stimuli. Pain is out of proportion to the degree of tissue damage (3,4). Chronic pain is characterized by physiologic, affective, and behavioral responses that differ from those associated with acute pain (44). An inflammatory lesion, such as endometriosis, for example, can set up an environment of chronic neurogenic inflammation or stimulation, which can result in "plastic" changes in the peripheral and central nervous system (CNS) and the persistence of chronic pain (5–8). Genetic predisposition, adverse environmental pressures, and hormonal milieu are thought to increase the vulnerability and predisposition for chronic pain disorders (9).

ACUTE PAIN

The differential diagnosis of acute pelvic pain is outlined in Table 12-1. Assessing the character of the pain helps create a differential diagnosis. **[1] Rapid onset of pain is most consistent with perforation or rupture of a hollow viscus or ischemia following the torsion of a vascular pedicle. Colic or severe cramping pain is commonly associated with muscular contraction or obstruction of a hollow viscus, such as the intestine, ureter, or uterus. Pain perceived over the entire abdomen suggests a generalized reaction to an irritating fluid within the peritoneal cavity such as blood, purulent fluid, or contents of an ovarian cyst.**

Table 12-1 Differential Diagnosis of Acute Pelvic Pain

Gynecologic
Acute Pain
1. *Complication of pregnancy* a. Ectopic pregnancy b. Abortion, threatened, or incomplete
2. *Acute infections* a. Endometritis

b. Pelvic inflammatory disease (acute PID) or salpingo-oophoritis c. Tubo-ovarian abscess
3. *Adnexal disorders* a. Hemorrhagic functional ovarian cyst b. Torsion of adnexa c. Rupture of functional, neoplastic, or inflammatory ovarian cyst
Recurrent Pelvic Pain
1. Mittelschmerz (midcycle pain) 2. Primary dysmenorrhea 3. Secondary dysmenorrhea
Gastrointestinal
1. Gastroenteritis 2. Appendicitis 3. Bowel obstruction 4. Diverticulitis 5. Inflammatory bowel disease 6. Irritable bowel syndrome
Genitourinary
1. Cystitis 2. Pyelonephritis 3. Ureteral lithiasis
Musculoskeletal
1. Abdominal wall hematoma 2. Hernia
Other
1. Acute porphyria 2. Pelvic thrombophlebitis 3. Aortic aneurysm 4. Abdominal angina

The first perception of visceral pain is a vague, deep, poorly localizable sensation associated with autonomic reflex responses. When the pain becomes localized to a region of the abdominal wall, the pain is called referred pain. Referred pain is well localized, more superficial, and is appreciated within the nerve distribution or dermatome of the spinal cord segment innervating the involved viscus. The location of the referred pain provides insight into the location of the primary disease process. The innervations of the pelvic organs are outlined in Table 12-2. The upper vagina, cervix, uterus, and adnexa share the same visceral innervations with the large intestine, rectum, bladder, lower ureter, and lower small intestine. Pain from the reproductive organs, genitourinary (GU), and gastrointestinal (GI) tracts are referred to the same dermatomes

(10).

Table 12-2 Nerves Carrying Painful Impulses from the Pelvic Organs

Organ	Spinal Segments	Nerves
Abdominal wall	T12–L1	Iliohypogastric, ilioinguinal, genitofemoral
Lower abdominal wall, anterior vulva, urethra, clitoris	L1–L2	Ilioinguinal, genitofemoral
Lower back	L1–L2	
Pelvic floor, anus, perineum, and lower vagina	S2–S4; L1–L2	Pudendal, inguinal, genitofemoral, posterofemoral cutaneous
Upper vagina, cervix, uterine corpus, inner third of fallopian tubes, broad ligament, upper bladder, terminal ileum, and terminal large bowel	T11–L2; S2–S4	Thoracolumbar autonomics (sympathetics) via hypogastric plexus; sacral autonomics (parasympathetics) via pelvic nerve
Ovaries, outer two-thirds of fallopian tubes, and upper ureter	T9–T10	Thoracic autonomics (sympathetics) via renal and aortic plexus and celiac and mesenteric ganglia, aortic and superior mesenteric plexuses

Evaluation of Acute Pelvic Pain

In the evaluation of acute pelvic pain, early diagnosis is critical because significant delay increases morbidity and mortality. Fundamental to correct diagnosis is an accurate history. The date and character of the last and previous menstrual periods and the presence of abnormal bleeding or discharge should be ascertained. The menstrual, sexual, contraceptive history, and any history of sexually transmitted conditions and previous gynecologic disorders are relevant. Pain history should include how and when the pain started, pregnancy-related symptoms (amenorrhea, irregular bleeding, nausea, breast tenderness), GI symptoms (anorexia, nausea, vomiting, constipation, obstipation, absence of flatus, hematochezia), urinary symptoms (dysuria, urgency frequency, hesitancy, hematuria), signs of infection (fever, chills, purulent vaginal discharge), and symptoms attributable to a hemoperitoneum (dizziness, syncope, abdominal distention, and right upper quadrant or shoulder pain). Document any past medical and surgical history, and current medications.

Baseline laboratory studies will include, at minimum, a complete blood count (CBC) with differential, clean catch midstream routine urine analysis (RUA), sensitive urine or serum pregnancy test, gonorrhea and chlamydia screening, and a transvaginal pelvic ultrasound. Other tests such as computerized tomography (CT) with and without contrast, chemistry panel, or blood type and screen (if transfusion is likely) may be

indicated depending on the patient's symptoms and the specific differential diagnosis.

Reproductive Tract Causes of Acute Pelvic Pain

Ectopic Pregnancy

[2] All reproductive-aged women presenting with acute pain should be screened for pregnancy.

An ectopic pregnancy is defined as implantation of the fetus in a site other than the uterine cavity (see Chapter 32).

Symptoms

Ectopic pregnancies can implant anywhere other than inside the uterus including the abdomen, cervix, ovary, or cornua of the uterus. Nearly all ectopic pregnancies (98%) are found within the fallopian tube, which will be discussed in this section (11).

Implantation of the fetus in the fallopian tube produces pain with acute dilation of the tube. If tubal rupture occurs, localized abdominal pain tends to be temporarily relieved and is replaced by generalized pelvic and abdominal pain and dizziness with the development of a hemoperitoneum. A period of amenorrhea followed by irregular bleeding and acute onset of pain compose the classic triad of symptoms. A mass in the cul-de-sac may produce an urge to defecate. Referred pain to the right shoulder often develops if the intra-abdominal blood collection transverses the right colic gutter and irritates the diaphragm (C3–C5 innervation).

Signs

Vital signs often reveal orthostatic changes in the case of a ruptured ectopic. Orthostasis is diagnosed by obtaining a patient's pulse and blood pressure while they are supine, after sitting for 3 minutes, and finally after standing for 3 minutes. If the systolic blood pressure decreases by 20 mmHg or the diastolic blood pressure decreases by 10 mmHg when standing from a supine position, orthostasis is confirmed. Although pulse rate is not specifically included in the definition of orthostasis, it is easy to obtain and an increase in pulse rate can be suggestive of orthostasis. Elevated temperature is generally absent with an ectopic.

Abdominal examination is notable for tenderness and guarding in one or both lower quadrants. With the development of hemoperitoneum, generalized abdominal distention and rebound tenderness are prominent and bowel sounds are decreased. Pelvic examination generally reveals mild tenderness on the motion of the cervix. Adnexal tenderness is present, usually more pronounced on the side of the ectopic pregnancy, and a mass may be palpated. Positive pregnancy test and transvaginal ultrasound are usually confirmatory. Ultrasound findings can include an adnexal mass, pseudosac in the endometrium, and an extrauterine sac with a yolk sac within the embryo in the fallopian

tube. If the patient has intra-abdominal bleeding, peritoneal free fluid can be seen on the ultrasound. The diagnostic approach and the medical and surgical management of ectopic pregnancy are discussed in Chapter 32 (12,13).

Leaking or Rupture of an Ovarian Cyst

Functional cysts (e.g., follicle or corpus luteum) are the most common ovarian cysts and are more likely to rupture than benign or malignant neoplasms. The pain associated with the rupture of the ovarian follicle at the time of ovulation is called *mittelschmerz*. The small amount of blood leaking into the peritoneal cavity and high concentration of follicular fluid prostaglandins contribute to this midcycle pelvic pain. The pain is usually mild to moderate and self-limited, and with an intact coagulation system, hemoperitoneum is unlikely.

Normal menstrual cycles produce follicles which mature to release an ovum, which becomes the corpus luteum that eventually involutes. When the follicle does not rupture to release an ovum it can become a follicular or physiologic cyst and continue to grow. Likewise, the corpus luteum fails to involute and continues to grow after ovulation. Both of these can become hemorrhagic cysts. Uncomplicated ruptured ovarian cysts which are hemodynamically stable can be managed with close observation, hospitalization, or repeat imaging.

[2] A hemorrhagic cyst can become symptomatic, causing worsening vital signs, and require surgery. The rapidly expanding ovarian capsule or, with rupture, the blood in the peritoneal cavity is responsible for the acute pain. Rupture of this cyst can produce either a small amount of intraperitoneal bleeding or frank hemorrhage, resulting in significant blood loss and hemoperitoneum. Cystic ovarian neoplasms or inflammatory ovarian masses, such as endometriomas or abscesses, can leak or rupture. A history of a dermoid cyst or endometrioma that has not yet undergone surgical extirpation is not uncommon. **Surgical exploration is indicated if the rupture leads to significant hemoperitoneum (corpus luteum) or chemical peritonitis (endometrioma or dermoid), which could impair future fertility, or an acute abdomen (abscess), which is life-threatening.**

Symptoms

An ovarian cyst that is not undergoing torsion, rapidly enlarging, infected, or leaking does not usually cause acute pain. **A corpus luteum cyst is the most common cyst to rupture and leads to hemoperitoneum. Symptoms of a ruptured corpus luteum cyst are similar to those of a ruptured ectopic pregnancy.** The patient is in the luteal phase or can have delayed menses as a result of the persistently functioning corpus luteum. The onset of pain is usually sudden and is associated with increasing pelvic pain, which becomes generalized abdominal pain and dizziness or syncope with the development of significant hemoperitoneum.

A ruptured endometrioma or benign cystic teratoma (dermoid cyst) produces similar symptoms; however, dizziness and signs of hypovolemia are not present because blood loss is minimal.

Signs

Orthostasis resulting from hypovolemia is present only when there is intravascular volume depletion, such as with a hemoperitoneum. Fever is rare. **The most important sign is the presence of significant abdominal tenderness, often associated with localized or generalized lower quadrant rebound tenderness because of peritoneal irritation.** The abdomen can be moderately distended with decreased bowel sounds. On pelvic examination, a mass is often palpable if the cyst is leaking and has not completely ruptured.

Diagnosis

The diagnosis and the type of ruptured cyst are ascertained by blood tests and transvaginal ultrasound. Pregnancy test, CBC, and, if orthostasis is present, type and screening should be ordered. Leukocytosis is uncommon. The hematocrit is decreased if active bleeding is present. If orthostasis is absent and the peripheral hematocrit is relatively normal, clinically significant hemoperitoneum is unlikely. Culdocentesis was used historically to support findings by aspirating clear, blood tinged, or purulent fluid in helping with diagnosis. It has largely been replaced by improvements in pelvic imaging, image-guided aspiration, or diagnostic laparoscopy.

A skillful reading of transvaginal ultrasound images can help characterize a cystic structure in the pelvis as a dermoid, endometrioma, corpus luteum, or pelvic abscess and quantify the amount of intraperitoneal fluid.

Management

Orthostasis, significant anemia, or a large amount of free peritoneal fluid on ultrasound suggests significant hemoperitoneum and usually requires surgical management by laparoscopy or laparotomy. Patients who are not orthostatic or febrile, not pregnant or anemic, and have only a small amount of fluid in the cul-de-sac can often be observed in the hospital, with surgical intervention, or discharged home from the emergency room after observation.

Adnexal Torsion

[2] Torsion (twisting) of the vascular pedicle of an ovary, ovary with cyst, fallopian tube, paratubal cyst, or rarely a pedunculated uterine myoma results in ischemia of the structures distal to the twisted pedicle and acute onset of pain. A benign cystic teratoma is the most common neoplasm to undergo torsion. Because of adhesions, ovarian carcinoma and inflammatory masses such as endometriomas or abscesses rarely undergo torsion. It is unusual for a normal tube and ovary to torque, although a

polycystic ovary can undergo torsion. Diagnosis of adnexal torsion is challenging. The clinician must base the diagnosis on history, clinical examination, and additional investigations such as pelvic ultrasound (14). There is no specific size criteria for ovarian torsion, but one study found that 83% of torsion occurred in ovaries that were 5 cm or larger (15). In the pediatric population, the clinician should be aware that torsion can happen with no ovarian lesion or mass.

Symptoms

The pain of torsion is usually severe and constant or, if the torsion is partial and intermittent, the pain can wax and wane. The onset of the torsion and subsequent abdominal pain frequently coincides with activities such as lifting, exercise, or intercourse. Autonomic reflex responses (e.g., nausea, emesis, tachycardia, and apprehension) are usually present.

Signs

Mild temperature elevation, tachycardia, and leukocytosis may accompany the necrosis of tissue. Pregnancy test is negative unless there is a coexistent pregnancy. The diagnosis must be suspected in any woman with acute pain and unilateral adnexal mass.

On examination, the localized direct and rebound tenderness can be noted in the lower quadrant(s). Another important sign is the presence of a large pelvic mass on bimanual examination.

Diagnosis

The process of torsion occludes the lymphatic and venous drainage of the involved adnexa; therefore, the torqued viscus rapidly increases in size and can be easily palpated on examination or visualized by ultrasound. The presence of Doppler blood flow to the ovary on ultrasound does not definitely rule out torsion. CT has been shown to have low overall sensitivity and is not recommended for the workup for suspected ovarian torsion in one meta-analysis (16) However, in another case-control study, CT was not shown to be significantly different from ultrasound in identifying ovarian torsion (17).

The ovarian torsion composite index (OT-CI) is a scoring system that combines clinical and radiologic findings to accurately predict ovarian torsion. Scores greater than or equal to 3 had 100% sensitivity and 65.3% specificity and could be considered for surgical interventions (18).

The diagnosis of ovarian torsion is challenging as clinical symptoms are neither sensitive nor specific and there are no definitive criteria with imaging. Surgical diagnosis (laparoscopy or laparotomy) remains the diagnostic and therapeutic method of choice if there is suspicion of ovarian torsion.

Management

Adnexal torsion must be treated surgically. The adnexa may be untwisted and a cystectomy performed if appropriate. Even when it appears that necrosis occurred, there is evidence that it remains functional and sparing the adnexa can preserve its hormonal and reproductive function. Treatment can be accomplished by laparoscopy or laparotomy, depending on the size of the mass.

Acute Salpingo-Oophoritis and Pelvic Inflammatory Disease

The diagnosis and management of acute salpingo-oophoritis and pelvic inflammatory disease (PID) are discussed in Chapter 15.

Symptoms

[2] All cases of PID are polymicrobial, involving gram-negative and gram-positive aerobic and anaerobic bacteria. PID initiated by *Neisseria gonococcus* or chlamydia is manifested by the acute onset of pelvic pain that increases with movement, fever, purulent vaginal discharge, and sometimes nausea and emesis. Subclinical PID can be seen with chlamydial salpingo-oophoritis, with more insidious symptoms that can be confused with the symptoms of irritable bowel syndrome (IBS) (19).

Signs

Elevated temperature and tachycardia are typical. Abdominal examination may show distention and decreased bowel sounds caused by secondary ileus. Direct and rebound abdominal tenderness with palpation are marked. **The most important signs of acute salpingo-oophoritis are cervical motion tenderness and bilateral adnexal tenderness.** Evaluation of the pelvis may be difficult because of pain and guarding, but lack of a discrete mass or masses differentiates acute salpingo-oophoritis from tubo-ovarian abscess (TOA) or torsion. Right upper quadrant can be a distinct sign of PID-related perihepatitis involving the liver capsule and peritoneal surfaces, called Fitz-Hugh–Curtis syndrome.

Diagnosis

Leukocytosis and elevated erythrocyte sedimentation rate (ESR), a nonspecific, although more sensitive, sign of inflammation, are found in patients with acute PID. Pregnancy test is usually negative because PID as coexistent with intrauterine pregnancy (IUP) is rare. If the pregnancy test is positive, an infected or very inflamed ectopic pregnancy, or instrumented IUP, or infected, incomplete abortion should be suspected. Appendicitis and diverticulitis can be mistaken for PID. Laparoscopy can be useful if the diagnosis is uncertain. The Centers for Disease Control and Prevention (CDC) guidelines for diagnosing PID state that PID should be suspected and treatment started if the patient is at risk for PID and she has uterine, cervical motion, or adnexal tenderness without any apparent cause (20). Findings that support the diagnosis include cervical or vaginal

mucopurulent discharge, elevated ESR or C-reactive protein (CRP), laboratory confirmation of gonorrhea or chlamydia, oral temperature of 38.3°C or higher, or white blood cells (WBCs) on wet mount of vaginal secretions. One study showed that an ESR >19.5 mm per 1/2 h and CRP >11.5 mg/L were predictors of TOA where below these cutoffs were predictors of PID without TOA (21). Most specific criteria for the diagnosis include endometritis on endometrial biopsy, laparoscopic evidence of PID (tubal edema, erythema, and purulent discharge), or thickened, fluid-filled fallopian tubes on pelvic ultrasound or magnetic resonance imaging (MRI).

Tubo-Ovarian Abscess

[2] TOA, a complication of acute salpingo-oophoritis, is usually bilateral but can be unilateral (20). The symptoms and signs are similar to those of acute salpingitis. A ruptured TOA is a life-threatening surgical emergency because gram-negative endotoxic shock can develop rapidly.

Signs

Vital signs reveal fever, tachycardia, and low blood pressure if the patient is septic. TOAs can often be palpated on bimanual examination as firm, exquisitely tender, bilateral fixed masses. The abscesses can be palpated or "pointed" in the pelvic cul-de-sac and are appreciated on rectovaginal examination. Approximately 90% of patients will have abdominal or pelvic pain and 60% to 80% will present with fever and/or leukocytosis.

Diagnosis

The diagnostic imaging of choice for TOAs is ultrasound. CT with and without contrast can be used to establish the diagnosis (22). The differential diagnosis of a unilateral mass includes TOA and adnexal torsion, ectopic pregnancy, endometrioma, leaking ovarian cyst, and periappendiceal or diverticular abscess. If physical and ultrasound examination results are not definitive, laparoscopy or laparotomy must be performed.

Management

TOAs should always be treated as an inpatient, and conservative medical therapy with intravenous broad-spectrum antibiotics can be attempted (see Chapter 15) (23). If the patient is persistently febrile or not improving clinically, CT or ultrasound-guided drainage of the abscesses should be undertaken. CT-guided percutaneous drainage can be achieved transabdominally or transvaginally. Drainage along with intravenous antibiotics is considered first-line therapy (23,24). If fertility is not desired, bilateral salpingo-oophorectomy (BSO) and hysterectomy will provide definitive therapy.

[2] A ruptured TOA rapidly leads to diffuse peritonitis, evidenced by tachycardia

and rebound tenderness in all four quadrants of the abdomen. With endotoxic shock, hypotension and oliguria ensue, and the result can be fatal. Exploratory laparotomy with resection of infected tissue is mandatory (see Chapter 15).

According to the CDC, women should show clinical improvement in regards to pelvic pain and vital signs within 3 days of initiation of therapy. If there is no improvement, additional diagnostics should be performed, such as diagnostic laparoscopy and other imaging for alternative diagnoses. Women who receive a diagnosis of chlamydia or gonorrhea should be retested 3 months after treatment and their partner should also be treated (20).

Uterine Leiomyomas

Leiomyomas (fibroids) are uterine smooth muscle tumors, as discussed in detail in Chapter 11. **Discomfort may be present when myomas are in the broad ligament or encroaching on adjacent bladder, rectum, or supporting ligaments of the uterus**. The discomfort is usually reported as noncyclic pressure or pain symptoms and less often, urinary frequency, dysmenorrhea, dyspareunia, or constipation (25). **There is no association between the degree of pain and fibroid volume or number** (26). A retrospective review of patients who had **[2]** symptomatic fibroids were diagnosed with histology-proven endometriosis (27).

Acute pelvic pain caused by uterine leiomyomas is rare but can develop if the myoma undergoes degeneration or torsion (27). Rare cases of uterine rupture have been documented which require prompt treatment (28). Degeneration of myomas occurs secondary to loss of blood supply, usually attributable to rapid growth associated with pregnancy. **In a nonpregnant woman, degenerating uterine leiomyoma is often a misdiagnosis, because it can be confused with subacute salpingo-oophoritis.** A pedunculated subserosal leiomyoma can undergo torsion with ischemic necrosis and can be associated with pain similar to that of adnexal torsion. When a submucous leiomyoma becomes pedunculated within the endometrial cavity, the uterus contracts forcefully as if to expel a foreign body and the resulting pain is similar to that of labor. The cramping pain is usually associated with vaginal hemorrhage.

Signs

Vital signs are usually normal, although a low-grade temperature and mild tachycardia can be present with degeneration. Abdominal or bimanual examination and ultrasound reveal an irregular solid mass or masses arising from the uterus. If degeneration occurs, the inflammation can cause abdominal tenderness in response to palpation and mild localized rebound tenderness.

Diagnosis and Management

With degeneration there is usually leukocytosis. **Ultrasound can distinguish adnexal**

from uterine etiology of an eccentric mass. If diagnosis is still uncertain, a pelvic MRI is more accurate (29). The fibroid can be excised laparoscopically; however, surgery is not mandatory. A submucosal leiomyoma with pain and hemorrhage should be excised transcervically with hysteroscopic guidance.

Endometriosis-Related Acute Pain

In women with endometriosis, endometrial glands and stroma implant outside the uterine cavity, most commonly at the cul-de-sac, ovaries, or pelvic visceral and parietal peritoneum. Each menstrual cycle potentially results in further proliferation, causing inflammation, scarring, fibrosis, and adhesion formation. Women with endometriosis often experience dysmenorrhea, dyspareunia, and dyschezia, irregular bleeding, or subfertility. Acute pain attributable to endometriosis is usually premenstrual and menstrual; if nonmenstrual acute generalized pain occurs, a ruptured endometrioma (chocolate endometrial cyst within the ovary) should be considered. The management of endometriosis is discussed under dysmenorrhea and CPP (see also Chapter 13).

Diagnosis

The abdomen is often tender in one or both the lower quadrants. Significant distention or rebound tenderness may be present if there is there is a ruptured endometrioma. **Bimanual and rectovaginal examinations can reveal a fixed, retroverted uterus with tender nodules in the uterosacral region or thickening of the cul-de-sac.** An adnexal mass, if present, usually is fixed to the broad ligament and cul-de-sac. **The clinical diagnosis of endometriosis is accurate approximately 50% of the time. Definitive diagnosis is made by laparoscopy or laparotomy.** In the setting of chronic pain symptoms with an acute exacerbation, a leaking endometrioma should be suspected. If there is a characteristic mass on ultrasound, laparoscopy is indicated.

Gastrointestinal Tract Causes of Acute Pelvic Pain

Appendicitis

[2] The most common intestinal source of acute pelvic pain in women is appendicitis. Lifetime incidence in the United States is 7%, and it is the most common cause of emergent abdominal surgery (30). **The symptoms and signs of appendicitis can be similar to those of PID, but the nausea and emesis are often more prominent with appendicitis.**

Symptoms

The first symptom of appendicitis is typically diffuse abdominal pain, periumbilical pain, followed by anorexia, nausea, and vomiting. Within a matter of hours, the pain

generally shifts to the right lower quadrant. Fever, chills, emesis, and obstipation (no flatus or stool per rectum) may ensue. However, this classic symptom pattern is often absent. Atypical abdominal pain can occur when the appendix is retrocecal or entirely within the true pelvis (which occurs in 15% of the population). In this setting, tenesmus and diffuse suprapubic pain may occur.

Signs

A low-grade fever is generally present, but the temperature may be normal. High temperatures are typically seen with appendiceal perforation. **Local tenderness is usually elicited on palpation of the right lower quadrant (McBurney point). The appearance of severe generalized muscle guarding, abdominal rigidity, rebound tenderness, right-sided mass, tenderness on rectal examination, positive psoas sign (pain with forced hip flexion or passive extension of hip), and obturator signs (pain with passive internal rotation of flexed thigh) indicate appendicitis.** The pelvic examination usually does not show cervical motion or bilateral adnexal tenderness, but right-sided unilateral adnexal area tenderness can be present.

Diagnosis

Many patients with acute appendicitis have normal total leukocyte counts but a left shift is usually present. The mean platelet volume has been shown to be helpful in diagnosis; a decrease in MPV was noted with patients with acute appendicitis (31). **Ultrasound examination of the pelvic organs is normal, whereas the appendix may appear abnormal on ultrasound or CT with contrast. CT with oral contrast with normal filling of the appendix rules out appendicitis.** Diagnostic laparoscopy can be useful to rule out other sources of pelvic pathology, but it may be difficult to visualize the appendix sufficiently to rule out early appendiceal inflammation, so appendectomy can be indicated if the diagnosis is uncertain.

Management

Initial management is intravenous administration of fluids, strict restriction of any oral intake, and preoperative antibiotics followed by laparoscopy or laparotomy. **Surgery with a false-positive rate of 15% is considered acceptable and is preferable to prolonged observation with the risk of rupture and peritonitis. A ruptured appendix is life-threatening and can have profound consequences for the fertility of women of reproductive age. With the advent of imaging, negative appendectomy rates are less than 10%** (32).

Acute Diverticulitis

[2] Acute diverticulitis is a condition in which there is inflammation of a diverticulum or outpouching of the wall of the colon, usually involving the sigmoid colon. Diverticulitis typically affects postmenopausal women but can occur in women

during their 30s and 40s.

Symptoms

The severe, left lower quadrant pain of diverticulitis can occur following a long history of symptoms of irritable bowel (bloating, constipation, and diarrhea), although diverticulosis usually is asymptomatic. Diverticulitis is less likely to lead to perforation and peritonitis than is appendicitis. Fever, chills, and constipation typically are present, but anorexia and vomiting are uncommon.

Signs

Bowel sounds are hypoactive and are substantially decreased with peritonitis related to a ruptured diverticular abscess. Abdominal examination reveals distention with left lower quadrant tenderness on direct palpation and localized rebound tenderness. Abdominal and bimanual rectovaginal examinations may reveal a poorly mobile, doughy inflammatory mass in the left lower quadrant. Leukocytosis and fever are common. Stool guaiac may be positive as a result of inflammation of the colon or microperforation. Hemodynamic instability can be seen with perforation.

Diagnosis and Management

CT with and without contrast is an important adjunct to history and physical examination (33). It will reveal a swollen, edematous bowel and can rule out an abscess. A barium enema is contraindicated. Diverticulitis is initially managed medically with intravenous administration of fluids, strict restriction of oral intake, and broad-spectrum intravenous antibiotics. A diverticular abscess, obstruction, fistula, or perforation requires general surgical intervention.

Intestinal Obstruction

The most common causes of intestinal obstruction in women are postsurgical adhesions, hernia, inflammatory bowel disease, or carcinoma of the bowel or ovary.

Symptoms

[2] Intestinal obstruction is heralded by the onset of colicky abdominal pain followed by abdominal distention, vomiting, constipation, and obstipation. Higher and more acute obstruction results in early vomiting. Colonic obstruction presents with a greater degree of abdominal distention and obstipation. Initially vomiting consists of gastric contents, followed by bile, then material with feculent odor, depending on the level of obstruction.

Signs

Fever is often present in the late stages. At the onset of mechanical obstruction, bowel sounds are high pitched and maximal during an episode of colicky pain. As the obstruction progresses, bowel sounds decrease and, when absent, suggest ischemic

bowel. Marked abdominal distention often ensues.

Diagnosis and Management

An upright abdominal x-ray series shows a characteristic gas pattern, distended loops of bowel, and air–fluid levels; and it helps to determine whether obstruction is partial or complete (no colonic gas seen). CT can be useful. WBC count will be elevated in patients with ischemic bowel. **Complete obstruction requires surgical management, whereas partial obstruction often can be managed with intravenous fluids, bowel rest, and selective use of nasogastric suction.** A water-soluble contrast such as Gastrografin has been shown to be therapeutic and shown in studies to improve bowel function, decreased hospital stay, and lower rate of surgery (34). The cause of the obstruction should be determined and treated, if possible. Underlying GI or reproductive tract malignancy may be present.

Urinary Tract Causes of Acute Pelvic Pain

Ureteral colic resulting from ureteral lithiasis is caused by a sudden increase in intraluminal pressure and associated inflammation. Urinary tract infections (UTIs) producing acute pain include cystitis and pyelonephritis. The most common microbes causing UTIs are *Escherichia coli* followed by *Proteus*, *Klebsiella*, and *Pseudomonas* (35).

Symptoms and Signs

[2] The pain of lithiasis is typically severe and crampy; it can radiate from the costovertebral angle (CVA) to the groin. Hematuria is often present. UTI comprises bladder or kidney infection. Cystitis is associated with dull suprapubic pain, urinary frequency, urgency, dysuria, and occasionally hematuria. Pyelonephritis is associated with flank and CVA pain, although lateralizing lower abdominal pain occasionally is present. Urethritis caused by chlamydia or gonorrhea infection can have similar symptoms to those of a UTI. These infections must be ruled out, if relevant.

Diagnosis

The diagnosis of stone can be made by urinalysis revealing red blood cells and demonstration of the stone via abdominal ultrasound, CT urography, or intravenous pyelography (uric acid stones may not be detected by CT). There is pain with firm pressure over the CVA in the case of lithiasis or pyelonephritis. Peritoneal signs are absent. Suprapubic tenderness may accompany cystitis.

The diagnosis of UTI is based on RUA revealing bacteria and leukocytes with or without leukocyte esterase and nitrites, in the absence of significant squamous epithelial cells. Findings can subsequently be confirmed by culture. The diagnostic

thresholds for WBC and vaginal squamous cells vary with each laboratory. An elevated number of squamous cells in the urinary specimen suggests contamination of the urine specimen with vaginal secretions and can result in false-positive urine analysis and culture.

Management

Expectant medical treatment consists of oral hydration or intravenous fluids (if the patient is unable to tolerate oral intake), antibiotics for UTI, and pain control. Surgical management, such as lithotripsy or open surgery, is an option for renal and urethral lithiasis. Nonpregnant women (and pregnant women who are afebrile with a normal WBC count) with pyelonephritis and all women with cystitis can be treated on an outpatient basis. **Nonpregnant women with pyelonephritis can be treated with a 14-day course of a *fluoroquinolone* or *trimethoprim/sulfamethoxazole*** (some sources recommend one intravenous dose of a third-generation cephalosporin before discharging patients with oral antibiotics) (see Chapter 15) (36). Caution should be used with *trimethoprim/sulfamethoxazole* given the rising resistance patterns**. It is important to follow up urine culture sensitivities and treat accordingly.** If there is no improvement, raising concerns for patient compliance, inability to tolerate oral medications and fluids, or whether the patient may be immunocompromised as related to AIDS, intravenous drug use/abuse, diabetes, pregnancy, or chronic steroid use, then the patient should be hospitalized and given intravenous antibiotics.

Tuberculosis should be excluded as a cause of pyelonephritis if the characteristic sterile pyuria is present and the patient's condition does not improve with antibiotics.

Acute Pelvic Pain: Summary

[1] All women of reproductive age with acute pelvic pain should have a CBC with differential, ESR, urinalysis, and a sensitive qualitative urine or serum pregnancy test. If not diagnosed expeditiously, an acute process can often result in significant morbidity or mortality. For patients who have CPP and develop acute exacerbation, it is important to rule out a superimposed acute process. Symptoms of fever, chills, diaphoresis, abnormal vaginal bleeding, dizziness, syncope, emesis, significant diarrhea, obstipation, dysuria, hematuria, hematochezia, and signs of elevated temperature, tachycardia, orthostasis, abdominal distention, abnormal bowel sounds, ascites, peritonitis, or abnormal pregnancy are all indicative of an acute process.

[1] Laboratory tests for the evaluation of acute pelvic pain include a CBC with differential, ESR, clean catch midstream RUA, gonorrhea and chlamydia nucleic acid amplification testing (NAAT) from cervix or urine, and urine or serum pregnancy test. The sedimentation rate is nonspecific, but often is the only abnormal laboratory finding in women with subacute PID. **[1]** If the pregnancy test is positive, a quantitative β-

human chorionic gonadotropin (βhCG) should be ordered. Other studies that are recommended include transvaginal pelvic ultrasound. CT with and without contrast, abdominal x-rays, or upper or lower Gastrografin studies help rule out gastrointestinal pathology when gastrointestinal symptoms predominate. CT is useful for evaluation of retroperitoneal masses or abscesses related to the gastrointestinal tract. Pelvic MRI can be diagnostic if the pelvic ultrasound cannot determine whether a mass is uterine or adnexal.

[1] Diagnostic laparoscopy is reserved for establishing the diagnosis in patients who have acute abdomen of uncertain cause, for elucidating the nature of an ambiguous adnexal mass, or for delineating whether a pregnancy is intrauterine or extrauterine (if ultrasound results and βhCG are equivocal). Visualization is hampered if diagnostic laparoscopy is performed for a large pelvic mass (>12 cm) and is relatively contraindicated in patients with peritonitis, severe ileus, or bowel obstruction. In these settings, laparotomy is preferable. The majority of patients with pelvic pain and a normal pelvic ultrasound have improvement or resolution of symptoms with conservative therapy and do not require surgical intervention (37).

CYCLIC PAIN: PRIMARY AND SECONDARY DYSMENORRHEA

[3] **Dysmenorrhea is a common gynecologic disorder affecting as many as 60% of menstruating women (38). Primary dysmenorrhea refers to menstrual pain without pelvic pathology, whereas secondary dysmenorrhea is defined as painful menses associated with underlying pathology.** Primary dysmenorrhea usually appears within 1 to 2 years of menarche, when ovulatory cycles are established. The disorder affects younger women but may persist into their 40s. Secondary dysmenorrhea usually develops years after menarche and can occur with anovulatory cycles. The differential diagnosis of secondary dysmenorrhea is outlined in Table 12-3.

Primary Dysmenorrhea

[3] **The etiology of primary dysmenorrhea includes excessive or imbalanced amount of prostanoids secreted from the endometrium during menstruation. The prostanoids result in increased uterine contractions with a dysrhythmic pattern, increased basal tone, and increased active pressure. Uterine hypercontractility, decreased uterine blood flow, and increased peripheral nerve hypersensitivity contribute to pain** (39). Prostaglandin compounds are found in higher concentrations in secretory endometrium than in proliferative endometrium. The decline of progesterone levels in the late luteal phase triggers lytic enzymatic action, resulting in a release of phospholipids with the generation of arachidonic acid and activation of the cyclooxygenase (COX) pathway. The biosynthesis and metabolism of prostaglandins

and thromboxane derived from arachidonic acid are depicted in Figure 12-1. Increased synthesis of prostanoids in women with primary dysmenorrhea results in higher uterine tone with high-amplitude contractions causing dysmenorrhea (40). It is theorized that women suffering from dysmenorrhea have upregulated COX enzyme activity and prostanoid synthase activity. This led to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which act as COX enzyme inhibitors, for therapy (41).

Symptoms

The pain of primary dysmenorrhea usually begins a few hours before or just after the onset of a menstrual period and may last 48 to 72 hours. The pain is similar to labor, with suprapubic cramping, and may be accompanied by lumbosacral backache, pain radiating down the anterior thigh, nausea, vomiting, diarrhea, and rarely syncopal episodes. The pain of dysmenorrhea is colicky in nature and, unlike abdominal pain that is caused by chemical or infectious peritonitis, is relieved by abdominal massage, counterpressure, or movement of the body.

Table 12-3 Differential Diagnosis of Chronic Pelvic Pain

Gynecologic	Genitourinary
Noncyclic	Recurrent or relapsing cystourethritis
Adhesions	Urethral syndrome
Endometriosis	Interstitial cystitis/painful bladder syndrome
Salpingo-oophoritis	Ureteral diverticuli or polyps
Ovarian remnant or retained ovary syndrome	Carcinoma of the bladder
Pelvic congestion	Ureteral obstruction
Ovarian neoplasm benign or malignant	**Neurologic**
Pelvic relaxation	Nerve entrapment syndrome, neuroma, or other neuropathies
Cyclic	Trigger points
Primary dysmenorrhea	**Musculoskeletal**
Mittelschmerz	Myofascial pain and trigger points

Secondary dysmenorrhea	**Low-back pain syndrome**
Endometriosis/adenomyosis	Congenital anomalies
Uterine or vaginal anomalies with obstruction of menstrual outflow	Scoliosis and kyphosis
Intrauterine synechiae (Asherman syndrome)	Spondylolysis
Endometrial polyps or nonhormonal intrauterine device (IUD)	Spondylolisthesis
Uterine leiomyomata	Spinal injuries
Pelvic congestion syndrome	Inflammation
Gastrointestinal	Tumors
Irritable bowel syndrome	Osteoporosis
Ulcerative colitis	Degenerative changes
Crohn disease	Coccydynia
Carcinoma	Myofascial syndrome
Infection	**Systemic**
Recurrent partial bowel obstruction	Fibromyalgia
Diverticulitis	Acute intermittent porphyria
Hernia	Abdominal migraine
Abdominal angina	Connective tissue disease including systemic lupus erythematosus
	Lymphoma
	Neurofibromatosis

Signs

On examination, the vital signs are normal. The suprapubic region may be tender to palpation. Bowel sounds are normal, and there is no upper abdominal tenderness and no abdominal rebound tenderness. **Bimanual examination at the time of the dysmenorrheic episode often reveals uterine tenderness; severe pain does not occur with movement of the cervix or palpation of the adnexal structures.** The pelvic organs are normal in primary dysmenorrhea.

Diagnosis

[3] To diagnose primary dysmenorrhea, it is necessary to clinically rule out

underlying pelvic pathology and confirm the cyclic nature of the pain. History taking is important to rule out abnormal uterine bleeding, presence of dyspareunia, or nonmidline focal pelvic pain that can point to other causes of pain. During the pelvic examination, the size, shape, and mobility of the uterus; the size and tenderness of adnexal structures; and the nodularity or fibrosis of uterosacral ligaments or rectovaginal septum should be assessed. NAAT for gonorrhea and chlamydia and if relevant, CBC and ESR, help rule out endometritis and subacute PID. Pelvic ultrasound should be performed if symptoms do not resolve with NSAIDs. If no abnormalities are found, a tentative diagnosis of primary dysmenorrhea can be established. Laparoscopy is not necessary at this point.

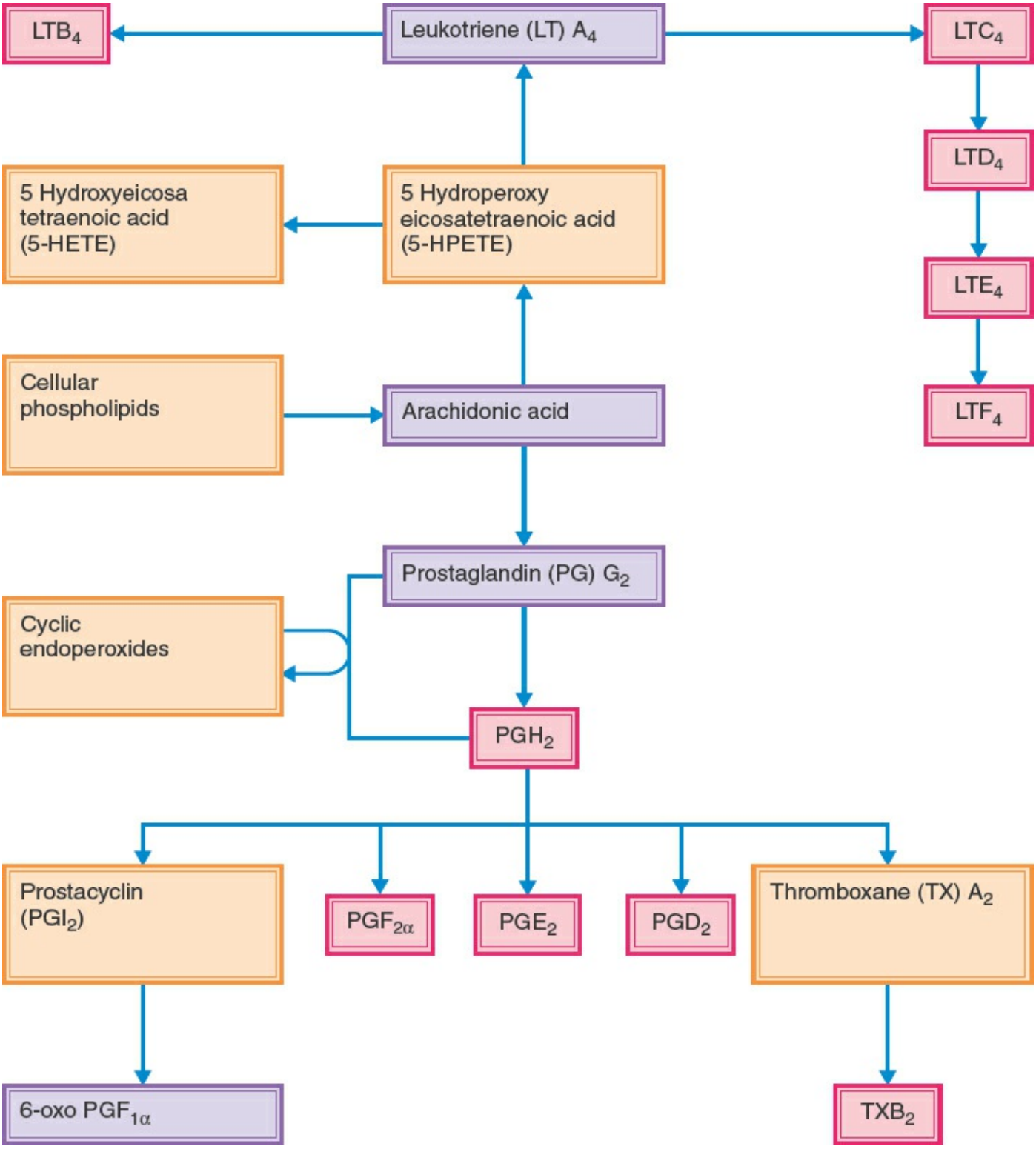


FIGURE 12-1 The biosynthesis and metabolism of prostaglandins and thromboxane derived from arachidonic acid. (From **Chaudhuri G.** Physiologic aspects of prostaglandins and leukotrienes. *Semin Reprod Endocrinol* 1985;3:219, with permission.)

Management

[3] Prostaglandin synthase inhibitors, also called NSAIDs, are effective for the

treatment of primary dysmenorrhea (42). **The inhibitors should be taken up to 1 to 3 days before or, if menses are irregular, at the first onset of minimal pain or bleeding and continuously every 6 to 8 hours to prevent reformation of prostaglandin byproducts.** The medication should be taken for the first few days of menstrual flow. A 4- to 6-month course of therapy is warranted to determine whether the patient will respond to treatment. Changes in dosages and types of NSAIDs should be attempted if initial treatment is not successful. The medication may be contraindicated in patients with gastrointestinal ulcers or bronchospastic hypersensitivity to aspirin. Side effects are usually mild and include nausea, dyspepsia, diarrhea, and occasionally fatigue.

Hormonal contraceptives have been shown to be equally effective to NSAIDs. They are indicated for patients with primary dysmenorrhea who have no contraindications to hormonal contraceptives and who desire contraception. Hormonal contraceptive agents (such as combined estrogen and progestin) or progesterone-only oral contraceptives (OCs) (either cyclic or continuous regimens), transdermal patch, vaginal ring, injectable progestin preparations, or levonorgestrel-releasing intrauterine devices are more effective than placebo alone and result in less absence from work or school (43). Continuous or extended cycle combined OC pills are just as efficacious for this pain syndrome (44). Hormonal contraceptives inhibit ovulation, decrease endometrial proliferation, and create an endocrine milieu similar to the early proliferative phase of the menstrual cycle, when prostaglandin levels are lowest. Decreased prostaglandin levels result in less uterine cramping.

Treatment with both NSAIDs and hormonal contraception may be more effective than either one alone. If the patient does not respond to this regimen for 2 to 3 months, hydrocodone or codeine may be added for 2 to 3 days per month; before addition of the narcotic medication, psychological factors should be evaluated, and diagnostic laparoscopy to rule out pathology should be considered.

Nonpharmacologic pain management, in particular heat, acupuncture, or transcutaneous electrical nerve stimulation (TENS), may be useful (45–47). Acupuncture is thought to excite receptors or nerve fibers, blocking pain impulses through interactions with mediators like serotonin and endorphins. The perception of pain signals is altered with TENS. It does not directly affect uterine contractions. Abdominal electrical or chemical heating pads are effective in treating primary dysmenorrhea. There is insufficient data to support any herbal or vitamin regimen.

Methods rarely used to treat primary dysmenorrhea include surgical laparoscopic uterine nerve ablation and presacral neurectomy and hysterectomy (48).

Secondary Dysmenorrhea

[3] Secondary dysmenorrhea is cyclic menstrual pain that occurs in association with underlying pelvic pathology. The pain of secondary dysmenorrhea often begins 1 to 2 weeks before menstrual flow and persists until a few days after the cessation of bleeding. [3] Underlying causes include endometriosis, adenomyosis, subacute endometritis and PID, copper intrauterine devices (IUDs), ovarian cysts, congenital pelvic malformations, and cervical stenosis. Whereas the diagnosis of primary dysmenorrhea is based on the history and presence of a normal pelvic examination and ultrasound, the diagnosis of secondary dysmenorrhea may require review of a pain diary to confirm cyclicity, and transvaginal ultrasound examination, laparoscopy, and hysteroscopy may be indicated.

[3] The most common cause of secondary dysmenorrhea is endometriosis, followed by adenomyosis and nonhormonal intrauterine devices. NSAIDs and hormonal contraceptives are less likely to provide pain relief in women with secondary dysmenorrhea than in those with primary dysmenorrhea. The differential diagnosis of secondary dysmenorrhea is outlined in Table 12-3. The management of secondary dysmenorrhea is treatment of the underlying disorder.

Endometriosis

[3] In women with endometriosis, endometrial glands and stroma are found outside the uterine cavity, especially at the cul-de-sac, ovaries, and pelvic visceral and parietal peritoneum. They can occur outside the pelvis such as the bowel, diaphragm, and even the pleural cavity. There are several theories of pathogenesis, but none explains all the different types of endometriosis. Given that confirmation requires visual diagnosis, the prevalence of endometriosis is unknown. It is thought to occur in approximately 10% of the general female population, 15% to 20% of infertile women, and more than 30% of women with CPP. In some cases, regression can occur spontaneously (see the section on endometriosis under the heading of chronic pelvic pain and Chapter 13) (49).

Symptoms

Patients typically complain of severe dysmenorrhea and cyclic pelvic pain that starts up to 2 weeks prior to menses. Symptoms depend on the site of endometriosis. The pain can be sharp or pressure-like, localized to the midline or involving the lower abdomen, back, and rectum. Other symptoms include deep thrust dyspareunia, subfertility, irregular bleeding despite ovulatory cycles, and nongynecologic symptoms such as cyclic dyschezia, urinary urgency, frequency, bloating, and rarely hematochezia or hematuria. Patients with thoracic endometriosis can have symptoms of chest pain, pneumothorax, and hemothorax that coincides with menses (50).

Signs

Bimanual and rectovaginal examinations may reveal uterosacral nodularity and focal tenderness. Fibrosis resulting from endometriosis can cause a fixed retroverted uterus or laterally deviated cervix or uterus. Bimanual examination can demonstrate a fullness consistent with ovarian cystic endometrioma. Patients can have focal uterosacral or broad ligament area tenderness. Abdominal wall endometriosis implants can present with a cyclically painful discrete abdominal mass on examination.

Diagnosis

Diagnosis of endometriosis is categorized by nonsurgical or surgical diagnosis. The clinical, or nonsurgical, diagnosis of endometriosis is accurate in approximately 50% of cases. Though a definitive diagnosis of endometriosis cannot be made on imaging studies, endometriomas are generally distinguishable from hemorrhagic corpus lutea by the appearance on ultrasound. Homogeneous hemorrhagic-appearing cysts that fail to resolve after one to two menstrual cycles are suspicious for endometriomas. CA125 can be elevated but is a nonspecific and nonsensitive marker for endometriosis. **Definitive or surgical diagnosis is made by direct operative visualization either laparoscopically or via laparotomy with histologic confirmation.** Active red flame, or colorless vesicles, or petechial lesions usually indicate early disease, while powder-burn, fibrotic lesions suggest more longstanding lesions. Suspicious findings should be biopsied for confirmation. Deep infiltrating lesions and peritoneal windows are most often found within the posterior cul-de-sac, especially at the uterosacral ligaments, and may cause pain by penetrating the many nerve endings in this area (51). Patients with endometriosis have nerve fibers in their endometrial tissue, and studies show endometrial biopsy is a potential, but as yet unproven, diagnostic tool. A double-blind study of 99 women undergoing laparoscopy and endometrial biopsy for evaluation of endometrial nerve fibers found that the biopsy was just as effective as laparoscopy for diagnosing endometriosis (52).

Management of Secondary Dysmenorrhea Caused by Endometriosis: Pharmacologic

Medications can be used to reduce the cyclic hormonal stimulation of these lesions and eventually decidualize or atrophy the lesions. Surgical resection of endometriosis has surgical risks but can reduce pain by removing implants. One study showed short-term improvement in dyspareunia and quality of sex life in patients up to 12 months after radical resection of endometriosis (53). Given the excellent response rate, relatively low cost, and fair tolerability with medical hormonal therapy, an expert consensus panel recommended that women with suspected endometriosis who are not actively trying to conceive and who do not have an adnexal mass start with first-line medical management before laparoscopy. **First-line treatment consists of a trial of combined estrogen–progestin formulations with or without NSAIDs** (54). Both cyclic and continuous combined OCs can be used with equal efficacy (55). Most studies

used OCs containing low-dose estrogen and more androgenic progestins; newer-generation progestins are also effective. Continuous rather than cyclic OC regimens can be tried, without a hormonal break or with menstruation every 3 months. Two reviews have shown that continuous OCs may be more effective at reducing pain symptoms than cyclic regiments in maintaining symptoms after initial surgery (56,57).

Second-line medical therapy involves high-dose progestins or gonadotropin-releasing hormone (GnRH) analogs. This can be initiated for refractory symptoms or for patients with contraindication to estrogen. Progestins alone are associated with few metabolic concerns and are safe and inexpensive alternatives to surgical intervention. Progestins or progestins plus estrogen effectively manage pain symptoms in approximately three-quarters of the women with endometriosis (58). High-dose *medroxyprogesterone acetate* and *norethindrone acetate* are equally effective to the GnRH analogs (59). **Progestins should be given at a dose to achieve amenorrhea, then the dose can be tapered to control symptoms.**

A randomized controlled trial comparing *levonorgestrel* intrauterine system (LNG-IUS) with depot GnRH for the treatment of endometriosis-related chronic pain found that both were effective treatments (60). Etonogestrel implants are shown to be as effective as medroxyprogesterone acetate (61).

GnRH agonist and add-back treatment can be used as pharmacologic treatments for endometriosis (62). A randomized controlled trial of GnRH agonist therapy for 6 months in cases of confirmed endometriosis showed decreased size of endometriotic lesions and pain symptoms. Side effects are related to the hypoestrogenic state and include vasomotor symptoms, mood swings, vaginal dryness, decreased libido, myalgias, and, eventually, bone loss. These side effects can be reduced with supplemental calcium and hormonal add-back therapy with *norethindrone acetate* 2.5 to 5 mg daily with or without low-dose estrogen (0.625 mg of conjugated estrogen or 1 mg of 17 β-estradiol) (62). Given the side effects, GnRH agonists usually are not used for more than 8 to 12 months, but with add-back hormones and/or bisphosphonate, GnRH therapy can be considered for use for more than 1 year. Recurrence of symptoms after discontinuation of GnRH agonist ranges from 36% to 70%, 5 years after completion of treatment.

Androgenic hormones such as danazol are thought to inhibit the luteinizing hormone surge and steroidogenesis and may have anti-inflammatory effects. These medications increase free testosterone, resulting in possible side effects such as deepening of voice, weight gain, acne, and hirsutism. Vaginal *danazol* in lower doses may be effective.

Aromatase p-450 and prostaglandin E2 (PgE_2) pathways are thought, to be involved in the genesis of endometriotic implants. Aromatase plays an important role in estrogen biosynthesis by catalyzing the conversion of androstenedione and testosterone to estrone

and estradiol. Although aromatase activity is not detectable in normal endometrium, it is found in eutopic endometrium and endometriotic lesions. **Thus, aromatase inhibitors (AIs) are being used as adjunctive therapy with medical therapies in refractory cases** (63). A 2008 review of eight studies evaluated AIs for management of endometriosis and found that AIs combined with progestins or OCs or GnRH analogs decreased mean pain scores and lesion size and improved the quality of life. In the only randomized controlled trial (97 women) evaluated in this meta-analysis, AI (*anastrozole*) in combination with GnRH agonist significantly improved pain ($p < 0.0001$) compared with GnRH agonist alone at 6-month follow-up, and there was no significant reduction in the spine or hip bone density (64).

Management of Endometriosis: Surgical

Laparoscopy and laparotomy are appropriate for some patients, and can be considered for treatment in the management of secondary dysmenorrheal pain related to endometriosis that is unresponsive to hormonal agents (see also Chapter 13). Excellent operative skill is required to manage endometriosis surgically. Endometriotic lesions should be ablated or resected. Endometriomas must be removed with their capsule. Resection of endometriomas by ovarian cystectomy improves pain and fertility in women with CPP and endometriosis when compared to fenestration, drainage, and coagulation. In a randomized controlled trial of laser ablation for minimal to moderate endometriosis, over 90% of women felt improved at 1-year follow-up, and 87% of women with stage III to IV endometriosis were satisfied with the results at 1-year follow-up. Recurrent pain after 24 months is close to 50% (65). A meta-analysis found that there was no difference in pain levels when comparing patients with surgical and medical management of endometriosis (66). Given these findings, the risks and benefits of surgical management should be thoroughly discussed with patients when coming up with a treatment plan.

In women who no longer desire fertility with severe secondary dysmenorrhea, hysterectomy with BSO and removal of endometriosis lesions is the preferred treatment. Hysterectomy without BSO results in a higher rate of disease recurrence and a 30% reoperation rate. The risk of recurrent endometriosis with hormone replacement is small if combined estrogen–progestin preparations are used and unopposed estrogen is avoided.

There are limited data regarding outcomes for repeated conservative surgical procedures, including pelvic denervation procedures (65). Although reoperation is often considered the best option, the long-term outcome appears suboptimal with a cumulative probability of recurrent pain between 20% and 40%, and of further surgical procedure at least 20%. Hysterectomy with BSO decreased the need for reoperation to treat pelvic pain by sixfold. Postoperative medical treatment with OCs can be effective (67). Reoperation in a symptomatic patient after previous conservative surgery should take

into account the psychological state of the patient, desire for future fertility, and whether the pain responded to prior surgical therapy with at least 1, but preferably 3 to 5 years of pain relief.

Rectovaginal endometriosis is often deeply infiltrating, highly innervated, and associated with severe cyclic pelvic pain and dyspareunia (see also Chapter 13). These lesions can be surgically challenging for laparoscopic resection. Hormonal therapy can be effective. One study reviewed hormonal therapy in 217 patients: 68 in 5 observational studies, 59 in a cohort study, and 90 in a randomized controlled trial (68). The study compared AI, vaginal *danazol*, GnRH agonist, intrauterine progestin, and two estrogen–progestin combinations, transvaginally or transdermally, and an oral progestin. With the exception of an AI used alone, the pain relief with medical therapies was satisfactory over the 6- to 12-month course of the treatment, with 60% to 90% of women reporting substantial decrease or complete relief from pain symptoms.

Adenomyosis

[3] Adenomyosis is defined as the presence of endometrial stroma and glands within the myometrium, at least one low-power field from the basis of the endometrium, whereas endometriosis is characterized by ectopic endometrium appearing within the peritoneal cavity. Adenomyosis, endometriosis, and uterine leiomyomas frequently coexist. Although occasionally noted in women in their younger reproductive years, the average age of symptomatic women is usually older than 40 years. Increasing parity, early menarche, and shorter menstrual cycles may all be risk factors according to one study (69–71).

Symptoms

Symptoms typically associated with adenomyosis include excessively heavy or prolonged menstrual bleeding, dyspareunia, and dysmenorrhea. Symptoms often begin up to 2 weeks before the onset of a menstrual flow and may not resolve until after the cessation of menses. Patients may present with CPP.

Signs

The uterus is typically diffusely enlarged, although usually less than 14 cm in size, and is often soft and tender, particularly at the time of menses. Mobility of the uterus is not restricted, and there is no associated adnexal pathology (72).

Diagnosis

Adenomyosis is a clinical diagnosis. Definitive diagnosis can only be made histologically. Imaging studies including pelvic ultrasound or MRI, although helpful, are not definitive. Because of the cost of MRI and negligible improvement in diagnostic accuracy, this study is not recommended routinely. Transvaginal ultrasound has been shown to have an accuracy rate of 68% to 86% in diagnosing adenomyosis. The

accuracy decreases in women who have coexisting fibroids or who have focal adenomyosis (73). In women with diffuse uterine enlargement and negative pregnancy test results, secondary dysmenorrhea may be attributed to adenomyosis; **however, the pathologic confirmation of suspected adenomyosis can be made only at the time of hysterectomy.**

Management

The management of adenomyosis depends on the patient's age and desire for future fertility. **Relief of secondary dysmenorrhea caused by adenomyosis can be ensured after hysterectomy, but less invasive approaches can be tried initially. NSAIDs, hormonal contraceptives, and menstrual suppression using oral, intrauterine, or injected progestins or GnRH agonists are all useful.** Treatment follows the same protocol as treatment for endometriosis. Uterine artery embolization can be effective (74).

CHRONIC PELVIC PAIN

[3] CPP is defined as pelvic pain that persists in the same location for greater than 6 months' duration, causing functional disability or requiring treatment. CPP is an inclusive, general term that encompasses many more specific causes, ranging from reproductive, gastrointestinal, and urinary tract etiologies to myofascial pain and nerve entrapment syndromes. CPP affects 12% to 20% of women in the United States. The differential diagnosis of CPP is outlined in Table 12-3. **[3] Nongynecologic causes of pain, such as IBS, interstitial cystitis (IC)/bladder pain syndrome (BPS), abdominal wall or pelvic floor myofascial syndrome, or neuropathy, are frequently overlooked but common causes of CPP.** This can in part explain why 60% to 80% of patients undergoing laparoscopy for CPP have no intraperitoneal pathology (2).

Patients with CPP are often anxious and depressed. Their marital, sexual, social, and occupational lives are disrupted. While some patients with CPP present with psychiatric comorbidities, some women develop secondary symptoms as a result of CPP. These patients frequently have poor treatment outcomes from traditionally effective gynecologic and medical therapy and may undergo multiple unsuccessful surgical procedures for pain. About 12% to 19% of hysterectomies are performed for pelvic pain, and 30% of patients who present to pain clinics have had a hysterectomy (75).

CPP states are characterized by upregulation of CNS responsiveness to peripheral stimuli. **[3] The relationship between the pain and pathology, such as endometriosis, adhesions, or venous congestion, is inconsistent and treatment is associated with pain recurrence. Recent investigations suggest that "plasticity" of the nervous system or alterations in signal processing may be involved in the maintenance of**

chronic pain states (2,6). Maladaptive changes within the peripheral and CNS predispose to allodynia (pain with usually nonpainful stimuli), hyperalgesia (excessive pain with a potentially painful stimulus), widening of the receptive field (pain experienced over a larger territory), and abnormal reflex responses in surrounding musculature (5–7,76).

The spinal cord is not a simple conduit between the periphery and the brain. It is an important site of "gating" mechanisms, such as excitation, inhibition, convergence, and summation of neural stimuli (77). With visceral tissue injury, a subset of nociceptive C-fibers that are usually dormant, called "silent" afferents, can become activated. The dorsal horn of the spinal cord is then flooded with noxious chemical stimuli that, over time, can lead to upregulation of the signaling in the dorsal horn and brain, and pain sensation can be persistent and amplified, even after the peripheral pathology has resolved. The dorsal horn neurons demonstrate a number of electrophysiologic changes in this setting, such as the development of spontaneous activity, enlarged receptive fields, and lowered threshold for firing.

[3] In chronic pain states, the pain is no longer adaptive. The initial painful input produces a persistent abnormal state of increased responsiveness called central sensitization (8). It is not known why in some individuals or in certain settings, prolonged stimuli or injury will result in sensitization. Different regions of the CNS are important in modulating the sensory and affective components of the pain response. Pain persistence is fostered by adverse or traumatic early experience, conditioning, fear, arousal, depression, and anxiety.

Evaluation of Chronic Pelvic Pain

[4] On the first visit, a thorough pain history should be performed, taking into consideration the nature of each pain symptom: location, radiation, severity, aggravating and alleviating factors; effect of menstrual cycle, stress, work, exercise, intercourse, and orgasm; the context in which pain arose; and the social and occupational toll of the pain (Table 12-4). A visual or verbal analog pain scale to record pain severity 0 through 10 and stating "no pain" and "worst possible pain" is important in assessing the severity of pain and comparing the changes in severity over subsequent visits. **[4]** The evaluation should include a comprehensive questionnaire that addresses depression, anxiety, emotional, physical and sexual trauma, quality of life, and criteria to assist with the diagnosis of IBS and IC/BPS. The International Pelvic Pain Society published a comprehensive pain assessment tool in order to facilitate the history and physical examination, which can be found on the International Pelvic Pain Society's Web site and reprinted or reproduced (78).

Diagrams of a woman's abdomen, back, and genital area should be used to help the patient define the location of pain (2). The patient should be questioned about symptoms

specific to the types of pathology listed in Table 12-3.

1. [4] **Genital (abnormal vaginal bleeding, abnormal vaginal discharge, dysmenorrhea, dyspareunia, sub-fertility, sexual functioning)**
2. **Enterocoelic (constipation, diarrhea, flatulence, hematochezia, and relationship of pain to times of altered bowel function or form and pain relief with bowel movements)**
3. **Musculoskeletal/neuropathic (physical trauma—surgical or injury, exacerbation with exercise or postural changes, weakness, numbness, lancinating pain)**
4. **Urologic (urgency, frequency, nocturia, hesitancy, dysuria, hematuria, incontinence)**
5. **Psychological (previous diagnoses, hospitalizations, and medications, current depression, anxiety, panic, including suicidal ideation, past and current emotional, physical, or sexual trauma)**

Record a thorough gynecologic, medical, and surgical history; medication, ethanol, or recreational drug intake; prior evaluations for pain with outcome; and review prior operative and pathology reports. Prior physical, emotional, and sexual trauma or abuse should be ascertained (79–81). The attitude of the patient and her family toward the pain, resultant behavior of the patient and her family, and current upheavals in the patient's life should be discussed. The part of the history relating to sensitive issues may have to be revisited after establishing rapport with the patient.

Table 12-4 Pain History Mneumonic

OLD CAARTS	Pain History
Onset	When and how did pain start? Did it change over time?
Location	Localize specifically. Can you put a finger on it?
Duration	How long does it last?
Characteristic	Cramping, aching, stabbing, burning. "like lightening," tingling, itching
Alleviating/Aggravating factors	What makes it better (medication, stress reduction, heat/ice, position change) or worse (specific activity, stress, menstrual cycle)?
Associated symptoms	Gynecologic (dyspareunia, dysmenorrhea, abnormal bleeding, discharge, infertility), GI (constipation, diarrhea, bloating, gas, rectal bleeding), GU (frequency, dysuria, urgency, incontinence), neurologic (specific nerve distribution)
Radiation	Does it move to other areas (dermatomal)?

Temporal	What time of day (elation to menstrual cycle and activities of daily living)?
Severity	Scale of 0–10

GI, gastrointestinal; GU, genitourinary.
From Rapkin AJ, Howe CN. Chronic pelvic pain: A review. Part 2. In: *Family Practice Recertification*. Monroe Township, New Jersey: Medical World Communications, 2006;28:59–67.

Whatever the original cause of the pain, when pain has persisted for any length of time, it is likely that other psychosocial factors are now contributing to the maintenance of the pain. Pain is commonly accompanied by anxiety and depression, and these conditions need to be carefully assessed and treated (2,82,83). In a typical gynecologic setting, referral to a psychologist or psychiatrist for parallel evaluation can evoke resistance. The inference is drawn that the referring physician is ascribing the pain to psychological causes. The patient needs to understand the reason for this referral and to be reassured that it is a routine and necessary part of the evaluation. **A psychologist is one of the key personnel in a multidisciplinary pain clinic.**

[4] A complete physical examination should be performed, with particular attention directed to the abdominal and lumbosacral areas, vulva, pelvic floor, and internal organs via vaginal, bimanual, and rectovaginal examination. The examination should include the *Carnett test,* which is an evaluation of the painful sites on the abdominal wall before and after tensing of the abdominal muscles (head raised off the table or with bilateral straight leg raise) to differentiate abdominal wall and visceral sources of pain. Abdominal wall pain is augmented and visceral pain is diminished with palpating the tender points during these maneuvers (84). While standing, the patient should be examined for hernias, both abdominal (inguinal and femoral) and pelvic (cystocele and enterocele). An attempt should be made to locate by palpation the tissues that reproduce the patient's pain. If abdominal wall sources of pain are noted, it is useful to block these areas with injection of local anesthetics and then perform the pelvic examination (84). Neuropathic symptoms (sharp or lancinating or electrical pain, burning, or tingling sensations) should be localized to the peripheral nerve subserving the involved area.

Reproductive Tract

The most common findings noted at the time of laparoscopy for CPP are endometriosis and adhesions. Patients with other gynecologic pathologies, such as benign or malignant ovarian cysts, uterine leiomyomas of a size sufficient to encroach on supporting ligaments or other somatic structures, or significant pelvic relaxation should be evaluated and treated in a manner that is appropriate for the underlying condition. Pain associated with these latter conditions is generally not severe, and appropriate surgical management is therapeutic.

Endometriosis

See the section on secondary dysmenorrhea above and for a more thorough discussion of the diagnosis and management of endometriosis refer to Chapter 13.

[4] Endometriosis can be demonstrated in 15% to 40% of patients undergoing laparoscopy for CPP. Endometriosis is a surgical diagnosis based on identification and histology of characteristic lesions (85). Endometriosis produces a low-grade inflammatory reaction; over time this results in adhesions between confluent pelvic organs (86). However, the cause of the pain is not well established. **[4] There is no correlation between the location of disease and pain symptoms.** (87,88). **There appears to be no relationship between the incidence and severity of pain or the stage of the endometriotic lesions, and as many as 30% to 50% of patients have no pain regardless of stage. Similarly, 40% to 60% of patients have no tenderness on examination regardless of stage** (88). Deeply infiltrating endometriosis lesions that involve the rectovaginal septum and the bowel, ureters, and bladder are strongly associated with pain (86,89,90) Pelvic adhesions related to endometriosis are a predictor of pelvic pain (91). Vaginal and uterosacral deep lesions are associated with dyspareunia and dyschezia.

Prostaglandin E and $F_{2\alpha}$ production from explants of petechial lesions present in mild, low-stage disease was found to be significantly greater than from the explants of powder-burn or black lesions, which are more common in patients with higher-stage endometriosis. Prostaglandin and cytokine production may account for severe pain in some patients with mild disease. More importantly, endometriotic implants acquire a vascular and nerve supply that may contribute to peripheral and CNS sensitization and persistence of pain even after surgical therapy (92–94).

Endometriosis-related pain syndrome is a new and evolving concept that is defined as pain that does not respond adequately to appropriate medical and surgical therapy, especially in the setting of minimal or mild disease. In this situation, neural plasticity results from central sensitization, hypothetically initiated by the peripheral inflammatory insult (93). The disease is no longer just the endometriosis, but is fostered by the alterations in the peripheral and CNS. Endometriosis-related pain syndrome is often co-existent or "comorbid" with other chronic conditions such as IC/PBS, IBS, myofascial pain, fibromyalgia and vulvodynia, and anxiety disorders. These disorders need to be managed concurrently.

Adhesions

[4] Adhesions noted at the time of laparoscopy may be in the same general region of the abdomen as the source of the pelvic pain; however, neither the specific location (i.e., adnexa structures, parietal, visceral peritoneum, or bowel) nor density of the adhesions correlates consistently with the presence of pain symptoms (95,96). In one nonrandomized, noncontrolled study of adhesion lysis, a

subgroup of women with anxiety, depression, multiple somatic symptoms, and social and occupational disruption responded poorly to adhesiolysis. The group without these characteristics had significant improvement in pain (97). Prospective randomized controlled trials do not support adhesiolysis for women with CPP. A randomized controlled trial of laparoscopic adhesiolysis showed an improvement in both the groups (i.e., laparoscopy with and laparoscopy without lysis of adhesions), suggesting a large placebo effect (98–100). One randomized controlled trial that did not consistently demonstrate a significant long-term reduction in pain did find some improvement if the adhesions were dense and involved the small bowel (101). In a nonrandomized study of patients who underwent adhesiolysis for pelvic pain, 41% of patients still had residual abdominal symptoms during a 15 year follow up (102).

Most women with adhesions had a prior surgical procedure with possible injury to abdominal wall nerves, such as the iliohypogastric or ilioinguinal nerves, and those are more likely to be the cause of the pain. The abdominal wall must be carefully evaluated for myofascial or nerve injury, or entrapment, as the source of pain before assuming that adhesions contribute to the genesis of pain.

Diagnosis

Diagnostic laparoscopy is recommended if GI, GU, and myofascial and neuropathic causes are ruled out or treated and the results of the psychological evaluation are negative. Mini-laparoscopy using local anesthesia and conscious sedation is used to perform "conscious pain mapping," whereby specific adhesions are tweaked and pelvic pain response is recorded (103). In an observational study of 50 women using local anesthesia, manipulation of appendiceal and pelvic adhesions contributed to pelvic pain. However, lysis of these adhesions did not improve outcomes over traditional laparoscopic therapy (2,104).

Management

The causal role of adhesions in the genesis of pelvic pain is uncertain, and surgery will lead to further adhesion formation and perhaps organ injury. Therefore, lysis is not recommended unless there is intermittent partial bowel obstruction or infertility. Although some observational studies showed that laparoscopic lysis of adhesions can alleviate CPP, randomized controlled trials have not revealed any long-term benefit. If surgery is performed, barrier materials such as oxidized regenerated cellulose or hyaluronic acid with carboxymethyl cellulose have been shown in meta-analysis studies to be effective for prevention of adhesion reformation (105). Repeated surgical procedures for lysis of adhesions are not indicated.

Pelvic Congestion

Pelvic congestion syndrome involves congestion or dilation of uterine and/or ovarian venous plexuses (106–110). First proposed in the 1950s, this condition was a

suggested result of emotional stress that could lead to smooth muscle spasm and congestion of ovarian and uterine pelvic venous plexuses. A subsequent blind study was undertaken to compare results of transuterine venography in patients with unexplained CPP and negative laparoscopy with controls. This study demonstrated that women with CPP had a larger mean ovarian vein diameter, delayed disappearance of contrast medium, and greater ovarian plexus congestion compared to controls. The existence of this condition is controversial as this condition does not have definitive diagnostic criteria (110).

Pelvic congestion syndrome results from compression of the left renal vein at the origin of the superior mesenteric artery (also known as "nutcracker syndrome"). This leads to pelvic venous congestion.

Signs and Symptoms

[4] Pelvic congestion affects women of reproductive age. Typical symptoms include bilateral lower abdominal and back pain that is increased with standing for long periods, secondary dysmenorrhea, dyspareunia, abnormal uterine bleeding, chronic fatigue, and irritable bowel symptoms (110). Pain usually begins with ovulation and lasts until the end of menses. The uterus is often bulky, and the ovaries are enlarged with multiple functional cysts. The uterus, parametria, and uterosacral ligaments are tender.

Diagnosis

Diagnosis can be made clinically. However, imaging can be used to help diagnosis and aid in therapy. Transuterine venography or MRI are the primary method for diagnosis, although other modalities, such as pelvic ultrasound and laparoscopy, may disclose varicosities (106,110). Because of the cost and possible side effects of treatment, further management should be based on related symptoms and not solely on the presence of varicosities.

Management

Treatment of suspected pelvic congestion ranges from the less invasive hormonal suppression and cognitive–behavioral pain management to the more invasive ovarian vein embolization or hysterectomy and salpingo-oophorectomy (106–110). Low-estrogen, progestin-dominant continuous OCs, high-dose progestins, and GnRH analogs often provide pain relief (107). Hormonal suppression should be the initial mode of treatment for women with suspected pelvic congestion. *Medroxyprogesterone acetate,* 30 mg daily, is useful (108). Goserelin acetate (3.5 mg a month for 6 months) has been shown to be effective in treating pelvic congestion in pelvic venography improvements and in symptom improvement (107). A multidisciplinary approach incorporating psychotherapy, behavioral pain management, or both is highly recommended. Percutaneous transcatheter embolization can be considered for women who do not respond to medical or hormonal therapy (109,110). Technically more

invasive, transcatheter embolotherapy selectively catheterizes the ovarian and internal iliac veins, followed by contrast venography and embolization. This treatment showed some promise in small uncontrolled studies, but larger randomized controlled trials are necessary to validate its benefits. For women who have completed their childbearing, hysterectomy with oophorectomy is a reasonable option if multidisciplinary management has failed (110).

Subacute Salpingo-Oophoritis

Patients with salpingo-oophoritis usually present with symptoms and signs of acute infection. Atypical or partially treated infection may not be associated with fever or peritoneal signs. **Subacute or atypical salpingo-oophoritis is often a sequel of chlamydia or mycoplasma infection.** Abdominal tenderness, cervical motion, and bilateral adnexal tenderness are typical of pelvic infection (see Chapter 15).

Ovarian Remnant and Residual Ovary Syndromes

[4] In a reproductive-aged patient who has had a BSO, with or without a hysterectomy, for severe endometriosis or PID, CPP may be caused by ovarian remnant syndrome (111). **This syndrome results from residual ovarian cortical tissue that is left in situ after a difficult dissection in an attempt to perform an oophorectomy. This tissue can become encased in adhesions and result in painful cysts.** Often, the patient had multiple pelvic operations with the uterus and adnexa removed sequentially. Laparoscopic oophorectomy, combined with a difficult dissection, is a strong risk factor.

Residual ovary syndrome is uncommon considering the number of women undergoing hysterectomy with ovarian preservation. **Theoretically, after a hysterectomy with one or both ovaries intentionally left in situ, adhesions develop and encase the ovaries, then cyclical expansion of the ovaries can result in pain and, in some cases, a tender persistent mass. This can be seen in patients with endometriosis in which ovarian implants are left in place.**

Symptoms

The patient usually reports lateralizing pelvic pain, often cycling with ovulation or the luteal phase that is described as sharp and stabbing or constant, dull, and nonradiating, occasionally with associated genitourinary or gastrointestinal symptoms. Symptoms tend to arise 2 to 5 years after initial oophorectomy. A tender mass in the lateral region of the pelvis is pathognomonic. The patient may report deep dyspareunia, constipation, or flank pain.

Diagnosis

Ultrasonography usually confirms a mass with the characteristics of ovarian tissue.

The accuracy of ultrasound can be improved by treating the patient with a 5- to 10-day course of *clomiphene citrate,* 100 mg daily, to stimulate follicular development. In a patient who has had BSO and is not taking hormone therapy, estradiol and follicle-stimulating hormone (FSH) assays reveal a characteristic premenopausal picture (FSH <40 mIU/mL and estradiol >20 pg/mL), although on occasion the remaining ovarian tissue may not be active enough to suppress FSH levels (111). The patient may have a persistent estrogenized state based on the vulvar and vaginal examination and lack postmenopausal symptoms such as hot flashes, night sweats, and mood changes. **Medical therapy that suppresses ovarian function can be diagnostic and therapeutic.** Imaging with pelvic ultrasound can be used if pelvic mass is found on exam.

Management

Patients who are not candidates for, or decline, surgery can be managed through medical treatment such as high-dose progestins or OCs, which usually provides good results. Patients experience pain relief with a GnRH agonist, although these medications are impractical for long-term therapy. Those who achieve relief with GnRH agonists also experience relief with subsequent surgery (112). Laparoscopic examination usually is not productive because the ovarian mass may be missed or adhesions may prevent accurate diagnosis. A few articles documented successful laparoscopic treatment of this condition (113,114). **Removal of the remnant ovarian tissue is necessary for treatment, and the corrective surgery tends to be arduous, with risks of cystotomy, enterotomy, and postoperative small bowel obstruction** (111). Surgical pathology usually reveals the presence of ovarian tissue, sometimes with endometriosis, corpus lutea or follicle cysts, and fibrous adhesions. *Clomiphene citrate* can be used 7 to 10 days before surgery to induce folliculogenesis, allowing ovarian tissue to be more easily detected.

Gastroenterologic Etiology

The uterus, cervix, and adnexa share visceral innervation with the lower ileum, sigmoid colon, and rectum. These pain signals travel through sympathetic nerves to spinal cord segments T10 to L1. [4] It is often difficult, therefore, to determine whether lower abdominal pain is of gynecologic or enterocoelic origin. Skillful medical history and examination are necessary to distinguish gynecologic from gastrointestinal causes of pain. Inflammatory bowel disease, such as Crohn disease or ulcerative colitis, infectious enterocolitis, intestinal neoplasms, appendicitis, and hernia must be ruled out with appropriate history and physical examination, complete blood cell count, and stool cultures and visualization of colonic mucosa when appropriate.

Irritable Bowel Syndrome

[4] IBS is one of the more common causes of lower abdominal pain and may account for up to 60% of referrals to the gynecologist for CPP. An estimated 35% of patients with CPP have a concurrent diagnosis of IBS (115,116). Women who had a hysterectomy for CPP are twice as likely to have IBS. Women are at a slightly higher risk of IBS than men (117). The pathophysiology of IBS appears to be influenced by CNS sensitization and decreased descending inhibition, which ultimately leads to visceral hypersensitivity. Visceral hypersensitivity and abnormal reflex responses, demonstrated in both animal and human studies, result in an increased intensity of pain, lowered threshold for sensation, and an enlarged viscera-somatic region of pain referral, all of which lead to the IBS symptoms (118,119).

Symptoms

The predominant symptom of IBS is abdominal pain. Other symptoms include abdominal distention, excessive flatulence, alternating diarrhea and constipation, increased pain before a bowel movement, decreased pain after a bowel movement, and pain exacerbated by events that increase gastrointestinal motility, such as eating, stress, anxiety, depression, and menses. The pain is usually intermittent, occasionally constant, cramp-like, and more likely to occur in the left lower quadrant. The patient with IBS can be placed into one of three categories: constipation-predominant, diarrhea-predominant, and pain-predominant (alternating bowel habits) depending on their main symptoms. The new Rome IV criteria for diagnosis (Table 12-5) includes at least 3 days of recurrent abdominal pain or discomfort per month over the past 3 months with at least two of the following features: relief with defecation, onset associated with change in stool frequency, or onset associated with change in the form and appearance of stool (120).

Table 12-5 Rome IV Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain for at least 1 day per week (on average) for the previous 3 months with onset of symptoms at least 6 months before the diagnosis and associated with two of three features:
1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

Signs

On physical examination, the findings of a palpable tender sigmoid colon or discomfort during insertion of the finger into the rectum and hard feces in the rectum are suggestive of IBS.

Diagnosis

The diagnosis of IBS is usually based on history and physical examination, and although suggestive, especially in young women, the findings are not specific. A CBC, thyroid function study, stool sample to test for white cells and occult blood, and sigmoidoscopy or colonoscopy or barium enema are usually required, particularly in older individuals and in young individuals who have not responded to initial treatment. The results of these studies are all normal in patients with IBS.

Management

Treatment consists of reassurance, education, stress reduction, bulk-forming agents and other symptomatic treatments, and low-dose tricyclic antidepressants (TCAs). A multidisciplinary management approach consisting of medical and psychological approaches is recommended. Patients should eliminate triggers in their diet, such as food containing lactose, sorbitol, alcohol, fat, and fructose. Products that contain caffeine can cause abdominal bloating, cramping, and more frequent bowel movements. After the patient has tried these lifestyle changes, if she remains symptomatic, a short-term trial of antispasmodics such as *dicyclomine* or *hyoscyamine* can be given (117–119). Multidisciplinary therapy addresses the cognitive, affective, and behavioral components of the pain. Therapy may decrease the intensity of nociceptor stimulation and change the patient's interpretation of the meaning of pain (119).

Antispasmodic agents relax the smooth muscle and reduce contractility of the gastrointestinal tract. While antispasmodics and laxatives may produce symptomatic relief of bowel symptoms, the pain symptoms of IBS may respond to antidepressants. **Low-dose TCAs can alleviate the pain of IBS as shown in a number of randomized controlled trials. TCAs can reduce excessive gastrointestinal contractility and are approved for use as antispasmodics.** TCAs may be used for women with moderate to severe pain, who were refractory to other therapies. Although the dose to achieve the analgesic response is much lower than that used for antidepressive effects, TCAs may be increased to higher dosages in patients with coexisting depression. **Selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) were used successfully in the treatment of IBS and can be used in those patients failing TCA treatment or those who are depressed or are unable to tolerate the side effects of TCAs** (117–119).

Urologic Etiology

[4] CPP of urologic origin may be related to recurrent cystourethritis, urethral syndrome, sensory urgency of uncertain cause, and IC/PBS. With an appropriate diagnostic workup, infiltrating bladder tumors, ureteral obstruction, renal lithiasis, and endometriosis can easily be ruled out as possible causes.

Urethral Syndrome

Urethral syndrome is defined as a symptom complex including dysuria, frequency and urgency of urination, suprapubic discomfort, and often dyspareunia in the absence of any abnormality of the urethra or bladder (121). The cause of urethral syndrome is uncertain and is attributed to a subclinical infection, urethral obstruction, and psychogenic and allergic factors. The symptoms of urethral syndrome may evolve into the initial stages of IC/PBS.

Symptoms

Urinary urgency, frequency, suprapubic pressure, and other less frequent symptoms such as bladder or vaginal pain, urinary incontinence, postvoid fullness, dyspareunia, and suprapubic pain are commonly observed. According to the American Urological Association, these symptoms must be present for at least 6 weeks.

Signs

Physical and neurologic examinations should be performed. Anatomic abnormalities, including pelvic relaxation, urethral caruncle, and hypoestrogenism, should be evaluated. The patient should be evaluated for vaginitis. The urethra should be carefully palpated to detect purulent discharge.

Diagnosis

A clean catch or catheterized urine specimen for RUA and culture should be obtained to rule out UTI. Urine cytology can help exclude malignancy or hematuria. A postvoid residual can easily be done in clinic to check for urinary retention. As indicated, urethral and cervical studies for chlamydia should be obtained, and a wet prep for vaginitis should be performed. Urethral syndrome should be considered if infection is ruled out, the evaluation does not disclose vulvovaginitis, and no allergic phenomenon causing contact dermatitis of the urethra can be detected. The possibility of ureaplasma, chlamydia, candida, trichomonas, gonorrhea, and herpes should be eliminated. Cystoscopic evaluation should be performed to rule out urethral diverticulum, stones, and cancer. Pelvic floor muscles should be evaluated, as spasm of these muscles can lead to urethral pain and tenderness. The urethral pain can be a manifestation of IC/PBS.

Management

Various forms of therapy are suggested for urethral syndrome. **Those patients in whom no infectious agent is present but who have sterile pyuria may respond to a 2- to 3-week course of *doxycycline* or *erythromycin.*** Long-term, low-dose antimicrobial prophylaxis often is used in women with urgency and frequency symptoms who had careful documentation of recurrent UTIs. Some of these women may continue to have symptoms when their urine is not infected, and bacterial infection redevelops over time.

Posttreatment test of cure cultures are useful. **It is recommended that all postmenopausal women with this condition be given a trial of local estrogen therapy for at least 2 months.** If there is no improvement after antibiotic or estrogen therapy, physical therapy (PT), and cognitive–behavioral therapy, then urethral dilation can be considered but recent studies are lacking. Positive results were noted with biofeedback techniques. Other treatments including acupuncture and laser therapy proved successful (122). Psychological support is very important in this group of women. **Management requires a multidisciplinary approach, as is true of CPP in general.**

Interstitial Cystitis/Bladder Pain Syndrome or Painful Bladder Syndrome

IC/BPS occurs more often in women than men. Most patients are between 40 and 60 years of age. In 2002, painful bladder disorders were defined by the International Continence Society (ICS) in a set of new recommendations (123). The most widely used definition, **painful bladder syndrome (PBS) is described as a clinical syndrome (i.e., a complex of symptoms) consisting of "suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and nighttime frequency in the absence of proven infection or other obvious pathology." By comparison, the term "IC" refers to patients who have PBS symptoms, but who also have "typical cystoscopic and histologic features" during bladder hydrodistention** (123).

The etiology of IC/PBS is unknown, but several hypotheses exist. A defective glycosaminoglycan (GAG) epithelial layer, which allows irritating substances in the urine to penetrate the urothelium to the subepithelial nerve endings, may be responsible for the syndrome (124). This theoretical mechanism is based on the fact that many IC sufferers are sensitive to certain foods and beverages. Immunologic mechanisms were proposed because abnormal mast cell activity, increased substance P–expressing nerve fibers and increased nerve growth factor, were all found in bladder biopsies of IC-affected individuals (124). Autoimmune mechanisms may be responsible in some individuals given that there is a higher incidence of systemic lupus erythematosus, allergies, inflammatory bowel and IBD, and fibromyalgia in patients with bladder symptoms. Another possible mechanism is central sensitization with altered sympathetic and hypothalamic adrenal axis, substantiated by the existence of "phantom" bladder pain even after surgical removal of the bladder (125).

Symptoms

Symptoms include pain and severe and disabling urinary frequency and urgency, nocturia, and occasional dysuria and hematuria. Suprapubic, pelvic, urethral, vaginal, vulvar, or perineal pain is common and can be relieved to some extent by emptying of the bladder (125).

Signs

Pelvic examination usually reveals anterior vaginal wall and suprapubic tenderness. Pelvic floor muscles are invariably involved, and tender to palpation. Urinalysis may reveal microhematuria without pyuria, although results are usually normal.

Diagnosis

The diagnosis is one of exclusion and is no longer based on cystoscopy. Definitions and diagnostic criteria continue to change. **In 2011, the American Urological Association defined criteria as an unpleasant sensation perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes.**

National Institutes of Health (NIH) Consensus Criteria for diagnosis of IC states that patients must have at least two of the following: (1) pain on bladder filling relieved by emptying; (2) pain in suprapubic, pelvic, urethral, vaginal, or perineal region; (3) glomerulations on endoscopy or decreased compliance on cystometrogram (126).

Patients can be evaluated with cystoscopy with hydrodistention and biopsy. Petechial bladder mucosal hemorrhages (glomerulations) are characteristic of IC. The use of a pelvic pain and urgency or frequency symptom scale and a bladder potassium intravesical test can promote early diagnosis (127); it is debatable whether a positive potassium test is definitive for IC or if a positive test is a manifestation of bladder hyperalgesia (126).

Management

Although there is no definitive cure for IC/PBS, patients can achieve remission with multidisciplinary therapy. First-line treatments are primarily behavioral modification such as bladder training and stress management, cognitive–behavioral therapy, dietary modifications or restriction of acidic, spicy, and fermented foods, and pelvic floor muscle PT. These first-line treatments are individually specific. For example, studies have shown that the foods that can cause irritation differ between individuals (128). Urinary alkalinization can be useful (129). TCAs have been efficacious. *Amitriptyline* 10 mg can be taken at bedtime and titrated as tolerated up to 150 mg or to relief of symptoms. *Amitriptyline* has antihistaminic, anticholinergic, and sodium channel blocking properties that are potentially therapeutic for opposing the histamine from mast cell degranulation, urinary frequency, and neuropathic pain, respectively (129). Oral *pentosan polysulfate sodium* (PPS) is the only U.S. Food and Drug Administration (FDA)-approved oral therapy for IC and is modestly beneficial (129,130). *Pentosan polysulfate* is a heparin-like moiety that resembles the GAG layer, but should not be used with NSAIDs because of the bleeding risk.

Intravesical therapy can be first- or second-line. With an intravesical mixture of *lidocaine,* bicarbonate, and *heparin* instilled three times a week for 3 weeks, 57% of

women reported resolution of pain (131). *Dimethyl sulfoxide* (*DMSO*) is the only FDA-approved intravesical treatment of IC. Intravesical 50% *DMSO* showed significant symptomatic improvement compared to placebo in two randomized controlled trials. Intravesical solutions containing dissolved PPS showed some promise but are not FDA approved and are under investigation (132). Hydrodistention of the bladder to maximum capacity under epidural anesthesia has been used to treat ICS/PBS and has shown to be helpful in improving symptoms (133,134).

Sacral neuromodulation is an invasive, yet promising, technique under investigation for treatment of refractory IC (135). Sacral neuromodulation is not FDA approved for IC, and larger studies are required to confirm efficacy.

Treatments that require more data to support safety and efficacy include intravesical instillation of GAGs and intradetrusor botulinum toxin.

Neurologic and Musculoskeletal Causes

Nerve Entrapment

[4] Abdominal cutaneous nerve injury or entrapment of the iliohypogastric or ilioinguinal nerves can occur with transverse suprapubic laparotomy incisions or laparoscopy incisions placed inferior to the anterior superior iliac spine. Injury can follow heavy lifting or traumatic injury, such as with a motor vehicle accident. The ilioinguinal (thoracic 12, lumbar 1 and lumbar 2, T12, L1, L2) or iliohypogastric (T12 and L1, L2) nerves may become trapped between the transverse and internal oblique muscles, especially when the muscles contract. Alternatively, the nerve may be ligated or traumatized during the surgery (136). **Localized pain in the L1–L2 dermatome lateral to the rectus muscle immediately following surgery should be evaluated expeditiously, as removal of the offending fascial suture will be curative. Neuropathic pain may not begin until weeks after surgery or even years following surgery, following vigorous abdominal wall stress with lifting or reinjury.**

Femoral nerve injury can result when deep lateral retractor blades compress the nerve between the blade and the lateral pelvic side wall (137). Femoral nerve damage results in an inability to flex at the hip joint or to extend at the knee.

Symptoms of nerve entrapment or injury include sharp, burning, aching pain, and paresthesia in the dermatomal distribution of the involved nerve. With nerve entrapment, hip flexion and exercise or activity exacerbates pain and rest or infiltration with a local anesthetic relieves pain. The pain is usually judged as coming from the abdomen, not the skin (138).

Pudendal neuropathy can result from vaginal surgery (especially with lateral mesh attachments), childbirth, exercise, and chronic constipation or pelvic floor muscle abnormalities. Vulvar surgical procedures including episiotomies, laser hair

removal, and Bartholin gland removal can lead to injury of the vestibular, rectal, or clitoral nerves, terminal branches of the pudendal nerve (139**)**.

Nantes criteria for pudendal nerve entrapment in and around the Alcock canal are: (1) pain in the sacral 2–4 dermatomal area innervated by the pudendal nerve (i.e., ipsilateral clitoris/ penis, distal urethra, labia/scrotum, perineum, and anus); (2) pain is increased while sitting; (3) patient is not awakened by pain; (4) no sensory loss on clinical examination (sensory deficits are suggestive of a sacral nerve root lesion); (5) resolution of pain with administration of pudendal nerve block (140). Entrapment can potentially be relieved by surgical release but neuralgia caused by nerve injury will not recover from surgery. It is not possible with examination or imaging to completely differentiate pudendal entrapment from neuralgia related to nerve injury.

Signs

On examination, the point of maximal tenderness or pain should be localized with the fingertip. The maximal point of tenderness in an iliohypogastric or ilioinguinal injury is at the rectus margin, medial and inferior to the anterior iliac spine. Carnett test will be positive with increased pain over the area of entrapment or injury. Carnett test involves palpation of the tender area followed by repalpation during an abdominal wall tensing maneuver, that is abdominal crunch (3/4 "sit up") or bilateral straight leg raise. Abdominal wall pain is more severe with palpation during muscle contraction in the setting of L1, L2 nerve entrapment, injury, hernia, or myofascial pain. For the pudendal nerve, the maximal tenderness is near the ischial spine and the Alcock canal.

A tentative diagnosis or neuropathy can be confirmed by a diagnostic nerve block with 3 to 5 mL of 0.25% *bupivacaine*. Patients usually report immediate relief of symptoms after injection, and at least 50% of patients experience relief lasting longer than a few hours over the following weeks.

Management

Many patients may require no further intervention after a series of weekly nerve blocks and avoiding activities that lead to compression of the nerve. Many patients require PT or medications that downregulate nerve firing. Medications for neuropathic pain include topical local anesthetics, oral anticonvulsants, or antidepressants. PT can be helpful in cases of pudendal neuropathy involving abnormal functioning of levator or obturator internus muscles. If injection and other pharmacologic approaches produce only limited pain relief and there are no contributory visceral or psychological factors, surgical decompression of the involved nerve may be recommended.

Myofascial Pain

Myofascial pain of the abdominal wall or pelvic floor muscles are commonly overlooked in the evaluation of CPP. **[4]** **Myofascial pain syndrome (MPS) consists of pain originating from muscle trigger points in the skeletal muscle and fascia. By**

definition, a myofascial trigger point is a "hyperirritability focus within a tender, taut band-like hardness within one or more skeletal muscles or the associated fascia" (141). Intra-abdominal pathology, muscular overload, and direct trauma can result in the development of trigger points but are not required for development or perpetuation.

Depending on the study, 13% to 75% of women with CPP have myofascial pelvic tenderness and/or trigger points (142). **Pelvic floor muscle pain can result from surgical trauma, poor posture, severe constipation, or viscerosomatic reflex responses.** The muscles sharing thoracolumbar and sacral nerve supply with the reproductive, gastrointestinal, and urinary systems can lead to pelvic floor and abdominal wall muscle pain (143). Trigger points can develop in muscles in the zone of the referred pain from the underlying organ and in turn the trigger point can lead to abdominal fullness, bloating, swelling, and gas. IC/PBS, IBS, endometriosis, and vulvodynia are associated with pelvic floor dysfunction and trigger points and many women with these diagnoses have, or will develop, generalized chronic myofascial pain and fibromyalgia (143). Trigger points in the lower rectus abdominis between the umbilicus and symphysis can develop in women with severe dysmenorrhea.

Symptoms

History should investigate overuse, repetitive strains, injuries, and dysfunctional posturing which can result in myofascial trigger points in the abdominal wall, back, and pelvic floor. History of IBS, IC/PBS, or endometriosis should prompt a search for abdominal wall and pelvic floor myofascial pain. **Abdominal wall and pelvic floor myofascial pain is exacerbated by activity, or by stimuli to the dermatome of trigger points** (e.g., full bladder, bowel, luteal phase, or menses; any stimulation to organs that share the dermatome of the involved nerve) (144).

Signs

Pelvic muscle assessment should include both external and internal muscles. In addition to testing for tenderness, muscle strength, for which both the squeeze and lift components are essential, and function testing are important (145). Unfortunately, techniques for the discovery of pelvic floor trigger points are not standardized, making it difficult to describe the musculoskeletal system for the diagnostic workup.

Management

Massage therapy can help relieve the pain in some cases. "Myofascial release" is a special vigorous message that can be effective (141). Depending on the location of the myofascial trigger points, pelvic floor PT is indicated (145,146).

PT entails manual techniques to inactivate trigger points, restore muscle length, and correct predisposing factors. Pelvic floor PT involves a variety of muscle relaxation and lengthening exercises to pelvic floor muscles as well as releasing trigger

points by connective tissue release. A retrospective chart review of 75 women with chronic myofascial pelvic pain noted significantly improved pain scores proportional to the number of PT visits completed (144). A randomized study noted 57% patients with CPP benefited from myofascial PT (147,148). The response rate was significantly greater with PT compared to therapeutic massage. Sustained pressure with adequate force to a trigger point for a specified period or injection can inactivate the irritable point (149).

NSAIDs, gabapentin, pregabalin, low-dose TCAs, SNRIs, and benzodiazepines may be useful in patients requiring pharmacologic interventions. Injection of the trigger point with 3 mL of 0.25% bupivacaine provides relief that usually outlasts the duration of the anesthetic action. After four to five biweekly injections, the procedure should be abandoned if long-lasting relief is not obtained. A 60-patient randomized controlled trial compared lidocaine patch and placebo patch versus anesthetic injection for the treatment of Myofascial Pain Syndrome (MPS). The study revealed similar efficacy of anesthetic patch to the gold standard treatment with trigger point injection and was associated with less discomfort than injection therapy (151). Acupuncture can be effective (152). Concomitant with injection at trigger points; relaxation, stress reduction, and cognitive–behavioral pain management should be undertaken, especially if anxiety, depression, history of emotional trauma, physical or sexual abuse, sexual dysfunction, or social or occupational disruption are present.

Fibromyalgia

[4] Fibromyalgia is an *MPS*, made up of the triad of diffuse pain, fatigue, and nonrestorative sleep. Women with abdominal wall or pelvic floor myofascial pain, IC/PBS, and IBS often have comorbid *fibromyalgia*. Women are affected more commonly than men. To diagnose the syndrome, the patient must have tender points in all four quadrants. The cause is thought to be a CNS sensitization that results in abnormal perception of chronic pain. Fibromyalgia is closely associated with *chronic fatigue syndrome,* a combination of regional myofascial problems including infections and autoimmune disorders or dysautonomias. The management includes education, environmental changes (well-balanced diet, adequate time for sleep, and an environment conducive to restful sleep), exercise and stretching, and counseling or cognitive behavioral therapy for relaxation and maximizing coping mechanisms. Medications used include NSAIDs, low-dose TCAs, selective SNRIs, anticonvulsants, and benzodiazepines to improve sleep (150).

Low-Back Pain Syndrome

In women who experience lower-back pain without pelvic pain, gynecologic pathology rarely is the cause of their pain. However, low-back pain may accompany gynecologic pathology. Back pain may be caused by gynecologic, vascular,

neurologic, psychogenic, or spondylogenic (related to the axial skeleton and its structure) pathology (153).

Symptoms

Women with low-back pain syndrome often have pain occurring after trauma or physical exertion, in the morning on arising, or with fatigue. Nongynecologic low-back pain can intensify with the menstrual cycle.

Signs

Examination consists of inspection, evaluation with movement, and palpation. Various anatomic structures in the spine should be considered as sources of pain. Muscles, vertebral joints, and discs (including the lumbosacral junction, paravertebral sacrospinal muscles, and sacroiliac joints) are common sources of spondylogenic pain that must be examined carefully (2).

Diagnosis

Diagnostic imaging studies performed while the patient is standing, lying, and sitting with maximal flexion can be helpful. An elevated ESR suggests pain of inflammatory or neoplastic origin. Though most patients with acute back pain do not require imaging, plain films can be obtained to evaluate for infection, fracture, malignancy, spondylolisthesis, degenerative changes, disc space narrowing, and prior surgery. For patients who require advanced imaging, MRI without contrast is considered to be the best imaging modality.

Management

Consultation with the patient's primary care provider should be sought before initiating management for back pain unless the source could be referred gynecologic pain. For more complex cases, an orthopedic or neurosurgery consult may be required.

Vulvodynia

[4] Vulvodynia has a prevalence of 15% and is classified as vulvar pain for at least 3 months without a clear source (154). Specific causes of vulvar pain must be excluded before a diagnosis of vulvodynia can be made. **Specific causes of vulvar pain that should be ruled out include inflammatory conditions (dermatitis, dermatoses), malignancy, neuralgia, trauma, iatrogenic causes (e.g., chemotherapy, radiation, surgery), infection (candida, herpes), and hormonal deficiency.** Factors that can initiate or maintain vulvodynia include comorbid pain or psychiatric disorders, genetic predisposition to pain or inflammation, sex steroid hormone deficiency, pelvic floor musculoskeletal abnormalities, relevant neurologic changes in the pudendal or sacral 2–4 nerves, and psychosocial issues. **Vulvodynia is classified by pain localization,**

triggers, and timing of onset. If there is localized pain of the vulvar vestibule (vestibulodynia) or clitoris (clitorodynia), vulvodynia is classified as localized. Pain over the entire vulva is called generalized vulvodynia. Mixed vulvodynia refers to pain that is localized and generalized. Pain is further classified as provoked which means pain with genital contact or spontaneous, whereby the pain occurs without contact. Pain can be provoked and spontaneous. If the pain occurs from the first genital penetration attempt, it is classified as primary. If the pain starts after a period of painless genital contact, it is classified as secondary.

The pathophysiology of vulvodynia is unclear but likely complex and multifactorial. **Provoked vestibular pain, the most common type of vulvodynia, has been hypothesized to start with a chronic inflammatory process or immunologic challenge such as yeast infection or injury.** Proliferation of nociceptive nerve fibers, increased inflammatory infiltrate dominated by mast cells, and increased neuroinflammatory neurokines, cytokines, chemokines, and prostanoids can develop in predisposed individuals (155). Altered pelvic floor musculature contractility often is associated but may be etiologic. There is evidence for central and peripheral sensitization with hypersensitivity to tactile, thermal, and chemical stimuli.

A history and examination are adequate for the diagnosis of vulvodynia. Patients should be questioned about their medical, psychological, sexual, and pain history (156). **The vulva and vagina should be examined for any lesions, infections, or dermatoses. A cotton swab is used to test the vestibule for pain at 12, 2, 5, 6, 7, and 10 o'clock. Pain of at least 4/10 on a numeric rating scale when the swab is pressed to a depth of 1/3 of the cotton tip for 1 second is consistent with provoked vestibulodynia.** Pelvic floor muscle tone and tenderness should be ascertained with a single lubricated finger in the vagina. A wet mount of vaginal discharge should be performed to look for yeast or bacterial vaginosis and for signs of inflammation (excessive white blood cells) or estrogen deficiency (multiple parabasal or intermediate cells). Imaging studies can be considered to diagnose the pain if not limited to vestibule.

The treatment of vulvar pain is multifactorial. Address any underlying disorder which may be causing the pain such as infection, dermatoses, psychological, or hormonal issues. Long-term hormonal contraceptives may contribute to vestibular thinning and pain. Vulvar hygiene is an important part of the treatment. Patients should be taught to eliminate pads, allergens, fabric softeners, soaps, and other potentially irritating chemicals. **The pharmacologic treatments of vulvodynia can include topical lidocaine 5%, anticonvulsants such as gabapentin topical (6% compounded) or oral, TCAs either as a topical or oral formulation, botulinum toxin injections, hormonal therapy if estrogen deficiency is noted, and injections of local anesthetic with or without steroid. Pelvic floor PT is usually recommended for treatment of**

vulvodynia. Further treatments include surgery (vestibulectomy) for provoked vestibulodynia, psychological (cognitive–behavioral, psychotherapy, mindfulness-based relaxation therapy), EMG biofeedback, and complementary/alternative treatments such as acupuncture or hypnotherapy (157–161).

Psychological Factors

[3] Psychological factors that increase pain vulnerability and lower resilience promote the chronicity of pain (162). The meaning attached to the pain, pain-related catastrophizing, low self-efficacy in managing pain, poor pain coping, anxiety, negative affect, childhood emotional, physical or sexual traumatic experiences, and poor social support all play a role in maintaining and amplifying chronic pain (163–165). Recent investigations are beginning to shed light on how current and previous psychological, behavioral, and psychosocial factors affect chronic pain. Crucial are the changes in brain networks concerning reward, motivation, learning, and pathways descending from the brain to the periphery that modulate pain (162). **[3] There is a close relationship between depression and pain**. The Beck Depression Inventory can be used as a tool for evaluation; a score over 12 suggests dysphoria and over 18, depression (166). Antidepressants, particularly SNRIs often relieve depression and pain.

[3] Childhood physical abuse has been noted to be more prevalent in women with CPP than in those with other types of pain (39% vs. 18.4%) (81). In a comparison of women with CPP, women with nonpelvic chronic pain (headache), and pain-free women, a higher lifetime prevalence of major sexual abuse and physical abuse was found in the CPP group. Childhood traumas may lead to an increased vulnerability to psychosocial stress and impaired coping strategies and promote chronicity of pain after an injury.

If patients are taught self-efficacy and adaptive pain coping skills through psychological treatment interventions, pain can be reduced and functioning improved. Cognitive-behavioral therapy can be useful in treating CPP (167). Dramatizing the pain is a coping mechanism that is used by pain sufferers to generate support from others around them (168). This practice, combined with pain-related anxiety and fear, propagates pain.

Management of Chronic Pelvic Pain

Multidisciplinary Approach

[3] The multidisciplinary management approach recognizes the importance of cognitive, psychological, and myofascial contributions to chronic pain. The treatment milieu for women with chronic pain must be therapeutic, optimistic, and supportive. The patient should be instructed to complete a daily pain rating form

for two menstrual cycles and bring to her subsequent visit. This form provides the clinician and patient with important information for pain diagnosis and management. Each day, the average pain level (0 to 10), mood (0 to 10), vaginal bleeding (yes or no), and briefly, events that trigger pain such as stress, foods, and physical activities should be recorded. The pain ratings can encourage the patient's sense of control and decrease feelings of helplessness. Daily recording improves self-efficacy and compliance, and help the patient to recognize the connection between pain and stressors. The ratings reveal the relationship of the pain to the menstrual cycle. Cyclical pain associated with ovulation, premenstrual, or menstrual phase can be improved with hormonal suppression.

[3] Offering regular follow-up appointments is preferable to asking the patient to return only if pain persists because the latter reinforces pain behavior. Specific pain management skills should be taught using cognitive–behavioral approaches by a psychologist or with techniques as mindfulness-based meditation or yoga. **Patients should be instructed in ways to enhance opportunities for control of pain.** Various strategies, including cognitive-behavioral therapy, mindfulness-based relaxation techniques, stress management, hypnosis, and other psychotherapeutic approaches affect CNS pain networks and increase descending inhibition of peripheral pain signals. **Psychological group treatment is a very cost-effective approach for helping patients learn stress reduction techniques and develop coping behavioral mechanisms** (169). Psychotherapy is indicated for women who have pronounced depression, sexual difficulties, or previous trauma. Acupuncture can be helpful. Myofascial evaluation can be supplemented by PT evaluation and if appropriate, PT treatment should be initiated.

Various studies of multidisciplinary pain management in CPP were performed in the past (170). This approach incorporates the skills of the gynecologist, psychologist, and physical therapist, and may include an anesthesiologist for specialized nerve blocks. Retrospective, uncontrolled studies revealed relief of pain in 85% of the participants (171). One prospective randomized study revealed a similar response rate, which was significantly better than that of traditional therapy for pain and associated symptom reduction, improvement of daily functioning, and the quality of life (170).

[3] The following groups of patients should be considered for multidisciplinary therapy early in the management process: (1) no obvious pathology; (2) pathology that has an equivocal role in pain production; (3) poor response to traditionally effective medical or surgical management; (4) more than one visceral or somatic structure involved in the production of pain (i.e., more than one "pain generator"); (5) significant stress, anxiety, posttraumatic stress disorder, or depression; (6) history of past or current physical, emotional, or sexual trauma. There is a dearth of evidence based on controlled trials for the treatment of noncyclic pelvic pain (172).

Pharmacologic Interventions

Any patients with dysmenorrhea or pain that worsens in the luteal or menstrual phase should be given pre-emptive NSAIDs in adequate doses and/or hormonal agents to suppress ovulation and/or menses. The choice of the hormonal agent used to suppress the menstrual cycle will vary with patient preference, concurrent medical conditions, and side effects.

Patients with neuropathic pain or those with evidence of central sensitization or myofascial pain benefit from agents that alter neural processing (173). **A low dose of a TCA, most anticonvulsants, and selective SNRIs are often effective, especially if combined with cognitive-behavioral therapy or mindfulness.** These pharmacologic agents lower the threshold for nerve firing and can help reduce reliance on narcotic pain medication, increasing activity, and relieving the impact the pain has on women's lifestyle (104).

Anticonvulsants such as *gabapentin* or *pregabalin* are useful for treatment of CPP. *Gabapentin* plus *amitriptyline* can be more efficacious than *amitriptyline* alone (173). The anticonvulsants likely impact pain via blockade of calcium channels.

Local anesthetics are sodium channel blockers and they downgrade nerve firing. Ilioinguinal, iliohypogastric, pudendal nerve blocks and trigger point injections can be easily learned by the gynecologist and used liberally where appropriate to downregulate neural signaling.

Women with significant depression or anxiety should be treated with an appropriate therapeutic dose of antidepressant or anxiolytic medication. Psychiatry can be consulted in this setting.

The role of opioid therapy in chronic pain is controversial and randomized controlled trials are lacking. Long-term management of CPP with narcotic medications is considered a last resort after failure of all other treatment modalities. Opioids should be given on a scheduled basis, and patients should have consistent follow-up with evaluation of the extent of pain relief, level of function, and quality of life. Physicians should carefully document failure of other treatment options and patient counseling. Narcotics should be prescribed only with a narcotic contract. The patient should sign a written contract agreeing to obtain pain medications from only one provider and describing other expectations with respect to treatment. Some other points that the patient should agree to include no early refills or increasing dosage of medication without discussion with the doctor, no alcohol or illegal drugs, random blood or urine drug screens if needed, and psychiatric or psychological evaluation if needed. Updated opioid guidelines for chronic noncancer pain are available (174,175).

Physical Therapy

PT procedures restore tissue and joint flexibility, improve posture and body mechanics, restore strength and coordination, reduce nervous system irritability, and restore function (175). **PT is an important component of the management of patients with myofascial pain in the abdominal wall, pelvic floor, or lower back or fibromyalgia** (146).

Laparoscopy

Women with disabling pain that is premenstrual and/or menstrual and that does not respond to NSAIDs or hormonal contraceptives should be considered for laparoscopic evaluation. Diagnostic laparoscopy is a standard procedure in the evaluation of patients with chronic noncyclic pelvic pain; however, laparoscopy is generally withheld until other nongynecologic somatic or visceral causes of pain are excluded. During diagnostic laparoscopy, endometriotic lesions should be excised for biopsy, and if infection is suspected, cultures should be performed. The laparoscopy is essentially a debulking procedure, and all visible endometriosis may not be able to be removed safely; but if possible the implants should be excised or electrocoagulated.

Presacral neurectomy and laparoscopic uterosacral nerve ablation (LUNA) are techniques to interrupt the nerve supply to the uterus. A large study showed that LUNA was no more effective for CPP than laparoscopy alone (176). A 2007 review revealed that there is insufficient evidence to recommend pelvic nerve disruption for the treatment of dysmenorrhea (177).

The role of pelvic adhesions in pain is unclear, and the efficacy of lysis of adhesions is even more in doubt. Adhesiolysis, even via laparoscopy, is frequently complicated by adhesion reformation and may not be effective for relief of pain in controlled trials (96–102). Other causes must be treated first, and psychological consultation and management should precede or accompany the lysis of adhesions.

Hysterectomy

Although 19% of hysterectomies are performed to cure pelvic pain, 30% of patients presenting to pain clinics have already undergone hysterectomy without experiencing pain relief. A multidisciplinary approach including a gynecologist, physical therapist, and a psychologist decreased the frequency of hysterectomy in one study from 16.3% of patients with CPP to 5.8% (178).

[4] Hysterectomy is particularly useful for women who have completed childbearing and have secondary dysmenorrhea or chronic pain related to endometriosis, uterine pathology, such as adenomyosis, or pelvic congestion. However, hysterectomy is generally not indicated for patients with CPP (179–181). Before recommending hysterectomy for pain or unilateral adnexectomy for unilateral pain, it is useful to apply the **PREPARE** mnemonic in discussions with the patient (182): the ***P*rocedure** that is being done, ***R*eason** or indication, ***E*xpectation** or desired

outcome of the procedure, ***P*robability** that the outcome will be achieved, ***A*lternatives** and nonsurgical options, and ***R*isks** as well as ***E*xpense** (see Chapter 3). Hysterectomy for central pelvic pain in women with dysmenorrhea, dyspareunia, and uterine tenderness provided relief of pain in 77% of women in one retrospective study and in 74% of women in one prospective cohort study (183). Nevertheless, 25% of women in the retrospective study noted that pain persisted or worsened at 1-year follow-up (183). Persistent pain in the prospective study was associated with multiparity, prior history of PID, absence of pathology, and Medicaid payer status. The Maine Women's Health Study, a prospective cohort study, studied outcomes of 199 women with frequent pain at baseline who underwent hysterectomy. In this cohort, only 11% reported persistent symptoms after their surgery (184).

The American College of Obstetricians and Gynecologists outlined criteria that should be met before performing a hysterectomy for pelvic pain (185). **They require at least 6 months of pelvic pain without any otherwise correctable pathology.** When deciding on the surgical approach, consideration should be given to a vaginal or laparoscopic hysterectomy over an abdominal approach, if there are no extensive adhesions expected or large uterine/fibroid size does not preclude it. There are many studies that confirm less morbidity and shorter hospital stays with vaginal compared with abdominal hysterectomies (186). A prospective study of abdominal versus vaginal versus laparoscopically assisted surgery did not find any statistical difference or worsening of outcomes of urinary or sexual function between the different approaches at 6 months (186).

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CHAPTER 13

Endometriosis



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KEY POINTS

1 Endometriosis is diagnosed by visualization of lesions during laparoscopy, ideally with histologic confirmation; positive histology confirms the diagnosis, but negative histology does not exclude it.

2 Endometriosis can be associated with infertility, pelvic pain, that is, dysmenorrhea, dyspareunia and nonmenstrual pain, and reduced quality of life.

3 Severe or deep endometriosis should be managed in a facility with the necessary expertise to provide treatment in a multidisciplinary context, including advanced laparoscopic surgery and laparotomy.

4 The American Society for Reproductive Medicine (ASRM) staging system for endometriosis is subjective and correlates poorly with pelvic pain and infertility.

5 The Endometriosis Fertility Index (EFI) predicts non-in vitro fertilization (IVF) pregnancy rates after surgical treatment of endometriosis.

6 Suppression of ovarian function reduces pain associated with endometriosis. Different classes of hormonal drugs—combination oral contraceptives, progestins, gonadotropin-releasing hormone (GnRH) agonists—are equally effective in reducing pain but have differing side effects and costs.

7 Ablation or resection of endometriotic lesions plus adhesiolysis in minimal to mild endometriosis is more effective than diagnostic laparoscopy alone in improving fertility.

8 Suppression of ovarian function is not effective in improving subsequent fertility in patients with endometriosis.

Endometriosis is defined as the presence of endometrial-like tissue (glands and/or stroma) outside the uterus. The most frequent sites of implantation are the pelvic viscera and the peritoneum but, although rare, it can also be found in the pericardium, pleura, lung, and even the brain. Endometriosis varies in appearance from a few minimal lesions on otherwise intact pelvic organs, to deep infiltrating nodules and massive ovarian endometriotic cysts with extensive adhesions involving bowel, bladder, and ureter resulting in significant distortion of the pelvic anatomy. It is estimated to occur in 10% of reproductive-age women and is associated with pelvic pain and infertility. Considerable progress in understanding the pathogenesis, spontaneous evolution, diagnosis, and treatment of endometriosis has occurred. **The European Society for Human Reproduction and Embryology (ESHRE) guidelines for the clinical management of endometriosis are published and regularly updated to present emerging clinical evidence** (1).

EPIDEMIOLOGY

Prevalence

Endometriosis is found predominantly in women of reproductive age but is reported in adolescents and in postmenopausal women receiving hormonal replacement therapy (2). It is found in women of all ethnic and social groups. **Estimates of the frequency of endometriosis vary widely, but the prevalence of the condition is assumed to be around 10% women of reproductive age** (3,4). Although no consistent information is available on the incidence of the disease, temporal trends suggest an increase among women of reproductive age (4). The World Endometriosis Research Foundation (WERF) EndoCost study calculated the costs of women with histologically proven endometriosis treated in referral centers (5). The study showed that the costs to women with endometriosis are substantial, resulting in an economic burden similar to the estimated annual health care costs for diabetes mellitus, Crohn disease, and rheumatoid arthritis (5).

In women with pelvic pain or infertility, a high prevalence of endometriosis (from a low of 20% to a high of 90%) is reported (6,7). **In women with unexplained infertility (regular menstrual cycle, normal pelvic imaging, normospermic partner) with or without pain, the prevalence of endometriosis is reported to be as high as 50%** (8). **In asymptomatic women undergoing tubal ligation (women of proven fertility), the prevalence of endometriosis ranges from 3% to 43%** (9–14). This variation in the reported prevalence may be explained by several factors. First, it may vary with the diagnostic method used: laparoscopy, the operation of choice for diagnosis, is a better method than laparotomy for diagnosing minimal to mild endometriosis. Second, minimal or mild endometriosis may be more thoroughly evaluated in asymptomatic patients than in asymptomatic patients during tubal sterilization. Third, the interest and experience of the surgeon has relevance because there is a wide variation in the appearance of subtle endometriosis implants, cysts, and adhesions. Most studies that evaluate the prevalence of endometriosis in women of reproductive age lack histologic confirmation (9–11,15–20).

Risk and Protective Factors

The following are possible risk factors for endometriosis: infertility, red hair, early age at menarche, shorter menstrual cycle length, hypermenorrhea, nulliparity, müllerian anomalies, low birth weight (less than 7 pounds), being one of multiple fetal gestation, *diethylstilbestrol* (DES) exposure, endometriosis in first-degree relative, tall height, dioxin or polychlorinated biphenyls (PCB) exposure, a diet high in fat and red meat, and prior surgeries or medical therapy for endometriosis (21,22). Prior use of contraception or intrauterine device (IUD), or smoking is not associated with increased risk of endometriosis (23,24). **Protective factors against the development of endometriosis include multiparity, lactation, tobacco exposure *in utero,* increased body mass index, increased waist-to-hip ratios, and diet high in vegetables and fruits** (21,25). Some evidence suggests that women with a "pinpoint cervix" have an increased risk for endometriosis, but more studies are needed to confirm this observation (26).

Endometriosis and Cancer

Several publications link endometriosis with an increased risk for certain gynecologic and nongynecologic cancers (27,28). These associations are controversial and no good data exist to inform clinicians regarding the best management of patients who might be at risk of developing such cancers (1). Endometriosis should not be considered a medical condition associated with a clinically relevant risk of any specific cancer (29). **Data from large cohort and case-control studies indicate an increased risk of**

ovarian cancers in women with endometriosis. The observed effect sizes are modest, varying between 1.3 and 1.9 (30). **Evidence from clinical series consistently demonstrates that the association is confined to the endometrioid and clear-cell histologic types of ovarian cancer** (31). A causal relationship between endometriosis and these specific histotypes of ovarian cancer should be recognized, but the low magnitude of the risk observed is consistent with the view that ectopic endometrium undergoes malignant transformation with a frequency similar to its eutopic counterpart (32). Evidence for an association with melanoma and non-Hodgkin lymphoma has been reported but needs to be verified, whereas an increased risk for other gynecologic cancer types is not supported (31).

ETIOLOGY

Although signs and symptoms of endometriosis have been described since the 1800s, its widespread occurrence was acknowledged only during the 20th century. **Endometriosis is an estrogen-dependent disease. Three theories were proposed to explain the pathogenesis of endometriosis:**

1. **Ectopic transplantation of endometrial tissue**
2. **Coelomic metaplasia**
3. **The induction theory**

No single theory can account for the location of endometriosis in all cases.

Transplantation Theory

The transplantation theory, originally proposed by Sampson in the mid-1920s, is based on the assumption that endometriosis is caused by the seeding and implantation of endometrial cells by transtubal regurgitation during menstruation (33). **Substantial clinical and experimental data support this hypothesis** (6,34). Retrograde menstruation occurs in 70% to 90% of women, and it may be more common in women with endometriosis than in those without the disease (9,35). The presence of endometrial cells in the peritoneal fluid, indicating retrograde menstruation, is reported in 59% to 79% of women during menses or in the early follicular phase, and these cells can be cultured in vitro (36,37). The presence of endometrial cells in the dialysate of women undergoing peritoneal dialysis during menses supports the theory of retrograde menstruation (38). Endometriosis is most often found in dependent portions of the pelvis —the ovaries, the anterior and posterior cul-de-sac, the uterosacral ligaments, the posterior uterus, and the posterior broad ligaments (39). The menstrual reflux theory combined with the clockwise peritoneal fluid current explains why endometriosis is predominantly located on the left side of the pelvis (refluxed endometrial cells implant

more easily in the rectosigmoidal area) and why diaphragmatic endometriosis is found more frequently on the right side (refluxed endometrial cells implant there by the falciform ligament) (40,41).

Endometrium obtained during menses can grow when injected beneath abdominal skin or into the pelvic cavity of animals (42,43). Endometriosis was found in 50% of *Rhesus* monkeys after surgical transposition of the cervix to allow intra-abdominal menstruation (44). Increased retrograde menstruation by obstruction of the outflow of menstrual fluid from the uterus is associated with a higher incidence of endometriosis in women and in baboons (45–47). Women with shorter intervals between menstruation and longer duration of menses are more likely to have retrograde menstruation and are at higher risk for endometriosis (48). Menstruation is associated with intraperitoneal inflammation in women and baboons, but a limited quantity of endometrial cells can be identified in peritoneal fluid during menstruation in women, possibly because endometrial–peritoneal attachment is reported to occur within 24 hours (49–51). Ovarian endometriosis may be caused by either retrograde menstruation or by lymphatic flow from the uterus to the ovary; metaplasia and bleeding from a corpus luteum may be a critical event in the development of some endometriomas (52–54).

Deep endometriosis, with a depth of at least 5 mm beneath the peritoneum, can present as nodules in the cul-de-sac, rectosigmoid, and bladder area and occurs with other forms of peritoneal or ovarian endometriosis (55). According to anatomic, surgical, and pathologic findings, deep endometriotic lesions originate intraperitoneally rather than extraperitoneally. The lateral asymmetry in the occurrence of ureteral endometriosis is compatible with the menstrual reflux theory and with the anatomic differences of the left and right hemipelvis (40). Adolescents and young women can have peritoneal disease (56). This observation, together with evidence from the development and spontaneous evolution of endometriosis in baboons, supports the notion that endometriosis starts as peritoneal disease and that the three different phenotypes and locations of endometriosis (peritoneal, ovarian, and deep) represent a homogeneous disease continuum with a single origin (i.e., regurgitated endometrium), rather than three different disease entities (40,57,58).

Extrapelvic endometriosis, although rare (1% to 2%), may result from vascular or lymphatic dissemination of endometrial cells to many gynecologic (vulva, vagina, cervix) and nongynecologic sites. The latter include bowel (appendix, colon, small intestine, hernia sacs), lungs and pleural cavity, skin (cesarean section, episiotomy or other surgical scars, inguinal region, extremities, umbilicus), lymph glands, nerves, and brain (59).

Coelomic Metaplasia

The transformation (metaplasia) of coelomic epithelium into endometrial tissue is a proposed mechanism for the origin of endometriosis. One study evaluating structural

and cell surface antigen expression in the rete ovarii and epoophoron reported little commonality between endometriosis and ovarian surface epithelium, suggesting that serosal metaplasia is unlikely in the ovary (60). The results of another study involving the genetic induction of endometriosis in mice suggest that ovarian endometriotic lesions may arise directly from the ovarian surface epithelium through a metaplastic differentiation process induced by activation of an oncogenic *K-ras* allele (53).

Induction Theory

The induction theory is an extension of the coelomic metaplasia theory. It proposes that an endogenous (undefined) biochemical factor can induce undifferentiated peritoneal cells to develop into endometrial tissue. This theory is supported by experiments in rabbits but is not substantiated in women or nonhuman primates (61,62).

Genetic Factors

Endometriosis is a complex disorder caused by a combination of multiple genetic and environmental factors. These genetic factors need to be divided into germline and somatic genetic variants. The former is inherited and results in a higher chance of developing endometriosis, the latter are somatic alterations that possibly play a role in the pathophysiology of endometriosis.

Germline Variants

Inherited genetic variants associated with endometriosis confer a genetic susceptibility to develop the disease but represent only approximately 50% of the risk associated with the disease (63). The heritable component of endometriosis is demonstrated by familial clustering in humans and in *Rhesus* monkeys, a founder effect detected in the Icelandic population, higher concordance in monozygotic versus dizygotic twins, a similar age at onset of symptoms in affected nontwin sisters, an increased prevalence of endometriosis among first-degree relatives and a 15% prevalence of magnetic resonance imaging (MRI) findings suggestive of endometriosis in the first-degree relatives of women with ASRM stage III or IV disease (64). The induction of human-like endometriosis in mice by genetic activation of an oncogenic *K-ras* allele lends further support to the genetic basis of this disorder (53).

The risk of endometriosis is seven times greater if a first-degree relative is affected by endometriosis (65). **Because no specific mendelian inheritance pattern is identified, multifactorial inheritance is postulated.** Family linkage studies and genome-wide association studies (GWAS) have provided insights on the genetic variants contributing to the hereditary risk of endometriosis. Family linkage studies identify genetic variants that lead to clustering of endometriosis in certain families, but these variants are often rare in the general population. GWAS studies uncover common genetic variants in the general population related to an increased risk of endometriosis

(63).

A meta-analysis of 11 GWAS identified 19 independent single nucleotide polymorphisms associated with endometriosis (66). However, all these polymorphisms combined explain only approximately 5% of variance in endometriosis. These genetic variants are located in or near a wide variety of genes with functions in diverse pathways: sex steroid hormone signaling (FSHB, ESR1), inflammation (NFE2L3), oncogenesis (ID4), uterine development (HOXA10, HOXA11), WNT signaling (WNT4, MIR148), estrogen responsive genes (GREB1, KDR) and genes involved in the actin cytoskeleton or cellular adhesion (FN1, VEZT, ANRIL). Large genome-wide linkage studies, including more than 1,300 families with multiple women affected by endometriosis, have identified three linkage regions of endometriosis: on chromosome 10q26, chromosome 20p13, and chromosome 7p13-15 (63,67,68). The genes in these linkage regions have roles in estrogen metabolism (CYP2C19 in the 10q26 region) and in endometrial or uterine development (INHBA, SFRP4 and HOXA10 in the 7p13-15 region).

Functional studies of the genes in these endometriosis risk loci are needed to elucidate their precise role and determine the effects of the variants in underlying pathways. These targeted functional gene studies have the potential to provide us with important new insights on the pathogenesis of endometriosis.

Somatic Alterations

Aneuploidy

Epithelial cells of endometriotic cysts are monoclonal on the basis of phosphoglycerate kinase gene methylation, and normal endometrial glands are monoclonal (69,70). In a comparison of endometriotic tissue with eutopic endometrium, flow cytometric DNA analysis failed to show aneuploidy (71). Studies using comparative genomic hybridization, or multicolor *in situ* hybridization, showed aneuploidy for chromosomes 11, 16, and 17, increased heterogeneity of chromosome 17 aneuploidy, and losses of 1p and 22q (50%), 5p (33%), 6q (27%), 70 (22%), 9q (22%), and 16 (22%) of 18 selected endometriotic tissues (72–74). In another study, trisomies 1 and 7, and monosomies 9 and 17 were found in endometriosis, ovarian endometrioid adenocarcinoma, and normal endometrium (75). The proportions of aneusomic cells were significantly higher in ovarian endometriosis compared with extragonadal endometriosis and normal endometrium (p <0.001), suggesting a role of the ovarian stromal milieu in the induction of genetic changes, which may lead to invasive cancer in isolated cases (75).

Microsatellite DNA assays reveal an allelic imbalance (loss of heterozygosity) in *p16 (Ink4), GALT, p53,* and *APOA2* loci in patients with endometriosis and in stage II of endometriosis (76). Another report found a loss of heterozygosity in 28% of endometriotic lesions at one or more sites: chromosomes 9p (18%), 11q (18%), and

22q (15%) (70).

Somatic Mutations

Somatic mutations in genes or chromosomes are, by definition, never passed on to progeny but can play an important role in pathogenesis of diseases such as cancer. **The role of somatic mutations in endometriosis is not well understood.**

Patients with clear cell ovarian carcinoma or endometrioid ovarian carcinoma often have concomitant endometriosis and endometriosis is well recognized as a risk factor for these types of ovarian cancer. Investigation of endometriosis lesions occurring synchronously with clear cell ovarian carcinoma or endometrioid ovarian carcinoma showed somatic mutations in ARID1A, PIK3CA, and in the MET oncogenes (77–79). However, data on the presence of somatic alterations in noncancer-associated endometriosis are very limited. One study revealed the presence of somatic mutations in noncancer-associated deep endometriotic lesions in 19 of 24 patients (79%) (80). Five patients harbored known cancer driver mutations in ARID1A, PIK3CA, KRAS, or PPP2R1A although deep infiltrating endometriosis has virtually no risk for malignant transformation. All the tested somatic mutations appeared to be confined to the epithelial compartment of endometriotic lesions.

Immunologic Factors and Inflammation

Retrograde menstruation appears to be a common event in women and not all women who have retrograde menstruation develop endometriosis. The immune system may be altered in women with endometriosis, and it is hypothesized that the disease may develop as a result of reduced immunologic clearance of viable endometrial cells from the pelvic cavity (81,82). Endometriosis can be caused by decreased clearance of peritoneal fluid endometrial cells resulting from reduced natural killer (NK) cell activity or decreased macrophage activity (83). Decreased cell-mediated cytotoxicity toward autologous endometrial cells is associated with endometriosis (83–87). These studies used techniques that have considerable variability in target cells and methods (88,89). Whether NK cell activity is lower in patients with endometriosis than in those without endometriosis is controversial. Some reports demonstrate reduced NK activity and others found no increase in NK activity in women with moderate to severe disease (85–87,90–95). There is great variability in NK cell activity among normal individuals that may be related to variables such as smoking, drug use, and exercise (88).

In contrast, endometriosis can be considered a condition of immunologic tolerance, as opposed to ectopic endometrium, which essentially is self-tissue (81). It can be questioned why viable endometrial cells in the peritoneal fluid would be a target for NK cells or macrophages. Autotransplantation of blood vessels, muscles, skin grafts,

and other tissues is extremely successful (84–86). There is no in vitro evidence that peritoneal fluid macrophages actually attack and perform phagocytosis of viable peritoneal fluid endometrial cells. High-dose immunosuppression can slightly increase the progression of spontaneous endometriosis in baboons (96). There is no clinical evidence that the prevalence of endometriosis is increased in immunosuppressed patients. The fact that women with kidney transplants, who undergo chronic immunosuppression and are not known to have increased infertility problems can be considered indirect evidence that these patients do not develop extensive endometriosis.

Substantial evidence suggests that endometriosis is associated with a state of subclinical peritoneal inflammation, marked by an increased peritoneal fluid volume, increased peritoneal fluid white blood cell concentration (especially macrophages with increased activation status), and increased inflammatory cytokines, growth factors, and angiogenesis-promoting substances. It is reported in baboons that subclinical peritoneal inflammation occurs during menstruation and after intrapelvic injection of endometrium (94). A higher basal activation status of peritoneal macrophages in women with endometriosis may impair fertility by reducing sperm motility, increasing sperm phagocytosis, or interfering with fertilization, possibly by increased secretion of cytokines such as tumor necrosis factor α (TNF-α) (97–101). Tumor necrosis factor may facilitate the pelvic implantation of ectopic endometrium (100,101). The adherence of human endometrial stromal cells to mesothelial cells in vitro is increased by the pretreatment of mesothelial cells with physiologic doses of TNF-α (102). Macrophages or other cells may promote the growth of endometrial cells by secretion of growth and angiogenetic factors such as epidermal growth factor (EGF), macrophage-derived growth factor (MDGF), fibronectin, and adhesion molecules such as integrins (102–108). After attachment of endometrial cells to the peritoneum, subsequent invasion and growth appear to be regulated by matrix metalloproteinases (MMP) and their tissue inhibitors (109,110).

There is increasing evidence that local inflammation and secretion of prostaglandins (PGs) is related to differences in endometrial aromatase activity between women with and without endometriosis. Expression of aromatase cytochrome P450 protein and mRNA is present in human endometriotic implants but not in normal endometrium, suggesting that ectopic endometrium produces estrogens, which may be involved in the tissue growth interacting with the estrogen receptor (111). Inactivation of 17β-estradiol is impaired in endometriotic tissues because of deficient expression of 17β-hydroxysteroid dehydrogenase type 2, which is normally expressed in eutopic endometrium in response to progesterone (112). The inappropriate aromatase expression in endometriosis lesions can be stimulated by prostaglandin E_2 (PGE_2). This reaction leads to local production of E_2, which stimulates PGE_2 production, resulting in a positive-feedback system between local inflammation and estrogen-driven local

growth of ectopic endometrium (113).

The subclinical pelvic inflammatory status associated with endometriosis is reflected in the systemic circulation. Increased concentrations of C-reactive protein, serum amyloid A (SAA), TNF-α, membrane cofactor protein-1, interleukin-6 (IL-6), IL-8, and chemokine (C-C motif) receptor 1 (CCR1) are observed in peripheral blood samples of patients with endometriosis when compared with controls (114). This observation offers a basis for the development of noninvasive diagnostic tests.

Both hypothesis-driven research and system biology approaches using mRNA microarray and proteomic techniques studies show that eutopic endometrium is biologically different in women with endometriosis when compared to controls with respect to proliferation, apoptosis, angiogenesis, and inflammatory pathways (115–118). Several studies show a higher prevalence of nerve fibers and neurotrophic factors in the eutopic endometrium from women with endometriosis when compared to controls (49,119).

Environmental Factors and Dioxin

There is an increasing awareness of potential links between reproductive health, infertility, and environmental pollution. Attention was directed toward the potential role of dioxins in the pathogenesis of endometriosis, but the issue remains controversial. A meta-analysis concluded that there is insufficient evidence in women or in nonhuman primates that endometriosis is caused by dioxin exposure (120).

Human Data

A 1976 explosion of a factory in Seveso, Italy, resulted in the highest recorded levels of dioxin exposure in humans, but data are not published (121). The Seveso Women's Health Study will correlate prospective individual data on exposure to dioxin with reproductive endpoints such as the incidence of endometriosis, infertility, and decreased sperm quality. One case-control study failed to show an association in the general population between endometriosis and exposure to PCB and chlorinated pesticides during adulthood. No differences in mean plasma concentrations of 14-PCB and 11-chlorinated pesticides were found between women with and those without endometriosis (122). In another study, increased exposure to dioxin-like compounds is associated with (moderate to severe) endometriosis in a case-control study in women (123). Genetic mechanisms may play a role in dioxin exposure and the development of endometriosis. Transcripts of the *CYP1A1* gene, a dioxin-induced gene, are significantly higher (nine times higher) in endometriotic tissues than in eutopic endometrium (113). Other investigators report a similar expression of aryl hydrocarbon receptor and dioxin-related genes (using semiquantitative reverse transcriptase polymerase chain reaction) in the endometrium from women with or without endometriosis (124). In Japanese women, no association was found between endometriosis prevalence or severity and

polymorphisms for aryl hydrocarbon receptor repressor, aryl hydrocarbon (x2) receptor, and aryl hydrocarbon nuclear translocator or *CYP1A1* genes (125). Based on these data, there is insufficient evidence supporting the association between endometriosis and dioxin exposure in humans.

Nonhuman Primates

An initial retrospective case-control study reported that the prevalence of endometriosis was not statistically different ($p = 0.08$) between monkeys chronically exposed to dioxin for 4 years (11 of 14, 79%) and unexposed animals (2 of 6, 33%) after a period of 10 years. A positive correlation was found between the severity of endometriosis and dioxin dose, serum levels of dioxin, and dioxin-like chemicals (126,127). Two prospective studies evaluated the association between dioxin exposure and development of endometriosis in *Rhesus* monkeys. In one study, monkeys exposed for 12 months to low-dose dioxin (0.71 ng/kg/day) had endometriosis implants with smaller maximal and minimal diameters and similar survival rate when compared with endometriotic lesions in unexposed controls, suggesting no effect of dioxin on endometriosis (128). After 12 months of exposure to high-dose dioxin (17.86 ng/kg/day), larger diameters and a higher survival rate of endometriosis implants were observed in exposed *Rhesus* monkeys compared with unexposed controls. The second randomized study performed in 80 *Rhesus* monkeys compared those with no treatment with those treated with 0, 5, 20, 40, and 80 µg of *aroclor* (1,254 kg/day) for 6 years. Endometriosis occurred in 37% of controls and in 25% of treated monkeys as determined by laparoscopy and necropsy data (129). No association was observed between endometriosis severity and PCB exposure. These data question the importance of dioxin exposure, except at high doses, in the development of endometriosis in primates.

Rodents

Continuous exposure to 2,3,7,8-tetrachlorodibenzo-P-dioxin inhibited the growth of surgically induced endometriosis in ovariectomized mice treated with high-dose estradiol. No correlation was observed between the dose of dioxin and survival of endometrial implants, adhesions, and serum E_2 levels (130). In ovariectomized mice induced with endometriosis, similar stimulating effects of estrone and 4-chlorodiphenyl ether (4-CDE) were observed on survival rates of endometriotic mice, suggesting an estrogen-like effect of 4-CDE (131). Potential mechanisms mediating dioxin action to promote endometriosis in rodents are complex and probably different in rats and mice, and furthermore in women. The mouse appears to be a better model to elucidate these mechanisms, but both models have important limitations (132,133).

Stem Cells

In 2004 the first evidence for the presence of adult stem cells in endometrium was published (134). In one study, stem cells were identified in endometrium isolated from hysterectomy tissue. Concurrently, it was reported that some epithelial and stromal cells in human endometrium of bone marrow transplant recipients were of donor origin (135). In the next decade, a key role of adult stem cells in normal endometrial physiology was discovered (136).

Following the discovery of endometrial stem cells, it was proposed that these stem cells play a role in the pathogenesis of endometriosis. The first hypothesis is an extension of Sampson theory of retrograde menstruation: endometrial stem cells, with intrinsic abnormalities such as germline or somatic mutations, may have increased propensity to implant on the peritoneum after retrograde menstruation. Studies showed that women with endometriosis shed basalis endometrium at menstruation, increasing the likelihood of endometrial epithelial progenitor cells gaining access to the peritoneal cavity and stem cells have been identified in endometriotic lesions (136). However, the presence of endometrial stem/progenitor cells in peritoneal fluid has not yet been reported, which is crucial for identifying their role in the pathogenesis of endometriosis. A second hypothesis focuses on abnormal stem cell recruitment in patients with endometriosis (137). Stem cells from the bone marrow or alternate sources could be preferentially recruited in ectopic over eutopic endometrium through altered expression of chemotactic ligands such as CXCL12 (137). Abnormal endometrial function caused by impaired recruitment of stem cells to the eutopic endometrium could be a contributing endometrial factor to endometriosis-associated infertility (137).

Several studies have addressed the role of stem cells in endometriosis, but **no strong direct evidence for the role of endometrial stem/progenitor cells in the pathogenesis of endometriosis has been reported.**

Future Research

The study of endometriosis is compounded by the need to determine the presence or absence of pathology. The pathogenesis of endometriosis, the pathophysiology of related infertility, and the spontaneous evolution of endometriosis are being studied. At the time of diagnosis, most patients with endometriosis had the disease for an unknown period, making it difficult to initiate clinical experiments that would determine the etiology or progression of the disease (34). Because endometriosis occurs naturally only in women and nonhuman primates, and invasive experiments cannot be performed easily, it is difficult to undertake properly controlled studies.

There is a need for the development of good in vitro and in vivo models for endometriosis. The main advantage of the rodent models used to study endometriosis is their low cost relative to nonhuman primates, but the disadvantages are numerous (138–141). First of all, in these models, the type of lesion appears to be quite different from

the variety of pigmented and nonpigmented lesions observed in women (138–140). Secondly, there is a lack of standardization in rodent endometriosis models and no consensus on relevant outcome measures. Nonhuman primates are phylogenetically close to humans, have a comparable menstrual cycle, are afflicted with spontaneous endometriosis, and when induced with endometriosis, develop macroscopic lesions that are similar to those found in human disease (44,142–146). Spontaneous endometriosis in the baboon is minimal and disseminated, similar to the different stages of endometriosis in women (142,147–149).

The techniques for in vitro experiments have significantly improved, including the development of endometrial organoids (150,151). Application of these promising new techniques on endometriotic tissue and further improvement of in vitro models for endometriosis hold great potential for future research.

DIAGNOSIS

Clinical Presentation

[2] Endometriosis should be suspected in women with infertility, dysmenorrhea, dyspareunia, or chronic pelvic pain, although these symptoms can be associated with other diseases. Endometriosis may be asymptomatic, even in women with more advanced disease (i.e., ovarian endometriosis or deep endometriosis).

Endometriosis can be associated with significant gastrointestinal symptoms (pain, nausea, vomiting, early satiety, bloating and distention, altered bowel habits). A characteristic motility change (ampulla of Vater–duodenal spasm, a seizure equivalent of the enteric nervous system, along with bacterial overgrowth) is documented in most women with the disease (152). Women of reproductive age with endometriosis are not osteopenic (153).

The average delay between onset of pain symptoms and surgically confirmed endometriosis is quite long: 8 years or longer in the United Kingdom and 9 to 12 years in the United States (154). Similar durations were observed in Scandinavia and in Brazil (155,156). A delay in diagnosis of endometriosis of 6 and 3 years in women with pain and women with infertility, respectively, was reported. Over previous decades, there was a steady decrease in the delay in diagnosis and a decline in the prevalence of advanced endometriosis at first diagnosis (157). Patient awareness of endometriosis was increased. Many patients' quality of life is affected by pain, emotional impact of infertility, anger about disease recurrence, and uncertainty about the future regarding repeated surgeries or long-term medical therapy and its side effects (158). **Endometriosis should be perceived as a chronic disease, at least in a subset of highly symptomatic women, and quality-of-life should be evaluated using reliable and validated questionnaires** (159).

Pain

[3] In adult women, dysmenorrhea may be especially suggestive of endometriosis if it begins after years of pain-free menses. Dysmenorrhea often starts before the onset of menstrual bleeding and continues throughout the menstrual period. In adolescents, the pain may be present after menarche without an interval of pain-free menses. Evidence suggests that absenteeism from school and the incidence and duration of oral contraceptive (OC) use for severe primary dysmenorrhea during adolescence is higher in women who later develop deep endometriosis than in women without deep endometriosis (160).

The distribution of pain is variable but most often is bilateral. Local symptoms can arise from rectal, ureteral, and bladder involvement, and lower back pain can occur. Some women with extensive disease have no pain, whereas others with only minimal to mild disease may experience severe pelvic pain. **All endometriosis lesion types are associated with pelvic pain, including minimal to mild endometriosis** (161). Endometriomas are not associated with dysmenorrheal severity, and dysmenorrhea is less frequent in women with only ovarian endometriomas compared with other locations (162,163). Endometriomas can be considered a marker for greater severity of deep lesions (164). Deep lesions are consistently associated with pelvic pain, gastrointestinal symptoms, and painful defecation (165). The role of adhesions in pain and endometriosis is poorly understood (166).

Many studies failed to detect a correlation between the degree of pelvic pain and the severity of endometriosis (12,163,167). **Some studies reported a positive correlation between endometriosis stage and endometriosis-related dysmenorrhea or chronic pelvic pain** (168,169). In one study, a significant but weak correlation was observed between endometriosis stage and severity of dysmenorrhea and nonmenstrual pain, whereas a strong association was found between posterior cul-de-sac lesions and dyspareunia (170).

Possible mechanisms causing pain in patients with endometriosis include local peritoneal inflammation, deep infiltration with tissue damage, adhesion formation, fibrotic thickening, and collection of shed menstrual blood in endometriotic implants, resulting in painful traction with the physiologic movement of tissues (171,172). The character of pelvic pain is related to the anatomic location of deep endometriotic lesions (165). Severe pelvic pain and dyspareunia may be associated with deep endometriosis (7,171,173). In rectovaginal endometriotic nodules, a close histologic relationship was observed between nerves and endometriotic foci and between nerves and the fibrotic component of the nodule (174). Increasing evidence suggests a close relationship between the density of innervation of endometriotic lesions and pain symptoms (170).

Infertility

Many arguments support the hypothesis that there is a causal relationship between the presence of endometriosis and infertility (175). The following factors have been reported:

1. Increased prevalence of endometriosis in infertile women (33%) when compared to women of proven fertility (4%), a reduced monthly fecundity rate (MFR) in baboons with mild to severe (spontaneous or induced) endometriosis when compared to those with minimal endometriosis or a normal pelvis.
2. Trend toward a reduced MFR in infertile women with minimal to mild endometriosis when compared to women with unexplained infertility.
3. Endometriotic ovarian cysts that negatively affect the rate of spontaneous ovulation (176).
4. Dose–effect relationship: A negative correlation between the r-AFS stage of endometriosis and the MFR and cumulative pregnancy rate (175,177).
5. Reduced MFR and cumulative pregnancy rate after donor sperm insemination in women with minimal to mild endometriosis when compared to those with a normal pelvis.
6. Reduced MFR after husband sperm insemination in women with minimal to mild endometriosis when compared to those with a normal pelvis.
7. Reduced implantation rate per embryo after in vitro fertilization (IVF) in women with endometriosis when compared to women with tubal factor infertility (175,178).
8. Increased MFR and cumulative pregnancy rate after surgical removal of minimal to mild endometriosis.

When endometriosis is moderate or severe, involving the ovaries and causing adhesions that block tubo-ovarian motility and ovum pickup, it is associated with infertility (176,179). This effect was shown in primates, including cynomolgus monkeys and baboons (145,180). Numerous mechanisms (ovulatory dysfunction, luteal insufficiency, luteinized unruptured follicle syndrome, recurrent abortion, altered immunity, and intraperitoneal inflammation) are proposed as explanations, but an association between fertility and minimal or mild endometriosis remains controversial (181).

Spontaneous Abortion

A possible association between endometriosis and spontaneous abortion was suggested in uncontrolled or retrospective studies. Some controlled studies evaluating the association between endometriosis and spontaneous abortion have important methodologic shortcomings: heterogeneity between cases and controls, analysis of the abortion rate before the diagnosis of endometriosis, and selection bias of study and control groups (81,182,183). **Based on controlled prospective studies, there is no**

evidence that endometriosis is associated with (recurrent) pregnancy loss or that medical or surgical treatment of endometriosis reduces the spontaneous abortion rate (184–186). Some data suggest that miscarriage rates may be increased after treatment with assisted reproductive technology (187).

Endocrinologic Abnormalities

Endometriosis is associated with anovulation, abnormal follicular development with impaired follicle growth, reduced circulating E_2 levels during the preovulatory phase, disturbed luteinizing hormone (LH) surge patterns, premenstrual spotting, luteinized unruptured follicle syndrome, and galactorrhea, and hyperprolactinemia (188). Increased incidence and recurrence of the luteinized unruptured follicle syndrome is reported in baboons with mild endometriosis, but not in primates with minimal endometriosis or a normal pelvis (189). Luteal insufficiency with reduced circulating E_2 and progesterone levels, out-of-phase endometrial biopsies, and aberrant integrin expression was reported in the endometrium of women with endometriosis by some researchers, but these findings were not confirmed by other investigators (188,190,191). No convincing data exist to conclude that the incidence of these endocrine abnormalities is increased in women who have endometriosis.

Extrapelvic Endometriosis

Extrapelvic endometriosis, although often asymptomatic, should be suspected when symptoms of pain or a palpable mass occur outside the pelvis in a cyclic pattern. Endometriosis involving the intestinal tract (especially colon) is the most common site of extrapelvic disease and may cause abdominal and back pain, abdominal distention, cyclic rectal bleeding, constipation, and obstruction. Ureteral involvement can lead to obstruction and result in cyclic pain, dysuria, and hematuria. Endometriosis lesions on the diaphragm often result in cyclic shoulder pain. Pulmonary endometriosis can manifest as pneumothorax, hemothorax, or hemoptysis during menses. Umbilical endometriosis should be suspected when a patient has a palpable mass and cyclic pain in the umbilical area (59).

Clinical Examination

In many women with endometriosis, no abnormality is detected during the clinical examination. However, the vulva, vagina, and cervix should be inspected for any signs of endometriosis, although the occurrence of endometriosis in these areas is rare (e.g., episiotomy scar). The presence of a narrow pinpoint cervical ostium can be a risk factor for endometriosis (26). **Other signs of possible endometriosis include uterosacral or cul-de-sac nodularity, lateral or cervical displacement caused by uterosacral scarring, painful swelling of the rectovaginal septum, and unilateral**

ovarian cystic enlargement (192). In more advanced disease, the uterus is often in fixed retroversion, and the mobility of the ovaries and fallopian tubes is reduced ("frozen pelvis"). Evidence of deep endometriosis (deeper than 5 mm under the peritoneum) in the rectovaginal septum with cul-de-sac obliteration or cystic ovarian endometriosis should be suspected when there is clinical documentation of uterosacral nodularities during menses (193–195). In these cases, black-blue–colored lesions can sometimes be observed in the vagina during speculum examination.

Imaging

Based on the symptoms at presentation and the clinical examination the diagnosis of endometriosis can be suspected. However, endometriosis symptoms are not specific and the clinical examination may have false-negative results. The next step in the diagnostic workup is medical imaging. However, **no imaging modality detects endometriosis accurately enough to replace surgical visual detection and biopsy for diagnosis** and thus the gold standard for diagnosis of endometriosis remains laparoscopic visualization of lesions with histologic confirmation (196).

Ultrasound

The guidelines from the European Society of Human reproduction and Embryology (ESHRE) and American College of Obstetricians and Gynecology (ACOG) recommend transvaginal ultrasound (TVUS) as a first imaging step in the diagnostic work up of women with suspected endometriosis. However, **the sensitivity and specificity of TVUS for diagnosis of endometriosis are strongly dependent on the interest and experience of the sonographer and on the quality of the ultrasound equipment.**

In a systematic review the accuracy of TVUS for detecting the different phenotypes of endometriosis (peritoneal, endometrioma, deep infiltrating) was assessed (196). **TVUS could not reliably visualize peritoneal endometriosis (sensitivity = 65%, specificity = 95%). Compared to laparoscopy, TVUS has no value in diagnosing peritoneal endometriosis. However, TVUS is reliable in detecting or excluding the presence of an endometrioma (sensitivity = 93%, specificity = 96%). The typical ultrasound features of an endometriotic ovarian cyst in premenopausal women were described as "ground-glass echogenicity of the cyst fluid, one to four locules and no solid parts" (197). Studies evaluating the accuracy of TVUS for diagnosis of deep endometriosis mainly focus on rectovaginal or bladder nodules. TVUS can detect these deep endometriotic lesions with moderate reliability (sensitivity = 79%, specificity = 94%).** The role of TVUS in diagnosis of deep endometriosis in more distant locations is limited.

In summary, the main role of TVUS in the diagnostic workup of endometriosis is detecting the presence of an endometrioma or deep endometriotic nodule because it

establishes the diagnosis with high certainty. Moreover, **an endometrioma or a deep nodule are very rarely isolated findings.** Patients with an endometrioma or a deep nodule often have other endometriotic lesions and adhesions. Identification of an endometrioma or a deep nodule on TVUS should always be followed by a detailed investigation for other (peritoneal and deep) endometriotic lesions.

Local guidelines for the management of suspected ovarian malignancy should be followed in cases of ovarian endometrioma (1). Ultrasound scanning with or without serum CA125 testing is usually used to identify rare instances of ovarian cancer; however, CA125 levels are frequently elevated in the presence of endometriomas (1).

The absence of endometriosis on TVUS does not rule out the presence of peritoneal or deep endometriosis. Based on the patients' symptoms and clinical examination further investigation and a diagnostic laparoscopy should be considered.

Other Imaging Techniques

Other imaging techniques, including **computed tomography (CT) and MRI,** can be used to provide additional and confirmatory information, but they are not considered first line imaging modalities because of the high costs and their added value is unclear (1). Moreover, CT results in an important radiation dose, which should be avoided as much as possible in a population of young reproductive women.

MRI has a good sensitivity and specificity for the diagnosis of deep endometriosis and endometriomas, but the value in addition to TVUS is limited. A growing number of studies suggest that MRI has a role in the diagnosis of endometriosis because of a greater ability to detect small lesions and lesions on distant locations (extrapelvic endometriosis) (196). However, **a negative MRI does not rule out peritoneal endometriosis** because lesions are identified only if they are hemorrhagic, greater than 5 mm or when associated with extensive adhesions distorting the normal anatomy. **Hysterosalpingography is not recommended as a diagnostic test for endometriosis,** although the presence of filling defects (presence of hypertrophic or polypoid endometrium) has a significant positive correlation with endometriosis (positive and negative predictive values of 84% and 75%, respectively) (198).

Assessment of Intestinal and Urologic Involvement

Medical imaging plays an important role in establishing the diagnosis of endometriosis and imaging-based mapping of the extent of endometriosis is indispensable for appropriate planning of surgical management. **If there is clinical evidence of deep endometriosis, ureteral, bladder, and bowel involvement should be assessed.** Ureteral involvement may be asymptomatic in up to 50% of patients with deep endometriosis (199). Consideration should be given to performing ultrasound (transrectal, transvaginal, or renal), a CT urogram, or an MRI. A barium enema study

might be useful, depending on the individual circumstances, to map the extent of disease present, which may be multifocal (1). There is no proof that one technique is superior to another; it is recommended that the technique that is most familiar to the radiologist involved be used.

Blood and Other Tests

There is no specific blood test for the diagnosis of endometriosis. A general endometriosis screening test may be neither appropriate (risk for overdiagnosis) nor feasible. A blood test with a high sensitivity would be useful if that would identify women with symptomatic endometriosis (pelvic pain, infertility) that is not detectable by ultrasound imaging (200). This would include all cases of minimal to mild endometriosis and those cases of moderate to severe endometriosis without detectable ovarian endometriotic cysts or nodules (201). These are patients who could benefit from laparoscopic surgery to reduce endometriosis-associated pain and infertility or to diagnose and treat other pelvic causes of pelvic pain or infertility, like pelvic adhesions. From that perspective, a lower specificity would be acceptable because the main goal of such a test would be to rule in all women with potential endometriosis or other pelvic diseases who might benefit from surgery (202).

CA125

Levels of CA125, a glycoprotein from coelomic epithelium and common to most nonmucinous epithelial ovarian carcinomas, are significantly higher in women with moderate or severe endometriosis and normal in women with minimal or mild disease (203,204). It is presumed that endometriosis lesions produce peritoneal irritation and inflammation and this leads to an increased shedding of CA125 (204). During menstruation, an increase in CA125 levels was shown in women with and without endometriosis (205–209). Other studies did not find an increase during menses, or found an increase only with moderate to severe endometriosis (210–213). The levels of CA125 vary widely: in patients without endometriosis (8 to 22 U/mL in the nonmenstrual phase), in those with minimal to mild endometriosis (14 to 31 U/mL in the nonmenstrual phase), and in those with moderate to severe disease (13 to 95 U/mL in the nonmenstrual phase). **Compared with laparoscopy, measurement of serum CA125 levels has no value as a diagnostic tool** (214).

Laparoscopy

General Considerations

Unless disease is visible in the vagina or elsewhere, laparoscopy is the standard technique for visual inspection of the pelvis and establishment of a definitive

diagnosis (1). There is insufficient evidence to justify timing the laparoscopy at a specific time in the menstrual cycle. Laparoscopic recognition of endometriosis will vary with the experience of the surgeon, especially for subtle bowel, bladder, ureteral, and diaphragmatic lesions (1). A meta-analysis of its value against a histologic diagnosis showed (assuming a 10% pretest probability of endometriosis) that a positive laparoscopy increases the likelihood of disease to 32% (95% confidence interval [CI], 21–46) and a negative laparoscopy decreases the likelihood to 0.7% (95% CI, 0.1–5.0) (1,215). Diagnostic laparoscopy is associated with an approximately 3% risk of minor complications (e.g., nausea, shoulder tip pain) and a risk of major complications (e.g., bowel perforation, vascular damage) of 0.6 to 1.8 per 1,000 cases (1,216,217). Endometriosis can be treated during laparoscopy, thus combining diagnosis and therapy.

Laparoscopic Technique

During diagnostic laparoscopy, the pelvic and abdominal cavity should be systematically investigated for the presence of endometriosis. This examination should include a complete inspection and palpation with a blunt probe to check for nodularity as a sign of deep endometriosis of the bowel, bladder, uterus, tubes, ovaries, cul-de-sac, or broad ligament (Fig. 13-1). The type, location, and extent of all lesions and adhesions should be documented in the operative notes; ideally, the findings should be recorded with photographs or on video (1).

Laparoscopic Findings

The laparoscopic findings of endometriosis include peritoneal lesions, ovarian endometriotic cysts, and deep endometriosis invading the peritoneal surface with a depth of at least 5 mm. **Most patients with ovarian endometriotic cysts or deep endometriosis also have peritoneal disease.**

Peritoneal Endometriosis

Characteristic findings include typical ("powder-burn" or "gunshot") lesions on the serosal surfaces of the peritoneum. These lesions are black, dark brown, or bluish nodules or small cysts containing old hemorrhage surrounded by a variable degree of fibrosis (Fig. 13-2). Endometriosis can appear as subtle lesions, including red implants (petechial, vesicular, polypoid, hemorrhagic, red flame-like), serous or clear vesicles, white plaques or scarring, yellow-brown discoloration of the peritoneum, and subovarian adhesions **(Fig. 13-3)** (139,140,142,218,219). Histologic confirmation of the laparoscopic impression is essential for the diagnosis of endometriosis, for subtle lesions, and for the typical lesions reported to be histologically negative in 24% of cases (220,221).

Deep Endometriosis

Mild forms of deep endometriosis may be detected only by palpation under an

endometriotic lesion or by discovery of a palpable mass beneath visually normal peritoneum, most notably in the posterior cul-de-sac (Fig. 13-4) (194). **At laparoscopy, deep endometriosis may have the appearance of minimal disease, resulting in an underestimation of disease severity** (194). Reduced size of the cul-de-sac in women with deep endometriosis suggests that such lesions develop not in the rectovaginal septum but intraperitoneally and that burial of anterior rectal wall adhesions creates a false bottom, giving an erroneous impression of extraperitoneal origin (222).

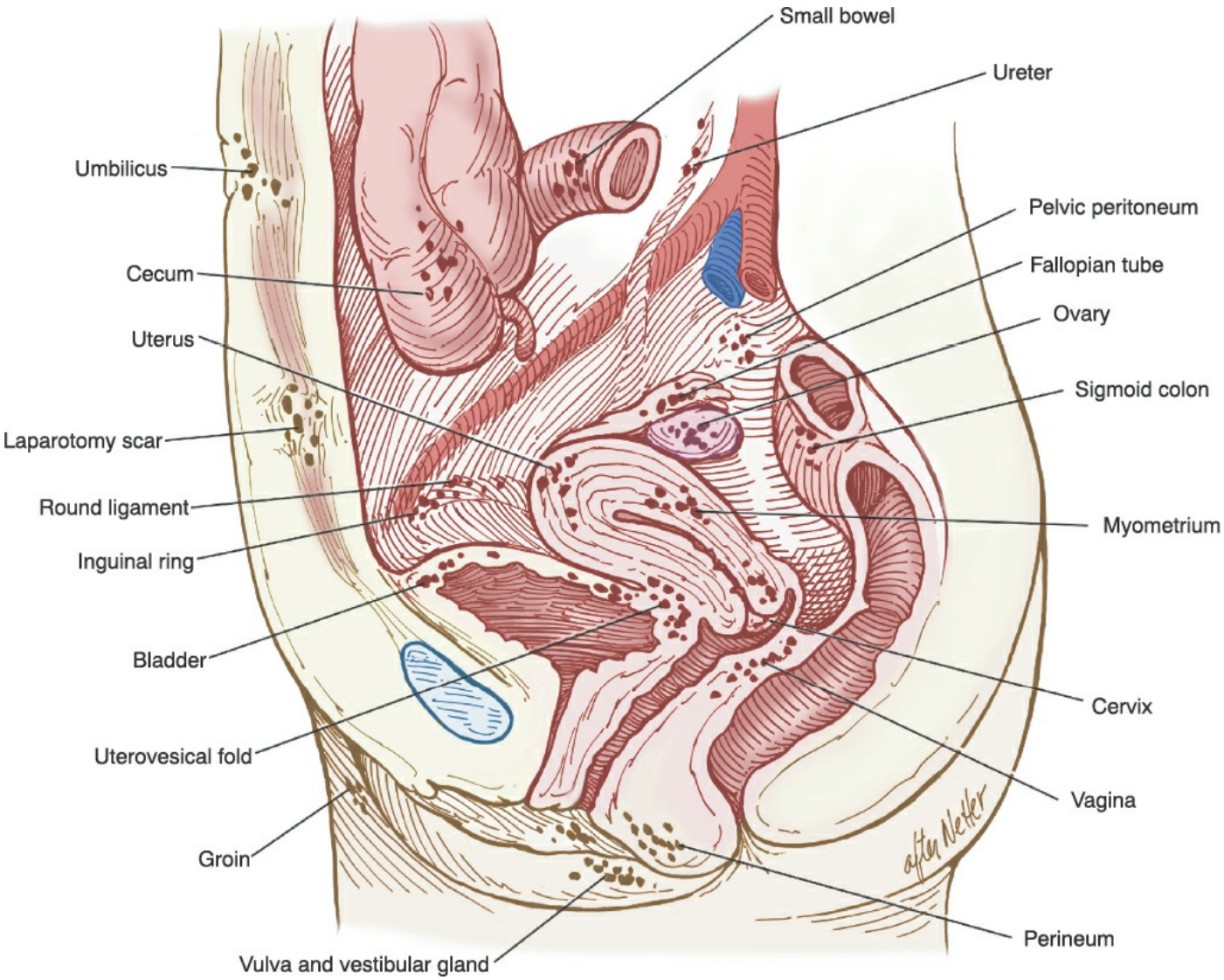


FIGURE 13-1 Pelvic endometriosis.

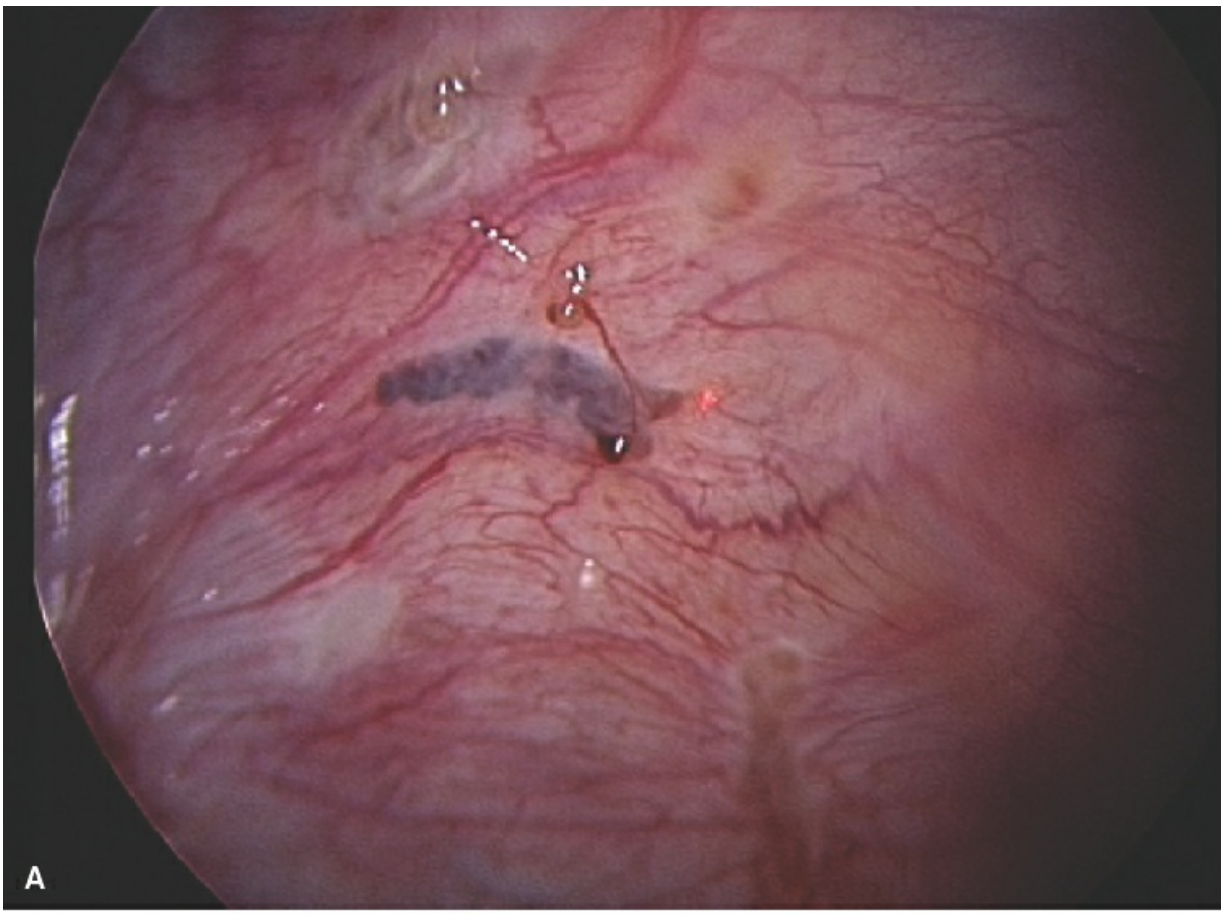
Ovarian Endometriosis

The diagnosis of ovarian endometriosis is facilitated by careful inspection of all sides of both ovaries, which may be difficult when adhesions are present in more advanced stages of disease (Fig. 13-5). With superficial ovarian endometriosis, lesions can be both typical and subtle. Larger ovarian endometriotic cysts (i.e.,

endometriomas) usually are located on the anterior surface of the ovary and are associated with retraction, pigmentation, and adhesions to the posterior peritoneum. **These ovarian endometriotic cysts often contain a thick, viscous dark brown fluid (i.e., "chocolate fluid"), composed of hemosiderin derived from previous intraovarian hemorrhage.** Because this fluid may be found in other conditions, such as in hemorrhagic corpus luteum cysts or neoplastic cysts, **biopsy and preferably removal of the ovarian cyst for histologic confirmation are necessary for the diagnosis** in the revised endometriosis classification of the American Society for Reproductive Medicine (ASRM). If that is not possible, the presence of an ovarian endometriotic cyst should be confirmed by the following features: cyst diameter of less than 12 cm, adhesion to pelvic sidewall or broad ligament, endometriosis on the surface of the ovary, and tarry, thick, chocolate-colored fluid content (223). Ovarian endometriosis appears to be a marker for more extensive pelvic and intestinal disease. Exclusive ovarian disease is found in only 1% of endometriosis patients, with the remaining patients having extensive pelvic or intestinal endometriosis (224).

Histologic Confirmation

[1] Positive histology confirms the diagnosis of endometriosis; negative histology does not exclude it (1). **Whether histology should be obtained when peritoneal disease alone is present is controversial; visual inspection is usually adequate but histologic confirmation of at least one lesion is ideal** (1). **In cases of ovarian endometrioma (>4 cm in diameter) and in deep endometriosis, histology is recommended to exclude rare instances of malignancy** (1).


A

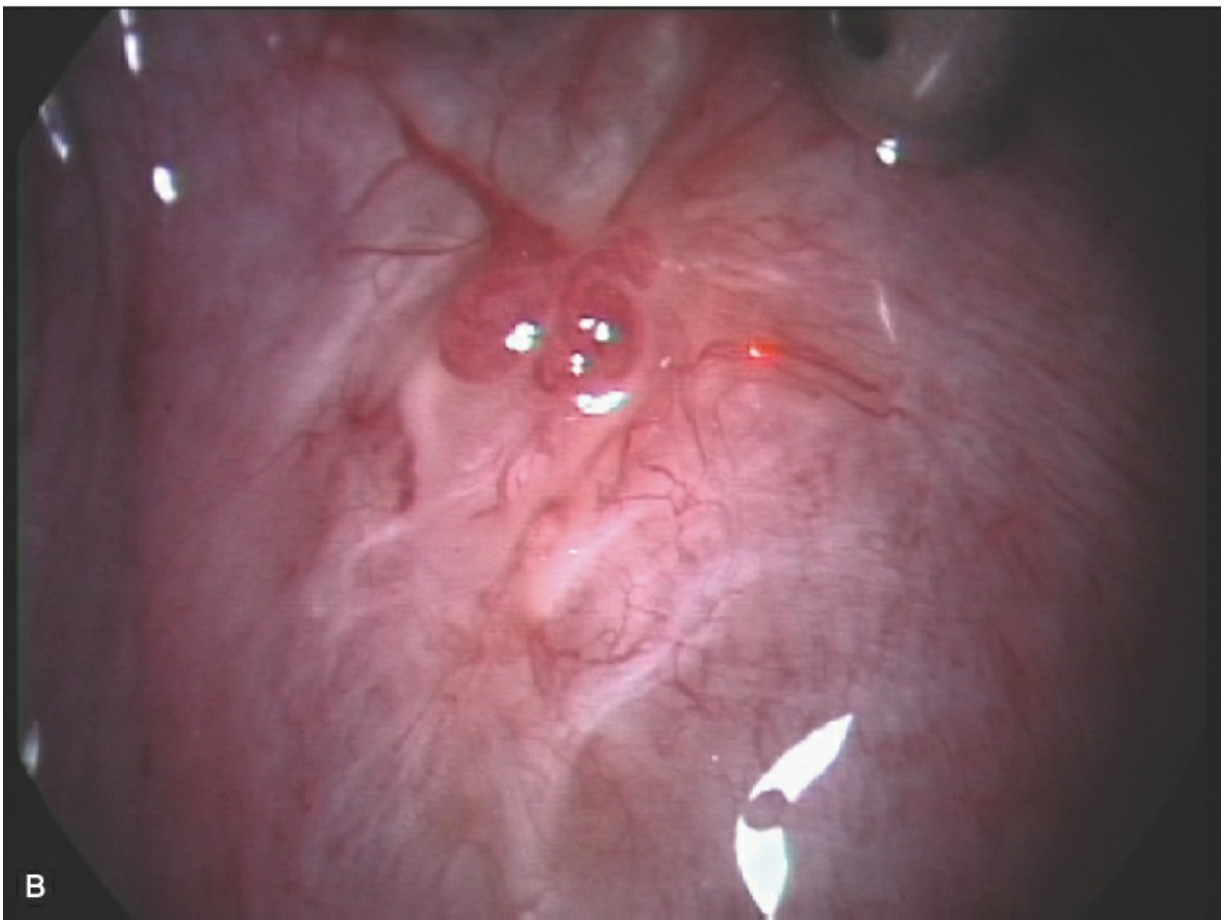
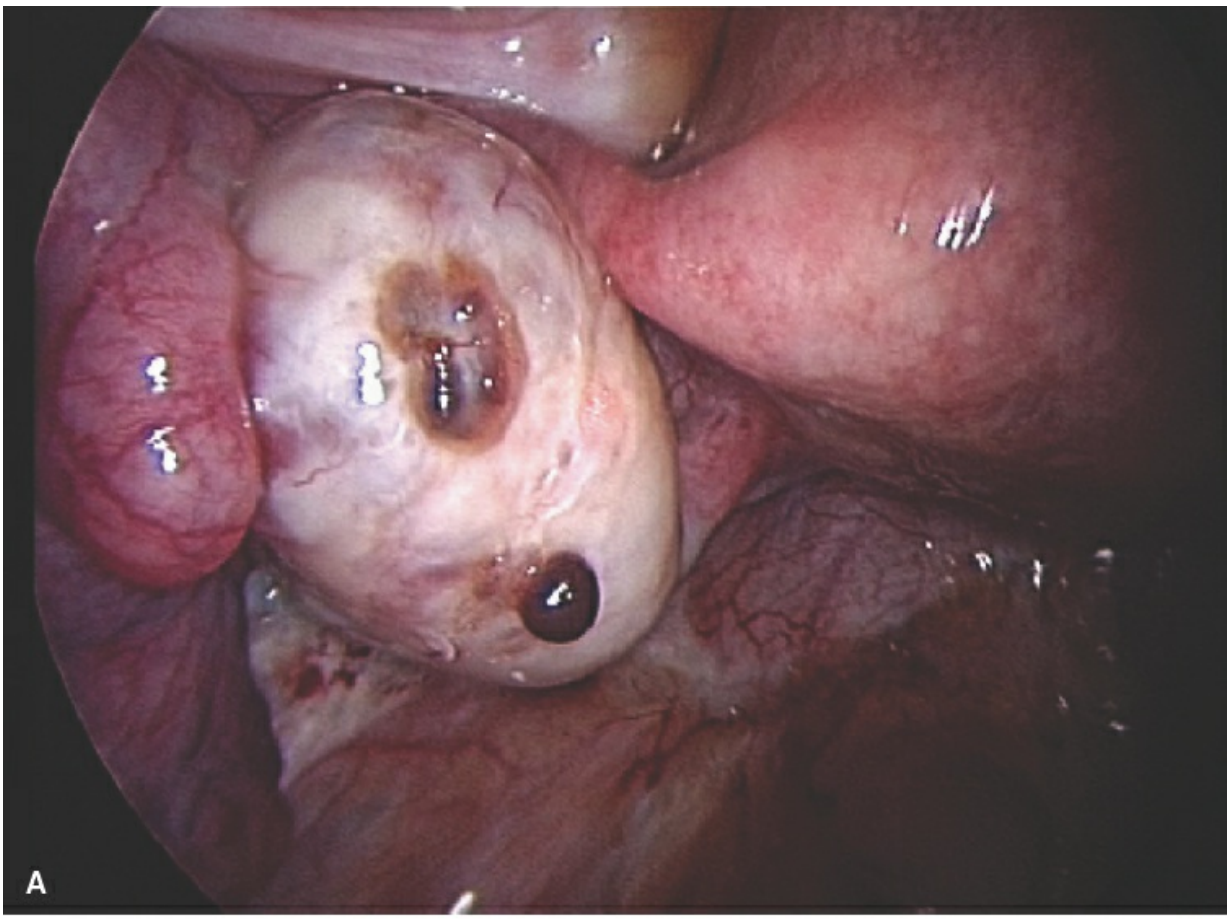
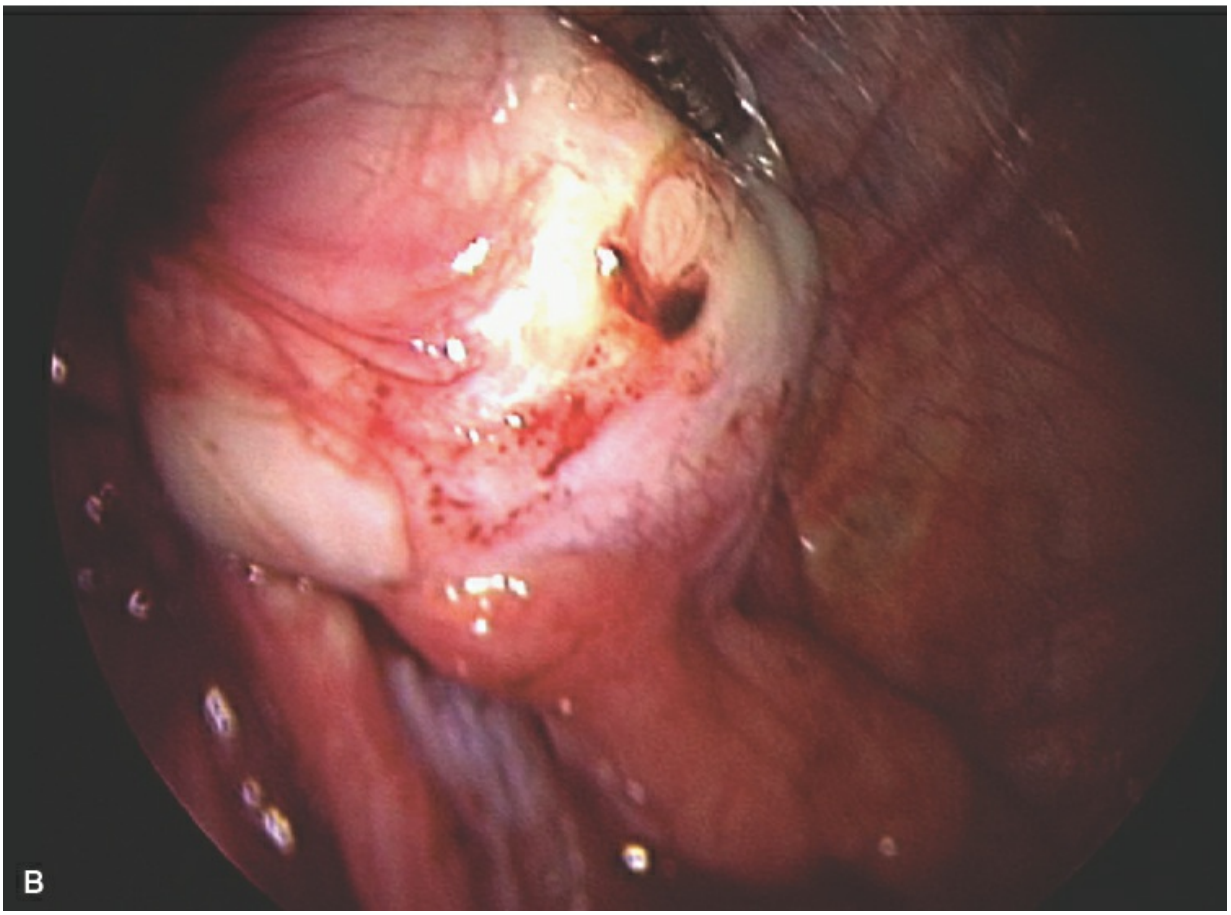
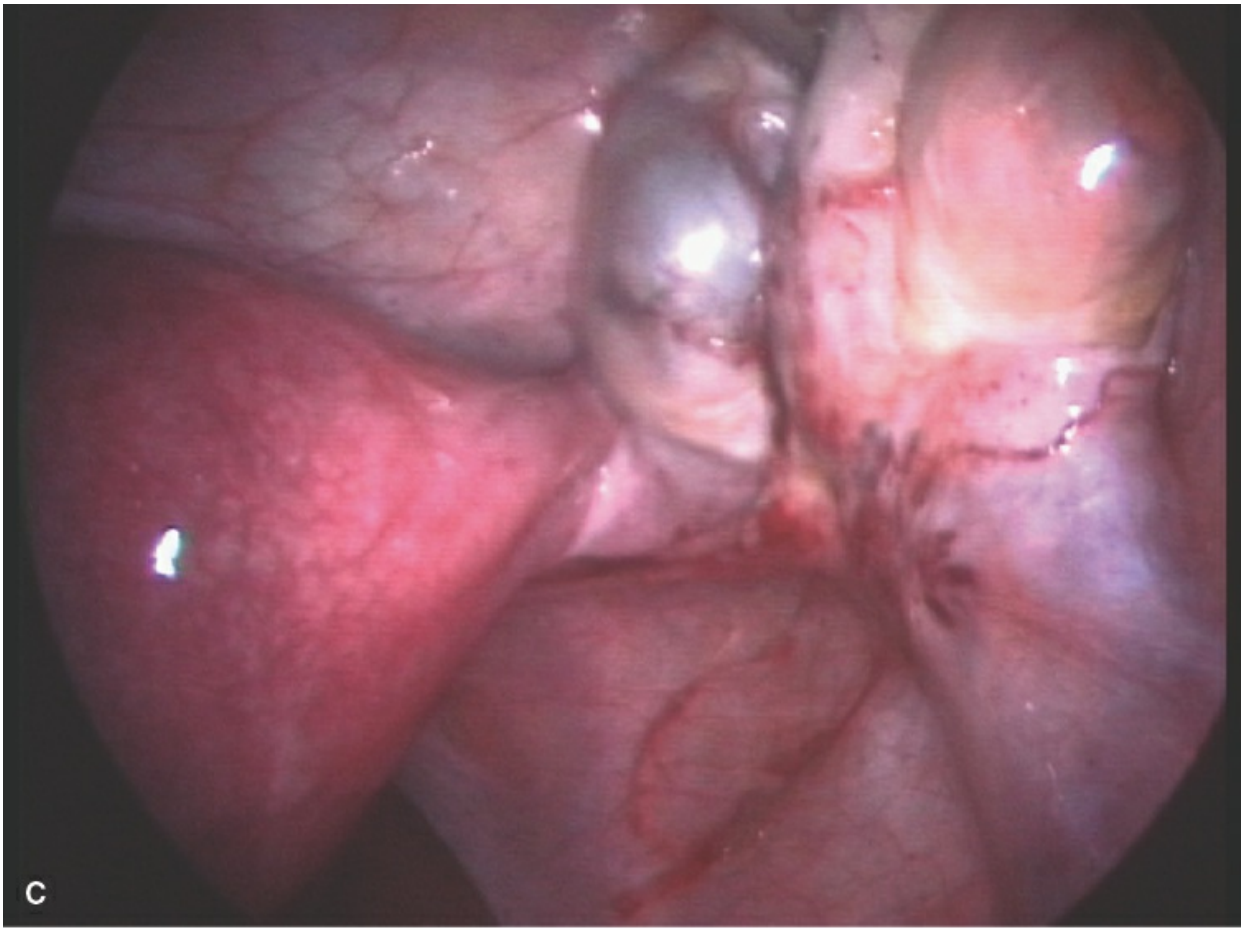
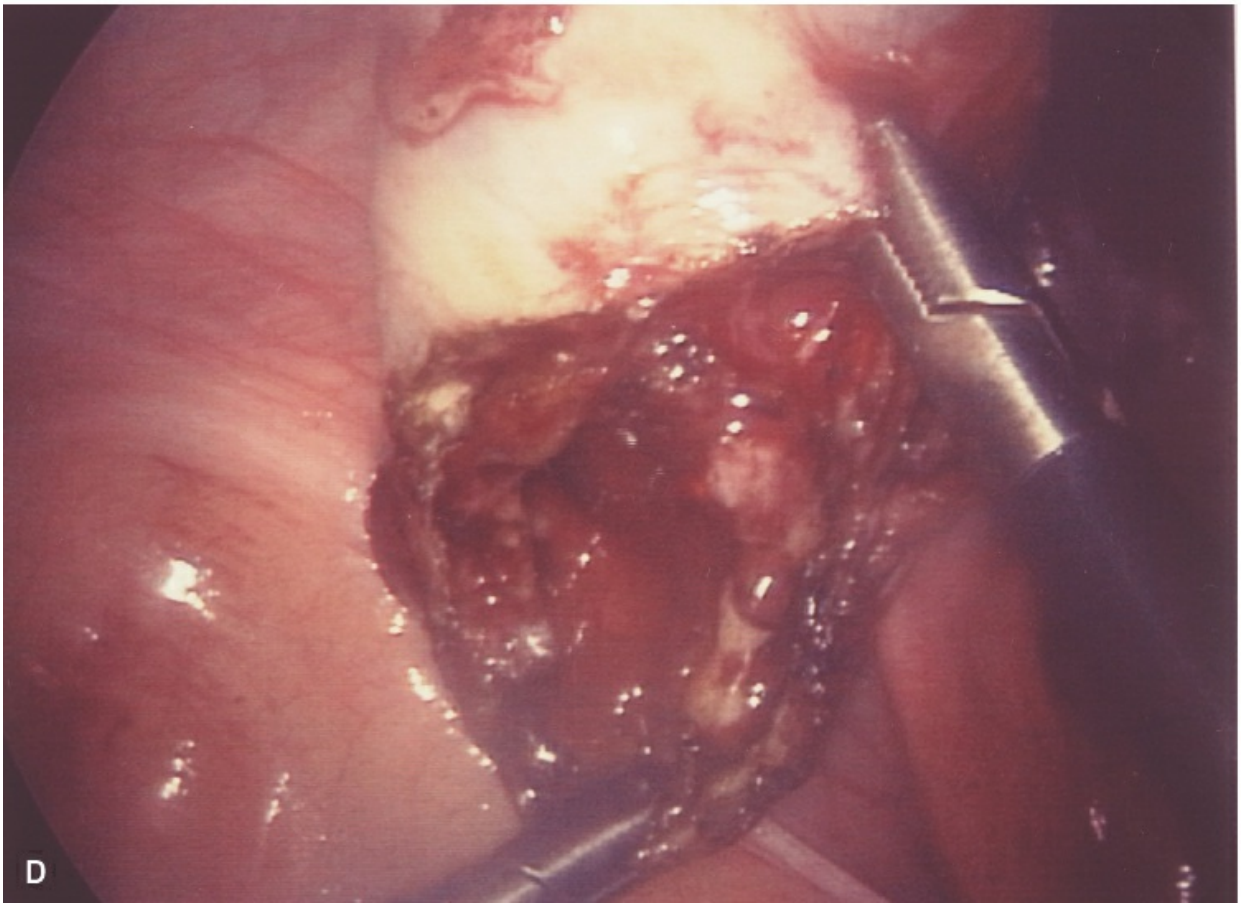

B

FIGURE 13-2 Typical and subtle endometriotic lesions on peritoneum. **A:** Typical black-puckered lesions with hypervascularization and orange polypoid vesicles. **B:** Red polypoid lesions with hypervascularization. (Photographs from Dr. Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium.)


A


B


C


D

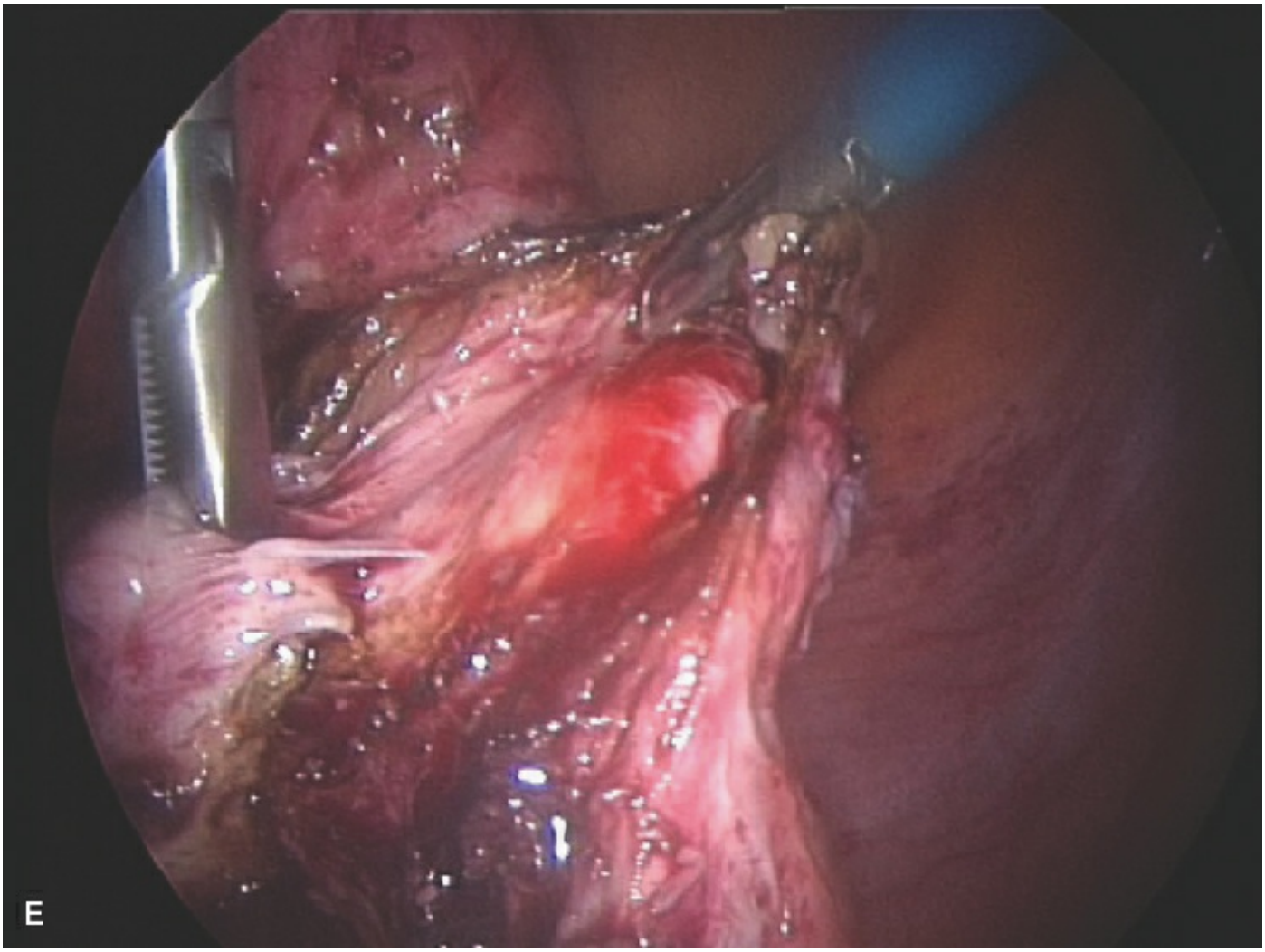
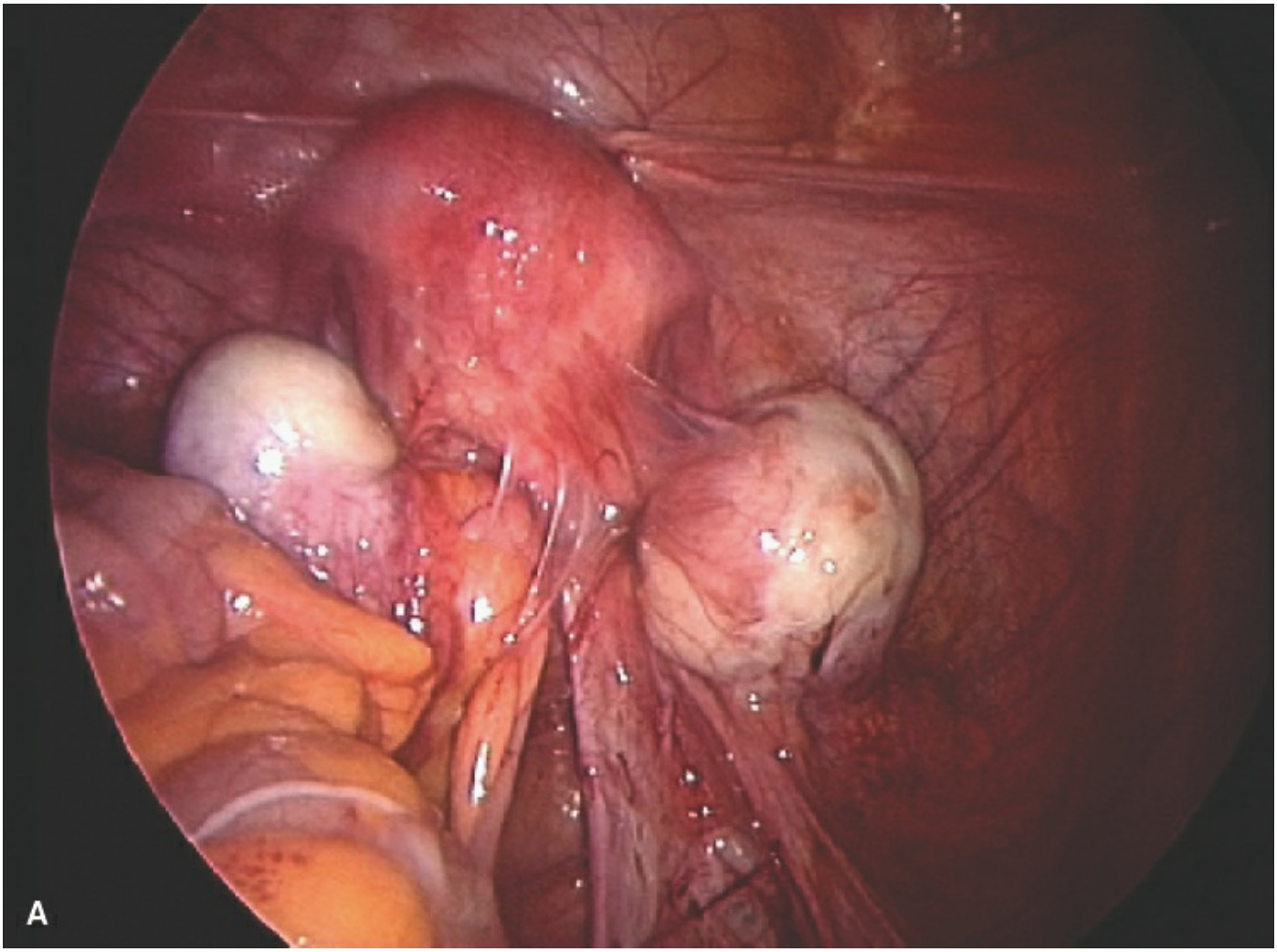
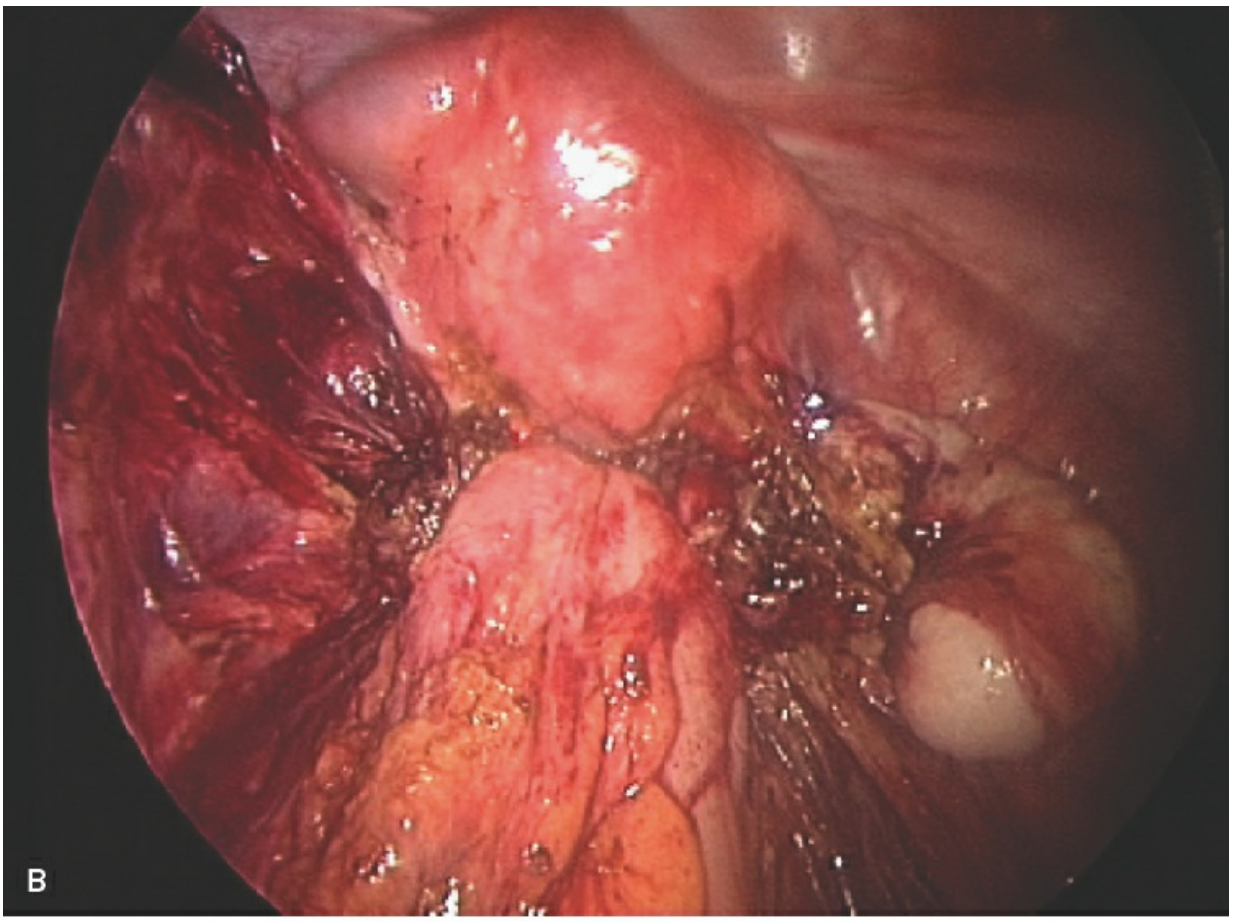


FIGURE 13-3 Ovarian endometriosis. **A:** Superficial ovarian endometriosis. **B:** Superficial ovarian endometriosis and endometrioma—laparoscopic image prior to adhesiolysis. **C:** Laparoscopic image of uterus and right ovary with dark endometrioma. **D:** Ovarian endometriotic cystectomy. **E:** Ovarian endometriotic cystectomy. (Photographs from Dr. Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium.)


A


B

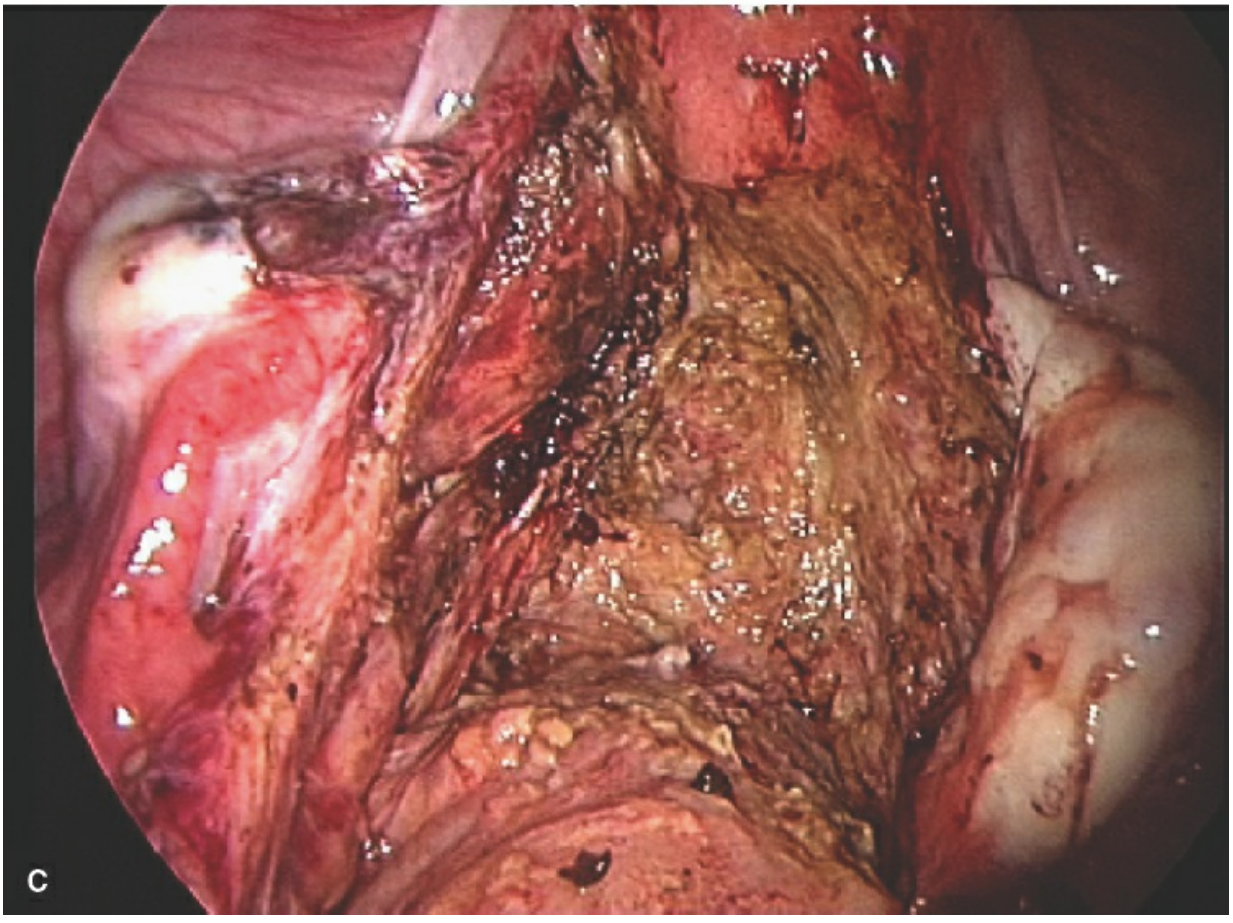

C

FIGURE 13-4 Laparoscopic excision of deep endometriosis from the cul-de-sac. **A:** Extensive endometriosis with deep nodule at the right uterosacral ligament, masked by adhesions. **B:** Deep nodule still present in dense adhesion between rectum and uterosacral ligaments. **C:** Cul-de-sac after resection of deep nodule with CO_2 laser. (Photographs from Dr. Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium.)

American Society for Reproductive Medicine
Revised Classification of Endometriosis

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40

Total _____

Laparoscopy _____ Laparotomy _____ Photography _____

Recommended Treatment _____

_____

Prognosis _____

PERITONEUM	**ENDOMETRIOSIS**	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	POSTERIOR CUL-DE-SAC OBLITERATION	Partial	Complete
		4	40

OVARY	**ADHESIONS**	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____

_____

_____

_____

Associated Pathology: _____

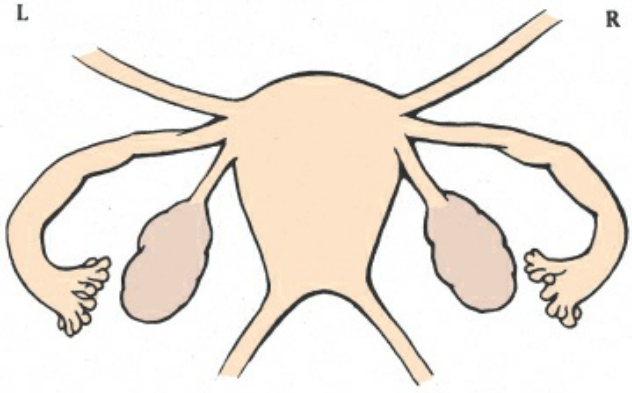
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To Be Used with Normal Tubes and Ovaries

L R



To Be Used with Abnormal Tubes and/or Ovaries

L R

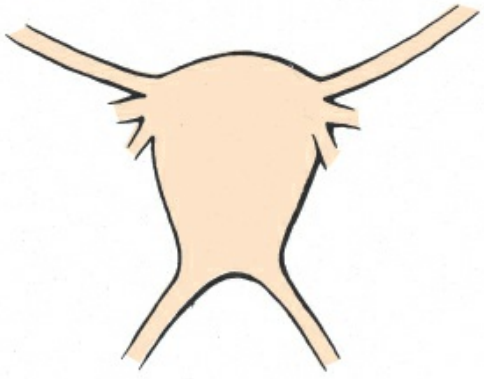


FIGURE 13-5 Revised American Society for Reproductive Medicine Classification. (From the American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis. Am Soc Reprod Med 1997;5:817–821.)

In a study of 44 patients with chronic pelvic pain, endometriosis was laparoscopically diagnosed in 36%, but histologic confirmation was obtained in only 18%. This approach resulted in a low diagnostic accuracy of laparoscopic inspection with a positive predictive value of only 45%, explained by a specificity of only 77% (225).

Microscopically, endometriotic implants consist of endometrial glands and/or stroma, with or without hemosiderin-laden macrophages (Fig. 13-6). It is suggested that using these stringent and unvalidated histologic criteria may result in significant underdiagnosis of endometriosis (6). Problems in obtaining biopsies (especially small vesicles) and variability in tissue processing (step or partial instead of serial sectioning) may contribute to false-negative results. Endometrioid stroma may be more characteristic of endometriosis than endometrioid glands (226). The presence of stromal endometriosis, which contains endometrial stroma with hemosiderin-laden macrophages or hemorrhage, was reported in women and in baboons and may represent a very early event in the pathogenesis of endometriosis (148,220,221). Isolated endometrial stromal cell nodules, immunohistochemically positive for vimentin and estrogen receptor, can be found in the absence of endometrial glands along blood or lymphatic vessels (227).

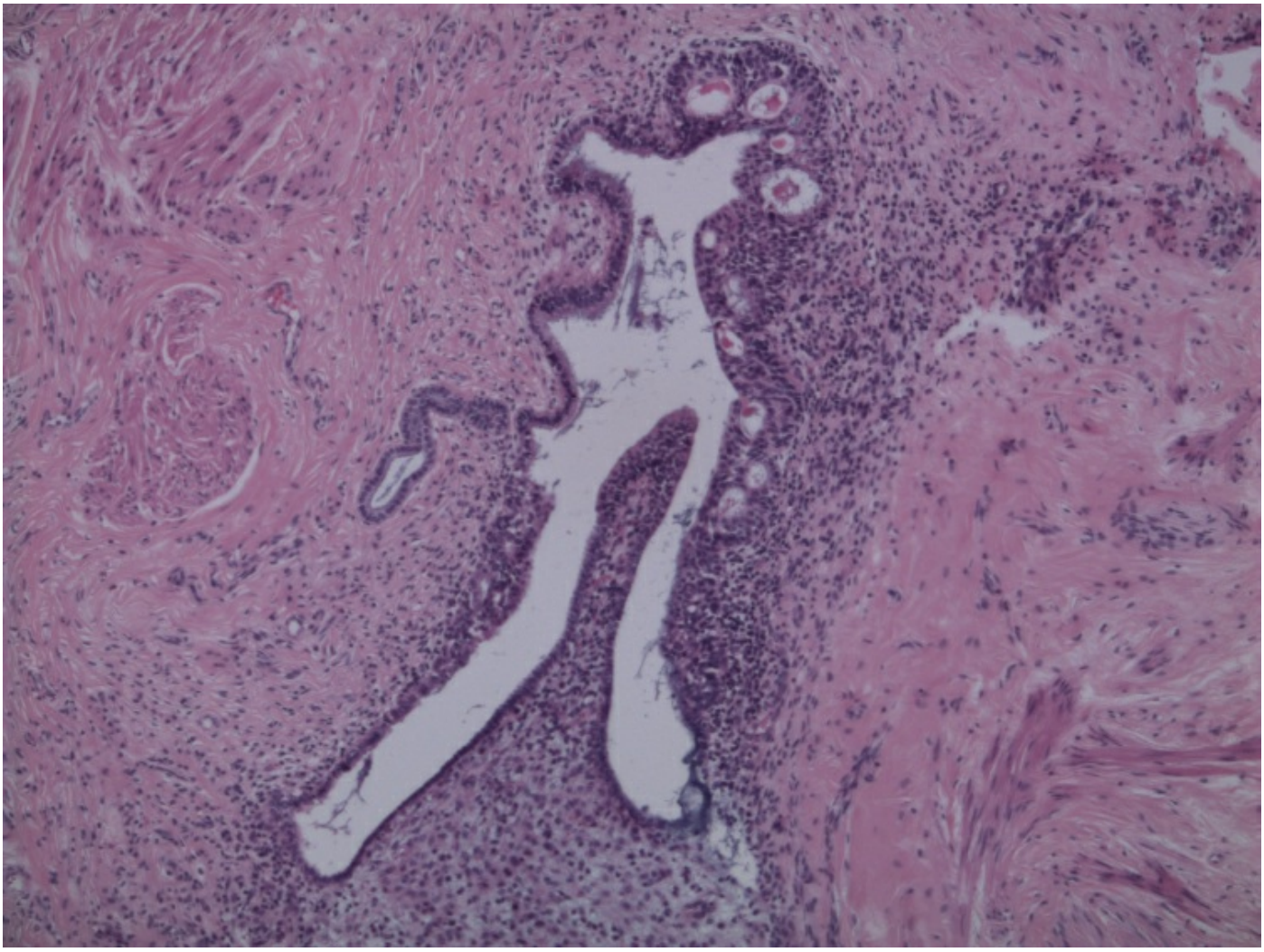


FIGURE 13-6 Histologic appearance of endometriosis: endometrial glandular epithelium, surrounded by stroma in typical lesion and clear vesicle.

Different types of lesions may have different degrees of proliferative or secretory glandular activity (226). Vascularization, mitotic activity, and the three-dimensional structure of endometriosis lesions are key factors (171,228,229). **Deep endometriosis is described as a specific type of pelvic endometriosis characterized by proliferative strands of glands and stroma in dense fibrous and smooth muscle tissue** (20). Smooth muscles are frequent components of endometriotic lesions on the peritoneum, ovary, rectovaginal septum, and uterosacral ligaments (174).

Microscopic endometriosis is defined as the presence of endometrial glands and stroma in macroscopically normal pelvic peritoneum. It is important in the histogenesis of endometriosis and its recurrence after treatment (230,231). The clinical relevance of microscopic endometriosis is controversial because it is not observed uniformly. Using undefined criteria for what constitutes normal peritoneum, peritoneal biopsy specimens of 1 to 3 cm were obtained during laparotomy from 20 patients with moderate to severe endometriosis (231). Examination of the biopsy results with low-

power scanning electron microscopy revealed unsuspected microscopic endometriosis in 25% of cases not confirmed by light microscopy. Peritoneal endometriotic foci were demonstrated by light microscopy in areas that showed no obvious evidence of disease (232).

In serial sections of laparoscopic biopsies of normal peritoneum, 10% to 15% of women had microscopic endometriosis, and endometriosis was found in 6% of those without macroscopic disease (219,233,234). Other studies were unable to detect microscopic endometriosis in 2-mm biopsy specimens of visually normal peritoneum (235–238). Examination of larger samples (5 to 15 mm) of visually normal peritoneum revealed microscopic endometriosis in only 1 of 55 patients studied (239). A histologic study of serial sections through the entire pelvic peritoneum of visually normal peritoneum from baboons with and without disease indicated that microscopic endometriosis is a rare occurrence (96). **Macroscopically appearing normal peritoneum rarely contains microscopic endometriosis** (239).

Laparoscopic Classification

Endometriosis is a complex disease and at present there is no perfect staging system available. **The most widely used staging system is the revised American Society for Reproductive Medicine classification (rASRM).** The Endometriosis Fertility Index (EFI) has been shown to predict non-IVF pregnancy rates for patients following surgical staging and treatment of endometriosis (177,240). To supplement the rASRM classification with regard to the description of deep endometriosis, the ENZIAN score was introduced (241–243). Although the ENZIAN score appears to be a good complement to the rASRM score for morphologic description of deep endometriosis and planning of surgery, it is not widely used. Recently the World Endometriosis Society (WES) published a consensus statement in which they recommend that **all women undergoing surgery should have the rASRM classification completed, women with deep endometriosis should additionally have ENZIAN completed, and women for whom future fertility is a concern should additionally have the EFI completed** (244).

American Society for Reproductive Medicine Staging

The revised ASRM staging system, is based on the appearance, size, and depth of peritoneal and ovarian implants; the presence, extent, and type of adnexal adhesions; and the degree of cul-de-sac obliteration (179,201). **In this classification system, the morphology of peritoneal and ovarian implants should be categorized as red (red, red-pink, and clear lesions), white (white, yellow-brown, and peritoneal defects), and black (black and blue lesions), according to color photographs provided by ASRM.**

This system reflects the extent of endometriotic disease but has considerable

intraobserver and interobserver variability (245,246). **[4] The ASRM classification for endometriosis is subjective and correlates poorly with pain and fertility outcomes** (175). Despite these important shortcomings the WES recommends its use because of two important reasons: it is the most widely used staging system in clinical practice and endometriosis research, and it is the rASRM system (partially) incorporated in the EFI and ENZIAN.

Endometriosis Fertility Index

[5] The EFI staging system predicts non-IVF pregnancy rates after surgical staging and treatment of endometriosis (Fig. 13-7) (177). **The EFI is based on historical and surgical factors. The historical factors are age, years of infertility, and prior pregnancies. The surgical factors consist of the total ASRM score, the ASRM endometriosis score, and the least function score, which describes functionality of the fallopian tubes, fimbriae, and ovaries.**

The EFI was designed specifically for infertility patients who have had surgical staging and treatment of their disease. It is not intended to predict any aspect of endometriosis associated pain. It is required that the male and female gametes are sufficiently functional to enable attempts at non-IVF conception. Severe uterine abnormality that is clinically significant is not included in the EFI. However, when this condition is found it does need to be taken into account in predicting pregnancy rates.

ENZIAN Classification

The ENZIAN staging system supplements the rASRM staging with a precise description of the location and extent of deep endometriosis lesions and the involvement of retroperitoneal structures or other organs.

The anatomic location of the deep endometriotic lesions is described in three compartments: A = rectovaginal septum and vagina; B = sacrouterine ligament to pelvic wall; and C = rectum and sigmoid colon. The depth of invasion is rated for all compartments (grade 1 = invasion <1 cm; grade 2 = invasion 1 to 3 cm; grade 3 = invasion >3 cm). Deep endometriotic lesions outside the pelvis and invasion of organs is registered separately: FA = adenomyosis; FB = bladder; FU = intrinsic involvement of the ureter; FI = intestinal disease cranial to the rectosigmoid junction; and FO = other locations, such as abdominal wall endometriosis. The ENZIAN classification seems to be useful in planning endometriosis surgery, but more research is needed on the correlation with pain or infertility and clinical relevant outcomes.

Spontaneous Evolution

Endometriosis appears to be a progressive disease in a significant proportion (30% to 60%) of patients. During serial observations, deterioration (47%), improvement (30%), or elimination (23%) was documented over a 6-month period (247,248). In

another study, endometriosis progressed in 64%, improved in 27%, and remained unchanged in 9% of patients over 12 months (249). A third study of 24 women reported 29% with disease progression, 29% with disease regression, and 42% with no change over 12 months. Follow-up studies in both baboons and women with spontaneous endometriosis over 24 months demonstrated disease progression in all baboons and in 6 of 7 women (250–252). Several studies reported that subtle lesions and typical implants may represent younger and older types of endometriosis, respectively. In a cross-sectional study, the incidence of subtle lesions decreased with age (253). This finding was confirmed by a 3-year prospective study that reported that the incidence, overall pelvic area involved, and volume of subtle lesions decreased with age, but in typical lesions, these parameters and the depth of infiltration increased with age (7). Remodeling of endometriotic lesions (transition between typical and subtle subtypes) is reported to occur in women and in baboons, indicating that endometriosis is a dynamic condition (254,255). Several studies in women, cynomolgus monkeys, and rodents showed that endometriosis is ameliorated after pregnancy (255–258).

The characteristics of endometriosis are variable during pregnancy, and lesions tend to enlarge during the first trimester but regress thereafter (259). Studies in baboons revealed no change in the number or surface area of endometriosis lesions during the first two trimesters of pregnancy (260). These results do not exclude a beneficial effect that may occur during the third trimester or in the immediate postpartum period. Establishment of a "pseudopregnant state" with exogenously administered estrogen and progestins is based on the belief that symptomatic improvement may result from decidualization of endometrial implants during pregnancy (261). This hypothesis is not substantiated, and it is possible that amenorrhea can explain the beneficial effect of pregnancy and lactation on endometriosis-associated pain symptoms.

MANAGEMENT

Primary Prevention

No strategies to prevent endometriosis are uniformly successful. A reduced incidence of endometriosis was reported in women who engaged in aerobic activity from an early age, but the possible protective effect of exercise was not investigated thoroughly (48). There is insufficient evidence that OC use offers protection against the development of endometriosis. One report showed an increased risk for endometriosis in a select population of women taking OCs, possibly explained by the observation that dysmenorrhea as a reason to initiate estroprogestins is significantly more common in women with endometriosis than in women without the disease (262,263). OCs inhibit ovulation, substantially reduce the volume of menstrual flow, and may interfere with implantation of refluxed endometrial cells, but the hypothesis of recommending OCs for primary prevention of endometriosis is not sufficiently substantiated (264). Although the

risk of endometriosis appears reduced during OC use, it is possible that this effect results from postponement of surgical evaluation caused by temporary suppression of pain symptoms (265). Confounding by selection and indication biases may explain the trend toward an increase in risk of endometriosis observed after discontinuation, but further clarification is needed (265).

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description
4	=	Normal
3	=	Mild Dysfunction
2	=	Moderate Dysfunction
1	=	Severe Dysfunction
0	=	Absent or Nonfunctional

	Left	Right		
Fallopian Tube				
Fimbria				
Ovary				
Lowest Score		+		=
	Left	Right		LF Score

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors

Factor	Description	Points
Age		
	If age is ≤ 35 years	2
	If age is 36 to 39 years	1
	If age is ≥ 40 years	0
Years Infertile		
	If years infertile is ≤ 3	2
	If years infertile is > 3	0
Prior Pregnancy		
	If there is a history of a prior pregnancy	1
	If there is no history of prior pregnancy	0
Total Historical Factors		

Surgical Factors

Factor	Description	Points
LF Score		
	If LF Score = 7 to 8 (high score)	3
	If LF Score = 4 to 6 (moderate score)	2
	If LF Score = 1 to 3 (low score)	0
AFS Endometriosis Score		
	If AFS Endometriosis Lesion Score is < 16	1
	If AFS Endometriosis Lesion Score is ≥ 16	0
AFS Total Score		
	If AFS total score is < 71	1
	If AFS total score is ≥ 71	0
Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: ( ) Historical + ( ) Surgical = ( ) **EFI Score**

ESTIMATED PERCENT PREGNANT BY EFI SCORE

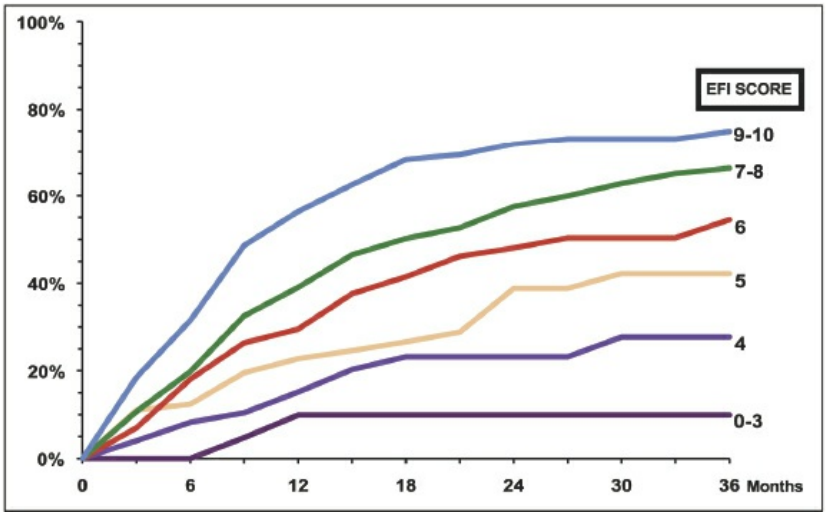


FIGURE 13-7 Endometriosis Fertility Index. (From Adamson D, Pasta D. Endometriosis fertility index: The new, validated endometriosis staging system. Fertil Steril 2010;94:1609–1615.)

Principles of Treatment

Treatment of endometriosis must be individualized, taking into consideration the clinical problem in its entirety, including the impact of the disease and the effect of its treatment on quality of life. Evidence-based recommendations that are continuously updated can be found in the ESHRE guidelines for the clinical management of endometriosis (1).

In most women with endometriosis, preservation of reproductive function is desirable (1). **Many women with endometriosis have pain and infertility at the same time or may desire children after sufficient pain relief, which complicates the choice of treatment.** Endometriosis surgery should be considered as reproductive surgery, defined by the World Health Organization (WHO) as "all surgical procedures carried out to diagnose, conserve, correct and/or improve reproductive function" (266). The least invasive and least expensive approach that is effective with the least long-term risks should be chosen (1). **Symptomatic endometriosis patients can be treated with analgesics, hormones, surgery, assisted reproduction, or a combination of these modalities** (1). **Regardless of the clinical profile (infertility, pain, asymptomatic findings), treatment of endometriosis may be justified because endometriosis appears to progress in 30% to 60% of patients within a year of diagnosis and it is not possible to predict in which patients it will progress** (249). Elimination of the endometriotic implants by surgical or medical treatment often provides only temporary relief. In addition to eliminating the endometriotic lesions, the goal should be to treat the sequelae (pain and infertility) often associated with this disease and to prevent recurrence of endometriosis (1). **Endometriosis is a chronic disease and the recurrence rate is high after both hormonal and surgical treatment** (1).

Treatment of extragenital endometriosis will depend on the site. If complete excision is possible, this is the treatment of choice; when this is not possible, long-term medical treatment is necessary using the same principles of medical treatment for pelvic endometriosis (1).

It is important to involve the patient in all decisions, to be flexible in considering diagnostic and therapeutic approaches, and to maintain a good relationship. It may be appropriate to seek advice from more experienced colleagues or to refer the patient to a center with the necessary expertise to offer treatments in a multidisciplinary context, including advanced laparoscopic surgery and laparotomy (1,267). Because the management of severe or deep endometriosis is complex, referral is strongly

recommended when disease of such severity is suspected or diagnosed (1).

Treatment of Endometriosis-Associated Pain

Pain may persist despite seemingly adequate medical or surgical treatment of the disease. A multidisciplinary approach involving a pain clinic and counseling should be considered early in the treatment plan. The least invasive and least expensive approach that is effective should be used (1).

Surgical Treatment

Depending on the severity of disease, diagnosis and removal of endometriosis should be performed simultaneously at the time of surgery, provided that preoperative consent was obtained (1,268–271). **The goal of surgery is to excise all visible endometriotic lesions and associated adhesions—peritoneal lesions, ovarian cysts, deep rectovaginal endometriosis—and to restore normal anatomy** (1). **Laparoscopy is preferred over laparotomy because the two techniques are equally effective and laparoscopy is associated with quicker recovery, better cosmesis, less postoperative pain, decreased costs, lower morbidity, and fewer postoperative adhesions** (1). Laparotomy is only indicated in the rare cases of advanced-stage disease where laparoscopy is impossible.

Conservative Surgery

Peritoneal Endometriosis

Endometriosis lesions can be removed during laparoscopy by surgical excision with scissors, bipolar coagulation, or laser methods (CO_2 laser, potassium-titanyl-phosphate laser, or argon laser). Some surgeons claim that the CO_2 laser is superior because it causes only minimal thermal damage, but **no evidence is available to show the superiority of one technique over another.** Surgical ablation of peritoneal endometriosis is considered equally effective as surgical excision. However, surgical excision of lesions could be preferred because it allows histologic analysis and confirmation of endometriosis.

Ovarian Endometriosis

Superficial ovarian lesions can be vaporized. The surgical management of pain associated with ovarian endometriotic cysts is controversial. The most common procedures for the treatment of ovarian endometriomas are either excision of the cyst wall or drainage and ablation of the cyst wall. During excision, the ovarian endometrioma is aspirated, followed by incision and removal of the cyst wall from the ovarian cortex with maximal preservation of normal ovarian tissue. During drainage and ablation, the ovarian endometrioma is aspirated and irrigated. Its wall can be inspected

with ovarian cystoscopy for intracystic lesions, and it is vaporized to destroy the mucosal lining of the cyst.

According to a systematic review, there is good evidence that excisional surgery for endometriomas with a diameter of 3 cm provides a more favorable outcome than drainage and ablation with regard to the recurrence of the endometrioma, recurrence of pain symptoms, and in women who were previously subfertile or had subsequent spontaneous pregnancy (272). Laparoscopic excision of the cyst wall of the endometrioma was associated with a reduced recurrence rate of the symptoms of dysmenorrhea (odds ratio [OR] 0.15; 95% CI, 0.06–0.38), dyspareunia (OR 0.08; 95% CI, 0.01–0.51), and nonmenstrual pelvic pain (OR 0.10; 95% CI, 0.02–0.56), a reduced rate of recurrence of the endometrioma (OR 0.41; 95% CI, 0.18–0.93), and with a reduced requirement for further surgery (OR 0.21; 95% CI, 0.05–0.79) than surgery to ablate the endometrioma. For those women subsequently attempting to conceive, it was associated with an increased spontaneous pregnancy rate in women who had documented prior infertility (OR 5.21; 95% CI, 2.04–13.29).

Based on this evidence, the **ESHRE guideline recommends cystectomy over drainage and coagulation because a cystectomy reduces endometriosis-associated pain and has a lower recurrence rate.** In case of very large endometriomas where excision is technically difficult without removing a large part of the ovary, a three-step procedure (marsupialization and rinsing followed by hormonal treatment with GnRH analogs and cyst wall electrocoagulation or laser vaporization 3 months later) can be considered (1,273).

It is possible that the surgical techniques used to treat ovarian endometriotic cysts may influence postoperative adhesion formation and/or ovarian function. In a randomized study comparing surgical methods to achieve ovarian hemostasis after laparoscopic endometriotic ovarian cystectomy, closure of the ovary with an intraovarian suture resulted in a lower rate and extension of postsurgical ovarian adhesions at 60 to 90 days follow-up when compared to only bipolar coagulation on the internal ovarian surface (274).

Deep Endometriosis

Deep endometriosis is usually multifocal and complete surgical excision must be performed in a one-step surgical procedure in order to avoid more than one surgery, provided the patient is fully informed (1,173,269). Because management of deep endometriosis is complex, referral to a center with sufficient expertise to offer all available treatments in a multidisciplinary approach is strongly recommended (1). Surgical management is only for symptomatic deep endometriosis. Asymptomatic patients must not undergo surgery, except for cases with complete obstruction of a ureter resulting in asymptomatic loss of renal function. Progression of the disease and appearance of specific symptoms rarely occurred in patients with asymptomatic

rectovaginal endometriosis (270). When surgical treatment is decided, the treatment must be radical with excision of all lesions (1). It is difficult to perform randomized studies to detect the best surgical technique to treat deep endometriosis because these severe cases are all managed individually and not all surgeons are familiar with all treatment options (1). Complete excision while preserving the uterus and ovarian tissue might include the resection of the uterosacral ligaments, the resection of the upper part of the posterior vaginal wall, and urologic and bowel operations.

The patients' surgical agreement must be obtained preoperatively to perform this difficult and high-risk procedure, especially in cases of expected or possible bowel or urologic surgery. Preoperative imaging is necessary to assess bowel and urologic impact of deep endometriosis. As endometriosis sometimes involves nongynecologic organs (i.e., the bowel, the urinary tract, or pelvic bones), other surgical specialists should be consulted as appropriate. These severe cases should be handled in centers with special expertise. Preoperative intestinal preparation may be recommended. Placement of ureteric catheters may facilitate the excision of periureteral endometriosis to facilitate ureterolysis and end-to-end ureteral reanastomosis that may be needed in cases of infiltrative periureteral endometriosis. The pattern of pain in endometriosis is complicated and pain does not always respond to treatment, so consultation with pain specialists may be useful.

In patients with severe endometriosis, it is common clinical practice that surgical treatment be preceded by a 3-month course of medical treatment (194). It is believed that this facilitates surgery by reducing inflammation and vascularization of lesions. The role of preoperative hormonal treatment was evaluated in a Cochrane review that concluded that there was no evidence of a benefit of preoperative medical therapy on the outcome of surgery. Therefore, although common clinical practice, the ESHRE guideline does not recommend preoperative hormonal therapy.

Surgical treatment of bladder endometriosis is usually in the form of excision of the lesion and primary closure of the bladder wall. Removal of full-thickness bladder detrusor endometriosis entails excision of the bladder dome or posterior wall, generally well above the trigone. Transurethral resection is contraindicated. Ureteral lesions may be excised after stenting the ureter. In the presence of intrinsic lesions or significant obstruction, segmental excision with end-to-end anastomosis or reimplantation with antireflux vesicoureteral plasty may be necessary (275).

Surgical excision of deep rectovaginal and rectosigmoidal endometriosis is difficult and can be associated with major complications such as bowel perforations with resulting peritonitis (276). It is debated whether this type of endometriosis is best treated by shaving, conservative excision, or resection reanastomosis, by laparoscopy and laparotomy, or laparoscopically assisted vaginal technique (277). Appendicular endometriosis is usually treated by appendectomy.

In a randomized study comparing colorectal resection for endometriosis by

laparoscopy or laparotomy, clinical outcome was similar with respect to dyschezia, bowel pain and cramping, and dysmenorrhea and dyspareunia, but laparoscopy was associated with less blood loss, fewer complications, and a higher pregnancy rate than laparotomy (278).

There are very few methodologically valid studies evaluating clinical outcome after surgery for deep endometriosis with colorectal extension, as demonstrated in a systematic review (279). In a review on the clinical outcome of surgical treatment of deep endometriosis with colorectal involvement, most of the 49 reviewed studies included complications (94%) and pain (67%); few studies reported recurrence (41%), fertility (37%), and quality of life (10%); only 29% reported (loss of) follow-up. Of 3,894 patients, 71% underwent bowel resection and anastomosis, 10% had full-thickness excision, and 17% were treated with superficial surgery. Comparison of clinical outcome between different surgical techniques was not possible. Postoperative complications were present in 0% to 3% of the patients. Although pain improvement was reported in most studies, pain evaluation was patient based in less than 50% (visual analog scale [VAS] in only 18%). Although quality of life was improved in most studies, prospective data were available for only 149 patients. Pregnancy rates were 23% to 57% with a cumulative pregnancy rate of 58% to 70% within 4 years. The overall endometriosis recurrence rate in studies (longer than 2 years follow-up) was 5% to 25%, with most of the studies reporting 10%.

Because high quality prospective studies reporting standardized and well-defined clinical outcomes after surgical treatment of deep endometriosis with long-term follow-up are needed, the Consensus On Recording Deep Endometriosis Surgery (CORDES) statement was published in 2016 (280). This consensus statement provides definition and standards for recording deep endometriosis surgery and outcome reporting in clinical trials on the surgical management of deep endometriosis.

Adhesiolysis

Endometriosis is often associated with pelvic adhesions, which can be very extensive and result in severe distortion of the pelvic anatomy. The removal of endometriosis-related adhesions (adhesiolysis) should be performed carefully and focused at restoration of the normal anatomy. However, adhesions lysed at surgery can form again. Cutting, surgical denudation, ischemia, desiccation, or abrasion can cause peritoneal trauma during surgery and the subsequent healing mechanism in the peritoneal cavity can result in adhesion formation between damaged serosal surfaces. Minimally invasive techniques such as laparoscopy reduce the risk of adhesion formation but do not eliminate it entirely.

Several barrier agents have been tested for adhesion prevention during surgery. The ESHRE guideline acknowledges that clinicians can consider the use of oxidized regenerated cellulose and potentially other barrier agents. However, **a recent**

systematic review including 18 randomized controlled trials (RCTs) with a total of 1,262 enrolled women found no effects of any barrier agent used during pelvic surgery on either pain or fertility outcomes (281). Low-quality evidence suggests that oxidized regenerated cellulose, expanded polytetrafluoroethylene and sodium hyaluronate with carboxymethylcellulose may all be more effective than no treatment in reducing the incidence of adhesion formation following pelvic surgery.

Based on this systematic review, routine use of barrier agents to prevent postoperative adhesions after pelvic surgery can be considered but cannot be recommended.

Interruption of Pelvic Nerve Pathways

Surgical interruption of pelvic nerve pathways has been suggested as an additional procedure to conservative surgery for endometriosis. Two techniques have been suggested for endometriosis-associated pain: laparoscopic uterine nerve ablation (LUNA) and presacral neurectomy (PSN). The effectiveness of LUNA and PSN was evaluated in several clinical trials and data of six RCTs were analyzed in a Cochrane review (282). Based on the systematic review it can be concluded that laparoscopic excision or ablation of endometriosis should not be combined with LUNA because this procedure offers no additional benefit. PSN is effective as an additional procedure, but it requires a high degree of surgical skill and is associated with increased adverse effects such as bleeding, constipation, urinary urgency, and less pain during the first stage of labor (1).

Outcome of Conservative Surgery

The outcome of surgical therapy in patients with endometriosis and pain is influenced by many psychological factors relating to personality, depression, and marital and sexual problems. It is difficult to evaluate scientifically the objective effect of different surgical approaches because the extirpation and destruction of the pathologic tissue can impact the results as can surgery per se, the doctor–patient relationship, complications, and other factors. There is a significant placebo response to surgical therapy: diagnostic laparoscopy without complete removal of endometriosis may alleviate pain in 50% of patients (283–285). Similar results were reported using oral placebos (286). Although some reports claimed pain relief with laser laparoscopy in 60% to 80% of patients with very low morbidity, none were prospective or controlled or allowed a definitive conclusion regarding treatment efficacy (194,287–290). The longstanding effect of surgery on pain is difficult to evaluate because the follow-up time is too short, usually just a few months. The major shortcoming of surgical treatment in endometriosis-related pain is the lack of prospective randomized studies with sufficient follow-up time to draw clear clinical conclusions.

In a systematic review assessing the efficacy of laparoscopic surgery in the treatment of pelvic pain associated with endometriosis and including five randomized controlled studies, meta-analysis demonstrated an advantage of laparoscopic surgery when compared to diagnostic laparoscopy only at 6 months (OR 5.72; 95% CI, 3.09–10.60; 171 participants, three trials) and 12 months (OR 7.72; 95% CI, 2.97–20.06; 33 participants, one trial) after surgery (291). Few women diagnosed with severe endometriosis were included in the meta-analysis and any conclusions from this meta-analysis regarding treatment of severe endometriosis should be made with caution. It was not possible to draw conclusions from the meta-analysis in which specific laparoscopic surgical intervention was most effective (291).

The extent and duration of the therapeutic benefit of surgery for endometriosis-related pain are poorly defined, and the expected benefit is operator dependent (292). In a systematic review based on three randomized controlled studies, the absolute increased benefit from destruction of lesions compared with diagnostic only operation in terms of proportion of women reporting pain relief was between 30% and 40% after short follow-up periods (292). The pain relief tended to decrease with time, and the reoperation rate, based on long-term follow-up studies, was as high as 50% (292). In most case series on excisional surgery for rectovaginal endometriosis, substantial short-term pain relief was experienced by approximately 70% to 80% of the patients who continued the study. At 1-year follow-up, approximately 50% of the women needed analgesics or hormonal treatments (292). Medium-term recurrence of lesions was observed in approximately 20% of the cases, and approximately 25% of the women underwent repetitive surgery (292). It appears that pain recurrence and reoperation rates after conservative surgery for symptomatic endometriosis are high and probably underestimated (292).

Prevention of Recurrence After Conservative Surgical Treatment

The addition of postoperative hormonal therapy to conservative surgery for endometriosis has been suggested for two main reasons. First, short-term postoperative hormonal therapy (up to 6 months after the operation) could potentially improve the outcomes of the operation through their effect on any residual endometriosis. Secondly, long-term hormonal therapy after surgery could be prescribed for secondary prevention: suppression of ovarian function and menstruation could prevent the development of new lesions.

Systemic Medical Therapy

In a systematic review published in 2004 to determine the effectiveness of systemic medical therapies used for hormonal suppression before or after surgery for endometriosis, or before and after surgery for the eradication of endometriosis, improvement of symptoms, pregnancy rates, and overall tolerability, by comparing them with no treatment or placebo, 11 trials were included (293). **Five trials compared**

postsurgical medical therapy with surgery alone (without medical therapy) and assessed the outcomes of pain recurrence, disease recurrence, and pregnancy rates (294–297). There was no statistically significant reduction in pain recurrence at 12 months (relative risk [RR] 0.76; 95% CI, 0.52–1.10), but the difference at 24 months approached statistical significance (RR 0.70; 95% CI, 0.47–1.03). **There was no statistically significant difference between the use of these medical therapies after surgery compared to surgery alone with regard to disease recurrence** (RR 1.02; 95% CI, 0.27–3.84) or pregnancy rates (RR 0.78; 95% CI, 0.50–1.22). Postsurgical medical therapy was compared to surgery plus placebo in three studies (295,298,299). There was no difference between medical therapy and placebo with regard to the measures for pain; multidimensional pain score (WMD −0.40; 95% CI, −2.15–1.35); linear scale score (0.10; 95% CI, −2.24–2.44); or change in pain (−0.40; 95% CI, −1.48–0.68). There was no difference between medical therapy and placebo for pregnancy rates (RR 1.05; 95% CI, 0.44–2.51) or total AFS scores (WMD −2.10; 95% CI, −4.56–0.36). There was no significant difference between preoperative hormonal suppression and postoperative hormonal suppression for the outcome of pain in one trial (300).

These results were confirmed in another RCT with 5 years of follow-up, showing that GnRH analog treatment with *triptorelin* depot 3.75 intramuscular after operative laparoscopy for stages III and IV endometriosis was comparable to placebo injections with respect to time to relapse of endometrioma, pain recurrence, and time to pregnancy (301).

There is circumstantial evidence that regular postoperative use of OCs effectively prevents endometrioma recurrence (302). In a prospective controlled cohort study with a median follow-up of 28 months after laparoscopic excision of ovarian endometriomata, the 36-month cumulative proportion of subjects free from endometrioma recurrence was 94% in women who always used cyclic oral contraception compared with 51% in those who never used it (p <0.001; adjusted incidence rate ratio [IRR] 0.10; 95% CI, 0.04–0.24) (302).

Some randomized controlled studies suggest that postoperative hormonal treatment can be useful in delaying the recurrence of endometriosis and/or pelvic pain. One study supported the long-term postoperative use of OCs to reduce the frequency and the severity of recurrent endometriosis-related dysmenorrhea (303). The prevention of endometriosis-related pain recurrence by postoperative long-term (24 months) cyclic and continuous administration of OCs was compared to no treatment in women after surgery for ovarian endometrioma. A significant reduction in recurrence rate and VAS scores for dysmenorrhea was evident in the continuous users versus the other groups at 6 months, and in cyclic users versus nonusers at 18 months postoperatively. No significant differences in recurrence rate and VAS scores for dyspareunia and chronic pelvic pain were demonstrated among the groups. The increase of VAS scores for

dysmenorrhea, dyspareunia, and chronic pelvic pain during the postoperative follow-up of 6 to 24 months was significantly higher in nonusers than in the users (303).

In a second study, **long-term cyclic and continuous postoperative use of OCs was shown to effectively reduce and delay endometrioma recurrence** (304). The crude recurrence rate within 24 months was significantly lower in cyclic (14.7%) and continuous users (8.2%) compared with nonusers (29%). The recurrence-free survival was significantly lower in nonusers compared with cyclic and continuous users. The mean recurrent endometrioma diameter at first observation and the mean diameter increase every 6 months of follow-up were significantly lower in cyclic and continuous users compared with nonusers, whereas **no significant differences between cyclic users and continuous users in terms of endometrioma recurrence were demonstrated** (304).

In a third study, women who underwent conservative pelvic surgery for symptomatic endometriosis stages III and IV (r-AFS) were treated postoperatively during 6 months with either placebo, GnRH agonist (*triptorelin* or *leuprorelin,* 3.75 mg every 28 days), continuous estroprogestin (*ethinylestradiol,* 0.03 mg plus *gestodene,* 0.75 mg) or dietary therapy (vitamins, minerals salts, lactic ferments, fish oil) (305). At 12 months after surgery, patients treated with postoperative hormonal suppression therapy showed a lower VAS score for dysmenorrhea than patients in the other groups. Hormonal suppression therapy and dietary supplementation were equally effective in reducing nonmenstrual pelvic pain. **Postoperative medical and dietary therapy allowed a better quality of life when compared to placebo treatment** (305).

In a systematic review to determine whether postoperative use of an *levonorgestrel* intrauterine system in women with endometriosis improves pain symptoms associated with menstruation and reduces recurrence compared with surgery only, placebo, or systemic hormones, one small RCT was identified showing a statistically significant reduction in the recurrence of painful periods in the *levonorgestrel* intrauterine system treated group compared with the control group receiving a GnRH agonist (OR 0.14; 95% CI, 0.02–0.75) (306,307). The proportion of women who were satisfied with their treatment was higher in the *levonorgestrel* intrauterine system treated group than in the control group, but this difference did not reach statistical difference (OR 3.00; 95% CI, 0.79–11.44) (306,307). In another small randomized trial, postsurgical treatment with either *levonorgestrel* intrauterine system or depot *MPA* for 3 years indicated symptom control and recurrence were comparable, but compliance and change in bone mineral density were better in the *levonorgestrel* intrauterine system treated group than in the depot *MPA* group (308).

Based on all this evidence, it can be concluded that there is no strong evidence that short-term postoperative hormonal therapy improves the outcome of conservative surgery for endometriosis, hence it is not recommended in the ESHRE guideline. However, there is a role for postoperative hormonal therapy for secondary prevention

of endometriosis. There is no good evidence to recommend one intervention and the ultimate choice will be influenced by patient preferences, side effects, and costs. **The ESHRE guideline recommends the use of postoperative hormonal therapy in two indications: (1) after cystectomy for an endometrioma in women not immediately seeking conception; and (2) after conservative surgery for endometriosis, for at least 18 to 24 months, for secondary prevention of endometriosis-associated dysmenorrhea.**

Radical Surgery: Oophorectomy and Hysterectomy

Radical procedures such as oophorectomy or total hysterectomy are indicated only in severe situations and can be performed laparoscopically or by laparotomy. Women aged 30 years or younger at the time of hysterectomy for endometriosis-associated pain are more likely than older women to have residual symptoms, to report a sense of loss, and to report more disruption from pain in different aspects of their lives (309). If a hysterectomy is performed, all visible endometriotic tissue should be removed. Although associated with improved pain relief and a reduced chance of future surgery, a bilateral salpingo-oophorectomy (BSO) in young women should be considered in only the most severe or recurrent cases (310,311). Resection is an effective treatment for rectovaginal endometriosis, in combination with hysterectomy (312).

Medical Treatment of Endometriosis-Associated Pain

If the patient desires treatment of pain symptoms that are suggestive of endometriosis in the absence of a definitive diagnosis, empirical treatment is appropriate and includes counseling, analgesia, and progestins or combined OCs. Before starting empirical treatment, other causes of pelvic pain symptoms should be ruled out, as far as possible. **It is unclear whether OCs should be taken in a conventional, continuous, or tricycle regimen. A GnRH agonist may be taken, but is not recommended,** because this class of drug is more expensive and associated with more side effects and concerns about bone density than OCs (1).

Primary Dysmenorrhea

Analgesics

Women suffering from dysmenorrhea are treated with analgesics; many women treat themselves with over-the-counter oral analgesics. Primary dysmenorrhea is defined as menstrual pain without organic pathology, based on physical examination alone, and it can be argued that some women with so-called primary dysmenorrhea probably have endometriosis (313). In a systematic review, it was concluded that **nonsteroidal anti-inflammatories (NSAIDs) were more effective than placebo for relief of primary**

dysmenorrhea, but there was insufficient evidence to suggest whether any individual NSAID was more effective than another (314). In another review, selective cyclooxygenase-2 inhibitors *rofecoxib* and *valdecoxib* were as effective as *naproxen* and more effective than placebo for the treatment of primary dysmenorrhea (315). Concerns were raised about the safety of these medications, and its manufacturers withdrew *rofecoxib* from the market.

According to another systematic review based on two relatively small, RCTs comparing *paracetamol* and *coproxamol* with placebo, *coproxamol* (*paracetamol* 650 mg and *dextropropoxyphene* 65 mg) but not *paracetamol* (500 mg 4 times daily) was more effective than placebo in reducing primary dysmenorrhea (315). This observation may be explained by the suboptimal dosage of *paracetamol* used. A small randomized trial demonstrated that *paracetamol* (*acetaminophen*) 1,000 mg four times daily was superior to placebo for the treatment of primary dysmenorrhea (316).

Oral Contraceptives

There is a paucity of information for the use of modern OCs for primary dysmenorrhea. A Cochrane review suggested that first- and second-generation OCs with 50 µg or more estrogen may be more effective than placebo treatment for dysmenorrhea. It concluded that the studies included for analysis were of poor quality and heterogeneous so that no recommendation could be made regarding the efficacy of modern, lower-dose OCs (evidence level 1a) (317). An RCT comparing a low-dose OC containing 20 µg *ethinyl estradiol* and 100 µg *levonorgestrel* with placebo showed better pain relief in adolescent girls with dysmenorrhea using the OC than placebo (318).

There is some evidence in general populations that OCs can effectively treat dysmenorrhea (319). OCs have the advantage of long-term safety; hence they can be used indefinitely in low-risk women. In clinical practice, when they are used for menstrual pain, they may be taken continuously or with one pill-free week per three cycles to reduce the number of periods or avoid them altogether. There is no direct comparison of these options with the conventional approach.

Other Treatments

Several Cochrane reviews and one clinical evidence review suggest that other treatment modalities that might be helpful in primary dysmenorrhea include supplemental thiamine or vitamin E, high-frequency transcutaneous nerve stimulation, topical heat and herbal remedy *toki-shakuyaku-san.* They suggest that treatment modalities with unknown benefits are vitamin B_{12}, fish oil, magnesium, acupuncture, other herbal remedies, and behavioral interventions, and that spinal manipulation is unlikely to be beneficial (317,319–321).

Treatment of Endometriosis-Associated Pain

Nonsteroidal Anti-Inflammatory Drugs

Considering that endometriosis is a chronic inflammatory disease, anti-inflammatory drugs would appear to be effective for treatment of endometriosis-related dysmenorrhea. Although NSAIDs are used extensively and are often the first-line therapy for reduction of endometriosis-related pain, the analgesic effect of NSAIDs was not studied extensively. Only one small, double-blind, placebo-controlled, four-period, crossover clinical study was published (322). This study claimed complete or substantial pain relief of endometriosis-related dysmenorrhea in 83% of cases treated with *naproxen* compared with 41% in cases treated with placebo. A different analysis of the data from the same study by **the Cochrane Collaborative Network did not confirm a positive effect of *naproxen* on pain relief** (OR 3.27; 95% CI, 0.61–17.69) **in women with endometriosis** (323). There was inconclusive evidence to indicate whether women taking NSAIDs (*naproxen*) were less likely to require additional analgesia (OR 0.12; 95% CI, 0.01–1.29) or to experience side effects (OR 0.46; 95% CI, 0.09–2.47) when compared to placebo (323).

Endometriosis-related pain is nociceptive, but persistent nociceptive input from endometriotic lesions leads to central sensitization manifested by somatic hyperalgesia and increased referred pain (324). The potential effectiveness of NSAIDs in the reduction of endometriosis-related pain may be explained by a local antinociceptive effect and a reduced central sensitization in addition to the anti-inflammatory effect. NSAIDs have significant side effects, including gastric ulceration and possible inhibition of ovulation. PGs are involved in the follicle rupture mechanism at ovulation, which is why women who wish to become pregnant should not take NSAIDs at the time of ovulation (325).

Hormonal Treatment

Effect of Hormonal Treatment on Pain

Because estrogen is known to stimulate the growth of endometriosis, hormonal therapy is designed to suppress estrogen synthesis, thereby inducing atrophy of ectopic endometrial implants or interrupting the cycle of stimulation and bleeding (1). Implants of endometriosis react to gonadal steroid hormones in a manner similar, but not identical, to normally stimulated ectopic endometrium. Ectopic endometrial tissue displays histologic and biochemical differences from normal ectopic endometrium in characteristics such as glandular activity (proliferation, secretion), enzyme activity (17β-hydroxysteroid dehydrogenase), and steroid (estrogen, progestin, and androgen) hormone receptor levels. Withdrawal of estrogen stimulation causes cellular inactivation and degeneration of endometriotic implants but not their disappearance.

There is strong evidence that suppression of ovarian function for 6 months reduces pain associated with endometriosis. **[6]** Combined OCs *danazol, gestrinone, medroxyprogesterone acetate,* and GnRH agonists are all equally effective but their side effects and cost profiles differ (1). **Pain relief may be of short duration,**

presumably because endometriosis and endometriosis-associated pain recur after the cessation of medical treatment. The use of *DES, methyltestosterone,* or other androgens is no longer advocated because they lack efficacy, have significant side effects, and pose risks to the fetus if pregnancy occurs during therapy. A new generation of aromatase inhibitors, oral GnRH antagonists, estrogen receptor modulators, and progesterone antagonists (PRAs) may offer new hormonal treatment options.

Hormonal Treatment for Pain From Rectovaginal Endometriosis

Surgical treatment may reduce the pain associated with rectovaginal endometriosis, but it is associated with a high risk of morbidity and major complications. The effect of medical treatment in terms of pain relief in women with rectovaginal endometriosis appears to be substantial (326). In a systematic review including 217 cases of medically treated rectovaginal endometriosis, the antalgic effect of the considered medical therapies (vaginal danazol, GnRH agonist, progestin, and estrogen–progestin combinations used transvaginally, transdermally, or orally) for the entire treatment period (from 6 to 12 months) was 60% to 90%, with patients reporting considerable reduction or complete relief from pain symptoms, with the exception of when an aromatase inhibitor was used alone (326).

Oral Contraceptives

Although OCs are effective in inducing a decidualized endometrium, the estrogenic component in OCs may stimulate endometrial growth and increase pelvic pain in the first few weeks of treatment. The long-term significance of this effect is undetermined. OCs are less costly than other treatments and may be helpful in the short-term management of endometriosis with potential long-term benefits in some women.

The use of cyclic OCs may provide prophylaxis against the development or recurrence of endometriosis. Estrogens in OCs may stimulate the proliferation of endometriosis. The reduced menstrual bleeding that often occurs in women taking OCs may be beneficial to women with prolonged, frequent menstrual bleeding, which is a known risk factor for endometriosis (48).

Further research is warranted to assess the effect of low-dose OCs in preventing endometriosis and treating associated pain, because the evidence for its efficacy is limited. In a systematic review to assess the effects of OC's in comparison with other treatments for painful symptoms of endometriosis in women of reproductive age, only one study met the inclusion criteria (all truly RCTs of the use of OCs in the treatment of women of reproductive age with symptoms ascribed to the diagnosis of endometriosis and made visually at surgical procedure were included) (327,328). In this study, a total of 57 women were allocated to two groups to compare an OC to a GnRH analog (328). Methods of randomization and allocation concealment were unclear and the analog group became amenorrheic during the treatment period of 6 months, while women in the OC group reported a decrease in dysmenorrhea (327,328). No evidence of a significant

difference between the two groups was observed in terms of dysmenorrhea at 6 months follow-up after stopping treatment (OR 0.48; 95% CI, 0.08–2.90). Some evidence for a decrease in dyspareunia was found at the end of treatment in women in the GnRH analog group; although no evidence of a significant difference in dyspareunia was observed at the end of the 6 months follow-up (OR 4.87; 95% CI, 0.96–24.65). According to these data, there is no evidence of a difference in outcomes between the OC studied and GnRH analog in the treatment of endometriosis-associated painful symptoms (327). The lack of studies with larger sample sizes or studies focusing on other comparable treatments is concerning, and further research is needed to evaluate the role of OCs in managing symptoms associated with management of endometriosis (327).

In a double-blind, randomized, placebo-controlled trial, patients with suspected or surgically proven endometriosis were randomly assigned to receive either monophasic OC (*ethinylestradiol* plus *norethisterone*) or placebo during four cycles (329). Total dysmenorrhea scores assessed by verbal rating scale were significantly decreased at the end of treatment in both groups. From the first cycle through the end of treatment, dysmenorrhea in the OC group was significantly milder than in the placebo group. The volume of ovarian endometrioma was significantly decreased in the OC group but not in the placebo group (329).

Continuous Contraceptives

The treatment of endometriosis with continuous low-dose monophasic OCs (one pill per day for 6 to 12 months) was originally used to induce pseudopregnancy caused by the resultant amenorrhea and decidualization of endometrial tissue (261). The concept was to induce an adynamic endometrium through elimination of the normal cyclic hormonal changes characteristic of the menstrual cycle (330). This induction of a pseudopregnancy state with combination OC pills is effective in reducing dysmenorrhea and pelvic pain. The subsequent amenorrhea induced by OCs could decrease the risk for disease progression by preventing or reducing (retrograde) menstruation. Pathologically, OC use is associated with decidualization of endometrial tissue, necrobiosis, and possibly absorption of the endometrial tissue (331). **There is no convincing evidence that medical therapy with OCs offers definitive therapy. Instead, the endometrial implants survive the induced atrophy and, in most patients, reactivate after termination of treatment.**

Any low-dose OC containing 20 to 35 lg of *ethinyl estradiol* used continuously can be used for the management of endometriosis. The objective of the treatment is the induction of amenorrhea, which should be continued for 6 to 12 months. Continuous or extended cyclic use of OCs is well tolerated when compared to the cyclic use of OCs for contraceptive purposes (332). In an RCT of women with recurrent moderate or severe pelvic pain after unsuccessful conservative surgery for symptomatic rectovaginal endometriosis, continuous treatment with oral *ethinyl E2,* 0.01 mg plus

cyproterone acetate, 3 mg per day, or *norethindrone acetate,* 2.5 mg per day during 12 months resulted in substantially reduced dysmenorrhea, deep dyspareunia, nonmenstrual pelvic pain, and dyschezia scores without major between-group differences in patient satisfaction rates (62% and 73%, respectively) (333).

Table 13-1 Medical Treatment of Endometriosis-Associated Pain: Effective Regimens (Usual Duration: 6 Months)

	Administration	Dose	Frequency
Progestogens			
Medroxyprogesterone acetate	PO	30 mg	Daily
Dienogest	PO	2 mg	Daily
Megestrol acetate	PO	40 mg	Daily
Lynestrenol	PO	10 mg	Daily
Dydrogesterone	PO	20–30 mg	Daily
Antiprogestins			
Gestrinone	PO	1.25 or 2.5 mg	Twice weekly
Danazol	PO	400 mg	Daily
Gonadotropin-Releasing Hormone			
Leuprolide	SC	500 mg	Daily
	IM	3.75 mg	Monthly
Goserelin	SC	3.6 mg	Monthly
Buserelin	IN	300 µg	Daily
	SC	200 µg	Daily
Nafarelin	IN	200 µg	Daily
Triptorelin	IM	3.75 mg	Monthly

PO, oral; SC, subcutaneous; IM, intramuscular; IN, intranasal.

In a patient preference cohort study to evaluate the efficacy and tolerability of a contraceptive vaginal ring (supplying 15 µg of *ethinyl E* and 120 µg per day of *etonogestrel*) and transdermal patch (delivering 20 µg of *ethinyl E* and 150 µg per day *norelgestromin*) in the treatment of women with recurrent moderate or severe pelvic pain after conservative surgery for symptomatic endometriosis and endometriosis-associated pain, patients who preferred the ring were significantly more likely to be satisfied and to comply with treatment than those who chose the patch (264). Both systems were associated with poor bleeding control when used continuously.

Progestins

Progestins may exert an antiendometriotic effect by causing initial decidualization of endometrial tissue followed by atrophy. **Progestins can be considered as the first choice for the treatment of endometriosis** because they are as effective as *danazol* or GnRH analogs and have a lower cost and possibly a lower incidence of side effects than these agents (334).

There is no evidence that any single agent or any particular dose is preferable to another. The effective doses of several progestins are summarized in Table 13-1. In most studies, the effect of treatment was evaluated after 3 to 6 months of therapy. Progestins appear to be an effective therapy for the painful symptoms associated with endometriosis (335).

Medroxyprogesterone Acetate

***MPA* is the most studied agent.** It is effective in relieving pain starting at a dose of 30 mg per day, increasing the dose based on the clinical response and bleeding patterns according to data from nonrandomized trials (336,337). A randomized placebo-controlled study reported a significant reduction in stages and scores of endometriosis in both the placebo group and the group treated with *MPA* 50 mg per day and placebo at laparoscopy within 3 months after cessation of therapy (338). These findings raise questions about the need for medical therapy with *MPA* in this dose.

Evidence suggests a possible role for depot *MPA* in the treatment of endometriosis. In a randomized controlled study, depot *MPA* (150 mg every 3 months) was more effective in the relief of dysmenorrhea than treatment with a cyclic 21-day OC (*ethinyl estradiol* 20 µg plus *desogestrel* 0.15 mg) combined with very low-dose *danazol* (50 mg per day) (339). In another multicenter, randomized, evaluator-blinded, comparator-controlled trial, depot *MPA* (150 mg) or *leuprolide acetate* (11.25 mg), given every 3 months for 6 months were equivalent in reducing endometriosis-associated pain during the study and the 12-month posttreatment follow-up period, with less impact on bone mineral density and fewer hypoestrogenic side effects, but more bleeding being observed in the depot *MPA* treated group (340). Add-back therapy would prevent the negative effects on bone density and hypoestrogenic side effects associated with GnRH-agonist therapy. In a pilot study, pain relief, side effects, and treatment satisfaction were comparable during a 12-month treatment with *etonogestrel* implantate subcutaneous (68 mg) or depot *medroxyprogesterone acetate* 150 mg intramuscular depot *MPA* in 41 patients with dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia associated with histologically proven endometriosis (341). **Although depot *MPA* treatment is effective for the treatment of pain associated with endometriosis, it is not indicated in infertile women because it induces profound amenorrhea and anovulation, and a varying length of time is required for ovulation to resume after discontinuation of therapy.**

Dienogest

In two randomized noninferiority trials, treatment during 6 months with *dienogest* 2 mg per day orally demonstrated equivalent efficacy to depot *leuprolide acetate* (3.75 mg, depot intramuscular injection, every 4 weeks) or intranasal *buserelin acetate* (900 µg per day, intranasally) in relieving the pain associated with endometriosis, offering a different safety and tolerability profile (less bone loss, fewer hot flushes, more irregular genital bleeding) (342,343). *Dienogest* treatment was not compared to the recommended treatment of GnRH agonist combined with add-back in these two trials.

Other Progestins

Megestrol acetate was administered in a dose of 40 mg per day with good results (339). Pain was reduced significantly during luteal phase treatment with 60 mg *dydrogesterone,* and this improvement was still evident at 12-month follow-up (286). Other treatment strategies included *dydrogesterone* (20 to 30 mg per day, either continuously or on days 5 to 21) and *lynestrenol* (10 mg per day).

Side effects of progestins include nausea, weight gain, fluid retention, and breakthrough bleeding caused by hypoestrogenemia. Breakthrough bleeding, although common, is usually corrected by short-term (7-day) administration of *estrogen.* Depression and other mood disorders are a significant problem in about 1% of women taking these medications.

Intrauterine Progesterone

The *levonorgestrel* intrauterine system releasing 20 lg per day of *levonorgestrel* reduces endometriosis-associated pain caused by peritoneal and rectovaginal endometriosis and reduces the risk of recurrence of dysmenorrhea after conservative surgery (344). *Levonorgestrel* induces endometrial glandular atrophy and decidual transformation of the stroma, reduces endometrial cell proliferation, and increases apoptotic activity (344). A systematic review identified two randomized trials and three prospective observational studies, all involving small numbers and a heterogeneous group of patients (345). The evidence suggests that the *levonorgestrel* intrauterine system reduces endometriosis associated pain with symptom control maintained over 3 years (346–349). Twelve months of treatment results in a significant reduction in dysmenorrhea, pelvic pain, and dyspareunia; a high degree of patient satisfaction; and a significant reduction in the volume of rectovaginal endometriotic nodules (346,347). After the first year of use, a 70% to 90% reduction in menstrual blood loss is observed.

Progesterone Antagonists and Selective Progesterone Receptor Modulators

PRAs and selective progesterone receptor modulators (SPRMs) may suppress endometriosis based on their antiproliferative effects on the endometrium, without the risk for hypoestrogenism or bone loss that occurs with GnRH treatment. Four PRA/SPRMs have been approved by the FDA: *mifepristone, ulipristal acetate (UPA),*

gestrinone, and *asoprisnil*. A Cochrane review assessed the available evidence for the use of PRAs/SPRMs in the treatment of endometriosis-associated pain (350). The authors included 10 RCTs with 960 women: two RCTs compared *mifepristone* versus placebo or versus a different dose of *mifepristone,* one RCT compared *asoprisnil* versus placebo, one compared *ulipristal* versus *leuprolide acetate*, and four compared *gestrinone* versus *danazol*, gonadotropin-releasing hormone (GnRH) analogs, or a different dose of *gestrinone.* The quality of evidence ranged from high to very low. The authors conclude that there are insufficient data about the safety and effectiveness of UPA and *asoprisnil.*

Mifepristone

Mifepristone is a potent antiprogestogen with a direct inhibitory effect on human endometrial cells and, in high doses, an antiglucocorticoid action (351). One study compared *mifepristone* with placebo and reported lower rates of dysmenorrhea (OR 0.08, 95% CI, 0.04–0.17) and dyspareunia (OR 0.23, 95% CI 0.11–0.51) in the *mifepristone* group (350). However, the mifepristone group had higher rates of side effects: nearly 90% had amenorrhea and 24% had hot flushes. Two studies compared doses of *mifepristone* and found insufficient evidence to show differences between different doses in terms of effectiveness or safety, if present. However, subgroup analysis of comparisons between *mifepristone* and placebo suggest that the 2.5-mg dose may be less effective than 5 mg or 10 mg for treating dysmenorrhea or dyspareunia.

Gestrinone

Gestrinone is a 19-nortestosterone derivative with androgenic, antiprogestogenic, antiestrogenic, and antigonadotropic properties. It acts centrally and peripherally to increase free testosterone and reduce sex hormone–binding globulin levels (androgenic effect), reduce serum estradiol values to early follicular phase levels (antiestrogenic effect), reduce mean LH levels, and obliterate the LH and follicle-stimulating hormone (FSH) surge (antigonadotropic effect). *Gestrinone* causes cellular inactivation and degeneration of endometriotic implants but not their disappearance (352). Amenorrhea occurs in 50% to 100% of women and is dose dependent.

Resumption of menses generally occurs 33 days after discontinuing the medication (353,354). An advantage of *gestrinone* is its long half-life (28 hours) when given orally. The standard dose is 2.5 mg twice a week. Although 1.25 mg twice weekly is effective, a randomized study demonstrated in women with mild to moderate endometriosis that 2.5 mg *gestrinone* twice weekly for 24 weeks is more effective and has a better effect on bone mass (+7% vs. −7%) when compared with 1.25 mg *gestrinone* twice weekly for 24 weeks (355). The clinical side effects of *gestrinone* are dose dependent and similar to but less intense than those caused by *danazol* (355). They include nausea, muscle cramps, and androgenic effects such as weight gain, acne, seborrhea, and oily hair and skin.

In a multicenter, randomized, double-blind study, *gestrinone* was as effective as GnRH for the treatment of pelvic pain associated with endometriosis, with fewer side effects and the added advantage of twice-weekly administration (356). Pregnancy is contraindicated while taking *gestrinone* because of the risk for masculinization of the fetus.

Danazol

Recognized pharmacologic properties of *danazol* include suppression of GnRH or gonadotropin secretion, direct inhibition of steroidogenesis, increased metabolic clearance of estradiol and progesterone, direct antagonistic and agonistic interaction with endometrial androgen and progesterone receptors, and immunologic attenuation of potentially adverse reproductive effects (99,357). The multiple effects of *danazol* produce a high-androgen, low-estrogen environment (estrogen levels in the early follicular to postmenopausal range) that does not support the growth of endometriosis, and the amenorrhea that is produced prevents new seeding of implants from the uterus into the peritoneal cavity.

The immunologic effects of *danazol* were studied in women with endometriosis and adenomyosis and include a decrease in serum immunoglobulins, a decrease in serum C3, a rise in serum C4 levels, decreased serum levels of autoantibodies against various phospholipid antigens, and decreased serum levels of CA125 during treatment (209,358–364). *Danazol* inhibits peripheral blood lymphocyte proliferation in cultures activated by T-cell mitogens but does not affect macrophage-dependent T-lymphocyte activation of B lymphocytes (365). *Danazol* inhibits IL-1 and TNF production by monocytes in a dose-dependent manner and suppresses macrophage- and monocyte-mediated cytotoxicity of susceptible target cells in women with mild endometriosis (366,367). These immunologic findings may be important in the remission of endometriosis with *danazol* treatment and may offer an explanation of the effect of *danazol* in the treatment of a number of autoimmune diseases, including hereditary angioedema, autoimmune hemolytic anemia, systemic lupus erythematosus, and idiopathic thrombocytopenic purpura (368–372). Doses of 800 mg per day are used frequently in North America, whereas 600 mg per day is prescribed in Europe and Australia. It appears that the absence of menstruation is a better indicator of response than drug dose. A practical strategy for the use of *danazol* is to start treatment with 400 mg daily (200 mg twice a day) and increase the dose, if necessary, to achieve amenorrhea and relieve symptoms (357).

In a systematic review to determine the effectiveness of *danazol* compared to placebo or no treatment for the symptoms and signs, other than infertility, of endometriosis in women of reproductive age, five randomized trials were included in which *danazol* (alone or as adjunctive therapy to surgery) was compared to placebo or no therapy (373). Treatment with *danazol* (including adjunctive to surgical therapy) was

effective in relieving painful symptoms related to endometriosis when compared to placebo (373). Laparoscopic scores improved with *danazol* treatment (including as adjunctive therapy) when compared with either placebo or no treatment (373). Side effects were more commonly reported in those patients receiving *danazol* than for placebo (373).

The significant adverse side effects of *danazol* are related to its androgenic and hypoestrogenic properties. The most common side effects include weight gain, fluid retention, acne, oily skin, hirsutism, hot flashes, atrophic vaginitis, reduced breast size, reduced libido, fatigue, nausea, muscle cramps, and emotional instability. Deepening of the voice is another potential side effect that is nonreversible. *Danazol* can cause increased cholesterol and low-density lipoprotein levels and decreased high-density lipoproteins levels, but it is unlikely that these short-term effects are clinically important. *Danazol* is contraindicated in patients with liver disease because it is largely metabolized in the liver and may cause hepatocellular damage. *Danazol* is contraindicated in patients with hypertension, congestive heart failure, or impaired renal function because it can cause fluid retention. The use of *danazol* is contraindicated in pregnancy because of its androgenic effects on the fetus.

Because of the many side effects of oral *danazol,* alternative routes of administration were studied. In an uncontrolled pilot study, local *danazol* treatment using a vaginal *danazol* ring (1,500 mg) was effective for pain relief in deep endometriosis. This treatment did not cause the classic *danazol* side effects or detectable serum *danazol* levels, and it allowed ovulation and conception to occur (374).

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone agonists bind to pituitary GnRH receptors and stimulate LH and FSH synthesis and release. The agonists have a much longer biologic half-life (3 to 8 hours) than endogenous GnRH (3.5 minutes), resulting in the continuous exposure of GnRH receptors to GnRH-agonist activity. This exposure causes a loss of pituitary receptors and downregulation of GnRH activity, resulting in low FSH and LH levels. Ovarian steroid production is suppressed, providing a medically induced and reversible state of pseudomenopause. A direct effect of GnRH agonists on ectopic endometrium is possible, because expression of the GnRH receptor gene is documented in ectopic endometrium and because direct inhibition of endometriosis cells was shown in vitro (375). In rat models used to study surgical adhesion formation and endometriosis, GnRH-agonist therapy decreased activity of plasminogen activators and matrix MMPs and increased the activity of their inhibitors, suggesting potential GnRH-agonist–regulated mechanisms for reducing adhesion formation (376).

Various GnRH agonists were developed and used for treating endometriosis. These agents include *leuprolide, buserelin, nafarelin, histrelin, goserelin, deslorelin,* and *triptorelin.* These drugs are inactive orally and must be administered intramuscularly,

subcutaneously, or by intranasal absorption. The best therapeutic effect is often associated with an *estradiol* dose of 20 to 40 pg/mL (75 to 150 pmol/L). These so-called depot formulations are attractive because of the reduced frequency of administration and because nasal administration can be complicated by variations in absorption rates and problems with patient compliance (354). The results with GnRH agonists are similar to those with OC *progestin* or *gestrinone* therapy. **Treatment for 3 months with a GnRH agonist is effective in improving pain for 6 months** (295).

Although GnRH agonists do not have an adverse effect on serum lipids and lipoproteins levels, their side effects are caused by hypoestrogenism and include hot flashes, vaginal dryness, reduced libido, and osteoporosis (6% to 8% loss in trabecular bone density after 6 months of therapy). Reversibility of bone loss is equivocal and therefore of concern, because treatment periods of longer than 6 months may be required (377,378). The goal is to suppress endometriosis and maintain serum estrogen levels of 30 to 45 pg/mL. More extreme estradiol suppression will induce bone loss (377). **The dose of daily GnRH agonist can be regulated by monitoring estradiol levels, by the addition of low-dose *progestin* or *estrogen–progestin* in an add-back regimen, or by draw-back therapy.**

The goal of add-back therapy is to treat endometriosis and endometriosis-associated pain effectively while preventing vasomotor symptoms and bone loss related to the hypoestrogenic state induced by GnRH analogs. Add-back therapy can be achieved by administering progestins only, including *norethisterone,* 1.2 mg, and *norethindrone acetate,* 5 mg, but bone loss is not prevented by *medrogestone,* 10 mg per day (378–380). Add-back therapy can be achieved by *tibolone,* 2.5 mg per day, or by an estrogen–progestin combination (i.e., *conjugated estrogens,* 0.625 mg, combined with *medroxyprogesterone acetate,* 2.5 mg, or with *norethindrone acetate,* 5 mg; *estradiol,* 2 mg, combined with *norethisterone acetate,* 1 mg) (374,377,379–383). Treatment for up to 2 years with combined estrogen and progestogen add-back appears to be effective and safe in terms of pain relief and bone density protection; progestogen only add-back is not protective (384).

GnRH agonists should not be prescribed to girls who have not yet attained their maximal bone density, as some concern remains about the long-term effects of GnRH analogs on bone loss. In one report, bone mineral density reduction occurred during long-term GnRH-agonist use and was not fully recovered up to 6 years after treatment (385). Use of add-back therapy (2 mg *estradiol* and 1 mg *norethisterone acetate*) did not affect this process (385). Draw-back therapy was suggested as an alternative in a study showing that 6 months of intake of 400 µg per day of *nafarelin* was as effective as a draw-back regimen consisting of 1 month of intake of 400 µg per day of *nafarelin* followed by 5 months of 200 µg per day of *nafarelin,* with similar estradiol levels (30 pg/mL) but less loss of bone mineral density (386).

Aromatase Inhibitors

Treatment of rats with induced endometriosis using the nonsteroidal aromatase inhibitor *fadrozole hydrochloride* or *YM511* resulted in a dose-dependent volume reduction of endometriosis transplants (387,388). In one case report, treatment of severe postmenopausal endometriosis with an aromatase inhibitor, *anastrozole,* 1 mg per day, and elemental *calcium,* 1.5 g per day for 9 months resulted in hypoestrogenism, pain relief after 2 months, and after 9 months a 10-fold reduction in the 30-mm diameter size of red, polypoid vaginal lesions, along with remodeling to gray tissue (389).

There is concern with the use of aromatase inhibitors such as *anastrozole* or *letrozole* in the treatment of premenopausal women because these drugs are known to stimulate ovulation and continuous administration can result in the development of functional ovarian cysts. This side effect can be prevented by combining aromatase inhibitors with ovarian suppressing drugs such as OCs or *progestins*. A systematic review assessing the effects of aromatase inhibitors in women symptomatic of pain with endometriosis included eight studies including 137 women (390). In case series (seven studies, 40 women), aromatase inhibitors combined with progestins or OCs or GnRH analogs reduced mean pain scores and lesion size and improved quality of life (390). An RCT including 97 women demonstrated that aromatase inhibitors in combination with GnRH analogs significantly improved pain (p <0.0001), compared with GnRH analogs alone, with significant improvement in multidimensional patient scores (p <0.0001), without significant reduction in spine or hipbone densities (391). Aromatase inhibitors appear to have a promising effect on pain associated with endometriosis, but the strength of this inference is limited because of a dearth of evidence and because aromatase inhibitors need to be combined with other hormonal medication (390).

Selective Estrogen Receptor Modulators

The role of selective estrogen receptor modulators (SERMs) in the treatment of endometriosis is unclear. In animal models, *raloxifene* therapy resulted in regression of endometriosis. The effect was seen in a surgically prepared, rat uterine explant model and in *Rhesus* macaques diagnosed with spontaneous endometriosis before exposure (392). In a placebo-controlled randomized trial in women with chronic pelvic pain and surgically treated biopsy-proven endometriosis, postoperative treatment with *raloxifene* for 6 months resulted in a shortened time to return of pain (defined as 2 months of pain equal to or more severe than that at study entry) and to repeat laparoscopy, suggesting that *raloxifene* is not effective in the treatment of endometriosis-associated pain (393). Biopsy-proven endometriosis was not associated with return of pain, suggesting that other factors were implicated in recurrent pelvic pain after surgery in this study (393).

GnRH Antagonists

Gonadotrophin-releasing hormone (GnRH) antagonists inhibit the action of endogenous GnRH through competitively and reversibly binding to GnRH receptors in the pituitary gland (394). Unlike the GnRH agonists, which cause an initial stimulation of the hypothalamic-pituitary-gonadal axis, GnRH antagonists have an immediate onset of action, rapidly reducing sex hormone levels without an initial surge. Gonadotropin-releasing hormone antagonists are available as injectables (*ganirelix, cetrorelix*) and increasingly as oral nonpeptide forms (*elagolix, abarelix, ozarelix*). The use of GnRH antagonists for a variety of reproductive indications, mostly in medically assisted reproduction, has greatly increased over the past decade.

The development of oral GnRH antagonists made these drugs potential candidates for treatment of endometriosis. In contrast to the GnRH agonists and injectable GnRH antagonists, that completely suppress pituitary function, **oral GnRH antagonists can produce a dose-dependent suppression of pituitary function and production of ovarian hormones** (394,395). Similar to the effect of add-back therapy during GnRH agonist treatment, oral GnRH antagonist could be used to suppress the estrogen production to a level that is adequate to control endometriosis-related pain symptoms but minimizes hypoestrogenic effects.

An RCT, including 872 women in total, showed that *elagolix* at low (150 mg once daily) and high dose (200 mg twice daily) was more effective than placebo in improving dysmenorrhea and nonmenstrual pelvic pain during a 6-month period in women with endometriosis-associated pain (395). Women who received *elagolix* had higher rates of hot flushes, higher levels of serum lipids, and greater decreases from baseline in bone mineral density than did those who received placebo. Further studies comparing oral GnRH antagonists with other treatments are required.

Nonhormonal Medical Therapy

Progress in understanding the pathogenesis of endometriosis led to the expectation that new pharmaceutic agents affecting inflammation and angiogenesis activity may prevent or inhibit the development of endometriosis. Most of these compounds were tested only in rodent models, and more research is needed in the baboon model for endometriosis and in women to ensure their safety and efficacy, as they may interfere with normal physiologic processes like ovulation, menstruation, and implantation (57).

Selective Inhibition of Tumor Necrosis Factor α

In rats with experimental endometriosis, recombinant human TNF-α–binding protein can reduce 64% of the size of endometriosis-like peritoneal lesions (396). Several prospective randomized placebo- and drug-controlled studies in baboons showed that TNF-α antagonists effectively prevent and treat induced endometriosis and endometriosis-related adhesions and are effective in the treatment of spontaneous endometriosis in baboons (57). These results were not confirmed in a small placebo-

controlled randomized trial in women with deep endometriosis, who were awaiting surgery, possibly because the endometriosis phenotype in these women (deep and fibrotic disease) was different from the endometriosis phenotype in the baboon studies (inflammatory peritoneal disease with adhesions) (397). TNF-α antagonists are less effective in fibrotic inflammatory bowel disease than in earlier nonfibrotic inflammatory bowel disease.

Pentoxifylline

In a systematic review determining the effectiveness and safety of *pentoxifylline,* which has anti-inflammatory effects in the management of endometriosis in infertile, premenopausal women, four trials involving 334 participants were included (398). *Pentoxifylline* had no significant effect on reduction in pain (one randomized trial, MD −1.60; 95% CI, −3.32–0.12), improvement of fertility (three randomized trials, OR 1.54; 95% CI, 0.89–2.66) or recurrence of endometriosis (one randomized trial, OR 0.88; 95% CI, 0.27–2.84) (398). No trials reported the effects of *pentoxifylline* on the odds of live birth rate per woman, improvement of endometriosis-related symptoms, or adverse events (398).

Peroxisome Proliferator Activated Receptor-γAgonists

Peroxisome proliferator activated receptor-γ (PPAR-γ) agonists prevent and treat endometriosis in rodent and baboon models for endometriosis and show promise for treatment of human endometriosis (399–402).

Other

Many substances potentially capable of modulating immunologic or inflammatory mechanisms involved in the onset or progression of the disease could be the targets for future research in endometriosis (403,404). Preliminary trials with cyclooxygenase-2 (COX-2) inhibitors, leukotriene receptor antagonists, TNF-α inhibitors, antiangiogenic agents and kinase inhibitors show promising results in vitro in rodent and in nonhuman primate models, but their safety is an important issue regarding human use (405).

Treatment of Endometriosis-Associated Infertility

Surgical Treatment

The treatment of endometriosis-related infertility is dependent on the age of the woman, the duration of infertility, the stage of endometriosis, the involvement of ovaries and tubes in the endometriosis process, previous therapy, associated pain symptoms, and the priorities of the patient, taking into account her attitude toward the disease, the cost of treatment, her financial means, and the expected results. If surgery is performed and spontaneous pregnancy does not occur within 2 years of surgery, there is little chance of subsequent natural conception (406).

[7] Surgical management of infertile women with minimal to mild endometriosis is controversial. Based on the results of a meta-analysis of two randomized trials, ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal to mild endometriosis is effective compared to diagnostic laparoscopy alone (185,186,407). One Canadian study reported that laparoscopic surgery enhanced fecundity in infertile women with minimal or mild endometriosis (185). They studied 341 infertile women, 20 to 39 years of age, with minimal or mild endometriosis. During diagnostic laparoscopy, the women were randomly assigned to undergo resection or ablation of visible endometriosis or diagnostic laparoscopy only. They found that **resection or ablation of minimal and mild endometriosis increased the likelihood of pregnancy in infertile women.** They were followed for 36 weeks after the laparoscopy or, for those who became pregnant during that interval, for up to 20 weeks of pregnancy. The study participants were recruited among infertile women scheduled for diagnostic laparoscopy with strict eligibility criteria. The women in the study had no previous surgical treatment for endometriosis, no medical treatment for endometriosis in the previous 9 months, and no other medical or surgical treatment for infertility in the previous 3 months. They had no history of pelvic inflammatory disease and no severe pelvic pain precluding expectant management. The diagnosis of endometriosis required the presence of one or more typical bluish or black lesions. The stage of endometriosis was determined according to the revised American Society of Reproductive Medicine classification. The MFR and the cumulative pregnancy rate after 36 weeks were significantly higher and twice as high after surgical excision of minimal to mild endometriosis (4.7% and 30.7%, respectively) than after diagnostic laparoscopy (2.4% and 17.7%, respectively). In the treated group, 31% of the patients became pregnant, compared with 18% in the nontreated group (p = 0.006). Limitations of this study include the lack of blinding of the patients, and the fecundity rate after surgery was below that observed in control groups from other studies (1,408).

In a multicenter study in Italy, a similar study design was used to compare the effect of diagnostic laparoscopy with surgical resection and ablation of visible endometriosis (on fertility parameters) in infertile women with minimal to mild endometriosis (186). Eligible patients were less than 36 years old, were trying to conceive, and had a laparoscopically confirmed diagnosis of minimal or mild endometriosis. None of the women had therapy for endometriosis or infertility. Treatment was randomly allocated during laparoscopy. There was a follow-up period of 1 year after the laparoscopy. **The results of this study did not show a beneficial effect of surgery regarding fertility.** During the follow-up period after laparoscopy, no statistically significant differences in conception and live birth rates were observed in the treated group (24% and 20%, respectively) or in the control group (29% and 22%, respectively). The methodologic

quality of the Italian study was inferior to the Canadian study (175,185,186). First, the study was underpowered, including only 91 patients, compared to 341 patients in the Canadian study. Second, it is remarkable and unexplained that the Italian study included after randomization more patients undergoing surgical excision of endometriosis (n = 54) than patients undergoing diagnostic laparoscopy (n = 47). Third, the duration of infertility was longer in the Italian study (4 years) than in the Canadian study (32 months). Duration of infertility is an important factor influencing MFR and cumulative pregnancy rates independently from other causes of infertility. The bias introduced by the long duration of infertility in couples participating in the Italian trial may have reduced the possibility to find any significant effect of surgical treatment, especially in view of the lack of proper power calculation in the Italian study. Fourth, the Italian study did not present any data on MFR or cumulative pregnancy rates using life table analysis, but only published the crude live birth rate per patient, not controlled for number of cycles per patient. Fertility outcome should be measured by more controlled variables such as MFR and the cumulative pregnancy rates or time to pregnancy. Fifth, 41 of 91 patients in the Italian study had received GnRH analog treatment after surgery (18 from the surgical excision group, 23 from the diagnostic laparoscopy group) (186). There was no specification for how long this medical treatment was given and how ovarian function was affected. The lack of this information introduces another bias influencing fertility outcome. Taking into account the relative methodologic weaknesses of the Italian study when compared to the Canadian study, extreme caution is needed before combining these two studies in a meta-analysis, especially because the fertility outcome data are reported so differently. It seems preferable to use the data of the better study demonstrating that **surgical treatment of minimal to mild endometriosis appears to offer a small, but significant, benefit with regard to fertility outcome** (1,175,185,409). The surgical removal of peritoneal endometriosis may be important to prevent progression of endometriosis. Care is needed to prevent adhesion formation that could result as a consequence of overenthusiastic excision of minimal to mild endometriosis.

Surgery for Moderate to Severe Endometriosis

When endometriosis causes mechanical distortion of the pelvis, surgery should be performed to achieve reconstruction of normal pelvic anatomy. No randomized trials or meta-analyses are available to answer the question of whether surgical excision of moderate to severe endometriosis enhances pregnancy rate (1). Most studies present only crude pregnancy rates without detailed information regarding time of follow-up and are therefore not relevant (1).

Based on three studies, there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis, but statistical significance was reached in only one study (410–412).

Other studies reported a significant negative correlation between endometriosis stage and pregnancy rate and decreased pregnancy rates when the revised scores exceeded 15 or 70 (177,410,413). Data from different studies cannot be compared easily because of retrospective design, lack of a control group, significant variability and lack of standardization with respect to inclusion criteria, surgical procedures, extent of surgery, skill of the surgeon, variable duration of follow-up without life table analysis, postoperative hormonal suppression or medically assisted reproduction, and lack of control for other infertility-related factors such as male infertility or ovarian dysfunction. These limitations explain why management differed and was not standardized, and why the cumulative pregnancy rates 9 to 12 months after surgery for moderate to severe endometriosis vary between 24% and 30% (1,414–416).

Surgery for Ovarian Endometriomas in Infertile Patients

In patients with an endometrioma receiving surgery for infertility or pain, cystectomy of the endometrioma increased the postoperative spontaneous pregnancy rate, compared to ablation of the endometrioma (417). Therefore, the **ESHRE guideline recommends cystectomy over ablation of endometriomas in infertile women with an ovarian endometrioma undergoing surgery** (1).

A randomized study demonstrated an increased ovarian follicular response to gonadotrophin stimulation for women who underwent excisional surgery when compared to ablative surgery (weighted mean difference [WMD] 0.6; 95% CI, 0.04–1.16) (418). There is insufficient evidence to favor excisional surgery over ablative surgery with respect to the chance of pregnancy after controlled ovarian stimulation and intrauterine insemination (OR 1.40; 95% CI, 0.47–4.15) or treatment with assisted reproductive technology (272).

Cystectomy and ablation of an endometrioma carry potential risks for the ovarian reserve, either by removal of normal ovarian tissue during excision or by thermal damage to the ovarian cortex during ablation. Although as little as one-tenth of an ovary may be enough to preserve function and fertility, there is concern that ovarian cystectomy with concomitant removal or destruction of normal ovarian tissue may reduce ovarian follicle reserve and reduce fertility (419). In a small prospective randomized clinical trial, 10 patients assigned to undergo laparoscopic cystectomy had a lower antral follicle count and a more pronounced reduction in serum anti-müllerian hormone (AMH) levels (from 3.9 to 2.9 ng/mL) 6 months after surgery when compared to the 10 patients treated with a "three-stage procedure" as described above (reduction in AMH levels from 4.5 to 3.99 ng/mL) (420,421). More randomized trials are needed to assess the effect of ovarian cystectomy on ovarian reserve and on reproductive function, especially with respect to conception after treatment with medically assisted reproduction.

Preoperative and Postoperative Medical Treatment

As described in the section on conservative surgery for endometriosis-associated pain, **there is no evidence of a benefit of preoperative medical therapy (*danazol*, progestins, GnRH agonists) on the outcome of endometriosis surgery.** However, in patients with severe endometriosis, it is common clinical practice that surgical treatment be preceded by a 3-month course of medical treatment because it is believed that this facilitates surgery by reducing inflammation and vascularization of lesions.

Postoperative medical treatment is not indicated because it is ineffective based on randomized trials, prevents pregnancy, and because the highest spontaneous pregnancy rates occur during the first 6 to 12 months after conservative surgery (296,298).

Hormonal Treatment

Conception is either impossible or contraindicated during medical treatment of endometriosis. [8] There is no evidence that medical treatment of minimal to mild endometriosis leads to better chances of pregnancy than expectant management (408). The published evidence does not comment on more severe disease (1).

Medically Assisted Reproduction

Medically assisted reproduction—including controlled ovarian hyperstimulation with intrauterine insemination, IVF, and gamete intrafallopian transfer—may be an option for infertility treatment in addition to surgical reconstruction and expectant management (266). Assisted reproductive technology (ART) is the method of choice when distortion of the tubo-ovarian anatomy contraindicates the use of superovulation with intrauterine insemination or gamete intrafallopian transfer (266).

The role of ART in the treatment of endometriosis-associated infertility may be limited in large tertiary care and referral centers for surgical treatment of endometriosis (422). After conservative surgery for endometriosis, 44% conceived *in vivo* (44%), and 51% of those who failed to conceive *in vivo* did not undergo ART treatment with the cumulative rate of IVF use at 36 months of infertility at 33%. The live birth/ongoing pregnancy rate per started cycle and per patient was 10% and 20%, respectively (422). For a full discussion on the application of ART in infertility, see Chapter 36.

Management of Adolescents

The most common presenting symptom in adolescents with endometriosis is cyclic pain (1). Less commonly acyclic pain, dyspareunia, gastrointestinal symptoms, irregular menses, urinary symptoms, and vaginal discharge are described (1,423–426). Similar presenting symptoms occur in adolescent patients evaluated for pelvic pain with and without endometriosis (426,427). **It is hard to predict the presence of endometriosis in adolescents with pelvic pain merely from the presenting symptoms, because**

similar symptoms occur in patients evaluated laparoscopically for pelvic pain with and without endometriosis (1,426,427). Laparoscopy should be considered for adolescents with chronic pelvic pain who do not respond to medical treatment (NSAIDs, OCs) because endometriosis is very common (up to 70%) under these circumstances (423,426–433). **Minimal and mild endometriosis, according to the revised ASRM classification, are the most common stages of the disease in adolescents.** Gynecologic surgeons should pay special attention to red, clear, or white lesions, which are more prevalent in adolescents than in adults with endometriosis (1,423–435). Mild disease can be treated by laparoscopic surgical removal of implants at the time of diagnosis, followed by continuous administration of low-dose combination OCs to prevent recurrence. More advanced disease can be treated medically for 6 months, followed by continuous OCs to prevent progression of disease. Surgery is indicated if this hormonal treatment is not effective. **GnRH agonists with add-back therapy can be considered for only adolescents older than 17 years of age who have completed pubertal and bone maturation, and then only if symptoms persist during other forms of hormonal suppression** (1,436–438).

Menstrual outflow obstructions such as müllerian anomalies may cause early development of endometriosis in adolescents. Regression of the disease was observed when surgical correction of the anomaly was accomplished (439–441).

Evidence suggests that **absenteeism from school and the incidence and duration of OC use for severe primary dysmenorrhea during adolescence is higher in women who later develop deep endometriosis than in women without deep endometriosis** (160).

Physicians treating adolescents with endometriosis should adopt a multidimensional approach, where surgery, hormonal manipulation, pain medication, mental health support, complementary and alternative therapies, and education in self-management strategies are useful components (1).

Management of Postmenopausal Women

Estrogen dependence is a central pathophysiologic hallmark of endometriosis, supported by a substantial body of molecular studies and clinical observations of symptom regression in hypoestrogenic states. Therefore, **endometriosis is typically regarded as a disease of the reproductive years, resolving after natural or iatrogenic menopause.** There is the concern that hormone replacement therapy (HRT) may reactivate endometriotic lesions, induce development of new lesions, or stimulate malignant transformation. However, a systematic review identified only 17 cases of recurrent endometriosis and 25 cases of malignant transformation in postmenopausal women taking some form of HRT (442). Only one RCT evaluated the potential risk of HRT in women with iatrogenic (bilateral oophorectomy) menopause. In a small RCT,

recurrence of pain was not significantly different in any of 57 patients in the no-treatment arm, or in 4 of 115 women receiving sequential administration of *estrogens* and *progesterone* with two 22-cm patches applied weekly to produce a controlled release of 0.05 mg per day, combined with oral administration of micronized *progesterone* administered orally (200 mg per day) for 14 days with a 16-day interval free of treatment (6,443). In this study, the endometriosis recurrence and reoperation rate were comparable in both groups (2 of 115 of the treatment group; 0 of 57of the no-treatment group) (443). Two observational studies support the findings of this RCT. The first study included 107 women with (n = 90) or without (n = 17) HRT after iatrogenic (hysterectomy and BSO) menopause (444). Recurrence was only identified in four women, 3 women had recurrent pain and one woman had a vaginal nodule. All patients with recurrence were receiving unopposed estrogen therapy. The second observational study reported on 42 women with deep infiltrating endometriosis (445). Nineteen of these 42 patients had a hysterectomy and BSO and 11 were subsequently treated with HRT. During the follow up period (mean = 4.3 years, range 1 to 18) no women were diagnosed with recurrence of endometriosis.

This systematic review shows that **postmenopausal recurrence or malignant transformation of endometriosis is possible but very rare**. The authors conclude that HRT in patients with a history of endometriosis has potential risks, but these risks are likely very small and the substantial benefits of HRT should not be overlooked, especially in women with iatrogenic menopause at a young age. This is in line with the ESHRE guideline, which states that **women should not be denied HRT treatment simply because of a history of endometriosis.** Based on the very limited available data, unopposed estrogen treatment in postmenopausal hysterectomized women with a history of endometriosis is dissuaded. **In young women with endometriosis undergoing iatrogenic (surgical) menopause the ESHRE guideline recommends HRT with combined estrogen/progestogen or *tibolone*, at least up to the age of natural menopause** (1).

Management of Recurrent Endometriosis

Recurrence After Medical Treatment

Because hormonal suppressive treatment does not cure endometriosis (it only suppresses the activity of endometriotic lesions during the treatment), “recurrence,” or rather persistence, of endometriosis can be expected in nearly all patients within 6 months to 2 years after the cessation of medical treatment, and this is positively correlated with the severity of endometriosis.

Recurrence After Conservative Surgery

Conservative surgery for endometriosis is associated with high recurrence rates.

Data regarding recurrence rates after conservative surgical treatment of endometriosis are scarce and systematic reviews identified considerable variation between different studies in the reporting of postoperative recurrence rates of endometriosis or endometriosis-associated symptoms, mostly because of the lack of clear definitions for recurrence. A consensus on precise definitions for suspected recurrence, based on symptoms or imaging, and proven recurrence of endometriosis, based on laparoscopic visualization or histology, was published.

The overall endometriosis recurrence rate is estimated between 2% to 20% per year. Cumulative recurrence rates vary from 4% to 25% at 2 years follow-up to 40% after 5 years (279,446). Recurrence of endometriosis can be the result of incomplete surgery or caused by the development of new lesions. The ASRM classification system has low value to predict pain recurrence and endometriosis relapse after conservative surgical treatment (447).

Recurrence After Hysterectomy

The medium-term outcome of hysterectomy for endometriosis-associated pain is satisfactory; the probability of pain persistence after hysterectomy is 15% and risk of pain worsening is 3% to 5%, with a six times higher risk of further surgery in patients with ovarian preservation as compared to concomitant bilateral ovarian removal (448). **At least one ovary should be preserved in young women, especially in those who cannot or will not receive *estrogen–progestin* therapy** (449). The risk of recurrence of endometriosis during hormonal therapy seems marginal if combined preparations or *tibolone* are used and *estrogen*-only treatments are avoided (449).

Risk Factors for Recurrence

The rate of recurrence increases with the stage of disease, the duration of follow-up, and the occurrence of previous surgery (15,450–453). The likelihood of recurrence appears to be lower when endometriosis is located only on the right side of the pelvis rather than when the left side is involved (453). The risk of endometriosis recurrence is significantly correlated to the age of the patient. The younger the patient is at diagnosis the higher the risk of recurrence.

Prevention of Recurrence

After first-line surgery for endometriosis, women should be invited to seek conception as soon as possible. Alternatively, OC use until pregnancy is desired should be considered because several lines of evidence suggest that ovulation inhibition reduces the risk of endometriosis recurrence (454). A recurrent endometrioma developed in 26 of 250 regular users (10%; 95% CI, 7–15) compared with 46 of 115 never users (40%; 95% CI, 31–50), with a common OR of 0.16 (95% CI, 0.04–0.65) (454).

Medical Treatment of Recurrence

It has been shown that medical treatments may provide a good efficacy for the treatment of pain in women presenting with recurrent endometriosis (455). In a randomized prospective clinical study, continuous treatment for 6 months with *desogestrel* (75 μg per day) (n = 20) versus a combined OC (*ethinyl estradiol* 20 μg plus *desogestrel* 150 μg) resulted in a significant and comparable improvement of pelvic pain and dysmenorrhea with breakthrough bleeding in 20% of the *desogestrel*-treated patients, and a significant body weight increase in 15% of the OC-treated women (455).

Surgical Treatment of Recurrence

The optimal surgical solution in women with recurrent symptoms after previous conservative procedures for endometriosis should be based on the desire for conception and on psychological characteristics (456). Repeat conservative surgery for DE has the same efficacy and limitations as primary surgery. **The long-term probability of pain recurrence after repeat conservative surgery for recurrent endometriosis varies from 20% to 40%, and a further surgical procedure will occur in 15% to 20% of the cases** (448,456). These figures are probably an underestimate related to drawbacks in study design, exclusions of dropouts, and publication bias and should be considered with caution (456). No studies evaluated the association of PSN to the surgical treatment of recurrent endometriosis among patients with recurrent disease (448). When a second surgical approach is intended, **definitive surgery (hysterectomy and bilateral oophorectomy) should be considered, particularly in women over 40 years old and who do not wish to conceive.** The spontaneous conception rate among women undergoing repetitive surgery for recurrent endometriosis associated with infertility is 20% (12- and 24-month cumulative pregnancy rates of 14% and 26%), whereas the overall crude pregnancy rate after a primary surgical procedure is 40% (12- and 24-month cumulative pregnancy rates of 32% and 38%) (448,456). Among infertile patients treated with repetitive surgery for recurrent endometriosis the spontaneous pregnancy rate was 19% (12- and 24-month cumulative pregnancy rates), whereas it was 34% for those untreated (12- and 24-month cumulative pregnancy rates of 25% and 30%). The probability of conception after IVF is not significantly lower after repetitive surgery (20%) when compared to primary surgery (30%) (hazard ratio [HR] 1.51; 95% CI, 0.58–3.91) (456).

COPING WITH DISEASE

Coping with endometriosis as a chronic disease is an important component of management. Patient self-help groups can provide invaluable counseling, support, and advice. ESHRE provides a comprehensive international list of self-help groups on their web site (1). Many women with endometriosis report that nutritional and complementary therapies such as reflexology, traditional Chinese medicine, herbal treatments, and homeopathy improve pain symptoms. Data on the effectiveness of alternative and complementary therapies for endometriosis-associated pain are scarce. The limited available evidence indicates that the effectiveness of transcutaneous electrical nerve stimulation (TENS), dietary supplements, acupuncture, and traditional Chinese medicine is not well established for treatment of endometriosis-associated pain. Hence ESHRE does not recommend the use of alternative and complementary therapies in the management of endometriosis. Although there is no good evidence to support the effectiveness of these treatments in endometriosis, they should not be ruled out if the woman feels they work in conjunction with more traditional therapies or that they could be beneficial to her overall pain management and quality of life.

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CHAPTER 14

Family Planning



Wing Kay Fok, Paul D. Blumenthal, Phillip G. Stubblefield

Efficacy
- Medical Eligibility for Contraception
- Cost
- Long-Acting Reversible Contraceptives

Nonhormonal Methods
- Coitus Interruptus
- Breastfeeding
- Fertility Awareness
- Condoms
- Vaginal Spermicides
- Vaginal Barriers
- Intrauterine Contraception

Hormonal Contraception
- Steroid Hormone Action
- Antifertility Effects
- Efficacy of Hormonal Contraception
- Alternative Routes for Hormonal Contraception
- Injectable Hormonal Contraceptives
- Emergency Contraception
- Hormonal Contraception for Men

Sterilization
- Female Sterilization
- Vasectomy

Abortion
- Safety

Techniques for First-Trimester Abortion
Second-Trimester Abortion
Complications of Second-Trimester Abortion

KEY POINTS

1 The most common methods of contraception used in the United States are sterilization, oral contraceptives (OCs), and condoms, in that order.
2 Latex condoms and other barriers reduce the risk of sexually transmitted diseases (STDs) and cervical cancer.
3 The intrauterine devices (IUDs) available in the United States are as effective as tubal sterilization and confer no increased long-term risk of pelvic infection.
4 The combination estrogen–progestin OC, patch, and vaginal ring all provide excellent contraception when used correctly but all can increase the risk of venous thrombosis and thromboembolism.
5 Present low-dose estrogen–progestin combinations do not increase the risk of heart attack among nonsmokers younger than age 35 years who have no other risks for vascular disease.
6 The association between breast cancer and OC use remains controversial, but OCs do not appear to substantially increase the risk of breast cancer. Furthermore, benefits of OC use, particularly protection against pregnancy and other noncontraceptive benefits, outweigh the risks for the majority of women.
7 Use of the progestin-only injectable or implant results in very low pregnancy rates without the estrogen-associated risk of thrombosis.
8 Hormonal contraceptives provide extensive contraceptive and noncontraceptive health benefits, including reduced risk for endometrial and ovarian cancer.
9 *Levonorgestrel 1.5 mg* and *ulipristal acetate 30 mg* are the most effective hormonal means of emergency contraception in the United States. Efficacy is greatest within 24 hours of intercourse but remains high at 5 days. The *copper T380A* IUD within 5 days after unprotected intercourse is even more effective than hormonal methods.
10 Long-acting reversible contraceptive (LARC) methods include subdermal progestin implants, and *copper*- or *levonorgestrel*-releasing IUDs. These offer pregnancy rates comparable to sterilization and are among the safest methods.
11 Safe and permanent contraception is provided with laparoscopy or mini-laparotomy, utilizing bipolar electrocautery, salpingectomy or partial salpingectomy, the Silastic band, or the *Filshie clip*.
12 Hysteroscopic sterilization techniques provide highly effective permanent contraception for women without the use of general anesthesia or abdominal incision. However, reports of adverse patient reactions have prompted the manufacturer to remove the product from the market.
13 Vasectomy provides highly effective, low-cost sterilization for men and is not associated with prostate cancer.
14 Abortion mortality rates fell rapidly with legalization; for safe abortions the overall mortality risk is less than 1 per 100,000.
15 The risk of abortion mortality increases with gestational age. The mortality rate for aspiration procedures was 0.3 per 100,000 at or before 8 weeks and increased to 6.7 per 100,000 at 18 weeks or greater.

The history of contraception is a long one, dating to ancient times. The voluntary control of fertility is especially important in modern society (1). A woman who expects to have no more than one or two children spends most of her reproductive years trying to avoid

pregnancy. Effective control of reproduction is essential to a woman's ability to accomplish her individual goals. From a larger perspective, the rapid growth of the human population in modern times threatens the survival of all. The world population is at 7.3 billion and is expected to reach 10 billion by 2056 (2). For both the individual and the planet, reproductive health requires careful use of effective means to prevent pregnancy and sexually transmitted infections (3).

From puberty until menopause, women are faced with challenges concerning childbearing or its avoidance: the only options are sexual abstinence, contraception, or pregnancy. The contraceptive choices made by couples in the United States in 2013 are shown in **Figure 14-1** (4). **[1]** Oral contraceptives (OCs) were the first choice among women, used by 25.9%. Female sterilization was the second choice, used by 25.1%. With the addition of the 8.2% of couples relying on male sterilization, 33.3% of couples were relying on sterilization, making this the first choice of couples. Condoms were third choice, used by 15.3%. OC use declines with age, and the rate of sterilization increases. Forty-seven percent of women under 25 who use contraceptives use OCs and only 1.6% is sterilized. Of women aged 35 to 44 years using contraception 12.4% uses OCs and 44.2% is sterilized, as is 17.9% of their consorts. About 10% of women use more than one method of contraception. Although contraceptive prevalence is high, a significant proportion of sexually active couples (6.9%) does not use contraception, and each year, 1.46 of every 100 women aged 15 to 44 years have an induced abortion (4,5). Abortion is an obvious indicator of unplanned pregnancy. Abortion ratios by age group indicate that the use of abortion is greatest for the youngest women and least for women in their late 20s and early 30s who are most likely to continue pregnancies **(Fig. 14-2)** (6). The use of abortion increases from the late 30s on. Young women are much more likely to experience unplanned pregnancy because they are more fertile than older women and because they are more likely to have unprotected intercourse.

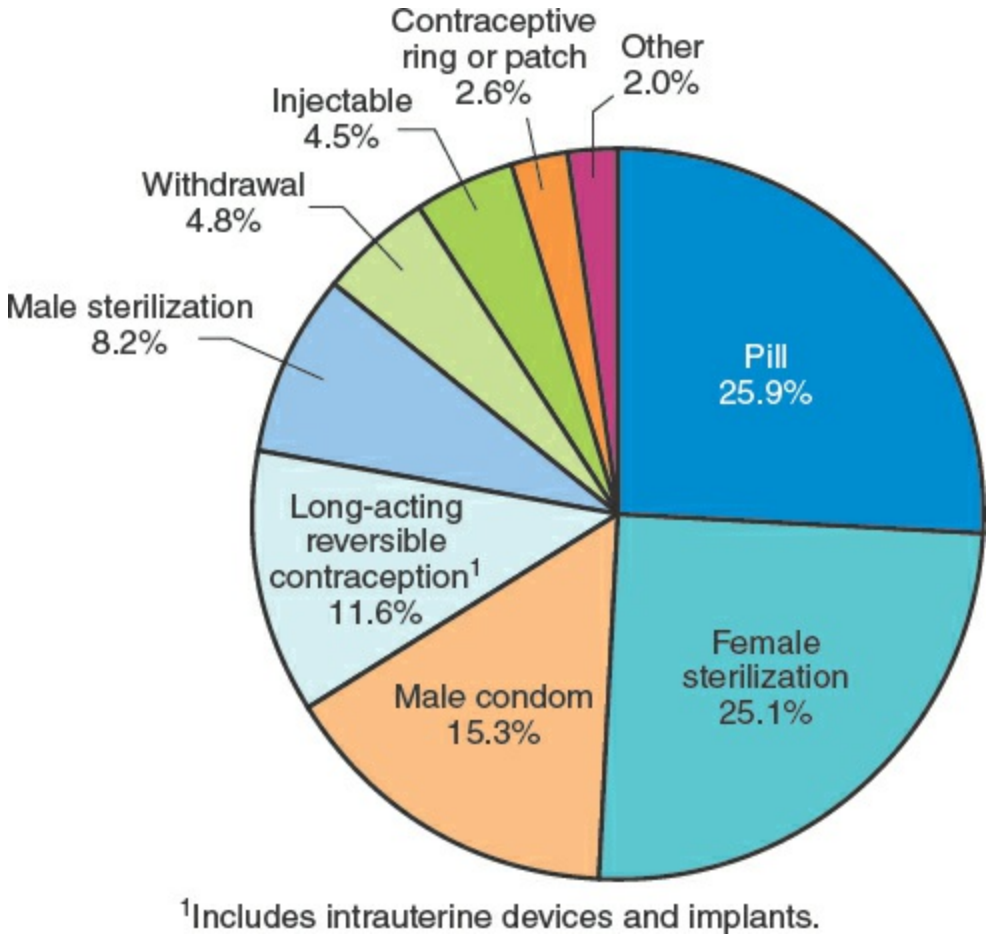


FIGURE 14-1 Percent distribution of women aged 15 to 44 years who are currently using contraception, by the type of contraceptive method used. United States, 2011 to 2013. (From **Daniels K, Daugherty J, Jones J, et al.** Current contraceptive use and variation by selected characteristics among women aged 15–44: United States, 2011–2013. *Natl Health Stat Report* 2015;[86]:1–14; Figure 1.)

EFFICACY

Factors affecting the likelihood of pregnancy include the fecundity of both partners, the timing of intercourse in relation to ovulation, the method of contraception used, the intrinsic effectiveness of the contraceptive method, and the correct use of the method. It is impossible to assess the effectiveness of a contraceptive method in isolation from the other factors. The best way to assess effectiveness is long-term evaluation of a group of sexually active women using a particular method for a specified period to observe how frequently pregnancy occurs. A pregnancy rate per 100 women per year can be calculated using the Pearl formula (dividing the number of pregnancies by the total number of months contributed by all couples, and then multiplying the quotient by 1,200). With most methods, pregnancy rates decrease with time as the more fertile or less careful couples become pregnant and drop out of the calculations. More accurate information is provided by the life-table method. This method calculates the probability of pregnancy in successive months, which are then added over a given interval.

Problems relate to which pregnancies are counted: those occurring among all couples or those in women the investigators deem to have used the method correctly. Because of this complexity, rates of pregnancy with different methods are best calculated by reporting two different rates derived from multiple studies (i.e., the lowest rate and the usual rate), as shown in **Table 14-1**.

Medical Eligibility for Contraception

Since 1996, the World Health Organization (WHO) has regularly published Medical Eligibility Criteria for Contraceptive Use (MEC). These recommendations are based on the best evidence available supplemented by expert opinion. The U.S. Centers for Disease Control undertook a formal process to review and revise the WHO MEC and adapt it to US practice (7). These eligibility criteria have become de facto US national (CDC) and international (WHO) standards for contraceptive practice. All present methods of contraception are assigned to one of four categories of suitability of use by women with more than 60 characteristics or conditions. The categories are:

1. A condition for which there is no restriction for the use of the contraceptive method;
2. A condition for which the advantages of using the method generally outweigh the theoretical or proven risks;
3. A condition for which the theoretical or proven risks usually outweigh the advantages of using the method;
4. A condition that represents an unacceptable health risk if the contraceptive method is used.

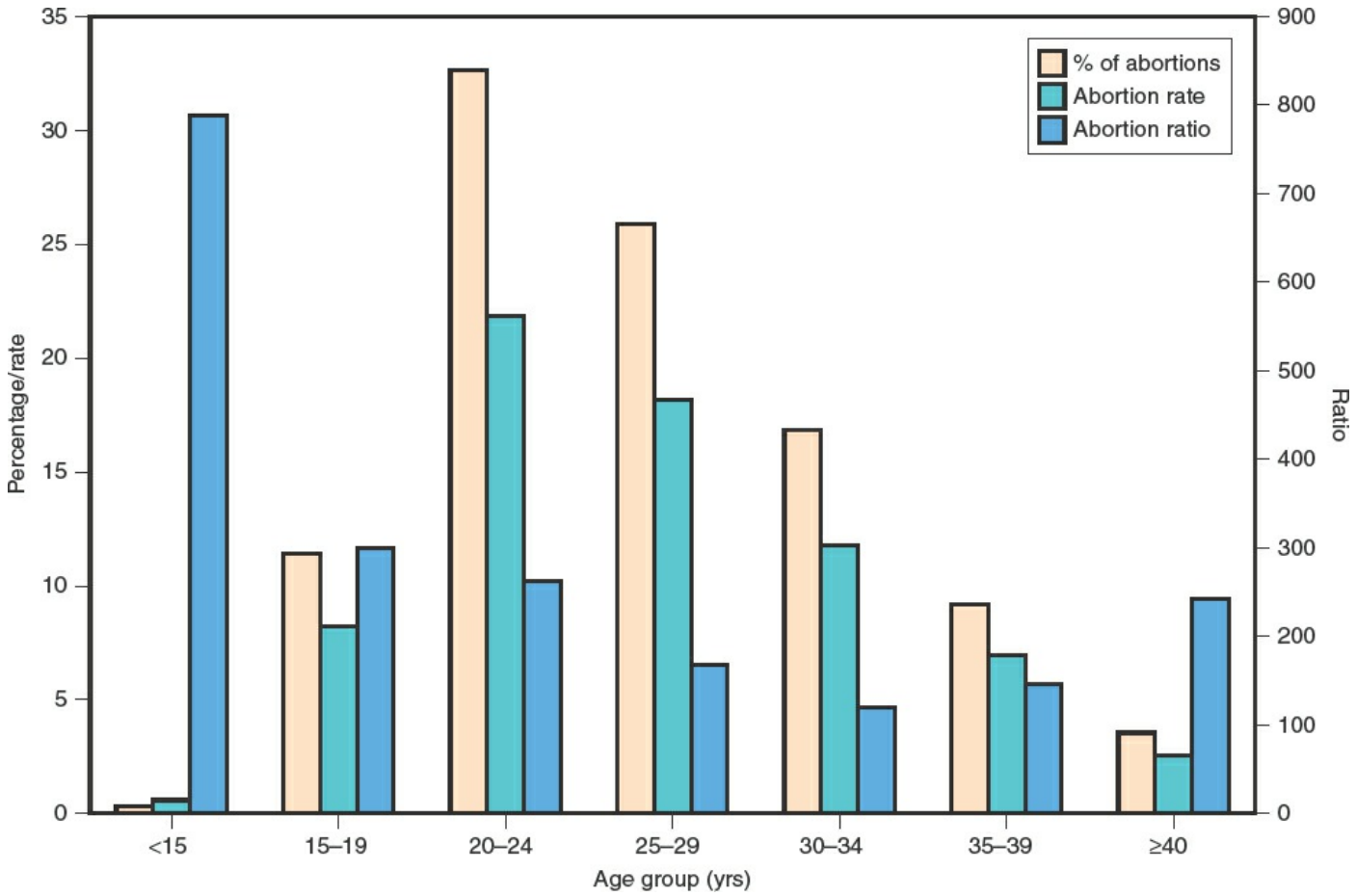


FIGURE 14-2 Percentage of total abortions, abortion rate,* and abortion ratio† by age group of women who obtained a legal abortion—selected reporting areas.§ United States, 2013. *Number of abortions per 1,000 women aged 15–44 years. †Number of abortions per 1,000 live births. §Data are for 47 areas; excludes five areas (California, Florida, Maryland, New Hampshire, and Wyoming) that did not report, did not report by age, or did not meet reporting standards. (From **Jatlaoui TC, Ewing A, Mandel MG, et al.** Abortion surveillance—United States, 2013. *MMWR Surveill Summ* 2016;65[12]:1–44; Figure 2.)

Cost

Some methods, such as intrauterine devices (IUDs) and subdermal implants, require an initial, "up-front" investment, which in some countries can be substantial, but then provide prolonged protection for a low annual cost. A complex cost analysis based on the cost of the method plus the cost of pregnancy if the method fails concludes that sterilization and IUDs are the least expensive over 5 years (Table 14-2) (8).

Long-Acting Reversible Contraceptives

[10] Several contraceptive methods are as effective as sterilization, but are completely reversible. All have the important advantage of being "forgettable," that is, little is required of the user after the method is begun, very much in contrast to methods like the condom that must be used with each act of intercourse, or the OC, which must

be taken daily. **[10]** These "forgettable" methods have typical-use pregnancy rates of less than 1%, are effective for at least several years without attention from the user, and are among the safest methods. They include the *etonogestrel* and *levonorgestrel* subdermal implants, copper-bearing IUDs such as the *copper T380A* and *levonorgestrel*-releasing intrauterine systems (9,10).

NONHORMONAL METHODS

Coitus Interruptus

Coitus interruptus is withdrawal of the penis from the vagina before ejaculation. This method, along with induced abortion and late marriage, is believed to account for most of the decline in fertility of preindustrial Europe (11). Coitus interruptus remains a very important means of fertility control in many countries. Eighty-five million couples are estimated to use the method worldwide, yet it has received little formal study. This method has obvious advantages: immediate availability and no cost. The penis must be completely withdrawn from the vagina and the external genitalia. Pregnancy has occurred from ejaculation on the female external genitalia without penetration. Efficacy is estimated to range from 4 pregnancies per 100 women in the first year with perfect use to 22 per 100 with typical use **(Table 14-1)**. Jones and colleagues offer a modern review of this practice and conclude that it likely is as effective as the condom (12).

Breastfeeding

Breastfeeding can be used as a form of contraception and can be effective depending on individual variables. The use of contraception during lactation should take into consideration the women's needs and the need to maintain lactation. Ovulation is variably suppressed during lactation. The suckling of the infant elevates prolactin levels and reduces gonadotropin-releasing hormone (GnRH) from the hypothalamus, reducing luteinizing hormone (LH) release and thus inhibiting follicular maturation (13). Even with continued nursing, ovulation eventually returns but is unlikely before 6 months, especially if the woman is amenorrheic and is fully breastfeeding with no supplemental foods given to the infant (14). For maximum contraceptive reliability, feeding intervals should not exceed 4 hours during the day and 6 hours at night, and supplemental feeding should not exceed 5% to 10% of the total amount of feeding (15). Six-month pregnancy rates of 0.45% to 2.45% are reported for couples relying solely on this method (16). To prevent pregnancy, another method of contraception should be used from 6 months after birth or sooner if menstruation resumes. Breastfeeding reduces the mother's lifetime risk of breast cancer (17).

Table 14-1 Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Use of Contraception and the Percentage Continuing Use at the End of the First Year

Method	Women Experiencing Unintended Pregnancy Within the First Year of Use (%)		Women Continuing Use at 1 Year (%)
	Typical Use	Perfect Use	
No method	85	85	
Spermicides	28	18	42
Fertility awareness–based methods	24		47
Standard Days method		5	
TwoDay method		4	
Ovulation method		3	
Symptothermal method		0.4	
Withdrawal	22	4	46
Sponge			36
Parous women	24	20	
Nulliparous women	12	9	
Condom			
Female	21	5	41
Male	18	2	43
Diaphragm	12	6	57
Combined pill and progestin-only pill	9	0.3	67
Patch (*Evra*)	8	0.3	67
NuvaRing	8	0.3	67
DepoProvera	6	0.2	56
Intrauterine devices			
ParaGard (Copper T380A)	0.8	0.6	78
Mirena (levonorgestrel T)	0.2	0.2	80
Implanon	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	

From **Hatcher RA, Trussell J, Nelson AL, et al.** *Contraceptive Technology.* 20th ed. New York: Ardent Media; 2011:791, with permission.

Contraception During Lactation (Lactation Amenorrhea)

Previously, the use of combination estrogen–progestin hormonal methods (OCs, the patch, and the ring) was not advised during lactation because of concern about reduction in the amount and quality of breast milk. However, clinical studies demonstrate conflicting results regarding effects on breastfeeding continuation or exclusivity in women exposed to COCs during lactation and the use of combined estrogen–progestin hormonal methods are category 2 in breastfeeding women beyond 30 days of delivery (7). Progestin-only OCs, implants, and injectable contraception do not affect milk quality or quantity (15). Barrier methods, spermicides, and the *copper T380A* IUD (*ParaGard*) are excellent options for nursing mothers. Few studies have specifically looked at the use of levonorgestrel-IUDs (LNG-IUDs) on breastfeeding. One randomized controlled trial (RCT) raised concerns that immediate insertion of the LNG-

IUD postpartum may be associated with poorer breastfeeding performance when compared with delayed insertion (18). However, while more studies are needed before definitive recommendations can be made, the safety and impact on breastfeeding with the use of other contraceptives such as implants (which produce higher blood levels) have been previously shown (19). Given the comparatively low level of circulating hormone in LNG-IUDs, no adverse effect on breastfeeding is anticipated.

Table 14-2 Cost Effectiveness (C/E) of Contraceptive Methods at 5 Years

Method	Method-related Costs (US$)	Failure Cost (US$)	Cost of Side Effects (US$)	Total Cost (C) (US$)	Effectiveness (E)[a]	C/E (US$)	ICER (US$)
Copper-T IUD	605	42	0	647	99.6	6.50	
Vasectomy	710	3	0	713	100	7.13	164
LNG-20 IUS	823	58	49	930	99.8	9.32	1,415
Male condom	358	1,217	0	1,575	86.6	18.19	Dominated[b]
Fertility awareness based methods	0	1,892	0	1,892	79.2	23.89	Dominated[b]
Withdrawal	0	2,017	0	2,017	77.8	25.92	Dominated[b]
Diaphragm	764	1,288	119	2,171	85.8	25.31	Dominated[b]
Implant	2,142	5	31	2,178	100	21.78	3,828
Spermicides	431	2,104	112	2,647	76.6	34.55	Dominated[b]
Female condom	1,043	1,633	0	2,676	76.8	34.85	Dominated[b]
Injectable contraceptive	2,341	300	40	2,681	97	27.64	Dominated[b]
Sponge	969	1,829	0	2,798	79.8	35.06	Dominated[b]
Tubal ligation	2,866	59	53	2,978	99.8	29.84	Dominated[b]
Vaginal ring	2,467	683	8	3,158	92.4	34.18	Dominated[b]
Oral contraceptive	2,630	682	69	3,381	92.4	36.59	Dominated[b]
Transdermal patch	2,774	683	1	3,458	92.4	37.42	Dominated[b]
No method	0	4,739	0	4,739	48	98.72	Dominated[b]

[a]Average annual rate of not becoming pregnant over 5 years.

[b]Dominated means that this contraceptive option costs more and was less effective than the reference contraceptive, in this case, copper-T IUD.

ICER, incremental cost-effectiveness ratio.

From **Trussell J, Lalla AM, Doan QV, et al.** Cost effectiveness of contraceptives in the United States. *Contraception* 2009;79(1):5–14.

Fertility Awareness

Periodic abstinence, described as "natural contraception" or "fertility awareness," requires avoiding intercourse during the fertile period around the time of ovulation. A variety of methods are used: the calendar method, the mucous method (Billings or ovulation method), and the symptothermal method, which is a combination of the first two methods. With the mucous method, the woman attempts to predict the fertile period by feeling the cervical mucous with her fingers. Under estrogen influence, the mucous increases in quantity and becomes progressively more slippery and elastic until a peak day is reached. The mucous becomes scant and dry under the influence of progesterone

until the onset of the next menses. Intercourse may be allowed during the "dry days" immediately after menses until mucous is detected. Thereafter, the couple must abstain until the fourth day after the "peak" day.

In the symptothermal method, the first day of abstinence is predicted either from the calendar, by subtracting 21 from the length of the shortest menstrual cycle in the preceding 6 months, or the first day mucous is detected, whichever comes first. The end of the fertile period is predicted by the use of basal body temperature. The woman takes her temperature every morning and resumes intercourse 3 days after the thermal shift, the rise in body temperature that signals that the corpus luteum is producing progesterone and that ovulation occurred. The postovulatory method is a variation in which the couple has intercourse only after ovulation is detected.

A system of hormone monitoring designed to better define the fertile period involves placement of disposable test sticks in a small battery-powered device to detect urinary estrone-3 glucuronide and LH. Changes in these hormones reliably predict the fertile period. These devices (*Persona* and *Clearblue Easy Fertility Monitor [CEFM]*) can serve as aids either to becoming pregnant or avoiding it (20). *Persona* is marketed in Europe for contraception. It is reported to have a correct-use effectiveness of 94% in avoiding pregnancy. CEFM is approved in the United States as an aid to becoming pregnant but is used off label to avoid pregnancy. Exact effectiveness rates are not known. The CEFM is used in the Marquette method, which combines observation of cervical mucous changes with the CEFM results. A correct-use pregnancy rate of 2% and a typical-use pregnancy rate of 12% were reported (21).

Efficacy

The ovulation method was evaluated by the WHO in a five-country study. Women who successfully completed three monthly cycles of teaching were enrolled in a 13-cycle efficacy study. There was a 3.1% probability of pregnancy in 1 year for the small proportion of couples who used the method perfectly and 86.4% probability of pregnancy for the rest (22). A review of 15 national surveys from developing countries estimated a 12-month gross failure rate of 24 pregnancies per 100 (23). One systematic review of RCTs that examined fertility awareness-based methods found that most participants in trials discontinued prematurely and thus comparative efficacy of these methods remains unknown (24).

Risks

Conceptions resulting from intercourse remote from the time of ovulation more often lead to a higher likelihood of spontaneous abortion than conceptions from midcycle intercourse (25). Malformations are not more common.

Condoms

In the 1700s, condoms made of animal intestine were used by the aristocracy of Europe, but condoms were not widely available until the vulcanization of rubber in the 1840s (1). Modern condoms usually are made of latex rubber, although condoms made from animal intestine are still sold and are preferred by some who feel they afford better sensation. New condoms made from nonlatex materials—such as polyurethane or synthetic elastomers that are thin, odorless, transparent, and transmit body heat—are available. Although the nonlatex condoms may break more easily than the latex varieties, substantial numbers of study participants preferred them and would recommend them to others (26).

The risk of condom breakage is about 3% and is related to friction (27). The use of water-based lubricants may reduce the risk of breakage. Petroleum-based products such as mineral oil must be avoided because even brief exposure to them markedly reduces the strength of condoms (28).

Sexually Transmitted Diseases

Gonorrhea, ureaplasma, and pelvic inflammatory disease (PID) and its sequel (tubal infertility) are reduced with consistent use of barrier methods (29–31). **[2]** Tested in vitro, *Chlamydia trachomatis,* herpes virus type 2, HIV, and hepatitis B did not penetrate latex condoms but did cross through condoms made from animal intestine (32). Follow-up of sexual partners of HIV-infected individuals showed that condom use provides considerable protection (33). Consistent condom use provides more protection than inconsistent use (34). In one study, couples who use condoms 0% to 50% of the time had an HIV seroconversion rate of 20.8 per 100 couple years, whereas those who used condoms 100% of the time had a conversion rate of only 2.3 per 100 couple years (35). *Nonoxynol-9 (N-9)* should not be used with condoms for HIV protection because it is associated with genital lesions. *N-9* does not add to the protection afforded by condoms alone (36).

[2] Condoms offer protection from cervical neoplasia (37). **The relative risk (RR) for invasive cervical cancer was 0.4 when those who used condoms or diaphragms were compared with those who never used them** (38). **The presumed mechanism of protection is reduced transmission of human papillomavirus (HPV).**

Risks

Latex allergy could lead to life-threatening anaphylaxis in either partner from latex condoms. Nonlatex condoms of polyurethane and *Tactylon* should be offered to couples who have a history suggestive of latex allergy.

Female Condom

The original female condom introduced in 1992 was a polyurethane vaginal pouch attached to a rim that partly covered the vulva. The FC2 female condom was U.S. Food and Drug Administration (FDA) approved in 2009 and is an improved version made

from softer synthetic latex that does not require hand assembly during manufacture and is therefore less expensive (39). It consists of a loose-fitting nitrile sheath with two flexible rings. It is recommended for prevention of pregnancy and STDs, including HIV. Although breakage may occur less often with the female condom than the male condom, slippage appears to be more common, especially for those new to its use (40). Male condoms should not be used with female condoms as concurrent use increases the risk of breakage. Exposure to seminal fluid is slightly higher than with the male condom (41). Initial US trials showed a pregnancy rate of 15% in 6 months. Subsequent analysis found that with perfect use, the pregnancy rate may be only 2.6%. This rate is comparable to perfect use of the diaphragm and cervical cap, the other female-controlled barrier methods (42). As with the male condom, failure rates fall with increasing experience. Colposcopic studies of women using the female condom demonstrate no signs of trauma or change in the bacterial flora (43).

Vaginal Spermicides

Vaginal spermicides combine a spermicidal chemical, either *N-9* or *octoxynol,* with a base of cream, jelly, aerosol foam, foaming tablet, film, suppository, or a polyurethane sponge. *N-9* is a nonionic surface-active detergent that immobilizes sperm. *N-9* spermicides alone appear considerably less effective in preventing pregnancy than condoms or diaphragms. Women using *N-9* spermicides frequently have higher rates of genital lesions than women not using spermicides. These lesions may increase their risk for STDs and HIV (44). In the same studies of serodiscordant couples in which condoms were proven effective in preventing transmission of HIV, *N-9* spermicides alone were not effective (35).

Concerns were raised about possible teratogenicity of spermicides. *N-9* is not absorbed from the human vagina (45). Several large studies found no greater risk of miscarriage, birth defects, or low birth weight in spermicide users than in other women (46,47).

N-9 is toxic to the lactobacilli that normally colonize the vagina. Women who use spermicides regularly have increased vaginal colonization with the bacterium *Escherichia coli* and may be predisposed to *E. coli* bacteriuria after intercourse (48).

Vaginal Barriers

At the beginning of the 20th century, four types of vaginal barriers were used in Europe: vaginal diaphragm, cervical cap, vault cap, and Vimule. Vaginal diaphragms, new varieties of cervical caps, and the synthetic sponge are used in the United States. When used consistently, vaginal barriers can be reasonably effective. A recent search for alternatives to condoms for HIV prevention in high-prevalence areas has rekindled interest in the other vaginal barriers (49).

Diaphragm

Traditional diaphragms consist of a circular dome covered with fine latex rubber (Fig. 14-3). There are several types of diaphragms, as determined by the spring rim: coil, flat, or arcing. Coil-spring and flat-spring diaphragms become a flat oval when compressed for insertion. Arcing diaphragms form an arc or half-moon when compressed; they are easiest to insert correctly. Traditionally, diaphragms require fitting by practitioners. Spermicide is always prescribed for use with the diaphragm; whether this practice is necessary is not well studied.

Fitting Diaphragms

Fitting a diaphragm should be performed as follows:

1. **A vaginal examination should be performed.** With the first and second fingers in the posterior fornix, the thumb of the examining hand is placed against the first finger to mark where the first finger touches the pubic bone. The distance from the tip of the middle finger to the tip of the thumb is the diameter of the first diaphragm that should be tried.
2. **A set of test diaphragms of various sizes is used, and the test diaphragm is inserted and checked by palpation.** The diaphragm should open easily in the vagina and fill the fornices without pressure. The largest diaphragm that fits comfortably should be selected. A size 65, 70, or 75 diaphragm will fit most women.
3. **The patient should practice insertion and should be reexamined to confirm proper position of the device.** About 1 teaspoon of water-soluble spermicidal jelly or cream is placed in the cavity of the dome. The diaphragm is inserted with the dome downward so that the cervix will sit in a pool of the spermicide.
4. **The diaphragm can be inserted several hours before intercourse. If intercourse is repeated, additional spermicidal jelly should be inserted into the vagina without removing the diaphragm. The diaphragm should be left in place at least 6 hours after intercourse to allow for immobilization of sperm.** When removed, it is washed with soap and water, allowed to dry, and stored away from heat. It should not be dusted with talc because genital exposure to talc may increase the risk of ovarian cancer.

In 2014, the FDA approved the Caya contoured diaphragm for use in the United States. It is a single-size reusable silicone diaphragm. Compared to traditional diaphragms, this contoured diaphragm does not require fitting by a practitioner to determine the size, which in low-resource settings may be especially important for improving access. Caya should be used with a spermicide. It should be kept in place for 6 hours after intercourse to ensure sperm cells are no longer active, but removed within

24 hours to prevent toxic shock syndrome.

Risks

Diaphragm use, especially prolonged use during multiple acts of intercourse, appears to increase the risk of bladder infections. A smaller-sized, wide-seal diaphragm or a cervical cap can be used if recurrent cystitis is a problem, although the problem may relate not only to mechanical obstruction but also to alterations in vaginal flora produced by the spermicide. An epidemiologic study comparing cases of toxic shock with controls found no increased risk from diaphragm use (50).

Other Barriers

FemCap

This version of the cervical cap made of silicone rubber was approved by the FDA in 2003. It looks like a sailor's hat with the dome covering the cervix and the brim fitting into the vaginal fornices. It is made in three sizes—22-, 26-, and 30-mm diameter—and is expected to be reusable for 2 years. It is used with spermicide and should be left in place for at least 6 hours after intercourse, but it may be left in place as long as 48 hours at a time. Additional acts of intercourse require insertion of more spermicide. *FemCap* requires a clinician's fitting and prescription for use. The only available efficacy study compared the *FemCap* to the vaginal diaphragm. The 6-month pregnancy rate for the *FemCap* was 13.5%, substantially higher than the 7.9% rate for the diaphragm. Both groups used *N-9* spermicide with the devices (52).

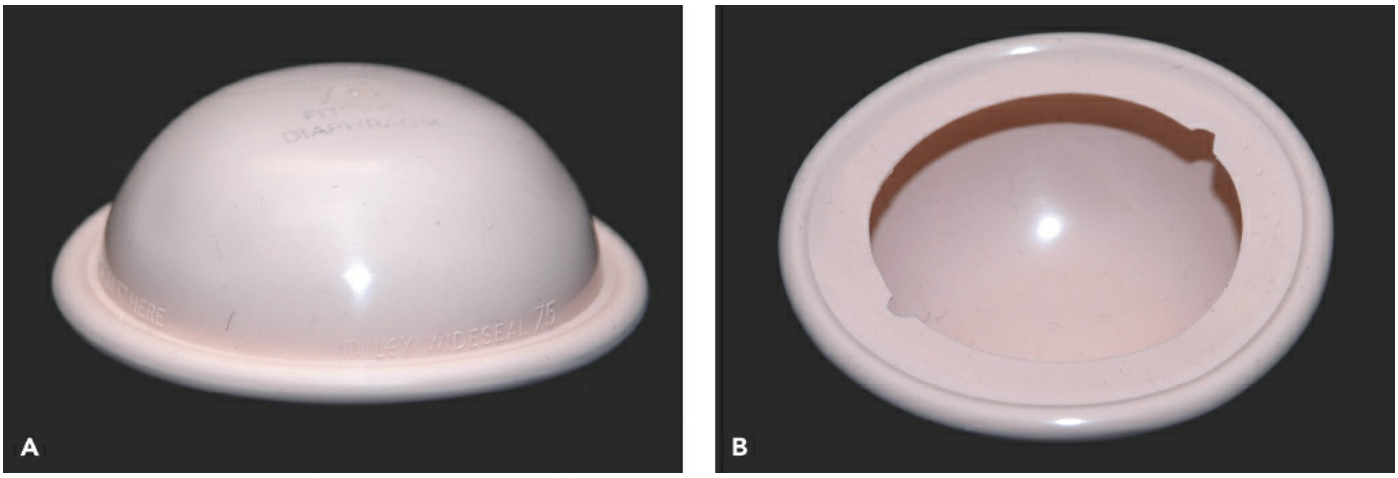


FIGURE 14-3 Wide-seal diaphragm. **A:** Outer caudal side. **B:** Inner cephalad side.

Future Development in Barrier Methods

The *Ovaprene* ring is a nonhormonal "one-size-fits-all" intravaginal organic silicone ring that continuously releases spermiostatic and spermicidal agents over a 4-week period. The phase I trial demonstrated patient acceptability and safety (51). It is expected to undergo a postcoital test clinical trial in 2018.

Sponge

The *Today* sponge is a polyurethane dome-shaped device containing *N-9*. It is moistened with water and then inserted high in the vagina to cover the cervix. It combines the advantages of a disposable barrier with spermicide and provides protection for 24 hours. The contraceptive efficacy appears to differ with parity. Nulliparous women are reported to have a perfect use pregnancy rate of 9% per year, whereas parous women have a pregnancy rate of 20% **(Table 14-1)**. Rates with typical use are estimated as 12% per year in nullipara and 24% in multipara (52). A trial comparing the sponge with a vaginal spermicide preparation used alone without barrier showed the sponge had a slightly lower pregnancy rate (53).

Intrauterine Contraception

Worldwide over 14% of married women use intrauterine contraception (54). In the United States, usage is increasing, but the estimates are that only 6.4% of women use intrauterine contraception (54). Candidacy includes nulliparous women, adolescents, and immunocompromised women. Immediate use postpartum or after a first- or second-trimester abortion broadened usage. Five IUDs are available in the United States: the copper T380A (*ParaGard*), two 52-mg levonorgestrel-releasing *IUDs* (*Mirena and Liletta*), a 19.5-mg levonorgestrel-releasing IUD (*Kyleena*), and a 13.5-mg levonorgestrel-releasing IUD (*Skyla*). The *copper T380A* has bands of copper on the cross arms of the T in addition to the copper wire around the stem, providing a total surface area of 380 mm of copper, almost double the surface area of copper in earlier copper devices **(Fig. 14-4)**. It is approved for up to 10 years of continuous use. The *Mirena* **(Fig. 14-5)** is approved in the United States for 5 years of use, although studies through 7 years of use show no loss of efficacy (55). The *Kyleena* is approved for 5 years of use, while the *Skyla* is approved for 3 years. *Liletta* is manufactured by Medicines360 and is approved for use up to 4 years, with eventual anticipated approval for 7 years, and possibly 10 years (56). **[3] All IUDs provide safe, long-term contraception with effectiveness equivalent to tubal sterilization.**

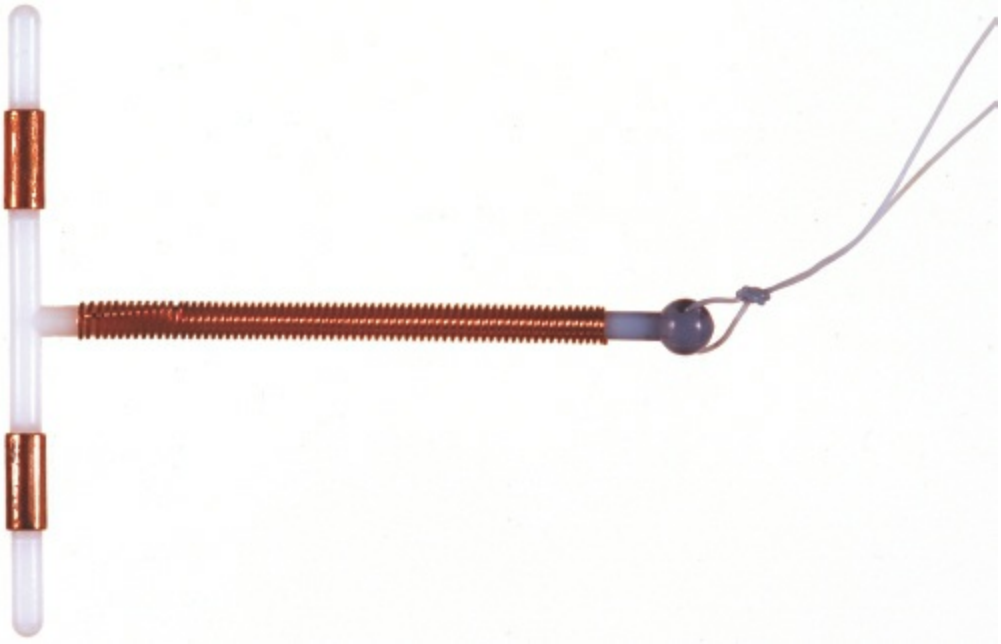


FIGURE 14-4 *Copper T380A* (*ParaGard*) intrauterine device.

Mechanism of Action

IUDs cause the formation of "biologic foam" within the uterine cavity that contains strands of fibrin, phagocytic cells, and proteolytic enzymes. All IUDs stimulate the formation of prostaglandins within the uterus, consistent with both smooth muscle contraction and inflammation. Copper IUDs continuously release a small amount of the metal, producing an even greater inflammatory response. Scanning electron microscopy studies of the endometrium of women wearing nonmedicated IUDs show alterations in the surface morphology of cells, especially of the microvilli of ciliated cells (57). There are major alterations in the composition of proteins within the uterine cavity and new proteins and proteinase inhibitors are found in washings from the uterus (58). **These altered intrauterine environments interfere with sperm passage through the uterus, preventing fertilization.**

The *levonorgestrel* in IUDs is much more potent than natural progesterone and has a profound effect on the endometrium. The hormone is released at an initial rate of 20 μg daily, which declines to half this rate by 5 years. For the 52-mg LNG-IUDs, blood hormone levels are significantly lower than with other progesterone-only contraception and remain stable at approximately 130 to 200 pg/mL (59). About 85% of cycles are ovulatory. The contraceptive effect of the LNG-IUD is a result of thickened and scant cervical mucous, endometrial atrophy, and an intrauterine inflammatory response (56,59).



FIGURE 14-5 *Levonorgestrel T* (*Mirena*) intrauterine device.

The IUD is not an abortifacient. The contraceptive effectiveness does not depend on interference with implantation, although this phenomenon can occur and is, in part, the theoretical basis for using copper IUDs for emergency contraception. Sperm can be obtained by laparoscopy in washings from the fallopian tubes of control women at midcycle; fewer sperm are present in the tubal washings from women wearing IUDs (60). Ova flushed from the tubes at tubal sterilization showed no evidence of fertilization in women wearing IUDs (61). Studies of serum β-human chorionic gonadotropin (β-hCG) levels in women wearing IUDs do not indicate pregnancy (62).

Effectiveness

The *copper T380A* and the 52-mg *LNG-IUDs* have remarkably low pregnancy rates, less than 0.2 per 100 woman-years. Total pregnancies over a 7-year period were only 1.1 per 100 for the *LNG-IUD* and 1.4 for the *copper T380A (*55*)*. Twelve-year data on the *copper T380A* showed a cumulative pregnancy rate of only 1.9 per 100 women and no pregnancies at all after year 8 (63).

Benefits

Modern IUDs provide excellent contraception without continued effort by the user. The *copper T380A* and the *LNG-IUDs* protect against ectopic pregnancy. **The *LNG-IUD,* by releasing *levonorgestrel,* reduces menstrual bleeding and cramping. It is used extensively to treat heavy menstrual bleeding and is used in Europe and the United Kingdom as an alternative to hysterectomy for menorrhagia** (64). The *LNG-IUD* has a beneficial effect on menorrhagia from uterine fibroids; the benefit may be diminished with distorting submucosal fibroids (65,66). **The *LNG-IUD* is an effective way to**

deliver the necessary progestin therapy in postmenopausal women on estrogen therapy (67). Additional noncontraceptive benefits include a reduced risk of endometrial cancer and improvement in symptoms of endometriosis and adenomyosis (68–71).

Risks

Infection

The Women's Health Study found the *Dalkon Shield* device (withdrawn from the market since 1974) to increase the risk of PID eightfold when women hospitalized for PID were compared with control women hospitalized for other illnesses (72). In contrast, risk from the other IUDs was markedly lower. Increased risk was detectable only within 4 months of insertion of the IUD. A prospective WHO study revealed that PID increased only during the first 20 days after insertion. Thereafter, the rate of diagnosis of PID was about 1.6 cases per 1,000 women per year, the same as in the general population (73).

[3] Exposure to sexually transmitted pathogens is the more important determinant of PID risk than IUD use. In the Women's Health Study, women who were married or cohabiting and who said they had only one sexual partner in the past 6 months had no increase in PID (72). In contrast, previously married or single women had marginal increase in risk, even though they had only one partner in the previous 6 months (74). The only pelvic infection that was unequivocally related to IUD use is actinomycosis (75). It appears that PID with actinomycosis was reported only in women wearing an IUD. Rates of colonization with actinomycosis increase with duration of use for plastic devices but appear to be much less for copper-releasing IUDs. Actinomyces may be found in cervical cytology of up to 7% of women with an IUD. Because of the low positive predictive value and a lack of sensitivity and specificity of cervical cytology to diagnose this organism, antibiotic treatment and IUD removal should be reserved for symptomatic women (76).

When PID is suspected in a woman using an IUD, appropriate cultures should be obtained, and antibiotic therapy should be administered. Removal of the IUD is not necessary unless symptoms do not improve after 72 hours of treatment (77). Pelvic abscess, if suspected, should be ruled out by ultrasound examination.

Ectopic Pregnancy

All contraceptive methods protect against ectopic pregnancy by preventing pregnancy. But when the method fails and pregnancy occurs, the risk of ectopic pregnancy is affected by the method of contraception. **IUDs and tubal sterilization increase the probability of the pregnancy being ectopic when pregnancy occurs, but the rate of any pregnancy is so low that women using either of these methods have much lower rates of ectopic pregnancy than women not using contraception** (78). Risk of any pregnancy with a *LNG-IUD* is between 0.1 and 0.2 per 100 woman-years. The rate of

an ectopic in users of this device is reported as 0.02 per 100 woman-years (79). In a large study of the *copper T380A,* the first-year pregnancy rate was 0.5 per 100 woman-years, and the rate of ectopic was 0.1 per 100 woman-years (80). Ectopic is a very rare event with either IUD, but should a woman wearing one present with pelvic pain and a positive β-hCG, an ectopic must be ruled out.

Fertility

Tubal factor infertility is not increased among nulligravid women who used copper IUDs, but exposure to sexually transmitted pathogens such as *C. trachomatis* can increase the risk (81). The contraceptive actions of the LNG-IUD reverse soon after removal of the device. One-year life-table pregnancy rates after removal are 89 per 100 for women less than 30 years of age—rates are similar to women who had not been using any form of birth control (82).

Expulsion and Perforation

The 36-month cumulative expulsion rate is 10.2 per 100 IUD users and did not vary by IUD type (LNG-IUD 10.1 vs. copper IUD 10.7, $p = 0.99$) (83). The cumulative rate of expulsion is lower in nulliparous women compared to parous women and higher in females aged 14 to 19 years compared to older women. The risk of uterine perforation associated with insertion is dependent on the inserter. The risk in experienced hands is on the order of 1 per 1,000 insertions or less (84). The risk of perforation is no different between the copper and the LNG-IUDs (85). Multiparity decreases the risk of perforation (84). Breastfeeding and time since delivery are independently associated with uterine perforation risk. The RR of perforation in lactating compared to nonlactating women at ≤36 weeks since delivery was 4.7 (86).

Clinical Management

Conditions listed as a category 4 (unacceptable health risk) for IUDs by the WHO include pregnancy, puerperal sepsis, PID, active purulent cervicitis, endometrial or cervical cancer, undiagnosed genital bleeding, gestational trophoblastic disease with persistent elevation in β-hCG, uterine anomalies, and fibroid tumors that distort the endometrial cavity (87). **Infection with HIV is not considered a contraindication for IUD use.** There are no differences in genital viral shedding, HIV disease progression or disease transmission among IUD users compared to users of other contraceptives (88). Copper allergy and Wilson disease are contraindications to the use of copper IUDs.

Candidate Selection

IUDs are appropriate for long-term contraception in most women given their ease of use, safety, high efficacy, and favorable side effect profile. Nulliparous women, adolescents, women undergoing a first- or second-trimester surgical abortion, women with a recent medical abortion, and women immediately postpartum should

all be considered candidates for IUDs (89). There is renewed interest in postpartum and postabortal insertion of IUDs. In both circumstances, the woman is clearly no longer pregnant, she may be highly motivated to accept contraception, and the setting is convenient for the woman and the provider (89). **Postpartum and postabortal insertions are safe.** Complications are not increased by comparison to interval insertion. The only disadvantage is that the expulsion rate is higher. Two recent RCTs, involving LNG-IUDs, reported expulsion rates after vaginal postplacental insertion of 24% and 27% (90,91). Postplacental expulsion rates after cesarean sections appear to be lower (92). While comparing postpartum to interval insertion, all the women requesting postpartum IUD received the device, but many women scheduled for interval insertion did not return. When surveyed at 6 months postpartum, more women who had immediate postpartum insertion were wearing IUDs than were those who had scheduled for interval insertion (93,94). Expulsion by 6 months was more likely following immediate insertion (odds ratio [OR], 4.89; 95% confidence interval [CI], 1.47–16.32); however, IUD use at 6 months was more likely with immediate insertion than with delayed insertion (OR, 2.04; 95% CI, 1.01–4.09) (95,96). Thus, in terms of actual continuation, overall, the benefits of IUD insertion immediately postplacental far outweigh the higher expulsion rates associated with such insertions (97). Goodman and colleagues found many fewer repeat abortions among women followed after postabortal IUD insertion compared to a cohort of women choosing non-IUD methods of contraception after an induced abortion (98).

Insertion

At the contraceptive visit, the patient's history is obtained and a physical examination, screening for *Neisseria gonorrhoeae* and chlamydia in high-risk women, and detailed counseling regarding risks and alternatives are provided. Clinicians have traditionally inserted IUDs at the time of menses to ensure the patient is not pregnant, but it can be inserted at any time in the cycle if pregnancy can be excluded (99). The *copper T380A* IUD can be inserted within 5 days of unprotected intercourse for almost 100% effective emergency contraception.

There are limited data on effective treatment of pain during IUD insertion. One randomized double-blind placebo-controlled study demonstrated that self-administered vaginal 2% lidocaine gel did not reduce pain with IUD insertion but did decrease pain with tenaculum placement (100). However, studies utilizing lidocaine–prilocaine creams have demonstrated a reduction in pain during tenaculum placement, sound insertion, and IUD insertion (101,102). Despite some practitioners' preference to premedicate with misoprostol or NSAIDs, these interventions do not reduce pain with insertion (103).

Antibiotic prophylaxis is not beneficial, probably because the risk of pelvic infection with IUD insertion is so low. A large randomized trial of 1,985 patients

receiving either oral *azithromycin* or placebo found no difference in rates of IUD removal during the first 90 days after insertion and no difference in rates of salpingitis (104). A meta-analysis found that antibiotic prophylaxis at the time of IUD insertion did not decrease the risk of PID nor did it reduce the likelihood of removal within the first 3 months (105). For women at high risk of STIs (e.g., aged 25 years or younger or having multiple sex partners), it is reasonable to screen for STIs and place the IUD on the same day. The International Planned Parenthood Federation, in collaboration with WHO and other international organizations, developed guidelines that include the restriction of IUD insertion within 3 months of puerperal sepsis (106).

The technique of insertion is as follows:

1. **The cervix is exposed with a speculum. The vaginal vault and cervix are cleansed with a bactericidal solution, such as an iodine-containing solution.**
2. **Traditionally, the next step is measurement of the uterine cavity with a uterine sound. The depth of the cavity should measure at least 6 cm from the external os.** However, a pilot study assessing a simplified insertion technique without the use of uterine sound or bimanual examination was found to be safe and effective (107).
3. **The use of a tenaculum for insertion is mandatory to prevent perforation. The cervix is grasped with a tenaculum and gently pulled downward to straighten the angle between the cervical canal and the uterine cavity. The IUD, previously loaded into its inserter, is gently introduced through the cervical canal.**
4. **With the *copper T380A,* the outer sheath of the inserter is withdrawn a short distance to release the arms of the T and is gently pushed inward again to elevate the now-opened T against the fundus. The outer sheath and the inner stylet of the inserter are withdrawn, and the strings are cut to project about 2 cm from the external cervical os.**
5. **The *Mirena* 52-mg LNG-IUD is inserted somewhat differently from the *copper T380A.* The inserter tube is introduced into the uterus until the preset sliding flange on the inserter is 1.5 to 2 cm from the external os of the cervix. The arms of the T device are released upward into the uterine cavity, and the inserter is pushed up under them to elevate the IUD up against the uterine fundus.**
6. **The Liletta 52-mg LNG-IUD can be inserted using a one-handed (United States) or a two-handed inserter (international).** In both cases, the deployment mechanism is more similar to that for *Mirena* than for the *copper T380A.*

In nulliparous women, insertion may be more challenging because of a narrower cervical canal than in parous women. Mechanical dilation may be necessary. While

misoprostol was initially proposed to benefit some women during IUD insertion, a systematic review found that routine pretreatment with misoprostol did not lead to improved ease or success of IUD insertion and resulted in more insertional discomfort (108).

Intrauterine Devices in Pregnancy

If an intrauterine pregnancy is diagnosed and the IUD strings are visible, the IUD should be removed as soon as possible to prevent later septic abortion, premature rupture of the membranes, and premature birth (109). When the strings of the IUD are not visible, an ultrasound examination should be performed to localize the IUD and determine whether expulsion has occurred. If the IUD is present, there are three options for management:

1. Elective abortion
2. Ultrasound-guided intrauterine removal of the IUD
3. Continuation of the pregnancy with the device left in place

If the patient wishes to continue the pregnancy, ultrasound evaluation of the location of the IUD should be considered (110). If the IUD is not in a fundal location, ultrasound-guided removal using small alligator forceps may be successful. If the location is fundal, the IUD should be left in place. When pregnancy continues with an IUD in place, the patient must be warned of the symptoms of intrauterine infection and should be cautioned to seek care promptly for fever or flulike symptoms, abdominal cramping, or bleeding. At the earliest sign of infection, high-dose intravenous antibiotic therapy should be given and the pregnancy evacuated promptly.

Duration of Use

Annual rates of pregnancy, expulsions, and medical removals decrease with each year of use (111). Therefore, a woman who has no problem by year 5, for example, is very unlikely to experience problems in the subsequent years. The *copper T380A* is FDA approved for 10 years and the *LNG-IUD* for 5 years, although good data support use of the *copper T380A* through 12 years and of the *LNG-IUD* through 7 years (63,85). Newer data from a prospective cohort study support the use of 52-mg LNG-IUD into year 6 and 7 (112,113).

Choice of Devices

All IUDs available in the United States, provide protection for many years, have remarkably low pregnancy rates, and substantially reduce the risk of ectopic pregnancy. The *LNG-IUDs* reduce the amount of menstrual bleeding and dysmenorrhea. Amenorrhea rates are 19% to 20%, 12%, and 6% for the 52-, 19.5-, and 13.5-mg LNG-IUDs at 1 year of insertion, respectively (56,59,114,115). The *copper T380A* can be

expected to initially increase menstrual bleeding. It is the most effective means for emergency contraception.

Management of Bleeding and Cramping With Intrauterine Devices

The most important medical reason that women give for requesting removal of an IUD is bleeding and pelvic pain. These symptoms are common in the first few months, but diminish over time, in most cases in months. Nonsteroidal anti-inflammatory drugs are usually helpful. When pain and bleeding occur later, the patient should be examined for signs of PID, partial expulsion of the device, or an intracavitary fibroid. Two ultrasonographic studies comparing women with these symptoms after 6 months to women with no bleeding complaints show downward displacement of the IUDs into the cervical canal in many symptomatic women and in some cases, intracavitary fibroids (116,117). When the patient wishes to continue with an IUD, removal of the displaced device and insertion of a new one is advisable. In situations where IUDs are inexpensive and ultrasound is expensive or not available, the best course is to offer immediate removal and replacement of the IUD without ultrasound proof of displacement.

Future of Intrauterine Devices

VeraCept

A novel nitinol-frame low-dose copper IUD, VeraCept (ContraMed, Campbell, California), is under investigation in a phase II multicenter study in the United States. Because of its thinner nitinol frame, the insertion tube has a small diameter. In a randomized comparison against copper T380S, VeraCept was associated with less pain with insertion, higher continuation rate at 12 months, lower expulsion rate at 12 months, and fewer removals for pain/bleeding (118). Despite containing less than half as much copper surface area (175 mm^2) as the T380S (380 mm^2), the contraceptive efficacy is similar. However, long-term efficacy has yet to be studied.

Intrauterine Ball With Copper Pearls

IUB (OCON Medical, Modiin, Israel) copper pearls are strung on a memory alloy nitinol wire, and when inserted into the uterine cavity, take the shape of the uterus. This device comes in three sizes, ranging from 12 to 18 mm in diameter with copper ranging from 300 to 380 mm^2. Preliminary results from a pilot study, however, are concerning for high expulsion rates and low user satisfaction (119).

FibroPlant

The FibroPlant 14 LNG-IUS (Contrel Research, Ghent, Belgium) is a frameless levonorgestrel-releasing IUD which contains a nonresorbable thread with a knot that is implanted into the myometrium of the uterine fundus. The attached implant delivers either 14 or 20 mcg of levonorgestrel each day and is approved for 5 years of use. The

reported pregnancy rate at 5 years is 0.4%, with similarly low expulsion and perforation rates (120).

HORMONAL CONTRACEPTION

Hormonal contraceptives are female sex steroids, synthetic estrogen and synthetic progesterone (progestin), or progestin-only without estrogen. They can be administered in the form of OCs, patches, implants, and injectables. The most widely used hormonal contraceptive is the combination OC containing estrogen and progestin. Combination OCs can be monophasic, with the same dose of estrogen and progestin administered each day, or multiphasic, in which varying doses of steroids are given through a 21-day or 24-day cycle. Combination OCs are packaged with 21 active tablets and 7 placebos, or 24 active tablets and 4 placebo tablets. The inclusion of placebos allows the user to take one pill every day without having to count. The medication-free interval while the user takes the placebo tablets allows withdrawal bleeding that mimics a 28-day menstrual cycle. To begin OC use, the user takes the first pill any time from the first day of menses through the Sunday after menstruation begins and thereafter starts a new pack as soon as the first pack is completed. The 7-day medication-free interval was standard for years, but studies showed that a shorter medication-free interval is adequate to trigger cyclic withdrawal bleeding and maintains better suppression of ovulation. Ovarian follicles mature more during the 7-day medication-free interval than during the 4-day interval. Hence the new 24/4 combination theoretically could be more effective in preventing pregnancy than the 21/7 combination, but this has not been demonstrated. Other variations of OC administration are the extended-cycle and the continuous-cycle methods. Users take active pills containing an estrogen–progestin combination for 3 months at a time (extended cycle) or indefinitely for a year or more (continuous cycle). Users on these regimens have more unscheduled days of spotting or bleeding than those on 28-day cycles in the beginning, but become amenorrheic. As a result, they experience fewer cycle-triggered symptoms such as headache and menstrual pain. Continuous combined regimens are preferred for women with chronic pelvic pain or when dysmenorrhea is not relieved by OCs taken in 28-day cycles (121).

Progestin-only OCs are taken every day without interruption. Other forms of hormonal contraception include transdermal administration with the patch, injectable progestins, injectable estrogen–progestin combinations, subdermal implants that release progestin, and vaginal rings that release either estrogen–progestin or progestin alone (122).

Where modern hormonal contraception is concerned, it is important to note that: (i) ALL hormonal contraceptives, even those containing estrogen are progestin-dominant, meaning that progestin effects are the dominant ones and (ii) the progestin is doing the

real contraceptive "work" by either suppressing ovulation or thickening the cervical mucous. The presence of the estrogen component assists with cycle control and adds to the ovarian suppressive effect, but overall the progestin component dominates.

Steroid Hormone Action

Sex steroids are characterized by their affinity for specific estrogen, progesterone, or androgen receptors, and by their biologic effects in different systems (123). Steroids are rapidly absorbed in the gut but go directly into the liver through the portal circulation, where they are rapidly metabolized and inactivated. Therefore, large doses of steroids are required when they are administered orally. The addition of the ethynyl group to carbon-17 of the steroid molecule hinders degradation by the liver enzyme 17-hydroxysteroid dehydrogenase and allows potent biologic activity after oral doses of only micrograms.

Progestins

Progestins are synthetic compounds that mimic the effect of natural progesterone but differ from it structurally. The progestins differ from one another in their affinities for estrogen, androgen, and progesterone receptors; their ability to inhibit ovulation; and their ability to substitute for progesterone and to antagonize estrogen. Some are directly bound to the receptor (*levonorgestrel, norethindrone*), whereas others require bioactivation as, for example, desogestrel, which is converted in the body to its active metabolite, etonogestrel. The 17-acetoxy progestins (e.g., *medroxyprogesterone acetate*) are bound by the progesterone receptor. *Norgestrel* exists as two stereoisomers, identified as dextronorgestrel and levonorgestrel. Only levonorgestrel is biologically active. Three newer progestins (*norgestimate, desogestrel,* and *gestodene*) are viewed as more "selective" than the other 19-nor progestins, in that they have little or no androgenic effect at doses that inhibit ovulation (124). The FDA-approved *norgestimate*- and *desogestrel*-containing OCs, and *gestodene* are available in Europe. *Gestodene* is a derivative of levonorgestrel that is more potent than the other preparations (i.e., very little of it is required for antifertility effects). Similarly, *norelgestromin* is an active metabolite of *norgestimate* and more potent than the parent compound. It is used in the transdermal patch. *Drospirenone,* a progestin introduced in the United States, is a derivative of the diuretic spironolactone. It has a high affinity for progesterone receptors, mineralocorticoid receptors, and androgen receptors. It acts as a progesterone agonist but is a mineralocorticoid antagonist and androgen antagonist (125). Comparative studies suggest a small decrease in body weight and in blood pressure, with equivalent cycle control and contraceptive efficacy, in women taking an OC containing 3 mg of *drospirenone*/30-µg *ethinylestradiol (EE)* versus women taking a 150-µg *levonorgestrel*/30-µg *EE* preparation (126). Pilot studies among women with polycystic ovary syndrome showed good cycle control and reduction in androgen levels

with no change in weight, blood pressure, or glucose metabolism (127). The FDA approved the 20-µg *EE*/3-mg *drospirenone* OC for premenstrual dysphoric disorder (PMDD) in women who chose OCs for contraception. When compared to an OC with 30-µg *EE*/150-µg *levonorgestrel,* women taking the *drospirenone* OC had better relief of menstrual symptoms, better improvement in acne, reduction in negative affect during the menstrual phase, and a greater feeling of well-being (128). *Dienogest,* another progestin introduced in the United States, is combined with *estradiol valerate,* not *EE.* Whether it offers any advantage over already marketed OC combinations is not yet evident. The *dienogest/estradiol valerate* combination is as effective as *levonorgestrel/EE* as a contraceptive, and in treating abnormal uterine bleeding (129).

Estrogens

In the United States, most OCs contain *EE.* An older formulation OC contains *mestranol,* which is *EE* with an extra methyl group. It requires bioactivation in the liver, where the methyl group is cleaved, releasing the active agent, *EE.* OCs with 35 µg of *EE* provide the same blood levels of hormone as do OCs containing 50 µg of *mestranol* (130). Other contraceptives contain 17 β-estradiol (Zoely) or its ester, *estradiol valerate* (Qlaira) or *estradiol cypionate* (Cyclofem), an injectable.

Antifertility Effects

Combination Estrogen–Progestin Contraceptives

Ovulation can be inhibited by estrogen or by progestin alone. Pharmacologic synergism is exhibited when the two hormones are combined and ovulation is suppressed at a much lower dose of each agent. Combination OCs, patches, and the *NuvaRing* suppress basal follicle-stimulating hormone (FSH) and LH. They diminish the ability of the pituitary gland to synthesize gonadotropins when it is stimulated by hypothalamic GnRH (131). Ovarian follicles do not mature, little estradiol is produced, and there is no midcycle LH surge. Ovulation does not occur, the corpus luteum does not form, and progesterone is not produced. This blockade of ovulation is dose related. Newer low-dose OCs do not provide as dense a block and allow somewhat higher baseline FSH and LH levels than higher-dose formulations (132). This makes ovulation somewhat more likely to occur if pills are missed or if the patient takes another medication that reduces blood levels of the contraceptive steroids.

Progestin-Only Preparations

Highly effective contraception can be provided by progestin alone, thus avoiding the risks of estrogen. The mode of action of progestin-only contraceptives is highly dependent on the dose of the compound (133). With low levels of progestin in the blood, ovulation will occur part of the time. At moderate levels of progestin in the

blood, normal basal levels of FSH and LH are present, and some follicle maturation may occur. At higher blood levels as seen with *DepoProvera,* the basal FSH is reduced, and there is less follicular activity, less estradiol production, and no LH surge.

Transdermal Hormonal Contraception

The patch (*Ortho Evra*), which adheres to the user's skin, and the vaginal *NuvaRing* contain combinations of *EE* and a potent progestin. Both provide sustained release of the steroids and result in relatively constant serum levels that are less than the peak levels seen with OCs but sufficient to prevent ovulation.

Hormonal Implants

With the *levonorgestrel* subdermal implants there is some follicular maturation and estrogen production, but LH peak levels are low and ovulation is often inhibited. In the first year of use, ovulation is believed to occur in about 20% of cycles. The proportion of ovulatory cycles increases with time, probably as a result of the decline in hormone release. By the fourth year of use, 41% of cycles are ovulatory. The more potent progestin released by the *etonogestrel* implant is even more effective at preventing ovulation (134). The mechanisms of action of low-dose progestins include effects on the cervical mucous, endometrium, and tubal motility. The scant, dry cervical mucous that occurs in women using implants inhibits sperm migration into the upper tract. Progestins decrease nuclear estrogen receptor levels, decrease progesterone receptors, and induce activity of the enzyme 17-hydroxysteroid dehydrogenase, which metabolizes natural 17 β-estradiol (133).

The sustained release offered by contraceptive implants allows for highly effective contraception at relatively low steroid blood levels. **Figure 14-6** depicts expected steroid blood levels with implants, injectables, and OCs. An additional mechanism for contraception was discovered with the antiprogesterone *mifepristone* (*RU486*). In the normal cycle, there is a small amount of progesterone production from the follicle just before ovulation. This progesterone appears essential to ovulation, because if *mifepristone* is given before ovulation this can be delayed for several days (135,136).

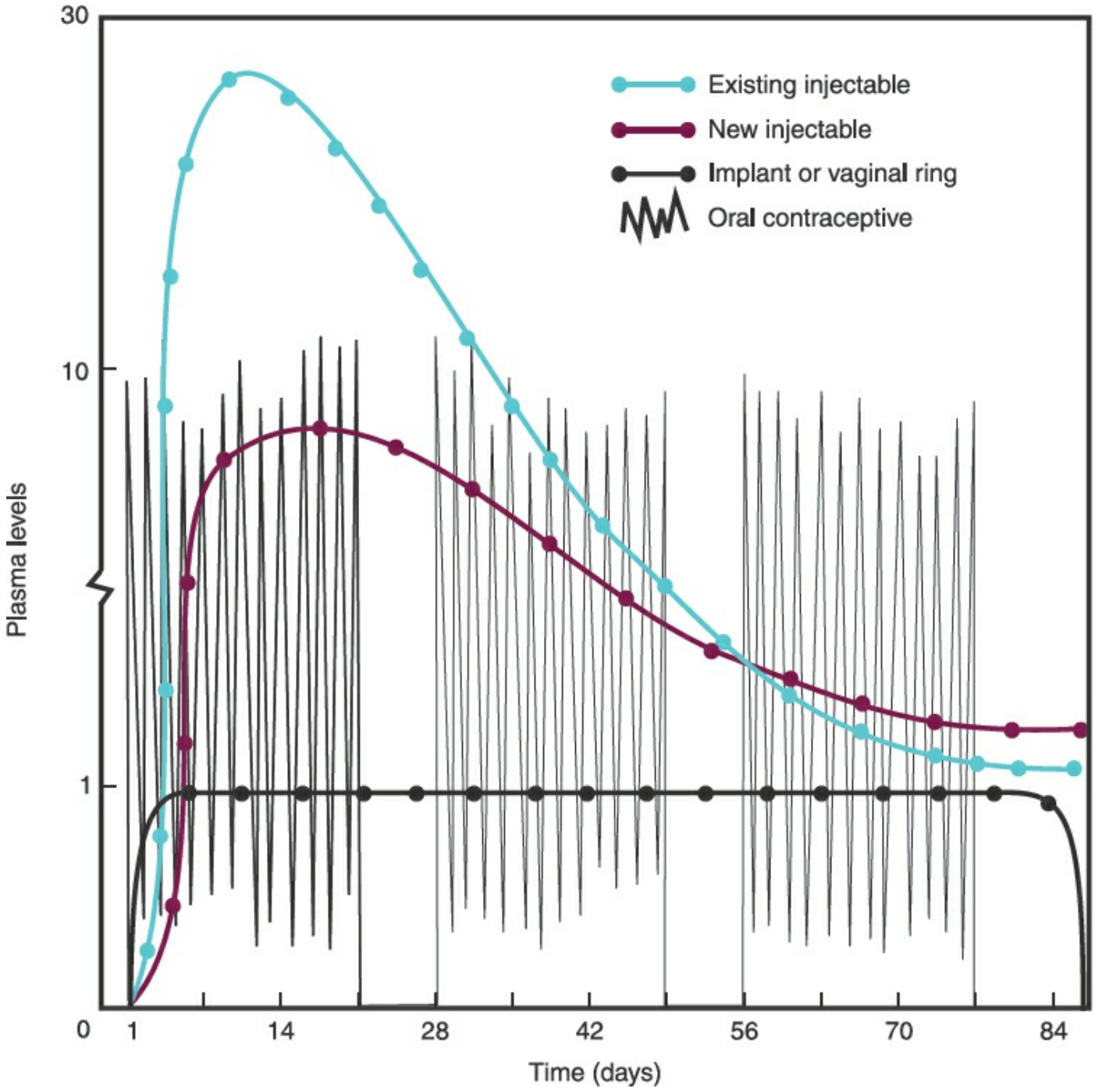


FIGURE 14-6 Schematic representation of the expected pharmacokinetic profiles of progestogens administered in different formulations. (From **Landgren BM**. Mechanism of action of gestagens. *Int J Gynaecol Obstet* 1990;32:95–110, with permission.)

Efficacy of Hormonal Contraception

[4] When used consistently, combination OCs have pregnancy rates as low as 2 to 3 per 100 women per year. Progestin-only OCs are less effective than combination estrogen–progestin preparations, with best results of 3 to 4 pregnancies per 100 woman-years. All methods have the potential for user error; therefore, there may be a

10-fold difference between the best results and results in typical users of OCs. Injectable progestins and implants are much less subject to user error than OCs. The difference between the best results and results in typical users is small and is comparable to pregnancy rates after tubal sterilization (Table 14-1). Pregnancy rates with the *Ortho Evra* patch and the *NuvaRing* were equivalent to those of OCs; however, because it is easier to use these methods consistently, larger studies may well demonstrate better typical user results than with OCs (137,138). Typical use pregnancy rates with *depomedroxyprogesterone acetate (DMPA)* are lower. The subdermal implants have the lowest failure rates of any hormonal contraceptive method.

Hormonal Contraception for Obese Women

The rate of obesity worldwide is increasing. Across the United States, more than one in three adults are obese (139). Most studies of contraceptive efficacy intentionally excluded obese women, so the available information is limited. Obese women are no less likely than other women to become pregnant, but they have an increased risk of pregnancy complications (140). A systematic review of hormonal contraception for overweight and obese women focused on 12 relevant studies (141). The data on the risk of pregnancy in overweight and obese women using OCs was mixed, with one study showing increased risk while another showing decreased risk. Analysis of data from other contraceptive methods indicated no association of pregnancy with overweight or obesity. These included depot medroxyprogesterone acetate (subcutaneous), LNG-IUD, the two-rod levonorgestrel implant, and the etonogestrel implant. One study evaluated a contraceptive patch containing EE and levonorgestrel, and found that obese women in the "treatment-compliant" subgroup had a higher reported Pearl Index than nonobese women.

Metabolic Effects and Safety

Venous Thrombosis

[4] Women who use estrogen-containing hormonal contraceptives are at increased risk for venous thrombosis and thromboembolism. Normally the coagulation system maintains a dynamic balance of procoagulant and anticoagulant systems. Estrogens affect both systems in a dose-related fashion. For most women, fibrinolysis (anticoagulation) is increased as much as coagulation, maintaining the dynamic balance at increased levels of production and destruction of fibrinogen (Fig. 14-7) (142). Older studies included women with what are now considered contraindications to the use of estrogen-containing hormonal contraceptives: previous thrombosis, preexisting vascular disease, coronary artery disease, cancers, and serious trauma (142,143). Low-dose OCs have a less measurable effect on the coagulation system, and fibrinolytic factors increase at the same rate as procoagulant factors. **Lower estrogen–dose (30- to 35-lg *EE*) OCs reduce the risk of a thromboembolic event when compared with higher-**

dose (50-lg estrogen) OCs (144). A very large Danish study showed for the first time that combination OCs with 20 µg of *EE* have an 18% further reduction in thrombosis risk compared with 30- to 40-µg OCs after adjustment for duration of use (145). The progesterone-only OCs and the *levonorgestrel*-releasing IUD were not associated with venous thrombosis.

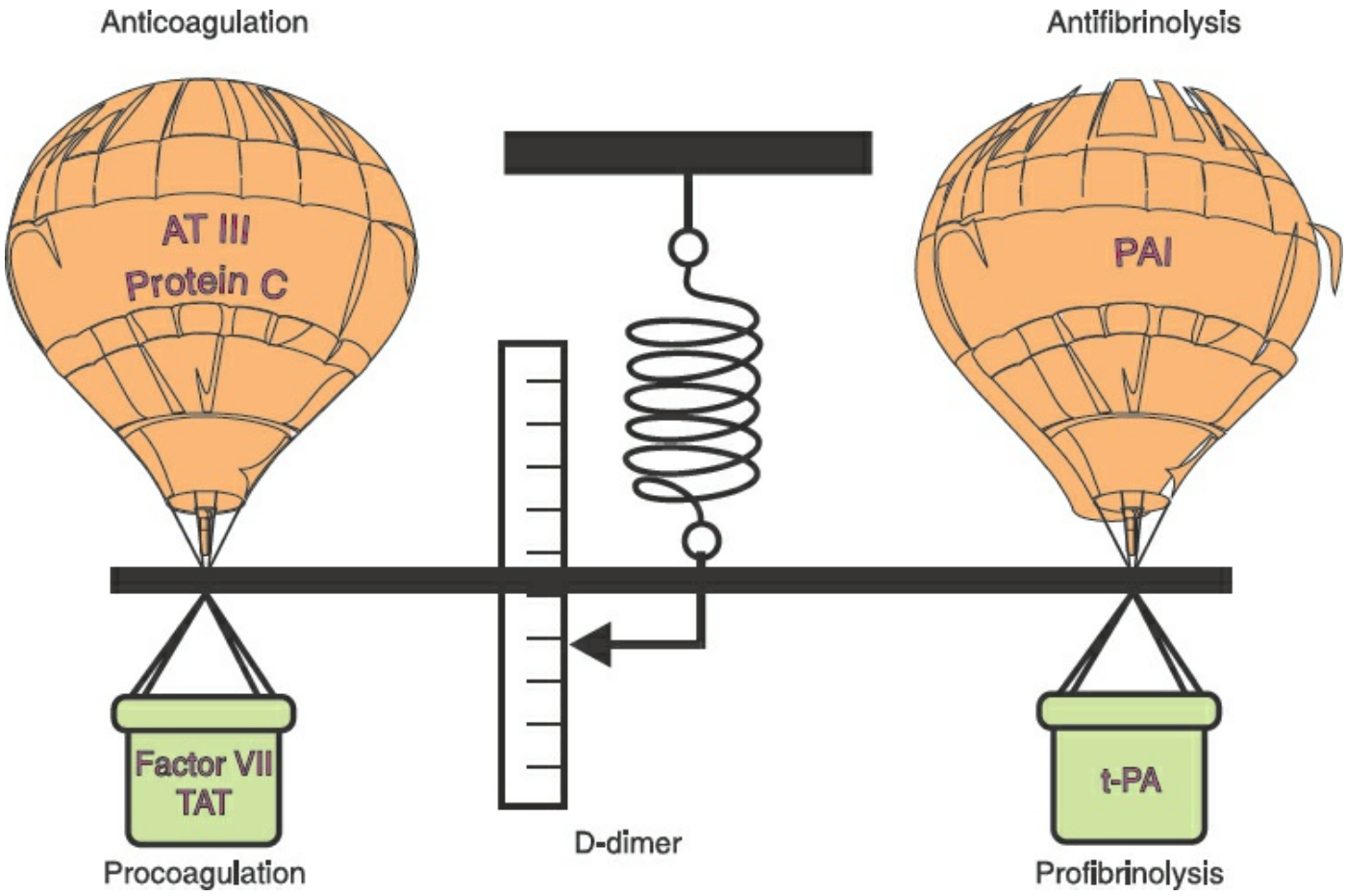


FIGURE 14-7 Dynamic balance of hemostasis. (From **Winkler UH, Buhler K, Schlinder AE**. The dynamic balance of hemostasis: implications for the risk of oral contraceptive use. In: Runnebaum B, Rabe T, Kissel L, eds. *Female Contraception and Male Fertility Regulation. Advances in Gynecological and Obstetric Research Series*. Oxfordshire, UK: CRC Press, 1991:85–92. Reproduced by permission of Taylor and Francis Group, LLC, a division of Informa plc.)

The absolute risk of deep vein thrombosis was strongly influenced by age, increasing from 1.84 per 10,000 women aged 15 to 19 years to 6.59 per 10,000 for women aged 45 to 49 years with current users, former users, and never users combined. With all types of OCs combined, the overall absolute rate of deep vein thrombosis was 6.29 per 10,000 woman-years for current OC users compared to 3.01 among nonusers, giving an adjusted rate ratio of 2.83 (95% CI, 2.65–3.01). This is a higher absolute risk than the 3 per 10,000 woman-years previously estimated and may reflect, among other things, the use of better means for diagnosis of deep vein thrombosis (145). This population-based study includes all Danish women aged 15 to 49 years, excluding only women with a

diagnosis of cancer or of cardiovascular disease diagnosed before the study interval. Thrombosis risk was highest during the first year of use and decreased thereafter.

Thrombophilia

Changes in the coagulation system are detectable in all women, including those taking lower-dose OCs; some women are genetically predisposed to thrombosis when challenged by pregnancy or administration of exogenous estrogen**. Women with inherited deficiencies of antithrombin III (ATIII), protein C, or protein S are at very high risk for thrombosis with pregnancy or estrogen therapy, but they make up a very small proportion of potential OC users.** A much more common variation, factor V Leiden exists in 3% to 5% of the Caucasian population. It codes for a one amino acid mutation in the factor V protein, inhibiting cleavage of the protein by activated protein C (APC), which is an essential step in maintaining the balance between coagulation and fibrinolysis (146). Risk for a first thromboembolic episode among women using OCs was 2.2 per 10,000 woman-years for women without the factor V mutation and 27.7 per 10,000 woman-years for women with the mutation (147). There are pronounced ethnic differences in the presence of this mutation. The Leiden allele is found in 3% to 5% of Caucasians but is rare in Africans, Asians, Amerindians, Eskimos, and Polynesians (148). A similar mutation is found in the prothrombin gene at position 20,210 and is described as prothrombin G20210A. This mutation occurs in 3% of the European population and is strongly associated with venous thrombosis in women taking OCs (149). Many more genetic conditions predisposing to thrombosis were described. Pregnancy is an even greater challenge for women with inherited defects of anticoagulation (150). A woman who sustains a venous event while using OCs should be evaluated thoroughly after she has recovered. Assessment should include at minimum the measurement of ATIII, protein C, and protein S levels, resistance to APC, serum homocysteine, factor V Leiden mutation, the prothrombin G20210A mutation and testing for antiphospholipid syndrome. It should not be assumed that hormonal contraception was the unique cause of the thrombotic episode.

Routine screening for all women before prescribing hormonal contraception is not justified because effective contraception would be denied to 5% of Caucasian women, and only a small number of fatal pulmonary emboli would be prevented (151,152). Screening women with a personal or family history of deep vein thrombosis before starting estrogen-containing hormonal contraception or pregnancy is strongly recommended. Women already diagnosed as having factor V Leiden should not receive estrogen-containing contraceptives, that is, the pill, patch, or ring.

Thrombosis and the New Progestins

Several studies found increased risk of venous thrombosis when users of OCs containing the newer progestins *desogestrel* or *gestodene* combined with 20 to 30 μg of *EE* were compared with users of *levonorgestrel* combined with the same doses of

estrogen (153,154). Subsequent studies showed mixed results. One study found no difference in thrombosis risk in users of OCs containing desogestrel or gestodene compared to users of OCs with other progestins in a large study of cases occurring between 2002 and 2006 in Austria (155). In 2013, a systematic review combining data from 26 studies (including the aforementioned ones) demonstrated that the RR of venous thrombosis for OCs containing 30 to 35 µg of EE and gestodene, desogestrel, cyproterone acetate or drospirenone were 50% to 80% higher than formulations containing levonorgestrel **(Fig. 14-8)**. However, this risk increase corresponds to approximately a difference of 3 cases per 10,000 women-years comparing second and third generation progestin users (in contrast to a VTE incidence of 20 cases per 10,000 in pregnancy) (156).

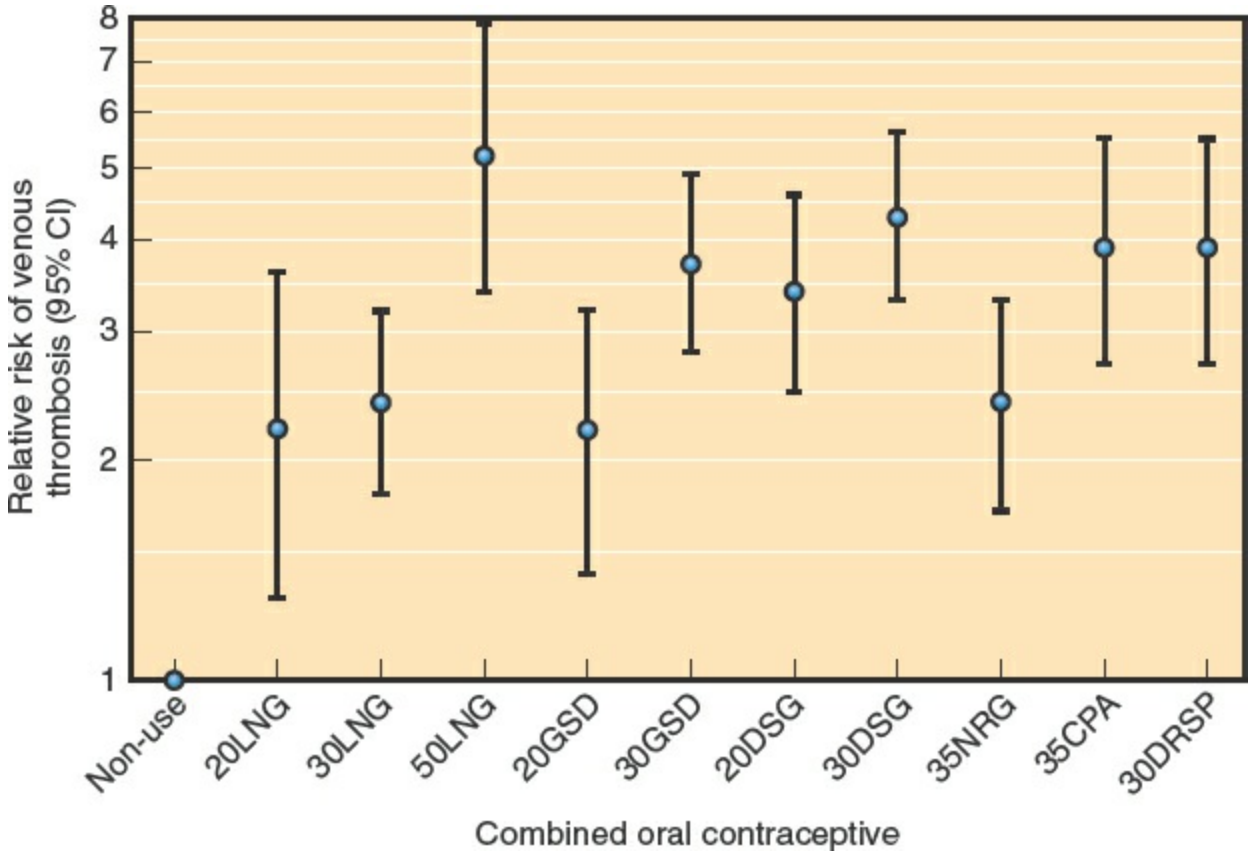


FIGURE 14-8 Network meta-analysis, per contraceptive plotted on a logarithmic scale. 20LNG, 20-µg ethinylestradiol with levonorgestrel; 30LNG, 30-µg ethinylestradiol with levonorgestrel; 50LNG, 50-µg ethinylestradiol with levonorgestrel; 20GSD, 20-µg ethinylestradiol with gestodene; 30GSD, 30-µg ethinylestradiol with gestodene; 20DSG, 20-µg ethinylestradiol with desogestrel; 30DSG, 30-µg ethinylestradiol with desogestrel; 35NRG, 35-µg ethinylestradiol with norgestimate; 35CPA, 35-µg ethinylestradiol with cyproterone acetate; 30DRSP, 30-µg ethinylestradiol with drospirenone; overall relative risk (95% confidence interval) of venous thrombosis (*dots* [*lines*]); non-use, reference group.

Ischemic Heart Disease

Ischemic heart disease and stroke were the major causes of death attributed to OC use in the past. It is known that the principal determinants of risk are advancing age and

cigarette smoking (157). **With higher-dose OCs used in the 1980s, smoking had a profound effect on risk. Women smoking 25 or more cigarettes per day had a 30-fold increased risk for myocardial infarction if they used OCs, compared with nonsmokers not using OCs** (158). **The use of OCs became safer because most women are taking low-dose pills and because physicians prescribe selectively, excluding women with major cardiovascular risk factors.** A very large study in the United States confirmed the safety of OCs as currently prescribed. A total of 187 women aged 15 to 44 years with confirmed myocardial infarction were identified during 3.6 million woman-years of observation in the Kaiser Permanente Medical Care Program in California from 1991 to 1994. This is a rate of 3.2 per 100,000 woman-years (159). Nearly all of the users took OCs with less than 50 µg of *EE.* After adjusting for age, illness, smoking, ethnicity, and body mass index, risk for myocardial infarction was not increased by OC use (OR, 1.14; 95% CI, 0.27–4.72). Of heart attack victims, 61% smoked; only 7.7% were current users of OCs. In a later study, the same investigators pooled results from the California study with a similar study from the Washington State. The results were the same. **[5] Current users of low-dose OCs had no increased risk for myocardial infarction after adjustment for major risk factors and sociodemographic factors** (160). Past use of OCs does not increase risk for subsequent myocardial infarction (161). These observations are supported by another population-based prospective study. OC use and myocardial infarction were studied prospectively among 48,321 randomly selected women aged 30 to 49 years in the Uppsala Health Care Region of Sweden (162). There was no association between current or past OC use and myocardial infarction. Most current users were taking low-dose estrogen pills (defined as less than 50 µg of EE or less than 75 µg of *mestranol*) with second or third generation progestins, more than half were aged 35 or older, and 26% were current cigarette smokers.

Oral Contraceptives and Stroke

In the 1970s, OC use appeared to be linked to the risk of hemorrhagic and thrombotic stroke, but these studies failed to take into consideration preexisting risk factors (163). A rare form of cerebrovascular insufficiency, the moyamoya disease, is linked to OC use, especially among cigarette smokers (164). **The evidence shows no risk of stroke among women who are otherwise healthy and who use low-dose pills.** One study identified all Kaiser Permanente Medical Care Program patients aged 15 to 44 years who sustained fatal or nonfatal stroke in California from 1991 to 1994 (165). Hypertension, diabetes, obesity, current cigarette smoking, and black ethnicity were strongly associated with stroke risk, but neither current nor past OC use was associated with stroke. A WHO study of cases from 1989 to 1993 from 17 countries in Europe and the developing world included women taking higher-dose OCs and low-dose OCs. European women using low-dose OCs had no increased risk for either type of stroke,

thrombotic or hemorrhagic. Those taking higher-dose OCs did have measurable risk (166,167). Women in developing countries had an apparent modest increase in risk, but this finding was attributed to undetected existing risk factors. Another study from Europe found less stroke risk from low-dose pills than from older, higher-dose pills, and that the risk was less if the patient's blood pressure was checked before starting OCs.

Women who smoke and those who have hypertension and diabetes are at increased risk for cardiovascular disease regardless of whether they use OCs. The important question is whether the risk is further increased if they use low-dose OCs, and if so, by how much. The WHO study provides some insight: smokers taking OCs had seven times the risk of ischemic (thrombotic) stroke when compared with smokers who did not use OCs, and hypertensive women had 10-fold increased risk if they took OCs, but a fivefold risk if they did not (166). Similarly, a study from Denmark found that women with diabetes had a fivefold increase risk for stroke, which increased to 10-fold if they took OCs (168). These data were not limited to low-estrogen OCs. The data suggest that although the risk is primarily determined by the predisposing condition—hypertension, diabetes, or cigarette smoking—the risk can be magnified by OC use, even when the OCs are low dose. These observations were confirmed in a systematic review (169). Hypertensive women using combination estrogen– progestin oral contraceptives (COCs) had higher risk for ischemic stroke and acute myocardial infarction than hypertensive women not using COCs. The US practice of limiting hormonal contraceptives containing estrogen by women older than 35 years of age to nonsmokers without other vascular disease risk factors is prudent (7).

Blood Pressure

OCs have a dose-related effect on blood pressure. With the older high-dose pills, as many as 5% of patients could be expected to have blood pressure levels greater than 140/90 mm Hg. The mechanism is believed to be an estrogen-induced increase in renin substrate in susceptible individuals. **Low-dose pills have minimal blood pressure effects,** but surveillance of blood pressure is advised to detect the occasional idiosyncratic response.

Glucose Metabolism

Oral estrogen alone has no adverse effect on glucose metabolism, but progestins exhibit insulin antagonism (170). Older OC formulations with higher doses of progestins produced abnormal glucose tolerance tests with elevated insulin levels in the average patient. The effect on glucose metabolism, similar to the effect on lipids, is related to androgenic potency of the progestin and to its dose.

Lipid Metabolism

Androgens and estrogens have competing effects on hepatic lipase, a liver enzyme

critical to lipid metabolism. **Estrogens depress low-density lipoproteins (LDL) and elevate high-density lipoproteins (HDL), changes that can be expected to reduce the risk of atherosclerosis** (171). Androgens and androgenic progestins can antagonize these beneficial changes, reducing HDL and elevating LDL levels. Estrogens elevate triglyceride levels. Low-dose formulations have minimal adverse effect on lipids, and the newer formulations (with *desogestrel* and *norgestimate* as the progestin) produce potentially beneficial changes by elevating HDL and lowering LDL (172,173). Although average values of a large group show only small lipid changes with the use of current OCs, an occasional patient may have exaggerated effects. Women whose lipid values are higher than the mean before treatment are more likely to experience abnormalities during treatment (172).

Other Metabolic Effects

OCs can produce changes in a broad variety of proteins synthesized by the liver. The estrogen in OCs increases circulating thyroid-binding globulin, thereby affecting tests of thyroid function that are based on binding, increasing total thyroxine (T_4) levels, and decreasing triiodothyronine (T_3) resin uptake. The results of actual thyroid function tests, as measured by free T_4 and radioiodine tests, are normal (174).

Oral Contraceptives and Neoplasia

Endometrial and Ovarian Cancers

Combination OCs reduce the risk of subsequent endometrial cancer and ovarian cancer (175,176). **[8] Two-year use of OCs reduces the risk of endometrial cancer by 40%, and 4 or more years of use reduces the risk by 60%. The evidence for this benefit continues to accumulate** (177). **[8] A 50% reduction in ovarian cancer risk for women who took OCs for 3 to 4 years and an 80% reduction with 10 or more years of use were reported** (178). There was some benefit from as little as 3 to 11 months of use. **A review of all available studies in the world published in English through 2008 concluded that ovarian cancer risk decreased by 20% for each 4 years of use and was seen for carriers of the BRCA1 and BRCA2 mutations as well. The benefit persisted for at least 30 years after last use** (179). A similar reduction of risk of ovarian epithelial cancer was found in a prospective study from Norway and Sweden, with borderline tumor risk equally reduced. Combination OCs with less than 50 µg of *EE,* or less than 100 µg of mestranol and reduced doses of progestin, provided as much protection as higher-dose pills (180). Today's lower-dose 20-µg *EE* pills were not separately studied. Whether or not they provide the same benefit remains unproven; however, progestin-only contraceptives are reported to provide risk reduction equivalent to that of combined OCs (181).

Colorectal Cancer

There is evidence that OC use is protective against colon cancer. A case-control study in Italy comparing women with colon cancer with controls found a 37% reduction in colon cancer and a 34% reduction in rectal cancer (colon cancer OR, 0.63; 95% CI, 0.45–0.87 and rectal cancer OR, 0.66; 95% CI, 0.43–1.01). Longer use produced more protection against colon cancer (182). Results of the US Nurses' Health Study disclosed some degree of protection. Women who used OCs for 96 months or more had a 40% lower risk of colorectal cancer (RR, 0.60; 95% CI, 1.15–2.14) (183). A large case-control study from Wisconsin found most of the benefit limited to women who were less than 14 years since discontinuing OCs (184). The mechanism of protection has not been identified. A long-term study that prospectively evaluated women for up to 44 years detected ever use of OCs was associated with reduced colorectal cancer (IRR, 0.81; 99% CI, 0.66–0.99) (185).

Cervical Cancer

There may be a weak association between OC use and cancer of the cervix. A systematic review of 28 epidemiologic studies of cervical cancer in OC users compared with those who never used OCs reported summary RRs of 1.1 (95% CI, 1.1–1.2) at less than 5 years of pill use, 1.6 (1.4–1.7) at 5 to 9 years, and 2.2 (1.9–2.4) at 10 or more years (186). A 2007 update by these same authors reported a pooled RR for all studies of 1.9 (95% CI, 1.69–2.13) for invasive cervical cancer or CIN3/carcinoma in situ (CIS) with 5 or more years of OC use. The risk declined after use ceased and by 10 years returned to that of never users (187). In a study that observed women for up to 44 years, an increased risk of cervical cancer that was seen in current and recent users appeared to be lost within 5 years of stopping oral contraception with no evidence of increased risk in ever users with time (185). Critics of these studies argued that causation is not proven because few adequately control for the key behavioral factors of partners, use of barrier contraception, and adequacy of cervical cancer screening (188). Important risk factors for cervical cancer are early sexual intercourse and exposure to HPV. Women who used OCs typically started sexual relations at younger ages than women who have not used OCs and, in some studies, report having had more partners. These factors increase one's chance of acquiring HPV, the most important risk factor for cervical cancer. Because barrier contraceptives reduce the risk of cervical cancer, the use of alternative choices for contraception compounds the difficulty in establishing an association with OC use alone (189). The presence of HPV types 16 or 18 is associated with a 50-fold increase in risk for precancerous lesions of the cervix (190). Adenocarcinomas of the cervix are rare, they are not as easily detected as other lesions by screening cervical cytology, and the incidence appears to be increasing. One study found a doubling of risk for adenocarcinoma with OC use that increased with the duration of use, reaching an RR of 4.4 if the total use of OCs exceeded 12 years (191). The results of this study were adjusted for history of genital warts, number of sexual

partners, and age at first intercourse. Another summary of case-control studies includes testing for HPV. HPV types 16 or 18 were present in 82% of the patients, yielding an RR of 81.3 (95% CI, 42.0–157.1) for the disease. Cofactors identified with adenocarcinoma included longer-term use of hormonal contraception. The use of hormonal contraception by women aged 20 to 30 years is estimated to increase the incidence of cervical cancer (any cervical cancer, or CIN3/CIS) diagnosed by age 50 from 7.3 to 8.3 per 1,000 women in lesser-developed countries and from 3.8 to 4.5 in developed countries (192). The use of OCs is, at most, a minor factor in causation of cervical cancer; these findings emphasize the need to immunize against HPV and to provide cervical cancer screening worldwide. To reduce the risk, women who are not in mutually monogamous relationships should be advised to use barrier methods in addition to hormonal contraception. A meta-analysis demonstrated that invasive cervical cancer may be approximately one-third less frequent in women who have used an IUD (193).

Breast Cancer

There is a large volume of conflicting literature on the relationship between OC use and breast cancer (194). No increase in overall risk is found from OC use, but some studies found that risk may increase in women who used OCs before their first term pregnancy, used OCs for many years, are nulligravid, are young at the time of diagnosis, or continue using OCs in their 40s. **[6]** A meta-analysis of 54 studies of breast cancer and hormonal contraceptive use reanalyzed data on 53,297 women with breast cancer and 100,239 controls from 25 countries, representing about 90% of the epidemiologic data available worldwide (195). Current use of OCs was associated with a very small, but statistically stable 24% increased RR (1.24; 95% CI, 1.15–1.33). The risk fell rapidly after discontinuation, to 16% 1 to 4 years after stopping and to 7% 5 to 9 years after stopping. Risk disappeared 10 years after cessation (RR, 1.01; 95% CI, 0.96–1.05). Results did not differ in any important way by ethnic group, reproductive history, or family history. Since the meta-analysis was published, subsequent studies found no increased risk. A case-control study of 4,575 women with breast cancer and 4,682 controls aged 35 to 64 years living in five cities in the United States concluded that breast cancer risk was not increased for current or past users of OCs and did not increase with prolonged or with higher-estrogen OC use (196). Neither family history of breast cancer nor beginning use at a young age was associated with increased risk. A similar study in Sweden compared 3,016 women aged 50 to 74 years who had invasive breast cancer with 3,263 controls of the same age. **[6]** No relation was found between the past use of OCs and breast cancer (197). Effect of hormone dose was explored in a 2008 US study of 1,469 women with breast cancer who were matched by race, age, and neighborhood to community controls. The investigators administered questionnaires and performed BRCA1 and BRCA2 testing. Subjects who

began OC use during or after 1975 were considered to have used low-dose pills. "Low dose" was not further defined. Neither OC use overall or "low-dose" OC use was associated with breast cancer risk, among the total group, or within any subset. Women with BRCA1 or BRCA2 did not have higher rates of cancer whether they were OC users or nonusers (198). **[6]** A prospective cohort study evaluating very–long-term risks or benefits associated with the use of combined OCs found an increased breast cancer risk in current and recent users that appeared to be lost within 5 years of stopping (185). **The controversy over the association between breast cancer and OC use is likely to continue. While concerns about a connection continue to circulate, the benefits of OC use, particularly protection against pregnancy and the other noncontraceptive benefits, outweigh the risks for the vast majority of women.**

Liver Tumors

OCs were implicated as a cause of benign adenomas of the liver. These hormonally responsive tumors can cause fatal hemorrhage. They usually regress when OC use is discontinued; the risk is related to prolonged use (199). The tumors are rare; about 30 cases per 1 million users per year were predicted with older formulations. Presumably, newer low-dose products pose less risk. A link to hepatic carcinoma was proposed. This cancer is closely associated with chronic hepatitis B and C infections and is usually seen in cirrhotic livers. There are case reports of hepatocellular carcinoma in young women with no risk factors other than long-term OC use (200). A large study from six countries in Europe found no association between the use of OCs and subsequent liver cancer (201). A systematic review looked for evidence of harm associated with hormonal contraceptive use among women already at risk because of liver disease (202). The authors concluded from the limited data available that OCs do not affect the course of acute hepatitis or chronic hepatitis, and do not affect the rate of progression or the severity of cirrhotic fibrosis, the risk of hepatocellular carcinoma in women with chronic hepatitis, or the risk of liver dysfunction in hepatitis B virus carriers.

Oral Contraceptives and Sexually Transmitted Infections

Chlamydial colonization of the cervix appears more likely in OC users than in nonusers but, despite this finding, several case-control studies found a reduced risk of acute PID among OC users (203,204). In contrast, a subsequent study found no protection with OC use (205). Whether hormonal contraceptives influence acquisition of HIV remains under debate. A recent systematic review increased concern about a potential causal association between DMPA use and HIV acquisition with hazard ratio (HR) estimated at 1.5 or less (206). In response to these findings, the WHO convened and updated recommendations for the use of progestogen-only injectables from category 1 to category 2. Women should not be denied the use of progestogen-only injectables but should be advised about the uncertainty over a causal relationship. There remains no

suspected increased risk of HIV acquisition with use of OCs or contraceptive implants.

Health Benefits of Oral Contraceptives

OCs have important health benefits (Table 14-3). These include contraceptive and noncontraceptive benefits.

Contraceptive Benefits

OCs provide highly effective contraception and prevent unwanted pregnancy, an important public health problem. Combination and progestin-only contraceptives decrease the risk of pregnancy and therefore, decrease the risk of ectopic pregnancy. Studies have reported an increased proportion of pregnancies that are ectopic, in women who became pregnant while using progestin-only implants, IUDs, and OCs (207). A systematic review of progestin-only injectables and implants reported higher proportions of ectopic pregnancies in the event that pregnancy occurs; however, the review confirmed that the absolute risk of ectopic pregnancy is lower for women using these methods compared with noncontraceptive users (208). Furthermore, the clinical and epidemiologic evidence indicated that LNG-containing implants are more likely to result in an ectopic pregnancy (or any pregnancy) than the etonogestrel implant or progestin-only injectables.

Noncontraceptive Benefits

OC use produces strong and lasting reduced risk for endometrial and ovarian cancer. In addition, protection was found for women with known hereditary ovarian cancer. The use of OCs in BRCA mutation carriers was associated with a significantly reduced risk of ovarian cancer (SRR, 0.50; 95% CI, 0.33–0.75) (209). Protection increased with longer duration of use. The exact mechanisms of action of OCs in the prevention of ovarian cancer is unknown, but one leading mechanism stems from the "incessant ovulation" theory, according to which chronic ovulation contributes to ovarian cancer by causing repeated trauma of the ovarian surface epithelium (210). Therefore, OCs may decrease the risk of ovarian cancer by suppressing ovulation.

Table 14-3 Established and Emerging Noncontraceptive Benefits of Oral Contraceptives

Established Benefits
Menses-related
Increased menstrual cycle regularity
Reduced blood loss
Reduced iron-deficiency anemia
Reduced dysmenorrhea

Reduced symptoms of premenstrual dysphoric disorder[a]
Inhibition of Ovulation
Fewer ovarian cysts
Fewer ectopic pregnancies
Other
Reduced fibroadenomas/fibrocystic breast changes
Reduced acute pelvic inflammatory disease
Reduced endometrial cancer
Reduced ovarian cancer
Emerging Benefits
Increased bone mass
Reduced acne
Reduced colorectal cancer
Reduced uterine leiomyomata
Reduced rheumatoid arthritis
Treatment of bleeding disorders
Treatment of hyperandrogenic anovulation
Treatment of endometriosis
Treatment of perimenopausal changes

[a]Only the low-dose *EE/droperidol* oral contraceptive has U.S. Food and Drug Administration approval for premenstrual dysphoric disorder treatment.

From **Burkman R, Schlesselman JJ, Zieman M.** Safety concerns and health benefits associated with oral contraception. *Am J Obstet Gynecol* 2004;190(Suppl):S12, with permission.

Other documented benefits of OC use include reduction of benign breast disease (211). The use of OCs helps relieve dysmenorrhea (212). OCs offer effective therapy for women with menorrhagia and dysfunctional uterine bleeding.

All combination OCs offer some protection from functional ovarian cysts, but this is dose related (213). Although OCs may prevent cyst formation, they are not helpful in treating large functional ovarian cysts and should not be used for this purpose (214).

All combination OCs reduce circulating androgen levels and usually improve acne. Three OCs were specifically FDA approved for acne treatment: the *norgestimate/EE triphasic* (*Ortho Tri-Cyclen*), the *norethindrone/EE multiphasic*

(*Estrostep*), and the 20-µg *EE*/3-mg drospirenone OC.

Fertility After Oral Contraceptive Use

After discontinuing OCs, the return of ovulatory cycles may be delayed for a few months. Women who have amenorrhea more than 6 months after discontinuation of OCs should undergo a full evaluation because of the risk for prolactin-producing pituitary tumors. This risk is not related to OC use but rather to the probability that the slow-growing tumor was already present and produced menstrual irregularity, prompting the patient to take OCs (215).

Sexuality

There is limited literature focusing on the topic of sexual function among OC users. A 2003 Spanish study demonstrated that in a comparative cohort of women using OCs and a cohort using IUDs, sexual desire decreased over time, but was not affected by the contraceptive method (216). OCs containing the new progestin *drospirenone* are reported to improve sexual functioning and feelings of well-being (217,218).

Teratogenicity

A meta-analysis of 12 prospective studies, including 6,102 women who used OCs and 85,167 women who did not, revealed no increase in the overall risk for malformation, congenital heart defects, or limb reduction defects with the use of OCs (219). Progestins were used to prevent miscarriage. A large study compared women showing signs of threatened abortion who were treated with progestins (primarily oral *medroxyprogesterone acetate*) with women who were not treated. The rate of malformation was the same among the 1,146 exposed infants as among the 1,608 unexposed infants (220). Conversely, exposure *in utero* to diethylstilbestrol, a nonsteroidal estrogen, can induce clear cell vaginal cancer and congenital anomalies of the reproductive tract in the female offspring (221). A literature search revealed no recent reports linking teratogenicity to hormonal contraception.

Interaction of Oral Contraceptives With Other Drugs

Some drugs (e.g., *rifampin*) reduce the effectiveness of OCs; conversely, OCs can augment or reduce the effectiveness of other drugs (e.g., *benzodiazepines*) (222,223). **Perhaps of greatest clinical significance are six antiepileptic drugs: *phenytoin, phenobarbital, carbamazepine, oxcarbazepine, felbamate,* and *topiramate*** (224). These drugs and the antibiotic *rifampin* all induce synthesis of liver cytochrome P450 enzymes and reduce plasma levels of *EE* in women taking OCs, increasing the likelihood of contraceptive failure. Some antiseizure agents have no effect on the levels of contraceptive steroids in the blood. These include *valproic acid, vigabatrin, lamotrigine, gabapentin, tiagabine, levetiracetam, zonisamide, ethosuximide,* and *benzodiazepines* (224). *St. John's wort* induces cytochrome P450

and is reported to increase clearance of *EE* and *norethindrone* (225). The antifungal agents *griseofulvin, ketoconazole,* and *itraconazole* induce these hepatic enzymes and may reduce OC efficacy (225). *Ampicillin* and *tetracycline* were implicated in numerous case reports of OC failure. They kill gut bacteria (primarily clostridia) that are responsible for hydrolysis of steroid glucuronides in the intestine, which allows reabsorption of the steroid through enterohepatic circulation. It was not possible to demonstrate reduced plasma levels of *EE* overall or differences in pregnancy rates (226). Certain drugs, such as protease inhibitor *atazanavir*, appear to increase plasma levels of contraceptive steroids but the clinical significance of such an interaction is unclear (227).

An example of OCs affecting the metabolism of other drugs is seen with *diazepam* and related compounds. OC use reduces the metabolic clearance and increases the half-life of those *benzodiazepines* that are metabolized primarily by oxidation: *chlordiazepoxide, alprazolam, diazepam,* and *nitrazepam. Caffeine* and *theophylline* are metabolized in the liver by two of the P450 isozymes, and their clearance is reduced in OC users. *Cyclosporine* is hydroxylated by another of the P450 isozymes, and its plasma concentrations are increased by OCs. Plasma levels of some analgesic drugs are decreased in OC users. *Salicylic acid* and *morphine* clearances are enhanced by OC use; therefore, higher doses could be needed for adequate therapeutic effect. Clearance of *ethanol* may be reduced in OC users.

The interactions of antiretroviral drugs with contraceptive steroids are complex. Some of the drugs increase plasma steroid levels and some reduce them. A complete list of interactions is available in the Centers for Disease Control and Prevention's "U.S. Medical Eligibility for Contraception" (7).

Oral Contraceptives and Clinical Chemistry Alterations

OCs have the potential to alter a number of clinical laboratory tests as a result of estrogen-induced changes in hepatic synthesis; however, a large study comparing OC users with pregnant and nonpregnant controls found minimal changes (228). Hormone users took a variety of OCs containing 50 to 100 µg of estrogen, higher doses than are used today. Compared with nonpregnant women who were not using OCs, the OC users had an increase in T_4 that is explained by increased circulating thyroid-binding protein, no change in creatinine and globulin levels, slight reduction in mean fasting glucose values and serum glutamic oxaloacetic transaminase, and a decrease in total bilirubin and alkaline phosphatase.

Choice of Oral Contraceptives

More recently introduced OCs include those containing *drospirenone,* more preparations with only 20 µg of *EE,* new multiphasic preparations, cyclic OCs with 24 days of active medication and 4 days of either placebo or 10 µg of *EE,* and extended-

cycle and continuous-cycle preparations plus branded generic versions of most OCs. A combination OC containing *estradiol valerate* with a new progestin, *dienogest,* was approved in 2010. There is new evidence that 20-µg *EE* pills offer reduced risk for venous thrombosis (145). An approach to OC selection for new patients is to begin with a 20-µg *EE* combination and then adjust depending on the patient's symptoms after the first 2 to 3 months. As reported in a large systematic review of 20-µg *EE* OCs compared to 30- to 35-µg *EE* pills, women taking the lower-dose OCs more often report changes in vaginal bleeding, episodes of irregular bleeding and heavy bleeding, and more amenorrhea (229). If a 20-µg pill is offered, the patient should understand that bleeding may be a problem and that she should return if this persists and try a different OC rather than stop the pill. The progestin component may become more important in determining cycle control when 20-µg *EE* is used. A comparison of 20-µg *EE* OCs, one containing 100 µg of *levonorgestrel,* the other with 1 mg of *norethindrone acetate* (*NEA*) found the *NEA* to have about twice as many days of unscheduled vaginal bleeding during the first 3 months, a critical time period for new users, which might be expected to lead to discontinuation (230). In a three-way trial, the 35-µg *EE*/*norgestimate* triphasic OC (*Tri-Cyclen*) was compared with two 20-µg *EE* pills, one containing 100 µg of *levonorgestrel* (*Alesse*), the other containing 150-µg *desogestrel,* followed by 2 hormone-free days and 5 days of 10-µg *EE* per day (*Mircette*) (231). Contraceptive efficacy was not significantly different. In the first two-pill cycles, more women taking *Alesse* had breakthrough bleeding and bleeding in the second half of the cycle than those taking the other two OCs in the first two cycles, but thereafter there was little difference. Women taking the higher-estrogen *Tri-Cyclen* consistently experienced more frequent estrogenic side effects—bloating, breast tenderness, and nausea—than did women taking either 20-µg *EE* OC. These authors concluded that for the specific OCs evaluated, changing to either one of the 20-µg preparations would be beneficial.

For the average patient, the first choice of preparation for contraceptive purposes is a very low estrogen OC (20-lg *EE*) unless there are other considerations, for example, previous pregnancy while taking the pill. Patients with persistent breakthrough spotting or bleeding could be offered a pill with the same low estrogen dose, but a more potent progestin, for example *levonorgestrel.* Patients with apparent weight gain from fluid retention while taking OCs, or with hirsutism or acne that did not respond to other OCs, may benefit from a change to the *drospirenone/EE* pill. The lower-*estrogen drospirenone* combination is FDA approved for treatment of PMDD and should be considered for women with these symptoms who want hormonal contraception. **Women with acne often benefit from the reduction in circulating testosterone that occurs with all combination OCs. Women who experience continuing pelvic pain, dysmenorrhea, or other menstrual-triggered symptoms or who simply prefer fewer menstruations may be offered an extended-**

cycle or continuous-cycle OC regimen.

Alternative Routes for Hormonal Contraception

The *Ortho Evra* patch and the *NuvaRing* provide combinations of ultrapotent progestins with *EE.* Both patch and ring provide almost constant low levels of the contraceptive steroids that are less than the peak levels seen with OCs. Both offer greater convenience to the user, which improves compliance. The patch has a surface area of 20 cm^2. It delivers a daily dose of 150-µg *norelgestromin,* the active metabolite of norgestimate, and 20 µg of *EE.* The patch is worn for 1 week then replaced with a new patch for 7 days, continuing for 3 consecutive weeks followed by a week with no patch. The patch was compared with a multiphasic OC containing *levonorgestrel* 50 to 125 µg, and 30- to 40-µg *EE* (*Triphasil*) in a randomized trial of 1,417 women (137). The overall and method failure Pearl indices were 1.24 and 0.99 pregnancies per 100 woman-years in the patch group and 2.18 and 1.23 in the OC group, respectively, numerically less in the patch group but not statistically significant. Patch users had more breakthrough bleeding or spotting in the first two cycles, but thereafter this did not differ from OC users. Patch users reported more breast discomfort, dysmenorrhea, and abdominal pain than the OC users, but other adverse events were uncommon and did not differ. Perfect compliance was reported for 88.2% of patch users' cycles versus 77.7% of the pill users' cycles (p <0.001). Pregnancy risk with the patch appears to be higher for women weighing more than 90 kg.

The *NuvaRing* is 54 mm in the outer diameter and has a cross section of 4 mm. It delivers daily doses of 120 µg of *etonogestrel,* the active metabolite of *desogestrel,* with 15 µg of *EE,* and thus is the lowest estrogen combination hormonal method available in the United States. The soft, flexible ring is worn in the vagina for 3 weeks, and then removed for 1 week, after which time a new ring is inserted. Alternatively, similar to OCs, women trying to avoid menstrual bleeding can simply use the ring for an entire month and then change immediately to a new ring. In a pharmacokinetic study comparing the ring with a combination OC containing 150 µg of *desogestrel* and 30 µg of *EE,* maximum blood levels of *EE* with the ring were about one-third of those seen with the OC, and the *etonogestrel* level was about 40% of that produced by the OC. Despite these findings, ovulation was inhibited in all women studied (232). Women wearing the ring are reported to have fewer days of irregular bleeding or spotting than women taking an OC with 150 µg of *levonorgestrel* and 30 µg of *EE* (233). A large study found a Pearl Index of 1.18 (95% CI, 0.73–1.80) for the vaginal ring (233). Some women prefer to remove the ring for intercourse, although this is not necessary. It should be reinserted within 3 hours to avoid loss of efficacy. If the ring is out of the vagina for more than 3 consecutive hours, contraceptive efficacy may be reduced and a barrier method should be used for 7 days.

Patch and Ring and Thrombosis

Since both methods provide constant low blood levels of *EE,* it was hoped that this might reduce the risk for thrombosis. The FDA took the unusual step of issuing a "black box warning" for the *EE/norelgestromin* patch after several thrombosis cases were reported, and a small study of pharmacodynamics was interpreted as showing higher mean *EE* blood levels for the patch than with the oral route of administration. A small crossover study found increased APC resistance when women were changed from a 30-µg *EE*/150-µg *desogestrel* pill to either the patch or the *EE/etonogestrel* ring. This was interpreted as prothrombotic (234). In another study, women on a variety of OCs had baseline measurement of APC resistance, and protein S. Then the patients were switched to either the patch or the ring. Those moving to the patch had changes in laboratory parameters that could be interpreted as prothrombotic, while those moved to the ring showed an improvement in the same studies, theoretically reducing the risk of clotting (235). Three data-based epidemiologic studies looked at thrombosis in patch users compared to oral contraception. The first found no difference, but two subsequent studies did find increased risk. One study found an overall doubling of the risk of deep vein thrombosis when patch users were compared to users of an OC containing 30-µg *EE*/150-µg *levonorgestrel,* but the risk estimate was of borderline statistical significance and disappeared when the analysis was restricted to women aged 39 years or less (236). Following the publication of these studies, the FDA convened in December 2011 to discuss the possibly increased risk of blood clots in users of Ortho Evra compared to women who use certain birth control pills. The Joint Advisory Committee recommended that Ortho Evra remain in the market as an option for contraception but that the label be revised to more clearly describe the risks and benefits associated with *Ortho Evra* (237).

No similar FDA warnings were issued about the ring. There are two case reports in the world literature of venous thrombosis with the ring. Both were women in their 30s who sustained cerebral venous thrombosis (238,239). It is best to assume that the ring has the same risk for thrombosis as the other combination hormonal contraceptives and to counsel women about risk in the same way.

Future of the Vaginal Ring

The Population Council has developed a one-year contraceptive vaginal ring that releases 150-mcg *Nestorone*, a nonandrogenic progestin that is inactive orally, and 15-mcg *EE* daily. It can be worn for 3 weeks, removed for 1 week, and then reinserted for up to 13 cycles (240). Refrigeration is unnecessary, and this method may be especially advantageous for women in low resource settings where access to a pharmacy and electricity are unreliable. The Population Council will submit a New Drug Application (NDA) to the U.S. FDA and pursue regulatory approval in low- and middle-income countries.

Injectable Hormonal Contraceptives

Depot Medroxyprogesterone Acetate

DMPA, a suspension of microcrystals of a synthetic progestin, was approved for contraception in 1992. A single 150-mg intramuscular dose will suppress ovulation in most women for 14 weeks or longer (241). **[7]** The regimen of 150 mg every 3 months is highly effective, producing pregnancy rates of about 0.3 per 100 women per year. Probably because of the high blood levels of the progestin, efficacy appears not to be reduced by administration of other drugs and is not dependent on the patient's weight. Women treated with *DMPA* experience disruption of the menstrual cycle and have initial spotting and bleeding at irregular intervals. Eventually, total amenorrhea develops in most women who take *DMPA;* with continued administration, amenorrhea develops in 50% of women by 1 year and in 80% by 3 years **(Fig. 14-9)**.

The most important medical reason women discontinue the use of *DMPA* and other progestin-only methods is persistent irregular vaginal bleeding. A variety of medications are used to stop this bleeding. Many are effective in terminating individual bleeding episodes, but a systematic review concluded that none improved continuation rates long term (242). New approaches include *mifepristone* and low-dose *doxycycline. Mifepristone* is of interest because irregular bleeding with *DMPA* was related to the downregulation of endometrial estrogen receptors. Treatment with 50 mg of *mifepristone* every 2 weeks increases endometrial estrogen receptors and reduces breakthrough bleeding in new users of both *DMPA* and the *levonorgestrel* progestin implant (243). Another line of investigation concerns endometrial matrix metalloproteinase, which appears to play a regulatory role in the breakdown of the endometrium to produce normal menstruation. Treatment with *doxycycline* inhibits matrix metalloproteinase production in the endometrium in women after insertion of *levonorgestrel* subdermal implants (244). Five-day courses of either *mifepristone* 25 mg twice a day for 1 day, followed by *EE* 20 μg per day for 4 days, or *doxycycline* 20 mg twice a day for 5 days, reduced bleeding days by about 50% when compared to placebos during a 6-month randomized trial in women treated for prolonged or frequent bleeding occurring with etonogestrel subdermal implants (245). Capsules of 20-mg *doxycycline* are sold in the United States for treatment of periodontal disease.

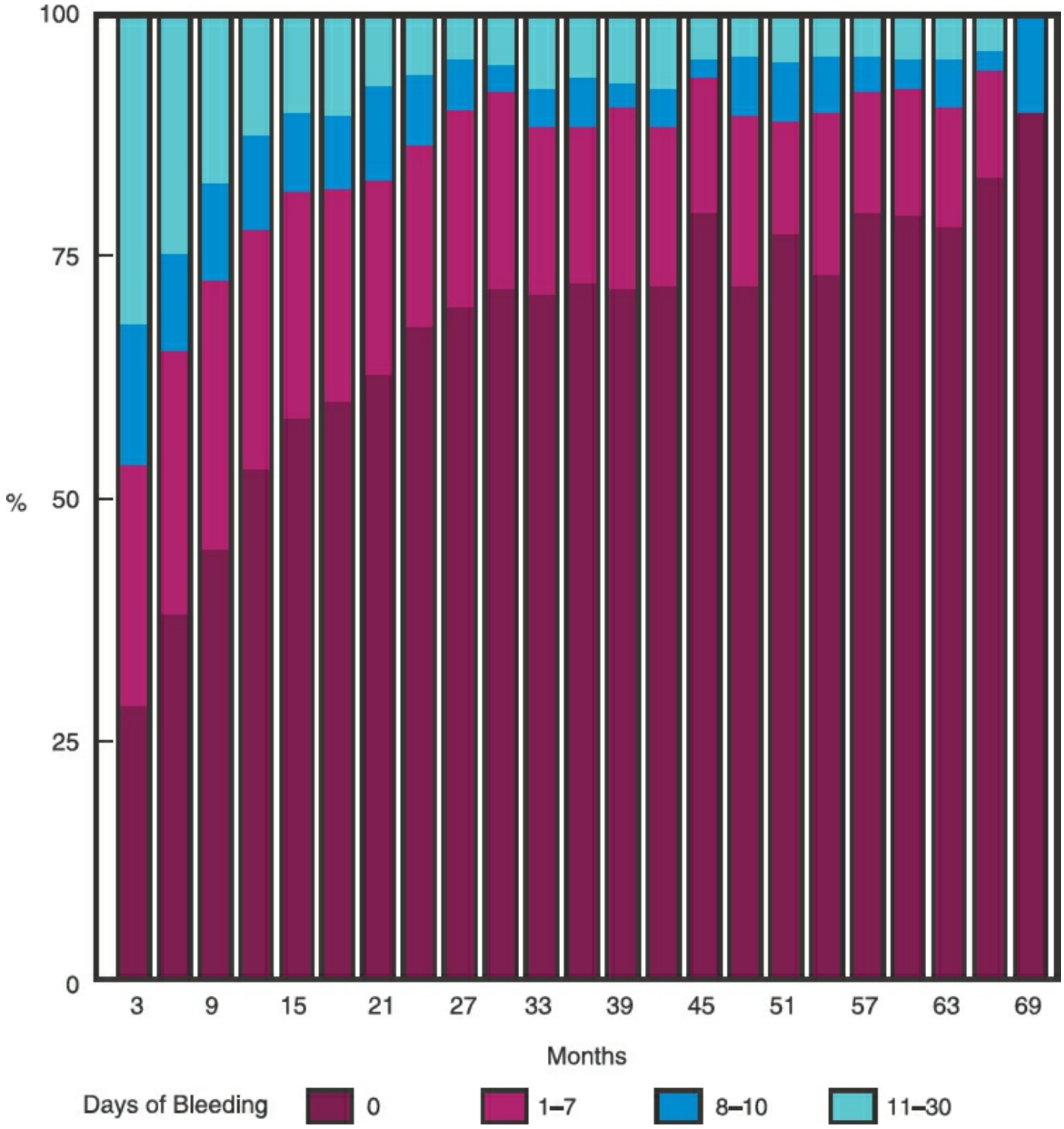


FIGURE 14-9 Bleeding pattern and duration of use of *depomedroxyprogesterone acetate (DMPA)*: percentage of women who have bleeding, spotting, or amenorrhea while taking *DMPA* 150 mg every 3 months. (From **Schwallie PC, Assenzo JR**. Contraceptive use-efficacy study utilizing *medroxyprogesterone acetate* administered as an intramuscular injection once every 90 days. *Fertil Steril* 1973;24:331–339, with permission.)

DMPA use is commonly associated with weight gain, and that is another principal reason women discontinue use. A large study is representative of the literature. Three cohorts of women who chose their method of contraception were followed for 36

months with measurements of weight and body fat. *DMPA* users gained an average of 5.1 kg. The cohort using OCs over the same interval gained only 1.47 kg, slightly less than the 2.05 kg gained by the cohort not using any hormonal contraception. Total body fat increased 4.14 kg in the *DMPA* cohort, while the increase in the OC users was 1.9 kg, only slightly more than the 1.17 kg in the nonhormonal contraceptive cohort. Many women were followed for 2 years after discontinuing *DMPA*. Those who chose nonhormonal methods after discontinuing *DMPA* lost a mean of 0.42 kg each 6 months. Those who chose to use OCs gained a mean of 0.43 kg each 6 months during the follow-up interval (246).

Weight gain during the first 6 months and self-reporting of increased appetite are strongly predictive of continued weight gain. Women who gained less than or equal to 5% of body weight in the first 6 months gained a mean of 2.49 kg by 36 months, while those who gained more than 5% by 6 months gained a total mean of 11.08 kg by 36 months (247). Studies are needed of interventions to prevent the weight gain. At minimum, women considering *DMPA* need to know the possibility of significant weight gain and be advised to avoid calorie-dense foods and weigh themselves regularly. Ideally they should be weighed when they return for subsequent injections so they can be counseled about the need for avoiding further gain. Women who gain 5% of body weight by 6 months should consider other contraceptive options.

DMPA persists in the body for several months in women who used it for long-term contraception, and return to fertility may be delayed. Studies of return to ovulation indicated a wide variation in time to ovulation post injection with the majority ranging from 15 to 49 weeks from the last injection for DMPA (248). In a cohort of Thai women, 70% of former users desiring pregnancy conceive within 12 months, and 90% conceive within 24 months after terminating *DMPA* use (249).

Safety

DMPA suppresses ovarian estrogen production. Prospective studies demonstrated bone loss during *DMPA* therapy, with recovery of bone mass after *DMPA* use is discontinued (250). Although bone loss was observed, it did not approach the fracture threshold. Similar bone loss and then recovery occurs with lactation. Adolescents are of special concern because they normally gain bone mass; most of adult bone mass is attained by age 20. Estrogen injections prevent the bone loss and allow adolescent women to gain bone density despite the use of *DMPA* (251). A long-term study in adolescents documented bone density loss and confirmed recovery of lumbosacral bone mineral density to baseline by 60 weeks after discontinuation of *DMPA* and significant gain above baseline by 180 weeks. Recovery of density at the hip was slower, 240 weeks to significant gain (252). A systematic review of *DMPA* clinical trials could find no studies where fracture was an outcome, so whether long-term use leads to fractures is still not known (253). The FDA black box warning added to *DMPA* labeling proposes

that *DMPA* treatment be limited to 2 years at a time, unless the patient has no other good options for contraception. For many women, especially in developing countries, *DMPA* is often the only option for highly effective contraception because it is inexpensive and easy to administer. The issue should be discussed with women who are considering *DMPA,* but *DMPA* should not be routinely discontinued after 2 years unless the patient wants to conceive or wants to change to another contraceptive method for other reasons.

The effect of *DMPA* on plasma lipids is inconsistent; *DMPA* users appear to have reduced total cholesterol and triglyceride levels, slight reduction in HDL cholesterol, and no change or slight increase in LDL cholesterol, all of which are consistent with a reduction in circulating estrogen levels. In some studies, the decrease in HDL and increase in LDL are statistically significant, although the values remain within normal ranges (254). *DMPA* is not associated with myocardial infarction. Glucose tolerance tests disclose a small elevation of glucose in *DMPA* users.

There is no change in hemostatic parameters, with the exception that ATIII levels are sometimes reduced with chronic therapy (254). As noted earlier, large epidemiologic studies have not found *DMPA* to be associated with thrombosis (145). *DMPA* is not associated with teratogenicity (255). Nor is it associated with affective disorders or mood changes (256).

DMPA and Lactation

There is widespread support for the use of *DMPA* during lactation when the *DMPA* is initiated at or after 6 weeks postpartum. There is good evidence that neither infant growth nor lactation is impaired by *DMPA* or progestin-only OCs (257). There is continued controversy as to how early *DMPA* should be given after delivery. Because lactation occurs in response to falling maternal estrogen and progesterone levels after birth, administration of *DMPA* in the first few days theoretically might interfere with the initiation of lactation. There is concern about the possible neonatal effects of the progestin, but investigators were unable to demonstrate the presence of *DMPA* or its metabolites in the urine of infants whose mothers received *DMPA* or any other suppression of reproductive hormones (257). In the United States, *DMPA* is commonly started at the time of hospital discharge, 48 to 72 hours after delivery. In a systematic review, including 11 nonrandomized clinical trials and observational studies, progestogen-only injectables were initiated in the first 6 weeks postpartum and most found either no effect on breastfeeding outcomes or improved outcomes among DMPA users (19). The "U.S. Medical Eligibility Criteria for Contraceptive Use 2016" considers *DMPA* use prior to 1 month postpartum as category 2: the benefit is thought to exceed the theoretical risk (7).

DMPA and Neoplasia

The use of *DMPA* is not associated with cervical cancer (258). Neither is it associated with ovarian cancer (259). The risk of endometrial cancer is substantially reduced by

past use of *DMPA* (260). A large study found no increase in breast cancer risk among *DMPA* users (261).

Benefits

DMPA has many of the noncontraceptive benefits of combination OCs (262). Decreases in anemia, PID, ectopic pregnancy, and endometrial cancer are reported. *DMPA* is reported to benefit women with sickle cell disease (263).

Subcutaneous DMPA

Depo-subQ Provera 104, a lower-dose *DMPA* preparation for subcutaneous administration, received FDA approval in 2005. The total dose is 30% less than that of the *DMPA* intramuscular preparation. Because the dose is administered subcutaneously, blood levels are adequate to completely suppress ovulation for more than 13 weeks in all subjects tested, with a mean time of 30 weeks for return to ovulatory function (264). Contraception efficacy is superb, with no pregnancies in a total of 16,023 woman-cycles in the phase III studies done in the United States (265). Blood levels were lower in very obese women but still sufficient to completely suppress ovulation. The weight gain reported with the 150-mg *DMPA* remains a problem with the lower-dose *DMPA.* Mean weight gain was 1.59 kg in the first year of use. Loss of bone density was observed with this dosage of *DMPA,* as with the larger intramuscular dose. In select countries, DMPA-SQ is available in a single-use Uniject device and is sold under the name Sayana Press (266). The Uniject is a small, prefilled, single-use injection device that any trained person, including community health workers, pharmacists, and even women themselves can administer. In an open-label observational study, current users of DMPA IM found Sayana Press to be acceptable, with most users preferring Sayana Press over DMPA IM, indicating promising uptake (267).

Once-a-Month Injectable

A once-a-month injectable contraception containing only 25 mg of *DMPA* in combination with 5 mg of the long-acting estrogen *estradiol cypionate* was briefly available in the United States, but was withdrawn by the manufacturer because of a packaging problem (268). Originally developed by the WHO, it is described as *Cyclofem* or *CycloProvera* in the literature and was marketed in the United States as *Lunelle* (269). Given once a month, this combination produces excellent contraceptive effects. Monthly withdrawal bleeding is similar to a normal menses, leading to high continuation rates despite the need for a monthly injection. Monthly injectable combinations continue to be widely used outside the United States.

Subdermal Implants

Three progestin-releasing subdermal implants systems are in use worldwide: *Jadelle* (Bayer, Leverkusen, Germany), *Sino-Implant* II (Dahua, Shanghai, China), and

Nexplanon (Merck, Kenilworth, USA). All three offer long-acting contraception that requires no continuing action by the user and are, hence, forgettable. All are very highly effective and have no serious risk. Each can produce irregular bleeding, which is the principal reason for discontinuation. The mechanism of action is suppression of ovulation in the initial years of use, plus thickening of the cervical mucous that prevents sperm penetration.

The original *levonorgestrel* implant (*Norplant*) six-rod system was replaced with a two-rod version (*Jadelle*), which is identical in its release rate and clinical activity to *Norplant* and is easier to insert and remove (270). *Jadelle* is widely used around the world. It is approved by the FDA but not marketed in the United States. It is approved for 5 years. The *Sino-Implant II* (*Levoplant*) is a less expensive two-rod *levonorgestrel* system manufactured in China and available in several countries. It is labeled for 3 years of use, with trials ongoing for a fourth year (271). In June 2017, the product received WHO prequalification, which recognizes that the product meets international quality standards for manufacturing and clinical performance. This allows additional donors to purchase the product for country programs. Thus, the availability of the *Sino-Implant II* (*Levoplant*) is likely to increase. *Nexplanon* (or *Implanon-NXT*) is a single-rod system containing *etonogestrel,* the active metabolite of *desogestrel.* It was first approved in 2006 as *Implanon*. In 2011, Merck replaced *Implanon* with Nexplanon, which contains 15 mg of barium sulfate to create a radiopaque quality and utilizes a simpler applicator for easier, and potentially safer insertion. All studies regarding safety and effectiveness of *Implanon* apply to Nexplanon.

A systematic review of 29,972 women and 28,108 woman-months of follow-up with *Norplant*, *Jadelle*, or *Implanon* found no differences in pregnancies or continuation rate over 4 years. No pregnancies occurred in any of the trials. There were no differences in side effects or adverse events. The most common side effect was unpredictable vaginal bleeding (272).

In 923 women followed for 20,648 treatment cycles in 11 studies, there were no pregnancies with the etonogestrel implant in place. Six pregnancies occurred within 14 days of removal of the devices. **[7]** When these are included, as required by the FDA, the cumulative Pearl Index was 0.38 pregnancies per 100 woman-years at 3 years (273). Irregular bleeding was a problem, but occurred most frequently in the first 90 days of use and decreased over time. In a randomized comparison with the six-rod *Norplant*, etonogestrel implant users had less frequent vaginal bleeding, but more became amenorrheic (274). Other commonly reported side effects are headache, weight gain, acne, breast tenderness, and emotional lability (273). Only 2.3% of subjects discontinued because of weight gain. Most women can use *Nexplanon*. The US MEC lists only a small number of conditions as category 3, and these are based on theoretical concerns without actual evidence of harm (7). Insertion in the postpartum period appears to have no adverse effects on the mother or infant. Among women who initiated

the ETG implant or LNG-IUD 6 weeks postpartum, there was no difference in the weight or height of their infants through 6 months (275). An RCT found no difference in growth at 12 months among breastfed infants whose mothers had etonogestrel implant inserted within 48 hours postpartum versus at 6 weeks postpartum (276). A study of etonogestrel implants compared with the copper IUD placed 4 to 8 weeks postpartum found no differences in infant growth, adverse events, respiratory or skin disorders, or developmental scores (277). One population in which special considerations should be taken when using progestin implants is HIV-positive women concurrently taking efavirenz-based antiretroviral therapy (ART), because efavirenz may reduce the effectiveness of contraceptive implants. Pharmacokinetic studies have reported reduced etonogestrel and levonorgestrel concentrations in implant users concurrently using efavirenz-based ART, which raises concerns about potential decreased contraceptive efficacy (278,279). In a retrospective cohort study of HIV-positive women with contraceptive implants, the adjusted pregnancy rates in efavirenz users were *triple* that of nevirapine users (280). Nevertheless, these findings should not preclude women taking efavirenz from using implants because even in this population, the implant remains more effective than non-LARC contraceptive methods.

Bone density is not affected by the etonogestrel implant, probably because ovarian follicular activity is not totally suppressed and estradiol synthesis continues (281). Enlarged follicular ovarian cysts are common during the first year of use of *Jadelle* or etonogestrel implant and usually resolve spontaneously (282).

[7] A comparative study of coagulation and fibrinolytic factors in users of *etonogestrel* and *levonorgestrel* implants showed no significant changes from the baseline, with the exception of a modest increase in ATIII and a small decrease in factor VII activity, changes that might reduce coagulability. Lipid levels and liver function studies were not changed, with the exception of small elevations of bilirubin, with somewhat more observed in *levonorgestrel* users than *etonogestrel* users (283). Another study of hemostatic factors found modest decreases in many measurements, within the range of normal, and a modest reduction in the generation of thrombin in users of the *etonogestrel* implant (284). Taken together these studies provide considerable reassurance that the progestin implants do not increase thrombosis risk. With several million women now using the implants, there are no published studies linking either implant to venous thrombosis or myocardial infarction.

Emergency Contraception

Postcoital use of sex steroids to prevent pregnancy began in the 1960s with high-dose estrogen taken daily for 5 days (285). This was replaced with the combination OC containing *EE* and *levonorgestrel* for greater convenience (286). **[9]** In the late 1990s, *levonorgestrel* alone became the method of choice after the WHO showed its

superiority in a large randomized trial with 1,998 women. The pregnancy rate was 3.2% with the *EE/levonorgestrel* method and only 1.1% with *levonorgestrel* alone (RR for pregnancy, 0.32; 95% CI, 0.18–0.70) for women treated within 72 hours of intercourse. Nausea and vomiting occurred much less frequently with *levonorgestrel* alone (23.1% vs. 50.5%, and 5.6% vs. 18.8%, respectively) (287). The efficacy of both methods declined as the time after intercourse increased. But even after 72 hours, the pregnancy rate with the *levonorgestrel* treatment was only 2.7% (288). A single dose of 1.5-mg *levonorgestrel* is just as effective as two doses of 0.75 mg, has no more side effects, and is more convenient for the patient. Both dosing regimens are FDA approved. While recognizing that *levonorgestrel* is more effective the sooner it is taken, the WHO allows for the use of 1.5 mg of *levonorgestrel* as a single dose, given up to 120 hours after intercourse (289). Research suggests that the main mechanism of action is delay of ovulation. Noe et al. established that *levonorgestrel* works only if it is administered prior to the day of ovulation (290). No pregnancies occurred to 87 women who received *levonorgestrel* from 1 to 5 days prior to the day of ovulation. Seven pregnancies occurred to 35 women treated on the day of ovulation or later. **Postcoital *levonorgestrel* is not an abortifacient because it is effective only when taken before ovulation.** *Levonorgestrel* alone is safer than the estrogen-containing preparations. There were several case reports of thrombotic events after use of the estrogen/levonorgestrel combination emergency contraception (291). No such complications with *levonorgestrel* alone were published.

Antiprogestins

The antiprogesterone *mifepristone* (*RU486*) is highly effective for postcoital contraception. The usual abortifacient dose is 200 mg, but a dose of only 10 mg is effective for emergency contraception. In one study, 2,065 women were randomized to *mifepristone,* 10 mg, or *levonorgestrel,* two doses of 0.75 mg, including women up to 120 hours after intercourse (292). The crude pregnancy rate was 1.3% for *mifepristone* and 2.0% for *levonorgestrel* ($p = 0.46$). Side effects were the same, and both methods were judged highly acceptable by the patients. *Mifepristone* is not being developed for this use and is not available at the appropriate dose.

[9] *Ulipristal acetate,* sold by the trade name of Ella, is a progesterone-receptor modulator that was approved by the FDA and the European Union for emergency contraception up to 120 hours after intercourse. It is a single 30-mg tablet, available by prescription only, whereas *levonorgestrel* 1.5 mg has been available without a prescription since 2013. When ovulation is imminent, ulipristal is more effective than levonorgestrel in delaying ovulation. The odds of pregnancy for ulipristal were 42% lower by 72 hours after intercourse and 65% lower in the first 24 hours (293). When *ulipristal* is administered prior to the LH peak, it delays the rupture of the preovulatory follicle for 5 days or more, which may be its primary mechanism of action (294). In

women with BMI >30, the risk of pregnancy is greater for those taking levonorgestrel (OR, 4.41) than for those taking ulipristal (OR, 2.62) (295). Thus, for obese women, ulipristal is preferred over levonorgestrel. Subsequent studies on EC and obesity have shown that the total concentration of levonorgestrel for obese women with one dose of levonorgestrel was significantly lower than the level observed in normal BMI women (296). However, the concentration of ulipristal was similar between obese and normal BMI women (297). *Ulipristal* is primarily metabolized by the CYP3A4 enzyme system; hence, patients on drugs such as barbiturates, *rifampin*, and several of the anticonvulsants may have reduced protection from pregnancy with it. With regards to starting hormonal contraception following the use of emergency contraceptive pills, hormonal contraception can be started immediately after administration of levonorgestrel. However, in one study where women were given either a placebo or a progestin-only pill, desogestrel, the day after ulipristal, ovulation occurred in 45% of cycles in women receiving desogestrel compared to 3% in the placebo group (298). Therefore, in 2015, the *Ella* label was updated to recommend that patients who use ulipristal wait 5 days before starting a hormonal contraceptive method (299).

The Copper Intrauterine Device for Emergency Contraception

Postcoital insertion of a copper IUD was first reported by Lippes et al. in 1976 (300). In initial trials, the copper IUD was inserted within 7 days of intercourse and was more effective than steroids for emergency contraception. Subsequent studies included women only within 5 days from intercourse. The multicenter trial by Wu and colleagues is an example of the superb efficacy offered by the *copper T380A* (301). Of 1,893 women who returned for a follow-up visit, there were no pregnancies within 1 month of IUD insertion. **[9] Efficacy for emergency contraception is 100% when the device is inserted up to 5 days after intercourse, and almost 100% up to 7 days after intercourse** (301). An added benefit was that 94% of the patients were continuing with the IUD at the 12-month follow-up. There were no uterine perforations. Zhou and colleagues reported similar excellent results in a large study with a different copper device, the *Multiload Cu-375* IUD (302). In much of the world, copper IUDs are very inexpensive. Even in the United States where IUDs are costly, the benefit to the patient of extremely effective emergency contraception, and long-term contraception with one intervention, makes emergency IUDs cost effective. Whether the *LNG-IUD* would work for emergency contraception is being studied.

Hormonal Contraception for Men

The same negative feedback of sex steroids that blocks ovulation in women suppresses spermatogenesis in men, but it will produce loss of libido and potentially extinguish sexual performance. The principle was first demonstrated in 1974 using oral estrogen and methyl testosterone (303). Testosterone given alone can suppress sperm production

to very low levels while maintaining normal libido and sexual performance. Over many years investigators have studied long-acting testosterone salts for male contraception (304). Ethnicity is an important predictor of efficacy of sperm suppression with testosterone therapy. Asian men virtually always achieve azoospermia or oligospermia when treated with *testosterone undecanoate* (*TU*) monthly injections, whereas only 86% of Caucasian men achieved azoospermia or oligospermia or with similar testosterone regimens (305). In a Chinese trial, 1,045 men were treated with monthly *TU* 500 mg. Only 4.8% failed to suppress to a sperm count less than 1×10^6 per mL. The cumulative pregnancy rate was only 1.1 per 100 men at 30 months (306). In Caucasian populations, testosterone was combined with progestins to further suppress gonadotropin and improve efficacy. In an important trial with Caucasian men, *etonogestrel* subdermal implants and *TU* injections were compared to placebo implants and injections. Only 3% failed to suppress to a sperm count of less than 1×10^6 (307). Side effects that were more common in the medicated group than placebo included acne, night sweats, libido changes (usually increased), and weight gain. In a study using Nestorone (progestin) and testosterone transdermal gels, 89% of men achieved suppression of their sperm concentrations to $\leq 1 \times 10^6$ per mL, with minimal side effects (308).

Nonhormonal male methods are being investigated. One product called reversible inhibition of sperm under guidance (RISUG) has been studied in both preclinical and human research in India (309). It consists of styrene maleic anhydride which when injected into the vasa differentia creates an incompatible pH level for sperm and blocks transport. *Vasalgel* involves a similar approach but uses a different formulation and is being developed in the United States. It is a high–molecular-weight polymer consisting of styrene-alt-maleic acid dissolved in dimethyl sulfoxide, which is injected into the vasa deferentia, where it remains as a soft gel-like state that allows water-soluble substances to pass but not sperm. It is meant to be reversible and in rabbit studies shows rapid restoration of sperm flow after an injection of sodium bicarbonate (310). Thus far, *Vasalgel* has been studied only in animal models (311). *Vasalgel* is expected to begin enrollment of men in clinical trials in the United States.

STERILIZATION

Surgical sterilization is the most common method of fertility control used by couples worldwide, with more than 250 million women and men relying on female sterilization or vasectomy for contraception (312). Laparoscopic and hysteroscopic techniques for women and vasectomy for men are safe and readily available throughout the United States. The mean age at sterilization is 30 years. Age younger than 30 years when sterilized, conflict within the marriage, and divorce and remarriage are predictors of sterilization regret, which may lead to a request for reversal of sterilization (313).

Female Sterilization

Hysterectomy is no longer considered for sterilization because morbidity and mortality are too high in comparison with tubal sterilization. Vaginal tubal sterilization, which was associated with occasional pelvic abscess, is rarely performed in the United States. **[11] Five procedures are used in the United States.**

1. **Tubal sterilization at the time of laparotomy for a cesarean delivery or other abdominal operation**
2. **Postpartum minilaparotomy soon after vaginal delivery**
3. **Interval minilaparotomy**
4. **Laparoscopy**
5. **Hysteroscopy**

Postpartum tubal sterilization at the time of cesarean delivery adds no risk other than a slight prolongation of operating time; cesarean birth poses more risk than vaginal birth, and planned sterilization should not influence the decision to perform a cesarean delivery. **Minilaparotomy can be performed in the immediate postpartum state. The uterus is enlarged, and the fallopian tubes lie in the midabdomen, easily accessible through a small, 3- to 4-cm subumbilical incision.**

Interval minilaparotomy, first described by Uchida, was rediscovered and popularized in the early 1970s in response to an increased demand for sterilization procedures and a simpler alternative to laparoscopy (314). Still widely practiced in lower resource settings, it is uncommon in the United States because of widespread availability of the endoscopic techniques.

Surgical Technique

The procedure usually elected for tubal sterilization by laparotomy is the Pomeroy or modified Pomeroy technique **(Fig. 14-10)**. In the classic Pomeroy procedure, a loop of tube is excised after ligating the base of the loop with a single absorbable suture. A modification of the procedure is excision of the midportion of the tube after ligation of the segment with two separate absorbable sutures. This modified procedure has several names: *partial salpingectomy, Parkland Hospital technique, separate sutures technique,* and *modified Pomeroy.* In the Madlener technique, now abandoned because of too many failures, a loop of tube is crushed by cross-clamping its base, ligated with permanent suture, and excised. Pomeroy and partial salpingectomy procedures have failure rates of 1 to 4 per 1,000 cases (313). In contrast, pregnancy is exceedingly rare after tubal sterilization by the Irving or Uchida methods. In the Irving method, the midportion of the tube is excised, and the proximal stump of each tube is turned back and led into a small stab wound in the wall of the uterus and sutured in place, creating a blind loop. With the Uchida method, a *saline–epinephrine* solution (1:1,000) is injected

beneath the mucosa of the midportion of the tube, separating the mucosa from the underlying tube. The mucosa is incised along the antimesenteric border of the tube, and a tubal segment is excised under traction so that the ligated proximal stump will retract beneath the mucosa when released. The mucosa is closed with sutures, burying the proximal stump and separating it from the distal stump. In Uchida's personal series of more than 20,000 cases, there were no pregnancies (314).

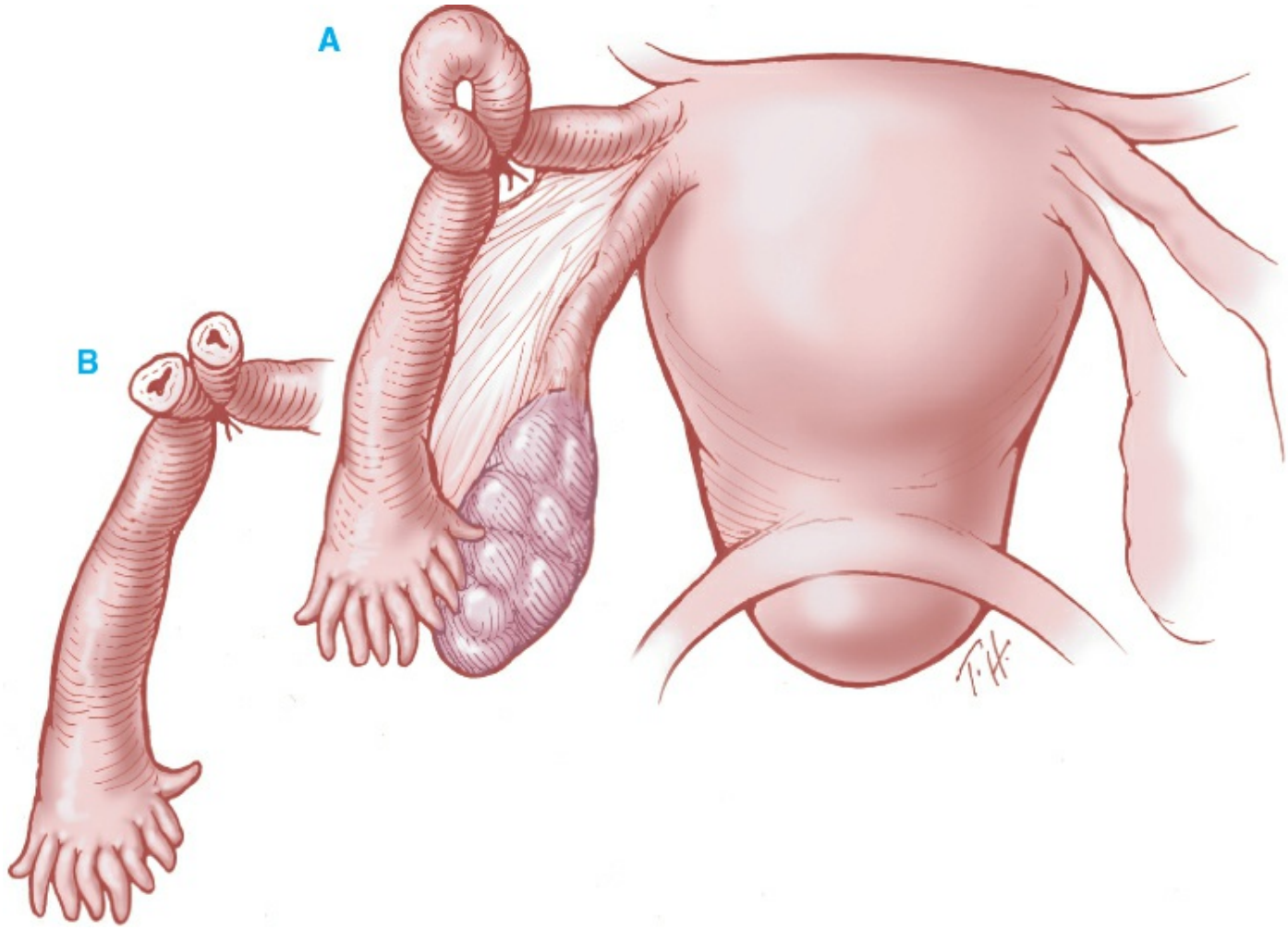


FIGURE 14-10 Pomeroy technique for tubal sterilization. **A:** Ligation of loop of fallopian tube. **B:** Subsequent excision of loop.

Laparoscopy

Laparoscopy is the most common method of interval sterilization in the United States. In the standard laparoscopy technique, after the abdomen is inflated with a gas, the laparoscope is inserted into the abdominal cavity through a trocar, usually at the lower margin of the umbilicus. Although single puncture laparoscopic sterilization procedures can be performed with an "operating laparoscope," it is increasingly common for a second, and sometimes third, trocar to be inserted in the suprapubic region or lateral lower quadrants to allow the insertion of special grasping forceps.

Laparoscopic sterilization is usually performed in the hospital under general anesthesia but can be performed under local anesthesia with conscious sedation. Overnight hospitalization for laparoscopy is rarely needed.

Techniques for Tubal Occlusion at Laparoscopy

Laparoscopic tubal occlusion is accomplished by any of four techniques: bipolar electrical coagulation, application of a small Silastic rubber band (Falope ring), the spring clip (Hulka clip), or the titanium clip (Filshie clip). The Filshie clip, first introduced in the United States in 1996, is used extensively in the United Kingdom and Canada (315). It is a hinged device made of titanium with a liner of silicone rubber tubing. Because of its lower pregnancy rate, the Filshie clip has largely supplanted the Hulka clip (316).

In the bipolar electrocoagulation technique, the midisthmic portion of the tube and adjacent mesosalpinx are grasped with special bipolar forceps, and radiofrequency electric current is applied to three adjacent areas, coagulating 3 cm of tube **(Fig. 14-11)**. The tube alone is recoagulated in the same places. The radiofrequency generator must deliver at least 25 W into a 100-Ω resistance at the probe tips to ensure coagulation of the complete thickness of the fallopian tube and not just the outer layer; otherwise, the sterilization will fail (317).

To apply the Falope ring, the midisthmic portion of the tube is grasped, with tongs advanced through a cylindrical sleeve that has the ring stretched around it **(Fig. 14-12A)**. A loop of tube is pulled back into the sleeve, and the outer cylinder is advanced **(Fig. 14-12B)**, releasing the Silastic ring around the base of the loop of the tube, producing ischemic necrosis over time **(Fig. 14-12C)**. If the tube cannot be pulled easily into the applicator, the operator should stop and change to electrical coagulation rather than persist and risk lacerating the tube with the Falope ring applicator. The banded tube must be inspected at close range through the laparoscope to demonstrate that the full thickness of the tube was pulled through the Falope ring.

The Hulka clip is placed across the midisthmus, ensuring that the applicator is at right angles to the tube and that the tube is completely contained within the clip before the clip is closed. The Filshie clip is placed at right angles across the midisthmus, taking care that the anvil of the posterior jaw can be visualized through the mesosalpinx beyond the tube to ensure that the complete thickness of the tube is completely within the jaws of the clip before it is closed **(Fig. 14-13)**.

The cautery band or clip techniques each have advantages and disadvantages. Bipolar coagulation can be used with any fallopian tube. The Falope ring and Hulka and Filshie clips cannot be applied if the tube is thickened from previous salpingitis. There is more pain during the first several hours after Falope ring application. This can be prevented by bathing the tubes with a few milliliters of 0.5% *bupivacaine* just before ring placement (318). Failure of the Falope ring or the clips generally results from

misapplication, and pregnancy, if it occurs, is usually intrauterine. After bipolar sterilization, pregnancy may result from tuboperitoneal fistula and is ectopic in more than 50% of cases. If inadequate electrical energy is used, a thin band of fallopian tube remains that contains the intact lumen and allows intrauterine pregnancy to occur. Thermocoagulation, the use of heat probes rather than electrical current, is employed extensively in Germany for laparoscopic tubal sterilization but is little used in the United States.

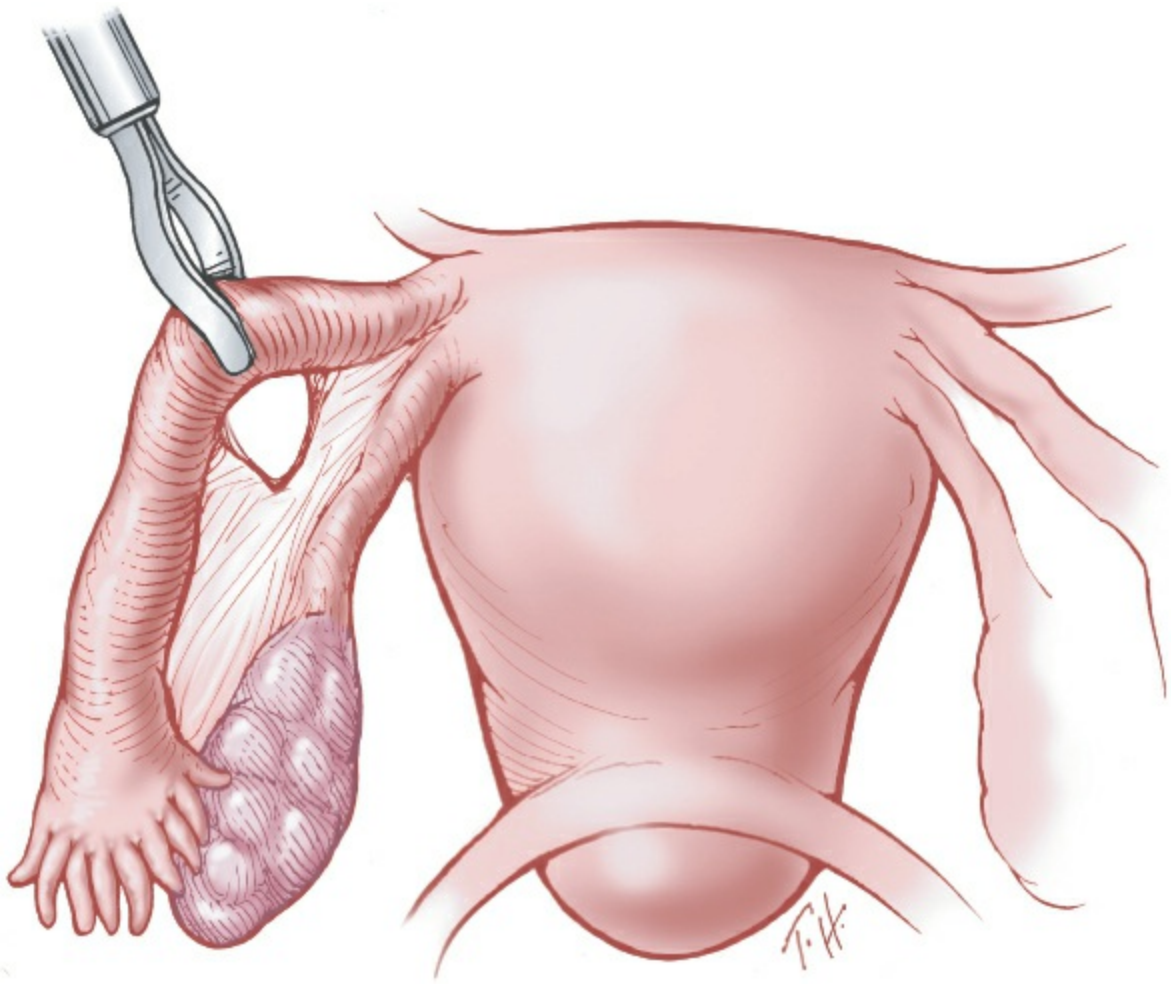


FIGURE 14-11 Technique for bipolar electrocoagulation tubal sterilization.

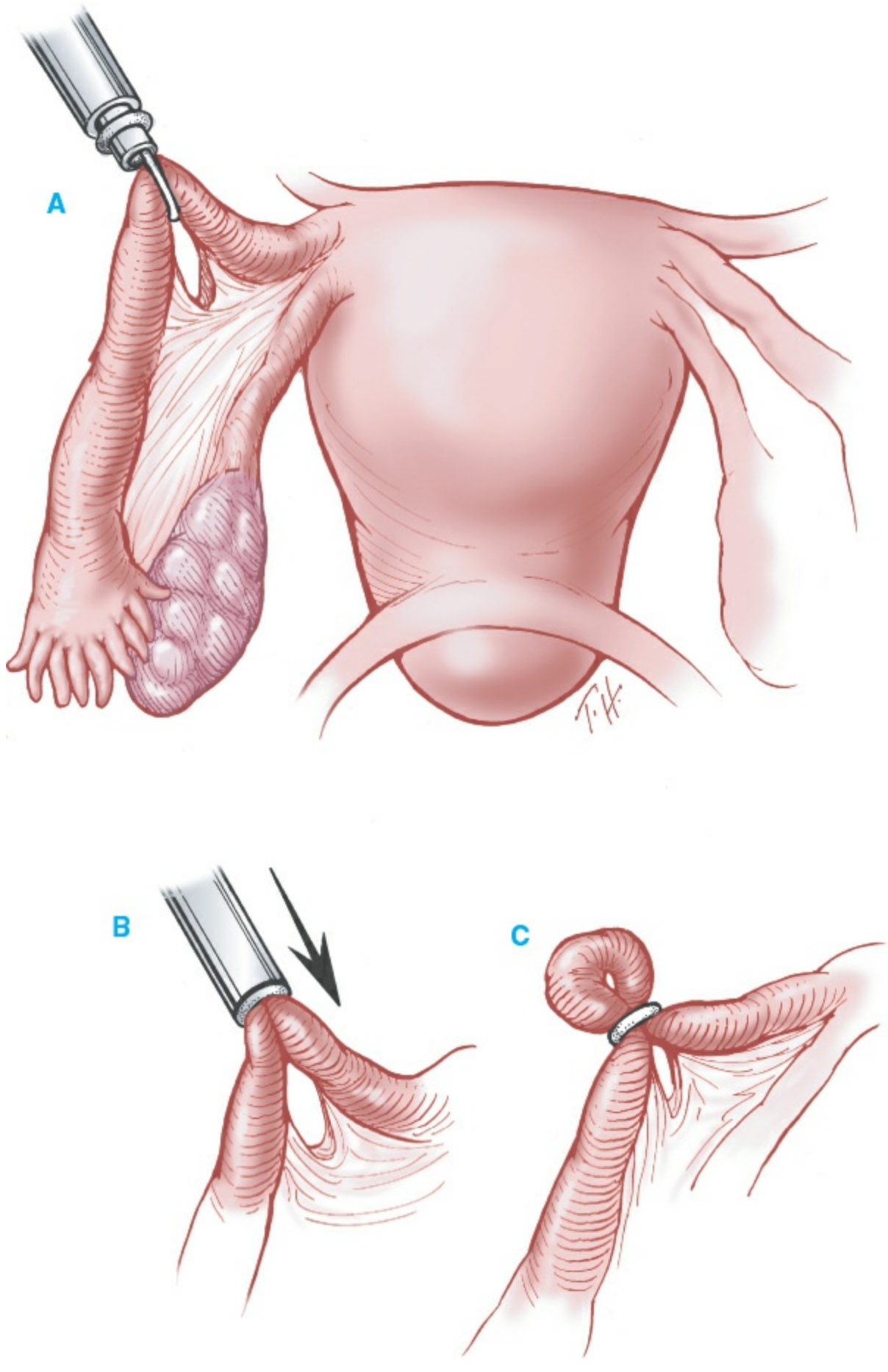

A
B
C

FIGURE 14-12 Placement of the Falope ring for tubal sterilization.

Laparoscopic Salpingectomy

Salpingectomy, either partial or complete, has not been traditionally used for sterilization because of perceived comparative ease and safety of occlusion methods. However, a large observational study compared salpingectomy with other methods and found no increase in complication rates but an increase in operative time of approximately 10 minutes (319). A recent study including salpingectomies and tubal occlusion cases showed comparable immediate and short-term complications rates across sterilization methods and an average increase of 6 minutes of operative time for salpingectomy (320). **Prophylactic salpingectomy may reduce the risk of ovarian/fallopian tube cancer because most epithelial ovarian cancers arise in the distal fallopian tube, and is now recommended when women are undergoing gynecologic surgeries for other benign indications.**

Noncontraceptive Benefits of Tubal Sterilization

In addition to providing excellent contraception, tubal ligation is associated with reduced risk for ovarian cancer. Among the largest studies to illustrate the relationship between tubal ligation and ovarian cancer were the Nurses' Health Study and Nurses' Health Study II. These two prospective cohort studies included 29,340 women who had tubal ligation and found that tubal ligation overall was associated with a decreased risk of ovarian cancer (HR, 0.76; 95% CI, 0.64–0.90) (321). In a large prospective cohort study in the United Kingdom, the association of tubal ligation with decreased risk varied by histology, with a significant decrease in the risk of high-grade serous carcinomas (RR, 0.77; 95% CI, 0.67–0.89), endometrioid (RR, 0.54; 95% CI, 0.43–0.69), and clear cell tumors (RR, 0.55; 95% CI, 0.39–0.77) (322).



FIGURE 14-13 Filshie clip for tubal sterilization. (Courtesy of Femcare Ltd, Romsey, UK.)

Furthermore, studies have explored the risks and benefits of opportunistic salpingectomy compared to tubal ligation with regards to ovarian cancer risk reduction. One study concluded that opportunistic salpingectomy at the time of sterilization is cost effective with an incremental cost effectiveness ratio of $31,432 per quality-adjusted life year (323). Another study comparing partial salpingectomy (modified Pomeroy method) to complete salpingectomy (use of LigaSure) at the time of cesarean delivery found no significant differences in short-term complications (postpartum fever, wound infection, relaparotomy, estimated blood loss) (324). In addition, one trial which aimed to evaluate short-term ovarian reserve by measuring antimüllerian hormone levels,

detected no significant difference between the groups, with an average increase of 0.58 ± 0.98 versus 0.39 ± 0.41 ng/mL in the salpingectomy and tubal ligation groups, respectively ($p = 0.45$). Surgeries including salpingectomy were longer by an average 13 minutes (66.0 ± 20.5 vs. 52.3 ± 15.8 minutes, $p = 0.01$) (325). A trend may develop that favors salpingectomy over tubal occlusion or ligation for sterilization.

Risks of Tubal Sterilization

Tubal sterilization is remarkably safe. The Collaborative Review of Sterilization (CREST) study, a 1983 review of 9,475 interval sterilizations from multiple centers in the United States, reported a total complication rate of 1.7 per 100 procedures (313). Complications were increased by the use of general anesthesia, previous pelvic or abdominal surgery, history of PID, obesity, and diabetes mellitus. The most common significant complication was unintended laparotomy for sterilization after intra-abdominal adhesions were found. In another series, 2,827 laparoscopic sterilizations were performed with the Silastic band using local anesthesia and intravenous sedation (326). Only four cases could not be completed (a technical failure rate of 0.14%), and laparotomy was never needed. Rarely, salpingitis can occur as a complication of the surgery. This occurs more often with electric coagulation than nonelectric techniques. The risk of death with female sterilization was 1 to 2 per 100,000 sterilizations in a national study based on data from 1979 to 1980 (313). Almost half of the deaths were from complications of general anesthesia, usually related to the use of mask ventilation. When general anesthesia is used for laparoscopy, endotracheal intubation is mandatory because the pneumoperitoneum increases the risk of aspiration. International data from the Association for Voluntary Surgical Contraception show a similar record of safety from third-world programs: 4.7 deaths per 100,000 female sterilizations and 0.5 deaths per 100,000 vasectomies (327).

Sterilization Failure

Many "failures" occur during the first month after surgery and are the result of a pregnancy already begun when the sterilization was performed. Contraception should be continued until the day of surgery, and a sensitive pregnancy test should be routinely performed on the day of surgery. Because implantation does not occur until 6 days after conception, a woman could conceive just before the procedure and there would be no way to detect it. Scheduling sterilization early in the menstrual cycle obviates the problem but adds to the logistic difficulty. Another cause of failure is the presence of anatomic abnormalities, usually adhesions surrounding and obscuring one or both tubes. An experienced laparoscopic surgeon with appropriate instruments usually can lyse the adhesions, restore normal anatomic relations, and positively identify the tube. In some circumstances, successful sterilization will not be possible by laparoscopy, and the surgeon must know before surgery whether the patient is prepared

to undergo laparotomy, if necessary, to accomplish sterilization. The CREST study reported on a cohort of 10,685 women sterilized from 1978 to 1986 at any of 16 participating centers in the United States who were followed from 8 to 14 years (313). The true failure rates for 10 years obtained by the life-table method are given in Table 14-4. Pregnancies resulting from sterilization during the luteal phase of the cycle in which the surgery was performed were excluded. Of all remaining pregnancies, 33% were ectopic. The most effective methods at 10 years were unipolar coagulation at laparoscopy and postpartum partial salpingectomy, generally a modified Pomeroy procedure. Bipolar tubal coagulation and the Hulka-Clemens clip were least effective. The Filshie clip was not evaluated because it was not in use in the United States. Younger women had higher risk for failure, as would be expected because of their greater fecundity.

Table 14-4 Ten-Year Life-Table Cumulative Probability of Pregnancy per 1,000 Procedures With Different Methods of Tubal Sterilization, United States, 1978–1986

Unipolar coagulation	7.5
Postpartum partial salpingectomy	7.5
Silastic band (Falope or Yoon)	17.7
Interval partial salpingectomy	20.1
Bipolar coagulation	24.8
Hulka-Clemens clip	36.5
Total: all methods	18.5

From **Peterson HB, Xia Z, Hughes JM, et al.** The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. *Am J Obstet Gynecol* 1996;174:1164; Table 2, with permission.

Since the CREST study began, sterilization by unipolar electrosurgery was abandoned because of the risk of bowel burns and was replaced with bipolar electrosurgery or the nonelectric methods (tubal ring, Hulka-Clemens clip, and the Filshie clip). **An analysis of the CREST data found that bipolar sterilization can have a very low long-term failure rate if an adequate portion of the tube is coagulated.** CREST study participants who were sterilized with bipolar electrosurgery from 1985 to 1987 had lower failure rates than those sterilized earlier (1978–1985). The important difference was in the application technique of the electric energy to the tubes. Women whose bipolar procedure involved coagulation at three sites or more had low 5-year failure rates (3.2 per 1,000 procedures), whereas women who had fewer than three sites of tubal coagulation had a 5-year failure rate of 12.9 per 1,000 (p = 0.01) (328).

Family Health International reported large randomized multicenter trials of the different means of tubal sterilization. The Filshie and Hulka clips were compared in two trials. A total of 2,126 women were studied, of which 878 had either clip placed by minilaparotomy and 1,248 had either clip placed by laparoscopy. The women were evaluated at up to 24 months (329). Pregnancy rates were 1.1 per 1,000 women with the Filshie clip and 6.9 per 1,000 with the Hulka clip at 12 months, a difference in rates that approached statistical significance ($p = 0.06$). This same group compared the Filshie clip with the Silastic tubal ring in a similar study with a total of 2,746 women, of which 915 had the devices placed at minilaparotomy and 1,831 at laparoscopy (330). Pregnancy rates at 12 months were the same for the Filshie clip and the tubal ring: 1.7 per 1,000 women. The ring was judged more difficult to apply. The Filshie clip was expelled spontaneously from the vagina by three women during the 12 months of follow-up.

Hysteroscopy

In 2002, the FDA approved *Essure*, a hysteroscopic method of permanent birth control. It can be provided in an office setting, with only local anesthesia or conscious sedation and both offer the prospect of greater safety, lower cost, and greater long-term effectiveness than the best laparoscopy **[12]** methods. ***Essure* is a microinsert consisting of a soft stainless steel inner coil and a dynamic nickel titanium alloy outer coil (Fig. 14-14)**. Soft fibers of polyethylene terephthalate run along and through the inner coil. To insert the device, a hysteroscope is introduced into the uterine cavity, which is distended with saline. The tubal ostia are visualized. The *Essure* device is inserted through the operating channel of the hysteroscope on the end of a slender delivery wire, guided into the tubal opening and advanced into the tube under direct vision **(Fig. 14-15)**. Once in place, an outer sheath is retracted, releasing the outer coils, which expand to anchor the device in the interstitial portion of the tube. The delivery wire is detached and removed and the procedure repeated for the other tube. When properly placed, three to eight of the end coils of the microinsert are visible inside the uterine cavity. The rest are inside the fallopian tube (331,332).

[12] ***Essure* can be installed under local anesthesia in an outpatient setting.** No incision is needed. Over time fibrous tissue grows, occluding the tubes permanently. The Essure Confirmation Test using either a transvaginal ultrasound (TVUS) or modified hysterosalpingogram (HSG) is required. The FDA approved the TVUS as an alternative confirmation test in July 2015. Patients must meet all criteria at the time of placement to be eligible for TVUS. Otherwise, they must undergo confirmation with modified HSG. A few notable criteria include certainty about bilateral placement, procedure time ≤15 minutes, and one to eight trailing coils bilaterally (333). Patients who are on active immunosuppressive therapy (systemic corticosteroids or chemotherapy) are not eligible for TVUS as a result of concern for failure of tissue

ingrowth. The modified HSG for *Essure* should document bilateral placement of the devices at the uterotubal junction and a lack of peritoneal spillage of dye. The patient with transcervical sterilization should continue to use a reliable method of contraception until successful occlusion is documented.



FIGURE 14-14 *Essure* device for hysteroscopic sterilization. (Courtesy of Conceptus, Inc.)



FIGURE 14-15 *Essure* device with guide wire and handle. (Courtesy of Conceptus, Inc.)

Risks of Hysteroscopy

Adverse events or side effects were reported on the day of procedure in 3% of the initial *Essure* patients. These consisted of vasovagal responses, cramping, nausea, and vaginal spotting (334). Possible but uncommon risks of the hysteroscopic tubal sterilization methods include perforation by the device at insertion and expulsion of the device. Tubal and uterine perforation was reported to range from 0% to 1.8% (335). Other potential combinations with transcervical sterilization are related to the hysteroscopy procedure, not the tubal occlusion process. These include hypervolemia, injury to surrounding organs, bleeding, and infection and occur in less than 1% of cases. **[12]** Between November 2002 and May 2015, the FDA received a total of 5,093 reports related to Essure, prompting it to convene a panel to review the safety and effectiveness

of Essure sterilization. In 2016, the FDA ordered the manufacturer to conduct a postmarket surveillance study to determine heightened risks for particular women, and issue a black box warning about risk of perforation, persistent pain and suspected allergic or hypersensitivity reactions (336). Subsequently, in July 2018, due to a decline in sales, the manufacturer removed the device from the market.

Sterilization Failure With Essure

A meta-analysis of 31 studies including more than 12,000 procedures reported bilateral placement rates of 81% to 98% with higher success rates reported from studies published since 2007 (337). Reasons for failure of insertion were tubal obstruction, stenosis, or difficulty in accessing the tubal ostia. In a review of over 66,000 Essure placements, there were 102 pregnancies (1.5 per 1,000). Seventy-six percent occurred in women who did not have postprocedure imaging to confirm tubal occlusion, did not have reliable contraception prior to confirmation imaging or had misread imaging (338). Other studies report similar rates of pregnancy, ranging from 1.2 to 1.5 per 1,000 (339).

Reversal of Sterilization

Reversal of sterilization is more successful after mechanical occlusion than after electrocoagulation, because the latter method destroys much more of the tube. With modern microsurgical techniques and an isthmus-to-isthmus anastomosis, the first-year pregnancy rate is about 44% (340). A retrospective review comparing microsurgical reanastomosis to in vitro fertilization (IVF) found similar total pregnancy rates, but a higher live birthrate with IVF because 10% of the pregnancies after microsurgery were ectopic (340). Hysteroscopic sterilization by *Essure* should be considered irreversible. However, reversal following hysteroscopic sterilization has been reported using tubouterine implantation. Thirty-six percent of those undergoing surgery subsequently conceived naturally (341).

Late Sequelae of Tubal Sterilization

Increased menstrual irregularity and pain are attributed to previous tubal sterilization. Study of the problem is complicated by the fact that many women develop these symptoms as they age, even though they did not have tubal surgery, and are treated with OCs that reduce pain and create an artificially normal menstrual cycle. Women who discontinue OC use after tubal sterilization will experience more dysmenorrhea and menstrual irregularity, which is unrelated to the sterilization. The best answer available comes from the CREST study (342). A total of 9,514 women who underwent tubal sterilization were compared with 573 women whose partners had undergone vasectomy. Both groups were followed up to 5 years with annual standardized telephone interviews. Women who underwent tubal sterilization were no more likely to report persistent changes in intermenstrual bleeding or length of the menstrual cycle than

women whose partners had vasectomy. The sterilized women reported decreases in the days of bleeding, amount of bleeding, and menstrual pain but were slightly more likely to report cycle irregularity (OR, 1.6; 95% CI, 1.1–2.3). In summary, the CREST study provided good evidence that there is no "posttubal ligation syndrome."

Vasectomy

About 500,000 vasectomies are performed each year in the United States (313). Vasectomy is a highly effective method. The literature on efficacy is often difficult to interpret because most studies report failure as failure to achieve azoospermia, rather than long-term pregnancy rates among the relevant women. **Vasectomy is not effective until all sperm are cleared by the reproductive tract, which can take up to 20 ejaculations or 3 months. It is estimated that up to half of pregnancies after vasectomy occur during the interval between the surgery and the clearance of all sperm** (343). Not all pregnancies after vasectomy can be attributed to the men who had the operation. **[13]** The best long-term information comes from the CREST study. The cumulative probability of failure was 7.4 per 1,000 procedures at 1 year and 11.3 at year 5, and comparable to the failure rate of tubal sterilization (313).

[13] Vasectomy is usually performed under local anesthesia. The basic technique is to palpate the vas through the scrotum, grasp it with fingers or atraumatic forceps, make a small incision over the vas, and pull a loop of the vas into the incision. A small segment is removed, and a needle electrode is used to coagulate the lumen of both ends. Improved techniques include the no-scalpel vasectomy, in which the pointed end of the forceps is used to puncture the skin over the vas. This technique reduces the risk of hematoma (344). Another variation is the open-ended vasectomy, in which only the abdominal end of the severed vas is coagulated while the testicular end is left open. This is believed to prevent congestive epididymitis and sperm granuloma (345). Fascial interposition creates a tissue barrier between the vasal ends and reduces vasectomy failure (346).

Reversibility

Vasectomy must be regarded as a permanent means of sterilization. However, among men undergoing surgical reanastomosis (vasovasostomy), subsequent patency has been reported in over 90% of cases when current microsurgical techniques are employed (347). Nevertheless, the longer the interval since vasectomy, the poorer is the chance of reversal (348).

Safety

Operative complications include scrotal hematomas, wound infection, and epididymitis, but serious sequelae are rare. There were no reports of deaths from vasectomy in the United States in many years, and the death rate in a large third-world series was only

0.5 per 100,000. Concerns about long-term safety recurred with the report of a possible association between prostate cancer and vasectomy (349). **[13] Large studies present the very clear conclusion that vasectomy is not associated with prostate cancer** (350–352).

ABORTION

It is extremely likely that couples will experience at least one unwanted pregnancy at some time during their reproductive years. In developing countries, desired family size is larger (although decreasing), but access to effective contraception is limited. As a result, abortion, often unsafe, is common. Because of population growth, the absolute number of abortions increased by 5.9 million, from 50.4 million per year from 1990 to 1994 to 56.3 million per year from 2010 to 2014 (353). Globally, 25% of pregnancies ended in abortion from 2010 to 2014. In the developed world, the percent of pregnancies ending in abortion declined by 11 points from 39% to 28%, whereas in the developing world, it increased significantly by 3 points from 21% to 24% (353). It is estimated that 25 million, or nearly half of all abortions are "unsafe" where either the persons terminating the pregnancy lack the necessary skills or the environment in which it is performed does not conform to minimal medical standards, or both (354).

As shown in **Figure 14-16**, there are large discrepancies in the rate of safe abortions compared with unsafe abortions worldwide. In the developed countries where there is access to legal abortion, unsafe abortions are rare. In developing countries, where abortion is often highly restricted or completely illegal, they are very common. The highest proportion of unsafe abortions are found in Middle and Western Africa, where mortality rates from abortion are highest. The subregions with the highest proportions of safe abortions (northern Europe and northern America) include countries with less restrictive laws on abortion, high contraceptive use, high economic development, high levels of gender equality, and well-developed health infrastructures (354). **[14]** **Where abortion is legal, it is generally safe; where it is illegal, complications are common.** Forty-seven thousand women die every year from complications of unsafe abortion (355). Societies cannot prevent abortion, but they can determine whether it will be illegal and dangerous or legal and safe. **[14]** Death from illegal abortion was once common in the United States. In the 1940s, more than 1,000 women died each year of complications from abortion (356). In 1972, 24 women died of complications of legal abortion and 39 died from known illegal abortions. In 2012, the most recent year for which complete data are available, there were four deaths from legally induced abortion and no deaths from illegal abortion (abortion induced by a nonprofessional) in the entire United States (6). The American Medical Association's Council on Scientific Affairs reviewed the impact of legal abortion and attributes the decline in deaths during this century to the introduction of antibiotics to treat sepsis; the widespread use of effective contraception beginning in the 1960s, which reduced the number of unwanted pregnancies; and the shift from illegal to legal abortion (357).

The number of abortions reported each year in the United States—926,000 in 2014—has been declining since the peak level of 1.61 million in 1990 (5). In 2014, the national

abortion ratio was 18.8 abortions for every 100 pregnancies, and the national abortion rate was 14.6 per 1,000 women aged 15 to 44 years (5). While abortion rates for all racial and ethnic groups have declined, they are significantly higher for non-Hispanic black women. Non-Hispanic white women have 37.5% of all abortions, non-Hispanic black women have 35.6%, and Hispanic women 19%. Most women who obtain abortions are unmarried, 85.2% in 2013 (6). The use of abortion varies markedly with age. In 2013, 11.3% of women obtaining abortions were between 15 and 19 years of age, and 44.7% were 24 years of age or younger. In 2013, the abortion ratio for women younger than 15 years of age was 789 per 1,000 live births **(Fig. 14-2)** (6). The lowest abortion ratio, 121 per 1,000 live births, is for women aged 30 to 34 years.

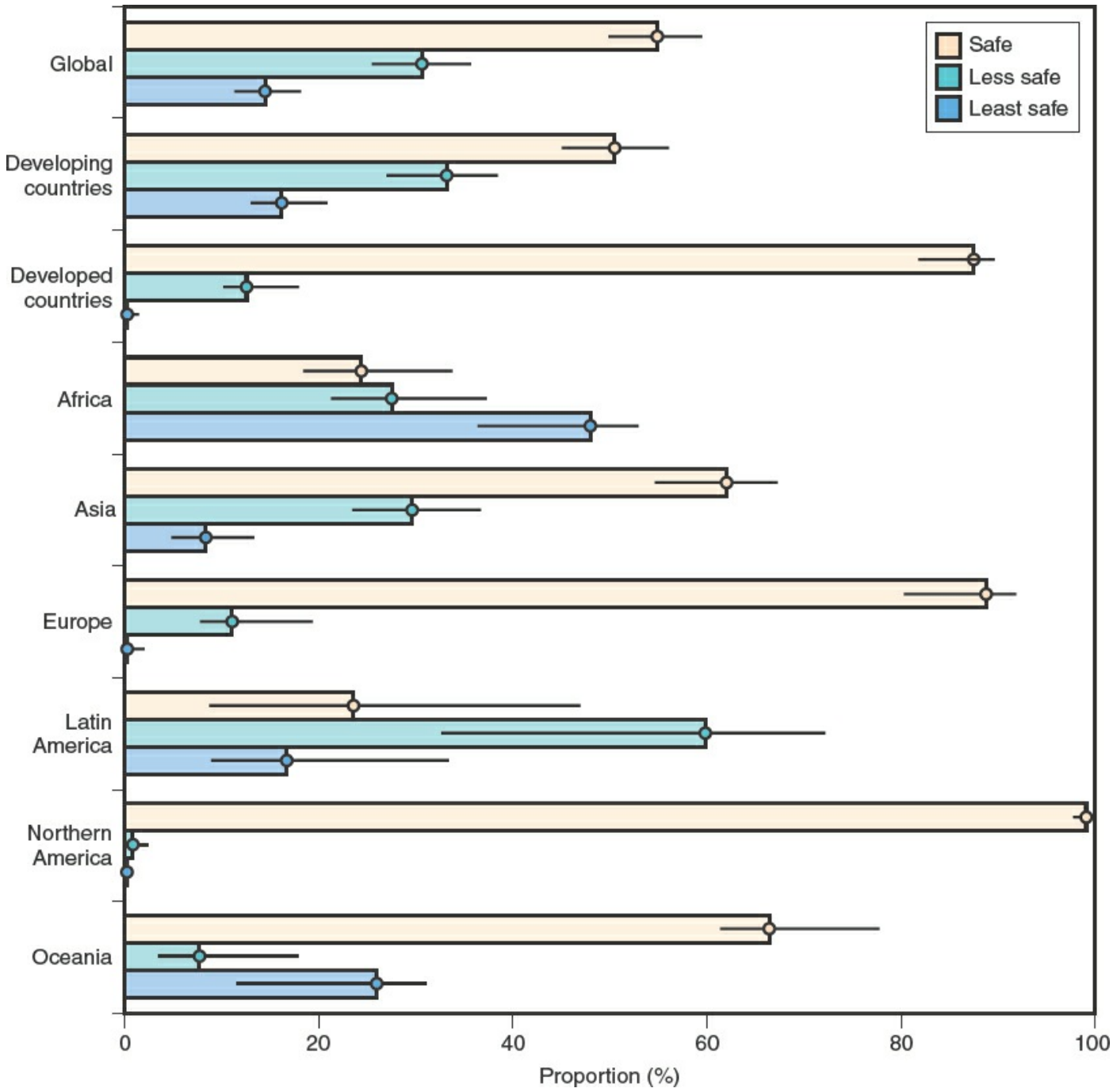


FIGURE 14-16 Distribution of abortion safety categories worldwide and by region. Bars and dots show the point estimates of the proportion of abortions in each category and horizontal lines are 90% uncertainty intervals. (From **Ganatra B, Gerdts C, Rossier C, et al.** Global, regional, and subregional classification of abortions by safety, 2010–14: estimates from a Bayesian hierarchical model. *Lancet* 2017;390[10110]:2372–2381.)

Regardless of personal feelings about the ethics of interrupting pregnancy, health professionals have a duty to know the medical facts about abortion and to share them with their patients (358). Providers are not required to perform abortions against their ethical principles, but they have a duty to help patients assess pregnancy risks and to make appropriate referrals.

Safety

[15] The overall annual risk of death with legal abortion decreased markedly, from 4.1 per 100,000 in 1972 to 1.8 in 1976, and remained less than 1 per 100,000 since 1987. Today, legal abortion remains an extremely safe procedure, with a mortality rate of 0.7 per 100,000 procedures (359). **[15]** Risk increases exponentially with gestational age. Pregnancy-associated mortality rate with aspiration procedures was 0.3 per 100,000 at or before 8 weeks and increased to 6.7 per 100,000 at 18 weeks or greater (359). Nevertheless, in comparison to a maternal mortality rate of 8.8 deaths per 100,000 live births, abortion by dilation and evacuation (D&E) beyond 18 weeks' gestation is safer than continuing pregnancy (360). It was estimated that 87% of the legal abortion deaths occurring after 8 weeks would have been prevented had the woman been able get abortion services by 8 weeks (361).

For individual women with high-risk conditions (e.g., cyanotic heart disease), even late abortion is a safer alternative to birth. Because of the availability of low-cost, out-of-hospital, first-trimester abortion, 88% of legal abortions are performed during the first trimester (before 13 weeks of amenorrhea), when abortion is the safest.

Techniques for First-Trimester Abortion

Vacuum Curettage

Most first-trimester abortions are performed by vacuum curettage. Most are performed with local anesthesia with or without moderate sedation, and usually on an outpatient basis in a freestanding specialty clinic or doctor's office (362). Cervical dilation is accomplished with metal or plastic dilators, or by osmotic cervical dilators or *misoprostol* 400 μg, given vaginally or by the buccal route 3 to 4 hours before the procedure (363). A plastic vacuum cannula of 5- to 12-mm diameter is used with a manual vacuum source or an electric vacuum pump. Manual vacuum provided by a modified 50-mL syringe is as effective as the electric pump through 10 menstrual weeks (364). The Society of Family Planning recommends a short course of antibiotics preoperatively to lower the risk of infection following surgical abortion (365). A single dose of doxycycline is a safe and effective prophylactic antibiotic and can be taken with dinner the night preceding a procedure. A large retrospective study of women's health care visits within 6 weeks after an abortion using California Medicaid data estimated abortion-related complication rates (366). Complications following first-trimester aspiration procedures are presented in Table 14-5. Major complications, defined as requiring hospital admission, surgery or blood transfusion, occurred in 0.16% of first-trimester aspiration abortions. The most common complications were other or undetermined diagnoses, most of which led to repeat abortions. More extensive descriptions of the management of complications are published elsewhere (367).

Table 14-5 Distribution of Abortion-Related Complication Diagnoses Among 34,755 First-Trimester Aspiration Procedures

Complication Diagnosis	
Incomplete abortion	116 (0.33)
Failed abortion	14 (0.04)
Hemorrhage	44 (0.13)
Infection	94 (0.27)
Uterine perforation	2 (0.01)
Anesthesia-related	2 (0.01)
Other or undetermined[a]	166 (0.48)
Total	438 (1.26)

[a]For major complications, this diagnosis includes undetermined diagnoses that required blood transfusions and surgery. For minor complications, the majority of this diagnosis consisted of cases treated with repeat abortion, but the exact diagnosis could not be determined. This category also includes diagnoses such as nonanesthesia-related allergic reactions and seizures.

Data are *n* (%).

Adapted from **Upadhyay UD, Desai S, Zlidar V, et al.** Incidence of emergency department visits and complications after abortion. *Obstet Gynecol* 2015;125(1):175–183.

Medical Abortion in the First Trimester

Mifepristone (RU486), an analog of the progestin *norethindrone,* has a strong affinity for the progesterone receptor but acts as an antagonist, blocking the effect of natural progesterone. Given alone, the drug was moderately effective in causing abortion of early pregnancy; the combination of *mifepristone* with a low dose of *prostaglandin* proved very effective, producing complete abortion in 96% to 99% of cases (368). In 2016, the FDA approved updated labeling for *mifepristone.* Changes included expansion of its use to 70 days from the start of the last menstrual period and a decrease in dose from 600 to 200 mg. Furthermore, misoprostol dose was increased from 400 mcg orally to 800 mcg buccally and home administration was allowed. Lastly, a posttreatment examination visit to the clinic was no longer required. These label changes were adopted because 200 mg of *mifepristone* was as effective as 600 mg, 800-mcg misoprostol by vaginal or buccal routes provide higher efficacy than 400-mcg oral dose, misoprostol can be taken at 24, 48, or 72 hours after mifepristone with equal efficacy, and women may safely self-administer misoprostol at home (369–373). Misoprostol can be taken by buccal or vaginal routes with similar blood levels and similar areas under the plasma concentration curve (AUC) (374,375). After case reports of death from *Clostridium sordellii,* a large cohort study was published by Planned

Parenthood describing the use of prophylactic *doxycycline* 100 mg twice a day for 1 week, and buccal rather than vaginal administration of *misoprostol* (376). No additional cases of *C. sordellii* have been recently reported. While individuals practitioners may decide to use antibiotics, the Society of Family Planning does not believe universal antibiotics are required for all women having a medical abortion.

Contraindications to medical abortion with *mifepristone/ misoprostol* include ectopic pregnancy; an IUD in place (remove IUD first); chronic adrenal failure; concurrent long-term corticosteroid therapy; history of allergy to *mifepristone, misoprostol,* or other *prostaglandins;* hemorrhagic disorder; and inherited porphyrias (377).

Methotrexate/Misoprostol and Misoprostol Alone

Alternatives to medical abortion when *mifepristone* is not available include regimens with *methotrexate/misoprostol* and *misoprostol* alone. The antifolate *methotrexate* provides another medical approach to pregnancy termination, but takes longer than the technique using *mifepristone/misoprostol* (378). Medical abortion can be induced with *misoprostol* alone, although it is less effective than the *mifepristone/misoprostol* combination. Vaginal *misoprostol,* 800 µg, repeated in 24 hours if fetal expulsion has not occurred, produces a complete abortion in 91% of pregnancies up to 56 days of amenorrhea (379).

Complications of Medical Abortion

Heavy or prolonged bleeding is the principal complication, with up to 8% of women experiencing some bleeding for as long as 30 days. Need for surgical curettage is predicted by the gestational age when the *mifepristone* is administered. Two percent of women treated at 49 days or less, 3% of those treated at 50 to 56 days, and 5% of those treated at 57 to 63 days needed curettage for bleeding or failed abortion in a large study with 200 mg of *mifepristone* and 800 µg of vaginal *misoprostol* (380). Late bleeding, at 3 to 5 weeks after expulsion of the pregnancy, accounted for more than half of the curettages. Under the updated protocol, serious complications requiring hospitalization for infection treatment or transfusion occur in fewer than 0.4% of patients (381). The updated regimen has been shown to cause fewer gastrointestinal side effects, such as nausea, vomiting, and diarrhea (382).

Medication Abortion and Telemedicine

With the 2016 mifepristone FDA label update excluding the requirement of in-clinic follow-up, telemedicine can facilitate the provision of medication abortions. Removing barriers to clinic access for rural women or mitigating the need for travel could reduce delays in receiving care and enable women to obtain an abortion at the earliest stages of pregnancy when it is safest (383). In one study, there were no differences in adverse events between in-person and telemedicine patients seeking medication abortion, and

telemedicine patients were more likely to recommend the service to a friend (384).

Second-Trimester Abortion

Abortions performed after 13 weeks include those done for fetal anomalies, medical illness, or delays resulting from pregnancy denial or difficulties making arrangements. Young maternal age is the single greatest factor determining the need for late abortion (6).

Dilation and Evacuation

D&E is the most commonly used method of midtrimester abortion in the United States. Prior to surgery, it is essential to prepare the cervix (to make it soft and pliable). There are a number of approaches to cervical ripening in this setting:

1. The cervix can be prepared by insertion of hygroscopic dilators, stems of the seaweed *Laminaria japonica* (laminaria), or Dilapan-S hydrophilic polymer rods. Placed in the cervical canal as small rods, these devices take up water from the cervix and swell, producing mechanical dilation, and induce endogenous prostaglandin synthesis, which aids in cervical softening. When the dilators are removed the following day, sufficient cervical dilation is accomplished to allow insertion of specialized forceps and a large-bore vacuum cannula to extract the fetus and placenta (385,386). Ultrasound guidance during the procedure is helpful (387). At the end of the midtrimester, procedures that combine serial insertion of two or more sets of laminaria or Dilapan-S for increased cervical dilation with a feticidal injection, or a combination of dilators with misoprostol to induce labor, followed by assisted expulsion of the fetus are possible (388).
2. Misoprostol can also be used for cervical preparation prior to midtrimester abortion. Osmotic dilator placement more effectively dilates and prepares the cervix before D&E than misoprostol alone (389,390). However, misoprostol in lieu of osmotic dilators has not been shown to increase the rate of serious complications. A large case series of D&Es between 17 and 23 weeks performed by highly experienced providers in women who received multidose misoprostol regimen as an alternative to overnight dilation reported a major complication rate less than 2% (391). However, the average dose of misoprostol used was 1,200 mcg.
3. Mifepristone is another option. A recent study comparing mifepristone as an adjunct or replacement for osmotic dilators in women undergoing D&E between 19 and 23 weeks found that, while median total procedure time was slightly longer for the mifepristone group compared to women who received mifepristone and osmotic dilators or only osmotic dilators, there were no differences in complications between the three groups (392). While some providers insert osmotic dilators sequentially over the course of 2 days, an RCT of D&Es from 19 to 23 weeks

showed that there were no differences in procedure times, initial cervical dilation, ease of procedure, or complications in women who received overnight synthetic osmotic dilators with mifepristone and misoprostol compared to women who received 2 days of dilators and misoprostol (393).

Intact D&E is another modification useful for procedures at the end of the midtrimester. After wide cervical dilation is achieved with serial placement of cervical dilators, the membranes are ruptured and an assisted breech delivery is performed, with decompression of the after-coming fetal head to allow delivery of the fetus intact (394). In response to the federal abortion ban of 2003, an increasing number of providers are using feticidal agents prior to late second-trimester terminations (395). Intra-amniotic or intrafetal *digoxin* and intracardiac *potassium chloride* are the two most common agents used for this purpose. Both are efficacious with little maternal adverse effects (396,397). The clinical utility of these agents is unproven. The only randomized controlled study looking at clinical outcomes found no change in procedure time or blood loss with the use of *digoxin* (398). Varying doses of *digoxin* were reported. In one study, 1.5-mg intra-amniotic *digoxin* was always successful in inducing fetal demise within 24 hours (399).

Labor-Induction Methods

In Europe and the United Kingdom, labor induction is much more common than D&E for midtrimester abortion (400). Induction abortion with hypertonic saline or urea was widely employed for labor induction abortion in the 1970s. These were supplanted by the use of synthetic prostaglandins, and by regimens that combine *mifepristone* and *misoprostol*.

Prostaglandins

Prostaglandins of the E and F series can cause uterine contraction at any stage of gestation. The 15 methyl analogs of prostaglandin $F_2\alpha$ (*carboprost*) and prostaglandin E_2 (*dinoprostone*) are highly effective for midtrimester abortion but frequently produce side effects of vomiting, diarrhea, and with *dinoprostone,* fever. *Misoprostol*, a 15 methyl analog of PGE_1, is much less expensive than other prostaglandins, stable at room temperature, and at doses effective for abortion, produces fewer side effects (401). Transient fetal survival is not infrequent after prostaglandin inductions. In the United States, it is common to induce fetal demise before induction with regimens similar to those used in late second-trimester D&E: intra-amniotic or intrafetal *digoxin,* 1 to 1.5 mg, or fetal intracardiac *potassium chloride* (3 mL of a 2-mmol solution).

Midtrimester Mifepristone/Misoprostol

Mifepristone pretreatment markedly increases the abortifacient efficacy of *gemeprost* and *misoprostol*. *Mifepristone,* 200 mg, is just as effective for this purpose as 600 mg

(402). A common protocol was developed using *mifepristone* and *misoprostol* that is now recommended by the Royal College of Obstetricians and Gynecologists (RCOG) and the WHO (403,404). Most women are cared for as hospital day-patients without need for overnight admission, a marked improvement over the labor induction methods of the past that often required 2 to 3 days of hospitalization. In the United States, ACOG recommends administering mifepristone, 200 mg orally, followed in 24 to 48 hours by either 800-mcg misoprostol vaginally followed by 400 mcg vaginally every 3 hours, or 400-mcg misoprostol buccally every 3 hours (405). Earlier studies evaluated intervals of 24 to 48 hours between dosing mifepristone and misoprostol. A systematic review including studies of 24- to 48-hour intervals calculated weighted median induction times of 7.6 hours for 1-day interval and 6.8 hours for 2-day interval (406). When comparing mifepristone–misoprostol intervals of 36 to 48 hours to intervals of 24 hours or less, shorter intervals on average had only minimally longer induction times (1 to 2 hours) but consistently much shorter overall total procedure times (mifepristone to pregnancy expulsion).

Combination of Induction and Assisted Delivery

Hern developed a procedure that combines a feticidal injection of *digoxin* with serial insertion of multiple laminaria tents over 2 to 3 days, followed by amniotomy, placement of *misoprostol* in the lower uterine segment, and intravenous *oxytocin* to induce labor, and then an assisted delivery (407). The procedure was successful in a large case series at 18 to 34 weeks with very few complications.

Complications of Second-Trimester Abortion

Surgical Abortion Complications

Complications of second-trimester surgical abortion are uncommon, but risk increases with gestational age. Complications and their frequency encountered in almost 3,000 midtrimester abortions performed by laminaria followed by D&E on a referral service are listed in Table 14-6. The gestational ages were 14 to 27 weeks and mean gestational age was 20.2 weeks. The most common complication was a cervical laceration that required suturing. A major complication, defined as one necessitating transfusion, disseminated intravascular coagulation, reoperations with uterine artery embolization, laparoscopy, or laparotomy, was encountered in 1.3% of patients. History of two or more cesareans, gestational period of 20 weeks or more, and insufficient initial cervical dilation by laminaria were independent risk factors for a major complication in a multivariate analysis (408). The rates of complication in Table 14-6 cannot be directly compared to the rates of complications with labor-induction abortion described below because half of the D&E group were 20 weeks or more gestation, while only a few of the induction patients were more than 20 weeks.

Table 14-6 Complications of 2,935 Midtrimester Dilation and Evacuation Abortion and Intervention Rates on a Referral Service

	Number (%)	95% Confidence Interval (%)
Complication		
Cervical laceration	99 (3.3)	2.7–4.0
Atony	78 (2.6)	2.1–3.3
Hemorrhage	30 (1.0)	0.6–1.4
Other	15 (0.5)	0.3–0.8
Disseminated intravascular coagulation	7 (0.2)	0.1–0.4
Retained products	6 (0.2)	0.04–0.4
Perforation	6 (0.2)	0.04–0.4
Treatment of Complications		
Reaspiration	46 (1.5)	1.1–2.0
Hospitalization	42 (1.4)	1.0–1.8
Transfusion	30 (1.0)	0.7–1.4
Uterine artery embolization	21 (0.7)	0.4–1.0
Laparoscopy or laparotomy	13 (0.4)	0.2–0.7

From **Frick AC, Drey EA, Diedrich JT, et al.** Effect of prior cesarean delivery on risk of second-trimester surgical abortion complications. *Obstet Gynecol* 2010;115:762; Table 2, with permission.

Induction Abortion Complications

The labor-induction methods share common hazards: failure of the primary procedure to produce abortion within a reasonable time, incomplete abortion, retained placenta, hemorrhage, infection, and embolic phenomena. With modern protocols, these are rare. In a series of 1,002 women treated with *mifepristone* and *misoprostol* at 13 to 21 weeks, 0.7% required a blood transfusion, 0.3% required ergot treatment for hemorrhage, and one required laparotomy for otherwise uncontrollable hemorrhage; 2.6% of patients received antibiotics for presumed pelvic infection after hospital discharge and 7.9% complained of prolonged bleeding (409). Uterine rupture has been reported in women with previous cesarean delivery treated with *misoprostol* in the midtrimester. In a case series of 101 women with one or more previous cesarean births and three smaller case series totaling 87 patients, no ruptures occurred (410). In another retrospective study of women 14 to 26 weeks undergoing induction, there were 3

ruptures, all in women who had 2 or more cesarean sections. These women had received 200 mcg vaginal misoprostol every 4 hours. The uterine rupture rate in these women alone was 11.5% (411). The Society of Family Planning recommends consideration of a 200 mcg or lower dose for women with a prior uterine scar, but concludes that data are insufficient to advise a change in dosing interval (412).

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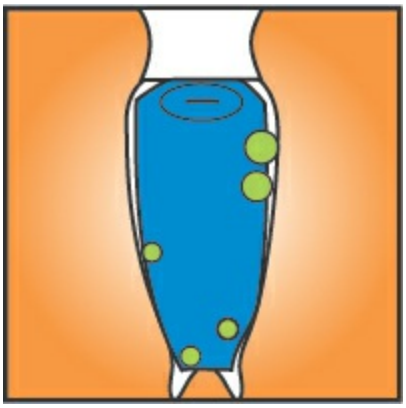
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CHAPTER 15

Genitourinary Infections and Sexually Transmitted Diseases



Oluwatosin Goje

The Normal Vagina
Vaginal Infections
- Bacterial Vaginosis
  - *Diagnosis*
  - *Treatment*
- Trichomonas Vaginitis
  - *Diagnosis*
  - *Treatment*
- Vulvovaginal Candidiasis
  - *Diagnosis*
  - *Treatment*
  - *Recurrent Vulvovaginal Candidiasis*
- Inflammatory Vaginitis
- Atrophic Vaginitis
- Cervicitis
  - *Diagnosis*
  - *Treatment*
- Pelvic Inflammatory Disease
  - *Diagnosis*
  - *Treatment*
- Tubo-Ovarian Abscess

Other Major Infections
- Genital Ulcer Disease
  - *Diagnosis*
  - *Treatment*

Genital Warts
Human Immunodeficiency Virus
Diagnosis
Treatment
Urinary Tract Infection
Acute Cystitis
Diagnosis
Treatment
Recurrent Cystitis
Urethritis
Acute Pyelonephritis

KEY POINTS

1 Vulvovaginitis is diagnosed by office-based testing.
2 More prolonged antifungal therapy is indicated for women with complicated vulvovaginal candidiasis (VVC) than for those with uncomplicated disease.
3 Women with normal physical examination findings and no evidence of fungal infection disclosed by microscopy are unlikely to have VVC and should not be treated empirically unless results of a vaginal yeast culture are positive.
4 Cervicitis is commonly associated with bacterial vaginosis (BV), which, if not treated concurrently, leads to significant persistence of the symptoms and signs of cervicitis.
5 Women with mild-to-moderate pelvic inflammatory disease (PID) can be treated as outpatients.
6 Trocar drainage, with or without placement of a drain, is successful in as many as 90% of patients with PID complicated by tubo-ovarian abscess that fails to respond to antimicrobial therapy within 72 hours.
7 Because false-negative results are common with herpes simplex virus (HSV) cultures, especially in patients with recurrent infections, type-specific glycoprotein G-based (IgG) antibody assay tests are useful in confirming a clinical diagnosis of genital herpes.
8 Suppressive treatment partially decreases symptomatic and asymptomatic viral shedding and the potential for transmission.

Genitourinary tract infections are among the most frequent disorders for which patients seek care from gynecologists. By understanding the pathophysiology of these diseases, and having an effective approach to their diagnosis, physicians can institute appropriate antimicrobial therapy to treat these conditions and reduce long-term sequelae.

THE NORMAL VAGINA

Normal vaginal secretions are composed of vulvar secretions from sebaceous, sweat, Bartholin, and Skene glands; transudate from the vaginal wall; exfoliated vaginal and cervical cells; cervical mucus; endometrial and oviductal fluids; and micro-organisms and their metabolic products. The type and amount of exfoliated cells, cervical mucus, and upper genital tract fluids are determined by biochemical processes that are influenced by hormone levels (1). Vaginal secretions may increase in the middle of the

menstrual cycle because of an increase in the amount of cervical mucus.

The vaginal desquamative tissue is made up of vaginal epithelial cells that are responsive to varying amounts of estrogen and progesterone. Superficial cells, the main cell type in women of reproductive age, predominate when estrogen stimulation is present. Intermediate cells predominate during the luteal phase because of stimulation by progesterone. Parabasal cells predominate in the absence of either hormone, a condition that may be found in postmenopausal women who are not receiving hormonal therapy.

The normal vaginal flora is mostly aerobic, with an average of six different species of bacteria, the most common of which is hydrogen peroxide–producing lactobacilli. The microbiology of the vagina is determined by factors that affect the ability of bacteria to survive (2). These factors include vaginal pH and the availability of glucose for bacterial metabolism. **The pH level of the normal vagina is lower than 4.5, which is maintained by the production of lactic acid.** Estrogen-stimulated vaginal epithelial cells are rich in glycogen. Vaginal epithelial cells break down glycogen to monosaccharides, which can be converted by the cells themselves, and lactobacilli to lactic acid.

[1] Normal vaginal secretions are floccular in consistency, white in color, and usually located in the dependent portion of the vagina (posterior fornix). Vaginal secretions can be analyzed by a wet-mount preparation. A sample of vaginal secretions is suspended in 0.5 mL of normal saline in a tube, transferred to a slide, covered with a slip, and assessed by microscopy. Some clinicians prefer to prepare slides by suspending secretions in saline placed directly on the slide. Secretions should not be placed on the slide without saline because this method causes drying of the vaginal secretions and does not result in a well-suspended preparation. Microscopy of normal vaginal secretions reveals many superficial epithelial cells, few white blood cells (less than one per epithelial cell), and few, if any, clue cells. **Clue cells are superficial vaginal epithelial cells with adherent bacteria, usually *Gardnerella vaginalis*, which obliterates the crisp cell border when visualized microscopically.** Potassium hydroxide 10% (KOH) may be added to the slide, or a separate preparation can be made, to examine the secretions for evidence of fungal elements. The results are negative in women with normal vaginal microbiology. Gram stain reveals normal superficial epithelial cells and a predominance of gram-positive rods (lactobacilli).

VAGINAL INFECTIONS

Bacterial Vaginosis

Bacterial vaginosis (BV) is a polymicrobial clinical syndrome resulting in alteration of normal vaginal bacterial flora that results in the loss of hydrogen peroxide–

producing lactobacilli and an overgrowth of predominantly anaerobic bacteria (3,4). **The most common form of vaginitis in the United States is BV** (5). Anaerobic bacteria can be found in less than 1% of the flora of normal women. In women with BV, however, the concentration of anaerobes, and *G. vaginalis* and *Mycoplasma hominis*, is 100 to 1,000 times higher than in normal women. Lactobacilli are usually absent.

It is not known what triggers the disturbance of normal vaginal flora. It is postulated that repeated alkalinization of the vagina, which can occur with frequent sexual intercourse or use of douches, plays a role. After normal hydrogen peroxide– producing lactobacilli disappear, it is difficult to reestablish normal vaginal flora, and recurrence of BV is common.

Numerous studies show an association of BV with significant adverse sequelae. Women with BV are at increased risk for pelvic inflammatory disease (PID), postabortal PID, postoperative cuff infections after hysterectomy, and abnormal cervical cytology (6–10). **Pregnant women with BV are at risk for premature rupture of the membranes, preterm labor and delivery, chorioamnionitis, and postcesarean endometritis** (8–9). In women with BV who are undergoing surgical abortion or hysterectomy, perioperative treatment with *metronidazole* eliminates this increased risk (10).

Diagnosis

Office-based testing is required to diagnose BV. It is diagnosed on the basis of the following findings (11): clinical criteria require three of the following signs or symptoms (Amsel Diagnostic Criteria):

1. **A fishy vaginal odor, which is particularly noticeable following coitus, and vaginal discharge are present.**
2. **Vaginal secretions are gray and thinly coat the vaginal walls.**
3. **The pH of these secretions is higher than 4.5 (usually 4.7 to 5.7).**
4. **Microscopy of the vaginal secretions reveals an increased number of clue cells, and leukocytes are conspicuously absent. In advanced cases of BV, more than 20% of the epithelial cells are clue cells.**
5. **The addition of KOH to the vaginal secretions (the "whiff" test) releases a fishy, amine-like odor.**

Clinicians who are unable to perform microscopy should use alternative diagnostic tests such as a pH and amines test card, detection of *G. vaginalis* ribosomal RNA, or Gram stain (12). Culture of *G. vaginalis* is not recommended as a diagnostic tool because of its lack of specificity.

Treatment

Ideally, treatment of BV should inhibit anaerobes but not vaginal lactobacilli. **The following treatments are effective:**

1. ***Metronidazole*, an antibiotic with excellent activity against anaerobes but poor activity against lactobacilli, is the drug of choice for the treatment of BV.** A dose of 500 mg administered orally twice a day for 7 days should be used. Patients should be advised to avoid using alcohol during treatment with oral *metronidazole* and for 24 hours thereafter.
2. ***Metronidazole* gel, 0.75%, one applicator (5 g) intravaginally once daily for 5 days, may alternatively be prescribed.**

The overall cure rates range from 75% to 84% with the aforementioned regimens (5). ***Clindamycin* in the following regimens is effective in treating BV:**

1. ***Clindamycin* ovules, 100 mg, intravaginally once at bedtime for 3 days**
2. ***Clindamycin* bioadhesive cream, 2%, 100 mg intravaginally in a single dose**
3. ***Clindamycin* cream, 2%, one applicator full (5 g) intravaginally at bedtime for 7 days**
4. ***Clindamycin*, 300 mg, orally twice daily for 7 days**

Many clinicians prefer intravaginal treatment to avoid systemic side effects such as mild to moderate gastrointestinal upset and unpleasant taste. Treatment of the male sexual partner does not improve therapeutic response and therefore is not recommended (5).

Trichomonas Vaginitis

Trichomonas vaginitis*, the most prevalent nonviral sexually transmitted infection in the United States is caused by the sexually transmitted, flagellated parasite, *Trichomonas vaginalis (5,13). The transmission rate is high; 70% of men contract the disease after a single exposure to an infected woman, which suggests that the rate of male-to-female transmission is even higher. The parasite, which exists only in trophozoite form, is an anaerobe that has the ability to generate hydrogen to combine with oxygen to create an anaerobic environment. It often accompanies BV, which can be diagnosed in as many as 60% of patients with trichomonas vaginitis (13–15). *T. vaginalis* infection is associated with a two to threefold increased risk for HIV acquisition (15).

Diagnosis

Local immune factors and inoculum size influence the appearance of symptoms.

Symptoms and signs may be much milder in patients with small inocula of trichomonads, and trichomonas vaginitis often is asymptomatic (13–15).

1. **Trichomonas vaginitis is associated with a profuse, purulent, malodorous vaginal discharge that may be accompanied by vulvar pruritus.**
2. **A purulent vaginal discharge may exude from the vagina.**
3. **In patients with high concentrations of organisms, a patchy vaginal erythema and colpitis macularis ("strawberry" cervix) may be observed.**
4. **The pH of the vaginal secretions could be variable or higher than 5.0.**
5. **Microscopy of the secretions reveals motile trichomonads and increased numbers of leukocytes.**
6. **Clue cells may be present because of the common association with BV.**
7. **The whiff test may be positive.**

Morbidity associated with trichomonas vaginitis may be related to BV. Patients with trichomonas vaginitis are at increased risk for postoperative cuff cellulitis following hysterectomy (7). **Pregnant women with trichomonas vaginitis are at increased risk for premature rupture of the membranes and preterm delivery**. Because of the sexually transmitted nature of trichomonas vaginitis, women with this infection should be tested for other sexually transmitted diseases (STDs).

Treatment

The treatment of trichomonas vaginitis can be summarized as follows:

1. ***Metronidazole* is the drug of choice for treatment of vaginal trichomoniasis.** Both a single-dose (2 g orally) and a multidose (500 mg twice daily for 7 days) regimen are highly effective and have cure rates of about 95%.
2. ***Tinidazole* 2 g orally in a single dose is another recommended regimen.**
3. **The sexual partner should be treated.**
4. **Women who do not respond to initial therapy should be treated again with *metronidazole*, 500 mg, twice daily for 7 days.** If repeated treatment is not effective, the patient should be treated with a single 2-g dose of *metronidazole* once daily for 5 days or *tinidazole*, 2 g, in a single dose for 5 days.
5. **Patients who do not respond to repeated treatment with *metronidazole* or *tinidazole* and for whom the possibility of reinfection is excluded should be referred for expert consultation.** In these uncommon refractory cases, an important part of management is to obtain cultures of the parasite to determine its susceptibility to *metronidazole* and *tinidazole.*
6. **Retesting for *T. vaginalis* is recommended within 3 months following initial**

treatment due to high rate of reinfection.

7. ***Metronidazole* gel should not be used for the treatment of vaginal trichomoniasis.**

Vulvovaginal Candidiasis

An estimated 75% of women experience at least one episode of vulvovaginal candidiasis (VVC) during their lifetimes (5,16). Nearly 45% of women will experience two or more episodes (16). Few are plagued with a chronic, recurrent infection. *Candida albicans* is responsible for 85% to 90% of vaginal yeast infections. Other species of *Candida*, such as *Candida glabrata* and *Candida tropicalis*, can cause vulvovaginal symptoms and tend to be resistant to therapy. Candida are dimorphic fungi existing as blastospores, which are responsible for transmission and asymptomatic colonization, and as mycelia, which result from blastospore germination and enhance colonization and facilitate tissue invasion. The extensive areas of pruritus and inflammation often associated with minimal invasion of the lower genital tract epithelial cells suggest that an extracellular toxin or enzyme may play a role in the pathogenesis of this disease. A hypersensitivity phenomenon may be responsible for the irritative symptoms associated with VVC, especially for patients with chronic, recurrent disease. Patients with symptomatic disease usually have an increased concentration of these micro-organisms ($>10^4$ per mL) compared with asymptomatic patients ($<10^3$ per mL) (17).

Factors that predispose women to the development of symptomatic VVC include antibiotic use, pregnancy, immunosuppressive states, and diabetes (18–20). Pregnancy and diabetes are associated with a qualitative decrease in cell-mediated immunity, leading to a higher incidence of candidiasis.

It is helpful to categorize women with VVC as having either uncomplicated or complicated disease (Table 15-1).

Table 15-1 Classification of Vulvovaginal Candidiasis

Uncomplicated	Complicated
Sporadic or infrequent in occurrence	Recurrent symptoms
Mild to moderate symptoms	Severe symptoms
Likely to be *Candida albicans*	Non-albicans Candida
Immunocompetent women	Immunocompromised, e.g., diabetic women, HIV, immunosuppressive therapy

From **Sobel JD, Faro S, Force RW, et al.** Vulvovaginal candidiasis: Epidemiologic, diagnostic, and

therapeutic considerations. *Am J Obstet Gynecol* 1998;178:203–211.

Diagnosis

The main symptom of VVC is vulvar pruritus associated with a vaginal discharge that typically resembles cottage cheese. A few patients may have minimal vaginal discharge.

1. **The discharge can vary from watery to homogeneously thick.** Vaginal soreness, dyspareunia, vulvar burning, and irritation may be present. External dysuria ("splash" dysuria) may occur when micturition leads to exposure of the inflamed vulvar and vestibular epithelium to urine. Examination reveals erythema and edema of the labia and vulvar skin. Discrete pustulopapular peripheral lesions may be present. The vagina may be erythematous with an adherent, whitish discharge. The cervix appears normal.
2. **The pH of the vagina in patients with VVC is usually normal (<4.5).**
3. **Fungal elements, either budding yeast forms or mycelia, appear in as many as 80% of cases.** The results of saline preparation of the vaginal secretions usually are normal, although there may be a slight increase in the number of inflammatory cells in severe cases.
4. **The whiff test is negative.**
5. **A presumptive diagnosis can be made in the absence of fungal elements confirmed by microscopy if the pH and the results of the saline preparation evaluations are normal *and* the patient has increased erythema based on examination of the vagina or vulva. A fungal culture is recommended to confirm the diagnosis. Conversely, women with normal physical examination findings and no evidence of fungal elements disclosed by microscopy are unlikely to have VVC and should not be empirically treated unless a vaginal yeast culture is positive.**

Treatment

The treatment of VVC is summarized as follows:

1. **Topically applied azole drugs are the most commonly available treatment for VVC and are more effective than *nystatin*** (Table 15-2) (5). Treatment with azoles results in relief of symptoms and negative cultures in 80% to 90% of patients who have completed therapy. Symptoms usually resolve in 2 to 3 days. Short-course regimens up to 3 days are recommended. The short-course formulations have higher concentrations of the antifungal agent, causing an inhibitory concentration in the vagina that persists for several days.
2. **The oral antifungal agent, *fluconazole*, used in a single 150-mg dose, is**

recommended for the treatment of VVC. It appears to have equal efficacy when compared with topical azoles in the treatment of mild to moderate VVC (26). Patients should be advised that their symptoms will persist for 2 to 3 days so they will not expect additional treatment.

3. **[2] Women with complicated VVC (Table 15-1) benefit from an additional 150-mg dose of *fluconazole* given 72 hours after the first dose. Patients with complications can be treated with a more prolonged topical regimen lasting 10 to 14 days. Adjunctive treatment with a weak topical steroid, such as 1% *hydrocortisone* cream, may help relieve some of the external irritative symptoms.**

Table 15-2 Vulvovaginal Candidiasis—Topical Treatment Regimens

Butoconazole
2% cream (single dose bioadhesive product), 5 g intravaginally in a single application[a,b]
Clotrimazole
1% cream, 5 g intravaginally for 7–14 days[a,b]
2% cream 5 g intravaginally for 3 days
Miconazole
2% cream, 5 g intravaginally for 7 days[a,b]
200-mg vaginal suppository, one suppository for 3 days[a]
100-mg vaginal suppository, one suppository daily for 7 days[a,b]
4% cream 5 g intravaginally daily for 3 days
1,200-mg vaginal suppository, one suppository for 1 day
Nystatin
100,000-U vaginal tablet, one tablet for 14 days
Tioconazole
6.5% ointment, 5 g intravaginally, single dose[a,b]
Terconazole
0.4% cream, 5 g intravaginally daily for 7 days[a,b]
0.8% cream, 5 g intravaginally daily for 3 days[a,b]

80-mg suppository, one suppository daily for 3 days

[a]Oil-based, may weaken latex condoms.

[b]Available as over-the-counter preparation.

Adapted from **Workowski KA, Bolan GA; Centers for Disease Control and Prevention.** Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015;64(RR-03):1–137.

Recurrent Vulvovaginal Candidiasis

A small number of women develop recurrent VVC (RVVC), defined as four or more episodes in a year. Non-albicans candida species are observed in 10% to 20% of RVVC. These women experience persistent irritative symptoms of the vestibule and vulva. **Burning replaces itching as the prominent symptom in patients with RVVC**. The diagnosis should be confirmed by direct microscopy of the vaginal secretions and by fungal culture. **[3] Many women with RVVC presume incorrectly they have a chronic yeast infection. Many of these patients have chronic atopic dermatitis or atrophic vulvovaginitis.**

The treatment of patients with RVVC consists of inducing a remission of chronic symptoms with *fluconazole* (150 mg every 3 days for three doses). Patients should be maintained on a suppressive dose of this agent (*fluconazole*, 150 mg weekly) for 6 months (21). On this regimen, 90% of women with RVVC will remain in remission. After suppressive therapy, approximately half will remain asymptomatic. Recurrence will occur in the other half and should prompt reinstitution of suppressive therapy (21). Patients with RVVC should have a fungal culture performed to look for non-albicans candida, and potential resistance to fluconazole. If recurrence persists or in patients with non-albicans candida, Boric acid 600-mg vaginal suppository is recommended for 2 weeks (22,23).

Inflammatory Vaginitis

Desquamative inflammatory vaginitis **is a clinical syndrome characterized by diffuse exudative vaginitis, epithelial cell exfoliation, and a profuse purulent vaginal discharge** (24). The cause of inflammatory vaginitis is unknown, but Gram stain findings reveal a relative absence of normal long gram-positive bacilli (lactobacilli) and their replacement with gram-positive cocci, usually streptococci. Women with this disorder have a purulent vaginal discharge, vulvovaginal burning or irritation, and dyspareunia. A less frequent symptom is vulvar pruritus. Vaginal erythema is present, and there may be an associated vulvar erythema, vulvovaginal ecchymotic spots, and colpitis macularis. The pH of the vaginal secretions is uniformly higher than 4.5 in these patients. Microscopy of the vaginal secretions, shows an increase in inflammatory cells and parabasal epithelial cells (immature squamous cells). Vaginal flora is abnormal and pH is always elevated above 4.5.

Topical vaginal clindamycin and local vaginal corticosteroids are used as treatment. Initial therapy is the use of 2% *clindamycin* cream, one applicator full (5 g) intravaginally once daily for 4 weeks. Relapse occurs in about 30% of patients, who should be retreated with intravaginal 2% *clindamycin* cream or vaginal hydrocortisone 10% cream 3 to 5 g daily for 6 weeks. When relapse occurs in postmenopausal patients, supplementary hormonal therapy should be considered (28). Some women with relapse may benefit from maintenance therapy.

Atrophic Vaginitis

Estrogen plays an important role in the maintenance of normal vaginal ecology. **Women undergoing menopause, either naturally or secondary to surgical removal of the ovaries, may develop inflammatory vaginitis, which may be accompanied by an increased, purulent vaginal discharge. In addition, they may have dyspareunia and postcoital bleeding resulting from atrophy of the vaginal and vulvar epithelium.** Examination reveals atrophy of the external genitalia, along with a loss of the vaginal rugae. The vaginal mucosa may be somewhat friable. Microscopy of the vaginal secretions shows a predominance of parabasal epithelial cells and an increased number of leukocytes.

Atrophic vaginitis is treated with topical *estrogen* vaginal cream. Use of 1 g of *conjugated estrogen* cream intravaginally each day for 1 to 2 weeks generally provides relief. Maintenance *estrogen* therapy, either topical or systemic, should be considered to prevent recurrence of this disorder.

Cervicitis

The cervix is made up of two different types of epithelial cells: squamous epithelium and glandular epithelium. The cause of cervical inflammation depends on the epithelium affected. The ectocervical epithelium can become inflamed by the same micro-organisms that are responsible for vaginitis. The ectocervical squamous epithelium is an extension of and is continuous with the vaginal epithelium. Trichomonas, candida, and herpes simplex virus (HSV) can cause inflammation of the ectocervix. Conversely, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infect only the glandular epithelium (25,26).

Diagnosis

The diagnosis of cervicitis is based on the finding of a purulent endocervical discharge, generally yellow or green in color and referred to as "mucopus" (26).

1. **After removal of ectocervical secretions with a large swab, a small cotton swab**

is placed into the endocervical canal and the cervical mucus is extracted. The cotton swab is inspected against a white or black background to detect the green or yellow color of the mucopus. The zone of ectopy (glandular epithelium) is friable or easily induced to bleed. This characteristic can be assessed by touching the ectropion with a cotton swab or spatula.

2. **Placement of the mucopus on a slide that can be Gram stained will reveal the presence of an increased number of neutrophils (>30 per high-power field).** The presence of intracellular gram-negative diplococci, leading to the presumptive diagnosis of gonococcal endocervicitis, may be detected. If the Gram stain results are negative for gonococci, the presumptive diagnosis is chlamydial cervicitis.
3. **Tests for gonorrhea and chlamydia, preferably using nucleic acid amplification tests (NAAT), should be performed.** The microbial etiology of endocervicitis is unknown in about 50% of cases in which neither gonococci nor chlamydia is detected. *Mycoplasma genitalium,* an emerging sexually transmitted disease, can be detected in 10% to 30% of women with clinical cervicitis (5).

Treatment

Treatment of cervicitis consists of an antibiotic regimen recommended for the treatment of uncomplicated lower genital tract infection with both chlamydia and gonorrhea (5). Dual therapy is recommended for the treatment of gonorrhea, and cefixime is no longer a first-line regimen (Table 15-3) (5). Fluoroquinolone resistance is common in *N. gonorrhoeae* isolates, and, therefore, these agents are no longer recommended for the treatment of women with gonococcal cervicitis. It is imperative that all sexual partners be treated with a similar antibiotic regimen. **[4]** Cervicitis is commonly associated with BV, which, if not treated concurrently, leads to significant persistence of the symptoms and signs of cervicitis.

Table 15-3 Treatment Regimens for Gonococcal and Chlamydial Infections

Neisseria gonorrhoeae endocervicitis
Ceftriaxone, 250 mg IM in a single dose, PLUS
Azithromycin 1g orally in single dose
If ceftriaxone is not available:
Cefexime, 400 mg in a single dose, PLUS
Azithromycin 1 g orally in single dose
Chlamydia trachomatis endocervicitis
Azithromycin, 1 g orally (single dose), or

Doxycycline, 100 mg orally twice daily for 7 days

Adapted from **Workowski KA, Bolan GA; Centers for Disease Control and Prevention.** Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015;64(RR-03):1–137; **Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC).** Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010;59(RR-12):1–110. Erratum in: *MMWR Recomm Rep* 2011 Jan 14;60(1):18. Dosage error in article text.

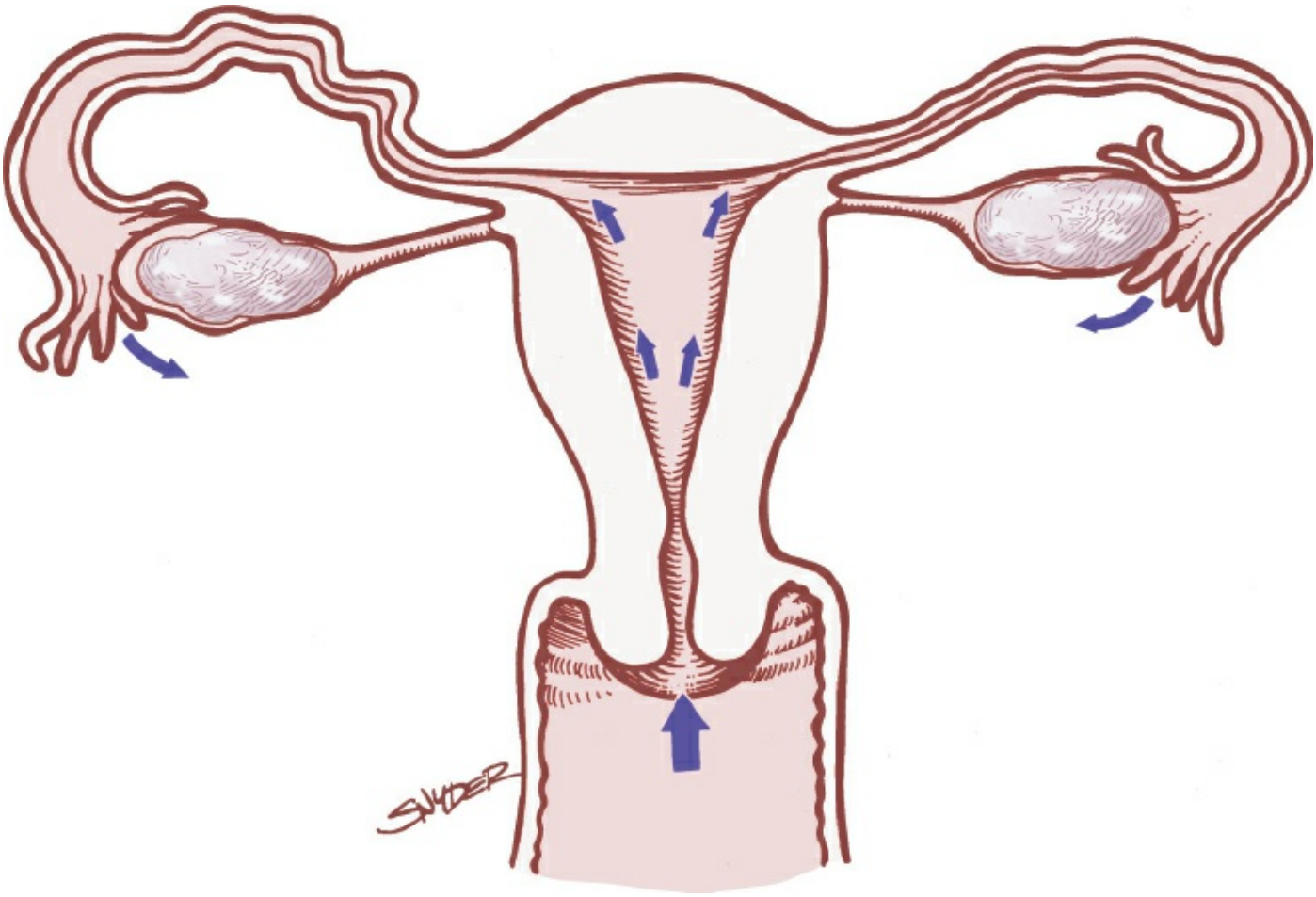


FIGURE 15-1 Micro-organisms originating in the endocervix ascend into the endometrium, fallopian tubes, and peritoneum, causing pelvic inflammatory disease (endometritis, salpingitis, peritonitis). (From **Soper DE**. Upper genital tract infections. In: Copeland LJ, ed. *Textbook of Gynecology*. Philadelphia, PA: Saunders, 1993:521, with permission.)

Pelvic Inflammatory Disease

PID is caused by microorganisms colonizing the endocervix and ascending to the endometrium and fallopian tubes. It is a clinical diagnosis implying that the patient has upper genital tract infection and inflammation. The inflammation may be present at any point along a continuum that includes endometritis, salpingitis, and peritonitis (Fig. 15-1).

PID is commonly caused by the sexually transmitted microorganisms *N.*

gonorrhoeae* and *C. trachomatis (27–29). Recent evidence suggests that *M. genitalium* can cause PID and presents with mild clinical symptoms similar to chlamydial PID (30). Endogenous microorganisms found in the vagina, particularly the BV microorganisms, are often isolated from the upper genital tract of women with PID. The BV microorganisms include anaerobic bacteria such as *Prevotella*, *Peptostreptococci,* and *G. vaginalis*. BV often occurs in women with PID, and the resultant complex alteration of vaginal flora may facilitate the ascending spread of pathogenic bacteria by enzymatically altering the cervical mucus barrier (31). Less frequently, respiratory pathogens such as *Haemophilus influenzae*, group A streptococci, and pneumococci can colonize the lower genital tract and cause PID.

Diagnosis

Traditionally, the diagnosis of PID is based on a triad of symptoms and signs, including pelvic pain, cervical motion and adnexal tenderness, and the presence of fever. It is recognized that there is wide variation in many symptoms and signs among women with this condition, which makes the diagnosis of acute PID difficult. Many women with PID exhibit subtle or mild symptoms that are not readily recognized as PID. Consequently, delay in diagnosis and therapy probably contributes to the inflammatory sequelae in the upper reproductive tract (32).

In the diagnosis of PID, the goal is to establish guidelines that are sufficiently sensitive to avoid missing mild cases but sufficiently specific to avoid giving antibiotic therapy to women who are not infected. Genitourinary tract symptoms may indicate PID; therefore, the diagnosis of PID should be considered in women with any genitourinary symptoms, including, but not limited to, lower abdominal pain, excessive vaginal discharge, menorrhagia, metrorrhagia, fever, chills, and urinary symptoms (33). **Some women may develop PID without having overt symptoms**.

Pelvic organ tenderness, either uterine tenderness alone or uterine tenderness with adnexal tenderness, is present in patients with PID. Cervical motion tenderness suggests the presence of peritoneal inflammation, which causes pain when the peritoneum is stretched by moving the cervix and causing traction of the adnexa on the pelvic peritoneum. Direct or rebound abdominal tenderness may be present.

Evaluation of both vaginal and endocervical secretions is a crucial part of the workup of a patient with PID (34). **In women with PID, an increased number of polymorphonuclear leukocytes may be detected in a wet mount of the vaginal secretions or in the mucopurulent discharge.**

More elaborate tests may be used in women with severe symptoms because an incorrect diagnosis may cause unnecessary morbidity **(Table 15-4)** (34). These tests include endometrial biopsy to confirm the presence of endometritis, ultrasound or radiologic tests to characterize a tubo-ovarian abscess, and laparoscopy to visually confirm salpingitis.

Treatment

Therapy regimens for PID must provide empirical, broad-spectrum coverage of likely pathogens, including *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, gram-negative facultative bacteria, anaerobes, and streptococci (5,35). Recommended regimens for the treatment of PID are listed in Table 15-5. **[5] An outpatient regimen of *cefoxitin* and *doxycycline* is as effective as an inpatient parenteral regimen of the same antimicrobials** (36). **Therefore, hospitalization is recommended only when the diagnosis is uncertain, pelvic abscess is suspected, clinical disease is severe, or compliance with an outpatient regimen is in question. Hospitalized patients can be considered for discharge when their fever has lysed (<99.5çF for more than 24 hours), the white blood cell count has become normal, rebound tenderness is absent, and repeat examination shows marked amelioration of pelvic organ tenderness** (37).

Table 15-4 Clinical Criteria for the Diagnosis of Pelvic Inflammatory Disease

Symptoms
None necessary
Signs
Pelvic organ tenderness
Leukorrhea and/or mucopurulent endocervicitis
Additional Criteria to Increase the Specificity of the Diagnosis
Endometrial biopsy showing endometritis
Elevated C-reactive protein or erythrocyte sedimentation rate
Temperature higher than 38°C (100.4°F)
Leukocytosis
Positive test for gonorrhea or chlamydia
Elaborate Criteria
Ultrasound documenting tubo-ovarian abscess
Laparoscopy visually confirming salpingitis

Sexual partners of women with PID should be evaluated and treated for urethral infection with chlamydia or gonorrhea (Table 15-3). One of these STDs usually is found in the male sexual partners of women with PID not associated with chlamydia or gonorrhea (38).

Tubo-Ovarian Abscess

An end-stage process of acute PID, tubo-ovarian abscess is diagnosed when a patient with PID has a pelvic mass that is palpable during bimanual examination. The condition usually reflects an agglutination of pelvic organs (tube, ovary, bowel) forming a palpable complex. Occasionally, an ovarian abscess can result from the entrance of microorganisms through an ovulatory site. **[6] Tubo-ovarian abscess is treated with an antibiotic regimen administered in a hospital (Table 15-5). About 75% of women with tubo-ovarian abscess respond to antimicrobial therapy alone. Failure of medical therapy suggests the need for drainage of the abscess** (39). Although drainage may require surgical exploration, percutaneous drainage guided by imaging studies (ultrasound or computed tomography) should be used as an initial option if possible. Trocar drainage, with or without placement of a drain, is successful in up to 90% of cases in which the patient failed to respond to antimicrobial therapy after 72 hours (40).

Table 15-5 Guidelines for Treatment of Pelvic Inflammatory Disease

Outpatient Treatment
Cefoxitin, 2 g intramuscularly, plus probenecid, 1 g orally concurrently, *or*
Ceftriaxone, 250 mg intramuscularly, *or*
Equivalent cephalosporin
Plus:
Doxycycline, 100 mg orally 2 times daily for 14 days, *or*
Azithromycin, 500 mg initially and then 250 mg daily for a total of 7 days
Inpatient Treatment
Regimen A
Cefoxitin, 2 g intravenously every 6 hrs, *or*
Cefotetan, 2 g intravenously every 12 hrs
Plus:
Doxycycline, 100 mg orally or intravenously every 12 hrs
Regimen B
Clindamycin, 900 mg intravenously every 8 hrs
Plus:

Ceftriaxone, 1–2 g intravenously every 12 hrs, *or*
Gentamicin, intravenously (5 mg/kg of body weight) daily

[a]Outpatient treatment only, that is, women treated for PID as an outpatient should also receive *metronidazole* gel for BV if they have BV.

Adapted from **Soper DE.** Pelvic inflammatory disease. *Obstet Gynecol* 2010;116:419–428.

OTHER MAJOR INFECTIONS

Genital Ulcer Disease

In the United States, most patients with genital ulcers have genital HSV or syphilis (5,41–44). Others causes of sexually transmitted ulcers include **chancroid, followed by the rare occurrence of lymphogranuloma venereum (LGV) and granuloma inguinale (donovanosis). These diseases are associated with an increased risk for HIV infection.** Other infrequent and noninfectious causes of genital ulcers include abrasions, fixed drug eruptions, carcinoma, and Behçet disease.

Diagnosis

A diagnosis based on history and physical examination alone is often inaccurate. **Therefore, all women with genital ulcers should undergo a serologic test for syphilis** (42). Because of the consequences of inappropriate therapy, such as tertiary disease and congenital syphilis in pregnant women, diagnostic efforts are directed at excluding syphilis. Optimally, the evaluation of a patient with a genital ulcer should include: dark-field examination; direct immunofluorescence testing for *Treponema pallidum*, or PCR; culture or PCR testing for HSV; and culture for *Haemophilus ducreyi*. Dark-field or fluorescent microscopes and selective media to culture for *H. ducreyi* often are not available in most offices and clinics. Even after complete testing, the diagnosis remains unconfirmed in one-fourth of patients with genital ulcers. For this reason, most clinicians base their initial diagnosis and treatment recommendations on their clinical impression of the appearance of the genital ulcer **(Fig. 15-2)** and knowledge of the most likely cause in their patient population (41).

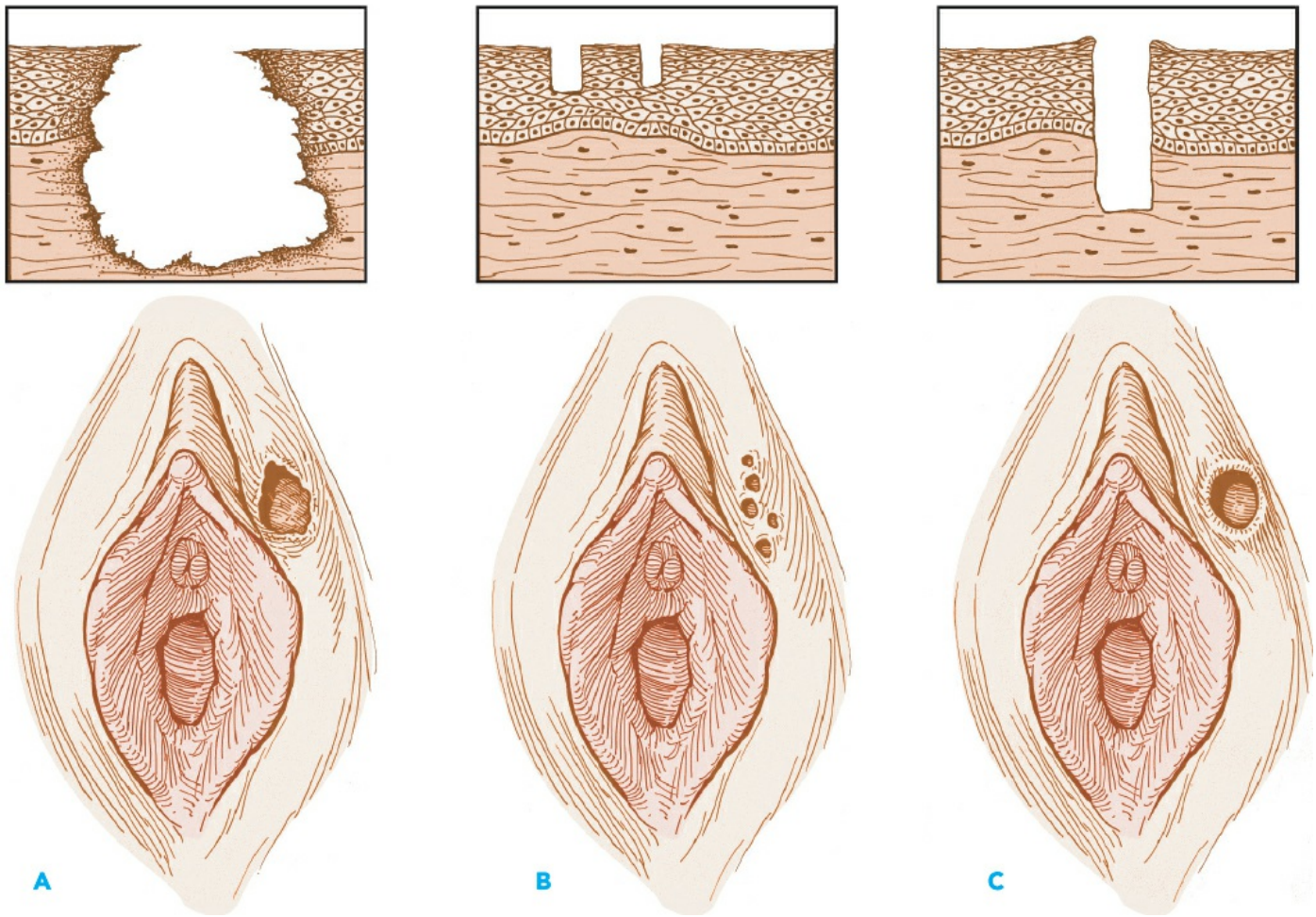


FIGURE 15-2 Showing the appearance of the ulcers of chancroid **(A)**, herpes **(B)**, and syphilis **(C)**. The ulcer of chancroid has irregular margins and is deep with undermined edges. The syphilis ulcer has a smooth, indurated border and a smooth base. The genital herpes ulcer is superficial and inflamed. (Modified from **Schmid GP, Shcalla WO, DeWitt WE**. Chancroid. In: Morse SA, Moreland AA, Thompson SE, eds. *Atlas of Sexually Transmitted Diseases*. Philadelphia, PA: Lippincott; 1990.)

Several clinical presentations are highly suggestive of specific diagnoses:

1. **A painless and minimally tender ulcer, not accompanied by inguinal lymphadenopathy, is likely to be syphilis, especially if the ulcer is indurated.** A nontreponemal rapid plasma reagin (RPR) test, or venereal disease research laboratory (VDRL) test, and a confirmatory treponemal test—fluorescent treponemal antibody absorption (FTA ABS) or microhemagglutinin–*T. pallidum* (MHA TP)—should be used to diagnose syphilis presumptively. Some laboratories screen samples with treponemal enzyme immunoassay (EIA) tests, the results of which should be confirmed with nontreponemal tests. The results of nontreponemal tests usually correlate with disease activity and should be reported quantitatively.
2. [7] **Grouped vesicles mixed with small ulcers, particularly with a history of such lesions, are almost always pathognomonic of genital herpes.** Nevertheless, laboratory confirmation of the findings is recommended because the **diagnosis of**

genital herpes is traumatic for many women, alters their self-image, and affects their perceived ability to enter new sexual relationships and bear children. Cell culture and PCR are preferred testing. HSV culture's sensitivity approaches 100% in the vesicle stage and 89% in the pustular stage and drops to as low as 33% in patients with ulcers. NAAT, including PCR assays for HSV DNA are more sensitive (5,43). Because false-negative results are common with HSV cultures, especially in patients with recurrent infections, type-specific glycoprotein G-based antibody assays are useful in confirming a clinical diagnosis of genital herpes.

3. **One to three extremely painful ulcers, accompanied by tender inguinal lymphadenopathy, are unlikely to be anything except chancroid.** This is especially true if the adenopathy is fluctuant.
4. **An inguinal bubo accompanied by one or several ulcers is most likely chancroid. If no ulcer is present, the most likely diagnosis is LGV.**

Treatment

Chancroid

Recommended regimens for the treatment of chancroid include *azithromycin,* 1 g orally in a single dose; *ceftriaxone*, 250 mg intramuscularly in a single dose; *ciprofloxacin*, 500 mg orally twice a day for 3 days; or *erythromycin* base, 500 mg orally four times daily for 7 days. Patients should be reexamined 3 to 7 days after initiation of therapy to ensure the gradual resolution of the genital ulcer, which can be expected to heal within 2 weeks unless it is unusually large.

Herpes

A first episode of genital herpes should be treated with *acyclovir*, 400 mg orally three times a day; or *famciclovir*, 250 mg orally three times a day; or *valacyclovir*, 1 g orally twice a day for 7 to 10 days or until clinical resolution is attained. Although these agents provide partial control of the symptoms and signs of clinical herpes, it neither eradicates latent virus nor affects subsequent risk, frequency, or severity of recurrences after the drug is discontinued. Daily suppressive therapy (*acyclovir*, 400 mg orally twice daily; or *famciclovir*, 250 mg twice daily; or *valacyclovir*, 1 g orally once a day) reduces the frequency of HSV recurrences by at least 75% among patients with six or more recurrences of HSV per year. **[8]** Suppressive treatment partially, but not totally, decreases symptomatic and asymptomatic viral shedding and the potential for transmission (5).

Syphilis

Parenteral administration of *penicillin G* is the preferred treatment of all stages of syphilis. *Benzathine penicillin G*, 2.4 million units intramuscularly in a single dose, is the recommended treatment for adults with primary, secondary, or early latent syphilis.

The Jarisch–Herxheimer reaction—an acute febrile response accompanied by headache, myalgia, and other symptoms—may occur within the first 24 hours after any therapy for syphilis; patients should be advised of this possible adverse reaction.

Latent syphilis is defined as those periods after infection with *T. pallidum* when patients are seroreactive but show no other evidence of disease. Patients with latent syphilis of longer than 1 year's duration or of unknown duration should be treated with *benzathine penicillin G*, 7.2 million units total, administered as three doses of 2.4 million units intramuscularly each, at 1-week intervals. All patients with latent syphilis should be evaluated clinically for evidence of tertiary disease (e.g., aortitis, neurosyphilis, gumma, and iritis). Quantitative nontreponemal VDRL or RPR serologic tests should be repeated at 6 months and again at 12 months. An initially high antibody titer (1:32) should decline at least fourfold (two dilutions) within 12 to 24 months.

Genital Warts

External genital warts are a manifestation of human papillomavirus (HPV) infection (5,45). The nononcogenic HPV types 6 and 11 are usually responsible for external genital warts. HPV types 16, 18, 31, 33, and 35 are occasionally found in anogenital warts. The warts tend to occur in areas most directly affected by coitus, namely the posterior fourchette and lateral areas on the vulva. Less frequently, warts can be found throughout the vulva, in the vagina, and on the cervix. Minor trauma associated with coitus can cause breaks in the vulvar skin, allowing direct contact between the viral particles from an infected man and the basal layer of the epidermis of his susceptible sexual partner. Infection may be latent or may cause viral particles to replicate and produce a wart. External genital warts are highly contagious; more than 75% of sexual partners develop this manifestation of HPV infection when exposed.

Table 15-6 Treatment Options for External Genital and Perianal Warts

Modality	Efficacy (%)	Recurrence Risk
Cryotherapy	63–88	21–39
Imiquimod 5% cream[a]	33–72	13–19
Podophyllin 10–25%	32–79	27–65
Podofilox 0.5%[a]	45–88	33–60

Trichloroacetic acid 80–90%	81	36
Electrodesiccation or cautery	94	22
Laser[b]	43–93	29–95
Interferon	44–61	0–67
Sinecatechin 15% ointment	60	ND

[a]May be self-applied by patients at home.

[b]Expensive; reserve for patients who have not responded to other regimens.

ND, no data.

The goal of treatment is removal of the warts; it is not possible to eradicate the viral infection. Treatment is most successful in patients with small warts that were present for less than 1 year. It is not determined whether treatment of genital warts reduces transmission of HPV. Selection of a specific treatment regimen depends on the anatomic site, size, and number of warts, and expense, efficacy, convenience, and potential adverse effects (Table 15-6). **Recurrences more often result from reactivation of subclinical infection than reinfection by a sex partner; therefore, examination of sex partners is not absolutely necessary.** However, many of these sex partners may have external genital warts and may benefit from therapy and counseling concerning transmission of warts. **HPV infection with types 6, 11, 16, 18, 31, 33, 45, 52, and 58 can be prevented by vaccination** (5).

Human Immunodeficiency Virus

It is estimated that almost 40% to 50% of individuals with human immunodeficiency virus (HIV) are women. Intravenous drug use and heterosexual transmission are responsible for most of the cases of AIDS in women in the United States (46,47). Infection with HIV produces a spectrum of disease that progresses from an asymptomatic state to full-blown AIDS. The pace of disease progression in untreated adults is variable. The median time between infection with HIV and the development of AIDS is 10 years, with a range from a few months to more than 12 years. In a study of adults infected with HIV, symptoms developed in 70% to 85% of infected adults, and AIDS developed in 55% to 60% within 12 years after infection. The natural history of the disease can be significantly altered by antiretroviral therapy (ART). **Early diagnosis**

and linkage to care are essential for a patient's health, and to reduce the risk of transmitting HIV to others. U.S. guidelines recommend all persons with HIV infection diagnoses be offered effective ART (47). Women with HIV-induced altered immune function are at increased risk for infections such as tuberculosis (TB), bacterial pneumonia, and *Pneumocystis jiroveci* pneumonia (PCP). Because of its impact on the immune system, HIV affects the diagnosis, evaluation, treatment, and follow-up of many other diseases and may decrease the efficacy of antimicrobial therapy for some STDs.

Diagnosis

Infection is most often diagnosed by HIV antibody tests. However, tests for HIV antibodies are often negative during the acute HIV phase (5). Antibody testing begins with a sensitive screening test such as enzyme-linked immunosorbent assay (ELISA) or a rapid assay. If confirmed by Western blot, a positive antibody test result confirms that a person is infected with HIV and is capable of transmitting the virus to others. HIV antibody is detectable in more than 95% of patients within 6 months of infection. Women diagnosed with any STI, particularly genital ulcer disease, should be offered HIV testing (5,15). **Routine HIV screening is recommended for women aged 19 to 64 years and targeted screening for women with risk factors outside of that age range** (46).

The initial evaluation of an HIV-positive woman includes screening for diseases associated with HIV, such as TB and STIs, administration of recommended vaccinations (hepatitis B, pneumococcal, meningococcal and influenza), and behavioral and psychosocial counseling. Intraepithelial neoplasia is strongly associated with HPV infection and occurs in high frequency in women with both HPV and HIV.

Treatment

ART is recommended for all HIV-infected individuals, regardless of CD4 T-lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection. ART is recommended for HIV-infected individuals to prevent HIV transmission (47). **When initiating ART, it is important to educate patients regarding the benefits and considerations regarding ART, and to address strategies to optimize adherence. Patients must be willing to accept therapy to avoid the emergence of resistance caused by poor compliance.** Dual nucleoside regimens used in addition to a protease inhibitor or nonnucleoside reverse transcriptase inhibitor provide a more durable clinical benefit, monotherapy is not recommended.

Patients with less than 200 CD4+ T cells per lL should receive prophylaxis against opportunistic infections, such as *trimethoprim/sulfamethoxazole* or aerosol *pentamidine* for the prevention of PCP pneumonia. Those with less than 50 CD4+ T cells per μL should receive *azithromycin* prophylaxis for mycobacterial infections (47).

URINARY TRACT INFECTION

Acute Cystitis

Women with acute cystitis generally have an abrupt onset of multiple, severe urinary tract symptoms including dysuria, frequency, and urgency associated with suprapubic or low-back pain. Suprapubic tenderness may be noted on physical examination. Urinalysis reveals pyuria and sometimes hematuria. Several factors increase the risk for cystitis, including sexual intercourse, the use of a diaphragm and a spermicide, delayed postcoital micturition, and a history of a recent urinary tract infection (48–50).

Diagnosis

***Escherichia coli* is the most common pathogen isolated from the urine of young women with acute cystitis, and it is present in 80% of cases** (51). *Staphylococcus saprophyticus* is present in an additional 5% to 15% of patients with cystitis. The pathophysiology of cystitis in women involves the colonization of the vagina and urethra with coliform bacteria from the rectum. For this reason, the effects of an antimicrobial agent on the vaginal flora play a role in the eradication of bacteriuria.

Treatment

High concentrations of *trimethoprim* and *fluoroquinolone* in vaginal secretions can eradicate *E. coli* while minimally altering normal anaerobic and microaerophilic vaginal flora. An increasing linear trend in the prevalence of resistance of *E. coli* (>10%) to the fluoroquinolones (e.g., *ciprofloxacin*) was noted (52). Despite a similar increase in *E. coli* resistance (9% to 18%) to *trimethoprim/ sulfamethoxazole*, therapeutic efficacy remains stable. In contrast, no such increase in resistance was noted with *nitrofurantoin*. *Nitrofurantoin* (macrocrystals, 100 mg orally twice daily for 5 days) or *trimethoprim/sulfamethoxazole* (160/800 mg orally twice daily for 3 days) are the optimal choices for empirical therapy for uncomplicated cystitis (52).

In patients with typical symptoms, an abbreviated laboratory workup followed by empirical therapy is suggested. The diagnosis can be presumed if pyuria is detected by microscopy or leukocyte esterase testing. Urine culture is not necessary, and a short course of antimicrobial therapy should be given. No follow-up visit or culture is necessary unless symptoms persist or recur.

Recurrent Cystitis

About 20% of premenopausal women with an initial episode of cystitis have recurrent infections. More than 90% of these recurrences are caused by exogenous reinfection. Recurrent cystitis should be documented by culture to rule out resistant microorganisms. **Patients may be treated by one of three strategies: (1) continuous prophylaxis; (2) postcoital prophylaxis; or (3) therapy initiated by the**

patient when symptoms are first noted.

Postmenopausal women may have frequent reinfections. **Hormonal therapy or topically applied estrogen cream, along with antimicrobial prophylaxis, is helpful in treating these patients.**

Urethritis

Women with dysuria caused by urethritis have a more gradual onset of mild symptoms, which may be associated with abnormal vaginal discharge or bleeding related to concurrent cervicitis. Patients may have a new sex partner or experience lower abdominal pain. Physical examination may reveal the presence of mucopurulent cervicitis or vulvovaginal herpetic lesions. *C. trachomatis*, *N. gonorrhoeae*, or genital herpes may cause acute urethritis. Nongonococcal, nonchlamydial urethritis could be caused by *M. genitalium* (5). Pyuria is present on urinalysis, but hematuria is rarely seen. Treatment regimens for chlamydia and gonococcal infections are presented in Table 15-3.

Occasionally, vaginitis caused by *C. albicans* or trichomonas is associated with dysuria. On careful questioning, patients generally describe external dysuria, sometimes associated with vaginal discharge, and pruritus and dyspareunia. They usually do not experience urgency or frequency. Pyuria and hematuria are absent.

Acute Pyelonephritis

The clinical spectrum of acute, uncomplicated pyelonephritis in young women ranges from gram-negative septicemia to a cystitis-like illness with mild flank pain. *E. coli* accounts for more than 80% of these cases (51). Microscopy of unspun urine reveals pyuria and gram-negative bacteria. A urine culture should be obtained in all women with suspected pyelonephritis; blood cultures should be performed in those who are hospitalized because results are positive in 15% to 20% of cases. In the absence of nausea and vomiting and severe illness, outpatient oral therapy can be given safely. Patients who have nausea and vomiting, are moderately to severely ill, or are pregnant should be hospitalized. Outpatient treatment regimens include *trimethoprim/sulfamethoxazole* (160/800 mg every 12 hours for 14 days) or a quinolone (e.g., *levofloxacin*, 750 mg daily for 7 days). Inpatient treatment regimens include the use of parenteral *levofloxacin* (750 mg daily), *ceftriaxone* (1 to 2 g daily), *ampicillin* (1 g every 6 hours), and *gentamicin* (especially if *Enterococcus* species are suspected) or *aztreonam* (1 g every 8 to 12 hours). Symptoms should resolve after 48 to 72 hours. If fever and flank pain persist after 72 hours of therapy, ultrasound or computed tomography should be considered to rule out a perinephric or intrarenal abscess or ureteral obstruction. A follow-up culture should be obtained 2 weeks after

the completion of therapy (53).

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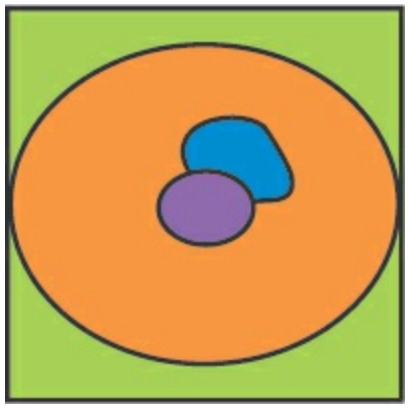
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CHAPTER 16

Intraepithelial Disease of the Cervix, Vagina, and Vulva



Francisco Garcia, Kenneth D. Hatch, Jonathan S. Berek

Cervical Intraepithelial Neoplasia
- Cervical Anatomy
  - *The Squamocolumnar Junction*
  - *Normal Transformation Zone*
- Human Papillomavirus
- Screening
  - *Cervical Cytology*
  - *Cervical Cytologic Screening Test Accuracy*
  - *Human Papillomavirus Testing in Screening*
  - *Cervical Cancer Screening Recommendations*
  - *Atypical Squamous Cells*
  - *Low-Grade Squamous Intraepithelial Lesions*
  - *High-Grade Squamous Intraepithelial Lesions*
- Colposcopic Diagnosis
  - *Colposcopy Findings*
  - *Clinical Pathologic Correlation*
- Management
  - *Clinical Disease Management Guidelines*
- Treatment Modalities
  - *Cryotherapy*
  - *Loop Electrosurgical Excision*
  - *Conization*
  - *Hysterectomy*

Vaginal Intraepithelial Neoplasia
- Diagnosis

Treatment
Vulvar Intraepithelial Disease
Vulvar Dystrophies
Vulvar Intraepithelial Neoplasia
VIN Treatment
Paget Disease of the Vulva
Histology
Clinical Features
Treatment

KEY POINTS

1 The criteria for the diagnosis of intraepithelial neoplasia may vary according to the pathologist, but the significant features are cellular immaturity, cellular disorganization, nuclear abnormality, and increased mitotic activity.

2 Metaplasia advances from the original squamocolumnar junction (SCJ) inward, toward the external os and over the columnar villi to establish the *transformation zone*. Cervical intraepithelial neoplasia (CIN) typically originates in the transformation zone at the advancing SCJ.

3 Infection with human papillomavirus (HPV) is the primary cause of cancer of the cervix and its precursor lesions. Persistent high-risk oncogenic HPV infection is the principal risk factor for the development of CIN. In the vast majority of cases, HPV infection will clear in 9 to 15 months.

4 Specific high-risk HPV types account for about 90% of high-grade intraepithelial lesions and cancer (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -68). HPV-16 is the most common HPV found in invasive cancer and in CIN 2 and CIN 3. Malignant transformation requires the expression of E6 and E7 HPV oncoproteins.

5 High-risk HPV testing is a critical component of the triage for equivocal (ASC-US) cytology, as a component of co-testing with simultaneous cytology, and as a stand-alone primary screening modality.

6 Evidence-based guidelines recommend that cervical cancer screening not begin until age 21 years, regardless of sexual history. For women 21 to 29 years, the recommendation is screening with cytology every 3 years. From 30 to 65 years co-testing with conventional cytology and high-risk HPV testing every 5 years or cytology alone every 3 years are appropriate alternatives. After the age of 65 it is appropriate to discontinue screening in women with a negative screening history as documented by either 3 negative cytology results or 2 negative co-tests in the previous 10 years.

7 The usefulness of high-risk HPV testing in the assessment of atypical squamous cells of unknown significance (ASC-US) Pap test results is well established, and aids in the identification of 90% of the patients with CIN 2 or 3 lesions.

8 Women with atypical squamous cells-high grade (ASC-H) should be referred to colposcopy because of the underlying risk of CIN 2 and/or 3, and should not be triaged with high-risk HPV testing.

9 Colposcopy is required for the evaluation of a low-grade squamous intraepithelial lesion (LSIL) cytology. Any woman with a cytology consistent with high-grade squamous intraepithelial lesion (HSIL) must undergo colposcopy and directed biopsy.

10 The minimum elements of a comprehensive colposcopic examination include visualization of squamocolumnar junction, identification of acetowhitening or other lesion(s), and an overall colposcopic impression (normal/benign, low grade, high grade, cancer).

11 It is a best practice for pathologists and colposcopists to review jointly the colposcopic examination findings, cytology, molecular testing, cervical biopsy, and endocervical sampling in order to develop a therapeutic and surveillance plan.

12 The evidence-based guidelines for the management of cervical cytologic and histologic entities lend

themselves to structured clinical algorithms that are available for download from the Web (www.asccp.org), on various mobile phone applications, and may be incorporated into a variety of electronic health record platforms.

13 CIN 1 is a histopathologic manifestation of HPV infection, not a cancer precursor. For CIN 1 that persists for 24 months or more, a patient with an adequate colposcopic examination may be given the choice of continued surveillance or destruction of the transformation zone with ablation or excision.

14 CIN 2 and CIN 3 lesions are neoplastic precursors and grouped for the purposes of diagnostic reporting and treatment. Women, 25 years of age and older, with adequate colposcopy and histologic documentation of CIN 2 and/or CIN 3 require destruction or excision of the transformation zone.

15 Although CIN 2 and CIN 3 can be treated with a variety of outpatient techniques, the preferred treatment is LEEP. Ablative therapy using cryotherapy, laser ablation, or any other technique is not appropriate if there is evidence of microinvasive or invasive cancer on cytology, colposcopy, endocervical curettage (ECC), or biopsy.

16 Adenocarcinoma *in situ* (AIS) is a cancer precursor, and the preferred management for women who have completed childbearing and have a histologic diagnosis of AIS on a specimen from a diagnostic excisional procedure is hysterectomy.

17 Loop excision should not typically be used before a high-grade intraepithelial lesion is identified with histopathology. However, treatment after an HSIL cytology may be appropriate among populations for whom colposcopic follow-up is not possible.

18 Conization is indicated for diagnosis in women with CIN 3 or atypical glandular cell (AGC)-adenocarcinoma *in situ*, but hysterectomy is the treatment of last resort for recurrent high-grade CIN.

19 Women with persistent abnormal cytology without evident cervical pathology and those with abnormal cytology after treatment of CIN should be examined carefully for vaginal intraepithelial neoplasia (VAIN). VAIN 1/HPV or VAIN 2 does not require treatment and may be managed with surveillance. VAIN 3 lesions that are adequately sampled to rule out invasive disease can be treated with laser therapy or excisional therapy.

20 Vulvar intraepithelial neoplasia (VIN) 3 is a neoplastic precursor and can be unifocal or multifocal. The therapeutic alternatives for VIN 3 are simple excision, laser ablation, and superficial vulvectomy.

CERVICAL INTRAEPITHELIAL NEOPLASIA

The concept of *preinvasive disease* of the cervix was introduced in 1947, when pathologists identified features suggestive of invasive cancer but confined to epithelium (1). Subsequent studies showed that these lesions left untreated could progress to cervical cancer (2). Improvements in cytologic assessment led to the identification of early precursor lesions known as *dysplasia,* a term that connotes the malignant potential of these lesions. Historically, carcinoma *in situ* (CIS) was treated very aggressively (most often with hysterectomy), whereas dysplasias were believed to be less significant and were not treated or were treated by colposcopic biopsy and cryosurgery. The concept of *cervical intraepithelial neoplasia* (CIN) was introduced in 1968, when Richart suggested that dysplasias have the potential for progression (3). **[1] The criteria for the diagnosis of intraepithelial neoplasia may vary according to the pathologist, but the significant features are cellular immaturity, cellular disorganization, nuclear abnormality, and increased mitotic activity.** The extent of the mitotic activity, immature cellular proliferation, and nuclear atypia identifies the

degree of neoplasia. If the presence of mitoses and immature cells is limited to the lower third of the epithelium, the lesion usually is designated as CIN 1. Involvement of the middle and upper thirds is diagnosed as CIN 2 and CIN 3, respectively **(Fig. 16-1)**.

Cervical Anatomy

The cervix is composed of *columnar epithelium,* which lines the endocervical canal, and *squamous epithelium,* which covers the exocervix (4). The point at which they meet is called the *squamocolumnar junction* (SCJ) (**Figs. 16-2** and **16-3**).

The Squamocolumnar Junction

The SCJ is not restricted to the external os. Instead, it is a dynamic point that changes in response to puberty, pregnancy, menopause, and hormonal stimulation **(Fig. 16-4)**. In neonates, the SCJ is located on the exocervix. At menarche, the production of estrogen causes the vaginal epithelium to fill with glycogen. Lactobacilli act on the glycogen to lower the pH, stimulating the subcolumnar reserve cells to undergo *metaplasia* (4).

[2] Metaplasia advances from the original SCJ inward, toward the external os and over the columnar villi to establish the *transformation zone.* The transformation zone extends from the original SCJ to the physiologically active SCJ, as demarcated by the SCJ. As the metaplastic epithelium in the transformation zone matures, it begins to produce glycogen and eventually resembles the original squamous epithelium, both colposcopically and histologically **(Fig. 16-5A,B)**.

CIN typically originates in the transformation zone at the advancing SCJ. The anterior lip of the cervix is twice as likely to develop CIN as the posterior lip, and CIN rarely originates in the lateral angles. Once CIN occurs, it can progress horizontally to involve the entire transformation zone, but it usually does not replace the original squamous epithelium. This progression usually results in CIN with a sharp external border. Proximally, CIN involves the cervical clefts, and this area tends to have the most severe CIN lesions. The extent of involvement of these cervical glands has significant therapeutic implications since the entire gland must be destroyed to ensure elimination of the CIN (4). The only way to determine where the original SCJ was located is to look for nabothian cysts or cervical cleft openings, which indicate the presence of columnar epithelium. After the metaplastic epithelium matures and forms glycogen, it is called the *healed* transformation zone and is relatively resistant to oncogenic stimuli.

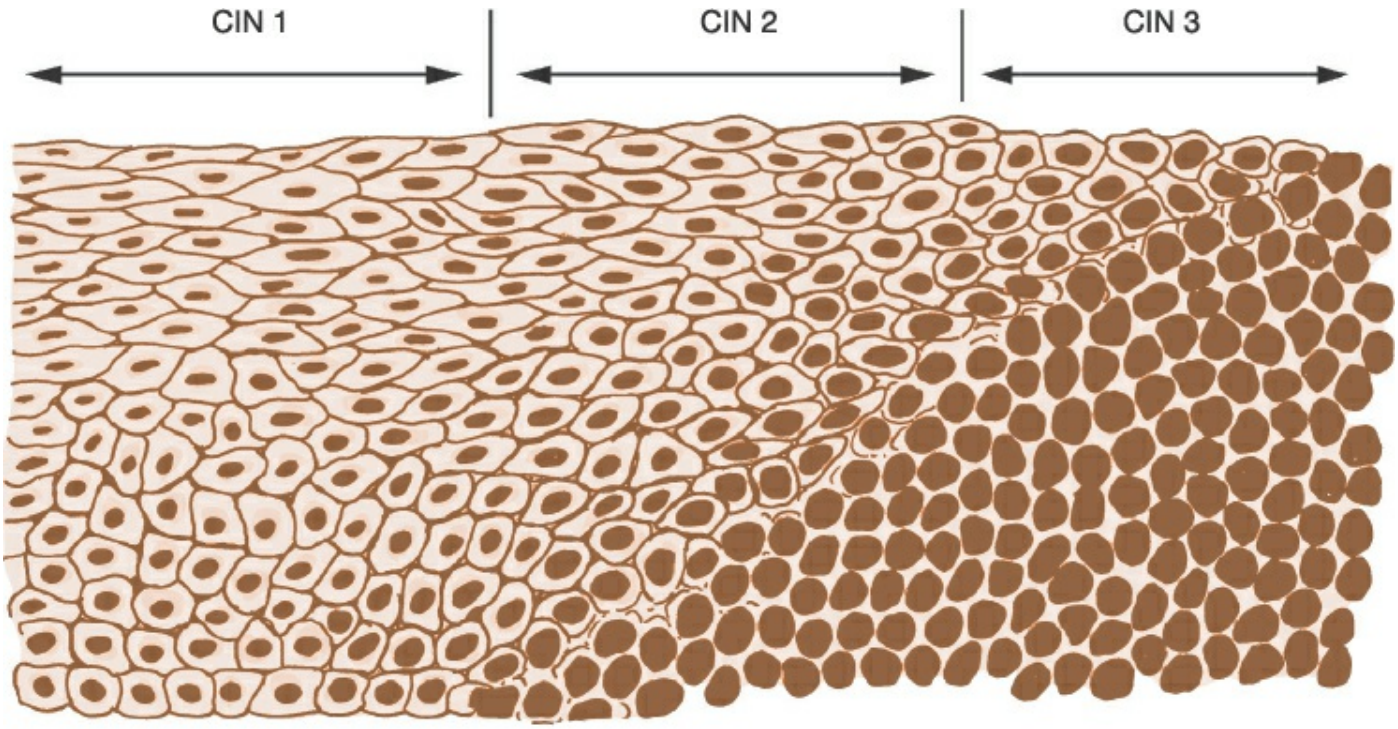


FIGURE 16-1 Diagram of cervical intraepithelial neoplasia compared with normal epithelium.

The entire SCJ with early metaplastic cells is susceptible to oncogenic factors, which may cause these cells to transform into CIN. Changes associated with CIN are most likely to begin either during menarche or after pregnancy, when metaplasia is most active. Conversely, after menopause a woman undergoes little metaplasia and is at a lower risk of developing CIN from de novo human papillomavirus (HPV) infection. HPV infection occurs through sexual contact in general and intercourse in particular. Although several agents, including sperm, seminal fluid histones, trichomonas, chlamydia, and herpes simplex virus, were studied, it is well established that **persistent high-risk oncogenic HPV infection is the overwhelming risk factor for the development of CIN.**

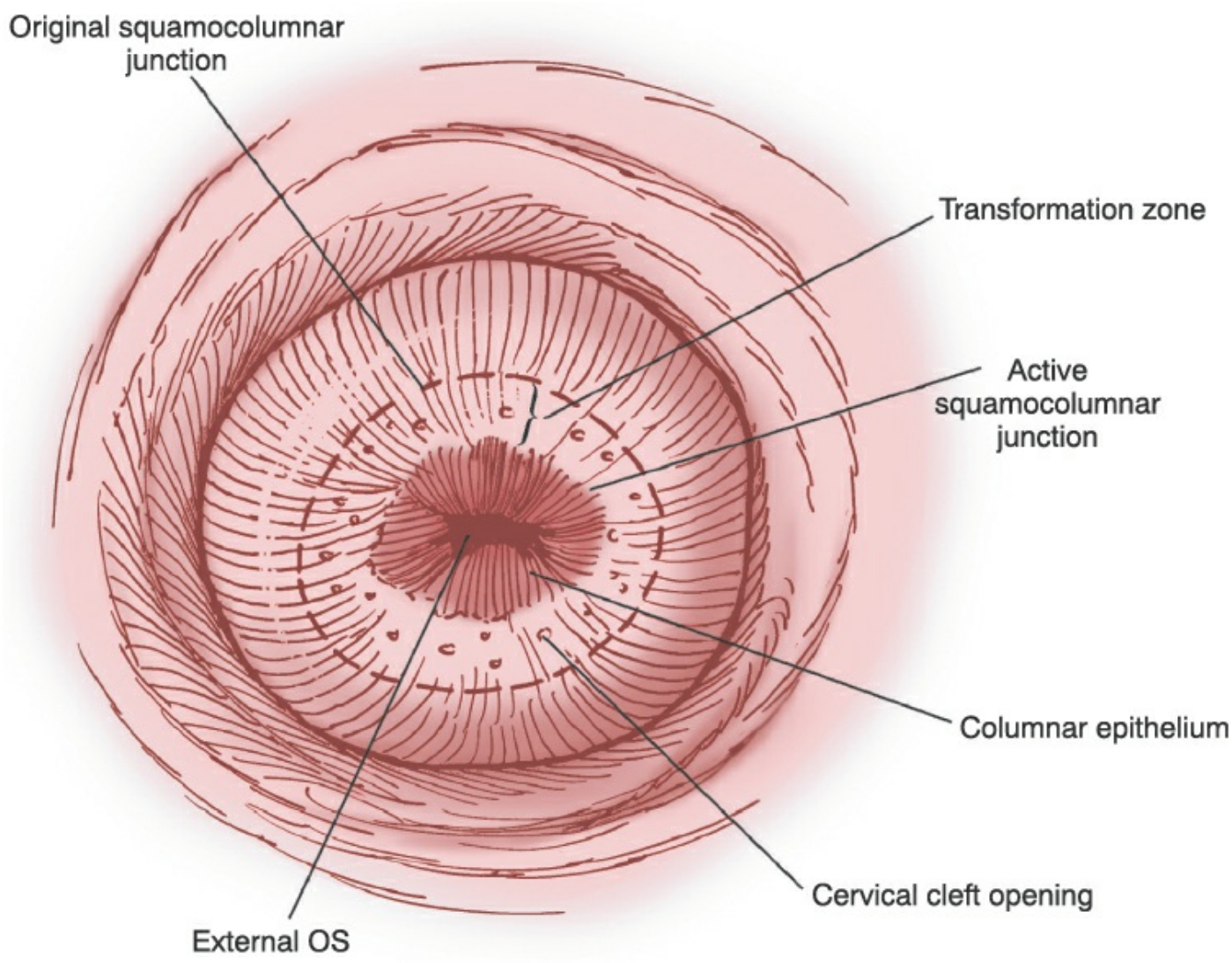


FIGURE 16-2 The cervix and the transformation zone.

Normal Transformation Zone

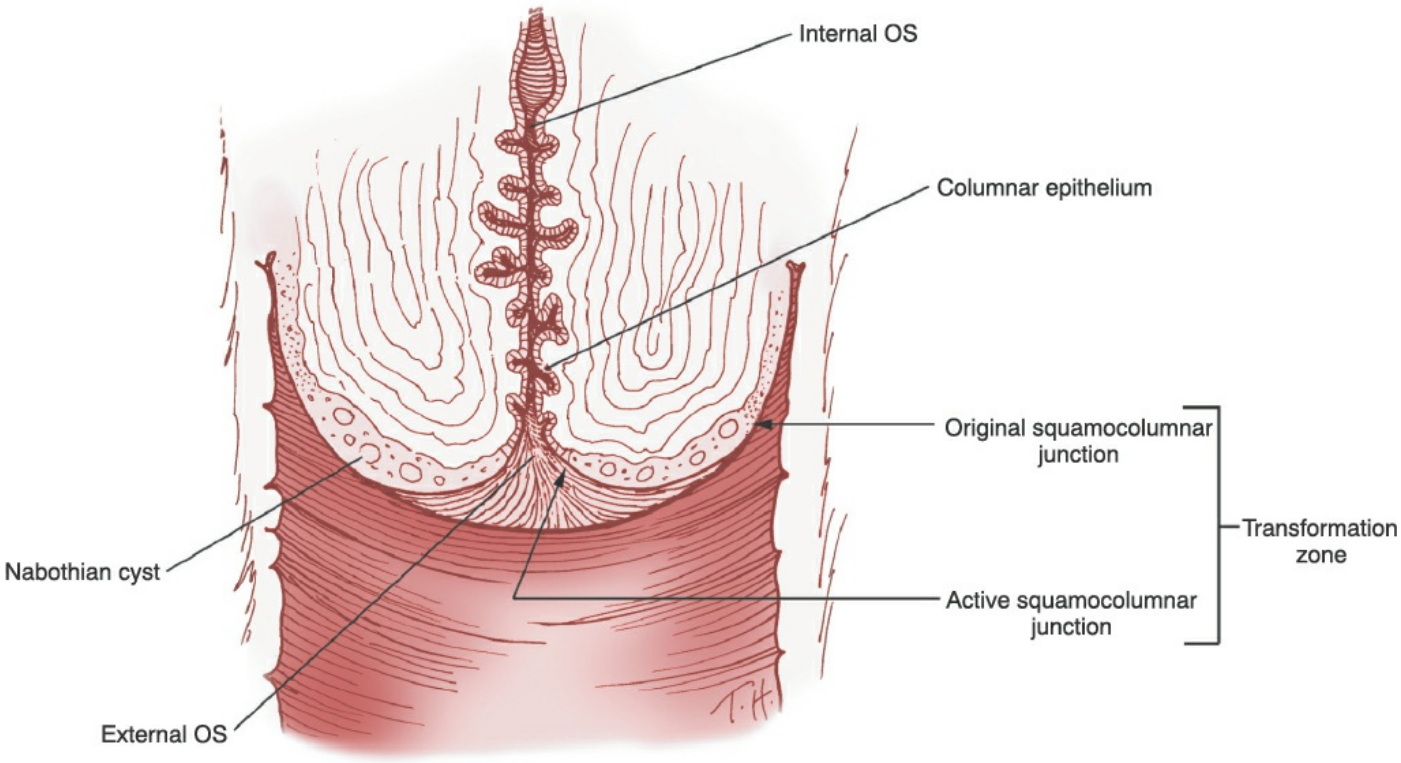


FIGURE 16-3 Diagram of the cervix and the endocervix.

The original squamous epithelium of the vagina and exocervix has four layers (4):

1. The *basal layer* is a single row of immature cells with large nuclei and a small amount of cytoplasm.
2. The *parabasal layer* includes two to four rows of immature cells that have normal mitotic figures and provide the replacement cells for the overlying epithelium.
3. The *intermediate layer* includes four to six rows of cells with larger amounts of cytoplasm in a polyhedral shape separated by an intercellular space. Intercellular bridges, where differentiation of glycogen production occurs, can be identified with light microscopy.
4. The *superficial layer* includes five to eight rows of flattened cells with small uniform nuclei and a cytoplasm filled with glycogen. The nucleus becomes pyknotic, and the cells detach from the surface (exfoliation). These cells form the basis for Papanicolaou (Pap) testing more accurately known as cervical cytology.

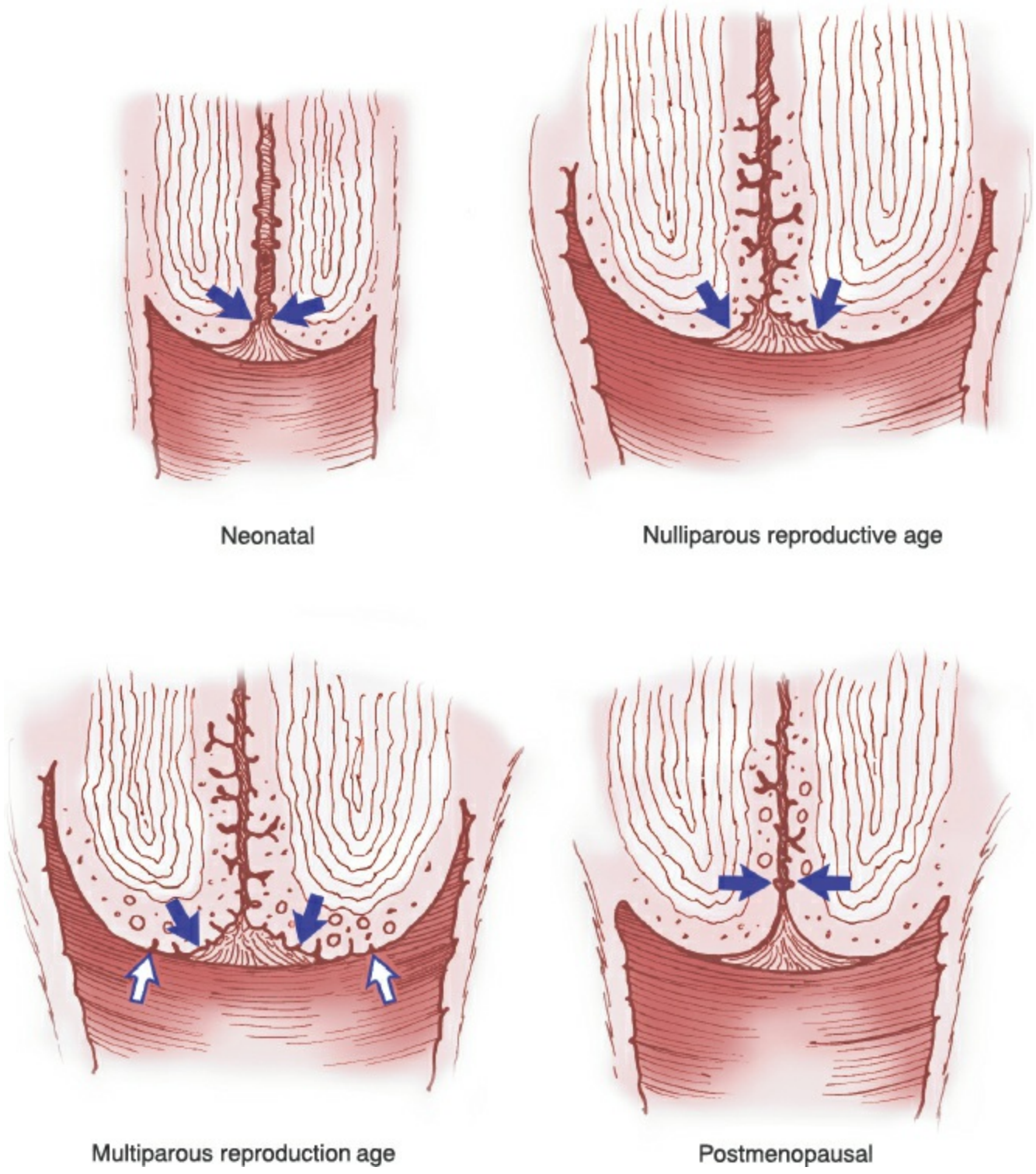
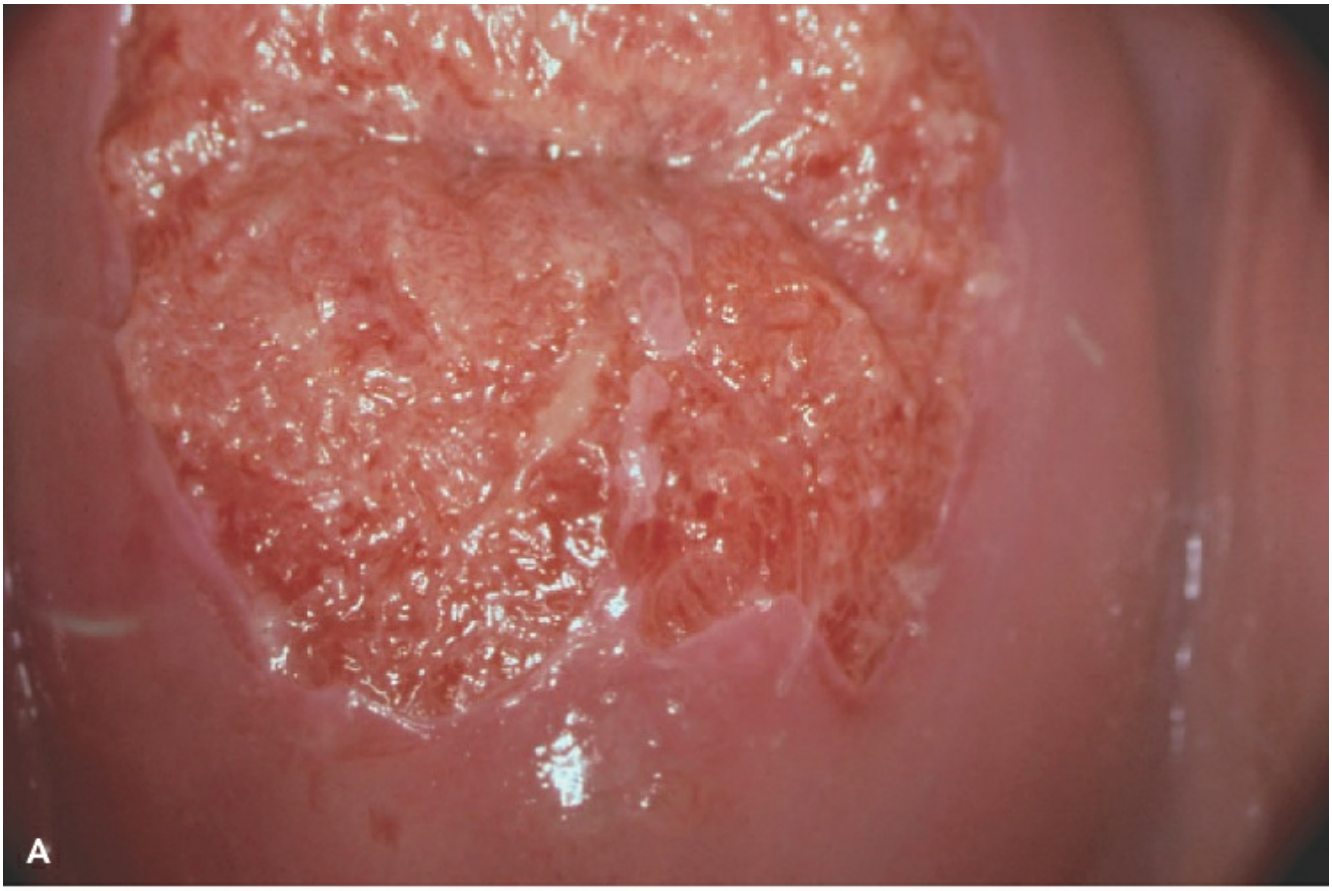


FIGURE 16-4 Different locations of the transformation zone and the squamocolumnar junction during a woman's lifetime. The *arrows* mark the active transformation zone. The *blue arrows* indicate internal boundaries of SCJ. The *white arrows* indicate external boundaries of the SCJ.


A


B

FIGURE 16-5 **A:** Active metaplasia in the transformation zone. **B:** Maturing metaplasia in the transformation zone.

Columnar Epithelium

Columnar epithelium has a single layer of columnar cells with mucus at the top and a round nucleus at the base. The glandular epithelium is composed of numerous ridges, clefts, and infoldings and, when covered by squamous metaplasia, leads to the appearance of gland openings. Technically, the endocervix is not a gland, but often the term *gland openings* is used.

Metaplastic Epithelium

Metaplastic epithelium, found at the SCJ, begins in the subcolumnar reserve cells. Under stimulation of lower vaginal acidity, the reserve cells proliferate, lifting the columnar epithelium. The immature metaplastic cells have large nuclei and a small amount of cytoplasm without glycogen. As the cells mature normally, they produce glycogen, eventually forming the four layers of epithelium. The metaplastic process begins at the tips of the columnar villi, which are exposed first to the acid vaginal environment. As the metaplasia replaces the columnar epithelium, the central capillary of the villus regresses, and the epithelium flattens out, leaving the epithelium with its typical vascular network. As metaplasia proceeds into the cervical clefts, it replaces columnar epithelium and similarly flattens the epithelium. The deeper clefts may not be completely replaced by the metaplastic epithelium, leaving mucus-secreting columnar epithelium trapped under the squamous epithelium. Some of these glands open onto the surface; others are completely encased, with mucus collecting in nabothian cysts. Gland openings and nabothian cysts mark the original SCJ and the outer edge of the original transformation zone **(Fig. 16-5A,B)** (4).

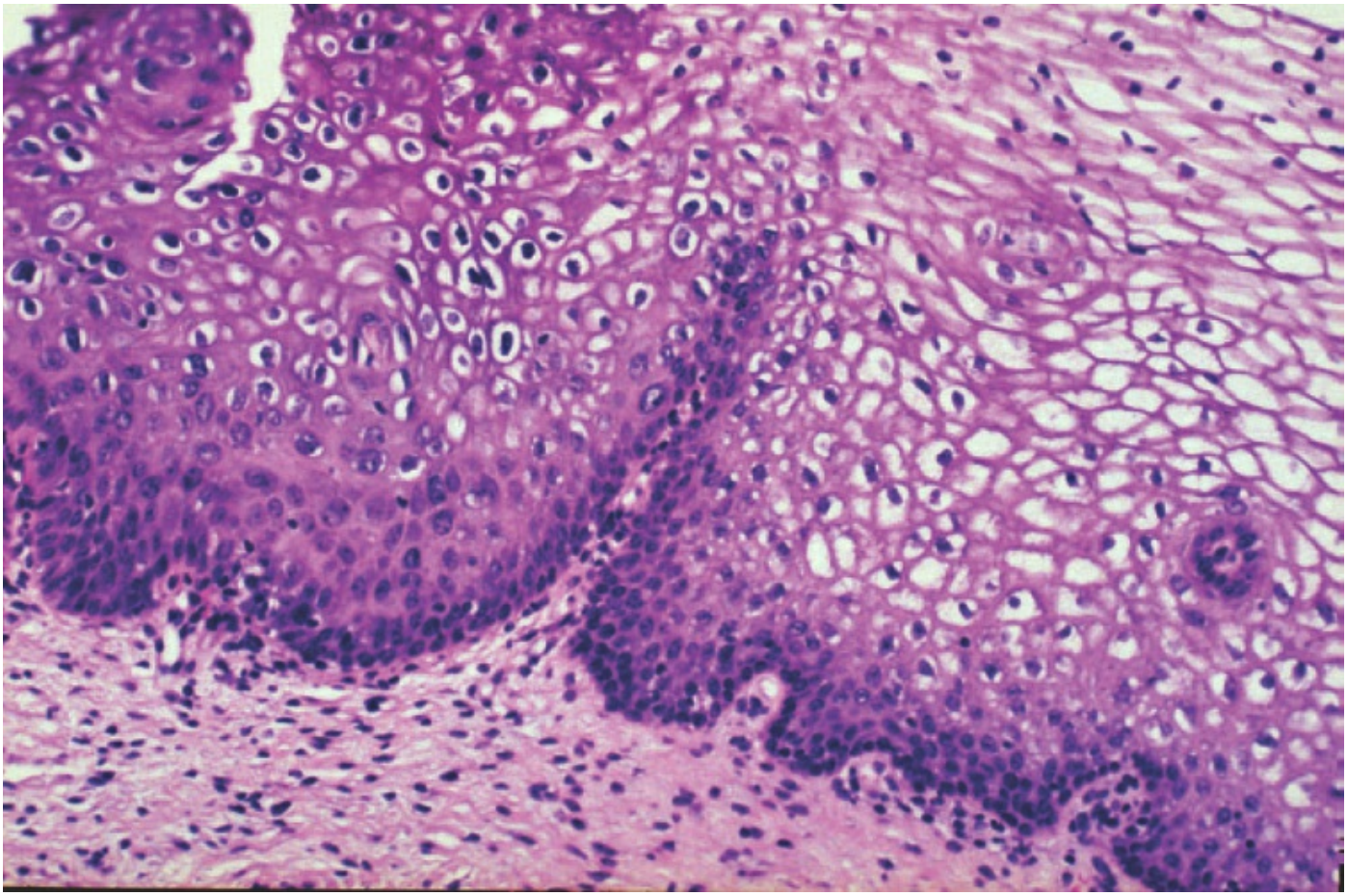


FIGURE 16-6 Cervical intraepithelial neoplasia grade 1 (CIN 1) with koilocytosis. The normal maturation process and differentiation from the basal and parabasal layers to the intermediate and superficial layers are maintained. In the upper layers, koilocytes are characterized by perinuclear halos, well-defined cell borders, and nuclear hyperchromasia, irregularity, and enlargement.

Human Papillomavirus

The cytologic changes of HPV were first recognized by Koss and Durfee in 1956 and given the term *koilocytosis* (5). Their significance was not recognized until 20 years later, when Meisels et al. reported these changes in mild dysplasia **(Fig. 16-6)** (6). Molecular biologic studies showed high levels of HPV DNA and capsid antigen, indicating productive viral infection in these koilocytic cells (7). HPV-related changes are found in all grades of cervical neoplasia (8). **[3] Infection with HPV is the primary cause of cancer of the cervix and its precursor lesions** (9). As the CIN lesions become more severe **(Fig. 16-7)**, the koilocytes disappear, the HPV copy numbers decrease, and the capsid antigen disappears, indicating that the virus is not capable of reproducing in less differentiated cells (10). Instead, portions of the HPV DNA become integrated into the host cell. Integration of the transcriptionally active DNA into the host cell appears to be essential for malignant transformation (11). **Malignant transformation requires the expression of E6 and E7 HPV oncoproteins**

(12). Because HPV will not grow in cell culture, there is no direct evidence of the carcinogenesis of HPV. However, a cell culture system for growing keratinocytes was described that allows for stratification and differentiation of specific keratinase types (13). When normal cells are transfected with the plasmid-containing HPV-16, the transfected cells produce cytologic abnormalities identical to those seen in intraepithelial neoplasia. The E6 and E7 oncoproteins are identifiable in the transfected cell lines, providing strong laboratory evidence of a cause-and-effect relationship (14). Cervical cancer cell lines that contain active copies of HPV-16 or -18 (SiHa, HeLa, C 4–11, Ca Ski) express HPV-16 E6 and E7 oncoproteins (15).

HPV DNA can be detected in the overwhelming majority of women with cervical neoplasia (16,17). There are more than 120 types of HPV identified, with 30 of these HPV types primarily infecting the squamous epithelium of the lower anogenital tract of men and women (18,19). Detection of HPV is associated with a 250-fold increase in risk of high-grade CIN (20). The percentage of intraepithelial neoplasia attributed to HPV infection approaches 90% (17).

Specific high-risk HPV types account for about 90% of high-grade intraepithelial lesions and cancer (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -68) (17). **[4] HPV-16 is the most common HPV found in invasive cancer and in CIN 2 and CIN 3** (21). It is the most common HPV type found in women with normal cytology.

HPV-16 infection is not a very specific finding and can be found in 16% of women with low-grade lesions and in up to 14% of women with normal cytology. HPV type-18 is found in 23% of women with invasive cancers, 5% of women with CIN 2 and CIN 3, 5% of women with HPV and CIN 1, and fewer than 2% of patients with negative findings (17). Therefore, HPV-18 is more specific than HPV-16 for invasive tumors.

Usually, HPV infections are typically transient and those that do persist may remain latent for many years. Most women who are exposed have no clinical evidence of disease, and the infection is eventually suppressed or eliminated (16). Other women exhibit low-grade cervical lesions that mostly regress spontaneously. **[3] In the vast majority of cases, HPV infection will clear in 9 to 15 months** (22). A small minority of women exposed to HPV develops persistent infection that may progress to CIN (16,23). Persistent high-risk HPV infection increases the risk of high-grade disease 300-fold and is required for the development and maintenance of CIN 3 (24,25). Factors that may have a role in persistence and progression include smoking, contraceptive use, infection with other sexually transmitted diseases, or nutrition (16,21). Any factor that influences the integration of HPV DNA into the human genome may contribute to progression to invasive disease (26).

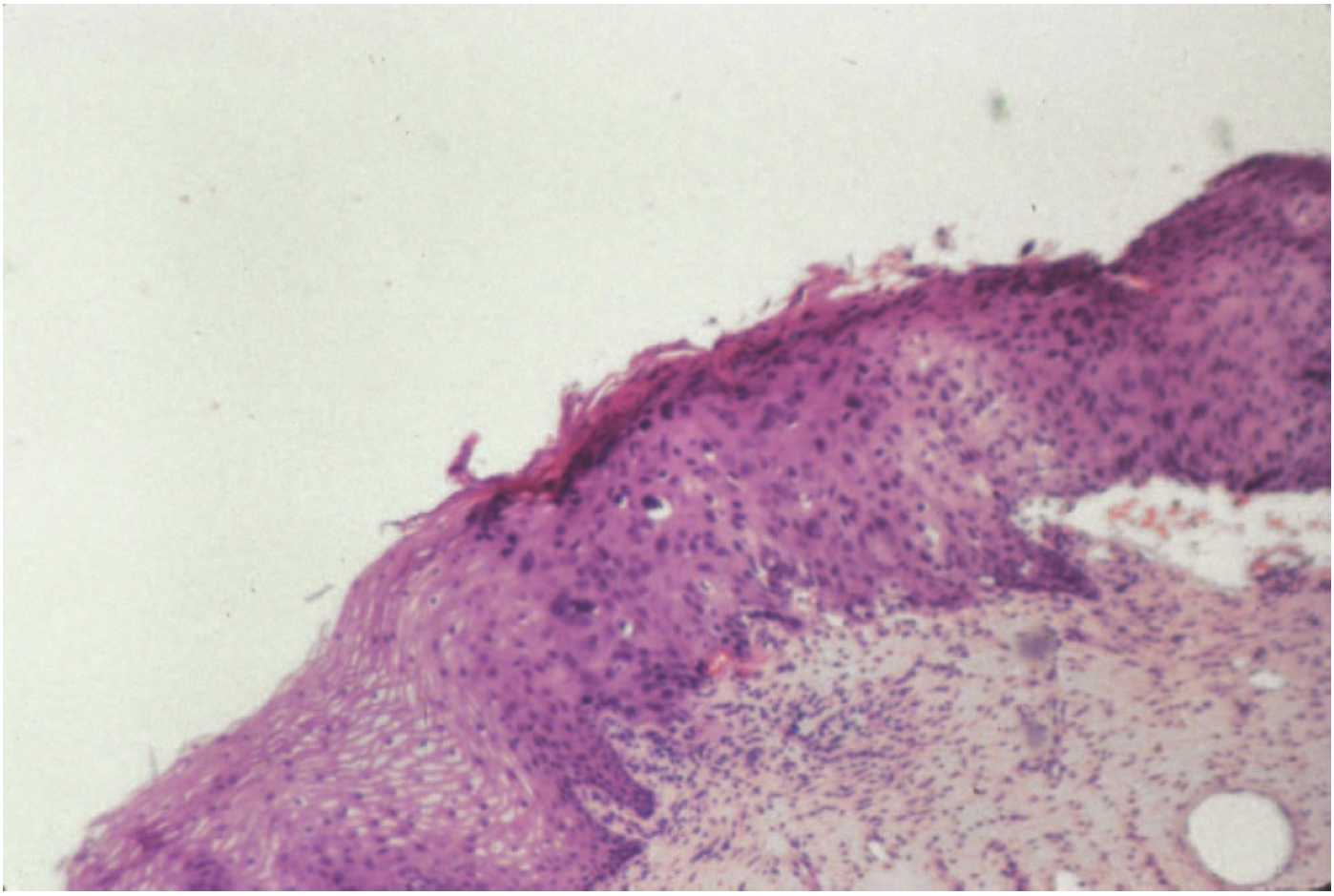


FIGURE 16-7 Cervical biopsy showing normal cells, cervical intraepithelial neoplasia 2 and 3 (CIN 2, CIN 3). In CIN 3, the normal maturation is lost.

Screening

Cervical Cytology

Cervical cytology has been the mainstay of cervical cancer screening since the mid-20th century. Its terminology has evolved to reflect an evolving and improved understanding of the pathogenesis of HPV-related disease in the lower genital tract. In 1988, the first National Cancer Institute (NCI) workshop held in Bethesda, Maryland, resulted in the development of the Bethesda System for cytologic reporting. That standardized method of reporting cytology findings facilitated peer review and quality assurance and was updated and refined in the Bethesda III System (2001) **(Table 16-1)**.

According to this system, potentially premalignant squamous lesions fall into specific categories: (i) *atypical squamous cells* (ASC), (ii) *low-grade squamous intraepithelial lesions* (LSILs), and (iii) *high-grade squamous intraepithelial lesions* (HSILs) (27). The ASC category is subdivided into two categories: those of unknown significance (ASC-US) and those in which high-grade lesions must be excluded (ASC-H). LSILs include CIN 1 (mild dysplasia) and the changes of HPV, termed *koilocytotic*

atypia. The HSIL category includes CIN 2 and CIN 3 (moderate dysplasia, severe dysplasia, and CIS). The terminology, AGUS, or atypical glandular cells of undetermined significance, was developed to characterize evidence of nonsquamous glandular neoplasia originating in the cervix.

Cellular changes associated with HPV (i.e., koilocytosis and CIN 1) are included within the category of LSIL because the natural history, distribution of various HPV types, and cytologic features are the same (26). Histopathologic and molecular virologic correlation showed a similar heterogeneous distribution of low- and high-risk HPV types in both koilocytosis and CIN 1 (28,29). On the basis of clinical behavior, molecular biologic findings, and morphologic features, HPV changes and CIN 1 are the same disease. The rationale for combining CIN 2 and CIN 3 into the category of HSIL is similar. The biologic studies reveal a comparable mix of high-risk HPV types in the two lesions, and the separation of the lesions is not reproducible (29,30). The management of CIN 2 and CIN 3 is similar.

Cervical Cytologic Screening Test Accuracy

Screening for cervical cancer precursors using exfoliative cervicovaginal cytology, the Pap test, was successful in reducing the incidence of cervical cancer by 79% and the mortality by 70% since 1950 (31). The annual incidence rate dropped from 8 to 5 cases per 100,000 women, so approximately 8,200 women per year are diagnosed with cervical cancer (31–33). A literature review of cervical cytology testing techniques was conducted by the Agency for Healthcare Research and Quality (34). The conclusion was that the sensitivity of conventional cytologic testing in detecting cervical cancer precursor lesions was 51%, with an estimated false-negative rate of 49%. In three reviews of the accuracy of cervical cytology assessment, **the sensitivity of the cervical cytology for the detection of CIN 2 or 3 ranged from 47% to 62% and the specificity ranged from 60% to 95%** (35–37). More than half of all cases of invasive cancer occur in women who were never screened or who were underscreened. The causes of missed cases of cervical cancer in women who have been screened are errors of sampling, fixation, interpretation or lack of follow-up (38).

Conventional cytology has improved in order to reduce false-negative errors. Sampling errors occur because a lesion is too small to exfoliate cells or the device did not pick up the cells and transfer them to the fixation media. Historically, preparation errors occurred because of poor fixation on the glass slide, leading to air drying and its consequences for interpretation. The slide preparations could be too thick and obscured by vaginal discharge, blood, or mucus. These problems were obviated with the widespread utilization of liquid-based media. Interpretive errors have been reduced by the large scale implementation of automated detection devices that assist the cytotechnologist in identifying significant cellular abnormalities. The ubiquitous use of liquid-based medium to collect the cytologic sample and preserve the collected cervical

cells significantly decreased specimen sampling and preparation errors. With this technique, liquid samples are processed to provide a uniform, thin layer of cervical cells without debris on a glass slide. The cell sample is collected with an endocervical brush used in combination with a plastic spatula or with a plastic broom. The sample is rinsed in a vial containing liquid alcohol-based preservative. With this technique, 80% to 90% of the cells are transferred to the liquid media, as compared with the 10% to 20% transferred to the glass slide with conventional cytologic testing. Use of liquid-based media eliminates air drying. The cells are retrieved from the vial by passing the liquid through a filter, which traps the larger epithelial cells, separating them from the small blood and inflammatory cells. This process yields a thin layer of diagnostic cells properly preserved and more easily interpreted by the cytologist. This technique reduces by 70% to 90% the rate of unsatisfactory samples encountered with conventional cytologic testing (39). Liquid-based cytology is commonly performed by most of the laboratories in the United States.

Another technology approved by the Food and Drug Administration (FDA) for primary screening and rescreening samples of cervical cytology initially interpreted as normal is the automated image-guided slide screening system. This technique uses an automated microscope coupled to a special digital camera. The system scans the slide and uses computer imaging techniques to analyze each field of view on the slide. Computer algorithms rank each slide on the probability that the sample may contain an abnormality. The selected slides are reviewed by a cytotechnologist or cytopathologist. This technique reduced the false-negative rate by 32% (40).

Human Papillomavirus Testing in Screening

An improved understanding of the critical role of high-risk human papillomavirus infection in the development of cervical cancer and its precursors has generated the proliferation of molecular tools that have come into clinical practice. Such methods have undergone extensive clinical trials, have been submitted to the rigorous approval process of the FDA, and have resulted in their licensure for specific roles in the screening process. **[5] High-risk HPV testing is a critical component of the triage for equivocal (ASC-US) cytology, as a component of co-testing with simultaneous cytology, and as a stand-alone primary screening modality** (Table 16-2).

Cervical Cancer Screening Recommendations

Guidelines based on the literature were developed to guide cervical cancer screening, follow-up, and treatment. The evolving state of the science and our improved understanding of HPV and cervical carcinogenesis, and clinical practice and liability considerations, occasionally lead to subtle differences in the interpretation of these guidelines. Ultimately, guidelines cannot substitute for an informed discussion of risks and benefits between a patient and health care provider in order to make decisions

about treatment.

The American College of Obstetricians and Gynecologists (ACOG) updated its guidelines (41). **[6]** The ACOG recommends that women not initiate cervical cancer screening until they are 21, regardless of the onset of sexual activity. This acknowledges the very low prevalence of invasive cancer in very young women, the long multiyear process of cervical carcinogenesis, and the very low but real risks for preterm birth associated with outpatient excisional procedures. Likewise, screening frequency was revised to every 2 years from ages 21 to 29 (with either conventional slide or liquid-based cytology), and every 3 years for women after age 30 years if 3 consecutive negative, that is, negative for intraepithelial lesion or malignancy (NILM) Pap tests can be documented. More frequent screening continues to be recommended for HIV-positive women (twice first year and annually after), those who are immune suppressed, *diethylstilbestrol* (DES) daughters, and for those with a history of CIN 2 or greater (screen annually for 20 years). Discontinuation of screening is reasonable between 65 and 70 years, with reassessment of risk factors annually to determine if reinitiating screening is appropriate. Likewise, in the setting of posthysterectomy for benign indications it is reasonable to discontinue screening in the absence of a history of high-grade CIN or cancer (Table 16-3).

Table 16-2 Commercially Available High-Risk HPV Assays and Their FDA-Approved Clinical Indications

Molecular Target *Technique*	Commercial Product	Typing	ASC-US Triage	Co-Test	Primary
DNA—genomic *DNA:RNA Hybridization*	*Hybrid Capture 2*	No	X	X	
DNA *Invader Technology*	*Cervista*	16/18 Reflex	X	X	
L1 DNA *PCR TaqMan*	*Cobas HPV*	16/18	X	X	X
E6/E7 mRNA *TMA*	*APTIMA*	16/18, 45 reflex	X	X	

Table 16-3 Comparison of Screening Guidelines From the American Cancer Society, American Society of Colposcopy and Cervical Pathology and American Society Clinical Pathology, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force

	ACS-ASCCP-ASCP 2012	ACOG 2009	USPSTF 2012	USPSTF 2017
Start Age	21	21	21	21
Ages 21–29	Cytology every 3 years (liquid or conventional) AGAINST annual Pap	Cytology every 2 years (liquid or conventional)	Cytology every 3 years (liquid or conventional)	Cytology every 3 years (liquid or conventional)
Ages 30–65	Co-test every 5 years (preferred) OR Every 3 years with cytology alone (acceptable) AGAINST more frequent screening	Co-test every 3 years OR Every 3 years with cytology alone	Co-test every 5 years OR Every 3 years with cytology alone	Cytology every 3 years (liquid or conventional) OR High-risk HPV testing every 5 years OR Co-test every 5 years
After 65	Discontinue after age 65 if 3 negative Pap tests or 2 negative HPV tests in last 10 years with most recent test in last 5 years	Discontinue at age 65–70 after 3 negative tests in last 10 years	Discontinue after age 65 if adequate prior screening	Recommend against screening if adequate prior screening and not at increased risk

The 2011 American Society for Colposcopy and Cervical Pathology (ASCCP), American Cancer Society (ACS), and the American Society for Clinical Pathology (ASCP) co-convened a guidelines development process in collaboration with more than 21 partner organizations. The goal of this process was to develop a set of updated evidence-based screening guidelines that reflected our best understanding of the science (42). Contemporaneously and independent of this effort the U.S. Preventive Services Task Force (USPSTF) is using an entirely different methodology and on the basis of an independent systematic evidence review in the process of updating that entity's cervical cancer screening recommendations (43). These near-parallel processes produced a set of remarkably concordant recommendations whose uniformity has been beneficial to patients and clinicians.

[6] These **evidence-based guidelines recommend that cervical cancer screening not begin until age 21 years, regardless of sexual history. For women 21 to 29 years, the recommendation is screening with cytology every 3 years. From 30 to 65 years co-testing with conventional cytology and high-risk HPV testing every 5 years or cytology alone every 3 years are appropriate alternatives. After the age of 65 it is appropriate to discontinue screening in women with a negative screening history as documented by either 3 negative cytology results or 2 negative co-tests in the previous 10 years** (42,43).

The USPSTF published its updated draft guidelines and made them available for stakeholder input **(Table 16-3)**. The major and historic innovation is the unprecedented incorporation of primary screening using molecular high-risk HPV testing (as an alternative to cytology every 3 years) in women between 30 and 65 years.

Atypical Squamous Cells

The ASC category does not include benign, reactive, and reparative changes, classified as normal in the Bethesda system. This cytologic diagnosis is relatively common, ranging from 3% to 25% in some centers (44). When standardized diagnostic criteria are used, the rate of ASC results should be 3% to 5% (45). The ASC category is subdivided into ASC-US and ASC-H.

The cytologic diagnosis of ASC-US is associated with a 10% to 20% incidence of CIN 1 and a 3% to 5% risk for CIN 2 or 3 (46–49). CIN 1 is most often a benign HPV infection and will regress spontaneously in more than 60% of cases; therefore, the goal of triage of an ASC-US Pap test result is to identify more advanced CIN 2 and CIN 3 lesions (50).

Immediate colposcopy is assumed to be the most sensitive method of detecting CIN 2 or 3 (46,49). Because 80% of patients will not have significant lesions, it is important to avoid overinterpretation of the colposcopic findings. **[7] The usefulness of high-risk HPV testing in the assessment of ASC-US Pap test results** (51–53) **is well established, and aids in the identification of 90% of the patients with CIN 2 or 3 lesions.** To compare the aforementioned triage method in a prospective, randomized fashion, the NCI funded an ASC-US/LSIL Triage Study (ALTS) (54). Patients with ASC-US or LSIL were randomized to three triage arms: (i) immediate colposcopy, (ii) HPV test, and (iii) conservative management by repeat Pap test. There were 1,163 women in the immediate colposcopy group, and 14 refused the examination. The results of colposcopy are assumed to reflect the prevalent disease rates, which were as follows: CIN 1, 14.3%; CIN 2, 16.1%; and CIN 3, 5%. Thus, 75% of the women with ASC-US had negative colposcopy results and either did not have a biopsy (25%) or had a biopsy with negative results. The HPV test results were positive in 56.1% of the patients, and 6.1% of the patients did not return for colposcopy. Of the 494 who underwent colposcopy, the results were as follows: CIN 1, 22.5%; CIN 2, 11.9%; and CIN 3, 15.6%. The sensitivity of HPV test was 95.9% for the detection of CIN 2 and 96.3% for the detection of CIN 3.

In the conservatively managed group, only one follow-up cytology was reported. The results of the single follow-up Pap test were included. Using a cutoff that includes any positive finding of ASC-US or greater, the sensitivity is 85% for CIN 2 and 85.3% for CIN 3, with 58.6% of patients referred for colposcopy. If LSIL is used as a cutoff, 26.2% of the patients are referred, with sensitivity of 64.0% for both CIN 2 and CIN 3. Using HSIL as the cutoff, 6.9% are referred, and the sensitivity falls to 44%. The conclusion of the ALTS trial is that HPV triage is highly sensitive in identifying CIN 2 and CIN 3 lesions and that it cuts the rate of referral for colposcopy by approximately one-half (55). When mathematical models are used to simulate the natural history of HPV and cervical cancer in a cohort of US women, a 2- to 3-year screening strategy using cytology with reflex high-risk HPV triages is more effective and less costly in reducing the rate of cancer than annual conventional cytology (56).

[8] Women with ASC-H should be referred to colposcopy because of the underlying risk of CIN 2 and/or 3, and should not be triaged with high-risk HPV testing.

Low-Grade Squamous Intraepithelial Lesions

The cytologic diagnosis of LSIL is reproducible and accounts for 1.6% of cytologic diagnoses (45). About 75% of the patients have CIN, with 20% being CIN 2 or 3 (46–48). These patients require additional evaluation. The ALTS trial closed the HPV test arm early because the HPV positivity rate was 82% and was not a valid discriminator in determining the presence of disease. The ALTS trial found that a cytology interpretation of LSIL is associated with a 25% risk of histologic CIN 2 or 3 within 2 years. No effective triage strategy was identified to spare many women from colposcopic referral without increasing their risk of CIN 3 and invasive carcinoma (57). **[9] Guidelines reaffirm the appropriateness of colposcopy to evaluate after an LSIL cytology** (52).

High-Grade Squamous Intraepithelial Lesions

[9] Any woman with a cytologic specimen suggesting the presence of HSIL must undergo colposcopy and directed biopsy (52). Two-thirds of patients with this cytologic finding will have CIN 2 or greater. After colposcopically directed biopsy and determination of the distribution of the lesion, excisional or ablative therapy that addresses the entire transformation zone should be performed. For populations who have completed childbearing and who are likely to be lost to follow-up, outpatient excision of the transformation may be considered after this cytologic diagnosis.

Colposcopic Diagnosis

The ASCCP convened a process to develop evidence-based and expert consensus recommendations for the practice of colposcopy in the United States (58). An outcome of this process was the development of standardized terminology for findings at colposcopic examination (59). It described **[10] the minimum elements of a comprehensive colposcopic examination, which include visualization of SCJ, the identification of acetowhitening or other lesion(s), and an overall colposcopic impression (normal/benign, low grade, high grade, cancer)** (Table 16-4) (59,60).

Table 16-4 Essential Elements of a Colposcopic Examination (Adapted from ASCCP)

Component	Content
Precolposcopic assessment	Evaluate/document the following: Indication; history of prior screening tests, colposcopy, and treatment; parity, contraception, pregnancy, menopause, hysterectomy, smoking, HIV, HPV vaccination.

	Informed consent.
Examination	Gross assessment of the vulva, vagina, perianal area, and cervix. Examination of the cervix and upper vagina with magnification after application of 3–5% acetic acid using white light and green/blue filter.
Documentation	Document cervix visibility, and visualization of squamocolumnar junction. Document (using diagram or photography) findings including presence, location, size, appearance, and characteristic of the lesion. Colposcopic impression.
Tissue sampling	Perform/document biopsy type, location of lesions. Perform/document endocervical sampling.
Postprocedure	Document modality and timing of how patient will be notified.

The guidelines formalize the practice of risk-based colposcopy. In general, colposcopists are asked to consider at least two and up to four biopsies of all suspected lesions (61). For women at the lowest risk of high-grade disease (those with less than HSIL cytology, no evidence for HPV16/18, and a normal colposcopic impression), random non-targeted biopsies are not recommended. Conversely, nonpregnant women at the greatest risk of disease may merit a more aggressive diagnostic workup.

The p16 protein is a cell cycle regulator, and under physiologic conditions, p16 acts as an inhibitor of cyclin-dependent kinases CDK4 and CDK6; this leads to cell cycle arrest in epithelial cells undergoing cellular differentiation. However, in response to a transforming infection by high-risk human papillomavirus (hrHPV) with overexpression of oncogenic protein E7, p16 levels rise. **The excess p16 is thus a surrogate marker of the transforming HPV infection. p16 is recommended for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (CIN 2/-IN2 or CIN 3/-IN3)** (62,63).

The 2012 ASCCP consensus guidelines recommended grouping CIN 2 and CIN 3 together as high-grade histology. However, it was recognized that there was a subset of CIN 2 patients that would not progress and thus did not need treatment. In 2012, the College of American Pathologists and ASCCP cosponsored the Lower Anogenital Squamous Terminology (LAST) standardization project and published the LAST recommendations for histopathology reporting of HPV-related squamous lesions of the lower anogenital tract. Specifically LAST calls for the use of a 2-tier nomenclature (low-grade squamous intraepithelial lesion/high-grade squamous intraepithelial lesion [LSIL/HSIL]) and expanded use of the biomarker p16 to classify equivocal lesions as either precancer (HSIL) or low-grade lesions (LSIL)/non-HPV changes. In one study, among 166 patients with subsequent pathology (including 131 excisions), 26.2% of p16-positive cases of grade 2 intraepithelial neoplasia versus 4.4% of p16-negative cases were associated with a subsequent

diagnosis of HSIL (-IN 3) or worse ($P = 0.002$) (64). **The results indicate that using the LAST recommendations would result in approximately one-third of equivocal (-IN 2) diagnoses being downgraded to LSIL over 1 year. The significant association of p16 expression with a higher risk for HSIL on a subsequent specimen suggests that the use of p16 to adjudicate equivocal (-IN 2) diagnoses in lower anogenital tract specimens as either LSIL or HSIL would likely predict lesion grade more accurately and avoid unnecessary excisional procedures. Therefore, strong and diffuse block-positive p16 results support a categorization of precancerous disease. Negative or non–block-positive staining strongly favors an interpretation of low-grade disease or a non–HPV-associated pathology such as immature squamous metaplasia, atrophy, or reparative changes.** Subsequent publications have confirmed the accuracy of p16 IHC (62,63).

Therefore, women with histologic diagnosis of CIN 2 with negative p16 staining have a very low risk of advancing to CIN 3 and no patient has developed invasive cancer in these studies. These women can avoid treatment, especially if they want further childbearing. Postmenopausal women often have atrophy or reparative changes and they may benefit from p16 testing as well.

Colposcopy Findings

Colposcopic assessment is a critical component of the follow-up of the abnormal cervical screening. Specialty providers in a variety of clinical settings have historically performed this procedure. In an effort to improve the quality and consistency of this procedure the American Society of Colposcopy and Cervical Pathology has developed and disseminated a new set of standards for services in this arena (59). This process developed standard terminology and definitions of findings. Table 16-4 summarizes the essential elements of a colposcopic evaluation.

Acetowhite Epithelium

Epithelium that turns white after application of acetic acid (3% to 5%) is called *acetowhite epithelium* (34). The application of acetic acid coagulates the proteins of the nucleus and cytoplasm and makes the proteins opaque and white (4).

The acetic acid does not affect mature, glycogen-producing epithelium because the acid does not penetrate below the outer one-third of the epithelium. The cells in this region have very small nuclei and a large amount of glycogen (not protein). These areas appear pink during colposcopy. Dysplastic cells are those most affected. They contain large nuclei with abnormally large amounts of chromatin (protein). The columnar villi become “plumper” after acetic acid is applied, making these cells easier to see. They appear slightly white, particularly in the presence of metaplasia. The immature metaplastic cells have larger nuclei and show some effects of the acetic acid. Because the metaplastic epithelium is very thin, it is not as white or opaque as CIN but instead

appears gray and filmy (4).

Leukoplakia

Translated literally, *leukoplakia* is white plaque (4). This plaque is white epithelium, visible before application of acetic acid. Leukoplakia represents a layer of keratin on the surface of the epithelium. Immature squamous epithelial cells have the potential to develop into keratin- or glycogen-producing cells. In the vagina and on the cervix, the normal differentiation is toward glycogen. Leukoplakia should not be confused with the white plaque of a monilial infection, which can be completely wiped off with a cotton-tipped applicator.

Keratin production is abnormal in the cervicovaginal mucosa. Leukoplakia results from this process and is commonly associated with HPV infection **(Fig. 16-8)** and related keratinizing intraepithelial or invasive lesions and should be biopsied. Other etiologies for this lesion include chronic trauma from diaphragm, pessary, or tampon use and radiotherapy.

Punctation

Dilated capillaries terminating on the surface appear from the ends as a collection of dots and are referred to as punctation **(Fig. 16-9)**. When these vessels occur in a well-demarcated area of acetowhite epithelium, they indicate an abnormal epithelium—most often high-grade CIN **(Fig. 16-10)** (4). The punctate vessels are formed as the metaplastic epithelium migrates over the columnar villi. Normally, the capillary regresses; however, when CIN occurs, the capillary persists and appears more prominent.

Mosaic

Terminal capillaries surrounding roughly circular or polygonal-shaped blocks of acetowhite epithelium crowded together are called mosaic because of their appearance **(Fig. 16-11)**. These vessels form a "basket" around the blocks of abnormal epithelium. They may arise from a coalescence of many terminal punctate vessels or from the vessels that surround the cervical gland openings (4). Mosaicism tends to be associated with high-grade lesions (CIN 2 and CIN 3) (**Figs. 16-12** and **16-13**).



FIGURE 16-8 Colposcopy of cervical intraepithelial neoplasia 2 (CIN 2) associated with human papillomavirus (HPV) infection of the cervix.

The International Federation for Cervical Pathology and Colposcopy published additional colposcopic criteria for CIN 3. They are ridge sign—dense acetowhite extending along the cervical ridges, and inner border sign—thick acetowhite with distinct border existing inside a finer, lacy acetowhite lesion **(Fig. 16-14)**. These are added to the previously described cuffed gland—dense acetowhite around the gland openings, and rag sign—peeling of the epithelium in an area of acetowhite **(Fig. 16-15)** (65).

Atypical Vascular Pattern

Atypical vascular patterns are characteristic of invasive cervical cancer and include looped vessels, branching vessels, and reticular vessels.

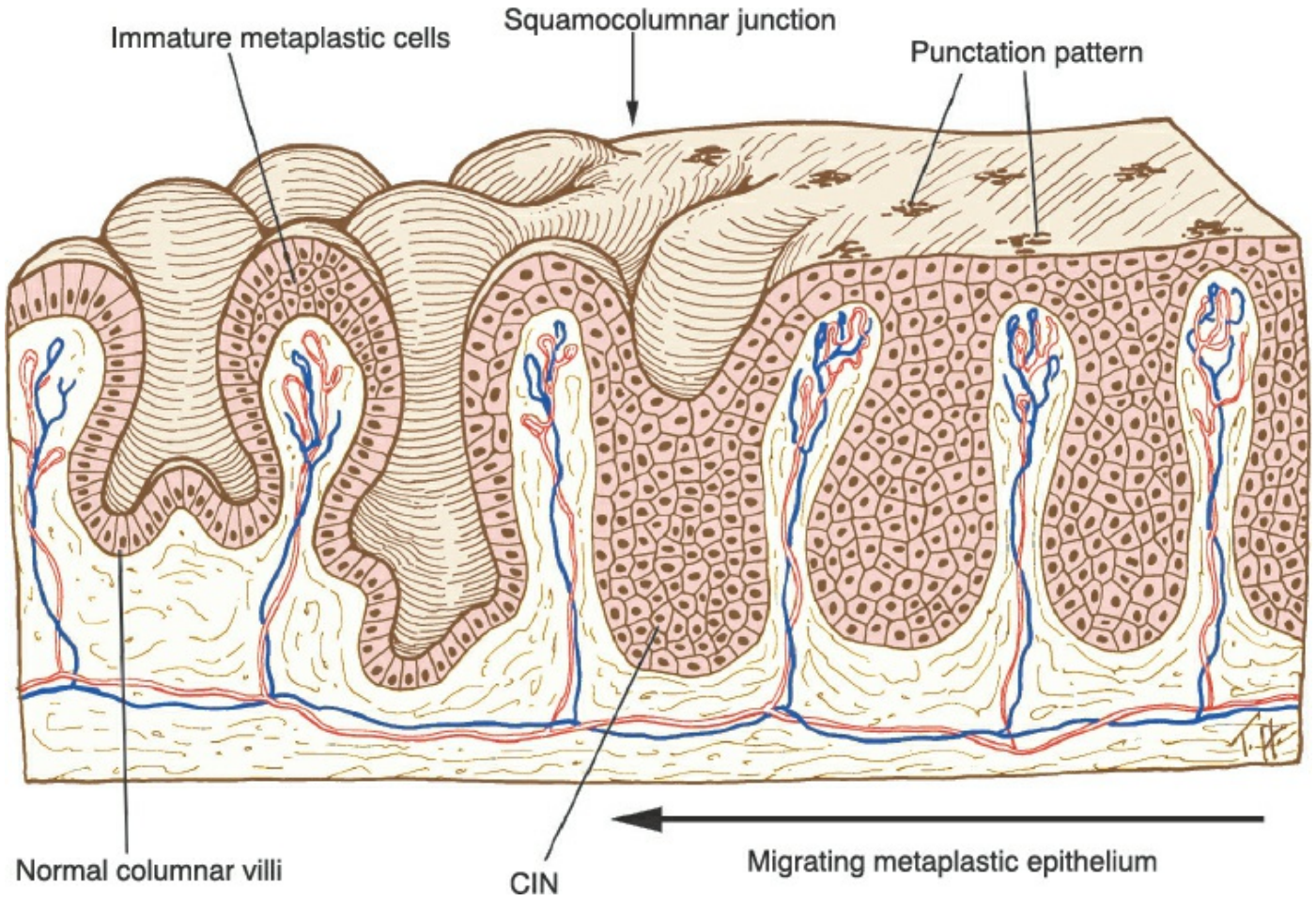


FIGURE 16-9 Diagram of punctation. The central capillaries of the columnar villi are preserved and produce the punctate vessels on the surface.

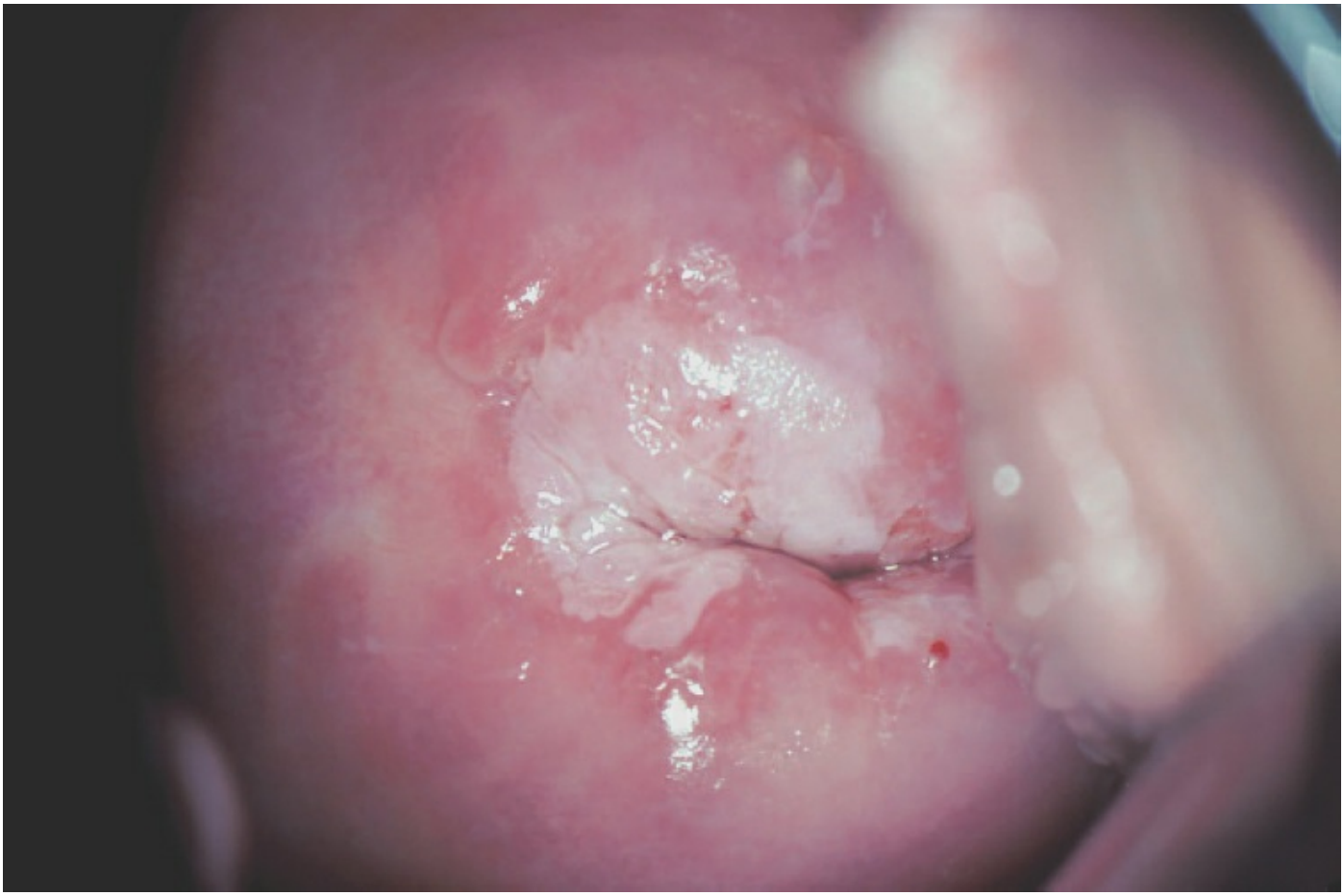


FIGURE 16-10 Human papillomavirus (HPV)/cervical intraepithelial neoplasia 2 (CIN 2) presents as a white lesion with surface spicules.

Clinical Pathologic Correlation

[11] It is a best practice for pathologist and colposcopist to jointly review the colposcopic examination findings, cytology, molecular testing, cervical biopsy, and endocervical sampling in order to develop a therapeutic plan. Cytology results should not be sent to one laboratory and the histology results to another. When the cytology, biopsy, and molecular testing results correlate, the colposcopist can be reasonably certain that the most clinically significant lesion was identified. If cytology indicates a more significant lesion than the histology, the patient may require further evaluation, including repeat colposcopy, additional biopsies, and excisional diagnostic procedures under certain circumstances.

Management

Clinical Disease Management Guidelines

In 2012, the ASCCP and the NCI sponsored a consensus conference to update evidence-based guidelines for abnormal cervical cancer screening. This gathering brought

together 47 experts and 23 professional societies, national and international health organizations, and federal agencies to review the latest natural history and clinical data, and consider how the newly updated cervical cancer screening impacted the clinical follow-up of abnormal screens (66). **[12] The new comprehensive evidence-based guidelines for the management of cervical cytologic and histologic entities lend themselves to structured clinical algorithms that are available for download from the Web (www.asccp.org), on various mobile phone applications, and can be incorporated into a variety of electronic health record platforms.**

CIN 1

[13] Although CIN 1 is a histopathologic manifestation of HPV infection, it is not a cancer precursor. The spontaneous regression rate of biopsy-proven CIN 1 is conservatively estimated to be 60% to 85% in prospective studies and regression typically occurs within a 2-year follow-up (4,52,67–70). Patients who have biopsy-proven CIN 1 (after a cytologic finding of ASC, LSIL) with satisfactory colposcopy are followed with cytology and high-risk HPV testing (co-testing) at 12 months. With a negative cytology and high-risk HPV test at the 12-month follow-up these women can be returned to age-appropriate screening. The patient is returned to colposcopy for appropriate reevaluation in the event of abnormality on surveillance testing (66). Young women of ages 21 to 24 years in this clinical scenario may undergo surveillance with repeat cytology only at 12 and 24 months, with referral to colposcopy for ASC-US or greater (66).

[14] For CIN 1 that persists 24 months or more, a patient with an adequate colposcopic examination may be given the choice of continued surveillance or destruction of the transformation zone with ablation or excision (66). However, if colposcopy is inadequate, ablative therapy should be avoided. Expectant management may not be appropriate for patients with chronic systemic immunosuppression, such as those requiring steroids, chemotherapy, or antirejection drugs, and others who may have persistent low-grade abnormalities (52).

Clinical situations where biopsy histopathology is CIN 1 preceded by ASC-H or HSIL cytology carry a higher risk. In these settings, follow-up with co-testing (with cytology and high-risk HPV) at 12 and 24 months or loop excision procedure may be more appropriate (66).

CIN 2 and CIN 3

Typically, **CIN 2 and CIN 3 lesions are neoplastic precursors and grouped for the purposes of diagnostic reporting and treatment. [14] Women, 25 years of age and older, with adequate colposcopy and histologic documentation of CIN 2 and CIN 3 require destruction or excision of the transformation zone** (66). Ablation should not be considered in cases where colposcopy is inadequate, CIN 2 and/or 3 is recurrent, or

endocervical sampling is positive. This recommendation is based on a meta-analysis showing that CIN 2 progresses to CIS in 20% of cases and to invasion in 5%. Progression of CIS to invasion is 5% (71). Surveillance with co-testing at 12 and 24 months is necessary prior to returning a patient to routine age-appropriate screening (66).


A

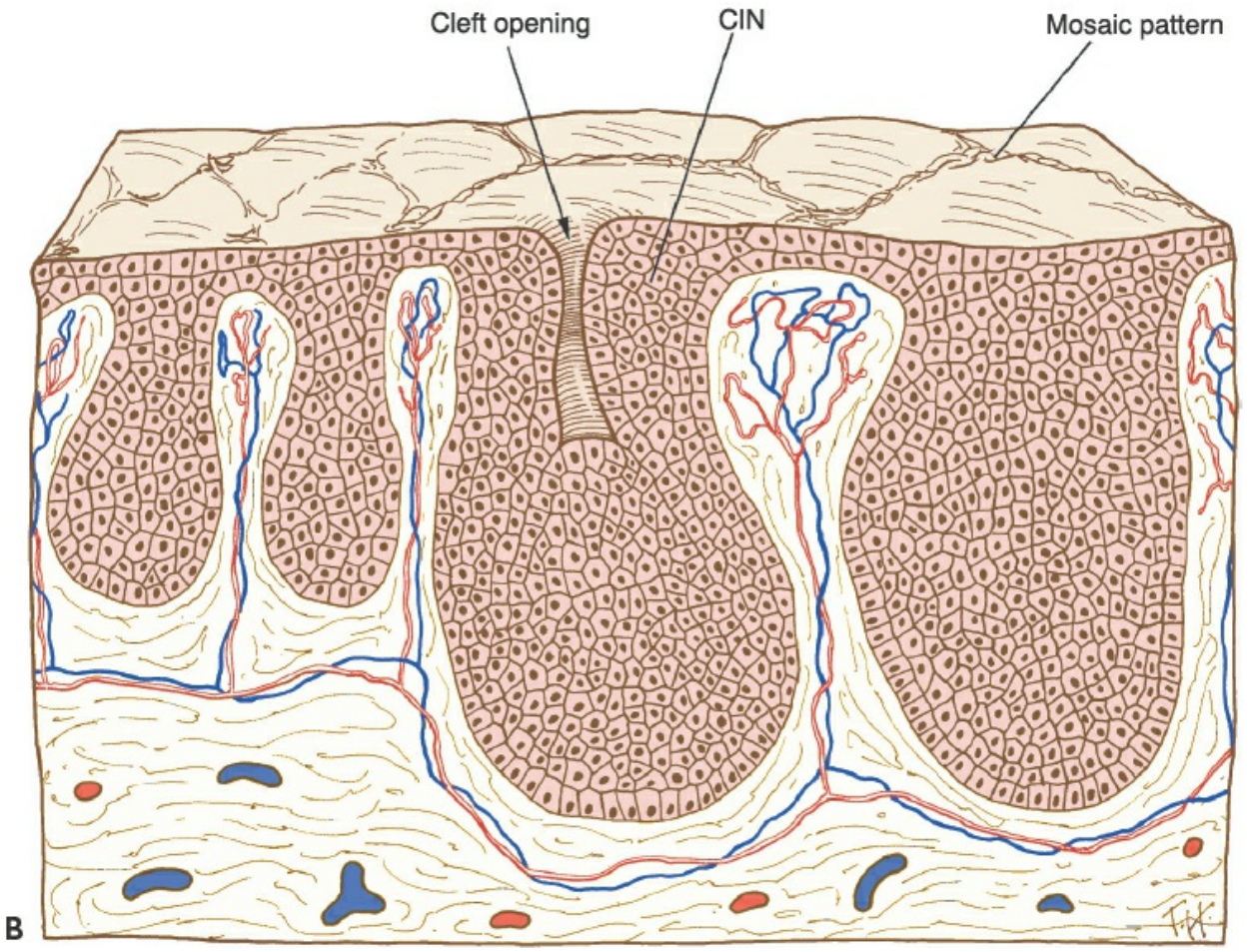

Cleft opening
CIN
Mosaic pattern
B

FIGURE 16-11 A: Mosaic pattern and punctation. This pattern develops as islands of dysplastic epithelium proliferate and push the ends of the superficial blood vessels away, creating a pattern that looks like mosaic tiles. **B:** Diagram of mosaic pattern.

There are exceptions to this therapeutic recommendation. The first is among pregnant women, who in the absence of invasive disease, are followed with cytology and colposcopy, until reevaluation at 6 weeks postpartum. Additionally, in recognition of the small but real risk for preterm birth, in young women less than 25 years of age with CIN 2–3, a program of intensive observation with colposcopy and cytology is performed at 6 and 12 months, and if normal, followed by co-testing in another year (66).



FIGURE 16-12 Human papillomavirus (HPV)/cervical intraepithelial neoplasia 3 (CIN 3). Cribriform pattern of HPV at periphery with mosaicism and punctation near the squamocolumnar junction.

[15] Although CIN 2–3 can be treated with a variety of outpatient techniques, the preferred treatment is LEEP. This allows pathologic evaluation to identify occult microinvasive cancer or adenomatous involvement. In the latter case, margin status has important prognostic implications. The persistent and recurrent disease rate post treatment is estimated at 4% to 10% (72,73).

Ablative therapy using cryotherapy, laser ablation, or any other technique is not

appropriate when there is CIN 2–3 in the endocervix based on colposcopy and endocervical curettage (ECC), or **evidence of microinvasive or invasive cancer on cytology, colposcopy, ECC, or biopsy.**

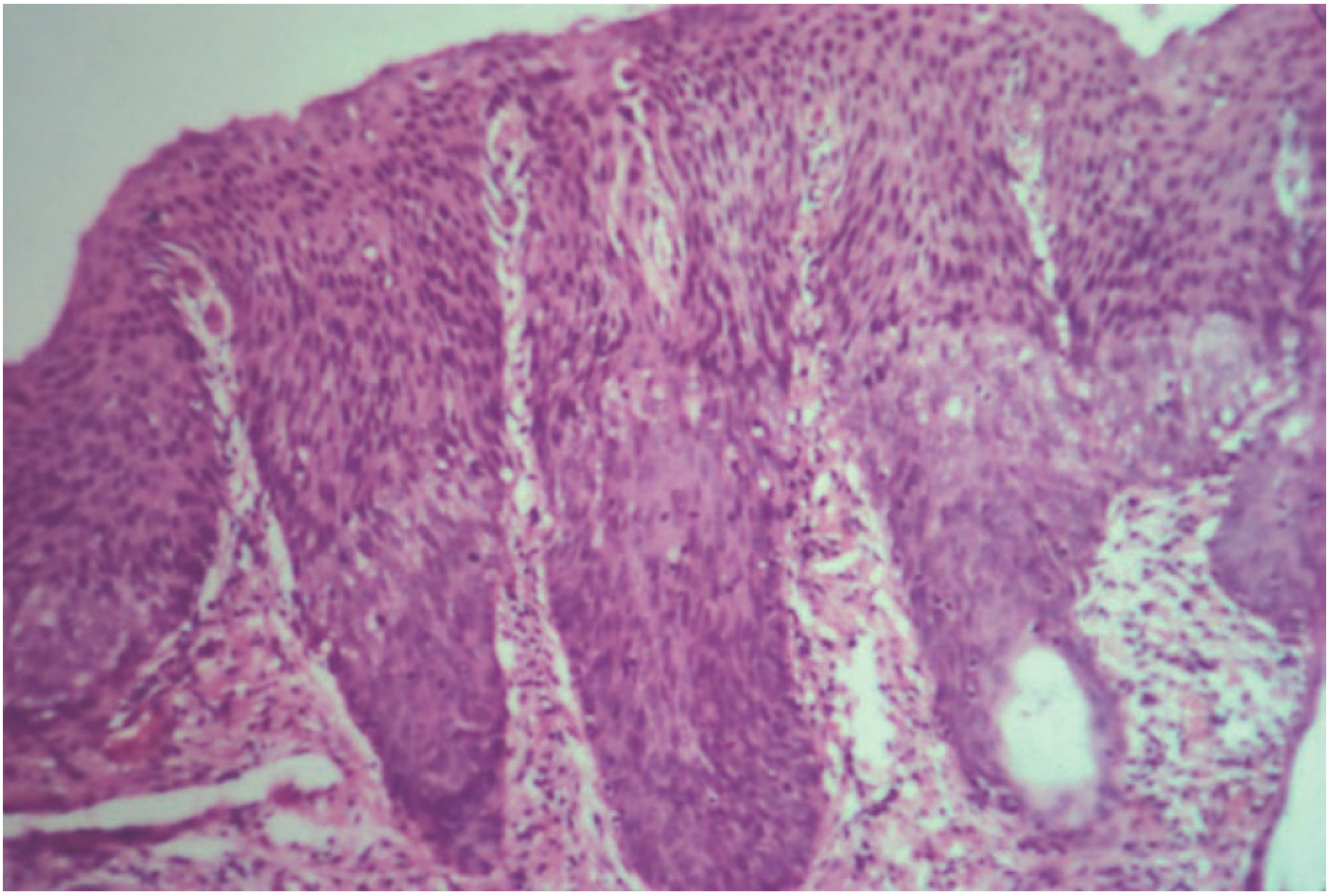


FIGURE 16-13 Cervical intraepithelial neoplasia grade 3 (CIN 3).

Cervical Adenocarcinoma In Situ

In adenocarcinoma *in situ* (AIS), the endocervical glandular cells are replaced by tall columnar cells with nuclear stratification, hyperchromasia, irregularity, and increased atypical mitotic activity (74). Cellular proliferation results in crowded, cribriform glands. The normal branching pattern of the endocervical glands is preserved. About 50% of women with cervical AIS have squamous CIN 2–3, and AIS lesions represent incidental findings in specimens removed for treatment of squamous neoplasia. Usually AIS is located near or above the transformation zone and conventional cervical specimens may not be effective for detecting glandular disease. Obtaining good endocervical specimens by Cytobrush may improve the detection of AIS during the screening process.

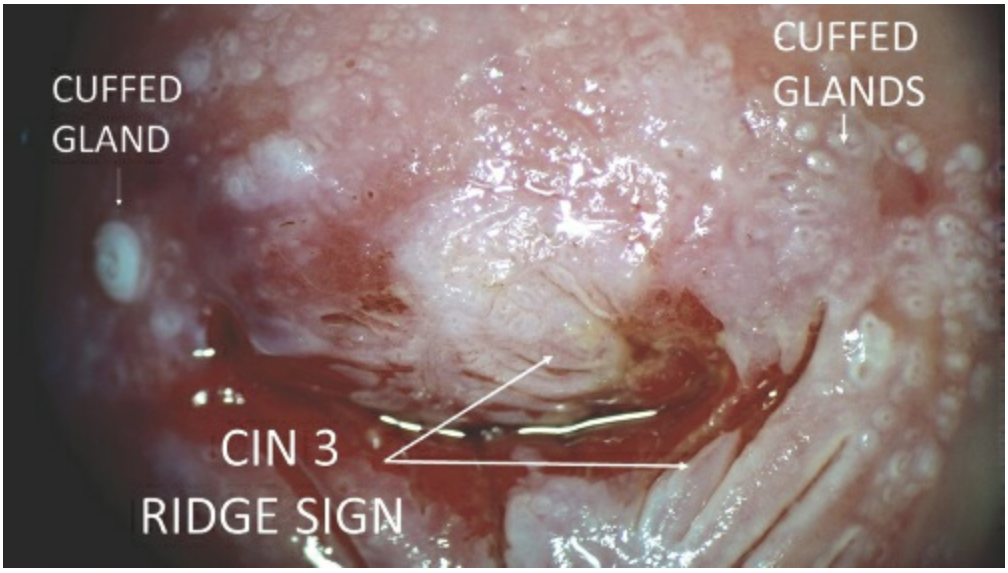


FIGURE 16-14 Colposcopic findings of CIN 3: cuffed gland openings and ridge sign.

[16] AIS is a cancer precursor, and the preferred management for women who have completed childbearing and have a histologic diagnosis of AIS on a specimen from a diagnostic excisional procedure is hysterectomy (66). A histologic diagnosis of AIS from a punch biopsy or a cytologic diagnosis of AIS is insufficient to justify hysterectomy in the absence of a diagnostic excisional procedure.

Conservative management with conization can be considered for women desiring future fertility (66). In such a setting, the status of surgical conization margins and endocervical sampling at the time of surgery are critical. If either is positive, reexcision is recommended because of the risk of cancer.

The limits of AIS lesions are difficult to establish by colposcopy or pathology because of frequent extension of disease within the endocervical canal and the presence of multifocal, "skip lesions" (i.e., lesions that are not contiguous). For this reason, negative margins on an excisional specimen may not be entirely reassuring.

There is good evidence that AIS may progress to invasive cancer (75). In a study of 40 patients with AIS who had cervical conization, 23 of 40 patients (58%) had coexisting squamous intraepithelial lesions and 2 had invasive squamous cell carcinoma (76). Of the 22 patients who underwent hysterectomy, the margins on the cone specimen were positive in 10 patients, and 70% had residual AIS, including 2 patients with foci of invasive adenocarcinoma. One of the 12 patients with negative margins had focal residual adenocarcinoma in the hysterectomy specimen, and 18 women had conization only with negative margins and no relapse of disease after a medium interval of 3 years. Thus, positive margins on the conization specimen are significant findings in these patients (77). In a more alarming study of 28 patients with AIS, of the 8 patients with positive margins who underwent repeat conization or hysterectomy, 3 had residual AIS and 1 patient had invasive adenocarcinoma (78). Of 10 patients with negative margins

who underwent hysterectomy or repeat conization, 4 had residual AIS. One patient in whom the cone margin could not be evaluated had invasive adenocarcinoma. Of the 15 patients treated conservatively with repeat conization of the cervix and close follow-up, 7 (47%) had a recurrent glandular lesion detected after the conization, including invasive adenocarcinoma in 2 women. A glandular lesion was not suspected in 48% of the patients, based on Pap test and ECC results obtained before conization of the cervix.

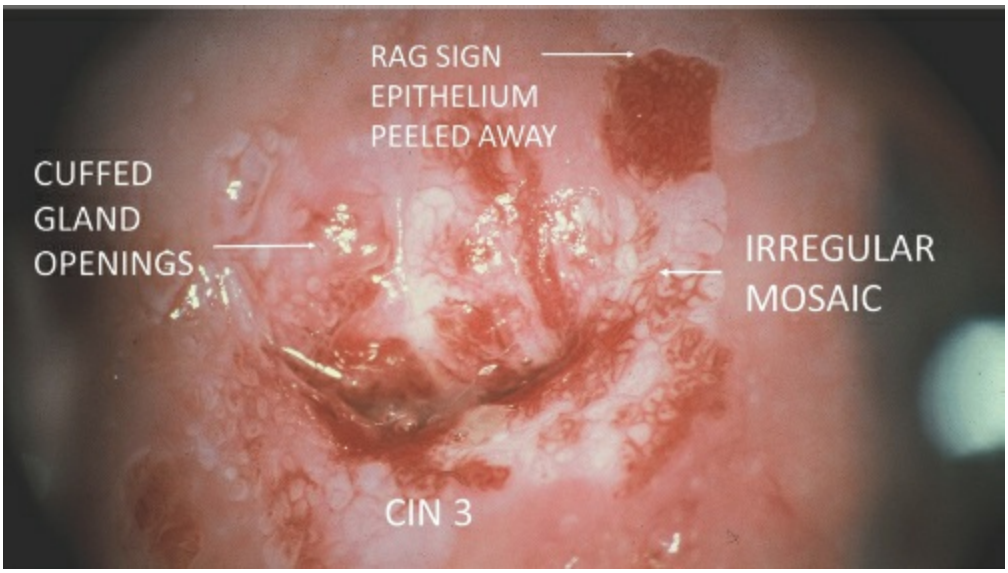


FIGURE 16-15 Colposcopy findings of CIN 3: rag sign and cuffed gland openings.

In all cases post conization for AIS, recommended surveillance requires reassessment at 6 months using a combination of cytology, colposcopy, HPV DNA testing, and endocervical sampling for women who do not undergo hysterectomy.

Treatment Modalities

Cryotherapy

Cryotherapy destroys the surface epithelium of the cervix by crystallizing the intracellular water, resulting in the eventual destruction of the cell. The temperature needed for effective destruction must be in the range of −20° to −30°C. Nitrous oxide (−89°C) and carbon dioxide (−65°C) produce temperatures below this range and, therefore, are the most commonly used gases for this procedure.

The technique believed to be most effective is a freeze-thaw-freeze method in which an ice ball is achieved 5 mm beyond the edge of the probe. The time required for this process is related to the pressure of the gas; the higher the pressure, the faster the ice ball is achieved. Cryotherapy is an effective treatment for CIN with very acceptable failure rates under certain conditions (79–82). It is a relatively safe procedure with few complications. Cervical stenosis is rare but can occur. Posttreatment bleeding is

uncommon and is usually related to infection.

Cure rates are related to the grade of the lesion; CIN 3 has a greater chance of treatment failure (Table 16-5). Townsend showed that cures are related to the size of the lesion; those covering most of the ectocervix have failure rates as high as 42%, compared with a 7% failure rate for lesions less than 1 cm in diameter (83). Positive findings on ECC can reduce the cure rate significantly. Endocervical gland involvement is important because the failure rate in women with gland involvement was 27%, compared with 9% in those who did not have such involvement (84).

Cryotherapy is acceptable when the following criteria are met:

1. CIN 1 that has persisted for 24 months, or CIN 2
2. Small lesion
3. Ectocervical location only
4. Negative endocervical sample
5. No endocervical gland involvement on biopsy

Table 16-5 Results of Cryotherapy for Cervical Intraepithelial Neoplasia (CIN) Compared With Grade of CIN

	CIN 1		CIN 2		CIN 3	
Author (Ref. No.)	No.	Failure (%)	No.	Failure (%)	No.	Failure (%)
Ostergard (80)	13/205	6.3	7/93	7.5	9/46	19.6
Creasman et al. (81)	15/276	5.4	17/235	7.2	46/259	17.8
Benedet et al. (82)	7/143	4.9	19/448	4.2	65/1,003	6.5
Anderson and Hartley (84)			9/123	7.3	17/74	23.0
Total	35/624	5.6	50/899	5.6	137/1,382	9.9

Loop Electrosurgical Excision

Loop electrosurgical excision is a valuable tool for the diagnosis and treatment of CIN (75,85–94). It offers the advantage of performing an operation that is simultaneously diagnostic and therapeutic during one outpatient visit (95–105).

The tissue effect of electricity depends on the concentration of electrons (size of the wire), the power (watts), and the water content of the tissue. If low power or a large-diameter wire is used, the effect will be electrocautery, and the thermal damage to tissue will be extensive. If the power is high (35 to 55 W) and the wire loop is small (0.5 mm), the effect will be electrosurgical, and the tissue will have little thermal damage. The actual cutting is a result of a steam envelope developing at the interface between the wire loop and the water-laden tissue. This envelope is pushed through the tissue, and the combination of electron flow and acoustical events separates the tissue. After the excision, a 5-mm diameter ball electrode is used, and the power is set at 50 W. The ball is placed near the surface so that a spark occurs between the ball and the tissue. This

process is called *electrofulguration,* and it results in some thermal damage that leads to hemostasis. If too much fulguration occurs, the patient will develop an eschar with more discharge, and the risk for infection and late bleeding will be higher.

Loop excision should not typically be used before a high-grade intraepithelial lesion is identified with histopathology. [17] However, treatment after an HSIL cytology may be appropriate in certain settings and among populations for whom colposcopic follow-up is not possible.

LEEP may be associated with an increased risk of overall preterm delivery, preterm delivery after premature rupture of membranes, and low–birth-weight infants in subsequent pregnancies at greater than 20 weeks' gestation (106). The excision of the entire transformation zone along with varying amounts of the cervical canal, may compromise birth outcomes (92,94). This is particularly true for young women, who may have large, immature transformation zones with extensive acetowhite areas. Complications following loop electrosurgical excision are relatively minor and compare favorably with those following laser ablation and conization. Intraoperative hemorrhage, postoperative hemorrhage, and cervical stenosis can occur but at low rates. The SCJ is visible in more than 90% of patients after this procedure. Effectiveness of LEEP and comparison of LEEP to other excision procedures are shown in **Tables 16-9** and **16-10**.

Conization

Conization of the cervix plays an important role in the management of CIN. It can be accomplished with a scalpel, electrosurgical needle, or laser. Before the availability of colposcopy, conization was the standard method of evaluating an abnormal Pap test result. Conization is a diagnostic and therapeutic procedure and has the advantage over ablative therapies of providing tissue for further evaluation to rule out invasive cancer and accurately assess surgical margins (100,101,103,107).

[18] Conization is indicated for diagnosis in women with CIN 3 or AGC-AIS and may be considered under the following conditions:

1. Limits of the lesion cannot be visualized with colposcopy.
2. The SCJ is not evaluable at colposcopy.
3. ECC histologic findings are positive for CIN 2 or CIN 3.
4. Substantial lack of correlation between cytology, biopsy, and colposcopy results.
5. Microinvasion is suspected based on biopsy, colposcopy, or cytology results.
6. The colposcopist is unable to rule out invasive cancer.

Lesions with positive margins are more likely to recur after conization (**Table 16-8**) (100,101,103). Endocervical gland involvement is predictive of recurrence (23.6% with gland involvement compared with 11.3% without gland involvement) (108). When

compared with conization, LEEP is the simpler technique, and short-term results are similar to those obtained with conization or laser excision (72,109). In a prospective study examining the long-term effects of LEEP, conization, and laser excision, no difference in recurrence of dysplasia or in pregnancy outcomes was found (**Tables 16-6** and **16-7**) (110).

Hysterectomy

[18] Hysterectomy is the treatment of last resort for recurrent high-grade CIN. In a study of 38 cases of invasive cancer occurring after hysterectomy among 8,998 women (0.4%), the incidence of significant bleeding, infection, and other complications, including death, is higher with hysterectomy than with other means of treating CIN (76). There are some situations in which hysterectomy remains a valid and appropriate (although not mandatory) method of treatment for CIN:

1. Microinvasion
2. Histologically confirmed recurrent high-grade CIN
3. Co-occurring gynecologic pathology requiring hysterectomy, such as fibroids, prolapse, endometriosis, and pelvic inflammatory disease

Table 16-6 Complications of Electrosurgical Excision

Author (Ref. No.)	No. of Patients	Operative Hemorrhage	Postoperative Hemorrhage	Cervical Stenosis
Prendiville et al. (85)	111	2	2	—
Whiteley and Olah (86)	80	0	3	—
Mor-Yosef et al. (75)	50	1	3	—
Bigrigg et al. (87)	1,000	0	6	—
Gunasekera et al. (88)	98	0	0	—
Howe and Vincenti (89)	100	0	1	—
Minucci et al. (90)	130	0	1	2
Wright et al. (91)	432	0	8	2
Luesley et al. (92)	616	0	24	7
Total	2,617	3 (0.001%)	48 (1.8%)	11/6,178 (1.0%)

Table 16-7 Unsuspected Invasion in Electrosurgical Excision Specimens

Author (Ref. No.)	Patients	Microinvasive	Invasive
Prendiville et al. (85)	102	1	—
Bigrigg et al. (87)	1,000	5	—
Gunasekera et al. (88)	98	—	1
Howe and Vincenti (89)	100	1	—
Wright et al. (91)	141	3	—
Luesley et al. (92)	616	1	—
Chappatte et al. (94)	100	4	6 (adenocarcinoma *in situ*)
Total	2,157	15 (0.7%)	1 (0.04%)

Table 16-8 Grade of Discomfort of Large Loop Excision Versus Laser Conization

Side Effect	Loop Excision (*n* = 98)	Laser (*n* = 101)
Not unpleasant	80 (92%)	32 (32%)
Moderately unpleasant	16 (16%)	50 (50%)
Very unpleasant	2 (2%)	19 (18%)
Operative time	20–50 sec	4–15 min
	(mean, 16 sec)	(mean, 6.5 min)

From **Gunasekera PC, Phipps JH, Lewis BV.** Large loop excision of the transformation zone (LLETZ) compared to carbon dioxide laser in the treatment of CIN: a superior mode of treatment. *Br J Obstet Gynaecol* 1990;97:995–998, with permission.

Table 16-9 Results of Loop Electrosurgical Excision

Author (Ref. No.)	Patients Treated	Patients Recurred
Prendiville et al. (85)	102	2
Whiteley and Olah (86)	80	4
Bigrigg et al. (87)	1,000	41
Gunasekera et al. (88)	98	7

Luesley et al. (92)	616	27
Murdoch et al. (93)	600	16
Total	2,496	97 (3.9%)

Table 16-10 Recurrence of Cervical Intraepithelial Neoplasia After Cone Biopsy

Author (Ref. No.)	No. of Patients	Negative Margins	Positive Margins
Larsson et al. (101)	683	56	246
Bjerre et al. (103)	1,226	64	429
Kolstad and Klem (104)	1,121	27	291
Total	3,030	147 (4.9%)	966 (31.9%)

VAGINAL INTRAEPITHELIAL NEOPLASIA

Vaginal intraepithelial neoplasia (VAIN) often accompanies CIN and shares a common etiology (111). Such lesions may be extensions onto the vagina from the CIN, or they may be satellite lesions occurring mainly in the upper vagina. Because the vagina does not have a transformation zone with immature epithelial cells to be infected by HPV, the mechanism of entry for HPV is by way of microabrasions resulting primarily from insertional sexual activity. As these abrasions heal with metaplastic squamous cells, the HPV may begin its growth in a manner similar to that in the cervical transformation zone. VAIN lesions are asymptomatic. Because they often accompany active HPV infection, the patient may report vulvar warts or an odoriferous vaginal discharge from vaginal warts.

Diagnosis

Women with an intact cervix should undergo routine cytologic screening. VAIN is nearly always accompanied by CIN and cytology is likely to be positive when VAIN is present. The vagina should be carefully inspected by colposcopic examination at the time of colposcopy for any CIN lesion. Particular attention should be paid to the upper vagina. **Women who have persistent abnormal cytology without evident cervical pathology and those with abnormal cytology after treatment of CIN should be examined carefully for VAIN.** For women in whom the cervix was removed for high-grade cervical neoplasia, Pap testing should be performed at regular intervals (e.g., yearly), depending on the diagnosis and severity of lesion.

Colposcopic examination and directed biopsy are the mainstays of diagnosis of VAIN. Typically, the lesions are located along the vaginal ridges, are ovoid in shape and slightly raised, and often have surface spicules. VAIN 1 lesions usually are accompanied by a significant amount of koilocytosis, indicating their HPV origin (Fig. 16-16). VAIN 2 exhibits a thicker acetowhite epithelium, a more raised external border, and less iodine uptake (Fig. 16-17A). When VAIN 3 occurs, the surface may become papillary, and the vascular patterns of punctation and mosaic may occur (Fig. 16-17B). Early invasion is typified by vascular patterns similar to those of the cervix.



FIGURE 16-16 Human papillomavirus (HPV)/vaginal intraepithelial neoplasia grade 1 (VAIN 1). Note the surface spicules with partial uptake of Lugol's stain.

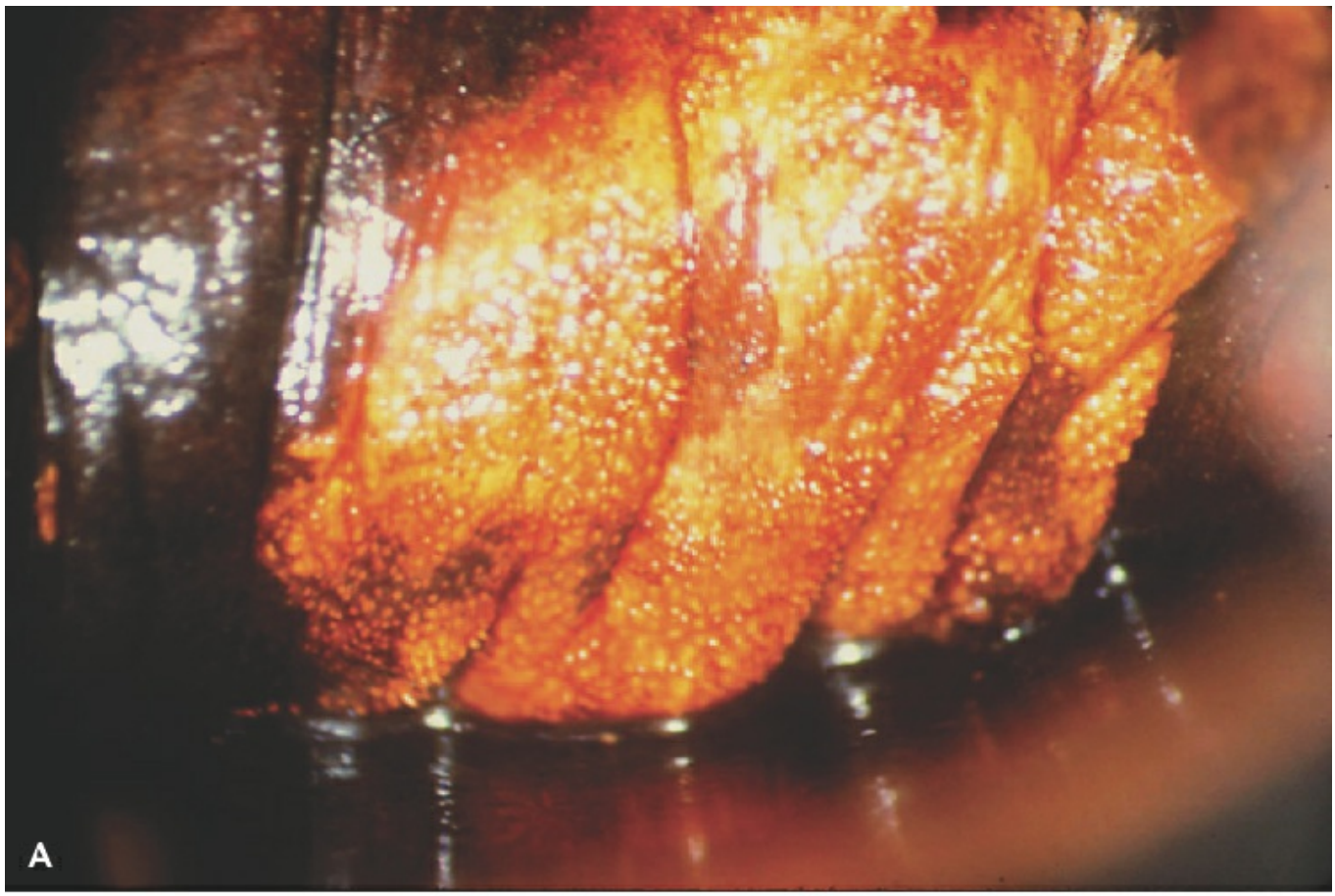
Treatment

[19] Patients with VAIN 1/HPV or VAIN 2 do not require treatment and may be managed with surveillance. These lesions often regress, are multifocal, and recur quickly when treated with ablative therapy. VAIN 3 lesions are more likely to be associated with early invasive disease. In a study of 32 patients who underwent upper vaginectomy for VAIN 3, occult invasive carcinoma was found in 9 patients (28%)

(112). It is recommended in older patients that VAIN 3 lesions located in the dimples of the vaginal cuff be excised to rule out occult invasive cancer. **[19] VAIN 3 lesions that are adequately sampled to rule out invasive disease can be treated with laser therapy or excisional therapy. The major advantage of laser vaporization therapy is the ability to control the depth and width of destruction by direct vision through the colposcope.** The other advantage of laser therapy is the rapid posttreatment healing phase. This process takes about 3 to 4 weeks, after which time a new epithelium has formed completely and, in most cases, has a mature glycogen-containing epithelium.

Tissue Interaction

When the laser beam contacts tissue, its energy is absorbed by the water in the cells, causing it to boil instantly. The cells explode into a puff of vapor (thus the term *laser vaporization*). The protein and mineral content are incinerated by the heat and leaves a charred appearance at the base of the exposed area. The depth of laser destruction is a function of the power of the beam (in watts), the area of the beam (in millimeters squared), and the length of time the laser remains in the tissue. The beam must be moved uniformly across the tissue surface to prevent deep destruction. The laser beam vaporizes a central area and leaves a narrow zone of heat necrosis surrounding the laser crater. The goal of laser vaporization is to minimize the area of tissue necrosis. This goal is accomplished by using high wattage (20 W) with medium beam size (1.5 mm) and moving the beam uniformly but quickly over the surface. The zone of thermal necrosis will be 0.1 mm when the laser is used in this manner. Some lasers have a function called *super pulse,* in which the laser beam is electronically switched off and on thousands of times per second, thereby allowing the tissue to cool between pulses to create less thermal necrosis.


A

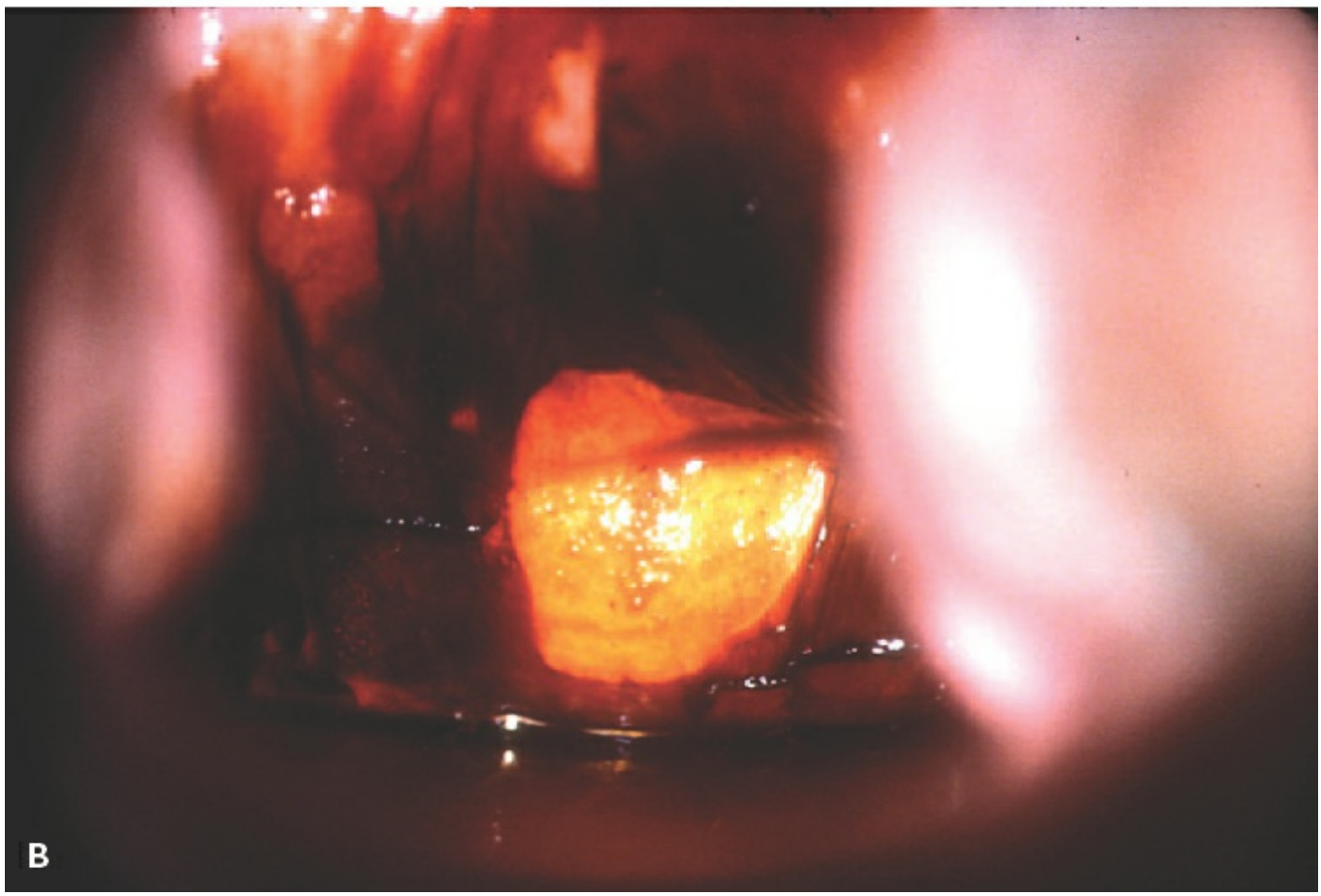

B

FIGURE 16-17 **A:** Vaginal intraepithelial neoplasia grade 2 (VAIN 2). **B:** Vaginal intraepithelial neoplasia grade 3 (VAIN 3).

Cryosurgery should not be used in the vagina because the depth of injury cannot be controlled and inadvertent injury to the bladder or rectum may occur. Superficial fulguration with electrosurgical ball cautery may be used under colposcopic control to observe the depth of destruction by wiping away the epithelial tissue as it is ablated. Excision is an excellent method for treatment of upper vaginal lesions in a small area. Occasionally, total vaginectomy will be required for a VAIN 3 lesion occupying the entire vagina. It should be accompanied by a split-thickness skin graft. This aggressive treatment for widespread vaginal lesions should not be used for VAIN 2.

The malignant potential of VAIN appears to be less than that of CIN. In a review of 136 cases of CIS of the vagina over a 30-year period, 4 cases (3%) progressed to invasive vaginal cancer despite the use of various treatment methods (111).

VULVAR INTRAEPITHELIAL DISEASE

Vulvar Dystrophies

In the past, terms such as *leukoplakia, lichen sclerosis et atrophicus, primary atrophy, sclerotic dermatosis, atrophic and hyperplastic vulvitis,* and *kraurosis vulvae* were used to denote disorders of epithelial growth and differentiation (113). In 1966, Jeffcoate suggested that these terms did not refer to separate disease entities because their macroscopic and microscopic appearances were variable and interchangeable (114). He assigned the generic term *chronic vulvar dystrophy* to the entire group of lesions.

The International Society for the Study of Vulvar Disease (ISSVD) recommended that the old *dystrophy* terminology be replaced by a new classification under the pathologic heading *nonneoplastic epithelial disorders of skin and mucosa.* This classification is shown in Table 16-11. In all cases, diagnosis requires biopsy of suspicious-looking lesions, which are best detected by careful inspection of the vulva in a bright light aided, if necessary, by a magnifying glass (115).

The malignant potential of these nonneoplastic epithelial disorders is low, and lesions with atypia are classified as vulvar intraepithelial neoplasia (VIN). Patients with lichen sclerosis and concomitant hyperplasia may be at particular risk (116).

Vulvar Intraepithelial Neoplasia

As with the vulvar dystrophies, there is confusion regarding the nomenclature for VIN. Four major terms are used: *erythroplasia of Queyrat, Bowen disease, carcinoma in situ simplex,* and *Paget disease.* In 1976, the ISSVD decreed that the first three lesions

were merely gross variants of the same disease process and that all of these entities should be included under the umbrella term *squamous cell carcinoma in situ* (stage 0) (92). In 1986, the ISSVD recommended the term *vulvar intraepithelial neoplasia* (Table 16-11).

Table 16-11 Classification of Epithelial Vulvar Diseases

Nonneoplastic epithelial disorders of the skin and mucosa
Lichen sclerosis (lichen sclerosis et atrophicus) Squamous hyperplasia (formerly hyperplastic dystrophy) Other dermatoses
Mixed nonneoplastic and neoplastic epithelial disorders
Intraepithelial neoplasia
Squamous intraepithelial neoplasia VIN 1 VIN 2 VIN 3 (severe dysplasia or carcinoma *in situ*)
Nonsquamous intraepithelial neoplasia Paget disease Tumors of melanocytes, noninvasive
Invasive tumors

VIN, vulvar intraepithelial neoplasia.
From **Committee on Terminology, International Society for the Study of Vulvar Disease.** New nomenclature for vulvar disease. *Int J Gynecol Pathol* 1989;8:83, with permission.

VIN is graded as 1 (mild), 2 (moderate), or 3 (severe or CIS) on the basis of cellular immaturity, nuclear abnormalities, maturation disturbance, and mitotic activity. In VIN 1, immature cells, cellular disorganization, and mitotic activity occur predominantly in the lower one-third of the epithelium, whereas in VIN 3, immature cells with scanty cytoplasm and severe chromatinic alterations occupy most of the epithelium (Fig. 16-18). Dyskeratotic cells and mitotic figures occur in the superficial layer. The appearance of VIN 2 is intermediate between VIN 1 and VIN 3. Additional cytopathic changes of HPV infection, such as perinuclear halos with displacement of the nuclei by the intracytoplasmic viral protein, thickened cell borders, binucleation, and multinucleation, are common in the superficial layers of VIN, especially in VIN 1 and VIN 2. These viral changes are not definitive evidence of neoplasia but are indicative of viral exposure (117). Most vulvar condylomas are associated with HPV-6 and -11, whereas HPV-16 is detected in more than 80% of VIN cases by molecular techniques.
[20] VIN 3 is a neoplastic precursor and can be unifocal or multifocal. Typically, multifocal VIN 3 presents with small hyperpigmented lesions on the labia majora (Fig.

16-19). Some cases of VIN 3 are more confluent, extending to the posterior fourchette and involving the perineal tissues. The term *bowenoid papulosis (bowenoid dysplasia)* was used to describe multifocal VIN lesions ranging from grade 1 to 3. Clinically, patients with bowenoid papulosis present with multiple small pigmented papules (40% of cases) that are usually less than 5 mm in diameter. Most women with these lesions are in their 20s, and some are pregnant. After childbirth, the lesions may regress spontaneously. The term *bowenoid papulosis* is no longer recommended by the ISSVD.

The American College of Obstetrics and Gynecology published a committee opinion on the management of VIN (118). **The report indicates that VIN 1 is no longer considered a precancerous lesion. It is most often an HPV lesion or may be overcalled, and does not require treatment. VIN 2 with p16 positive should be treated in the same manner as VIN 3. VIN 2 lesions with negative p16 can be observed.**

VIN Treatment

The treatment of VIN 3 varies from wide excision to the performance of a superficial or "skinning" vulvectomy (119–122). Although the treatment originally recommended for CIS of the vulva was wide excision, fears that the disease is preinvasive led to the widespread use of superficial vulvectomy (121). Because progression is relatively uncommon, typically occurring in 5% to 10% of cases, extensive surgery is not warranted (119). This is particularly important because many VIN 3 lesions are found in premenopausal women.

The therapeutic alternatives for VIN 3 are simple excision, laser ablation, and superficial vulvectomy with or without split-thickness skin grafting. Excision of small foci of disease produces excellent results and has the advantage of providing a histopathologic specimen. Although multifocal or extensive lesions may be difficult to treat by this approach, it offers the potential for the most cosmetic result. Repeat excision is often necessary but can usually be accomplished without vulvectomy (120,122).



FIGURE 16-18 Carcinoma *in situ* of the vulva (vulvar intraepithelial neoplasia grade 3, VIN 3).

The carbon dioxide laser can be used for multifocal lesions but is unnecessary for unifocal disease. The disadvantages are that it can be painful and costly and does not provide a histopathologic specimen (123).

Superficial vulvectomy is appropriate to treat extensive and recurrent VIN 3 (122). The goal of the surgery is to extirpate all of the disease while preserving as much of the normal vulvar anatomy as possible. The anterior vulva and the clitoris should be preserved if possible. In some patients, the disease extends up the anus, which must be resected. An effort should be made to close the vulvar defect primarily, reserving the use of skin grafts for instances in which the vulvar defect cannot be closed because the resection is so extensive. Split-thickness skin grafts can be harvested from the thighs or buttocks, but the latter is more easily concealed (124).

Paget Disease of the Vulva

Extramammary Paget disease of the vulva (AIS) was described 27 years after the description by Sir James Paget of the mammary lesion that now bears his name (125).

Some patients with vulvar Paget disease have an underlying adenocarcinoma, although the precise frequency is difficult to ascertain.

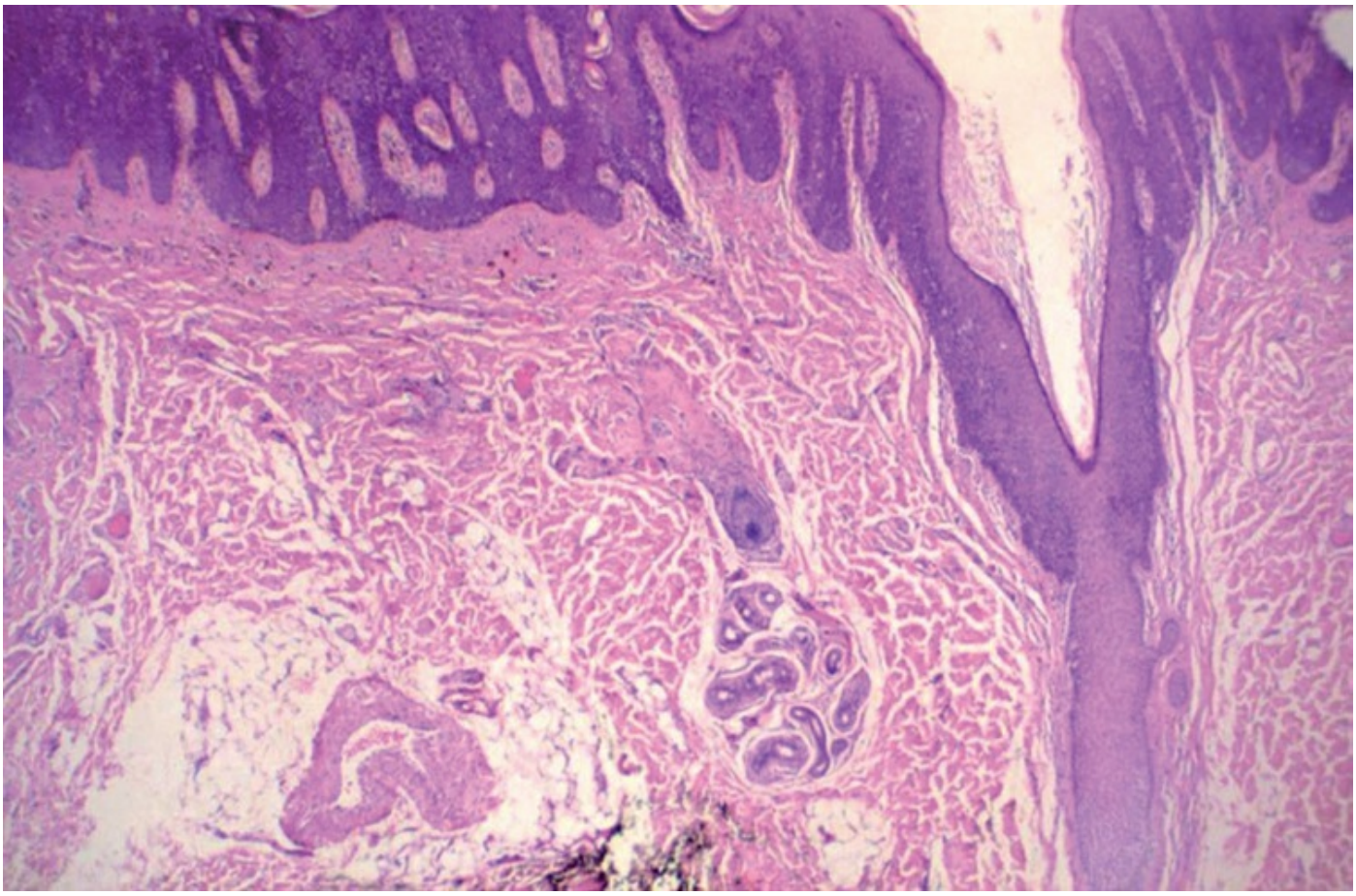


FIGURE 16-19 Vulvar carcinoma *in situ:* carcinoma *in situ* (VIN 3) extending into the hair follicle.

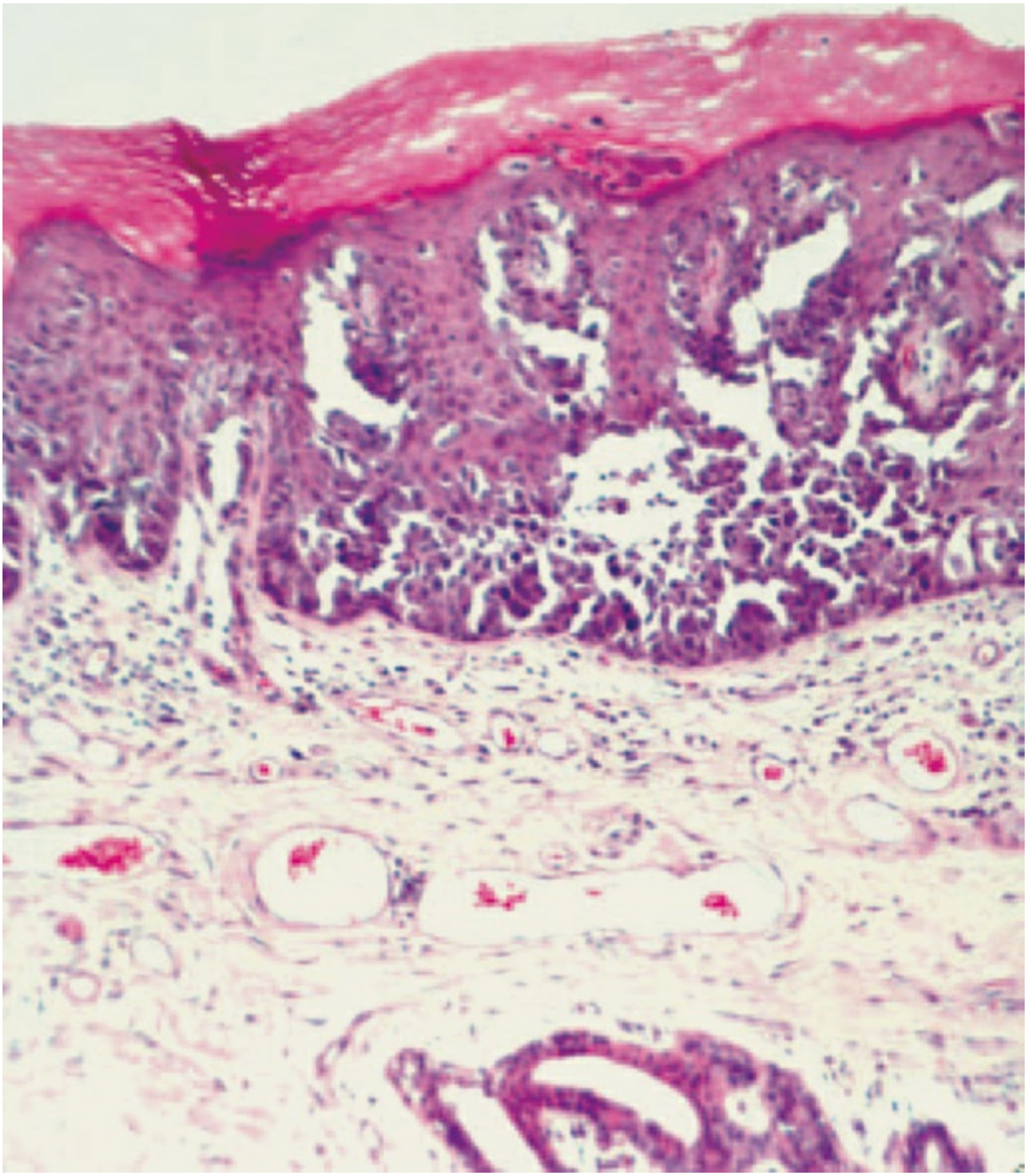


FIGURE 16-20 Paget disease of the vulva. The epidermis is permeated by abnormal cells with vacuolated cytoplasm and atypical nuclei. This heavy concentration of abnormal cells in the parabasal layers is typical of Paget disease.

Histology

Most cases of vulvar Paget disease are intraepithelial. Because these lesions demonstrate apocrine differentiation, the malignant cells are believed to arise from undifferentiated basal cells, which convert into an appendage type of cell during carcinogenesis (Fig. 16-20). The "transformed cells" spread intraepithelially throughout

the squamous epithelium and may extend into the appendages. In most patients with an underlying invasive carcinoma of the apocrine sweat gland, Bartholin gland, or anorectum, the malignant cells are believed to migrate through the dermal ductal structures and reach the epidermis. In such cases, metastasis to the regional lymph nodes and other sites can occur.

Paget disease must be distinguished from superficial spreading melanoma. All sections should be studied thoroughly using differential staining, particularly periodic acid–Schiff (PAS) and mucicarmine stains. Mucicarmine has routinely positive results in the cells of Paget disease and negative results in melanotic lesion.

Clinical Features

Paget disease of the vulva predominantly affects postmenopausal white women, and the presenting symptoms are usually pruritus and vulvar soreness. The lesion has an eczematoid appearance macroscopically and usually begins on the hair-bearing portions of the vulva (**Fig. 16-21**). It may extend to involve the mons pubis, thighs, and buttocks. Extension to the mucosa of the rectum, vagina, or urinary tract is described (126). The more extensive lesions are usually raised and velvety in appearance.

A second synchronous or metachronous primary neoplasm is associated with extramammary Paget disease in about 4% of patients, which is much less common than previously believed (127). Associated carcinomas were reported in the cervix, colon, bladder, gallbladder, and breast. When the anal mucosa is involved, there usually is an underlying rectal adenocarcinoma (116).

Treatment

Unlike squamous cell VIN 3, in which the histologic extent of disease correlates closely with the macroscopic lesion, Paget disease usually extends well beyond the gross lesion (128). This extension results in positive surgical margins and frequent local recurrence unless a wide local excision is performed (129). Underlying adenocarcinomas are apparent clinically, but this finding does not occur invariably; therefore, the underlying dermis should be removed for adequate histologic evaluation. For this reason, laser therapy is unsatisfactory in treating primary Paget disease. If underlying invasive carcinoma is present, it should be treated in the same manner as a squamous vulvar cancer. This treatment usually requires radical vulvectomy and at least an ipsilateral inguinal–femoral lymphadenectomy.



FIGURE 16-21 Paget disease of the labium majus.

Recurrent lesions are almost always *in situ,* although there was at least one report of an underlying adenocarcinoma in recurrent Paget disease (127). It is reasonable to treat recurrent lesions with surgical excision.

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CHAPTER 17

Sexuality and Sexual Dysfunction



Rosemary Basson

Sexuality
- Sexual Activity, Sexual Orientation, and Sexual Attraction
- Genital Anatomy
- Sexual Response Cycle
- Physiology

Factors Affecting Sexual Response
- Mental Health
- Aging
- Sex Hormones
- Age-Associated Health Conditions
- Personality Factors
- Relationships
- Sexual Dysfunction in the Partner
- Infertility
- Drugs
- Chronic Illness and Cancer
- Gynecologic Conditions: Sexual Dysfunction Can Arise From Gynecologic Diseases, Procedures, and Treatments
- Hysterectomy
- Gynecologic Cancer
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Assessment of Sexual Problems
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- Diagnostic Criteria
- Overview of Management of Sexual Dysfunction

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Management of Sexual Interest and Arousal Disorder
Management of Sexual Dysfunction Midlife and Later
Management of Genitourinary Syndrome of Menopause (GSM): AKA Vulvovaginal Atrophy
Female Genital Mutilation
Conclusion

KEY POINTS

1 Sexual problems are common, especially painful sex. Dyspareunia may affect two-thirds of women during their lifetime. Genito-pelvic penetration pain disorder includes the former term "vaginismus"—an involuntary reflex precipitated by real or imagined attempts at vaginal entry and other types of chronic dyspareunia including the most common type— vestibulodynia, which has a prevalence of 15%.

2 Sexual response reflects the fundamental interplay between the mind and body: psychological, interpersonal, cultural, environmental, and biologic (hormonal, vascular, muscular, neurologic) factors interact and modulate sexual experience.

3 Factors that can affect sexual response include mood, relationship duration and quality, age and stage in life, past sexual experiences—desired, coercive, or abusive— personal psychological factors stemming from relationships in childhood with parental figures, previous losses and traumas, and ways of coping with emotions, current and past illness, fertility concerns, and use of medication, alcohol, and illicit drugs.

4 Sexual dysfunction can arise from gynecologic diseases such as endometriosis; procedures such as those associated with infertility; and treatments including pelvic radiation, urinary incontinence surgeries, and medications, for example, aromatase inhibitors or gonadotropin-releasing hormone (GnRH) antagonists. Sexual abuse can have long-lasting effects on sexuality and women seen in gynecology clinics may have comorbid illnesses that interrupt their sexual function.

5 Physical, psychological, and economic stressors of pregnancy may negatively affect emotional and sexual intimacy. Sexual value systems, folklore, religious beliefs, physical changes, and medical restrictions influence sexual attitudes and behavior during pregnancy and postpartum.

6 Many of the sexual problems couples encounter result from a deficit of knowledge or experience, sexual misconceptions, or inability of the couple to communicate about their sexual preferences.

7 Despite the importance of issues relating to sexuality, many women find it difficult to initiate discussions with their physicians about sexual concerns, and many physicians are uncomfortable discussing sexual issues with their patients. Asking about sexual concerns gives physicians an opportunity to educate patients about the risk of sexually transmitted infections (STIs), encourage safer sex practices, evaluate the need for contraception, dispel sexual misconceptions, and identify potential sexual dysfunction. Many men and women have a number of serial sexual partners but use condoms inconsistently, thereby exposing themselves to STIs and unintended pregnancies.

8 Recent research confirms that 43% of 1,202 American women, including those in poor health, rated sexual health as an important component of quality of life—recording 4 or 5 on a 5-point Likert scale (1). There is need to provide patients with information about normal sexual changes that occur with puberty, pregnancy and postpartum, menopause, and older age as well as in association with gynecologic conditions.

SEXUALITY

The spectrum of normal sexual response varies from one woman to another

throughout a woman's lifetime. Physicians need to be sensitive to their patients' sexual values, attitudes about specific practices, and concerns about their sexuality. Maintaining open communication with patients about their sexuality confirms the physician's willingness to address problems when they arise.

Sexual Activity, Sexual Orientation, and Sexual Attraction

In keeping with recent large surveys, a continuous rather than categorical distribution of sexual orientation is described. Requesting women (and men) to choose between heterosexual, mostly heterosexual, bisexual, mostly gay/lesbian or gay/lesbian, showed that 71% of the total 803 women indicated heterosexual and 6% gay/lesbian while 20% checked "mostly heterosexual" (2). The latter group had more same-sex attraction and, although less frequent than the occurrence of same-sex attraction, more same-sex partners than strictly heterosexual women. This information is important to physicians, to avoid assumptions that sexual attraction and activity necessarily conform to a limited choice of hetero, bi, or gay label leading to potential misunderstanding risks of STI's pregnancy, and sexual dysfunction.

The average age for first intercourse for both men and women in the United States is 17 years and for at least 20% this is without contraception (3). **By age 19, 50% of women have had intercourse but while some 86% report using contraception on their last occasion of intercourse, only 1 in 5 women use dual protection** (4). **Many men and women have serial sexual partners and even older adults use condoms inconsistently, thereby exposing themselves to sexually transmitted infections (STIs) and unintended pregnancies.** A recent large British survey found that 22.8% of women reported one or more sexual difficulties including problematic orgasm, low sexual interest, and arousal or painful sex. Applying the new criteria to designate a sexual disorder as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual,* fifth version (DSM-5) (5), 3.6% of the total met all three criteria (6). These criteria include symptom persistence for >6 months, symptom presence in >75% of occasions, and associated distress. The study excluded nonsexually active women some of whom may have stopped activity as a result of sexual dysfunction.

Genital Anatomy

For most women, their clitoral tissue is the most sexually sensitive part of their anatomy, and its stimulation produces the most intense sexual feelings and the most intense orgasms. Many women first need to experience both nonphysical and nongenital physical stimulation before clitoral stimulation can be enjoyed. In the absence of arousal, direct clitoral stimulation can be unpleasant and be perceived as so

intense as to be painful. Immunohistologic studies identified neurotransmitters thought to be associated with sensation concentrated right under the epithelium of the glans clitoris. Clitoral tissue extends far beyond the visible portion when the clitoral hood is retracted. It includes the clitoral head, shaft, rami running along the pubic arch, periurethral tissue in front of the anterior vaginal wall, and the bulbar tissue under the superficial perineal muscles surrounding the anterior distal vagina—such that sexual sensations and arousal arise from massaging these areas, not just the clitoral shaft and head. Other sexually sensitive areas include the nipples, breasts, labia, much of the skin generally, and to some extent, the vagina. Although the lower third of the vagina is responsive to touch, the upper two-thirds are sensitive primarily to pressure. The rich supply of nerves in the fascia anterior to the upper vagina (Halban's fascia) and the proximity of the clitoral type of spongy tissue around the urethra anterior to the vagina contribute to the pleasurable sensations of intercourse. Many women experience orgasm more easily from direct clitoral touch, possibly provided at the same time as intercourse.

There is speculation about the existence of a "G-spot," an area of the vagina, located anteriorly midway between the symphysis pubis and cervix, which can be exquisitely sensitive to deep pressure. Stimulation of this area can be associated with orgasm and loss of fluid which can be dilute urine or fluid from Skene's glands (7). Women who are normally continent might leak urine at orgasm; urodynamic studies have demonstrated that orgasm may provoke uninhibited detrusor overactivity and sometimes sphincter relaxation. Usually medical intervention is not needed.

Sexual Response Cycle

[2] Sexual response reflects the fundamental interplay between the mind and body: psychological, interpersonal, cultural, environmental, and biologic (hormonal, vascular, muscular, neurologic) factors interact and modulate sexual experience. At the outset of sexual engagement, especially in new relationships, women may sense heightened sexual desire. However, in long-term relationships, women (and men), may be motivated by factors other than, or additional to, sexual desire (8). Women initiate or consent to sex for many reasons, including a wish to increase emotional intimacy with their partners (9,10). By directing her attention to sexual sensations from stimulation (physical, visual, fantasy, auditory), a woman's subjective sexual arousal/pleasure/excitement develops and triggers sexual desire. Desire and arousal coexist and compound each other **(Fig. 17-1)**. Sexual satisfaction (with one, many, or no orgasms) can be achieved if she can retain focus, continue to enjoy sensations of arousal, if the duration of stimulation is sufficiently long, and there is no negative outcome (e.g., pain or partner dysfunction). The response is circular, with phases overlapping and in variable order (e.g., desire may follow arousal, and higher arousal

may follow the first orgasm). Desire, once triggered, increases the motivation to respond to sexual stimuli and to agree to or request more intensely erotic forms of stimulation. Any initial spontaneous desire will augment the response. This circular type of sequence can be experienced multiple times on any one occasion of sexual interaction. This motivation/incentives module reflecting the importance of the mind's appraisal of sexual stimuli is supported by empirical research (10–12).

Physiology

Desire and Arousability

Sexual desire provides one of many motivations to be sexual. Feelings of desire and arousal may be triggered by internal (e.g., fantasies, memories, feelings of arousal) and external (e.g., an interested and interesting partner, visual or written erotica) stimuli. Sexual cues are dependent on adequate neuroendocrine function. Multiple neurotransmitters, peptides, and hormones modulate desire and subjective arousal (13). Substances that promote sexual response include norepinephrine, dopamine, oxytocin, melatonin, and serotonin acting on some receptors. Prolactin, serotonin acting on other receptors, endocannabinoids, opioids, and γ-aminobutyric acid inhibit sexual response. These peptides and neurotransmitters are themselves modulated by sex hormones that direct the synthesis of enzymes involved in the production of neurotransmitters and the synthesis of their receptors. Biologic factors do not act independently from environmental factors, a finding in human and animal models. Dopamine and progesterone, acting on receptors in the hypothalamus, facilitate sexual behavior in female rats following oophorectomy and received estrogen. The presence of a male animal in an adjacent cage caused an identical change in sexual behavior (14). Likewise, ability to be aroused and intensity of response can be increased in some women by giving them a modest dose of testosterone, by administering *bupropion* (dopaminergic), or by a change of partner (8,15,16). Even in rodents, complex networks exist whereby the female assesses the context of potential sexual activity and relates it to past experience and expectation of reward (17). In women, sexual interest is influenced by their mood, psychological mindset, beliefs and values, expectations, sexual orientation, preferences, and the presence of a safe and erotic environmental setting. Even in the absence of a clinical depression, negative affect is found to negatively modify sexual function while the sexual experiences modulate affect the next day (18,19). Moreover, other research concludes that cognitive factors (i.e., lack of erotic thoughts and being distracted or concerned about sexual behavior) were the best predictors of difficulty in triggering sexual desire: other dimensions including relationship factors, psychopathology, and medical problems appeared to have an indirect impact on sexual desire with the cognitive factors acting as the mediators (20). Sexual desire, interest, and arousability are most strongly influenced by mental health

and feelings for the partner, both generally and specifically, at the time of sexual interaction (21–23). Sexual desire is strongly influenced by fatigue; as a result, sex late at night is not usually attractive to busy individuals. Similarly, chronic illness typically reduces desire and arousability (24).

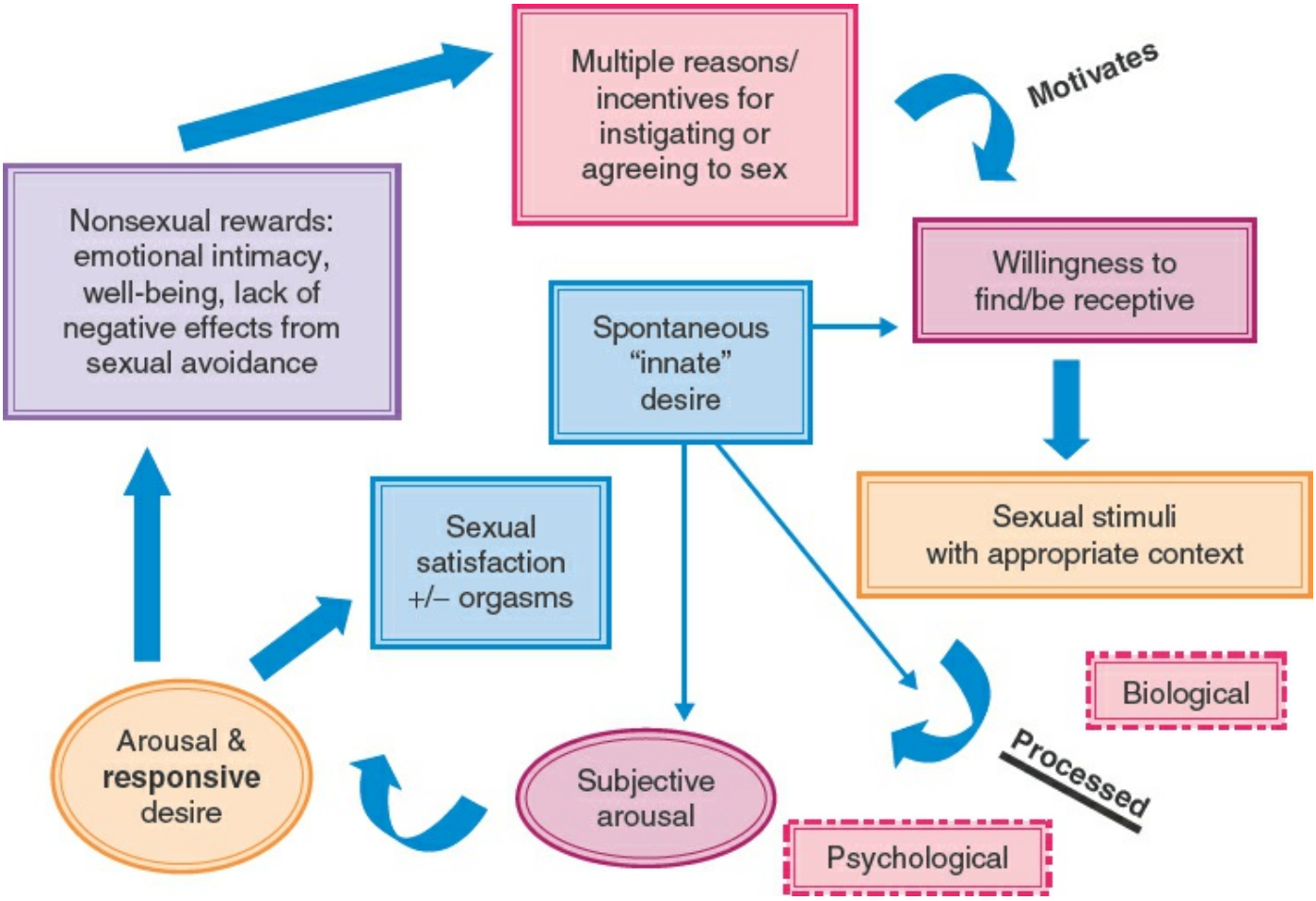


FIGURE 17-1 The blended sex response cycle showing the many reasons/incentives for initiating/accepting sexual activity.

Sexual Arousal

Recent brain imaging reflects the complexity of sexual arousal, confirming that multiple networks in the brain are involved in sexual response. Brain imaging of healthy people during visual sexual stimulation identifies a model of sexual arousal involving complex brain circuitry, including cortical, limbic, and paralimbic areas known to be involved in cognition, motivation, and emotions linked to changes within the autonomic nervous system (25). Specific inhibitory regions deactivate these sexual responses (26). In a small study, sexually functional surgically menopausal women, receiving no hormonal therapy, viewed erotic videos during functional magnetic resonance imaging. The women failed to show the brain activation typical of premenopausal women and also typical of themselves when they were treated with both

testosterone and estrogen, and yet, they reported sexual arousal from the erotic videos with, and without, hormonal supplementation (27). Recent work on brain activation during subliminal and supraliminal sexual stimuli shows an interesting difference between male and female subjects. Exposure to supraliminal sexual images was associated with activation in arousal-related areas and in inhibitory regions in both men and women. Exposure to subliminal sexual images was associated mainly with activation in the arousal-related areas, and in women there was increased activation in some inhibitory regions, but that did not appear in men. This suggests that when women appraise stimuli as sexual, there will be both arousal and control responses—even when the sexual cues are subliminal. The authors note that the various outcomes associated with sex including pregnancy and abuse, pose a relatively bigger potential threat to women than to men (28).

Accompanying the subjective excitement and erotic feelings of arousal are a number of physical changes. These changes include genital swelling; increased vaginal lubrication; engorgement of the breasts and nipple erection; increases in skin sensitivity to sexual stimulation; changes in heart rate, blood pressure, muscle tone, breathing, body temperature; mottling of the skin; and a "sex flush" of vasodilatation over the chest, breasts, and face. With sexual stimulation, brain function in the hypothalamus and other areas influencing the genital response is activated, triggering the autonomic nervous system to allow increased blood flow to the vagina. Vasodilatation of the arterioles in the submucosal vaginal plexus increases transudation of interstitial fluid, which moves from capillaries between the epithelial intercellular spaces and into the vaginal lumen. Simultaneously, the autonomic nervous system allows relaxation of the smooth muscle cells surrounding blood spaces (sinusoids) in the extensive clitoral tissue and labia, causing clitoral swelling and vasodilatation in the labia. Immunohistologic studies indicate nerves containing nitric oxide are present in the genital skin covering the clitoris and labia.

With arousal, the vagina lengthens, distends, and dilates, and the uterus elevates out of the pelvis. With increased sexual stimulation, vasocongestion reaches a maximum intensity. Genitally, the labia become more swollen and darker red and the lower third of the vagina swells and thickens to form an "orgasmic platform." The clitoris becomes more swollen and elevates to a position near the symphysis pubis, and the uterus elevates fully out of the pelvis. The breasts become more engorged, the skin more mottled, and the nipples more erect.

The neurobiology of arousal is incompletely understood but the genital vasocongestive responses appear to be highly automated, occurring within seconds of an erotic stimulus (12). Pelvic autonomic nerves release nitric oxide and vasoactive intestinal polypeptide (VIP), mediating vasodilatation. Acetylcholine (ACh) blocks noradrenergic vasoconstrictive mechanisms and promotes nitric oxide release from

endothelium. Some pelvic autonomic nerves primarily release (vasoconstrictive) noradrenaline and adenosine triphosphate, but others release ACh, nitric oxide, and VIP. Recent work suggests all pelvic autonomic nerves are sympathetic (29). Nitric oxide is thought to be the major neurotransmitter involved in vulvar engorgement. In the vagina, VIP, nitric oxide, and other unidentified neurotransmitters are involved.

Even in women without any sexual dysfunction, there is highly variable correlation between the degree of subjective sexual excitement and the increase in congestion around the vagina (12). This poor correlation was shown repeatedly over the past 39 years based on psychophysiologic studies using the vaginal photoplethysmograph. Congestion in response to a sexual video is reduced in women with disruption of the autonomic nerves supplying the vulva and vagina (e.g., from nonnerve-sparing radical hysterectomy). Otherwise healthy women complaining of absent sexual arousal show increases in vaginal congestion from erotic stimuli that are similar those in control women (12).

Laboratory-demonstrated reflexes may be involved in the physiology of arousal. A cervicomotor reflex can be elicited from cervical touch with a balloon-tipped catheter to replicate penile pressure, causing a reduction in pressure in the upper portion of the vagina and an increase in pressure in the middle and lower portions. Simultaneously, an increase in electromyographic activity in the levator ani and puborectalis muscles was recorded. It is thought that during intercourse penile thrusting on the cervix might cause contraction of the pelvic muscles to facilitate "ballooning" of the upper vagina, perhaps to facilitate pooling of semen. The same muscle contraction constricts the lower vagina, which may afford increased stimulation of the partner's penis, thereby maintaining rigidity (30). A further reflex demonstrated in laboratory studies shows reduced uterine tone in response to mechanical or electrical stimulation of the glans of the clitoris. Background activity of the uterine muscle was abolished by clitoral stimulation, but not if either the glans clitoris or the uterus was anesthetized. Uterine pressure decreased with clitoral stimulation. This reflex may underlie the known increase in size and the elevation of the uterus with sexual arousal (30).

Orgasm

Orgasm is a brain event, typically triggered by genital stimulation, but can occur during sleep or from stimulation of other body parts including the breast and nipple or by fantasy, occasionally by medication, and in spinal cord injured women by vibrostimulation of the cervix. In able-bodied women, it involves a myotonic response of smooth and striated muscle associated with feelings of sudden release of the sexual tension built up during arousal. It is described as the most intensely pleasurable of the sexual sensations. Reflex rhythmic contractions (3 to 20, 0.8/s) of the muscles surrounding the vagina and anus occur. Some women may subjectively perceive uterine contractions during orgasm and some may report a difference in their

perception of orgasm after hysterectomy, but this is not objectively documented. An objective quantitative measure was established that shows strong correspondence with the subjective experience of orgasm. Rectal pressure while volunteers imitated orgasm, tried to achieve orgasm and failed, or experienced orgasm was significantly different during orgasm as opposed to both control tasks (31).

Brain imaging studies of women during orgasm showed brain activations and deactivations similar but not identical to those found in men (32). There is profound deactivation in the anterior part of the orbitofrontal cortex (OFC). This area is thought to be involved in urge suppression and behavioral release. The medial OFC is part of the neuronal network underlying self-monitoring and is connected to the amygdala. The latter is deactivated during the genital stimulation and arousal and remains deactivated during orgasm. Deactivation of this network is associated with a more carefree state of mind. The subjective description of orgasm is very much in keeping with this depiction (33).

The majority of women experience orgasm more easily from direct clitoral stimulation. More direct contact with the clitoris is possible from contact of pubis to pubis after the man has ejaculated but the movements of intercourse resume while penile size is somewhat reduced but some firmness maintained. The bodies are more closely approximated and the woman can move her pelvis on his at a rate that is most conducive to her orgasm. Breast stimulation, kissing, and clitoral stimulation during intercourse are other commons means of experiencing orgasm. **Women are potentially multiorgasmic, capable of experiencing a number of orgasms close together during one sex response cycle. Some may resume sexual activity, possibly with more orgasms. Women do not typically have a refractory period. However, many mid-aged and older women may experience more rewarding sex when sexual activity is separated by a number of days. Following the interval there is more interest in being sexual, a more reliable and pleasurable response, and greater likelihood of more intense arousal and orgasm.**

Resolution

Following the sudden release of sexual tension brought about by orgasm, most women experience a feeling of relaxation and well-being (some may feel energized). The gradual lessening of pelvic engorgement contrasts with the quicker loss of penile firmness in men. Nongenital changes that took place during arousal are reversed, and the body can return to a resting state after some 5 to 10 minutes. Women who enjoy arousal without orgasm and without any sense that orgasm is very close but frustratingly absent, report a similar sense of well-being and relaxation.

FACTORS AFFECTING SEXUAL RESPONSE

[3] Numerous factors can affect sexual response (34,35): **These factors include mood; age; relationship duration and quality; personal psychological factors stemming from relationships in childhood with parental figures; previous losses, traumas, and ways of coping with emotions; illness; fertility concerns; and use of medication, alcohol, and illicit drugs**.

Mental Health

Studies find that mental health has the strongest links to women's sexual function (21,23,36–38). Depression independently determines the presence of sexual dysfunction in women with a number of chronic illnesses including multiple sclerosis (39), diabetes (40), renal failure (41), rheumatic disease (42). Lack of mental well-being, even if it does not meet the criteria of a clinical diagnosis of mental disorder, is strongly linked to women's symptoms of low desire (43). Epidemiologic studies confirm depression's negative effects upon orgasmic experience (44) and its strong association with increased sexual risk behaviors (45). Self-stimulation/masturbation may continue in the presence of depression (46). Many of the factors involved in partnered sex, including the relationship itself, the need to communicate sexual needs, the need to take care of the partner, concern about outcome, and dealing with feelings of inadequacy, do not apply to sex alone. Self-stimulation can cause calmness, relaxation, and improved sleep in women, but is often not a consequence of sexual urge or desire.

Aging

Aging is accompanied by the changes in ovarian function associated with menopause, and the marked reduction of adrenal production of prohormones (importantly dehydroepiandrosterone [DHEA]) that can become estrogen and testosterone and have as yet poorly understood actions on nonandrogen nuclear and membrane receptors. Previous population studies were conflicting: some showed little increase in sexual problems with age, whereas in others almost 40% of the sample reported reductions in responsiveness but an increased desire for nongenital sexual expression. Recent British research involving 6,777 women found some steady decrease in sexual function with age up to the 55 to 65 age group followed by some improvement in function during the following decade (37). Studying 3,205 women in the Boston area, researchers found a strong association between age and sexual problems (21). Another smaller study found that women's desire decreased significantly as a function of menopause status and age, low levels of desire were strongly associated with other sexual problems, including difficulties with arousal and orgasm (47).

Many studies of sexuality and aging show that older women report less distress about lack of desire when compared with younger women (37,48). Of 6,777 women

in the UK, 13.4% of those aged 16 to 24 reported distress about sexual problems compared to 6.7% of women aged 65 to 74 (37).

Despite reports of reduced sexual interest and desire by some older women, most retain some interest and maintain the potential for sexual pleasure their entire lives. In older women, a strong predictor of continued sexual interest is sexual behavior and enjoyment at an earlier age. A discrepancy between sexual interest and actual sexual activity occurs in many cases because an adequate partner is no longer available. In other instances, the cessation of sexual activity with age is more an expression of emotional problems resulting from lack of tenderness, communication, and attraction.

In addition to partner availability, an older woman's sexuality is influenced by her partner's general and sexual health and the relationship itself, which will determine how well the couple can adapt to changes in their sexual function as they age. Although some older women may retain negative societal attitudes toward sex that it is not "natural" (i.e., not focused intercourse), studies show a shift from intercourse to nonpenetrative sex and to a variety of activities that involve affection, romance, affectionate physical intimacy, and companionship (49). For some older women, it is clear that the setting, whether a nursing home or a grown-up child's home, strongly influences the opportunity and desirability for sexual expression.

Sex Hormones

Estrogen

If intercourse is perceived as a necessary component of sexual activity with a partner, some older women will lose motivation and interest as a result of discomfort and dyspareunia associated with lack of estrogen. Baseline vaginal blood flow is lower in estrogen-deficient women compromising needed lubrication. A male partner may be using a phosphodiesterase inhibitor to enhance erection. Penile girth may then be often maximal while vaginal size is reduced. Postmenopausal provoked vestibulodynia (PVD) is now recognized to be sometimes comorbid with genitourinary syndrome of menopause (GSM) (50) (AKA vulvovaginal atrophy). The latter is associated with loss of elasticity and thinning of the vaginal epithelium, which becomes vulnerable to damage from intercourse. Estrogen depletion predisposes women to vulvar vaginitis and urinary tract infections, both of which contribute to dyspareunia and reduced sexual self-image. Women who remain sexually active, alone or with a partner, may have less vulvar and vaginal atrophy than sexually inactive women but may still be symptomatic (51).

Testosterone

Adrenal production of testosterone precursors gradually decreases with age, beginning

in the late 30s. Large epidemiologic studies have not shown serum levels of testosterone to correlate with women's sexual function (52,53). Previously available assays were not sufficiently sensitive in the female range of serum testosterone to detect particularly low levels. When mass spectroscopy was used, the serum testosterone levels in 121 women who were carefully assessed and diagnosed with disorders of low desire and arousability were similar to the levels in 125 women similarly carefully assessed but who lacked any sexual dysfunction (54). Sexual dysfunction was not associated with mass spectroscopy measures of serum testosterone in a recent study investigating hormonal and psychosocial factors associated with desire (23). Another difficulty, besides past unreliable assays for serum testosterone, was the fact that intracellular production of testosterone in peripheral tissues (from adrenal and ovarian) precursor hormones—DHEA, DHEA sulfate (DHEAS), and androstenedione (A_4)—previously could not be measured. Total testosterone activity (ovarian and peripherally produced "intracrine" production) has been measured using mass spectrometry assays for androgen metabolites, most notably androsterone glucuronide (ADT-G). There appears to be a wide range of ADT-G among women of any given age, and levels decrease with age. **Importantly there were no group differences in ADT-G between 121 women carefully diagnosed with desire and arousal disorders and 124 sexually healthy controls** (52) nor in a second similar study with less stringent exclusion criteria (55), nor in a cross sectional study of 428 premenopausal women were androgen metabolites associated with sexual dysfunction (23).

11β-Hydroxyandrostenedione

An important recent finding is that neither accurately measured serum testosterone, nor testosterone metabolites as reflected by serum ADT-G, distinguish women with sexual dysfunction is of importance. However, it is possible that neither of these two values, nor "bio-available testosterone," that is, free testosterone plus that which is loosely bound to albumin is an adequate measure of androgen activity. The C19 adrenal steroid 11β-hydroxyandrostenedione, previously considered a by-product of adrenal steroid metabolism is now confirmed to serve as a precursor to the androgenic steroid 11-ketotestosterone. This molecule in turn is converted to 11-ketodihydrotestosterone (11KDHT) which acts on androgen receptors in a similar way to dihydrotestosterone (DHT) (56). Thus significant androgen action results from the peripheral synthesis of both DHT and 11KDHT which have minimal release into the circulation.

Dehydroepiandrosterone

The recent research of 246 women strictly recruited for presence or absence of desire disorder, found similar serum testosterone and serum androgen metabolites in the two groups, but found that serum DHEA was significantly higher in the controls. This is in keeping with previous large epidemiologic studies (52,53). Thus DHEA appears to be

acting in nonandrogenic ways. Research now turns to DHEA's many known but as yet not fully understood actions on nonandrogenic nuclear and membrane receptors (57).

Age-Associated Health Conditions

Illnesses that accompany aging may have an impact on sexual dysfunction. The association is weaker than that between male erectile dysfunction and hypertension, hyperlipidemia, diabetes, and coronary artery disease. **Depression is the major factor influencing sexual function in women with chronic illness, including end-stage renal disease** (41)**, multiple sclerosis** (39), **or diabetes** (40). Some sexual activities (e.g., intercourse) or responses (e.g., orgasmic intensity) may be limited by arthritic, cardiac, or respiratory disorders.

Personality Factors

Studies show that, compared with functional women, those who have concerns about low levels of desire and arousability are characterized as having vulnerable self-esteem, high levels of anxiety and guilt, negative body image, introversion, and somatization (58). Higher levels of anxiety can be particularly disruptive to healthy sexual response (59). Because sexual arousal involves increased sympathetic nervous system activity, in addition to increasing women's genital congestion there are nongenital sensations which may be misinterpreted as threatening and negate any potential sexual pleasure. These symptoms of "anxious arousal" include shortness of breath, increased temperature, muscle tension, and palpitations. The clinical impression of women with orgasmic disorder is that many are extremely uncomfortable in conditions in which they are not in control of circumstances or their bodily reactions, and research confirms strong links between orgasmic disorder and obsessive-compulsive traits and somatization (44). **For many women with vaginismus, there is a phobic quality to the fear of vaginal penetration. Many women with PVD show a marked fear of negative evaluation by others, ultra-conscientiousness, and self-criticism, as well as an increase in somatization and anxiety (**60).

Relationships

Most women who report loss of desire and arousability to physicians indicate that their partnerships are stable and satisfactory. However, an environment free of conflict, abuse, and the threat of separation or divorce is insufficient to nurture a woman's sexual desire. Commonly, the woman reports that her partner is not emotionally intimate with her, unwilling to reveal his (or her) feelings, fears, and hopes. In addition, the woman's need for eroticism and variety of sexual stimulation may not be met. These women frequently classify their relationship as being that of "very good

friends." Such a context is insufficiently sexual for nurturing or triggering a woman's sexual desire. Change of partner is shown to be a major factor in increasing women's desire and responsiveness, and there is a lessening of innate desire with the duration of a relationship (23,61). Not being happy in her relationship was a major determinant of sexual function in a recent large British survey (37). The woman's feelings for her partner, or a change of partner, were major determinants of a woman's sexual response in an 11-year longitudinal Australian study (61).

Sexual Dysfunction in the Partner

Of the multiple aspects of a woman's circumstances that can influence her sexual function, sexual dysfunction in a male partner is an important one. Successful treatment of a male partner's erectile dysfunction can result in reversal of the woman's sexual problems, including difficulties with sexual arousal, lubrication, orgasm satisfaction, and pain (62).

Infertility

Infertility evaluation and assisted reproductive techniques can have negative effects on a woman's body image and feelings of sexual self-worth. Infertility may cause her to feel hopeless and sexually undesirable. The loss of sexual spontaneity resulting from the goal-oriented approach to sex while trying to conceive with scheduled intercourse (coinciding with ovulation naturally or after hormonal stimulation) may lead to sexual dysfunction and is considered a major problem for many women (63). **Erectile dysfunction may be a consequence, compounding the couple's fertility difficulties and the woman's sexual satisfaction.** The stress of testing and waiting for results may disrupt emotional intimacy, causing further damage to sexual function. These changes do not always reverse with a successful pregnancy. Often there are unresolved feelings of guilt over personal responsibility for the infertility and feelings of resentment of the multiple procedures required for women compared with one semen analysis for men.

Drugs

1. **Prescription and nonprescription medications, including alcohol and illicit drugs, can alter the normal sexual response** (Table 17-1). Adjustments in dosage or formulation of medication may be required.
2. Two recently approved antidepressants appear to be sexually neutral. Vortioxetine has a range of effects on the serotonin system: an antagonist at 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors; an agonist at 5-HT_{1A} receptors; a partial agonist at 5-HT_{1B}

receptors; and an inhibitor of the 5-HT transporter (64). Vilazodone is a serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist (65).

3. Theoretically, pharmacologic agents might improve or reverse the loss of arousal, desire, and orgasm commonly associated with serotonergic antidepressants (SSRIs) and less frequently serotonergic noradrenergic antidepressants (SNRIs). A number of "antidotes" have been suggested but only three have evidence in the form of randomized controlled trials using approved medications: adding bupropion can reverse SSRI-induced dysfunction (66), as can the addition of aripiprazole (67). Recently vortioxetine has been shown to improve AISD from SSRIs in patients in remission from depression, to a greater degree than did escitalopram (68).

Table 17-1 Medications Potentially Affecting Sexual Response

• Antihypertensives: β-blockers, thiazides
• Antidepressants: serotonergic antidepressants
• Lithium
• Antipsychotics
• Antihistamines
• Narcotics
• Benzodiazepines
• Oral contraceptives and oral estrogen therapy
• Gonadotropin-releasing hormone (GnRH) agonists
• Spironolactone
• Cocaine
• Alcohol
• Anticonvulsants

Chronic Illness and Cancer

Chronic illness and living with a cancer diagnosis can affect sexual function in a number of ways (Table 17-2) (20).

Table 17-2 Sex and Chronic Illness

• Biologic disruption of the sexual response, e.g., multiple sclerosis damaging pelvic autonomic nerves
• Negative psychological consequences of the illness affecting sexual response, e.g., feeling sexually unattractive as a result of disfigurement from surgery, medication, stomas
• Increased fatigue
• Chronic pain
• Incontinence or stomas reducing sexual self-confidence
• Accompanying depressive illness
• Treatment of chronic illness, e.g., chemotherapy-inducing ovarian failure
• Limited mobility, e.g., arthritis precluding intercourse, Parkinson disease precluding masturbation
• Cardiac or respiratory compromise such that orgasm or movements of intercourse cause angina or intense dyspnea

Chronic Pelvic Inflammatory Disease and Endometriosis

Chronic dyspareunia, remitting temporarily or not at all with surgical or medical therapy, typically is associated with loss of sexual motivation or interest. Although definitive therapy is the overall goal, encouragement of nonpenetrative sex is very important for preservation of the woman's sexual enjoyment, sexual self-esteem, and relationship. GnRH therapy producing a temporary medical menopause can add further difficulties with reduced arousability and vaginal discomfort from the low estrogen state.

Polycystic Ovarian Syndrome

There is no evidence that the higher androgen levels associated with polycystic ovarian syndrome (PCOS) afford protection from low sexual desire or low sexual arousability. Some but not all studies of women with PCOS report reduced sexual satisfaction compared to controls. The limited data suggest that lower satisfaction is related to obesity and cosmetic androgen–related effects of hirsutism and acne. *Metformin* may improve sexual function in women with PCOS (69).

Recurrent Herpes

Fear of spreading an STI may reduce sexual motivation and arousability. Guidance regarding safer sexual practices is needed, along with a discussion of the causes of the woman's lowered sexual motivation. A recognized difficulty with recurrent herpes is asymptomatic viral shedding possibly despite long-term antiviral therapy.

Lichen Sclerosis

Tethering of the clitoral hood may cause pain with clitoral stimulation. Introital involvement may cause dyspareunia or prevent entry of penis, dildo, or fingers. Reduced sexual sensitivity of the involved vulvar skin is a common complaint. Topical *corticosteroid* administration is the primary treatment, although topical *testosterone* cream may benefit loss of sexual sensitivity.

Breast Cancer

Sexual dysfunction following breast cancer treatment is likely to persist more than 1 year after diagnosis of breast cancer (70). Chemotherapy appears to be responsible for most of the resulting sexual difficulties, including loss of desire, subjective arousal, vaginal dryness, and dyspareunia. A small study of women with past breast cancer and complex endocrine status resulting from ongoing antiestrogen therapy found that, whereas relationship factors predicted desire, a history of chemotherapy predicted disorders of arousal lubrication, orgasm, and dyspareunia. There was no connection between sexual function and androgen levels, including androgen metabolites (71). A model for predicting sexual interest, function, and satisfaction after breast cancer has evolved from two large independent groups of breast cancer survivors (70). The most important predictors of sexual health were absence of vaginal dryness, presence of emotional well-being, positive body image, better quality of relationship, and lack of partner sexual problems.

Dyspareunia is present in at least 45% of women with breast cancer (72). Mechanisms of pain include (1) changes from chemotherapy-induced estrogen deficiency; (2) chemotherapy-induced peripheral neuropathy which can affect the relatively lengthy pudendal nerve; (3) central sensitization underlying PVD possibly induced by the estrogen lack and all the stress of the illness. Management is initially with ointment such as Aquaphor or oils including olive, safflower, or coconut which can all be applied frequently—typically after voiding or bowel movements. *Low-dose topical estrogen* is often needed. In the past application has been to the vaginal canal only but given the sensitivity of the introitus and vestibule, direct application is often recommended (72). Pharmaceutical products may not be initially tolerated because of preservatives and a temporary use of custom-compounded hormones in a neutral base such as Glaxal base may be of benefit. Nightly application for some 2 to 4 weeks will frequently allow the use of pharmaceutical products including creams, intravaginal tablet, or silastic ring.

For women with breast cancer the American College of Obstetricians and Gynecologists consensus is that current low-dose estrogen vaginal products do not raise serum estrogen levels above those in untreated menopausal women and are not associated with higher breast cancer recurrence rates or endometrial stimulation (73). Within a few weeks of topical estrogen application the epithelium recovers and absorption becomes undetectable so that initiating treatment early during cancer

therapies before marked injury occurs from estrogen lack will allow the lowest systemic exposure. When the woman is on aromatase inhibitors the optimal management of her pain is unclear given the preference to avoid even minor systemic increase in estrogen. However, poor compliance in some 30% of women as a result of medication side effects is of concern (74). There is early evidence of safety in terms of minimal rise in serum estrogen plus and sexual benefit from the use of either an estradiol ring (7.5 microgram/d) or intravaginal testosterone (75). *Vaginal DHEA,* with recent FDA approval, appears useful for women with breast cancer given the lack of systemic increases in either testosterone or estrogen but its use has not been studied specifically in the context of breast cancer. A temporary switch from an aromatase inhibitor to a selective estrogen-receptor modulator such as *tamoxifen* can be used—*tamoxifen* does not consistently lead to dyspareunia (73).

Recent research showed *hyaluronic acid* to be as effective as low-dose estradiol when used nightly in an 8-week study (76). Topical lidocaine applied to the vestibule for 10 minutes before intercourse proved beneficial in a trial of women with breast cancer (77). *Ospemifene*—a selective estrogen-receptor modulator with estrogen agonist activity in the vagina appears to have a neutral effect on breast tissue but experience is limited.

Fertility preservation is considered along with the overall treatment plan for younger women, and a number of options are emerging. Delaying cancer treatment to allow one cycle of hormone stimulation followed by cryopreservation of either a mature oocyte or an embryo may be a very difficult decision. In some situations, including after a hormone receptor–positive breast cancer, pregnancy may increase the risk of recurrence. The more established option of using embryos can prove difficult as the embryo becomes shared property with the current partner. When time is insufficient for these two approved options, ovarian tissue cryopreservation can be considered (78).

Diabetes

The majority of studies clearly identified a strong link between sexual dysfunction and comorbid depression but not with diabetic control, duration, or complications. Data are limited in quality given that many studies have neither control groups nor clarify estrogen status, different assessments of sexual function are used, and many publications study only women who remain sexually active—excluding those who simply do not have a partner or may have discontinued activity as a result of severe dysfunction (79). Most studies find the prevalence of low sexual desire to be similar in women with and without diabetes, yet difficulties with lubrication are approximately two times more common in women with diabetes. Some but not all studies show increased prevalence of dyspareunia, orgasmic difficulties, and sexual dissatisfaction (80). In the long-term Epidemiology of Diabetes Interventions and Complications (EDIC) study, more than half of the women had problems with orgasm, arousal, and

lubrication. In multivariate analysis, only depression and marital status predicted sexual dysfunction (79). Recently, young women on multiple insulin dosage had impaired arousal and lubrication whereas those using an insulin pump had sexual function comparable to healthy age-matched women (40). Again depression was the independent predictor of sexual dysfunction.

[4] Gynecologic Conditions: Sexual Dysfunction Can Arise From Gynecologic Diseases, Procedures, and Treatments

Stress Incontinence Surgeries

Mid-urethral slings are now commonly placed for stress urinary incontinence. While most women report same or overall improved sexual function, orgasm preservation is more certain with transvaginal tapes than with transobturator tapes which may pose more risk to the neural integrity of the anterior vaginal wall (81).

Hysterectomy

Simple Hysterectomy

A recent review of English publications to 2015 concluded that in the shorter term the majority of women reported improved or unchanged sexual function. In the longer term deterioration in function was attributed to normative changes with aging (82). **Despite speculation that there might be different sexual outcomes depending on whether hysterectomy was vaginal, abdominal—open or laparoscopic, subtotal or total, any difference is not supported by study** (82).

Radical Hysterectomy

Techniques were developed to avoid the portions of the inferior hypogastric plexus in the cardinal and broad ligaments, and studies suggest minimal reduction of vaginal congestion in response to sexual stimulation in a laboratory setting (83).

Gynecologic Cancer

Some 55% of women with gynecologic cancer report dyspareunia (84) which has multiple causes in addition to estrogen deficiency. These include neuroma from transecting nerves, radiation-associated scarring causing nerve compression or entrapment, and damage to vasculature. Careful physical examination can identify which pelvic nerves may be generating the pain to allow targeted diagnostic injections of local anesthetic. Chemotherapy-induced peripheral neuropathy may follow the use of taxanes, vinca alkaloids, platinum analogs, and 5-fluorouracil. Vaginal stenosis may be caused by radiation and/or graft versus host disease and the use of dilators can be challenging

both technically and psychologically. Strong support from the oncology team, optimally with inclusion of a pelvic floor physiotherapist, is frequently recommended. Neuropathic pain does not respond to opioid medications, but there is some evidence of benefit from the use of duloxetine and low-dose amitriptyline (85). Mindfulness-based cognitive therapy programs have shown benefit for women's sexual dysfunction, including pain, that is subsequent to gynecologic cancer (86).

Cervical Cancer

Sexual symptoms encountered in women with cancer of the cervix include reduced vaginal lubrication secondary to surgical menopause, radiation damage, and/or interruption of the autonomic nerves. Compared to women who underwent cervical conization, women receiving radical hysterectomy reported worse sexual function in all domains with the female sexual function index questionnaire (87). Nerve sparing radical hysterectomy has been associated with improved sexual function compared to traditional radical hysterectomy (87). A meta-analysis of nerve sparing radical surgery for cervical cancer identified no worsening of prognosis and improved sexual function as compared to nonnerve-sparing surgery (88).

There is marked synergy between cancer of the cervix and sexual abuse as a cause of sexual dysfunction (89). An absence of sexual satisfaction was reported by 20% of women with neither abuse nor cancer of the cervix, by 31% of women who were sexually abused and did not have cancer of the cervix, by 28% of women with cancer of the cervix and who were not abused, but by 45% of women with a history of both abuse and cancer of the cervix. Dyspareunia was extremely rare in women without cancer of the cervix, but it was reported by 12% of those with cancer of the cervix and by 30% of those with cancer of the cervix and past sexual abuse.

Endometrial Cancer

The safety of vaginal estrogen for GSM is still in question although the evidence does not support any increase in recurrence rates with its use (90).

Ovarian Cancer

Sexual response and satisfaction is compromised with all forms of treatment but particularly when there is both surgery and chemotherapy and when disease is advanced such that only chemotherapy is possible (87). Importantly, the majority of ovarian cancer patients continue to feel sexual health is important (87).

Vulvar Cancer

There are conflicting results as to whether the extent of surgical resection determines the extent of sexual dysfunction, but women undergoing laser or partial resection of the clitoris have more severe dysfunction than women whose clitoris can be spared (91).

Pregnancy

[5] Physical, emotional, and economic stressors of pregnancy may negatively affect emotional and sexual intimacy. Sexual value systems, folklore, religious beliefs, physical changes, and medical restrictions influence sexual attitudes and behavior during pregnancy and postpartum. In the absence of preterm labor, antepartum bleeding, or an incompetent cervix, there is no evidence that sexual activity, orgasm, or intercourse increases the risk of pregnancy complications. Normal changes that occur with sexual activity during pregnancy include increased breast tenderness, increased sensitivity to uterine contractions with orgasm, general discomfort, less mobility, and fatigue. Sexual satisfaction in pregnancy is closely related to feeling happy about the pregnancy, continuing to feel attractive, and understanding that in a healthy pregnancy sexual activity and orgasm do not harm the fetus.

Toward the end of the third trimester the need for closeness, emotional support, and nurturing may be far greater than any desire for orgasms or intercourse. Nevertheless, a study noted that 39% of 188 women reported being engaged in intercourse during their birth week (92). Difficulties may arise from the partner's reaction to the woman's pregnancy, the physical changes of pregnancy, lack of information regarding sex and pregnancy, and lack of direction from the physician when complications arise. **A general lessening of sexual desire in both pregnancy and the postpartum period is common and considered normal. Couples can be encouraged to continue their usual patterns of lovemaking during pregnancy if they are emotionally and physically comfortable and there are no contraindications to either orgasm or intercourse.**

Dyspareunia and Method of Delivery

A recent prospective study found obstetric intervention including emergency cesarean section, vacuum extraction, or elective cesarean section to be associated with increased odds (2.4, 2.3, and 1.7 respectively) of the women reporting persistent dyspareunia at 18 months postpartum (93). Two previous studies showed that operative vaginal delivery conferred the highest risk of dysfunction (94,95).

Postpartum

The ongoing vaginal bleeding and discharge, perineal discomfort, hemorrhoids, sore breasts, and decreased vaginal lubrication associated with nursing, compounded by fatigue from disturbed nights, all contribute to decreased motivation for sexual activity. Further complicating factors include fear of waking the baby, a decreased sense of attractiveness, change of body image, or mood change. Many couples resume sexual activity and include intercourse by 6 to 8 weeks postpartum, but some couples wait as long as a year before resuming their prepregnancy level of sexual intimacy. Typically women who nurse report less sexual activity and less sexual satisfaction than those who bottle feed.

Physicians can provide considerable help to patients and their partners by acknowledging and discussing the normal fluctuations in sexual desire and frequency of sexual activity during and after pregnancy.

ASSESSMENT OF SEXUAL PROBLEMS

[7] **Despite the importance of issues relating to sexuality, many women find it difficult to announce their preferences or initiate discussions of sexual concerns with their physicians and many physicians are uncomfortable discussing sexual issues with their patients.** Through the use of a structured questionnaire and review of the records of 1,065 women who consecutively attended 37 family practices in areas of high, medium, and low socioeconomic status, 40% of women had at least one form of sexual dysfunction according to diagnostic criteria of the *International Statistical Classification of Disease* (ICD-10). Only 4% had a prior entry in their medical record relating to sexual problems (96).

There are numerous reasons physicians are reluctant to discuss issues relating to sexuality with their patients. Anxiety about physicians' perceived inability to treat sexual problems, unwillingness to spend the time required to accurately assess sexual concerns, personal discomfort when discussing sexual matters with patients, and distress arising from their patients' history of sexual-related violence are all potential barriers. Not asking about sexual function suggests to patients that sexuality is not important and should not to be discussed. [8] **Many gynecologic interventions and a number of gynecologic conditions interrupt sexual function, necessitating the inclusion of sexual health in gynecologic assessment. Asking about sexual concerns gives physicians an opportunity to educate patients about the risk of STIs, encourage safer sex practices, evaluate the need for contraception, dispel sexual misconceptions, and identify sexual dysfunction.** Many sexual concerns can be resolved by providing factual information and reassurance. Management of sexual dysfunction requires appropriate biopsychosocial assessment and intervention. Even when patients appear to have no sexual problems, if gynecologists routinely inquire about sexual health, they demonstrate that future sexual issues can be addressed in a professional, confidential, and nonjudgmental setting.

Interviewing Techniques

To be sufficiently comfortable to establish rapport and trust with patients, physicians need to be familiar with the components of a sensitive, detailed, sexual assessment and the general principles of management of dysfunction. Good listening skills and attention to nonverbal cues are helpful. The use of straightforward language that patients can understand while recognizing that many

people find it difficult to discuss these sensitive, intimate and extremely common issues is necessary.

A few open-ended questions can initiate the subject of sexual function (Fig. 17-2). Sexual inquiry is part of the medical history taken during a routine gynecologic assessment. There is evidence that an introductory sentence would greatly increase the chance a woman will identify her sexual problem. Listed in Table 17-3 are some examples of screening questions related to particular obstetric–gynecologic circumstances.

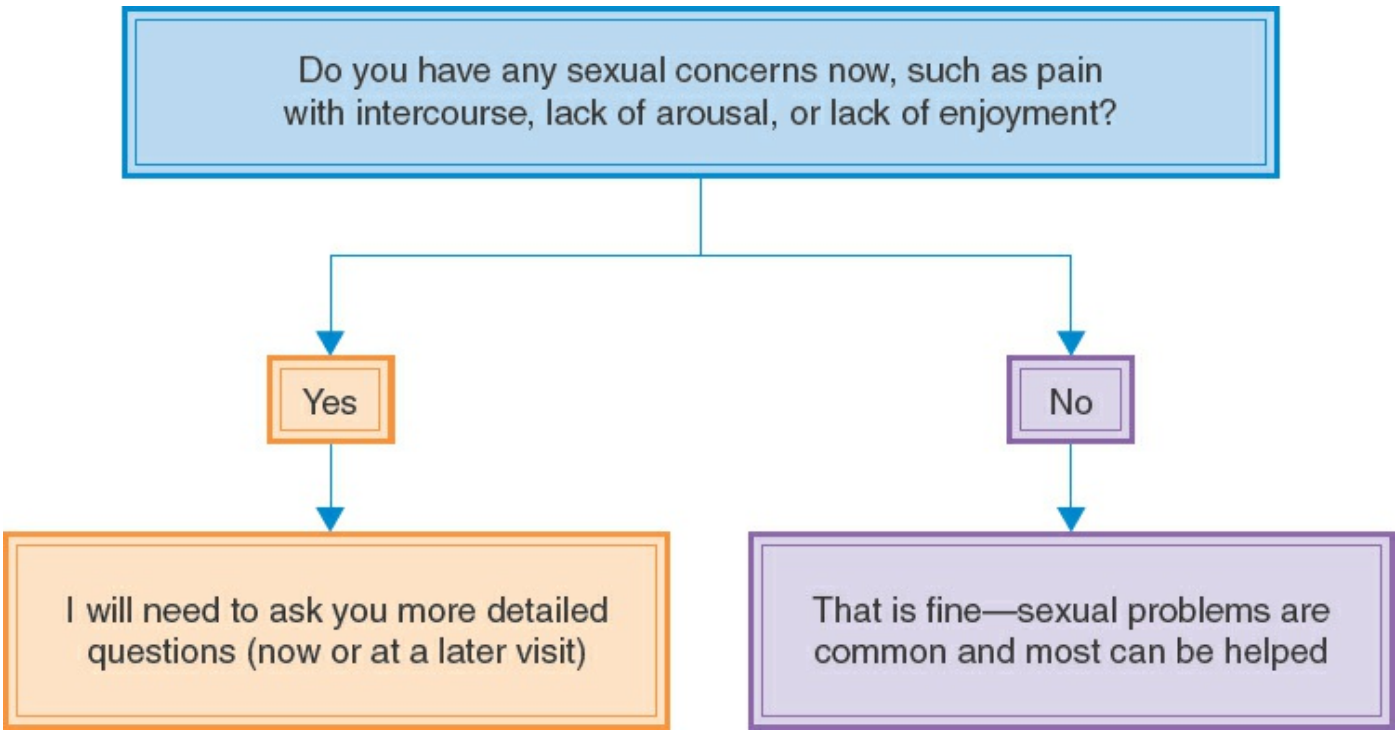


FIGURE 17-2 Algorithm for screening sexual dysfunction.

Table 17-3 Screening for Sexual Problems

Situation in Which Screening Question Is Necessary	Suggested Screening Question
Before surgery or instituting medication or hormone therapy	*Your surgery or medication is not expected to interfere with your sexual function. I need to check, though, whether you have any difficulties now with sexual desire, arousal, or enjoyment; or is there any pain?*
Routine antenatal visit	*Women's sexual needs can change during pregnancy. Do you have any problems or questions now? There is no evidence that intercourse or orgasm leads to miscarriage. Of course, any bleeding or spotting will require checking and*

	postponing sexual activity until we have evaluated you. Many women find fatigue and/or nausea reduce their sexual life in the first 3 months, but usually things get back to normal for the middle 3 months and sometimes right up to term.
Complicated antenatal visit	*These complications may well have already caused you to stop being sexual. Specifically, you should not (have intercourse/have orgasms).*
After one or more miscarriages	*Some women temporarily lose desire for sex after a miscarriage—this is quite normal. Many couples concentrate on affectionate touching while they both grieve about what has happened. Do allow yourselves some time. If any sexual problems persist, we can address them.*
Infertility	*All this testing and timed intercourse and disappointment, plus the financial burdens that are coming up, can be very stressful on your sex life. Try to have times when you and your partner are sexual just for pleasure and intimacy's sake—not when you are trying to conceive. Do you have any problems now?*
Postpartum	*It may be some weeks or months before you have the energy to be sexual, especially if your sleep is really interrupted. This is normal. If problems persist, or if you have pain, this can be addressed. Do you have any questions right now?*
Perimenopause or postmenopause	*We know many women have very rewarding sex after menopause—more time, more privacy. If you find the opposite or you begin to have pain or difficulty getting aroused, these things can be addressed. Do you have any concerns now?*
Woman who is depressed	*I know you are depressed right now, but our studies tell us that sex is still important for many women who are depressed. We also know that some of the medications we prescribe interfere with sexual enjoyment. Do you have any problems right now?*
Chronic illness	*Arthritis/multiple sclerosis can interfere with a woman's sex life. Are you having any problems?*
Potential damaging surgery	*Obviously the focus right now is to remove your cancer entirely when we do your surgery. The nerves and blood vessels that allow sexual sensations and lubrication may be temporarily and sometimes permanently damaged. If when you have recovered you notice any sexual problems that persist, they can be addressed. Do you have any sexual concerns now?*
Premenopausal bilateral oophorectomy	*Your surgery will remove a major source of estrogen and approximately one-half of the testosterone your body has been making. Testosterone will still be made by adrenal glands (small glands on top of the kidneys), and some of this gets converted into estrogen. Many women find that these reduced amounts of sex hormones are quite sufficient for sexual enjoyment, but others do not. Any sexual problems that do occur almost certainly can be addressed. Do you have any problems now?*

Optimally, the detailed assessment is obtained from both partners with opportunity to see each alone (Table 17-4). When dyspareunia is present, detailed questioning is necessary (Table 17-5).

Table 17-4 Biopsychosocial Assessment of Sexual Dysfunction

Sexual	Clarify further with direct questions; give options rather than leading questions.

problem in patient's own words	
Duration, consistency, priority	Duration of problems? Are problems present in all situations: with sex alone, with sex with a different partner if relevant?
Context of sexual problems	Emotional intimacy with partner, activity/behavior just before sexual activity, privacy, safety, birth control, risk of sexually transmitted disease, usefulness of sexual stimulation, sexual skills of partner, sexual communication, time of day
Rest of each partner's sexual response	Check this currently and before the onset of the sexual problems—sexual motivation, subjective arousal, enjoyment, orgasm, pain, and erection and ejaculation in male partner
Reaction of each partner to sexual problems	How each has reacted emotionally, sexually, and behaviorally
Previous help	Compliance with recommendations and effectiveness
Reason for presenting now	What has precipitated this request for help
Assessment of Each Partner Alone	
Partner's own assessment of the situation	Sometimes it is easier to acknowledge symptoms, e.g., total lack of desire, in the partner's absence
Sex response with self-stimulation	Also ask about sexual thoughts and fantasies
Past sexual experiences	Positive, negative aspects
Ask about sexual, emotional, and physical abuse[a]	Explain abuse questions are routine and do not necessarily imply causation of the problems.

[a]Omit if the dysfunction occurs after some decades of healthy function.

Table 17-5 Assessment of Dyspareunia: By History

• Ask if vaginal entry is possible at all (i.e., with finger, penis, dildo, speculum, tampon)
• Ask if sexual arousal is experienced when penetration is attempted and as it progresses

- Ask exactly when the pain is experienced:
  - With partial entry of the penis/dildo
  - With attempted full entry of penile head
  - With deep thrusting
  - With penile movement
  - With the man's ejaculation
  - With the woman's subsequent urination
  - For hours or minutes after intercourse attempts
- Ask if on some occasions there is less/no pain, and if so, what was different

Physical Examination

Routine pelvic examination is an essential component of general medical care; this is not the case with women who seek care for sexual concerns. Given the prevalence of negative past sexual experiences, including abuse, **a pelvic examination should be performed only in the presence of a definite indication, and the procedure should be clearly explained to the patient** (Table 17-6). Management of dyspareunia mandates careful vulvar, vaginal, and pelvic examination. A physical examination can confirm normal anatomy and the healthy nonaroused state of the genitalia, it does not confirm healthy sexual function. Nevertheless, such an examination can be both instructive and therapeutic.

Diagnostic Criteria

Just as phases of sexual response overlap, women's sexual dysfunctions are typically composite. Increasing evidence indicates that desire ahead of and at the outset of sexual engagement, although probably welcomed by both partners, is not mandatory for women's sexual enjoyment and satisfaction (97). It is the inability to trigger desire and arousal during sexual engagement, and an initial absence of desire, that constitutes disorder. Therefore, merging sexual arousal and desire difficulties into one disorder is evidence based as presented in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders:* DSM-5. Three disorders are now recognized —see Table 17-7. To fulfill a diagnosis symptoms must be present for at least 6 months, cause clinically significant distress, not be better explained by a nonsexual psychiatric disorder, by the effects a drug of abuse or by a medication or medical condition, or by relationship distress, partner violence, or other significant stressors. The disorder is designated as lifelong or acquired (5).

Overview of Management of Sexual Dysfunction

[6] Many of the sexual problems couples encounter result from a deficit of

knowledge or experience, sexual misconceptions, or inability of the couple to communicate about their sexual preferences. Brief counseling and education by the obstetrician–gynecologist regarding the circular sex response cycle can identify the areas where sexual dysfunction can occur.

The PLISSIT Model

Gynecologists may sometimes need to provide detailed management for certain conditions (e.g., for the chronic dyspareunia of PVD), frequently the first two levels of a model, known by its acronym as PLISSIT, are sufficient to address women's sexual problems. The model is as follows:

1. **P**ermission. The concept of permission is the validation of the patient's concerns and confirmation that the gynecologist's office is an appropriate setting to address them.
2. **L**imited **I**nformation. The patient is provided with information about sexual physiology and behavior so misunderstandings, myths, lack of knowledge, and inadequate sexual skills can be addressed.
3. **S**pecific **S**uggestions. This stage may involve altering the problematic sexual context, educating patients about specific attitudes and practices, advising different forms of sexual stimulation, screening for mental health issues, identifying interpersonal issues, and prescribing hormones and medications.
4. Referral for **I**ntensive **T**herapy. Examples where this step may be necessary include: (1) intrapsychologic issues stemming from childhood that impair a woman's ability to be aroused and experience sexual pleasure and satisfaction, including past traumas and abuse; (2) for couples who need more specialized help in sexual communication; and (3) for male sexual dysfunctions.

As an example of a PLISSIT approach, a woman with chronic dyspareunia from PVD is first given validation of her pain and is provided with the information that PVD is common and many women find that the pain precludes intercourse. The patient and her partner are encouraged to focus on nonpenetrative aspects of lovemaking. The next level is the provision of limited information about chronic pain mechanisms, the role of psychological stress, and genetic and possible immune factors. Specific suggestions could include ongoing encouragement to remove intercourse as one of the ways the couple interact sexually, explanation of basic cognitive behavioral therapy (CBT) concepts and/or referral to psychologist or counselor for the same, prophylaxis for overgrowth of candidiasis when this is relevant, and referral to a pelvic muscle physiotherapist. Temporary use of a local anesthetic can be discussed. Referral for intensive therapy may be indicated for further pain management, including programs for learning cognitive skills—those of CBT or mindfulness-based cognitive therapy

(MBCT), for couple counseling if the relationship cannot cope with the stress, or to a gynecologist specializing in vulvar surgery if vestibulectomy is considered.

Table 17-6 Physical Examination for Sexual Dysfunction

General examination	Signs of systemic disease leading to low energy, low desire, low arousability, e.g., anemia, bradycardia, and slow relaxing reflexes of hypothyroidism. Signs of connective tissue disease, such as scleroderma or Sjögren, which are associated with vaginal dryness. Disabilities that might preclude movements involved in caressing a partner, self-stimulation, intercourse. Disfigurements/presence of stomas; catheters that may decrease sexual self-confidence, leading to low desire; low arousability.
External genitalia	Sparsity of pubic hair, suggesting low adrenal androgens. Vulvar skin disorders, including lichen sclerosis, which may cause soreness with sexual stimulation (e.g., when it involves the clitoral hood) or loss of sexual sensitivity. Cracks/fissures in the interlabial folds suggestive of chronic candidiasis. Labial abnormalities that may cause embarrassment/sexual hesitancy (e.g., particularly long labia or asymmetry).
Introitus	Vulvar disease involving introitus (e.g., lichen sclerosis). Sign of estrogen deficit: pallor, loss of elasticity, skin turgor, vaginal rugae, atrophy of labia minora. Recurrent splitting of the posterior fourchette manifest as just visible white lines perpendicular to fourchette edge. Abnormalities of the hymen (e.g., hymenal band across the introitus). Adhesions of the labia minora. Swellings in the area of the major vestibular glands. Allodynia (pain sensation from nonpainful stimulus, i.e.,touch) of the crease between the outer hymenal edge and the inner edge of the labia minora +/– allodynia of the Skene duct openings (all typical of provoked vestibulodynia). Presence of cystocele, rectocele, or prolapse interfering with the woman's sexual self-image. Inability to tighten and relax perivaginal muscles (often associated with hypertonicity of pelvic muscles and midvaginal dyspareunia). Abnormal vaginal discharge associated with burning dyspareunia.
Internal examination	Pelvic muscle tone. Presence of tenderness or trigger points on palpating deep levator ani as a result of underlying hypertonicity.
Full bimanual examination	Presence of nodules and/or tenderness in the cul-de-sac or vaginal fornix, or along uterosacral ligaments. Retroverted fixed uterus as causes of deep dyspareunia. Tenderness palpating posterior bladder wall from anterior vaginal wall suggestive of bladder pathology.

Table 17-7 DSM-5 Definitions of Women's Sexual Dysfunction

Diagnosis	Definition	Comments
Female sexual interest/arousal disorder	At least 3 of the following must be present: • Absent/reduced interest in sexual activity • Absent/reduced sexual/erotic thoughts or fantasies • No/reduced initiation of	Minimal spontaneous sexual thinking or desiring of sex ahead of sexual experiences plus few fantasies (as in former DSM-IV) does not necessarily constitute disorder

	sexual activity and typically unreceptive to a partner's initiation • Absent/reduced sexual excitement, pleasure during sexual activity in all or almost all (approximately 75%) sexual encounters • Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues written/verbal/visual • Absent/reduced genital and/or nongenital sensations during sexual activity in all or almost all (approximately 75%) sexual encounters	
Female orgasmic disorder	At least one of the two must be experienced on all or almost all (approximately 75%) occasions of sexual activity: • Marked delay in, infrequency or absence of orgasm • Markedly reduced intensity of orgasmic sensation	Most commonly women complain of low desire and low arousal with rare or absent orgasms, but some women have healthy arousal but do not experience orgasm. SSRIs are a frequent cause
Genito-pelvic penetration disorder	Persistent or recurrent difficulties with one or more of the following must be present: • Marked difficulty with vaginal penetration during intercourse • Marked vulvovaginal or pelvic pain during vaginal intercourse/penetration attempts • Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during,	Now merged: **Dyspareunia** (persistent or recurrent pain with attempted or complete vaginal entry and/or penile–vaginal intercourse) and **vaginismus** (persistent or recurrent difficulty to allow vaginal entry of a penis or other object, often with phobic avoidance, anticipation/fear/experience of pain, plus variable and involuntary pelvic muscle contraction)

	or as a result of vaginal penetration • Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration	

PREVALENCE OF SEXUAL DYSFUNCTION

The larger surveys find approximately 10% of women report ongoing sexual dysfunction that is particularly upsetting, while an additional 20% report sexual problems that are less distressing (21,37,98). **A general muting of response—low interest, low subjective arousal along with infrequent or absent orgasm was the most common presentation** in many surveys (58,99). The large UK study of 6,777 women (NATSAL) found low interest to be the most common concern (30% to 38% peaking mid-age), and some 10% reported orgasmic dysfunction (37). About 10% of both sexually active and inactive women were distressed about their sexual difficulties. The prevalence of sexual disorders as per DSM-5 is unknown. The NATSAL study, using proxy measures of DSM-5 problems, found 3.6% of women met all three criteria for disorder (6). Postmenopausal vaginal dryness and associated dyspareunia affects some 15% to 30% of women with marked cultural differences to the extent that this leads to bothersome sexual difficulties (100). Lack of lubrication and associated dyspareunia is reported by 5% to 25% of younger women, with marked cultural differences leading to resulting sexual distress (100). Introital dyspareunia from PVD, the most common cause of dyspareunia in premenopausal women, is thought to affect some 15% to 18% of women (101). Isolated lack of orgasm despite high arousal is of unknown prevalence because studies generally include women who have low arousal accompanying their lack of orgasm.

Management of Sexual Interest and Arousal Disorder

Gynecologists can initiate therapy by construction of the woman's own sex response cycle showing the various breaks. This can be highly therapeutic for the woman and her partner. For example, **Figure 17-3** shows the various breaks subsequent to infertility testing. The couple learns that it is "normal" for the woman to have low interest in being sexual when emotional intimacy has suffered. If the issues distancing the couple cannot be addressed in the gynecologist's office (i.e., they extend over and beyond the common reactions to infertility testing and procedures), referral to a relationship counselor may be necessary. The gynecologist can address the sexual context and the type of stimulation that is provided. Often sex has become

"mechanical"—intercourse focused to achieve conception. Most women need more nonphysical stimulation, more nongenital physical stimulation, and more nonpenetrative genital sexual stimulation, and this can be stressed. Privacy issues, time of day, and emotional closeness at the time of lovemaking can all be discussed. Factors personal to the woman that may be impairing her ability to be aroused, such as low sexual self-image and distractions, can be identified: referral for CBT or MBCT may be necessary. Biologic factors influencing arousability, including fatigue, medication effect, and depression, may be involved. Fears regarding outcome, such as lack of adequate birth control or partner dysfunction, can be identified. Inquiring about the patient's thoughts at the time of potential lovemaking can be helpful. Some women admit to evoking negative thoughts or allowing spontaneously emerging negative thoughts to intrude when there is a sexual opportunity. Guilt about sex and about women having sexual pleasure may be present. If the woman is a new mother, she may feel on some level that sex now is "wrong." Experiences of assisted reproduction technique or delivery may lead to the woman feeling loss of control; this in turn may lead to a need to regain control in all aspects of her life, which may suppress her sexual feelings. CBT and mindfulness therapies are recommended (102,103).

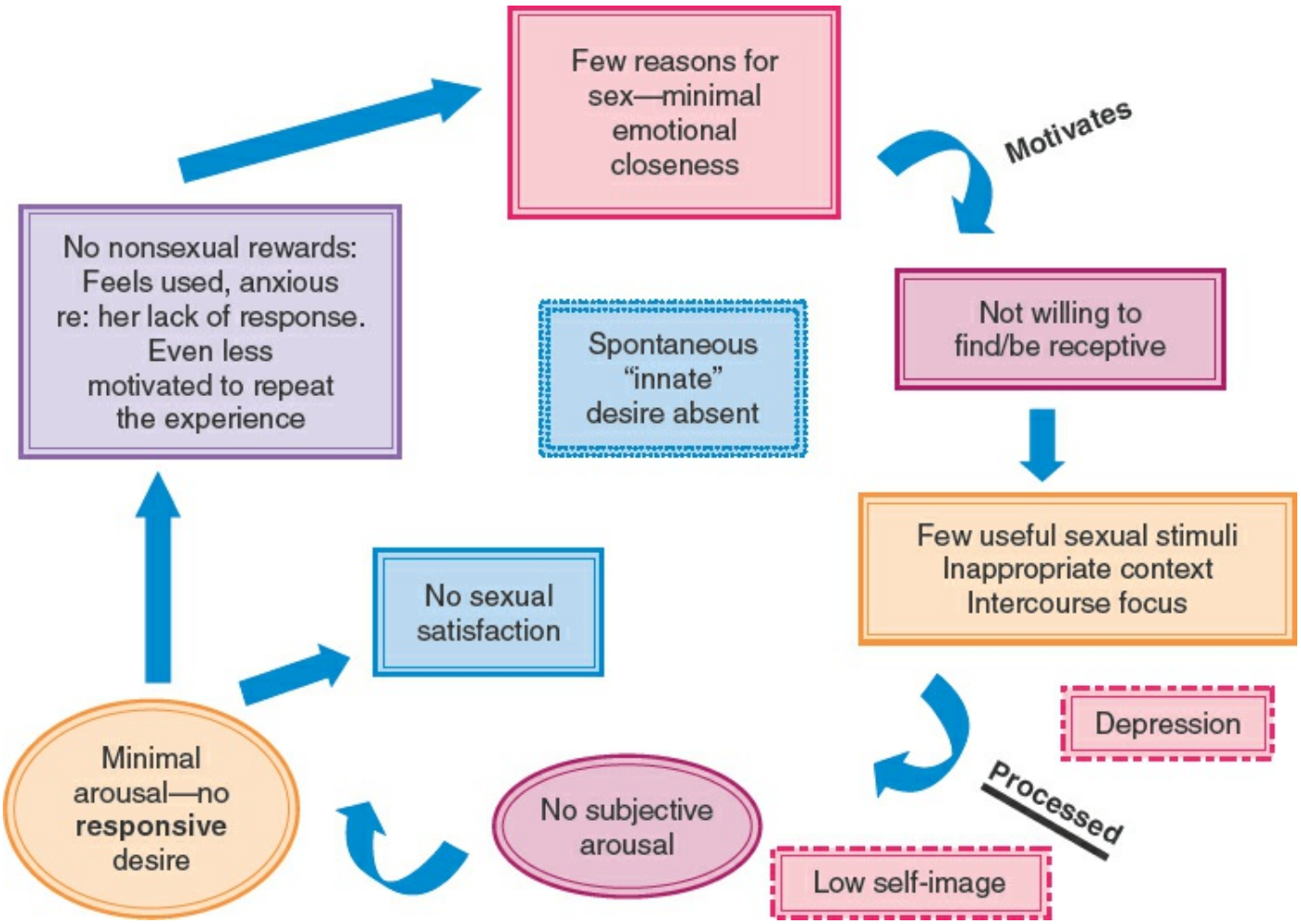


FIGURE 17-3 Breaks in the circular sex response cycle subsequent to infertility testing.

Qualitative research in sexually active mid-life women who reported sexual problems, found that the participants considered behavioral and psychological treatments more likely to be of benefit for both their physical and emotional sexual concerns (9).

Evidence-Based Psychological Treatments for Sexual Interest Arousal Disorder

It is recognized that establishing the benefit of psychological therapy is difficult and more complex than quantifying results in pharmaceutical trials (104). Improved sexual satisfaction does not necessarily mean lack of dysfunction nor does dysfunction necessarily mean lack of sexual satisfaction (105). The more traditional sex therapy techniques have been incorporated into programs that combine cognitive skills with behavioral changes as in traditional sex therapy. Cognitive behavioral therapy targets the common biased thoughts during sexual activity and inaccurate thoughts that women have about their own sexual selves. Two recent meta-analyses have reviewed the controlled outcomes on CBT for women with low sexual desire. The first found a large effect size on sexual desire and a moderate effect on improving sexual satisfaction (106). The second review found that including the male partner in CBT treatment for low desire led to better outcome (107). **CBT is a widely used treatment for women's concerns with low sexual desire and recommended as a grade B level by the 2015 International Consultation on Sexual Medicine** (108).

Combining some sexual therapy techniques with mindfulness skills and cognitive skills, that is, MBCT, has shown promise. Increasing mindfulness skills allows a person to focus on sexual sensations, but not critique them, and allows them to be better able to distance themselves from distracting thoughts. Thus, their focus becomes sensual pleasure and not a particular goal. There is a benefit compared with pretreatment levels of sexual function (109,110). Researchers using MBCT in sex therapy are reporting reduction of avoidance of sexual interaction and a new focus on the sexual sensory experience rather than any goal in a number of sexual dysfunctions including sexual interest and arousal disorder (111). **A recent meta-analytic review of studies using mindfulness-based therapy suggested that all aspects of sexual function and sexual well-being tended to improve—the largest improvements were seen in sexual desire and subjective arousal with more modest improvements in orgasm, pain, and lubrication. Partnered women showed greater benefit than did unpartnered women** (112).

Transdermal Testosterone

Neither accurately measured (by mass spectrometry) serum levels of testosterone nor total androgen metabolites that reflect ovarian and adrenal sources of androgens are linked to women's sexual disorders (23,54). Nevertheless, there is a decades' long

history of using off-label, often supraphysiologic testosterone supplementation. A series of studies beginning in 2005 showed modest benefit using lower hormonal dosage—a patch releasing 300 μg testosterone daily. However, a second series using an equivalent dose of testosterone gel, failed to show benefit. The latter has been published only in abstract form (113). Prior to the failed gel studies, the "patch" was approved in Europe, but as a result of low sales is no longer available. It was not approved in the USA.

The criteria for recruitment are a major drawback of the transdermal testosterone trials. It is not certain that the recruited women had any sexual disorder as the consistent focus was on the frequency of satisfying events, and the women were able to have such experiences at least half of the time (114). Because the absence or paucity of arousal and pleasure are two key criteria for the diagnosis, the participants did not have sexual interest arousal disorder as they were having satisfying experiences (5). The participants did not have consistent difficulties, indicating there was no biologic cause or requirement for a biologic remedy. Any psychological, relationship, or contextual factors are inherently variable. There was improvement in the secondary end points of desire and response subscales in the (unpublished) validated questionnaires used in all the trials. Increasing the degree of pleasure and arousal may not necessarily imply that absent pleasure and absent arousal would be remedied.

Long-term safety issues include those of the combination of testosterone and estrogen and concerns about estrogen itself. Beginning systemic estrogen 10 years postmenopause is known to increase cardiovascular risk: aromatization of exogenous testosterone to estrogen is likely. For postmenopausal women not receiving estrogen, long-term sequelae of creating a distinctly nonphysiologic profile of the testosterone:estrogen ratio are unknown. Endogenously high testosterone along with obesity in older women is associated with insulin resistance and increased cardiovascular morbidity (115). Until further safety and efficacy data become available, there is insufficient evidence to recommend testosterone in women for female sexual dysfunction (116).

Flibanserin

Initially targeted at depression, *flibanserin* is a 5-HT_{1A} agonist, a 5-HT_{2A} antagonist, and a very weak partial agonist on dopamine D4 receptors. Without benefitting depression, despite conflicting results in efficacy and considerable risks, its potential to increase sexual desire was pursued and the drug is now FDA approved. There are strict contraindications to alcohol, to medications which inhibit CYP3A4 inhibitors, including oral contraceptives and fluconazole. Overall risks of sedation or hypotension-related events were 28.6% with *flibanserin* versus 9.4% with placebo. Two recent meta-analyses have been based on published and unpublished randomized control trials. The first showed that *flibanserin* led to a mean increase of 0.49 satisfying sexual events per month (117). There was an increase of 0.3 (range 1.2 to 6.0) on the desire subscale of

the validated questionnaire. The women in the trials reported two to three rewarding sexual experiences each month at baseline, that is, as in the testosterone patch studies, the participants did not have sexual interest arousal disorder. The most recent meta-analysis noted the increase in desire on the desire scale of the questionnaire but concluded the magnitude of that increase did not differ from placebo (118). Given the need for daily dosage and the complete contraindication with alcohol, contraceptives, and the most commonly used oral medication to treat/prevent yeast infections and the seriousness of the risks, sales for *flibanserin* have been low.

Management of Orgasmic Dysfunction

Lifelong orgasmic disorder is more common than acquired loss of orgasm. Some women acquire orgasmic dysfunction in association with relationship problems, depression, substance abuse, medication (especially use of SSRIs), or chronic illness (e.g., multiple sclerosis). Aside from those using SSRIs, most women who experience lack of orgasm are found on careful questioning to have only modest degrees of subjective excitement such that cognitive and sex therapy is appropriate. It is important to remind women that most couples do not experience orgasm simultaneously, that most women experience orgasm far more easily from direct clitoral stimulation, and that this does not constitute dysfunction.

Common causes of lack of orgasm include obsessive self-observation and monitoring during the arousal phase, sometimes accompanied by anxiety and distracting negative and self-defeating thoughts. The woman may be so intent on monitoring her own and her partner's response and concerned about "failing" that she is unable to allow her natural reflexes to take over and trigger an orgasm. Lack of orgasm may be related to negative feelings toward sexuality, low self-esteem, poor body image, a history of sexual abuse, fear of losing control, and ineffective sexual technique. **The only clinically useful evidence-based therapy is encouragement of self-stimulation, accompanied by erotic fantasy, so-called directed masturbation.** Several excellent self-help books are available to help women become orgasmic through self-stimulation (119). A vibrator may be helpful if the plateau of high arousal is reached but there is still no orgasmic release. When the woman has experienced orgasm with self-stimulation with or without the use of a vibrator, she may or may not be able to teach the technique to her partner. Issues of trust may surface, and more intense psychological help may be needed. To counter the orgasmic delay or absence induced by SSRIs, one study showed that in highly selected women benefited from the prophylactic use of *sildenafil* (120).

Management of Genito-Pelvic Penetration Pain Disorder

Dyspareunia (persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse) and **vaginismus** (persistent or recurrent difficulty to

allow vaginal entry of a penis or other object, often with phobic avoidance, anticipation/fear/experience of pain, plus variable and involuntary pelvic muscle contraction) are now combined. Gynecologists are familiar with **the "vaginistic" response of involuntary reflexive contraction of pelvic muscles and often thighs, abdomen, buttocks, and even jaw, fists, and other muscle groups.** It may be generalized—the woman is unable to place anything in her vagina, even her own finger or a tampon—or it may be situational, maybe she can use a tampon and can tolerate a pelvic examination but cannot have intercourse. Couples frequently cope with this difficulty for many years before they seek help and then do so in order to begin a family. Often there are no obvious circumstances predisposing to vaginismus, such as an unpleasant past sexual experience or trauma, sexual abuse, or a painful first pelvic examination. Higher rates of psychopathology have sometimes been found (121) including more frequent agoraphobia without panic disorder, and obsessive-compulsive disorder. Some studies showed that women with vaginismus have higher scores on neuroticism, depression, state anxiety, phobic anxiety, social phobia, somatization, and hostility. They were shown to have increased catastrophic thinking compared to those women without dyspareunia and those with other forms of pain (e.g., PVD). Women with vaginismus had higher propensity for disgust. Women with vaginismus typically have an extreme fear of vaginal entry and misconceptions about their anatomy and the size of their vagina. They fear that harm will come from something the size of a penis entering the vagina, and similarly they fear that they would be damaged by vaginal delivery.

The term "vaginismus" was often loosely used to refer to reflex tightening secondary to dyspareunia (e.g., from PVD or GSM). However, the term was only correct when no such pathology was present. Thus, the diagnosis of vaginismus was provisional until a very careful introital and vaginal examination was done. This is not possible until the woman learns to be able to abduct her thighs, open the labia with her fingers or permit the examiner to do so, and to tolerate introital touch. **Despite typical histories of "phobic vaginismus" the allodynia of PVD is sometimes present.** Therefore the term is officially dropped from DSM-5 and genito-pelvic penetration pain disorder (GPPPD) is an umbrella term covering a number of types of pathophysiology, most commonly PVD, GSM and pelvic muscle reflexive hypertonicity (AKA "vaginismus"). In order to establish the type of GPPPD therapy, a detailed examination is needed.

When the "vaginistic" component is present:

1. **Encourage the couple to engage in sexual activities that exclude any attempt at intercourse.** They may need to have "dates" and deliberately provide sexual contexts.
2. **Explain to the patient the reflex contraction of pelvic muscles around the**

vagina to touch, especially when touch was associated only with negative emotions and physical pain. These women rarely use tampons and avoid the introitus and vagina in sexual play and have not experienced any neutral or positive sensations from this area of their bodies.

3. **Institute self-touch on a daily basis for a few minutes as close to the vaginal opening as possible.** This may be done while the woman is in the bathtub or relaxing by herself on the bed. This is not sexual, and at first it will be highly anxiety provoking. Providing she does this daily, the anxiety will quickly decrease.
4. **Suggest adding visual imagery to the previous exercise** so that she imagines being able to have a limited vaginal examination, sitting up on the examination couch at about a 70-degree angle, with the aid of a mirror, to view the vaginal opening and separate her labia, and be in control of what happens.
5. **As soon as she is ready, perform the partial vulvovaginal examination as in step 4.** If possible, encourage her to touch the vagina, moving her finger past the hymen, possibly afterward doing the same with the physician's gloved finger.
6. **Once the vagina is adequately examined, prescribe a series of vaginal inserts of gradually increasing diameter.** When symptoms suggestive of PVD are present—especially burning with semen ejaculation, dysuria, or vulvodynia after intercourse attempts—she should use only the smallest insert before a repeat examination takes place.
7. **When it is necessary to exclude PVD, repeat the examination with the woman checking for allodynia with a cotton swab.** Sometimes the physician can do this; it depends entirely on the amount of anxiety and apprehension the woman retains. The number of false-positive findings for allodynia can be limited if the patient touches the rim of the vaginal opening.
8. PVD or other gynecologic findings should be treated.
9. To continue therapy for the "vaginistic" response when the patient is able to use larger inserts, the following steps can be undertaken:
    a. **Encourage the woman to allow her partner to assist her in placing the insert in her vagina.**
    b. **Encourage the couple during their sexual times to briefly use the insert**—to prove to her that the insert will still go in when her body is physiologically aroused.
    c. **After she has used the insert on a number of occasions during sexual play, encourage her to follow it immediately with insertion of her partner's penis.** It is usually preferable for the woman to hold her partner's penis in the same position she used with the insert and to insert the penis herself. He must allow his pelvis to move forward with gentle pressure as she tries to insert it. The use of external lubrication is advised in these first attempts at penile entry.

Phosphodiesterase type 5 inhibitors may be used to treat temporary situational partner erectile dysfunction that occurs at the crucial moment when the woman is finally able to accommodate her partner's penis.

Management of Other Causes of GPPPD

Dyspareunia/GPPPD, one of the most common types of sexual dysfunction seen by gynecologists, affects some two-thirds of women during their lifetime. Both psychological and physical factors are involved—the mind being able to powerfully modulate both immune and neurologic systems, causing objective changes in the latter. The gynecologist's assessment of dyspareunia needs to be holistic: biologic, psychological, and sexual.

There are three aspects to the management of dyspareunia:

1. **Assisting the couple to have rewarding sexual intimacy even if intercourse initially is precluded**
2. **Identifying the psychological issues contributing to and arising from the chronic pain**
3. **Treating, whenever possible, the underlying pathophysiology that triggered the chronic pain circuits**

It is helpful to clarify that the popular depiction of sex as foreplay followed by "real sex" (i.e., intercourse) is not the reality for many sexually satisfied couples. The couple can be encouraged to consider the many varieties of human sexual interaction and ways of giving and receiving genital and nongenital sexual pleasure. It is important for the couple to see temporary removal of intercourse from the menu of sexual activity as an opportunity for more exploration and creativity, rather than as a loss. Inclusion of the partner in the assessment and evaluation of chronic dyspareunia allows his or her feelings to be addressed and their compliance with nonpenetrative sex encouraged. The couple rendered emotionally distant because of chronic dyspareunia may find it difficult to adapt to alternative forms of lovemaking.

Management of Provoked Vestibulodynia

[1] PVD has a prevalence of 15% (101), **and is defined as pain on vestibular touch (from tampon, examining finger, penis, tight seam on clothing, etc.) where physical findings are limited to variable (possibly absent) vestibular erythema and the presence of allodynia (feeling pain from a nonpain stimulus—typically a moistened Q-tip) on localized areas around the outer edge of the hymen and inner edge of the labia minora where the two meet.** The whole introital circumference may be affected: often the lower part (lower horseshoe or 4 to 8 o'clock location) is involved along with the areas immediately around the openings of Skene ducts. Typically pelvic muscle tone

is heightened. This is the most common cause of dyspareunia seen in clinics, with at least 50% of women reporting lifelong symptoms and others acquiring them after possibly multiple occasions of painless vaginal penetration. **PVD is considered a chronic pain syndrome and the end result of a number of possible pathophysiologic processes** (122). There is evidence of **central and peripheral sensitization within the nervous system.** This means there are physical changes within the nervous system that perpetuate the pain cycles, and that theoretically can be targeted by medications (chronic pain drugs) and mind skills including CBT and mindfulness. **The cause of the sensitization within the nervous system is not established with certainty, but early life and current stress appears to be a likely cause.** There is evidence of hypothalamic pituitary adrenal dysregulation in women with PVD. Studies show higher levels of perfectionism, reward dependency, fear of negative evaluation, harm avoidance, and higher levels of trait anxiety, and shyness (121). Three times higher rates of premorbid depression and ten times higher rates of premorbid anxiety disorders are found in women with PVD compared to controls (38). Women with PVD have more catastrophic thoughts about intercourse pain and the negative consequences on the partner and durability of the relationship than women with other types of dyspareunia (121). There is evidence of hypervigilance for pain. PVD may be precipitated and maintained by internal stress given the psychological consequences of self-described "sexual failure" (123,124). **Many women with PVD have other pain syndromes such as irritable bowel syndrome, temporomandibular joint pain, interstitial cystitis, dysmenorrhea, and fibromyalgia.**

The management of PVD includes psychological methods to change brain processing of the potentially painful stimulus and simultaneously alter the brain's triggering of stress responses. The psychological methods include CBT and MBCT. Particular attention is paid to the catastrophic thinking. Briefly describing brain activity during pain explains the role of thoughts and emotions to modulate the physical sensation of pain. Reduction of allodynia and increased intercourse has been documented for up to 2.5 years after 10 weeks of CBT (60). Mindfulness has been increasingly incorporated into Western medicine and several studies show moderate effect sizes for improvement in chronic pain. Given its use in other pain conditions, it was added to the holistic treatment of PVD (125). Benefit from a 4-week MBCT program has been shown using a waitlist control arm (126). Currently under review for publication is an 8-week program to compare 8 weeks of CBT versus 8 weeks of MBCT with follow-up for a year.

Medications: Randomized controlled trials of chronic pain medications—*tricyclic antidepressants* with or without additional local anesthetic and *antiseizure drugs* have not shown benefit beyond placebo. Individual women do nevertheless benefit suggesting probable variable types of pathophysiology underlying PVD. Recent research points to

future use of a local anti-inflammatory agent to block the action of angiotensin II on its receptors because angiotensin II is thought to cause the well-documented hyperproliferation of nociceptors in PVD (127). **Topical steroids need to be avoided because initial benefit moves onto worsening of the presumed neurogenic inflammation.** Evidence-based guidelines suggesting which medication to choose are lacking. **A typical outcome of the psychological therapy is that pain intensity and distress lessen sufficiently to allow the woman to regain her sexual confidence with nonpenetrative sex and sometimes to subsequently include intercourse when fully aroused. Prior to doing so she might use *topical local anesthetic* on residual areas of allodynia.** Her lessened reactivity to physical sensations and her expectation of less pain combine with her expectation of reward to reduce the intensity of the dyspareunia.

Introital pain may be caused by conditions other than PVD. The differential diagnosis includes recurrent tears of the posterior fourchette, which may be treated with the topical application of estrogen or testosterone and, if necessary, a perineorrhaphy. Other diagnoses are congenital abnormalities, including a hymenal ring that is rigid, scar tissue (e.g., from episiotomy repairs), a vaginal septum, and, much more commonly, vaginitis or vulvitis, sometimes resulting from the use of over-the-counter vaginal sprays and douches. **One important common cause of dyspareunia is friction from inadequate genital sexual arousal. Estrogen deficiency with inadequate lubrication, progressing to loss of elasticity and thinning of the epithelium from GSM is another common cause.** Deep dyspareunia resulting from pelvic disease, including endometriosis, is managed by treatment of the underlying conditions.

Management of Sexual Dysfunction Midlife and Later

Because sexual dysfunction in older women can be related to a variety of factors, broad-spectrum treatment approaches are needed in which individual, interpersonal, and sexual aspects can be addressed simultaneously. The following steps in therapy are recommended:

- **To encourage the woman to discover what provides sexual pleasure and arousal and to learn to guide her partner toward stimuli and contexts (surroundings and time of day) that are pleasurable to her now, as they may be different and more complicated than when she was a younger woman and possibly her relationship was relatively new.**
- **To assist her to understand that a more rewarding outcome will increase her sexual motivation.** Sexual dysfunction in the partner may need to be addressed.
- **To counsel her that women can begin rewarding sexual experiences in the absence of any initial desire. This can be reassuring and therapeutic.**

- **To acknowledge that resentment, frustration, and disappointment toward her partner will very likely preclude arousal and pleasure: relationship counseling can be suggested.**
- **Given low desire is strongly associated with low mood, treatment of the latter with nonpharmacologic therapy or sexually neutral medication is necessary.**
- **To avoid sex when tired and sleep is needed: plan earlier in the day.**
- **To avoid having a goal—be it intercourse, or orgasm, or that both partners must necessarily have orgasms: sharing physical and emotional sexual pleasure becomes the focus.**

Management of Genitourinary Syndrome of Menopause (GSM): AKA Vulvovaginal Atrophy

Loss of sexual motivation is frequently caused, at least in part, by the vulvar vaginal discomfort of dryness, itching, burning, and dyspareunia from estrogen deficit. Often the symptoms require local estrogen in pill, cream, or sialastic ring formulation to restore vaginal cell health, decreasing pH, and increasing vulvar and vaginal blood flow. When systemic estrogen is used for nonsexual reasons, additional topical vaginal estrogen may still be required. Postmenopausal vulvovaginal atrophy–associated dyspareunia may be accompanied by PVD (50) and direct application of estrogen to the sites of allodynia is necessary.

Nonestrogen options include:

1. *Vaginal DHEA:* Research confirms a generalized sexual benefit in terms of coital comfort, ease of orgasm, and sexual motivation without any increase in mass spectrometry measured serum levels of testosterone and estrogen (128).
2. *Hyaluronic acid:* This has been shown to be noninferior to 0.5 mg estriol twice weekly with both treatments showing benefit within 2 weeks (129).
3. *Local anesthetic:* Topical lidocaine applied to the vestibule for 10 minutes before penetration, and then removed and replaced with a lubricant significantly lessened dyspareunia in a case series of women with a history of breast cancer (77).
4. *Laser therapy:* There is early report of benefit for up to 2 years from fractional microablative CO laser treatment (130).

FEMALE GENITAL MUTILATION

Increasing numbers of women who underwent female genital mutilation or female genital cutting (FGC) need gynecologic care in Western counties. This ancient tradition from at least 200 BC has cultural rather than religious origins and is not

restricted to any particular ethnic group or religious sect. **Type I** FGC involves removing part or all of the clitoris and prepuce; **Type II** is an excision of part or all of the clitoris and the labia minora with or without excision of the labia majora; **Type III** is known as infibulation and is the most extreme form, involving narrowing the vaginal orifice and creating a covering of the adjoined labia minora and or labia majora with or without including the clitoris. There are other "lesser" procedures often noted as **Type IV,** such as pricking of the female genitalia for nonmedical reasons. Although some 85% of FGC are Types I and II and 15% are Type III, recent immigration and refugee resettlement from countries where Type III predominates, including Somalia, resulted in many more women with Type III FGC in North America and Europe.

Data on psychosexual outcome are emerging but some women may be reluctant to admit to sexual dysfunction to avoid negative feelings toward their parents or condemnation of the religious orders (131). The taboos against discussing sexual displeasure or pain from FGC still limit data collection. Despite this, there is evidence that FGC may not destroy sexual function and prevent enjoyment in all women (132). FGC invariably damages many neural networks associated with the vulvar and perineal areas, potentially altering genital sensation. Neuroplasticity within the brain and spinal cord is thought to account for the fact that some, perhaps even the majority, of women have sexual response, sometimes including that from genital stimulation and other times from stimulation of breasts or other areas of the body.

A recent Egyptian case-controlled study using a validated questionnaire and careful genital examination confirmed significantly lower sexual function scores in the 197 women with FGC—76% with FGC Type I and 24% with Type II (131).

Surgery is recommended for women with Type III FGC complications such as dysmenorrhea, a desired vaginal birth that would not be possible without surgery, apareunia, dyspareunia, or difficulty voiding. The defibulation should be performed after counseling regarding risks and benefits, the former including bleeding infections, preterm labor if the woman is already pregnant, and scar formation. The benefits include lower risk of chronic urinary and vaginal infections, voiding difficulties, dysmenorrhea, dyspareunia, and intrapartum complications. Regional or general anesthesia is required, as local anesthesia may allow the sensation of touch to trigger flashbacks to the original traumatic procedure.

It is apparent to people helping women who underwent FGC that culture plays a very important role in their sexual health. It is imperative that the specific needs of the individual woman with FGC are understood in order to help her. Care should be given in a nonjudgmental manner that encourages trust and open discussion. Her own cultural significance of the FGC should be explored and often an interpreter is necessary to really understand her situation.

CONCLUSION

Although women's sexual dysfunction typically results from a number of psychological sexual and medical factors and can seem too complicated to address, very often careful assessment and provision of accurate information is highly therapeutic. Having current information increases physician comfort with the subject: this in turn encourages women to provide the sensitive personal details that frequently have not previously been disclosed but are necessary for diagnosis and treatment.

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CHAPTER 18

Menopause



Jan L. Shifren, Isaac Schiff

Health Concerns After Menopause
- Vasomotor Symptoms
- Genitourinary Syndrome of Menopause
- Sexual Dysfunction
- Osteoporosis
- *Cardiovascular Disease*
- Breast Cancer
- Dementia

Hormone Therapy Use
Summary

KEY POINTS

1 A woman in the developed world will spend approximately a third of her life beyond menopause, so addressing the health and quality of life concerns of menopausal women is critically important.

2 Health and quality of life concerns of menopausal and aging women include vasomotor symptoms, symptomatic vulvovaginal atrophy, sexual dysfunction, osteoporosis, cardiovascular disease, cancer, and cognitive decline.

3 Hot flashes and night sweats (vasomotor symptoms) affect up to 75% of perimenopausal women and may last 10 years or longer.

4 Hormone therapy is the most effective treatment for vasomotor symptoms. Low-dose paroxetine is another approved option. Lifestyle changes, relaxation response techniques, acupuncture, soy and

herbal products are popular interventions with limited efficacy beyond placebo.

5 Contraindications to systemic hormone therapy use include known or suspected breast or endometrial cancer, abnormal vaginal bleeding, cardiovascular disease (including coronary heart disease, cerebrovascular disease, and thromboembolic disorders), and active liver or gallbladder disease. Relative contraindications include high-risk states for the above disorders.

6 The genitourinary syndrome of menopause, which includes symptomatic vulvovaginal atrophy, affects at least 50% of menopausal women with an adverse impact on sexual function and quality of life.

7 Vaginal application of low doses of estrogen is an effective and safe treatment of vaginal dryness, dyspareunia, and certain urinary symptoms. Other options include systemic hormone therapy, vaginal lubricants and moisturizers, oral ospemifene, vaginal dehydroepiandrosterone, and pelvic physical therapy.

8 Sexual concerns are common after menopause, etiology is generally multifactorial, and effective treatment options are available.

9 Osteoporosis and fractures increase with menopause and aging. Modifying risk factors and pharmacologic interventions effectively prevent and treat osteoporosis and reduce fracture risk.

10 Cardiovascular disease is an important health concern for menopausal women. A healthy lifestyle and treatment of associated diseases including hyperlipidemia, hypertension, and diabetes reduce risk, morbidity, and mortality.

11 Breast cancer is a major health concern for menopausal women and regular screening is indicated.

12 Cognitive decline and dementia are highly prevalent in older women and risk reduction should be optimized beyond menopause.

Menopause, the permanent cessation of menstruation caused by ovarian failure, occurs at an average age of 52 years, with a range of 40 to 58 years. Despite a great increase in the life expectancy of women, the age at menopause has remained remarkably constant. **[1] A woman in the developed world will live approximately 30 years, or greater than a third of her life, beyond menopause. Therefore, it is important to ensure these years are as healthy and productive as possible.** The age at menopause appears to be genetically determined and is unaffected by race/ethnicity or age at menarche. Early menopause describes menopause occurring between the ages of 40 and 45 years and occurs in approximately 5% of women. **Premature menopause describes permanent loss of ovarian function before the age of 40, such as following bilateral oophorectomy. Primary ovarian insufficiency (POI) describes loss of ovarian function before the age of 40 years, which may not be permanent. POI occurs in approximately 1% of women.** Factors associated with early menopause or POI include toxic exposures, genetic abnormalities, autoimmune disorders, and pelvic surgery. Women who smoke experience an earlier menopause (1), as do many women exposed to chemotherapy or pelvic radiation. Fragile X premutations, Turner mosaic karyotypes, and ovarian surgery or hysterectomy, despite retention of ovaries, may result in early menopause or POI (2).

Although menopause is associated with changes in the hypothalamic and pituitary hormones that regulate the menstrual cycle, menopause is not a central event, but rather an indication of primary ovarian failure. At the level of the ovary,

there is a depletion of ovarian follicles, most likely secondary to apoptosis or programmed cell death. The ovary is no longer able to respond to the pituitary's follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and ovarian estrogen and progesterone production ceases. **The ovarian–hypothalamic–pituitary axis remains intact during the menopausal transition; thus, FSH levels rise in response to ovarian failure and the absence of negative feedback from the ovary.** Atresia of the follicular apparatus, in particular granulosa cells, leads to decreased production of estrogen and inhibin, resulting in elevated FSH levels, a cardinal sign of menopause. **Antimüllerian hormone (AMH) is produced by small ovarian follicles, so levels decrease with declining ovarian reserve** (3).

Androgen production from the ovary continues beyond the menopausal transition caused by sparing of ovarian stroma and theca cells. Androgen concentrations are lower in menopausal women than in women of reproductive age. This finding appears to be associated with aging and decreased functioning of the ovary and adrenal glands over time rather than with menopause per se. Menopausal women continue to have low levels of circulating estrogens, principally from peripheral aromatization of ovarian and adrenal androgens. Adipose tissue is a major site of aromatization, so obesity affects many of the sequelae of menopause. Obesity is a risk factor for breast cancer and a protective factor for osteoporosis, likely as a result of the impact of higher levels of endogenous free estrogens, though still within the menopausal range.

Menopause is defined retrospectively as the time of the final menstrual period followed by 12 months of amenorrhea. Postmenopause describes the period following the final menses.

The STRAW (Staging of Reproductive Aging Workshop) criteria describe the changes that encompass the transition from reproductive life to postmenopause (4). The late reproductive stage is marked by decreased fertility and onset of menstrual cycle changes. The early menopausal transition is characterized by increased variability in menstrual cycle lengths (≥7 days), and the late menopausal transition by amenorrhea of ≥60 days. Early postmenopause describes approximately 5 to 8 years after the final menstrual period and is followed by late postmenopause. **Rising FSH levels, a reduced ovarian antral follicle count, and declining levels of inhibin-B and AMH accompany menstrual cycle changes.**

The pathophysiologic consequences of menopause may be best understood by considering that the ovary is a woman's only source of oocytes, her primary source of estrogen and progesterone, and a major source of androgens. Menopause results in infertility secondary to oocyte depletion. Ovarian cessation of progesterone production appears to have no clinical consequences, except for the increased risk of endometrial proliferation, hyperplasia, and cancer associated with continued endogenous estrogen production or administration of unopposed estrogen therapy (ET) after menopause. The

effects of declining androgen concentrations that occur with aging have yet to be determined.

The clinical consequences of menopause are related primarily to estrogen deficiency. It is difficult to distinguish the impact of estrogen deficiency from that of aging, as aging and menopause are inextricably linked. Studying the effects of estrogen deficiency and replacement in young women with ovarian failure or of drugs that suppress estrogen synthesis (such as gonadotropin-releasing hormone antagonists) helps to distinguish between the effects of aging and estrogen deficiency. These models are imperfect, though, and differ from natural menopause in many ways.

[2] **Principal health and quality of life concerns of menopausal women include vasomotor symptoms, the genitourinary syndrome of menopause (GSM), sexual dysfunction, osteoporosis, cardiovascular disease (CVD), cancer, and cognitive decline.** Options for caring for menopausal women have increased greatly since hormone therapy (HT) was first introduced in the 1960s. There are many choices of hormone type, dose, and method of administration. In addition to HT, other pharmacologic options include estrogen agonist/antagonists, centrally acting agents, and bisphosphonates. Women are requesting more information on complementary and alternative (CAM) therapies, which are being studied more carefully. The many options available make caring for the postmenopausal woman more challenging and more rewarding.

HEALTH CONCERNS AFTER MENOPAUSE

Vasomotor Symptoms

[3] **Vasomotor symptoms affect up to 75% of perimenopausal women. Symptoms last for 1 to 2 years after menopause in most women, but may continue for up to 10 years or longer in others** (5,6). **Hot flashes are the primary reason women seek care at menopause. Hot flashes interrupt daily activities, disrupt sleep, and disturb women at work** (7,8). Many women report difficulty concentrating and emotional lability during the menopausal transition. **Treatment of vasomotor symptoms often will improve cognitive and mood symptoms if they are secondary to sleep disruption and resulting daytime fatigue. The incidence of thyroid disease increases as women age; therefore, thyroid function tests should be performed, if vasomotor symptoms are atypical or resistant to therapy.**

The physiologic mechanisms underlying hot flashes are incompletely understood. A central event, likely in the hypothalamus, drives an increased core body temperature, metabolic rate, and skin temperature; this reaction results in peripheral vasodilation and sweating. The central event may be triggered by noradrenergic, serotoninergic, and/or

dopaminergic activation. Hypothalamic neurons containing kisseptin, neurokinin B (NKB), and dynorphin receptors (KNDy neurons) appear to play an important role in hot flashes. Peripheral infusion of NKB intravenously induces a typical hot flash, while blocking NKB activity reduces hot flashes (9). Although an LH surge often occurs at the time of a hot flash, it is not causative, as vasomotor symptoms occur in women without pituitary glands. In symptomatic postmenopausal women, hot flashes likely are triggered by small elevations in core body temperature acting within a narrow thermoneutral zone (10). Exactly how estrogen and alternative therapies play a role in modulating these events is unknown. Vasomotor symptoms are a consequence of estrogen withdrawal, not simply estrogen deficiency. For example, a young woman with premature menopause caused by Turner syndrome will have very high FSH levels and low estrogen levels, but will not experience hot flashes until she is treated with estrogens and that therapy is withdrawn.

Lifestyle interventions may safely decrease vasomotor symptoms. Being in a cool environment is associated with fewer subjective and objective hot flashes (11), so women experiencing symptoms should be advised to keep the room temperature low and wear light, layered clothing (see **Table 18-1**). **Overweight women and those who smoke often have more severe vasomotor symptoms than women of normal weight and nonsmokers.** These findings provide additional reasons to encourage women to lose weight and stop smoking (12). Many menopausal women are interested in trying CAM therapies for relief of hot flashes. These are diverse medical and health care products and practices generally not considered part of conventional medicine. Vasomotor symptoms are particularly sensitive to placebo effects. **Numerous nutritional supplements and products claim to relieve hot flashes but these assertions are rarely supported by controlled trials** (13). Phytoestrogens are plant-derived substances that may act as estrogen agonist/antagonists, with their effects modulated through interactions with the estrogen receptor. Although they decrease hot flash severity and frequency, symptom improvement is comparable to that seen with placebo treatment (14). Black cohosh is another popular alternative treatment, with efficacy similar to placebo (15).

Table 18-1 Options for the Treatment of Vasomotor Symptoms

Hormone Therapy
Estrogen therapy *Progestin* therapy[a] Combination *estrogen/progestin* therapy Combination conjugated estrogen/bazedoxifene
Nonhormonal Prescription Medications
Centrally acting alpha agonist

Clonidine[a]
Selective serotonin and norepinephrine reuptake inhibitors
Paroxetine
Venlafaxine[a]
Escitalopram[a]
γ-aminobutyric acid analogs
Gabapentin[a]
Pregabalin[a]
Nonprescription Medications[a]
Isoflavone supplements
Soy products
Black cohosh
Lifestyle Changes
Reducing body temperature
Maintaining a healthy weight
Smoking cessation
Relaxation response techniques
Yoga
Acupuncture

[a]Not U.S. Food and Drug Administration–approved for treatment of vasomotor symptoms.

Acupuncture reduces vasomotor symptoms in several studies, although a traditional Chinese medicine approach may be no more effective than shallow or "sham" needling techniques (16,17). Exercise, yoga, and paced respiration demonstrated an improvement in hot flashes in several uncontrolled studies, with additional health benefits, including stress reduction. Women may choose to use alternative and complementary therapies for relief of symptoms, but they should be aware that the safety and efficacy of these approaches often are unproven.

[4] Systemic ET is the most effective treatment for vasomotor symptoms (see Table 18-2). **Although low-dose formulations are often effective, younger women and those with recent oophorectomy may require higher doses. Progestin therapy must be given concurrently if a woman has a uterus, although with low-dose ET, intermittent progestin treatment may be an option. Oral contraceptives (OCPs) are an excellent option for healthy, nonsmoking, perimenopausal women with bothersome hot flashes. The supraphysiologic doses of estrogens and progestins in OCPs treat vasomotor symptoms while controlling irregular bleeding. A tissue-selective estrogen complex that combines conjugated estrogen (CE) (0.45 mg) and the agonist/antagonist, bazedoxifene (BZA) (20 mg) (1 tablet orally daily) is approved for the treatment of vasomotor symptoms (VMS) in menopausal women with a uterus.** BZA provides endometrial protection, so a progestin is not needed (18).

HT should be used at the lowest effective dose for the duration necessary to meet treatment goals. For the majority of healthy women with bothersome hot flashes at the menopausal transition, the benefits of HT will outweigh risks.

Because vasomotor symptoms appear to be the result of estrogen withdrawal, rather than simply low estrogen levels, if cessation of ET is desired, the dose should be reduced slowly over time. This recommendation is based on clinical experience, as few controlled trials have been performed to examine the optimal way to discontinue HT. Abruptly stopping treatment may result in a return of disruptive vasomotor symptoms in approximately 50% of HT users (19). The dose and dosing interval may be reduced slowly over months or even years, depending on the patient's symptoms. **For women unable to discontinue HT without return of bothersome symptoms, long-term use may be an option, depending on health status, a careful review of risks and benefits, and shared decision making** (20).

For women who choose not to take estrogen or when it is contraindicated, other options are available (see **Table 18-1**) (13). Progestin therapy alone, including medroxyprogesterone acetate and micronized progesterone, reduces hot flash frequency and severity (21,22). Various agents that alter central neurotransmitter pathways reduce VMS. Agents that decrease central noradrenergic tone, such as clonidine, decrease hot flashes, although the effect size is limited. Potential side effects include orthostatic hypotension and drowsiness.

Table 18-2 Approved Estrogen/Progestogen Prescription Products for Menopausal Symptoms in the United States

Oral Estrogen Products			
Composition	**Product Name**	**Dose (mg/day)**	
17β-estradiol	*Estrace, generics*	0.5, 1.0, 2.0	
Conjugated estrogens (synthetic)	*Premarin* *Enjuvia*	0.3, 0.45, 0.625, 0.9, 1.25	
Esterified estrogens	*Menest*	0.3, 0.625, 1.25, 2.5	
Estropipate (Estrone)	*generics*	0.625, 1.25, 2.5	
Transdermal/Topical Estrogen Products			
Composition	**Product Name**	**Delivery Rate (mg E2/day)**	**Dosing**
17β-estradiol matrix patch	*Alora*	0.025, 0.05, 0.075, 0.1	Twice weekly
	Climara	0.025, 0.0375, 0.05, 0.075, 0.1	Once weekly
	Vivelle-Dot *Minivelle*	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	generics	0.025, 0.05, 0.1	Once or twice weekly
	Menostar	0.014	Once weekly
17β-estradiol transdermal gel	*EstroGel*	0.75	Daily application via metered-dose pump
	Elestrin	0.52	Daily application via metered-dose pump
	Divigel	0.25, 0.5, 1	Daily application of 1 packet
17β-estradiol transdermal spray	*Evamist*	1.53 (per spray)	Daily application via metered-dose pump (1–3 sprays daily)
Vaginal Estrogen Products			
Composition	**Product Name**	**Recommended Dose**	
Vaginal Creams			
17β-estradiol	*Estrace vaginal cream*	0.5-1 g, 2–3 times weekly	
Conjugated estrogens	*Premarin vaginal cream*	0.5-1 g, 2–3 times weekly	
Vaginal Rings			
17β-estradiol	*Estring*	Device releases 7.5 μg/day for 90 days	
Estradiol acetate	*Femring*	Device releases 0.05 or 0.1 mg/day for 90 days (systemic estradiol levels achieved, so progestogen needed, if uterus present)	
Vaginal Tablet			
Estradiol hemihydrate	*Vagifem*	1 tablet (10 μg) twice weekly	
Estradiol	*Imvexxy*	1 insert (10 μg or 4 μg) twice weekly	
Progestogens			
Composition	**Product Name**	**Dose**	
Micronized progesterone	*Prometrium*	100, 200 mg	
Medroxyprogesterone acetate	*Provera, generics*	2.5, 5, 10 mg	
Combination Estrogen–Progestogen Products			
Composition	**Product Name**	**Dose (per day)**	
Oral continuous-cyclic regimen			
Conjugated estrogens (E) + medroxyprogesterone acetate (P)	*Premphase*	0.625 mg E + 5.0 mg P (E alone days 1–14, E + P days 15–28)	
Oral continuous-combined regimen			
Conjugated estrogens (E) + medroxyprogesterone acetate (P)	*Prempro*	0.625 mg E + 2.5 or 5.0 mg P 0.3 or 0.45 mg E + 1.5 mg P	

Combination Estrogen–Progestogen Products		
Composition	**Product Name**	**Dose (per day)**
Ethinyl estradiol (E) + norethindrone acetate (P)	*FemHRTLo* *FemHRT* *generics*	2.5 μg E + 0.5 mg P 5 μg E + 1 mg P
17β-estradiol (E) + norethindrone acetate (P)	*Activella* *generics*	0.5 mg E + 0.1 mg P 1 mg E + 0.5 mg P
17β-estradiol (E) + drosperinone (P)	*Angeliq*	1 mg E + 0.5 mg P
Oral intermittent-combined regimen		
17β-estradiol (E) + norgestimate (P)	*Prefest*	1 mg E + 0.09 mg P (E alone for 3 days, followed by E + P for 3 days, repeated)
Transdermal continuous-combined regimen		
17β-estradiol (E) + norethindrone acetate (P)	*CombiPatch*	0.05 mg E + 0.14 P twice weekly
17β-estradiol (E) + levonorgestrel (P)	*Climara Pro*	0.045 mg E + 0.0015 mg P once weekly

E, estrogen; P, progestin. Products available in the United States.

Selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs/SNRIs) reduce hot flash frequency and severity and are the mainstay of nonhormonal VMS treatment. Although paroxetine, venlafaxine, and escitalopram have been shown in randomized controlled trials (RCTs) to be more effective than placebo and may be used off-label (23,24), only a very low dose of paroxetine (7.5 mg) is FDA approved for this indication (25). Side effects of SSRIs/SNRIs include nausea, drowsiness, dry mouth, insomnia, and sexual dysfunction. **Paroxetine inhibits the enzyme system that converts tamoxifen to its active form, so should not be used by women taking tamoxifen for breast cancer prevention or treatment.**

Gabapentin and pregabalin are γ-aminobutyric acid analogs approved for the treatment of seizures and neuropathic pain. These agents reduce hot flash frequency and severity significantly more than placebo in several RCTs, so are an off-label option for VMS treatment (26,27). As side effects include disorientation, dizziness, and drowsiness, use of gabapentin and pregabalin is best limited to bedtime for the treatment of night sweats and associated sleep disruption. Women principally bothered by night sweats and disrupted sleep may benefit from sleeping medication. In an RCT, the prescription insomnia treatment, eszopiclone, significantly improved sleep with a positive impact on next-day functioning, mood, and quality of life (28). Antihistamines, including diphenhydramine hydrochloride, are inexpensive, over-the-counter agents that may improve sleep in women with bothersome night sweats.

A potential therapy for VMS is an agent that blocks hypothalamic NKB activity. Although not yet commercially available, RCTs confirm that an oral antagonist to the NKB receptor (NK3R) significantly reduces hot flashes compared with placebo, independent of any hormonal effects (9).

Genitourinary Syndrome of Menopause

[6] GSM describes anatomic changes and symptoms secondary to estrogen deficiency affecting the labia, vagina, urethra, and bladder (29). **Symptoms include bothersome genital irritation, dryness, and burning; urinary urgency, dysuria, and recurrent urinary tract infections (UTIs); and dryness and pain with sexual activity. Vulvovaginal atrophy (VVA) is a component of GSM** (30). **Bothersome VVA symptoms are highly prevalent, affecting at least 50% of menopausal women, with a significant adverse impact on quality of life** (31,32). **Although vasomotor symptoms generally improve with time, GSM typically worsens in the absence of treatment.** Many effective therapies are available for GSM/symptomatic VVA (33).

Nonhormonal vaginal products available over-the-counter are often an initial treatment intervention. **Vaginal lubricants (water, silicone, or oil based) reduce friction and increase comfort with penetrative sexual activity, including intercourse. Long-acting vaginal moisturizers used two to three times weekly line the vagina, retaining moisture and reducing symptoms** (34).

Activity that stretches, stimulates, and strengthens the genital area promotes vulvovaginal health. If indicated, genital activity, with or without a partner, should be encouraged after menopause. Pelvic physical therapy (PT) and use of vaginal dilators effectively treat severe dyspareunia (35). The use of laser therapy for the treatment of GSM remains controversial with few controlled trials (36,37).

[7] If nonhormonal therapies are ineffective, ET is approved for the treatment of vaginal dryness, dyspareunia, and related symptoms. Low doses of estrogen applied vaginally are preferred to systemic ET in the absence of vasomotor symptoms because of minimal absorption and a high degree of safety (33). Several formulations are available, including vaginal estradiol tablets and creams, and a ring (see **Table 18-2**) (38). Low doses of vaginal estrogen cream (0.5 g) are effective when used only two or three times weekly. An estradiol vaginal tablet (10 µg, 4 µg) inserted twice weekly may be less messy than estrogen cream. An estradiol-containing vaginal ring (7.5 µg per day) is another convenient formulation, which is placed in the vagina every 3 months and slowly releases a low dose of estradiol (39).

Endometrial safety has been confirmed with the use of low-dose vaginal ET for up to 1 year, but long-term clinical trials have not been performed. An analysis of data from more than 45,000 women in the Women's Health Initiative (WHI) Observational Study was very reassuring, with no increased risk of endometrial cancer seen in users of vaginal ET compared with nonusers (40). There also was no increased risk of breast cancer or CVD in vaginal ET users. **Women using vaginal ET should be reminded to report any vaginal bleeding, and a thorough evaluation should be performed. Typically, concurrent progestin therapy is not prescribed with low-dose vaginal estrogen preparations.**

Vaginal ET reduces certain urinary problems in menopausal women, including frequency, urgency, and recurrent UTIs (41). **Incontinence does not appear to improve with vaginal ET, and is likely worsened by systemic HT** (42,43).

Studies of the low-dose estradiol vaginal ring and tablet confirm that serum estrogen levels generally remain within the normal range for postmenopausal women (44). **Given minimal systemic absorption, low doses of vaginal ET may be an option even for women with a history of estrogen-responsive cancers or CVD** (33,45).

Vaginal use of the hormone dehydroepiandrosterone (DHEA) (0.5% daily) effectively treats moderate to severe dyspareunia secondary to VVA and is approved for this indication (46). Circulating levels of estradiol, estrone, testosterone, and DHEA remain within the normal postmenopausal range. Endometrial biopsies showed inactive or atrophic uterine lining after one year of treatment (47).

The estrogen agonist/antagonist, ospemifene (60 mg/day) is an oral agent approved for the treatment of moderate to severe dyspareunia associated with VVA (48). Sexual function improves, including reduced sexual pain and increased arousal and desire (49). Endometrial safety was confirmed at 1 year (50). As with other estrogen agonist/antagonists, ospemifene may increase the risk of VTE and vasomotor symptoms, reduces breast density, and has favorable effects on bone.

Sexual Dysfunction

[8] Sexual problems are highly prevalent, reported in approximately 40% of US women, with 12% reporting a sexual problem associated with personal distress (51). Although sexual problems generally increase with aging, distressing sexual problems peak in midlife women (aged 45 to 64) and are lowest in women 65 years or older. **The etiology of female sexual dysfunction is often multifactorial, including depression or anxiety, relationship conflict, stress, fatigue, prior abuse, medications, or physical problems that make sexual activity uncomfortable, such as endometriosis or GSM. The impact of menopause per se on sexual function is uncertain** (52). Bothersome VMS causing sleep disruption and fatigue and dyspareunia secondary to GSM are aspects of the menopause transition that may directly affect sexual desire and pleasure. Aging, concurrent illness, psychological changes, and relationship and social factors impact sexual functioning in older women, irrespective of the direct physiologic and hormonal changes of menopause.

ET effectively treats vaginal dryness, dyspareunia, and vasomotor symptoms, but does not appear to have a direct effect on sexual interest, arousal, or orgasmic response, independent from its role in treating menopausal symptoms. In contrast to ET, androgen therapy may improve sexual function in selected populations of menopausal women (53). The impact of declining androgen levels with aging and the

efficacy of testosterone in treating female sexual dysfunction remain controversial. **Potential risks of androgen therapy include hirsutism, acne, irreversible deepening of the voice, and adverse changes in liver function and lipids. As most androgens are aromatized to estrogens, there is potential for an increased risk of cardiovascular events and breast cancer.** No androgen products are approved for use in women.

Although VVA and dyspareunia respond well to systemic or local ET, oral ospemifene, and vaginal DHEA, most other sexual problems may be effectively treated without hormones. Relationship quality and conflict, stress, and fatigue predict sexual satisfaction, so couples often benefit from counseling, lifestyle changes, and sex therapy. Underlying depression and anxiety should be treated, and antidepressant medication may need adjustment. **Bupropion may be an alternative to an SSRI, or added to SSRI treatment in the setting of FSD.** In women with and without depression, increased sexual arousal and orgasm are observed with bupropion in small RCTs (54). **Sildenafil citrate may benefit women who develop problems with arousal and orgasmic response on SSRIs, but generally it is no more effective than placebo for most female sexual problems** (55,56). Even though sexual problems are common, the majority of women with distressing sexual problems do not seek formal care, but when they do, it is typically the woman, rather than the physician, who initiates the conversation (57). **Clinicians should routinely ask their menopausal patients about sexual concerns, as many effective interventions are available** (58).

Osteoporosis

[9] Low bone mass and osteoporosis affect an estimated 35 million US women, or approximately 66% of women older than age 50 years (59). Because therapy is most likely to benefit those at highest risk, it is important to review a woman's risk factors for osteoporosis when making decisions regarding bone density screening and treatment (Table 18-3). **Low bone mass and osteoporosis are principal risk factors for fractures, which are associated with an enormous economic cost, pain, disability, and even increased mortality. Nonmodifiable risk factors include age, race (Asian, Caucasian), small body frame, early menopause, prior adult fracture, and family history of osteoporosis. Modifiable risk factors include inadequate intake of calcium and vitamin D, smoking, low body weight, excess alcohol use, and a sedentary lifestyle. Medical conditions associated with an increased risk of osteoporosis include anovulation during the reproductive years (e.g., secondary to excess exercise or an eating disorder), hyperthyroidism, hyperparathyroidism, chronic renal disease, rheumatoid arthritis, and diseases requiring systemic corticosteroid use.**

Table 18-3 Risk Factors for Osteoporosis

Nonmodifiable
Age Race (White, Asian) Small body frame Early menopause Prior adult fracture Family history of osteoporosis
Modifiable
Inadequate intake of calcium and vitamin D Smoking Low body weight Excess alcohol use Sedentary lifestyle
Associated Medical Conditions
Anovulation during reproductive years (e.g., due to excessive exercise or disordered eating) Hyperthyroidism Hyperparathyroidism Chronic renal disease Rheumatoid arthritis Conditions requiring systemic corticosteroid use

Bone mineral density (BMD) measurements may be used to determine fracture risk, diagnose osteoporosis, and identify women who would benefit from therapeutic interventions. Dual x-ray absorptiometry (DXA) of the hip and spine is the primary technique for BMD assessment. BMD is reported as absolute density (grams mineral/cm^2) and in relation to two norms. **T score is the standard deviation (SD) above or below the mean for a healthy 30-year-old woman.** Z score is the SD above or below the mean for a woman of similar age. **Normal BMD is defined by a T score ê-1, low BMD or osteopenia by a T score between -1 and -2.5, and osteoporosis by a T score Ä-2.5.** Although there is a strong association between BMD and fracture risk, a woman's age, risk for falls, and overall health status significantly influence fracture risk. **Evaluation of BMD by DXA is recommended for all women aged 65 and older, regardless of risk factors, and for younger postmenopausal women with one or more risk factors, other than being White and menopausal** (60).

Women should be counseled to alter modifiable risk factors as an important step in the prevention of osteoporosis and fractures (Table 18-4). Women with diets deficient in calcium and vitamin D will benefit from dietary modification and supplementation. Daily intake of calcium 1,200 mg and vitamin D 800 to 1,000 IU is recommended (60). **Calcium intake should be achieved principally through diet.**

Treatment with calcium and vitamin D does not appear to directly reduce fracture risk (61). Reducing the risk of osteoporosis and fractures is another of the many health benefits of regular weight-bearing and muscle-strengthening exercise, smoking cessation, and limiting alcohol intake. Other interventions to reduce fracture risk include a home safety assessment (installing a shower grab bar, carpeting stairs), vision correction, and avoiding central nervous system depressant medications.

Table 18-4 Recommendations to Reduce Risk of Falls and Fracture

Dietary calcium (1,200 mg/day) with supplementation only if dietary intake insufficient
Vitamin D (800–1,000 IU/day) through diet and/or supplements
Regular weight-bearing and muscle-strengthening exercises Improve balance Increase strength Reduce risk of falls and fractures
Stop smoking
Limit alcohol use
Limit central nervous system depressants
Visual correction, when needed
Home safety assessment Carpet stairs Install grab bars in tubs and showers Night lights

Cosman F, de Beur SJ, LeBoff MS, et al; National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 2014;25(10): 2359–2381.

Table 18-5 Options for Osteoporosis Prevention and Treatment

Bisphosphonates
Alendronate (Fosamax) (35 or 70 mg/week orally)
Risedronate (Actonel) (35 mg/week or 150 mg/month orally)
Ibandronate (Boniva) (150 mg/month orally or 3 mg/every 3 months intravenous)
Zoledronic Acid (4 mg every 1 to 2 years intravenous)
Additional potential benefits: none
Potential risks: esophageal ulcers, osteonecrosis of jaw (rare), atypical femoral fractures (rare) *Zoledronic acid:* hypocalcemia, atrial fibrillation, renal impairment
Side effects: gastrointestinal distress, arthralgias/myalgias

Hormone Therapy
Estrogen or estrogen/progestin therapy
Additional potential benefits: treatment of vasomotor symptoms and urogenital atrophy
Potential risks: breast cancer, gallbladder disease, venous thromboembolic events, coronary heart disease, stroke
Side effects: vaginal bleeding, breast tenderness
Tissue-Selective Estrogen Complex
Bazedoxifene (20 mg)/Conjugated estrogens (0.45 mg) (Duavee) (1/day orally)
Additional potential benefits: treatment of vasomotor symptoms and urogenital atrophy
Potential risks: breast cancer, endometrial cancer, gallbladder disease, venous thromboembolic events, coronary heart disease, stroke
Estrogen Agonist/Antagonist
Raloxifene (Evista) (60 mg/day orally)
Additional potential benefits: reduced risk of breast cancer
Potential risks: venous thromboembolic events, stroke
Side effects: vasomotor symptoms, leg cramps
Other
Forteo (Teriparatide) (20 µg/day subcutaneously)
Tymlos (Abzioparatide) (80 µg/day subcutaneously)
Additional potential benefits: none
Potential risks: osteosarcoma (after long-term use in rodents), hypercalcemia
Side effects: musculoskeletal pain
Prolia (Denosumab) (60 mg subcutaneously every 6 months)
Additional potential benefits: none
Potential risks: rash, serious infection, hypocalcemia
Side effects: musculoskeletal pain

Pharmacologic treatment is indicated for all women with osteoporosis (T score <–2.5), women with a prior hip or vertebral fracture, and women with low BMD at high fracture risk. FRAX, an online fracture risk assessment tool, provides the 10-year probability of a major osteoporotic fracture for an individual woman. FRAX

helps to identify women with low BMD (T score between –1 and –2.5) who will benefit from pharmacologic therapy (62). Prior to initiating treatment, excluding secondary causes of osteoporosis is advised. Evaluation may include a comprehensive metabolic panel, complete blood count, thyroid stimulating hormone level, parathyroid hormone level, 25-OH vitamin D level, and 24-hour urine collection for calcium.

Drugs used in the prevention and treatment of osteoporosis are principally antiresorptive agents that reduce bone loss and anabolic drugs that stimulate new bone formation (Table 18-5). **HT effectively prevents and treats osteoporosis** and is FDA approved for osteoporosis prevention. In observational studies, current ET use, especially if started soon after menopause and continued long term, reduces osteoporosis-related fractures (63). **The WHI trial confirmed a significant (34%) reduction in hip fractures in healthy women randomized to HT** (CE 0.625 mg per day) after a mean follow-up of 5.6 years (64). **Combined with calcium and vitamin D, even very low-dose ET (CE 0.3 mg per day; transdermal estradiol 0.014 mg per day) produces significant increases in BMD compared with placebo** (65).

The tissue-selective estrogen complex (BZA/CE) is approved for osteoporosis prevention in postmenopausal women with a uterus (18). **The estrogen agonist/antagonist raloxifene (60 mg orally daily) prevents vertebral fractures in women with low bone mass and osteoporosis, though does not appear to reduce the risk of nonvertebral fractures** (66). Raloxifene exercises estrogen-like actions on bone and lipids without stimulating the breast or endometrium. Raloxifene is approved to reduce the risk of invasive breast cancer in women at high risk. In an RCT of approximately 10,000 older postmenopausal women with heart disease or multiple risk factors, raloxifene had no significant effect on death from any cause, coronary events, or total stroke, though risk of fatal stroke and venous thromboembolic disease was increased. The risks of clinical vertebral fractures and invasive breast cancer were significantly reduced (67).

Bisphosphonates specifically inhibit bone resorption and are very effective for the prevention and treatment of osteoporosis. Many convenient formulations are available, including alendronate (35 mg and 70 mg orally weekly), risedronate (35 mg orally weekly, 150 mg orally monthly), ibandronate (150 mg orally monthly, 3 mg intravenous every 3 months), and zoledronic acid (5 mg intravenous every 1 to 2 years) (60). **Women should take oral bisphosphonates on an empty stomach with a large glass of water and remain upright with nothing else to eat or drink for at least 30 minutes.** Creatinine clearance must be normal. The major side effect is gastrointestinal distress. Very rare adverse events include esophageal ulceration, osteonecrosis of the jaw, and atypical femoral fractures. These rare complications are more likely with high-dose intravenous and long-term bisphosphonate use. As residual antifracture effects persist for several years after stopping bisphosphonates, it is

reasonable for women to take a "drug holiday" and discontinue treatment after 3 to 5 years, if fracture risk is reduced after initial treatment.

Denosumab (60 mg subcutaneously every 6 months) is a monoclonal antibody to the receptor activator of nuclear factor-κB ligand. It is approved for the treatment of postmenopausal osteoporosis and decreases both vertebral and hip fractures (68). Rare adverse events are similar to those with bisphosphonates. **Unlike most treatments for osteoporosis that inhibit bone resorption, parathyroid hormone (PTHrP 1–34) (teriparatide 20 lg and abaloparatide 80 lg subcutaneously daily) stimulates new bone formation, resulting in significant reductions in vertebral and nonvertebral fractures** (69). Treatment duration typically is 18 to 24 months. Women treated with denosumab, teriparatide, or abaloparatide should initiate an alternative treatment upon stopping, as rapid bone loss follows discontinuation. Calcitonin nasal spray (Miacalcin, 200 IU per day intranasal) is an approved, but rarely prescribed treatment for established osteoporosis.

Cardiovascular Disease

CVD is the leading cause of death for women and 90% of women have one or more risk factors. Nonmodifiable risk factors include family history and age. Modifiable risk factors include a sedentary lifestyle, obesity, and smoking. Medical conditions associated with an increased risk of heart disease include diabetes, hypertension, and hyperlipidemia. **[10] Advising women to alter modifiable risk factors for CVD and adequately treating diabetes, hypertension, and hyperlipidemia are important components of the comprehensive care of midlife women.**

Although epidemiologic studies identify an approximately 50% decrease in coronary heart disease (CHD) in woman who use HT (70), data from RCTs do not support the use of HT for CHD prevention. Observational studies are prone to bias, and women who used HT in the past were generally healthier and at lower risk for CHD than nonusers (71). **The WHI randomized, placebo-controlled trial of combination estrogen–progestin therapy (EPT) showed that rather than prevent CHD, EPT increased the risk of cardiovascular events in older women** (72). The WHI was a 15-year study sponsored by the National Institutes of Health to examine ways to prevent heart disease, osteoporosis, and breast and colorectal cancer in women. There were several different studies in WHI, involving more than 160,000 healthy postmenopausal women. The WHI clinical trial enrolled approximately 27,000 women nationwide between the ages of 50 and 79 years. The average age of women in the study was 63 years. The objective of the WHI RCT was to assess the major health benefits and risks of the most commonly used HT preparation at the time. Women with a uterus were randomized to EPT (CE 0.625 mg/MPA 2.5 mg) versus placebo while hysterectomized women were randomized to ET (CE 0.625 mg) versus placebo. **In the EPT trial, after an average of 5 years of**

follow-up, risks (hazard ratio [HR]) were increased for CHD (1.3), breast cancer (1.3), stroke (1.4), and pulmonary embolism (PE) (2.1), and decreased for hip fracture (0.7) and colorectal cancer (0.6) (72). **The absolute excess risk attributable to EPT was small, with seven to eight additional CHD events, breast cancers, strokes, and pulmonary embolisms per 10,000 woman-years. In the ET trial, after an average follow-up of 7 years, there was no increased risk of heart disease or breast cancer in estrogen users. Outcomes were similar to those seen in the EPT WHI trial with respect to venous thromboembolism, stroke, and osteoporotic fractures; there was no effect on colorectal cancer** (73).

Further analyses of WHI confirmed that the increased risk of CHD occurred principally in older women and those who were a number of years beyond menopause (Table 18-6). No increased risk of CHD was seen in women between the ages 50 and 59 or within 10 years of menopause (74). Although stroke was increased with HT regardless of age or years since menopause, the absolute excess risk of stroke in the younger women was minimal. **These data do not support a role for HT in the prevention of heart disease, but they do provide reassurance regarding the safety of HT use for bothersome hot flashes and night sweats in otherwise healthy women under age 60 or within 10 years of menopause.**

Table 18-6 Absolute Excess Risk of Coronary Heart Disease and Mortality with Hormone Therapy Use in WHI

	Age (yrs)			Years Since Menopause		
Outcome	50–59	60–69	70–79	<10	10–19	>20
Coronary heart disease	–2	–1	+19[a]	–6	+4	+17[a]
Total mortality	–10	–4	+16[a]	–7	–1	+14
Global index[b]	–4	+15	+43	+5	+20	+23

[a] $P = 0.03$ compared with age 50 to 59 years or less than 10 years since menopause.

[b] Global index is a composite of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, and mortality.

Absolute excess risk of coronary heart disease and mortality (cases per 10,000 woman years) by age and years since menopause in the combined trials (*estrogen + progestin* and *estrogen* alone) of the WHI. (**Rossouw J, Prentice R, Manson J, et al.** Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–1477).

From **Martin K, Manson J.** Approach to the patient with menopausal symptoms. *J Clin Endocrinol Metab* 2008;93:4567–4575. Copyright 2008, The Endocrine Society.

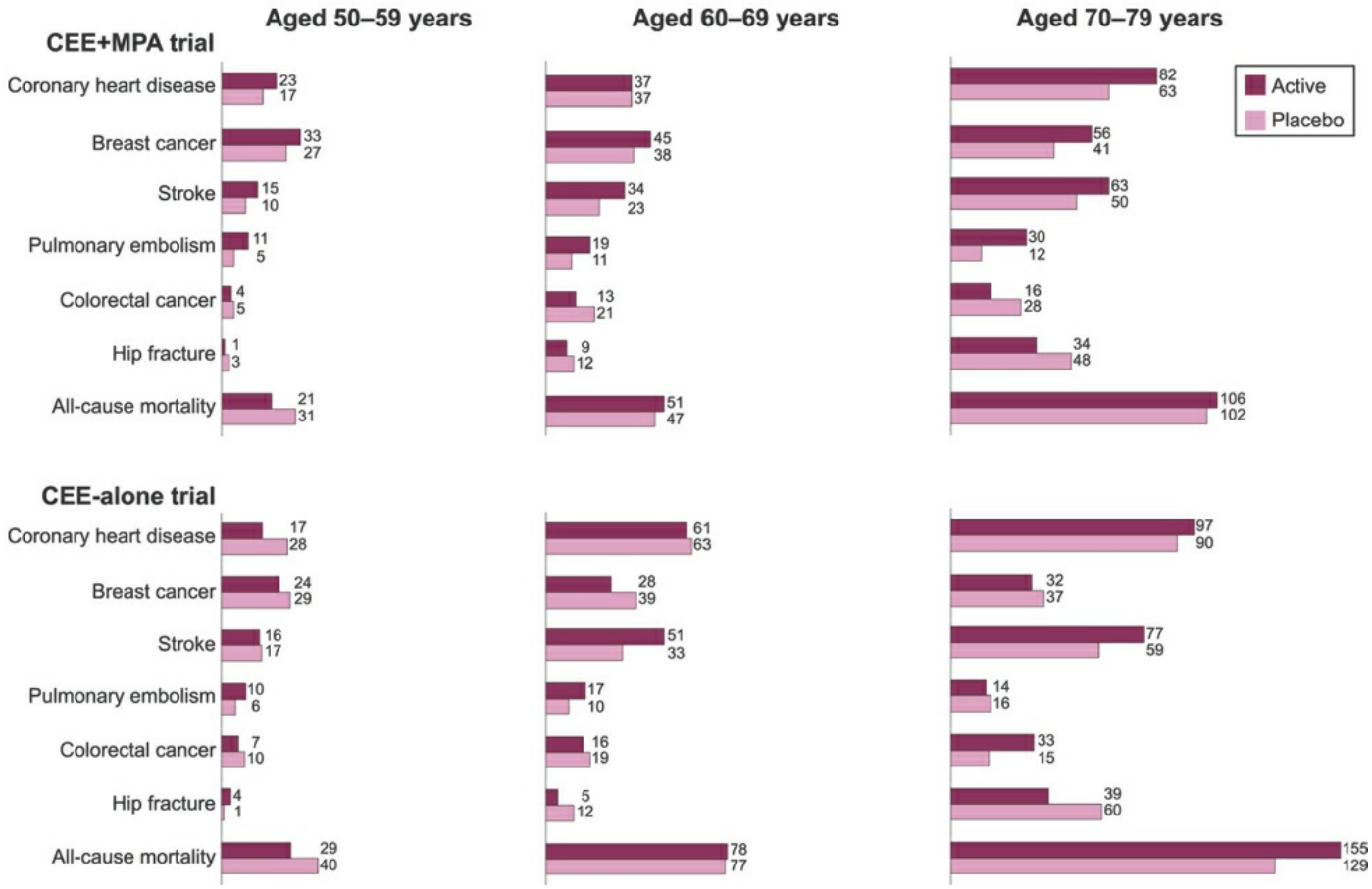


FIGURE 18-1 Women's Health Initiative hormone therapy trials: absolute risks (cases per 10,000 person-years) for outcomes in the intervention phases of the estrogen–progestin and estrogen-alone trials by age group. CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate. (Redrawn from **Kaunitz AM, Manson JE.** Management of menopausal symptoms. *Obstet Gynecol* 2015;126:859–876. In: **Manson JE, Chlebowski RT, Stefanick ML, et al.** Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310(13):1353–1368).

An overview of WHI findings, including both the EPT and ET trials and postintervention (median 13 years of cumulative follow-up), confirmed that the absolute risk of adverse events associated with HT use was considerably lower in younger women (ages 50 to 59 years) than in older women (75). In this reanalysis, in the intervention phase, **a statistically significant increase in CHD events was no longer seen with EPT use.** In both trials, women receiving HT had a lower risk of vasomotor symptoms, diabetes, and hip fractures and a higher risk of venous thromboembolism, gallbladder disease, and stroke. Breast cancer risk was increased in the EPT trial with a reduced risk in the ET trial observed during the poststopping phase (see Fig. 18-1) (75,76). **In an analysis of mortality with HT use, neither EPT (median 5.6 years) or ET (median use 7.2 years) was associated with risk of all-cause, cancer, or cardiovascular mortality with 18 years of cumulative follow-up** (77).

The WHI trials examined treatment only with CEs and medroxyprogesterone acetate. The effects of other oral estrogen agents, transdermal estradiol, other progestins, or cyclic HT may be different. **In observational studies, transdermal ET is not associated with an increased risk of venous thromboembolic disease** (78). The average age of women participating in these trials was more than 15 years beyond the age at which women typically initiate HT for the treatment of vasomotor symptoms. **The "timing hypothesis" proposes that early initiation of HT, presumably when there is less atherosclerosis in blood vessels, may result in a more favorable risk–benefit profile. The findings of the Early Versus Late Intervention Trial With Estradiol (ELITE) support this hypothesis.** HT for 5 years (oral estradiol 1 mg/day with cyclic progesterone vaginal gel in women with a uterus) was associated with less progression of subclinical atherosclerosis (carotid artery intima-media thickness [CIMT]) than placebo when initiated within 6 years after menopause. In contrast, HT had no effect on CIMT when initiated in women more than 10 years after menopause (79).

Breast Cancer

Breast cancer is a major health concern for menopausal women, as it is the most common cancer in women and the second leading cause of cancer death (80). The lifetime risk of invasive breast cancer for US women is 12%; therefore, any therapies that increase or reduce this risk will have a major impact on women's health. **[11] Regular screening mammography reduces the risk of death from breast cancer. The optimal screening interval remains controversial. It is generally recommended that women at average risk be offered initiation of screening mammography at age 40, beginning no later than age 50 years (**81). Screening every 1 or 2 years is advised until at least the age of 75 years. Whether annual or biennial screening is elected should be based on informed, shared decision making that includes a discussion of benefits and harms.

Risk factors for breast cancer include age, family history, early menarche, late menopause, certain genetic carrier states, and prior breast disease, including epithelial atypia and cancer. Risk is reduced in women who had bilateral oophorectomy or a term pregnancy before the age of 30. Many of these risk factors are consistent with the hypothesis that prolonged estrogen exposure increases breast cancer risk.

Current, long-term use of HT, generally defined as greater than 5 years, is associated with an increased risk of breast cancer (relative risk [RR] = 1.3) in observational studies (82). Use of estrogen alone appears to confer a lower risk than combined therapy with estrogen and progestin (83). **The WHI randomized controlled trial demonstrated an increased risk of breast cancer in women randomized to EPT after approximately 5 years of use (HR = 1.2) (72)**. The attributable risk of breast cancer in women randomized to EPT is less than 1 additional case per 1,000 women

per year. **In contrast, there was no increased risk of breast cancer with the use of estrogen alone in women with a prior hysterectomy after an average of 7 years of use (73). HT should not be prescribed to women with a history of breast cancer and should be used by women at high risk only after a careful assessment of potential benefits and risks.** A randomized trial of HT use in women with a history of breast cancer and bothersome hot flashes was stopped after only 2 years, as more new breast cancers were diagnosed in women randomized to HT (84).

The estrogen agonist/antagonist tamoxifen (20 mg per day orally) is used in the treatment of estrogen-receptor positive breast cancer. Tamoxifen and raloxifene reduce the risk of breast cancer in high-risk women by approximately 50% and are approved for this indication (85). **The risk of venous thromboembolism is increased approximately threefold with the use of tamoxifen and raloxifene, similar to the increase seen with HT.** Tamoxifen acts as an estrogen agonist in the endometrium, increasing the risk of endometrial polyps, hyperplasia, and cancer, whereas no endometrial stimulation is seen with raloxifene. **Aromatase inhibitors (AIs) have become the preferred adjuvant therapy for postmenopausal women with early-stage, hormone receptor–positive breast cancer (86). Circulating estrogen levels are very low with associated bone loss, vasomotor symptoms, and GSM.**

Dementia

[12] Cognitive decline and dementia are common concerns of menopausal and aging women. Alzheimer disease is the most common form of dementia and women are at greater risk for developing the disease than men. The number of affected individuals in the United States is estimated at over 5 million of which two-thirds are women. Although observational studies suggest that HT may decrease the risk of Alzheimer disease, this finding has not been supported by RCTs in older women. The WHI Memory Study (WHIMS) was a randomized placebo-controlled study of women aged 65 years or older enrolled in WHI to assess the effect of HT on cognitive function. **Women in WHIMS randomized to EPT experienced a significant twofold increased risk of probable dementia. The increased risk of dementia seen in women randomized to estrogen alone was not statistically significant** (75). HT should not be used to prevent or treat dementia. Women should be encouraged to engage in behaviors that are associated with a lower risk of dementia, including exercising regularly, not smoking, treating underlying hypertension and diabetes, avoiding head injury, improving hearing, active learning, and staying socially engaged (87).

HORMONE THERAPY USE

The use of unopposed estrogen is associated with an increased risk of endometrial hyperplasia and cancer. Therefore, combination EPT is necessary for all women with a uterus. Treatment may be provided in a sequential manner, with estrogen daily and progestin for 12 to 14 days of each month, or in a continuous-combined fashion with estrogen and a lower dose of progestin daily. Sequential regimens result in regular, predictable vaginal bleeding. The majority of women using continuous-combined regimens will experience amenorrhea by the end of 1 year of therapy, but the bleeding that does occur is irregular and unpredictable. Low-dose combination HT products (e.g., CE/MPA 0.45/1.5 and 0.3/1.5 mg per day) generally result in a lower incidence of breakthrough bleeding and breast tenderness (88).

To reduce overall progestin exposure, women using low doses of oral or transdermal estrogens may elect off-label intermittent progestin use (e.g., 14 days every 3 months) (89). **A progestin-releasing intrauterine system approved for contraception in premenopausal women provides endometrial protection in estrogen-treated menopausal women, although it is not approved for this indication** (90). Increased endometrial surveillance is advised with these alternative regimens.

There may be additional benefits and reduced risk with nonoral administration of ET. Systemic delivery of estradiol by skin patch, spray, gel, or vaginal ring avoids the "first pass hepatic effect" of oral estrogens on lipids, binding globulins, and clotting factors. Women with thyroid disease do not require adjustment of thyroid replacement when initiating nonoral ET, as thyroid globulin levels do not increase. Free testosterone levels do not decline with nonoral ET, as sex hormone–binding globulin levels are unchanged, which may be a benefit for women with low libido (91). In a trial of oral versus transdermal E2 in early menopausal women, transdermal, but not oral ET was associated with a significant yet moderate improvement in sexual function compared with placebo (92).

In contrast to oral administration, observational studies do not show an increased risk of venous thromboembolic events with transdermal estradiol (78) **and possibly a lower risk of stroke** (93). Gallbladder disease may not increase with use of transdermal ET, as with oral (94). **Although transdermal ET does not appear to increase the risk of venous thromboembolic events or gallbladder disease in observational studies, HT remains contraindicated in women at high risk for venous thromboembolic disease and in those with active liver or gallbladder disease.**

Popularized by the media, many women are interested in using "bioidentical hormones" for treatment of menopausal symptoms. Bioidentical generally refers to hormones structurally identical to "natural" hormones made by the ovary, including estradiol and progesterone. FDA-approved oral and transdermal estradiol products are available in a wide range of doses, as is an oral form of micronized progesterone. Progesterone should be taken at bedtime, as it may cause drowsiness. **There is**

potentially significant increased risk and no known benefit to the use of custom-compounded "bioidentical" HT formulations, preparations that are "custom" mixed and packaged by a compounding pharmacist for an individual patient (95). **Women who request natural HT formulations should be prescribed FDA-approved formulations containing estradiol and micronized progesterone.** All nonoral ET formulations (transdermal patches, topical spray and gels, and intravaginal ring) contain natural estradiol (see Table 18-2 for FDA-approved HT formulations).

[5] Contraindications to HT use include known or suspected breast or endometrial cancer, undiagnosed abnormal genital bleeding, CVD (including CHD, cerebrovascular disease, and thromboembolic disorders), and active liver or gallbladder disease. Relative contraindications include high-risk states for the above disorders. If alternative treatments for bothersome VMS are ineffective, HT may be appropriate for a woman with a relative contraindication, following a thorough assessment of potential risks and benefits.

HT is an appropriate option for most healthy woman with bothersome hot flashes. If she is under age 60 years or within 10 years of menopause, it is highly likely that benefits will outweigh risks. As with any therapy, HT should be used at the lowest effective dose for the duration necessary to meet treatment goals (20,76). **The need for continued HT use should be assessed at least annually. Although HT risks increase with advancing age and duration of use, long-term use may be appropriate for women with persistent hot flashes after thorough assessment of benefits and risks and shared decision making. As HT risks differ depending on formulation, dose, route of administration, and whether a progestin is needed, treatment should be individualized based on a woman's needs and preferences.**

SUMMARY

There are many options available to address the health and quality of life concerns of menopausal women. **The primary indication for HT is the alleviation of hot flashes and associated symptoms. Women should be informed of the potential risks and benefits of all therapeutic options. Care should be individualized based on a woman's medical history, needs, and preferences.**

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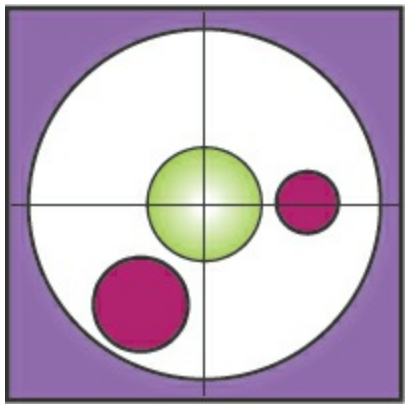
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CHAPTER 19

Benign Breast Disease



JoAnna L. Hunter-Squires, Carlie K. Thompson, Armando E. Giuliano

Evaluation
- History
- Physical Examination
  - *Inspection*
  - *Palpation*
- Breast Self-Examination
- Breast Imaging
  - *Mammography*
  - *Ultrasonography*
  - *Magnetic Resonance Imaging*

Breast Tissue Evaluation: Histology and Cytology
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Benign Breast Conditions

Breast Mass
- Fibrocystic Change
  - *Clinical Findings in Fibrocystic Disease*
  - *Differential Diagnosis*
  - *Diagnostic Tests*
  - *Cyst Fluid Analysis*
  - *Fibrocystic Change and Risk for Breast Cancer*
  - *Management of Fibrocystic Change*
- Fibroepithelial Lesions
  - *Fibroadenoma*
  - *Multiple Fibroadenomas*

Phyllodes Tumor
Fat Necrosis
Pain
Mastitis and Breast Abscess
Lactational Mastitis and Abscesses
Nonlactational Abscess
Subareolar Abscess and Lactiferous Duct Fistula
Granulomatous Mastitis
Mondor Disease
Mastalgia
Types of Mastalgia
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Macromastia
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Erosive Adenomatosis of the Nipple
Accessory Breast Tissue
Benign Mammographic Abnormalities
Diabetic Mastopathy/Lymphocytic Mastitis
Pseudoangiomatous Stromal Hyperplasia
Sclerosing Adenosis
Risk Lesions
Lobular Neoplasia
Atypical Ductal Hyperplasia
Radial Scars
Disorders of Breast Augmentation
Capsular Contracture
Rupture
Breast Implant–Associated Anaplastic Large Cell Lymphoma

KEY POINTS

1 Breast complaints are common, and the first priority in evaluation is to rule out malignancy and ensure concordance between physical examination, imaging, and pathology after a diagnosis has been reached.

2 Workup of a breast complaint includes a thorough history and physical, often accompanied by ultrasound, mammography in women over age 35 and, in some cases, biopsy and pathologic evaluation.

3 The most common benign breast problems include fibrocystic changes and mastalgia. These problems are usually best treated by reassurance. Pharmacologic agents are available but have side effects that usually are not well tolerated.

4 Histologic differences exist between fibroadenomas and phyllodes tumors; phyllodes tumors require excision, whereas small asymptomatic fibroadenomas can be observed if the diagnosis is confirmed by classic imaging findings or histologic assessment and there is no evidence of growth.

5 Breast abscesses are managed with aspiration and antibiotics; the use of incision and drainage is reserved for recurrence.

6 Spontaneous, unilateral, bloody discharge requires histologic evaluation to exclude malignancy, but

symptoms usually are caused by a benign process such as intraductal papilloma or duct ectasia.

7 Proliferative lesions such as ductal and lobular neoplasia represent an increased risk to the patient of subsequent diagnosis of breast cancer in either breast. Atypical lobular hyperplasia and lobular carcinoma in situ (LCIS) may be followed closely with repeat mammography and clinical examination, while atypical ductal hyperplasia (ADH) requires surgical excision because of the risk for concomitant cancer.

Benign breast diseases are among the most common diagnoses that the busy obstetrician-gynecologist will see in practice. An ability to accurately and promptly diagnose benign and malignant breast diseases is within the purview of the practicing gynecologist (1,2). Benign breast disease is a complex entity associated with a range of physiologic changes and clinical manifestations that have an impact on a woman's health independent of breast cancer risk (3). Patients may present with complaints ranging from pain to a palpable mass, skin or nipple changes, or, with increasing frequency, a mammographically-detected abnormality. Patients are often distressed regarding the possibility of cancer. Ultimately, the majority of breast complaints are benign conditions, and it is the practitioner's role to guide the patient through the process of excluding a malignancy, reaching a diagnosis, treating her symptoms, and managing future risk (4).

EVALUATION

History

Evaluation of a new breast symptom begins with a thorough clinical history. The history should include questions regarding current symptoms, duration of the condition, fluctuation of the signs and symptoms, and factors that aggravate or relieve the symptom. **[1] Assessment of breast problems should focus on the following points:**

- **Nipple discharge**
- **Characteristics of discharge (spontaneous or elicited, appearance, unilateral or bilateral, single or multiple duct involvement)**
- **Breast mass (size and change in size, density, or texture)**
- **Breast pain (cyclic versus continuous)**
- **Association of symptoms with menstrual cycle**
- **Change in breast shape, size, or texture**
- **Previous breast biopsies**
- **History of breast trauma**

The patient should be questioned about the following **risk factors for breast cancer** (see Chapter 42 for more details):

- **Increasing age (approximately 50% of breast cancers occur *after* age 65)**
- **Age of menarche less than 12 years of age**
- **Nulliparity or first pregnancy at greater than 30 years of age**
- **Late menopause (older than 55 years of age)**
- **Personal history of breast or other malignancies (ovary, colon, and prostate)**
- **Family history of breast cancer (especially in first-degree relatives who were premenopausal or had bilateral disease)**
- **Number of first-degree relatives with breast cancer and their ages when diagnosed**
- **Family history of male breast cancer**
- **Inherited conditions associated with a high risk for developing breast cancer, including *BRCA1* and *BRCA2* genes, Li-Fraumeni syndrome, PTEN hamartoma tumor syndrome (Cowden), hereditary diffuse gastric cancer syndrome, and Peutz–Jeghers syndrome**
- **Pathology of previous breast biopsy showing atypia or lobular carcinoma *in situ (LCIS)***
- **Hormone replacement therapy**
- **Alcohol consumption**
- **Postmenopausal weight gain**

Several clinical risk prediction models are readily available online. The most commonly used of these is the Breast Cancer Risk Assessment Tool or Gail Risk Assessment model from the National Cancer Institute (5). The Gail Risk Assessment model calculates the risk based on the patient's race, age, age of menarche, age of first live birth, number of first-degree relatives with breast cancer, number of previous breast biopsies, and presence of atypia on the biopsy. The Gail model likely underestimates the genetic contribution to risk and should not be used for patients with family members with breast, ovarian, tubal, or peritoneal cancer. Instead, the United States Preventative Services Task Force (USPSTF) recommends the use of either the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, or the Family History Screen 7 (6). Other useful risk calculators include BRCAPro and Tyrer–Cuzick (7,8).

While taking the clinical history, it is important to obtain a current list of medications used, including hormone replacement therapy and herbal medications such as phytoestrogens. The gestational history should take into consideration the possibility that the patient may be pregnant or has a prior history of miscarriage or abortion. A personal history of exposure to radiation, especially in the treatment of childhood malignancies, is associated with a higher incidence of developing breast cancer (9). The goal of breast evaluation is to determine clearly whether the symptom represents a

benign breast condition or may be indicative of a neoplastic process.

Physical Examination

[2] **Breast tumors, particularly malignant tumors, usually are asymptomatic and are discovered by the patient, physical examination, or screening mammography.** Typically, the breast changes slightly during the menstrual cycle. During the premenstrual phase, most women have increased innocuous nodularity and mild engorgement of the breast. Rarely these characteristics can obscure an underlying lesion and make examination difficult. Findings should be carefully documented in the medical record to serve as a baseline for future reference.

Inspection

Inspection is performed initially while the patient is seated comfortably with her arms relaxed at her sides. The breasts are compared for symmetry, contour, and skin appearance. Edema or erythema is identified easily, and skin dimpling or nipple retraction is shown by having the patient raise her arms above her head and then press her hands on her hips, thereby contracting the pectoralis muscles (Fig. 19-1). Palpable and even nonpalpable tumors that distort the Cooper ligaments may lead to skin dimpling with these maneuvers.

Palpation

[2] **While the patient is seated, each breast should be palpated methodically.** Some physicians recommend palpating the breast in long strips, but the exact palpation technique used is probably not as important as the thoroughness of its application over the entire breast. One very effective method is to palpate the breast in enlarging concentric circles until the entire breast is covered. A pendulous breast can be palpated by placing one hand beneath the breast and gently palpating the breast between both examining hands with the patient still seated. The axillary and supraclavicular areas should be palpated for enlarged lymph nodes. The entire axilla, the upper outer quadrant of the breast, and the axillary tail of Spence are palpated for possible masses. [2] **While the patient is supine with one arm over her head, the ipsilateral breast is again methodically palpated from the clavicle to the costal margin and from the sternum to the latissimus dorsi laterally.** If the breast is large, a pillow or towel may be placed beneath the scapula to elevate the side being examined; otherwise, the breast tends to fall to the side, making palpation of the lateral hemisphere more difficult. The major features to be identified on palpation of the breast are temperature, texture and thickness of skin, generalized or focal tenderness, nodularity, density, asymmetry, dominant masses, and nipple discharge. Most premenopausal patients have normally nodular breast parenchyma. The nodularity is diffuse but predominantly in the upper outer quadrants, where there is more breast tissue. These benign parenchymal nodules are

small, similar in size, and indistinct. By comparison, breast cancer usually occurs in the form of a nontender, firm mass with irregular margins. A cancerous mass feels distinctly different from the surrounding nodularity. A malignant mass may be fixed to the skin or to the underlying fascia. A suspicious mass is usually unilateral. Similar findings in both breasts are unlikely to represent malignant disease (3).

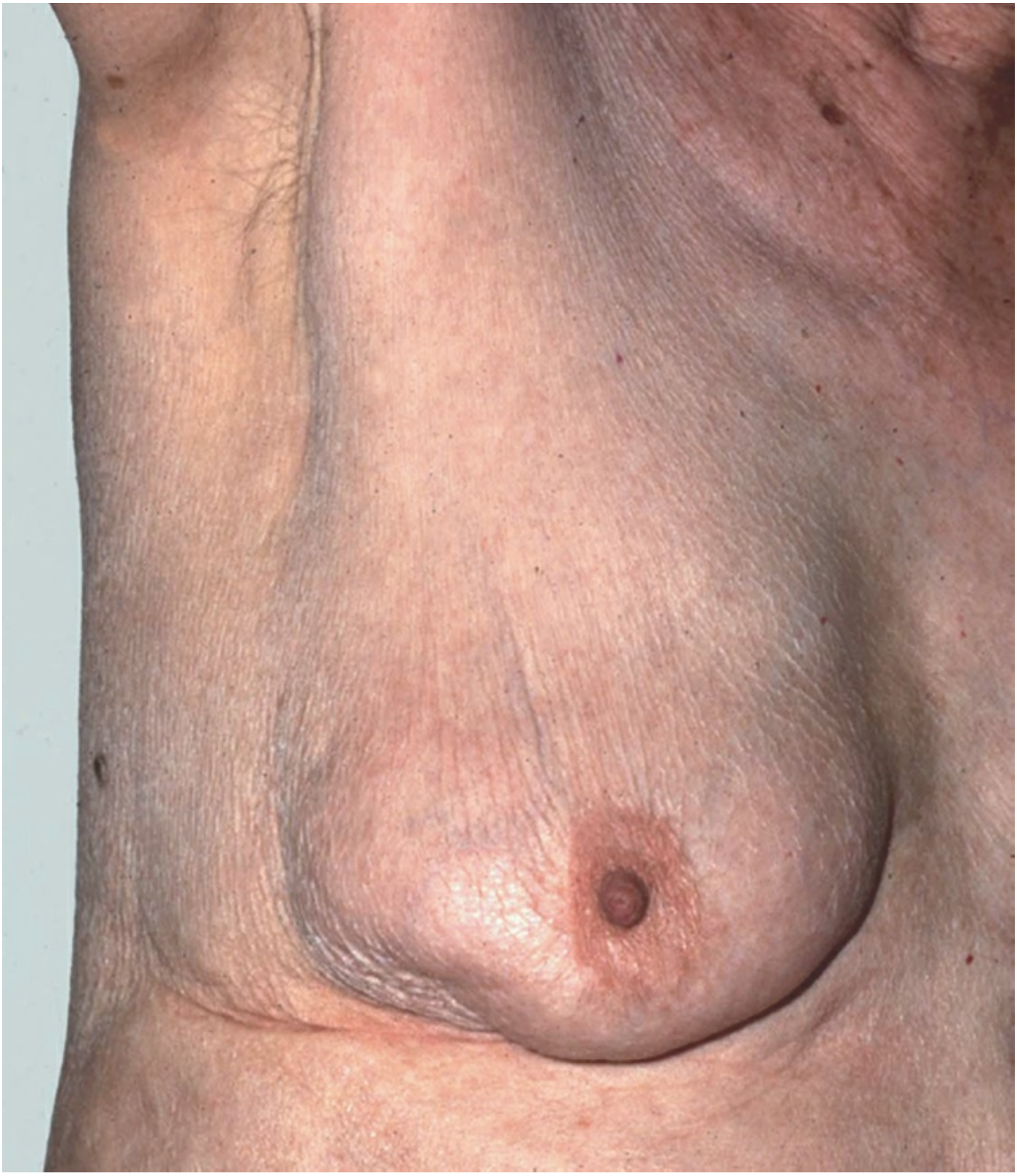


FIGURE 19-1 Raising the arm reveals retraction of the skin of the lower outer quadrant caused by a small palpable carcinoma. (From Giuliano **AE, Dang** CM. Breast disease. In: Berek JS, Hacker NF, eds. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2014:650.)

Breast Self-Examination

Breast self-examination (BSE) may help some women but is no longer recommended for the average-risk patient. BSE is associated with no improvement in breast cancer survival and increases biopsies for ultimately benign lesions (10). In patients wishing to do BSE, they should be educated regarding the natural cyclic changes of the breast and instructed to examine their breasts at the same time during each menstrual cycle. Premenopausal women who wish to perform BSE should examine their breasts monthly 7 to 10 days after the onset of the menstrual cycle. For postmenopausal women, selection of a specific calendar date is a helpful way to remember to perform a monthly BSE. Women should be instructed to report any abnormalities or changes to their physicians. If the physician cannot confirm the patient's findings, the examination should be repeated in 1 month or after her next menstrual period (11).

The following seven "P's" represent the essential components of breast examination:

- **Positions**
- **Palpation**
- **Pads of fingers for palpation**
- **Pressure**
- **Perimeter**
- **Pattern of search**
- **Patient education**

The woman should inspect her breasts while standing or sitting before a mirror, looking for any asymmetry, skin dimpling, or nipple retraction. Elevating her arms over her head or pressing her hands against her hips to contract the pectoralis muscles will highlight any skin dimpling. Finally, the woman should examine her breasts while bending over and leaning forward. While standing or sitting, she should carefully palpate her breasts with the fingers of the opposite hand. She should lie down and again palpate each quadrant of the breast as well as the axilla using the pads of the three middle fingers with three pressures—light, medium, and deep—covering the entire breast from the clavicle to the inframammary fold, from the sternum to the latissimus dorsi laterally. The area within the perimeter of the breast should be palpated, preferably using an up-and-down method called the vertical stripe, rather than the concentric circular or radial methods, in which the edges of the breast tissue often are omitted. Many women feel anxious about performing breast examination (12). The examination may be performed while showering; soap and water may increase the sensitivity of palpation, and the privacy of the shower may provide a less anxiety-

provoking environment.

Breast Imaging

Mammography

[2] Mammography remains the gold standard for screening for breast cancer. It is an excellent screening test and its sensitivity usually increases with age as does cancer incidence (13). Full-field digital mammography (FFDM), which records mammographic images on a computer, is a modification of the older screen-film mammography and has become standard in many centers. This technology has allowed many conveniences including the ability to manipulate a computerized image for optimal viewing and access to distant consultations through telemammography. Radiation exposure is less with digital than with conventional film mammography. Digital mammography has demonstrated superior sensitivity, but lower specificity for women with dense breasts and those aged 40 to 49 years at the expense of increased costs and more false-positive results (14).

Tomosynthesis, or three-dimensional (3D) mammography, is another breast imaging technique used in conjunction with standard mammography to improve the sensitivity of screening. This technique uses a moving x-ray source to collect 3D volumetric data and reconstruct thin sections of the breast. In tomosynthesis, increased lesion detection comes at the expense of increased radiation exposure (15). In prospective trials, tomosynthesis plus mammography resulted in a cancer detection rate of 8.0 to 8.8 per 1,000 screens versus 6.1 to 6.3 per 1,000 for mammography alone (15–17). Tomosynthesis has the theoretical advantage of eliminating false positives that occur as a result of superimposition of compressed breast tissue in standard mammography. This was supported by retrospective data, but thus far has failed to be consistently supported in prospective trials. Tomosynthesis does decrease the need to call patients back for additional views (18).

[2] Compression of the breast is necessary to obtain good mammographic images, and patients should be forewarned that breast compression is uncomfortable. With good technique and well-maintained modern equipment, exposure to radiation can be limited. FFDM has a 22% lower mean glandular radiation dose than film-screen mammography per acquired view. FFDM delivers 1.86 mGy average breast radiation dose per view compared to 2.37 mGy for film screen, while tomosynthesis delivers twice the dose of digital mammography on average (19,20).

[2] Slow-growing breast cancers can be identified by mammography at least 2 years before the mass reaches a size detectable by palpation. These tumors have a less aggressive biologic behavior than interval breast cancers (19–21). Mammography is the only reproducible method of detecting nonpalpable breast cancer, but its use

depends on the availability of state-of-the-art equipment and a dedicated breast radiologist.

This desire for supplemental screening modalities coupled with concerns about radiation exposure have prompted some centers to adopt whole-breast ultrasound screening programs using either handheld probes or automated systems wherein an automated transducer is used to acquire standardized images (22). These adjuncts can detect mammographically occult breast cancers, again at the risk of increased false-positive findings, leading to unnecessary core needle biopsy (CNB) (22,23).

Indications for Mammography

[2] The indications for mammography are as follows:

1. **To establish a baseline breast mammogram and reevaluate patients at regular intervals to diagnose a potentially curable breast cancer before it has been diagnosed clinically.**
2. **To screen women who are at high risk for developing breast cancer.**
3. **To evaluate a questionable or ill-defined breast mass or other suspicious change in the breast that is detected by clinical breast examination.**
4. **To search for occult breast cancer in a patient with metastatic disease in axillary nodes or elsewhere from an unknown primary origin.**
5. **To screen for unsuspected cancer before cosmetic operations or biopsy of a mass.**
6. **To monitor breast cancer patients who were treated with a breast-conserving surgery and radiation.**

Mammographic Abnormalities

A mammographic abnormality includes a mass (solid or cystic), microcalcifications (benign, indeterminate, or suspicious), asymmetric density, architectural distortion, and appearance of a new density. **[2] There are eight morphologic categories of mammographic abnormalities** (24)**:**

1. **Calcification distribution**
2. **Number of calcifications**
3. **Description of calcifications**
4. **Mass margin**
5. **Shape of mass**
6. **Density of mass**
7. **Associated findings**
8. **Special cases**

Mammographic abnormalities should be visible on two views, usually craniocaudal (CC) and mediolateral oblique (MLO). The lesion should triangulate to the same location on those two views. Calcifications can be macrocalcifications, which are coarse and usually represent benign degenerative breast conditions. Calcifications associated with breast cancer are clustered, pleomorphic microcalcifications; typically, five to eight or more calcifications are aggregated in one part of the breast (25). These calcifications may be associated with a mammographic mass density. A mass density may appear without evidence of calcifications. It can represent a cyst, benign tumor, or a malignancy. A malignant density usually has irregular or ill-defined borders and may lead to architectural distortion, which may be subtle and difficult to detect in a dense breast. Other mammographic findings suggesting breast cancer are architectural distortion, asymmetric density, skin thickening or retraction, or nipple retraction. Examples of mammographic abnormalities can be found in several electronic sources (26).

Mammographic Reports

The American College of Radiology recommended the **[2] Breast Imaging Reporting and Data System (BI-RADS)** as a standardized scheme for describing mammographic lesions. In the BI-RADS system, there are six categories for mammographic findings (other than incomplete) (24).

1. **Incomplete, needs further imaging**
2. **Negative**
3. **Benign finding**
4. **Probably benign, short-interval follow-up recommended**
5. **Suspicious finding and biopsy should be performed**
6. **Highly suggestive of malignancy and appropriate action should be undertaken**
7. **Known malignancy**

The patient should be referred for tissue diagnosis if the report identifies a lesion as a category 4 or 5 (20). A category 0 indicates incomplete evaluation, and further diagnostic studies are required. **Category 3 connotes a finding that is most likely benign; a short-interval follow-up is recommended, and breast examination by an expert should be considered.**

Correlation of Findings

[2] Biopsy must be performed on patients with a dominant or suspicious mass despite absence of mammographic findings (23). Mammography should be performed before biopsy so other suspicious areas can be noted and the contralateral breast can be checked **(Fig. 19-2)**. **Mammography is never a substitute for biopsy because it may**

not reveal clinical cancer, especially when it occurs in the dense breast tissue of young women with fibrocystic changes. The sensitivity of mammography is approximately 80%, with a specificity of 80% to 95% depending on the expertise of the radiologist interpreting the study and patient factors including breast density, patient age, use of hormone therapy, and the size, location, and mammographic appearance of the tumor (27). **Mammography is less sensitive in young women with dense breast tissue than in older women, who tend to have fatty breasts** (28). Small tumors, particularly those without calcifications, are more difficult to detect, especially in women with dense breasts.

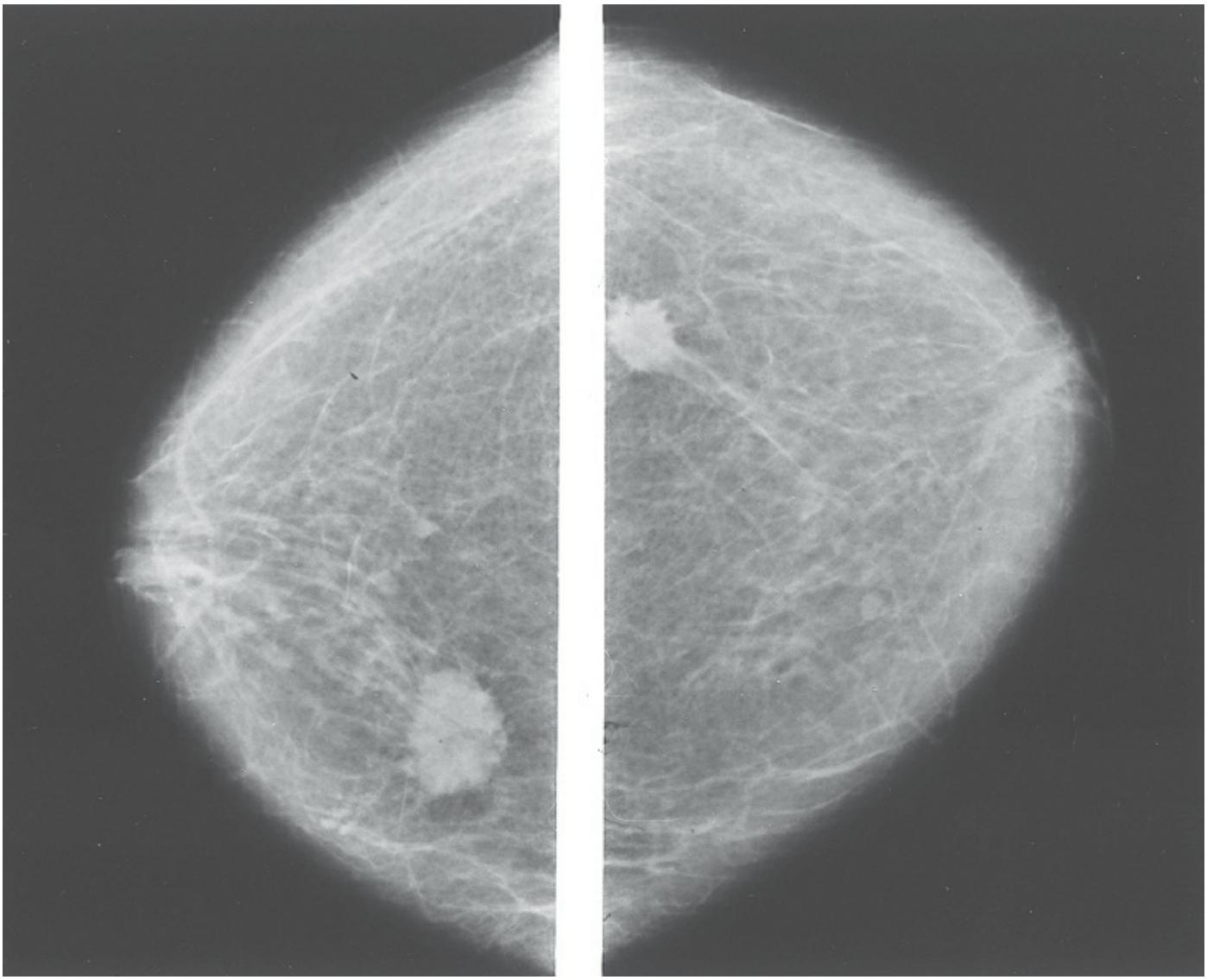


FIGURE 19-2 Bilateral mammography shows the extent of breast carcinoma, illustrating the importance of bilateral mammography in the workup of a clinically apparent mass. (From Giuliano AE**, Dang** CM. Breast disease. In: Berek JS, Hacker NF, eds. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2014:652.)

Ultrasonography

Breast ultrasonography is frequently used for focused scanning of a palpable lesion or mammographic finding (29). Reliable, portable, computer-enhanced ultrasonography with high-frequency transducers and improved imaging is available to evaluate and treat problems of the breast. It is a sensitive, minimally invasive technique that is used frequently to evaluate some breast symptoms, especially in younger women with dense breast tissue, but is dependent on the availability of a skilled ultrasonographer (29). Some lesions can be detected only with ultrasonography (23). It is the preferred modality to distinguish a solid from a cystic mass (29). Breast ultrasonography may be used as an adjunct for screening in women with dense breasts (30). Ultrasonography has a higher false-positive rate than mammography (22,30).

[2] Following are indications for breast ultrasonography:

- **Palpable abnormality**
- **Ambiguous mammographic findings**
- **Silicone leak**
- **Mass in woman younger than 30 years, lactating, or pregnant**
- **Guidance for interventional procedures**
- **Possible role for additional imaging in high-risk individuals**

Ultrasonography is useful in distinguishing benign from malignant lesions identified by mammography (29). Ultrasonography may be especially useful if the patient feels a mass, but the physician cannot detect an abnormality and the mammogram does not disclose one. It may identify cancers in the dense breast tissue of premenopausal women, but it is usually used to distinguish a benign cyst from a solid tumor. **Ultrasonography cannot reliably detect microcalcifications, and it is not as useful as mammography in assessing women with fatty breasts.**

[2] Handheld or real-time ultrasonography is very accurate in differentiating solid masses from cysts (31). If a lesion proves to be a simple cyst, no further evaluation is necessary. If the simple cyst is symptomatic, aspiration may be performed. Rarely ultrasonography may identify a small cancer within a cyst, an intracystic carcinoma. These complex cysts warrant surgical biopsy.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an appealing technique for imaging the breast because it is highly sensitive and does not utilize ionizing radiation. Several roles have been proposed for the use of breast MRI, but relatively few of these are clearly supported by the literature (32).

It has been suggested that MRI may be useful for further workup of inconclusive findings on mammography and ultrasonography (33). Gadolinium enhancement on breast MRI is associated with breast cancer, but has varying degrees of specificity (32).

Enhancement patterns are known to vary with the menstrual cycle and some noncancerous masses enhance with gadolinium (33).

[2] The National Comprehensive Cancer Network has recommended the addition of annual MRI screening for patients with >20% lifetime risk of breast cancer to routine mammographic screening (34). Screening MRI is not recommended for women with average risk of breast cancer. In retrospective studies of the high-risk population, 10 cancers are identified per 1,000 women screened, 70% of which are seen on MRI only (35). MRI screening has a sensitivity of greater than 90%, but a specificity of 60%, resulting in fivefold the number of biopsies and 10-fold the callback rate for a 6-month follow-up study (BI-RADS category 3 assessment) of mammographic screening alone (35,36). In prospective studies, 10-year survival is not improved, but fewer cancers detected on MRI are lymph node–positive compared to mammography with no additional screening (36). This finding has led to the hypothesis that earlier diagnosis in this population leads to improved quality of life by allowing less radical therapy.

Routine preoperative evaluation of patients diagnosed with breast cancer is a common practice that is not evidence based (37). Several large meta-analyses have demonstrated no oncologic benefit to routine preoperative MRI (38–40). These studies demonstrate no difference in disease-free survival, or local or distant recurrence, but do show increased rates of biopsy, mastectomy, overall number of surgical procedures, and cost (38–40). **[2] Routine preoperative breast MRI in patients diagnosed with breast cancer is not necessary.**

Breast MRI is commonly used to evaluate the in-breast response to neoadjuvant chemotherapy (NAC) (41). MRI enhancement does correlate with the extent of disease found at evaluation of the surgical specimen, but less frequently influences clinical decision making. In a study of 60 patients who received NAC in an attempt to allow breast conservation, mammographic findings and patient preference determined the decision for or against breast conserving surgery despite a favorable post-NAC MRI (41). No patient initially felt to require downstaging was denied breast conserving treatment on the basis of post-NAC MRI, and of those electing to undergo lumpectomy, 91% were successful (41).

One case in which pre-operative MRI clearly benefits patients is that of a woman presenting with breast cancer with axillary metastasis and no identifiable primary tumor. **[2] Breast MRI identifies a mammographically occult primary breast cancer in patients presenting with axillary metastasis in two-thirds of patients,** thus allowing breast conserving surgery (42).

MRI is extremely useful in identifying silicone released by ruptured breast implants in patients with augmented breasts **(Fig. 19-3)**. One interesting trial in which 208 asymptomatic women underwent breast MRI prior to scheduled explantation of recalled silicone breast implants, showed a sensitivity and specificity of 93% and a negative

predictive value of 98% (43). In practice, **breast MRI may be used reliably to rule out implant rupture.**

BREAST TISSUE EVALUATION: HISTOLOGY AND CYTOLOGY

The safest course is tissue biopsy evaluation of all dominant masses found on physical examination and, in the absence of a mass, evaluation of suspicious lesions shown by breast imaging. Over 1 million women have breast biopsies each year in the United States. Between 70% and 80% of these biopsies yield a benign lesion (44). **The diagnosis of a benign breast lesion versus breast cancer is often difficult to determine based on clinical examination and requires evaluation of tissue by core CNB.** The sensitivity of CNB performed using either stereotactic or ultrasound guidance is greater than 95% (45). **Fine-needle aspiration cytology is an alternative to CNB, which allows cytologic evaluation at about one-tenth the cost** of CNB and remains useful in health systems where the cost of CNB and pathologic analysis is prohibitive. The main limitations of FNA are high rate of insufficient sampling, inability to distinguish invasive from noninvasive cancers and insufficient tissue for immunohistochemistry staining to determine hormone receptor and HER2 status (46). CNB has replaced FNA and surgical biopsy as the diagnostic procedure of choice for evaluation of a breast mass (47,48). CNBs can be performed with mammographic or stereotactic, ultrasound or MRI guidance.



FIGURE 19-3 Mammography shows implant and extracapsular free silicone (*arrow*).

[2] About 30% of lesions suspected to be cancer prove to be benign on biopsy, and about 15% of lesions believed to be benign prove to be malignant (19). **Dominant masses or suspicious nonpalpable breast lesions require pathologic examination.** In

most cases, pathologic diagnosis should be obtained before the decision is made to monitor a breast mass (49). An exception may be a premenopausal woman with a nonsuspicious mass presumed to be fibrocystic disease or a fibroadenoma with classical imaging findings. **An apparently fibrocystic lesion that does not completely resolve within several menstrual cycles may be sampled for biopsy. Any mass in a postmenopausal woman who is not taking estrogen therapy should be presumed to be malignant.** When the results of the clinical diagnosis, breast imaging studies, and pathology are all in agreement, the workup is complete and treatment and follow-up planning may be initiated. **Figures 19-4 and 19-5 present algorithms for management of breast masses in premenopausal and postmenopausal patients**. Simultaneous evaluation of a breast mass using clinical breast examination, radiography, and needle biopsy can lower the risk of missing cancer to only 1%, effectively reducing the rate of diagnostic failure and increasing the quality of patient care (48).

[2] If the presence of breast cancer is strongly suggested by physical examination, the diagnosis can be confirmed by CNB, and the patient may be counseled regarding treatment. Treatment should not be determined based on results of physical examination and mammography alone, in the absence of biopsy results. The most reasonable approach to the diagnosis and treatment of breast cancer is outpatient CNB, followed by definitive operation at a later date if needed. Routine operative surgical biopsies are of historical interest only and should not be performed. The pathologic data obtained by CNB contributes to appropriate consideration of neoadjuvant therapies and allows patients to adjust to the diagnosis of cancer, carefully consider therapeutic options, and seek a second opinion (46,47). In cases of indeterminate diagnoses on CNB, surgical excision remains useful to clarify diagnosis and rule out coexistent malignancy.

Core Needle Biopsy

[2] The interpretation of results from CNB is classified by categories B1 to B5 (50):

B1: Normal tissue
B2: Benign lesions: fibroadenomas, fibrocystic change, sclerosing adenosis, duct ectasia, fat necrosis, abscess
B3: Uncertain malignant potential: atypical epithelial hyperplasia, lobular neoplasia, phyllodes tumor, papillary lesions, radial scar, complex sclerosing lesions
B4: Suspicious
B5: Malignant

Histologic Analysis

Histologic evaluation with hematoxylin and eosin (H&E) staining confirms benign or malignant disease. Images of benign and malignant breast lesions can be viewed through the Internet Pathology Laboratory for Medical Education (51).

BENIGN BREAST CONDITIONS

Benign breast disorders account for most breast problems. These conditions are frequently considered in the context of excluding breast cancer and often are unrecognized for their own associated morbidity (3). To provide appropriate management, it is important to consider benign breast disorders from four aspects: (i) clinical picture, (ii) medical significance, (iii) treatment intervention, and (iv) pathologic etiology (3). A framework for understanding benign breast problems is called Aberrations of Normal Development and Involution (ANDI) (52,53). It includes symptoms, histology, endocrine state, and pathogenesis in a progression from a normal to a disease state. Most benign breast conditions arise from normal changes in breast development, hormone cycling, and reproductive evolution (52).

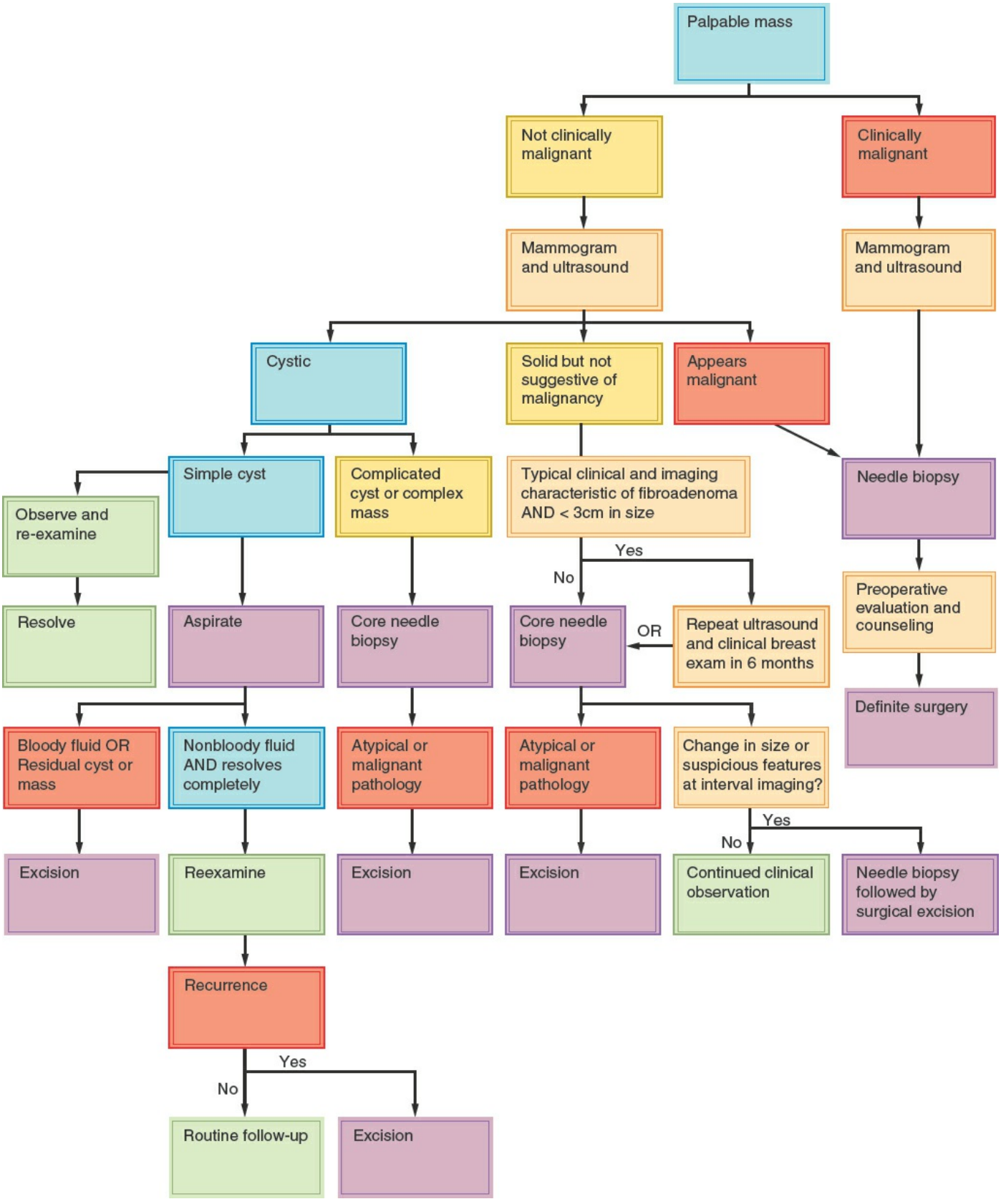


FIGURE 19-4 Algorithm for management of breast masses in premenopausal women.

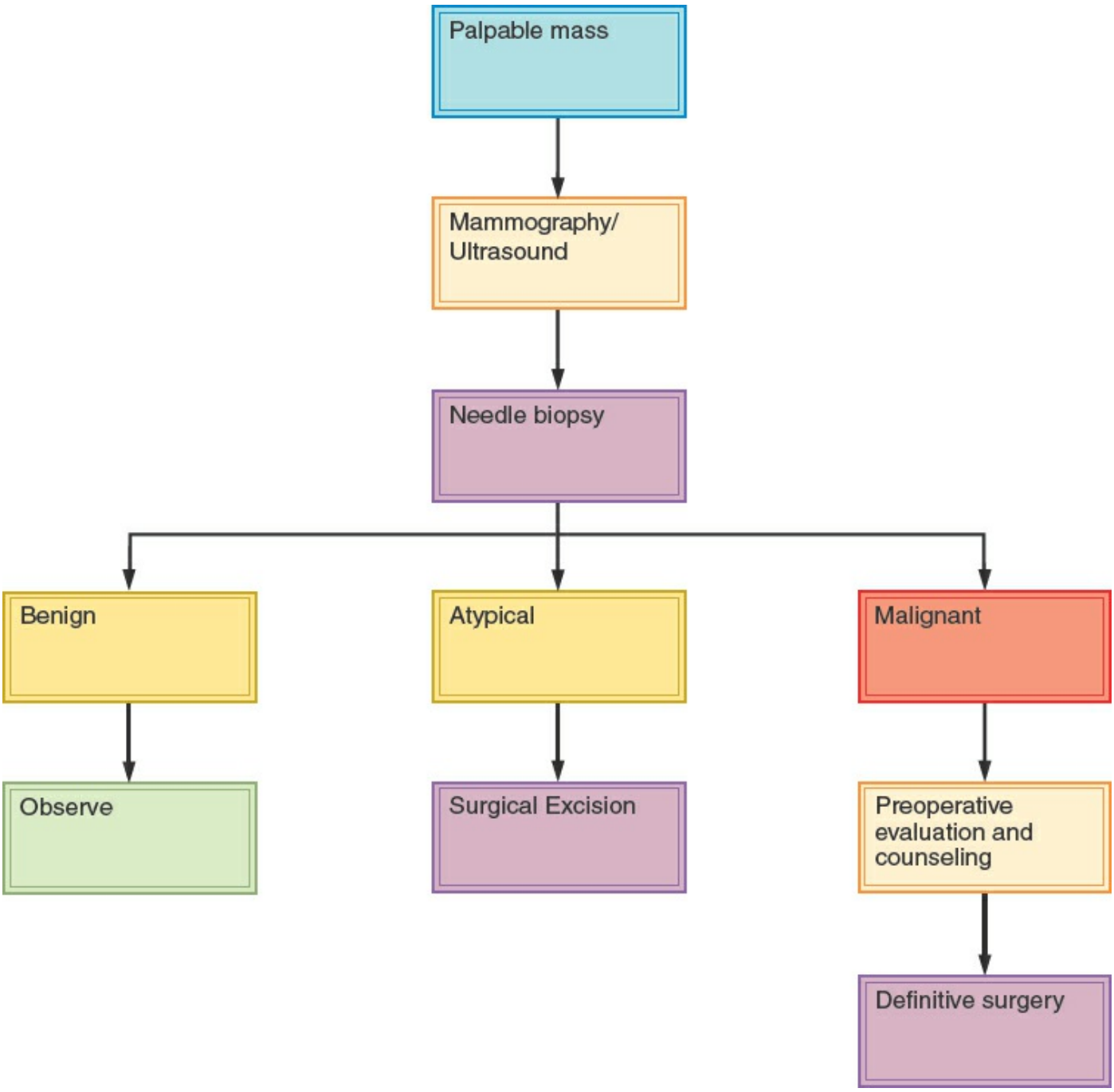


FIGURE 19-5 Algorithm for management of breast masses in postmenopausal women.

[3] Three life cycles reflect different reproductive phases in a woman's life and are associated with unique breast manifestations.

1. **During the early reproductive period (15 to 25 years), lobule and stromal formation occurs.** The ANDI conditions associated with this period are fibroadenoma (mass) and juvenile hypertrophy (excessive breast development). In this first stage, the progression from ANDI to a disease state results in the formation of giant fibroadenomas and multiple fibroadenomas.

2. **During the mature reproductive period (25 to 40 years), cyclic hormonal changes affect glandular tissue and stroma.** In this second period, the ANDI is an exaggeration of these cyclic effects, such as cyclic mastalgia and generalized nodularity.
3. **The third phase is involution of lobules and ducts or turnover of epithelia, which occurs during ages 35 to 55 years.** The ANDI associated with lobular involution are macrocysts (lumps) and sclerosing lesions (mammographic abnormalities). Those associated with ductal involution are duct dilation (nipple discharge) and periductal fibrosis (nipple retraction), and those with epithelial turnover are mild hyperplasia (pathologic description).

Disease conditions with increased epithelial turnover are epithelial hyperplasias with atypia. Breasts are under endocrine control and show a wide range of appearances during reproductive life. ANDI classification allows the clinician to understand the pathogenesis of these conditions and to understand that these disorders are aberrations of a normal process that does not usually require any specific treatment (53).

BREAST MASS

Fibrocystic Change

[3] **Fibrocystic change, the most common lesion of the breast, is an imprecise term that covers a spectrum of clinical signs, symptoms, and histologic changes** (52). The term refers to a histologic picture of fibrosis, cyst formation, and epithelial hyperplasia. Cysts arise from the breast lobules and are an aberration of normal breast involution (53). Macroscopic cysts occur in approximately 7% of women, and microscopic, nonpalpable cysts occur in about 40% of women (54). It is common in women 35 to 55 years of age, but rare in postmenopausal women not taking hormone therapy. The presence of estrogen seems necessary for the clinical symptoms to occur. This finding is supported by the observation that it is present bilaterally, increased in the perimenopausal age group, and responsive to endocrine therapy (55). In essence, a diagnosis of fibrocystic change can lead to significant patient anxiety but is of little clinical significance as long as malignancy is excluded (3). These lesions are associated with benign changes in the breast epithelium and patients with this entity should be reassured.

Clinical Findings in Fibrocystic Disease

[3] **Fibrocystic changes may produce an asymptomatic mass that is smooth, mobile, and potentially compressible. Fibrocystic change is more often accompanied by pain or tenderness and sometimes nipple discharge. In many cases, discomfort coincides with the premenstrual phase of the cycle, when the cysts tend to enlarge.**

Fluctuations in size and rapid appearance or disappearance of a breast mass are common. Multiple or bilateral masses appear frequently, and many patients have a history of a transient mass in the breast or cyclic breast pain. Cyclic breast pain is the most commonly associated symptom of fibrocystic changes.

Differential Diagnosis

Pain, fluctuation in size, multiplicity of lesions, and bilaterality are the features most helpful to differentiate fibrocystic disease from carcinoma. If a dominant mass is present, the diagnosis of cancer should be suspected until it is disproved by complete aspiration of a cyst, or pathologic analysis by CNB if a mass is present after aspiration. Microscopic findings associated with fibrocystic disease include cysts (gross and microscopic), papillomatosis, adenosis, fibrosis, and ductal epithelial hyperplasia (3).

Diagnostic Tests

[3] **Patients with cystic disease may have a discrete fibrocystic mass that is frequently indistinguishable from carcinoma, based on clinical findings.** Mammography may be helpful, but there are no mammographic signs diagnostic of fibrocystic change. Ultrasonography is useful in differentiating a cystic from a solid mass. **Characteristic findings on ultrasonography that confirm a simple cyst include the following:**

- **Mass with thin walls**
- **Smooth round shape**
- **Absence of internal echoes**
- **Posterior acoustic enhancement**

If these imaging criteria are not met, a tissue diagnosis of the mass, by CNB, is required. The finding of a simple cyst by ultrasonography rules out carcinoma. **Any lesion that is suspicious by mammography or ultrasonography should be biopsied.** When the diagnosis of fibrocystic change is established by ultrasonography, aspiration of a cyst is indicated **only** if the patient is symptomatic **or** the cyst obscures visualization of breast tissue on mammography and prevents adequate imaging. Aspiration may be performed with ultrasonographic guidance, but image guidance may not be absolutely necessary when the cyst is palpable (56). Aspiration of a cyst is a minimally invasive procedure performed with a 21- or 22-gauge needle without local anesthesia and is not associated with significant risks or complications. There is minimal pain and little risk for infection or bleeding. Benign cyst fluid is straw colored to dark green to brownish and does not need to be submitted for cytologic evaluation (57). The patient should be reexamined at a short interval thereafter for cyst recurrence. Cysts will reoccur in one-third of patients, cause anxiety, and require repeated

evaluations. **[3] Tissue biopsy should be performed in the presence of the following findings** (54–59):

- **No cyst fluid is obtained.**
- **The fluid is bloody.**
- **The fluid is thick.**
- **The cyst is complex.**
- **There is an intracystic mass.**
- **A mass persists after aspiration.**
- **A persistent mass is noted at any time during follow-up.**

If a needle biopsy is performed and results are negative for malignancy, a suspicious mass that does not resolve at short-interval follow-up imaging should be excised (56). Surgery should be conservative, because the primary objective is to exclude cancer. Simple mastectomy or extensive removal of breast tissue is not indicated for fibrocystic disease. Most patients do not require treatment for fibrocystic changes, just reassurance that fibrocystic change is a transient phenomenon of aging that is associated with hormonal effects on the breast glandular tissue that eventually subsides.

Cyst Fluid Analysis

Investigators have examined the electrolyte and protein content of cyst fluid, but this is of little significance in the clinical management of fibrocystic disease. The potassium-to-sodium ratio is a marker that may be used to distinguish cyst subtypes (60). Cysts are either secretive, lined by an apocrine epithelium with a high potassium-to-sodium ratio and a higher hormone or steroid concentration (type I); or transudative, lined by flattened lobule epithelium with a low potassium-to-sodium ratio and a higher concentration of albumin, carcinoembryonic antigen, CA125, and steroid hormone–binding globulin (type II) (60). Apocrine cysts produce and secrete large amounts of prostate-specific antigen (PSA) (61). The role of this serine protease in proliferative breast disease is not fully understood.

Fibrocystic Change and Risk for Breast Cancer

[3] Fibrocystic change is not associated with an increased risk of breast cancer unless there is histologic evidence of epithelial proliferative changes, with or without atypia (62). The common coincidence of fibrocystic disease and malignancy in the same breast reflects the fact that both processes are common events. Approximately 80% of biopsies show fibrocystic changes. In an evaluation of the relationship between fibrocystic change and breast cancer in 10,366 women who underwent biopsy between 1950 and 1968 and were followed for a median of 17 years, approximately 70% of the

biopsies showed nonproliferative breast disease, whereas 30% showed proliferative breast disease (62). Cytologic atypia were present in 3.6% of cases. Women with nonproliferative disease had no increased risk of breast cancer, whereas women with proliferative breast disease and no atypical hyperplasia had a twofold higher risk of breast cancer. **[6] Patients whose biopsy results showed atypical ductal or lobular hyperplasia had an approximately fivefold higher risk than women with nonproliferative disease to develop invasive breast cancer in either breast.** Patients with carcinoma *in situ* have an 8- to 10-fold risk of developing breast cancer. This risk is bilateral for lobular lesions and ipsilateral for ductal lesions. A family history of breast cancer added little risk for women with nonproliferative disease, but family history plus atypia increased breast cancer risk by 11-fold. The presence of cysts alone did not increase the risk of breast cancer, but cysts combined with a family history of breast cancer increased the risk about threefold (62). Women with these risk factors (family history of breast cancer and proliferative breast disease) should be followed carefully with physical examination and mammography. For such women, age-specific probability of developing invasive breast carcinoma in the next 10 years is 1 in 2,000 (age 20), 1 in 256 (age 30), 1 in 67 (age 40), 1 in 39 (age 50), and 1 in 29 (age 60) (62). The relative risk for developing breast cancer depends on the type of proliferative lesion diagnosed.

Management of Fibrocystic Change

[3] Fibrocystic change is a normal evolutionary change in breast development and involution and does not require a specific treatment other than a good clinical breast examination and age-appropriate mammographic screening or imaging studies directed to signs and symptoms. A number of nutritional and dietary supplements have been investigated to relieve symptoms. The role of caffeine consumption in the aggravation of fibrocystic change is controversial (63,64). Results of some studies suggest that eliminating caffeine from the diet is associated with improvement of symptoms. Many patients are aware of these studies and report relief of symptoms after discontinuing intake of coffee, tea, and chocolate. Vitamin E and B_6 supplementation have been suggested as possible treatments given the biochemical changes observed in fibrocystic breast tissue with direct administration (65). Observations about the clinical effects of these vitamins are difficult to confirm and are anecdotal (66). Investigations of nutritional interventions for fibrocystic breast conditions have had insufficient data to draw clear conclusions about their effectiveness (67). Exacerbations of pain, tenderness, and cyst formation may occur at any time until menopause, when symptoms usually subside, unless patients are taking *estrogen.* Patients with symptoms of pain that significantly diminish the quality of life may consider hormonal therapies for mastalgia (68).

Fibroepithelial Lesions

Fibroadenoma

[4] **Fibroadenomas are the most common benign tumors of the breast.** They usually occur in young women (age 20 to 35 years) and may occur in teenagers (69,70). In women younger than 25 years, fibroadenomas are more common than cysts. They rarely occur after menopause, although occasionally they are found, often calcified, in postmenopausal women (71). For this reason, it is postulated that fibroadenomas are responsive to estrogen stimulation. Fibroadenomas may appear as single masses or as multiple lesions.

Clinically, a young woman usually notices a mass while showering or dressing. Most masses are 1 to 3 cm in diameter when detected, but they can become extremely large (i.e., the giant fibroadenoma). On physical examination, they are firm, smooth, and rubbery. They do not elicit an inflammatory reaction, are freely mobile, and cause no dimpling of the skin or nipple retraction. They are often bilobed, and a groove can be palpated on examination. On mammographic and ultrasonographic imaging, the typical features are of a well-defined, smooth, oblong, solid mass with clearly defined margins.

[4] **Fibroadenoma is not associated with an increased risk for breast cancer** (3). The natural history of fibroadenoma can be regression, growth, or no change in size. Most fibroadenomas are static or cease growth at approximately 2 to 3 cm, about 15% of tumors regress spontaneously, and only 5% to 10% progress (72). A fibroadenoma that is classic on imaging need not be biopsied, but should be followed with short-interval repeat imaging to document stability. Because cancer occurring in a fibroadenoma is rare and regression is frequent, management recommendations are conservative unless there is evidence of growth (34). Rarely will the fibroadenoma increase to more than 2 to 3 cm in size. Large or growing fibroadenomas must be excised to exclude carcinoma or phyllodes tumor. Complete excision of a fibroadenoma with local anesthesia can be performed to treat the lesion and confirm the absence of malignancy. Less invasive local treatment of a fibroadenoma is advocated by some and can be performed with either ultrasonographically guided percutaneous vacuum-assisted biopsy devices or percutaneous cryoablation (73).

On gross examination of an excised mass, the fibroadenoma appears encapsulated and sharply delineated from the surrounding breast parenchyma. Microscopically, there is proliferation of the epithelial and stromal component. In longstanding lesions and in postmenopausal patients, calcifications may be observed within the stroma.

Multiple Fibroadenomas

Multiple fibroadenomas occur in some women and were reported to occur more frequently in premenopausal women undergoing immunosuppression for organ transplantation (74).

Phyllodes Tumor

[4] Phyllodes tumors are rare fibroepithelial tumors that display a spectrum of clinical and pathologic behaviors that may be either benign, borderline, or malignant (75). The majority of phyllodes **tumors are benign (60%), with fewer being malignant (20%) and borderline lesions (20%)** (76). Variation in histologic interpretation may influence these rates (71). Phyllodes tumors may occur at any age but tend to be more common in women who are in their late 30s, 40s, and 50s (76). **These lesions are rarely bilateral and usually appear as isolated masses that are difficult to distinguish clinically from a fibroadenoma.** Patients often relate a long history of a previously stable nodule that suddenly increases in size. Reported sizes range from 1 to 50 cm (77). Size is not a dependable on the diagnostic criterion, although phyllodes tumors tend to be larger than fibroadenomas, probably because of their rapid growth. There are no good clinical criteria by which to distinguish a phyllodes tumor from a fibroadenoma. Whereas observation of a fibroadenoma is acceptable, excision of a phyllodes tumor is necessary for local control and for determination of benign or malignant features. To avoid unnecessary excision of benign fibroadenomas that are indistinguishable from phyllodes tumors on clinical examination, imaging criteria were sought to aid in identifying patients who require EB for complete histopathologic evaluation and local control. Mammography may show a halo around a phyllodes tumor mass but cannot reliably distinguish a fibroadenoma from a phyllodes tumor (76). Ultrasonography evaluation has limitations even when color and pulse Doppler ultrasonography are used in conjunction with it (76).

[4] Microscopic evaluation of a lesion is important to determine the diagnosis. The histologic distinction between fibroadenoma, benign, borderline, and malignant phyllodes tumor can be very difficult on minimal tissue sampling with CNB (71,78). It may be easier to distinguish benign phyllodes from malignant phyllodes tumors than benign phyllodes tumors from fibroadenomas (71). Histologic features that stratify lesions include number of mitoses per high power field, stromal cellularity, pushing or infiltrating tumor margin, cellular atypia, tumor necrosis, and stromal overgrowth (71).

[4] If a lesion cannot be clearly characterized as a fibroadenoma, excision may be necessary. Factors that are considered in recommending excision include older age, new mass in a well-screened individual, rapid growth, size greater than 2.5 to 3 cm, suspicious CNB, and mammographic or ultrasonographic features that demonstrate lobulation and intramural cysts. If observation is elected, repeat clinical examination and imaging in a short interval is essential to evaluate the change in size.

[4] Treatment of core biopsy–proven phyllodes tumor is wide local excision, attempting to obtain a 1- to 2-cm margin since malignancy may not be excluded (79). Massive tumors, or large tumors in relatively small breasts, may require mastectomy; otherwise, mastectomy should be avoided, and axillary lymph node

dissection is not indicated. In most cases a phyllodes tumor is locally excised because it was felt to be a fibroadenoma. Reexcision is rarely necessary for benign phyllodes tumor, but is recommended for phyllodes tumors with borderline or malignant features (79–81).

The prognosis of benign and malignant phyllodes tumors is variable (82,83). [4] **Tumors judged to be benign phyllodes tumors can recur locally in up to 10% of patients** (81). Recurrence is associated with margin involvement, whereas mortality correlates with size and grade (82). In high-grade malignant phyllodes tumors, size and excision margins are associated with local recurrence and metastatic spread, and mastectomy may be required to achieve complete surgical excision in patients with small breasts (83). [4] **Malignant phyllodes tumors tend to recur locally and, although metastasis is unusual, they may occasionally metastasize to the lung, although brain, pelvic, and bone metastases may occur** (83). The stromal component of the tumor is malignant and metastasizes, behaving like a sarcoma. Axillary involvement is extremely unusual. Often, the appearance of metastasis is the first sign that a phyllodes tumor is malignant. Chemotherapy for metastatic phyllodes tumors should be based on regimens for sarcoma, not adenocarcinoma (84). Radiation therapy generally is not used in the treatment of phyllodes tumors, but in the presence of a bulky tumor, positive margins, recurrence, or malignant histology, it may be of some benefit (85).

Fat Necrosis

Fat necrosis of the breast is rare but clinically important because it produces a mass, clinically indistinguishable from carcinoma, often accompanied by skin or nipple retraction. Fat necrosis often presents as a confusing clinical finding. Trauma is presumed to be the cause, although only about one-half of patients have a history of injury to the breast. Ecchymosis is occasionally seen near the mass. Tenderness may or may not be present. If untreated, the mass associated with fat necrosis gradually disappears. Diagnostic imaging studies are usually insufficient (86). As a rule, the safest course is needle-core or excisional biopsy of the entire mass to rule out carcinoma. Fat necrosis is common after segmental resection and radiation therapy or native tissue reconstruction (87).

PAIN

Mastitis and Breast Abscess

Lactational Mastitis and Abscesses

Infection in the breast is rare unless the patient is lactating or has experienced an injury. Lactational mastitis must be distinguished from lactational abscess (3). During lactation, an area of redness, tenderness, and induration frequently develops in the breast. **[5] Lactational mastitis is caused by transmission of bacteria during nursing and poor hygiene. The organism most commonly found in lactational mastitis and abscesses is *Staphylococcus aureus*** (88). If lactational mastitis is diagnosed, manual pressure, antibiotics, and continued breastfeeding are recommended. In its early stages, the infection often can be treated while breastfeeding is continued by administering an antibiotic such as *dicloxacillin* 250 mg four times daily, or *oxacillin* 500 mg four times daily, for 7 to 10 days. **[5] If the lesion progresses to a localized mass with local and systemic signs of infection, an abscess is present. It should be drained, percutaneously, and breastfeeding should again be encouraged to continue** (89).

Nonlactational Abscess

Rarely, infections or abscesses may develop in young or middle-aged women who are not lactating (90). The approach to nonlactational abscess is conservative (91,92). A suspected abscess should be evaluated with ultrasonography to detect the presence of an inflammatory mass, frank pus, solitary cavity, or a multiloculated abscess (93). Aspiration of pus, if present, and antibiotic therapy is instituted with reaspiration, if necessary (93). When the fluid collection is large, percutaneous drain placement is an option (89). A single aspiration is sufficient in about one-half of patients (94). Recurrent abscess formation is low (10%), in general, but much higher in smokers (94). Bacteriologic analysis of 190 abscesses in nonlactating and lactating women showed a preponderance of gram-positive cocci. *S. aureus* was the most common organism isolated (51.3%). Of these, 8.6% were methicillin-resistant *S. aureus (MRSA)*, but rates of MRSA are expected to rise as colonization rates increase in the general population. Other common organisms included mixed anaerobes (13.7%) and anaerobic cocci (6.3%) (93). **[5] If these infections recur after multiple aspirations, incision and drainage followed by excision of the involved lactiferous duct or ducts at the base of the nipple may be necessary during a quiescent interval.** In virtually all cases, mammillary sinus (lactiferous duct fistula) can be confirmed as the cause of reinfection or persistent infection (95). Inflammatory carcinoma is a consideration when erythema of the breast is present. Patients should not undergo prolonged treatment for an apparent infection unless biopsy eliminated the possibility of inflammatory carcinoma. Patients who smoke should be counselled regarding smoking cessation.

Subareolar Abscess and Lactiferous Duct Fistula

Subareolar abscess and fistula of the lactiferous ducts secondary to squamous metaplasia can occur (95). The distal duct can be occluded with inspissated debris. Several large reviews report a high association of lactiferous duct fistulae with tobacco

smoking (95). The definitive treatment for lactiferous duct sinus is excision of the lactiferous duct and drainage of the abscess cavity. **[5] The recurrence rate is greater when only incision and drainage is performed** (3,95).

Granulomatous Mastitis

Granulomatous (lobular) mastitis is characterized by an inflammatory phlegmon of the breast that is often tender, painful, and associated with skin ulceration. It may be confused with multiple recurrent abscesses or even cancer. It occurs most frequently in parous women (96). Granulomatous mastitis may be associated with hyperprolactinemia but is idiopathic. Diagnosis is by CNB, which will demonstrate noncaseating granulomata surrounding the breast lobule. Culture of the tissue should be sent to rule out other causes of granulomata such as tuberculosis. Therapy for granulomatous mastitis is observation alone and the process usually resolves within 9 months to 1 year (96). A short course of antimicrobial therapy may be useful in patients with positive cultures.

Mondor Disease

The Mondor disease is superficial thrombophlebitis of the thoracoepigastric vein presenting as pain and erythema of the breast progressing to a palpable cord. Therapy is supportive care with warm compresses and nonsteroidal anti-inflammatory medication.

Mastalgia

Mastalgia is a recognized organic condition that is studied less thoroughly than other breast problems and a challenge to treat (97). The etiology is believed to be hormonal (63). Approximately 70% to 80% of women experience severe breast pain at some time in their lives and mastalgia is the most common breast symptom causing women to consult physicians (63,98). For one in six of these patients, the mastalgia is so severe that it alters lifestyle and requires repeated investigations and treatment. Mastalgia interferes with sexual function in 40% of affected women and sleep in 35% (99). Social relationship, work, and athletic performance have been reported to suffer (99).

Types of Mastalgia

[3] Breast pain is a distressing constellation of symptoms that is classified as cyclic, noncyclic, or extramammary (97). **Cyclic mastalgia** is related to exaggerated premenstrual symptoms beginning in the luteal phase of the menstrual cycle, associated with breast engorgement, pain, ache, heaviness, and tenderness that is bilateral and can last for more than 1 week in some women (63,97,100). Cyclical mastalgia is more prevalent in women in their third and fourth decades of life and accounts for two-thirds of all breast pain symptoms (63). **Noncyclic mastalgia** is independent of menstrual

cycles and is described as achy, burning soreness. It may be intermittent or constant, is usually unilateral, occurs in the fourth and fifth decades, and is more difficult to treat than cyclic mastalgia (63). **Extramammary pain** is perceived to be located in the breast but is related to an extramammary site. Chest wall muscular pain, costal cartilage symptoms, herpes zoster, radiculopathies, and rib fractures are among some of the more common causes of extramammary pain. Costochondritis (Tietze syndrome) is a manifestation of chest-wall pain that is frequently interpreted as breast pain.

Management of Mastalgia

[3] Breast pain is an unlikely symptom of malignancy, and when malignancy is excluded by a clinical breast examination and age-appropriate breast imaging for focal breast pain, the most important treatment is reassurance (98,101). Reassurance of the benign nature of mastalgia alone provides an improvement in complaints (97). For patients with persistent symptoms, suggested treatments have spanned the gamut of medications, lifestyle modifications, vitamins and supplements, and local excision. **Discontinuation of hormone therapy may be effective in some women. Maintenance of a pain-score diary is important to understand the relationship of pain to factors such as the menstrual cycle, activities of daily living, and stress.** Failure of therapy can lead to increased depression and anxiety in patients and treatment of this syndrome should not be neglected (100).

Effective nonpharmacologic therapy begins with appropriately sized external support garments (97). The breast has minimal structural support and is at significant risk for motion-related displacement resulting in mastalgia. The use of external support to minimize breast motion appears to be effective in reducing breast pain. An ill-fitting brassiere is associated with a threefold risk of mastalgia (102). Wearing a brassiere that gives good support and protection, both night and day, improved symptoms in the majority of women (97). The effect of a sports bra was greater than that of hormonal modulation with *danazol* in randomized trial (103). In a small randomized controlled trial, exercise was associated with an improvement in the symptoms of mastalgia. Exercising thrice weekly yielded greater improvement in the quality of life than reassurance and supportive garments alone (104).

Topical nonsteroidal therapy is another option for women with mastalgia (105). Gel formulations of NSAIDs often are used for analgesia. In one study, patients were stratified by cyclic versus noncyclic pain and then randomized to treatment with NSAIDs versus placebo. There was a significant reduction in cyclic and noncyclic pain in all groups, but the magnitude of change was greater in the treatment arms and similar for cyclic and noncyclic pain.

Hormone-modulating drugs, including *toremifene, ormeloxifene*, *danazol, bromocriptine, tamoxifen,* and *Depo-Provera,* are recognized drug treatments for mastalgia (97). All of these pharmacologic therapies are associated with significant

side effects that limit their general use and several are not approved by the FDA. **[3] Withdrawal of birth control pills or hormone therapy may be all that is required to alleviate symptoms** (63).

The next line of therapy for patients not responding to supportive garments, exercise, and analgesic, is selective estrogen receptor modulators (SERM). Treatment with the SERM tamoxifen demonstrated reduction in breast pain at 10 and 20 mg per day, with equivalent effects compared with *danazol* and *bromocriptine* in most studies (97). Despite this, *tamoxifen* is not approved for this use in the United States. *Ormeloxifene* is a nonsteroidal SERM, most often prescribed as an oral contraceptive pill that shows equivalent effect to *tamoxifen* for noncyclical breast pain (106). Notably, at 12 weeks of therapy 60% of patients reported relief of symptoms, but this was not durable, and by 24 weeks, the percentage of women reporting relief had dropped to 30% (106). Ten percent of women in this trail developed ovarian cysts and other bothersome side effects included menstrual irregularities and dizziness.

For patients with severe symptoms not responding to SERMs, a temporary course of a hormonal-regimen such as *danazol* or *bromocriptine* might then be considered, always weighing the benefits against the side effects. *Danazol* is a synthetic androgen that suppresses release of pituitary gonadotropin, prevents luteinizing hormone surge, and inhibits ovarian steroid formation (107). It is the only medication approved by the U.S. Food and Drug Administration (FDA) for mastalgia. The androgenic effects—acne, edema, change in voice, weight gain, headaches, depression, and hirsutism—often are intolerable, and many patients stop taking *danazol* even when symptoms are improved (108). It can be initiated at doses of 100 to 200 mg twice daily orally for patients with severe pain and then tapered to a lower dose of 100 mg per day (108).

Breast pain is increased in some individuals who have elevated prolactin (PRL) levels induced by thyrotropin-releasing hormone (TRH) (107). *Bromocriptine* is a dopamine antagonist that inhibits the release of PRL. *Bromocriptine* (2.5 mg twice daily) given for 3 to 6 months is effective in reducing mastalgia in women who have TRH-induced elevation of PRL with side effects of nausea, vomiting, and headache (109).

The side-effect profile of hormone modulating treatments has prompted a search for alternative therapies with vitamins, supplements, and herbal extracts. None of these has clearly been shown to be more efficacious than placebo, but they remain popular among patients because they are less likely to be associated with adverse drug-related side effects (97). Evening primrose oil containing essential fatty acids (γ-linolenic acid [GLA]) was originally studied because of its effect on prostaglandin synthesis, but has failed to demonstrate efficacy over placebo (97). GLA use was found to be safe, without any significant side effects, and was prescribed as therapy for mastalgia because of its lack of side effects. Chamomile extract, in very small randomized studies, has been found to lead to an improvement in symptoms and may represent the safest

nonhormonal supplement option, although the true efficacy of all investigated supplements is likely negligible (97,110).

Macromastia

Women with very large breasts frequently experience pain in the neck, shoulders, back, and breasts secondary to the excess weight of their breasts. This pain tends to worsen throughout the day (111). Macromastia may cause distortions in anatomy and posture resulting in shoulders that are pulled forward and compensatory hypertrophy of the trapezius muscle. Many women develop painful grooves in the shoulders from support garments, which may become permanent over time.

In patients with obesity, primary therapy should be directed at weight loss with a goal of achieving a normal body mass index. If symptoms persist and fail to improve with physical therapy, then a referral should be made for consideration of reduction mammoplasty. In a survey of 400 women who underwent reduction mammoplasty, 94% reported improvement in shoulder grooving, 93% in shoulder pain, 81% in back pain, and 88% in self-esteem. Despite postoperative complications in 53% of patients, 93% reported that they would have the surgery again (112).

DISORDERS OF THE NIPPLE–AREOLAR COMPLEX

Nipple Discharge

Nipple discharge is a presenting breast symptom in relatively few patients seeking evaluation of a breast symptom. In one report, 4.5% of patients presenting with a breast complaint reported nipple discharge, with roughly half being spontaneous and the remainder provoked (113). Nipple discharge that does not occur spontaneously has no pathologic significance. Provoked or self-induced nipple discharge should be managed by reassurance and instruction to discontinue manipulation. Spontaneous nipple discharge is more likely to be associated with an underlying pathologic problem than provoked discharge. **[6] Although it is a distressing finding, less than 10% of spontaneous nipple discharge is associated with carcinoma** (114). Nipple discharge can be caused by neoplastic or nonneoplastic processes (115). Usually discharge caused by malignancy is bloody, as is that caused by papillomas. Nonneoplastic processes include galactorrhea, physiologic changes resulting from mechanical manipulation, parous condition, periductal mastitis, subareolar abscess, fibrocystic change, and mammary duct ectasia. Neoplastic causes of nipple discharge in nonlactating women are solitary intraductal papilloma, carcinoma, papillomatosis, squamous metaplasia, and adenosis (113,115). Extramammary causes are related to hormones and drugs (115). **[6] Following are the important characteristics of the discharge and other factors to be evaluated by history and physical examination:**

1. **Nature of discharge (serous, bloody, or milky)**
2. **Association with a mass**
3. **Unilateral or bilateral**
4. **Single or multiple ducts**
5. **Discharge that is spontaneous (persistent or intermittent) or expressed by pressure at a single site or on the entire breast**
6. **Relation to menses**
7. **Premenopausal or postmenopausal**
8. **Hormonal medication (contraceptive pills or estrogen)**

Breast Papilloma

Unilateral, spontaneous, bloody, or serosanguineous discharge from a single duct is usually caused by an intraductal papilloma or, rarely, by an intraductal cancer. In either case, a mass may not be palpable. The involved duct may be identified by pressure at different sites around the nipple and at the margin of the areola. Bloody discharge is more suggestive of cancer but usually is caused by a benign papilloma in the duct. In premenopausal women, spontaneous multiple-duct discharge, unilateral or bilateral, is most marked just before menstruation. It often is caused by fibrocystic change. Discharge may be green or brownish. Papillomatosis and ductal ectasia are usually seen on biopsy. If a mass is present, it should be removed. Milky discharge from multiple ducts in nonlactating women presumably reflects increased secretion of pituitary PRL; serum PRL and thyroid-stimulating hormone levels should be evaluated to detect a pituitary tumor or hypothyroidism. Hypothyroidism may cause galactorrhea. Alternatively, *phenothiazines* may cause milky discharge that disappears when the medication is discontinued. Oral contraceptive agents may cause clear, serous, or milky discharge from multiple ducts or, less often, from a single duct. The discharge is more evident just before menstruation and disappears when the medication is stopped.

[6] Chronic unilateral nipple discharge, especially if it is bloody, is an indication for resection of the involved ducts. Mammography and ultrasonography are performed to rule out an associated mass. On occasion, ductography may be performed to identify a filling defect before excision of the duct system, but usually this technique is painful and of little value (116). Ductography is not a substitute for excision because it misses multiple lesions and cannot visualize the periphery (117).

The role of cytologic examination of nipple discharge is unclear. It may identify malignant cells and lead to an appropriate oncologic operation (116). Negative findings do not rule out cancer and a CNB should be performed of any underlying mass and may prompt further surgical therapy (117). Complete histopathologic evaluation of the involved ductal system is the preferred method of diagnosis if no mass is present. Cytologic assessment should not be relied on for diagnosis.

The usual approach for nipple discharge is surgical excision through a periareolar incision adjacent to the trigger point, the pressure point that elicits nipple discharge (115). A microdochectomy of a single duct or a central duct excision of the major subareolar ducts can be performed under local or general anesthesia. The putative duct can be cannulated, methylene blue can be injected, or a lacrimal probe can be inserted into the duct for localization. Ultrasound may assist in localizing a focally dilated duct and allow for needle localization (118). A resection of breast tissue for 3 to 5 cm, or until no bloody fluid can be identified in the ductal system, is performed. Complications are rare, but the patient must be warned of possible skin and nipple loss as a result of compromised vascularity, change in nipple sensation, deformity, inability to breastfeed, and recurrence if only a single duct is removed.

When there is a history of unilateral nipple discharge, localization is not possible, and no mass is palpable, the patient should be reexamined every week for several months. When unilateral discharge persists, even without definite localization or tumor, surgical exploration should be considered if the discharge is copious. The alternative is careful follow-up at intervals of 3 to 6 months. Mammography should be performed every 6 months. Purulent discharge may originate in a subareolar abscess and requires excision of the related lactiferous sinus (119).

Duct Ectasia

Duct ectasia is another common cause of nipple discharge in peri- and postmenopausal women. It is characterized by corkscrewing and dilation of the subareolar ducts, which can be demonstrated on ultrasound, and by thick or cheesy appearing discharge. Nipple retraction may be present due to involution and foreshortening of the affected ducts (120). This benign condition is best treated with reassurance, but occasionally may require excision for diagnosis.

Nipple Inversion and Retraction

In cases of nipple retraction, even a single tethered duct results in partial pulling in of the nipple and a slit-like appearance (121). The term nipple inversion, on the other hand, is reserved for cases in which the complete nipple is pulled in. This may be congenital or acquired. Congenital nipple inversion is present in about 5% of women, usually bilateral, and is a benign condition (122).

[6] Acquired nipple retraction or inversion must be carefully investigated, including a full clinical evaluation with ultrasound and the addition of mammography if the patient is more than 35 years old. This finding is most commonly a result of duct ectasia or periductal mastitis, but may less commonly be caused by carcinoma in 5% to 20%, or even by tuberculosis (122). If workup is normal, reassurance, with ongoing clinical surveillance, is the only treatment required.

Erosive Adenomatosis of the Nipple

Erosive adenomatosis is a rare benign condition of the nipple that mimics the Paget disease (123). Patients seek treatment for pruritus, burning, and pain. On clinical examination, the nipple can appear ulcerated, crusting, scaling, indurated, and erythematous. The nipple can be enlarged and more prominent during menstrual cycles (124). The differential diagnosis includes squamous cell carcinoma, psoriasis, contact dermatitis, seborrheic keratosis, adenocarcinoma metastatic to the skin, and unusual primary tumors of the nipple (123). Excisional biopsy should be performed to diagnose the lesion. Local excision is curative (124).

Accessory Breast Tissue

Approximately 1% of the population has accessory breast tissue (125). Most commonly, this is polythelia, or the presence of a rudimentary nipple areola complex, but may include varying degrees of breast glandular tissue in which case it is referred to as polymastia or supernumerary breast. This tissue may be found anywhere along the milk line running from the axilla to groin. Polythelia most commonly occurs just below the normal breast and may even be confused, at times, with a nevus. Polymastia occurs most frequently in the axilla (126). Not infrequently, the accessory breast tissue may go unrecognized until the hormonal changes of puberty or even pregnancy cause the tissue to become more noticeable. Despite this, the majority of polythelia and polymastia remain asymptomatic (125). It is important to note that normal benign and malignant diseases of the breast may occur in the accessory tissue and all breasts should be monitored should the patient elect not to have the tissue removed for cosmetic reasons. **Polythelia is associated with urogenital abnormalities and may be associated with an increased risk of urogenital malignancy** (127)**. Identification of the accessory breast tissue should prompt ultrasound evaluation** of the urogenital organs.

BENIGN MAMMOGRAPHIC ABNORMALITIES

Diabetic Mastopathy/Lymphocytic Mastitis

This benign breast lesion often appears as an asymptomatic breast mass found incidentally on imaging. Its ultrasonographic features can be quite concerning as it appears as a hypoechoic solid mass with irregular margins, inhomogeneous echotexture, and marked posterior shadowing (128). Diabetic mastopathy is strongly associated with diabetes mellitus and felt to be autoimmune in nature. It is hypothesized that, as a result of the hyperglycemic state, advanced glycosylated end products are formed and act as neoantigens triggering an autoimmune response (128). A CNB will show dense keloid-like fibrosis and periductal, lobular, or perivascular lymphocytic infiltration (129).

Diabetic mastopathy does not require excision, but requires CNB to establish the diagnosis.

Pseudoangiomatous Stromal Hyperplasia

Pseudoangiomatous stromal hyperplasia (PASH) is a benign stromal proliferation that shares some histologic appearance with angiosarcoma (130). PASH may present as an area of increased density on physical examination or may be incidentally identified on CNB done for another reason, but it is most commonly identified on breast imaging as a solid, well-defined, noncalcified mass (131). After a diagnosis has been clearly reached, it requires no further therapy.

Sclerosing Adenosis

Sclerosing adenosis may present as a palpable mass or mammographic abnormality (132). This is a benign sclerosing lesion and the risk for subsequent cancer is low (132). No treatment is needed.

Risk Lesions

[7] When found on CNB, these lesions represent an increased risk to the patient of subsequent diagnosis of breast cancer in either breast. Historically, these lesions were surgically excised because of the risk of finding concomitant invasive cancer at final pathologic review. This suggestion was based on largely retrospective data, but newer analysis suggests that surgical excision may be overtreatment in many patients in whom these diagnoses represent only generalized increased risk (133). Further prospective, multicenter trials are needed to clarify this problematic issue.

Patients diagnosed with risk lesions should be counseled regarding surveillance and risk reduction. The risk for development of invasive cancer is approximately 3.5 to 5 times that of the general population (133–136). Patients should continue with yearly mammography and clinical breast examination. Her risk for subsequent breast cancer may be decreased by avoidance of exogenous estrogens, initiation of an exercise program, and a generally healthy lifestyle (108). Patients with additional contributors to high risk may be considered for chemoprevention with *tamoxifen* therapy.

Lobular Neoplasia

Lobular neoplasia is a spectrum of atypia with lobular hyperplasia (ALH) on the more ordered end to the more distorted LCIS. Patients can be reassured that LCIS is not an obligate precursor to lobular carcinoma. Historically, upgrade rates for ALH were thought to range from 0% to 67%, with a mean of 9% (133). LCIS upgrade rates were, on average, higher, with a mean of 18% and range of 0% to 60% (134). When limited to

data for which imaging and pathologic concordance was confirmed, only one invasive cancer was found in 337 cases and upgrade rates to noninvasive cancer (ductal carcinoma in situ) in these patients was around 1% (133). Similar low rates have been reported in other recent retrospective series (135–136). The 2017 [7] **NCCN guidelines recommend close observation alone for patients with atypical lobular hyperplasia or classic LCIS found on CNB and felt to be concordant with imaging** (35). These lesions should be followed with repeat mammography at a 6-month interval to document stability. This approach does not apply in cases of pleomorphic LCIS, for which little natural history data is available. This is considered a more aggressive lesion, likely more closely related to ductal carcinoma in situ than lobular neoplasia, and is managed with excision to negative margins (138).

Atypical Ductal Hyperplasia

Unlike lobular neoplasia, ADH found with CNB has unacceptably high rates of upgrade to invasive carcinoma found at surgical excision (133,138). In a recent meta-analysis, the lowest possible upgrade rate of ADH to invasive carcinoma was calculated to be 8% (133), and historical averages have been in the range 20% to 25% (139). Consequently, **surgical excision is recommended for patients with ADH** (35).

Radial Scars

[7] Radial scars are sclerosing lesions most commonly encountered as incidental findings in biopsies performed for other indications. When larger in size, they may present as a mammographic speculated mass (3). Surgical excision is recommended because the upstaging rate to invasive cancer is approximately 7% (35,140). Following excision, patients remain at a mildly increased risk for developing breast cancer relative to the general population. In a study of 880 women with radial scars who followed for an average of 20 years, the relative risk of developing breast cancer at 10 years was 1.82 (141).

DISORDERS OF BREAST AUGMENTATION

Estimates indicate that greater than 11 million women worldwide have undergone augmentation mammoplasty. Breast implants are usually placed under the pectoralis muscle or in the subcutaneous tissue of the breast. Most implants are made of an outer silicone shell filled with a silicone gel or saline. The complications of breast implantation are significant.

Capsular Contracture

Rates of contracture vary in the literature from less than 10% to over 60%.

Capsular contraction or scarring around the implant, leading to firmness and distortion of the breast, can be painful and sometimes requires removal of the implant and capsule.

In a prospective study of nearly 1,000 patients, 6-year contracture rates were 4.6% for augmentation, 6.9% for revision-augmentation, 10.7% for reconstruction, and 18.3% for revision reconstruction, with the majority of these occurring within the first 3 years (142). Following the first 6 postoperative years, contracture rates are estimated to be an additional 1% per year indefinitely (142).

Rupture

Implant rupture may occur in as many as 10% of women, and bleeding of gel through the capsule is even more common (143). In 2006, the U.S. FDA reapproved silicone gel–filled implants for use in women 22 years or older for cosmetic purposes and for reconstruction after breast surgery or in women with traumatic or congenital breast defects and recommended MRI screening for implant rupture beginning 3 years after the first implant surgery and then every 2 years (144). The agency advised symptomatic women with ruptured implants to discuss the need for surgical removal with their physicians. When there is no evidence of associated symptoms, implant removal is generally not indicated because the risks of removal are probably greater than the risk of retention. Noncontrast MRI is very sensitive for detecting implant rupture, but is costly (43). High-resolution ultrasonography, which is slightly less sensitive has been suggested as a more cost-efficient alternative for use in asymptomatic individuals (145–147). Even without rupture, seepage of silicone particles may lead to palpable adenopathy caused by foreign-body reaction.

Breast Implant–Associated Anaplastic Large Cell Lymphoma

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a rare cancer, but has generated a large degree of patient and physician concern (148). Its true incidence is unknown, but a study from the Netherlands estimates one to three cases per million women with breast implants per year, while a US study calculated the lifetime risk to be approximately 1:30,000 in patients with implants (149,150).

The typical presentation is that of a seroma surrounding an implant more than 1 year after placement of implant without history of recent trauma, but BIA-ALCL may less commonly present as a mass (151). Patients with an unexpected seroma should be evaluated with aspiration of the fluid followed by immunohistochemistry for CD30. Diagnosis may be confirmed by a T-cell clonal population on flow cytometry and large anaplastic cells on cell block cytology. Treatment includes complete excision of the implant, capsule, and any associated mass and chemotherapy for more advanced disease (151).

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CHAPTER 20

Violence Against Women and Sexual Assault



Paula J. Adams Hillard

Terminology
Childhood Sexual Abuse
Human Trafficking
Female Genital Mutilation
Sexual Harassment and Misconduct
Reproductive and Sexual Coercion
Intimate Partner Violence
Sexual Assault and Rape
Rape
Medical Consequences of Sexual Assault
Mental Health Consequences of Sexual Assault
Examination
Elderly Abuse

KEY POINTS

1 Violence against women—particularly intimate partner and sexual violence—has been characterized by the World Health Organization (WHO) as a major public health problem and a violation of women's human rights. Global estimates by WHO indicate that approximately 35% of women worldwide have experienced either intimate partner, or nonpartner, physical or sexual violence in their lifetime.

2 Childhood sexual abuse has a profound and potentially lifelong effect on the survivor. Although most

cases of childhood sexual abuse are not reported by the survivor or her family, it is estimated that at least 20% of adult women were sexually abused as children.

3 Women who were sexually abused as children or sexually assaulted as adults often experience sequelae, including depression, anxiety, chronic pelvic pain, dyspareunia, and vaginismus. These symptoms may be unrecognized by the physician and patient.

4 All women should be screened for a history of sexual abuse or assault, and intimate partner violence (IPV).

5 Nearly one in four adult women and approximately one in seven men in the United States report having experienced severe physical violence from an intimate partner in their lifetime.

6 The terms *sexual abuse survivor* and *assault survivor* are preferable to *victim*.

7 The National Intimate Partner and Sexual Violence Survey (NISVS) from the U.S. Centers for Disease Control (CDC) found that approximately 18% of women have been raped during their lifetimes. The lifetime prevalence of rape by an intimate partner was 8.8% for women, with 0.8% reporting intimate partner rape in the last year. Among female victims of completed rape, 78.7% were first raped before age 25 years, and 40.4% before age 18.

TERMINOLOGY

[1] Violence against women includes a number of different acts to which girls and women may be subjected during their lifetimes. Violence against women—particularly intimate partner and sexual violence—has been characterized by the World Health Organization (WHO) as a major public health problem and a violation of women's human rights. Global estimates by WHO indicate that approximately 35% of women worldwide have experienced either intimate partner, or nonpartner, physical or sexual violence or sexual violence from a nonpartner in their lifetime (1). Most violence that women experience is perpetrated by intimate partners, and globally, as many as 38% of murders of women are committed by a male intimate partner (1). This chapter will address the topics of childhood sexual abuse, human trafficking, female genital mutilation (FGM), sexual harassment, reproductive coercion, intimate partner violence (IPV), sexual assault and rape, and elderly abuse. The term trauma informed care has been used to refer to medical care (as well as social services, education, and care in other settings) that acknowledges and takes into account the wide-ranging and potentially profound impact that past traumatic events can have on physical and mental health (2).

CHILDHOOD SEXUAL ABUSE

During childhood, the occurrence of adverse childhood experiences (ACE), experienced either as a single event or sustained over time—defined in a landmark 1998 study as including emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, violent treatment of the mother, household substance abuse, household mental illness, parental separation or divorce, or an incarcerated

household member—occur regularly for children of all races, economic classes, and geographic regions, although those who live in poverty have a much higher prevalence of ACEs (3). The experience of these ACEs may become toxic when there is "strong, frequent, or prolonged activation of the body's stress response systems in the absence of a supportive, adult relationship" (3,4). **A number of common adult health conditions, including obesity, heart disease, alcoholism, and other drug abuse have been directly linked to ACEs. In addition, they pose an increased risk for early initiation of sexual activity and adolescent pregnancy.**

[2] Childhood **sexual abuse has a profound and potentially lifelong effect on the survivor. Although most cases of childhood sexual abuse are not reported by the survivor or her family, it is estimated that at least 20% of adult women were sexually abused as children** (5). **Child sexual abuse is defined as any sexual activity with a child where consent is not or cannot be given, and includes forceful sexual contact and noncontact activities** (6). Younger children are more often exposed to genital fondling or noncontact abuse (exhibitionism, forced observation of masturbation, or posing in child pornography), and children older than 10 years of age are more likely to be forced to have intercourse or oral sex (7). **As children age, they are more likely to experience sexual abuse outside the home and more likely to be victimized by strangers. As adolescents, women survivors of childhood sexual abuse are at risk for early unplanned pregnancy, sexually transmitted diseases (STDs), prostitution, further sexual abuse (revictimization), antisocial behavior, running away from home, lying, stealing, eating disorders and obesity, and multiple somatic symptoms** (8). These women are more likely to engage in health risk behaviors such as smoking, substance abuse, and early sexual activity with multiple partners (9). They may be less likely to use contraception (10).

While the reported prevalence of child sexual abuse depends on varying definitions and usually relies on adult retrospective reporting, one large population study indicated that 10% of respondents reported experiencing contact child sexual abuse before age 18, and about ¾ of the sample reporting abuse were female (11). A meta-analysis of global prevalence studies reported a prevalence of combined contact and noncontact child sexual abuse of 19.7% of females (12,13). **A history of childhood sexual abuse increases the risks of developing posttraumatic stress disorder (PTSD), anxiety disorder, depression, distortions of self-perception including self-blame, and hospitalization for mental illness** (13). **Adult survivors of child sexual abuse are more likely to become victims of IPV and sexual assault**. Disorders that are frequently seen by obstetrician/ gynecologists including chronic pelvic pain, eating disorders, sexual effects (including disturbances of desire, arousal, and orgasm), dyspareunia, vaginismus, unintended pregnancy, and prostitution are associated with a history of sexual abuse (6). **[3] Women who were sexually abused as children or**

sexually assaulted as adults often experience sequelae, including depression, anxiety, chronic pelvic pain, dyspareunia, and vaginismus. These symptoms may be unrecognized by the physician and patient.

[4] The American College of Obstetricians and Gynecologists (ACOG) strongly recommends that all women be screened for a history of sexual abuse (6). **Recommendations include routinely incorporating such screening, normalizing the screening experience as occurring commonly, allowing patient control over disclosure, asking whether this history has previously been disclosed and whether she has experienced previous therapy, listening attentively, and being willing to postpone sensitive examinations** (6). Survivors often avoid pelvic examinations and are less likely to have Papanicolaou (Pap) tests because of the association between vaginal examinations and pain (14). They may not be able to tolerate pelvic examinations and may avoid seeking routine gynecologic care because these examinations may remind them of the sexual abuse they experienced as children; dissociation and flashbacks may occur during labor and birth (6,15). While data regarding adverse pregnancy outcomes for women with histories of childhood sexual abuse are inconsistent, pregnancy may be especially difficult, and the pain of labor and delivery may trigger memories of abuse (6,15).

Obstetrician–gynecologists can assist their sexual assault survivor patients by validating their feelings and concerns and giving them control over their examination. It is important to ask the patient for permission to perform the examination, give her the opportunity to have an advocate in the room with her, and let her know that she has the right to stop the examination at any time (6). Techniques to increase the patient's comfort include talking her through the steps of the examination, maintaining eye contact, allowing her to control the pace, or guide the examination (6). Survivors may be unable to trust or establish rapport with adults. Some women blame themselves for the abuse and come to believe that they are not entitled to assistance from others. Thus, they risk continuing to enter abusive relationships. **Women survivors of childhood sexual abuse often develop feelings of powerlessness and helplessness and may become chronically depressed.** They experience a high incidence of self-destructive behavior, including suicide and deliberate self-harm, such as cutting or burning themselves (14,16). The most extreme mental health symptoms in assault survivors are associated with the onset of abuse at an early age, frequent abuse over a long period, use of force, or abuse by a parent or other trusted individual. Survivors are at risk for becoming victimized again later in life (17). Of women who report being abused as children, 50% are abused again as adults. Women who are sexually abused as children carry the effects of abuse into adulthood. As adults, they have the same level of physical symptoms and psychological distress as women who do not report childhood sexual abuse but are currently experiencing sexual or physical

abuse (18).

Women who were sexually abused as children or sexually assaulted as adults often experience sexual dysfunction and difficulty with intimate relationships and parenting (19). Chronic sexual concerns may incorporate fear of intimate relationships, lack of sexual enjoyment, difficulty with desire and arousal, and anorgasmia. Compared with women who were not sexually assaulted, they are more likely to experience depression, suicide attempts, chronic anxiety, anger, substance abuse problems, dissociative personality disorder, borderline personality disorder, fatigue, low self-esteem, feelings of guilt and self-blame, and sleep disturbance (6,18,20,21). They often experience social isolation, phobias, feelings of vulnerability, fear, humiliation, grief, and loss of control (22,23). **Survivors of sexual assault represent a disproportionate number of patients with chronic headaches, fibromyalgia, and chronic pelvic pain (they have a lower pain threshold) and are more likely to have somatic symptoms that do not respond to routine medical treatment** (6,24). **Women with common gynecologic symptoms, such as dysmenorrhea, menorrhagia, and sexual dysfunction, are much more likely to have a history of sexual assault (**25). If they were forced to perform oral sex, they may have a dental phobia and avoid preventive dental care.

Survivors may develop PTSD, in which characteristic symptoms are exhibited following a psychologically traumatic event outside of normal human experience. Symptoms of PTSD involve blunting of effect, denial of symptoms, intrusive re-experiencing of the incident, avoidance of stimuli associated with the assault, and intense psychological distress and agitation in response to reminders of the event (26,27). Women affected by PTSD are more likely to commit suicide. The cognitive sequelae incorporate flashbacks, nightmares, disturbances in perception, memory loss, and dissociative experiences (28). They are more likely to use the medical care system for nongynecologic concerns (29). Women with PTSD are at greater risk for being overweight and having gastrointestinal disturbances (9).

Referral for mental health care is frequently helpful if there are physical, psychological, and behavioral symptoms potentially resulting from past abuse. The manner in which this referral is done may be more easily received if the statement indicates, “I think that a mental health professional could help assess whether your past abuse is contributing to your current health problems,” rather than suggesting that psychological problems are a cause of the symptoms (6).

HUMAN TRAFFICKING

Trafficking of children for labor and sexual exploitation is a global health issue and a violation of human rights. Child sex trafficking involves engaging a person

younger than 18 years in a commercial sex act (where there is an exchange of money or something of value) (30). **Activities that may be contained in this category include exploitation of a child for prostitution (as a buyer or a seller), mail-order bride trade and early forced marriage, the production of child pornography, or online sexual abuse. An estimated one million children, most of whom are girls, are being exploited yearly in the global commercial sex trade** (31). Children and adults may also be trafficked for labor, although persons trafficked for labor tend to be adult females and foreign nationals. Lesbian, gay, bisexual, transgender, or queer children and youth, children with a history of abuse or neglect, or who are homeless, are among those youth most likely to experience trafficking. In the United States, victims of sex trafficking are likely to seek medical attention during their period of exploitation, while those trafficked abroad may receive little or no medical care. The adverse health effects of child trafficking for sex and labor consist of trauma from sexual and physical assault, STDs, chronic untreated medical conditions, pregnancy, chronic pain, substance abuse, and malnutrition (30). Mental health consequences may involve depression and suicide attempts, self-harm, anxiety disorders, anger control problems, and PTSD.

The American Academy of Pediatrics (AAP) has advocated that information on human trafficking should be part of the medical education of health care professionals, to facilitate the identification and care of victims of human trafficking. ACOG's Committee Opinion on Human Trafficking notes that **signs of sex victimization and trafficking may include: young age, multiple sexual partners, multiple episodes of STDs, inappropriate attire for a health care visit, tattoos or other branding for which there is only a vague explanation, or evidence of sexual abuse or trauma** (31). An unusual dynamic between the patient and her partner can lead to a suspicion of abuse or trafficking. Other possible indicators of trafficking among children or adults encompass: lack of identification, vague answers to questions about their home situation, no eye contact, inconsistencies in the medical or personal history, no control of their money (someone else paying for the visit in cash), malnourishment, signs of physical abuse (bruises, burns, cuts, broken bones, or teeth), signs of depression or PTSD, or substance addiction (31). **Clinicians are mandated reporters and must contact Child Protective Services if abuse is suspected.** Patients can be given the National Human Trafficking Resource Center Hotline number (only when the patient is alone): 1-888-373-7888. Clinicians who provide health care for women and girls must be aware of the global issues of human trafficking, and alert to detecting and assisting patients who are or have been victims of human trafficking.

FEMALE GENITAL MUTILATION

FGM, also known as female genital cutting (FGC) or female circumcision, is genital

alteration performed on girls and young women for nontherapeutic indications (32). **The WHO estimates that approximately 200 million girls and women worldwide have been cut in the 30 countries in Africa, the Middle East, and Asia, the primary areas where FGM occurs** (33). This ancient tradition from at least 200 BC has cultural rather than religious origins and is not restricted to any particular ethnic group or religious sect. **FGM typically is performed between infancy and age 15, and has been characterized by the WHO as a violation of the human rights of girls and women.**

Increasing numbers of women who underwent FGM or FGC need gynecologic care in Western counties. **FGM has been classified into four types** (33). **Type I FGM, often referred to as clitoridectomy, involves removing part or all of the clitoris and prepuce. Type II, often referred to as excision, is removal of part or all of the clitoris and the labia minora with or without excision of the labia majora. Type III is known as infibulation and is the most extreme form, involving narrowing the vaginal orifice and stitching the adjoining labia minora and or labia majora with or without including the clitoris. There are other "lesser" procedures often noted as Type IV, such as pricking, piercing, incising, scraping, or cauterizing the female genitalia. Deinfibulation or defibulation refers to the practice of cutting open the sealed vagina of a woman who has been infibulated, which is necessary to allow intercourse or facilitate delivery.** Although some 85% of FGC are Types I and II and 15% are Type III, recent immigration and refugee resettlement from countries where Type III predominates, such as Somalia, resulted in many more women with Type III FGC in North America and Europe. Immediate complications of FGM are severe pain, hemorrhage, genital swelling, fever, and infections including tetanus, sepsis, urinary problems, poor wound healing, injury to surrounding genital tissue, shock, or even death. Long-term complications include painful urination, urinary tract infections, urinary retention, vaginal infection, painful menstruation, scar and keloid formation, sexual pain, increased risks of childbirth or hemorrhage, need for later surgeries, and psychological problems including depression, anxiety, PTSD, or low self-esteem (33).

Sound data are lacking on psychosexual outcome. The taboos against discussing sexual displeasure or pain from FGC limit data collection. Despite this, there is evidence that FGC may not completely destroy sexual function and prevent enjoyment in all women (34). FGC invariably damages many neural networks associated with the vulvar and perineal areas, potentially altering genital sensation. Neuroplasticity within the brain and spinal cord is thought to account for the fact that some women have sexual response, sometimes from genital stimulation and other times from stimulation of breasts or other areas of the body.

Results of studies of dyspareunia are conflicting, some suggesting it is only temporary after first intercourse during the initial period of marriage and after reinfibulation (35).

Some studies noted increased prevalence of dysmenorrhea, vaginal dryness, lack of sexual desire, difficulty reaching orgasm, and an increase of dyspareunia in comparison with noncircumcised women.

Surgery is recommended for women with Type III FGC complications such as dysmenorrhea, a desire for vaginal birth that would not be possible without surgery, apareunia, dyspareunia, or difficulty voiding. General obstetricians and gynecologists should be familiar with the types of FGM and their complications and should understand the surgical therapies for the excision of cysts, revision of introital or urethral scarring, repair of fistulae, procedures for correcting vaginal stenosis, and defibulation. Referral may be helpful to a physician with special expertise in reconstructive surgery or a clinician practicing in an area where FGC is prevalent. The surgical technique of defibulation has been detailed and summarized (36).

It is apparent to people helping women who underwent FGC that culture plays a very important role in their sexual health. It is imperative that the specific needs of the individual woman with FGC are understood in order to help her. Care should be given in a nonjudgmental manner that encourages trust and open discussion. Her own cultural significance of the FGC should be explored and often an interpreter is necessary to fully understand her situation.

The ACOG, WHO, AAP, American Medical Association (AMA), International Federation of Gynecology and Obstetrics (FIGO), and a number of other organizations oppose all forms of medically unnecessary genital surgery and support the development and accumulation of evidence related to eliminating FGC and caring for those who have experienced it.

SEXUAL HARASSMENT AND MISCONDUCT

Sexual harassment is unwelcome behavior of a sexual nature that includes sexual advances, requests for sexual favors, bullying or coercion of a sexual nature which may be tied to or a condition of employment, used as a basis for employment decisions, unreasonably interferes with work performance, or creates an intimidating, hostile, or offensive working environment (37). **The behaviors encompassed within the category of sexual harassment range from unwanted sexual looks or gestures, unwanted sexual teasing or jokes, sexual comments, unwanted touching, pressure for sexual favors, to actual or attempted rape or sexual assault.** As defined by the U.S. Equal Employment Opportunity Commission (EEOC), sexual harassment is illegal, and constitutes a violation of the Civil Rights Act of 1964. In the workplace, sexual harassment is considered illegal when it creates a hostile or offensive work environment or affects an employment decision. The concept of sexual harassment is culturally based, but in its modern understanding, dates to the

1970s.

During the second decade of the 21st century, the "#me too" movement has spread virally as a hashtag used in social media to bring awareness to the widespread prevalence of sexual assault and harassment. It gained momentum after multiple allegations of sexual misconduct against a prominent Hollywood producer. Sexual misconduct in established organizations and institutions such as the church, finance industry, politics and government, professional sports and the Olympics, the music industry, the military, and the medical field have all been cited as having ignored or tolerated sexual harassment (38). The movement has highlighted the prevalence of sexual violence that has often gone unpunished. Internationally, the movement has led to discussions of cultural norms and differences between men's and women's perceptions of similar behaviors. While the "#me too" movement initially focused on adults, sexual abuse is common among children and adolescents.

An online survey of nearly 6,000 13- to 18-year-old internet users in the United States found that sexual harassment was reported by 23% to 82% of youth, and that the highest rates were reported by lesbian/queer girls (72%), bisexual girls (66%), and gay/queer boys (66%) (39). **When examined by gender identity, transgender youth reported the highest rates of sexual harassment—81%** (39). In-person harassment was more common than online harassment in this study. Besides the increased risk for harassment among sexual and gender-minority individuals, there was an increased risk of sexual assault.

REPRODUCTIVE AND SEXUAL COERCION

Reproductive and sexual coercion consists of behaviors that are intended to promote pregnancy and to maintain power or control over a woman's reproductive choices. This is accomplished through attempts to impregnate her against her wishes, control the outcome of a pregnancy, coerce her to have unprotected sex, or interfere with contraceptive methods. Reproductive coercion (RC) has been reported by 11% of female veterans, 19% of high-school girls, and 8% of college women, with black women, younger women, and single women more likely to experience reproductive coercion (40–42). **ACOG counsels that obstetrician-gynecologists are in a unique position to screen for reproductive coercion and IPV that can be linked with reproductive issues (**43,44).

Unintended pregnancy has been found to occur more commonly in abusive relationships that may contain forced sex, fears of violence if the woman refuses sex, and difficulties negotiating contraception and condom use (45). Adolescent relationship abuse, such as cyber-dating abuse, may manifest in ways that may be less recognizable to clinicians (46). It has been suggested that reproductive health care clinicians should be educated about and trained to detect reproductive coercion. Tools such as safety

cards and posters educating women about reproductive coercion and provision of long-acting and hidden forms of contraception are potential educational and treatment options for some patients. Training in offering referrals to domestic violence hotlines and shelter resources should be part of the preparation to deal with reproductive health issues (45). Adolescents and young women can be engaged in a discussion of healthy versus unhealthy relationships, as they may not identify themselves as being in a coercive relationship. Reproductive coercion may be one aspect of young women's inconsistent use of contraception. Pilot projects have assessed family-planning-clinic–based interventions that have been shown to reduce the odds of pregnancy coercion and to increase the odds of clients ending an unhealthy or unsafe relationship in which they were at risk for IPV (47). The co-occurrence of IPV was found in approximately one-third of the 16% of women who experienced reproductive coercion in a large urban obstetrics and gynecology clinic (48). A clear temporal relationship has been shown between reproductive coercion and unintended pregnancy. In a survey of young women 16 to 29 years of age seeking care at family planning clinics in rural and urban settings, 5% reported reproductive coercion in the previous 3 months, and overall 12% reported an unintended pregnancy in the past year. Among those reporting recent reproductive coercion, 21% reported an unintended pregnancy, with and without a history of intimate partner physical and sexual violence (49). Globally, reproductive coercion is a major issue, and associated with IPV, contributing to adolescent and unintended pregnancies (50). Factors that will improve women's reproductive health related to IPV and reproductive coercion involve access to female-controlled contraceptive methods, and the transformation of social norms in which men feel entitled to control women's and girls' bodies and reproduction (50).

INTIMATE PARTNER VIOLENCE

IPV is the term that is used to refer to assaultive and coercive behavior such as physical abuse, psychological or emotional abuse, sexual assault, progressive isolation, stalking, intimidation, and reproductive coercion by a current or former intimate partner (43,51). **IPV has previously been termed wife/spouse abuse, domestic/family violence, or abuse or wife beating/battering.** IPV affects millions of individuals in the United States, and is described by the U.S. Centers for Disease Control (CDC) as a preventable public health problem that occurs across the lifespan (51). **[5] Data from the National Intimate Partner and Sexual Violence Survey (NISVS) indicate that nearly one in four adult women (23%) and approximately one in seven men (14%) in the United States report having experienced severe physical violence from an intimate partner in their lifetime** (51). Other estimates suggest that more than one in three women in the United States has experienced rape, physical violence, or stalking over a lifetime, although the true prevalence in not known,

as many individuals are afraid or ashamed to acknowledge their experiences of violence (52). Severe physical violence can be throwing objects, pushing, kicking, biting, slapping, strangling, hitting, beating, and threatening or using a weapon. Psychological abuse erodes an individual's sense of self-worth, and may consist of harassment, verbal abuse, threats, stalking, and isolation from friends and family. A range of sexual violence may occur, as may reproductive coercion. IPV is most prevalent among women of reproductive age and it contributes to multiple gynecologic problems, unintended pregnancy, pregnancy complications, and sexually transmitted infections (STIs), such as human immunodeficiency virus (HIV) (52).

Many racial/ethnic and sexual-minority groups are disproportionately affected by IPV, as are people living with physical or mental health impairments. The health and economic consequences of IPV include the costs of physical injuries. Beyond injuries, about one in six murder victims is killed by an intimate partner; 40% of female homicide victims in the United States is killed by an intimate partner. Chronic health problems, such as mental health problems, depression, and PTSD, are associated with IPV survivors (51).

The Institute of Medicine has recommended that IPV screening and counselling should be a part of women's health visits, and obstetrician-gynecologists are in a uniquely important position to screen for and provide care for women who have experienced IPV. ACOG provides recommendations and examples of IPV screening questions, and patient education cards about IPV and reproductive coercion, noting that even if a woman is not able to acknowledge abuse initially, she may ultimately be able to do so in the right setting. **ACOG recommends that clinicians should routinely and universally screen for IPV in a setting that is private, nonjudgmental, and safe where the women is seen alone, without her partner, friends, family, or caretaker.** Printed resource materials addressing safety, with hotline numbers and referral information should be placed in areas such as restrooms, and other educational materials should be displayed in clinic settings (52).

SEXUAL ASSAULT AND RAPE

Sexual assault of children and adult women has reached epidemic proportions in the United States and is the fastest growing, most frequently committed, and most underreported crime (26,53,54). Sexual assault is a crime of violence, conquest, control, and aggression, not passion, and encompasses a continuum of sexual activity that ranges from sexual coercion to contact abuse (unwanted kissing, touching, or fondling) and forcible rape. **[6] The terms *sexual abuse survivor* and *assault survivor* are preferable to *victim***.

The U.S. Federal Bureau of Investigation (FBI) has revised an old definition that

recognized forceful vaginal penetration of a woman by a man's penis as rape to a definition recognizes that rape survivors and perpetrators may be female or male, and that oral and anal penetration with an object are defined as rape (54). Physical force is no longer a requirement, thus encompassing vulnerable victims and those who are intoxicated or otherwise mentally or physically incapable of demonstrating consent. This change in definition affects national statistics, but state and federal criminal laws vary; the term sexual assault is sometimes used interchangeably with rape. Sexual assault and rape may be further characterized, related to the age of the victim and the relationship to the abuser, such as acquaintance rape, date rape, statutory rape, child sexual abuse, and incest. Acquaintance rape and date rape refer to sexual assaults committed by an individual known to the victim, and if the perpetrator is a family member, incest is the term used. Statutory rape refers to consensual intercourse, variably defined by states, related to the age at which an individual can give consent.

Rape

Although the legal definition of sexual assault may vary from state to state, most definitions of *rape* contain the following elements:

1. **The use of physical force, deception, intimidation, or the threat of bodily harm**
2. **Lack of consent or inability to give consent because the survivor is very young or very old, impaired by alcohol or drug use, unconsciousness, or mentally or physically impaired**
3. **Oral, vaginal, or rectal penetration with a penis, finger, or object**

The definitions of rape and sexual assault and methods of data collection are generating underestimates. **[7] The NISVS from the U.S. CDC is an ongoing national survey** (55). **As reported in this survey, approximately 18% of women have been raped during their lifetimes. The lifetime prevalence of rape by an intimate partner was 8.8% for women, with 0.8% reporting intimate partner rape in the last year** (55). **Among female victims of completed rape, 78.7% were first raped before age 25 years, and 40.4% before age 18. The highest incidence of acquaintance rape is among women in the 12th grade of high school or in the first year of college** (56). **Approximately one-half of female college students report that they were date raped.** Many of these women may have been unable to give consent because they were impaired by alcohol or so-called date-rape drugs (*Rohypnol* or other benzodiazepines, *ketamine,* or *gamma-hydroxybutyrate [GHB]*). Date rape may have even greater psychological consequences than rape by a stranger because it involves a violation of trust. **There are many myths about rape. Perhaps the most common myth is that women are raped by strangers. Most statistics indicate that a minority of women**

are raped by someone they do not know; in the NISVS, only 14% of women reported rape by someone they do not know. Among female rape survivors, 51% reported that at least one perpetrator was a current or former intimate partner, 41% reported an acquaintance, and 13% reported a family member (53). Acquaintance rape may seem to be less traumatic than stranger rape, but survivors of acquaintance rape often take longer to recover. A common misconception about rape is that most survivors sustain serious physical or life-threatening injury. Sixty percent of rape survivors report some physical injury. General body injury is more than twice as common as genital and anal injury (57). Serious injury is rare, although many rape survivors report being fearful of serious injury or death during the assault. **The most common genital injuries from a sexual assault are vaginal lacerations resulting in bleeding and pain.** Intraperitoneal extension of a vaginal laceration or damage to the anal mucosa is rare. Common nongenital injuries in survivors include cuts, bruises, scratches, broken bones and teeth, and knife or gunshot wounds (58). Sexual assaults rarely result in death (59).

Only 26% of rape survivors seek medical attention after an assault (60). Women are more likely to immediately seek treatment after sexual assault if weapons were involved, serious physical injury occurred, or physical coercion or confinement was used in the assault (61). Many rape survivors do not inform their physicians about the assault and may never volunteer information about the assault unless they are directly asked. **ACOG recommends that health care providers should routinely inquire about a history of childhood sexual abuse or adult sexual assault** (54). **These experiences are common and often have a lasting and profound effect on a woman's mental and sexual function and her general health and well being. When obtaining a medical history, physicians should routinely ask, "*Has anyone ever forced you to have sexual relations?*"**

Medical Consequences of Sexual Assault

After a sexual assault, women have many concerns, including pregnancy and STDs (such as HIV infection). Rates of rape-related pregnancy among girls and women aged 12 to 45 years have been estimated at 5% (62). Adolescents may have particularly high rates of pregnancy because of low rates of contraception, and the fact that they may be victimized in incestuous relationships (6). Gynecologic problems such as chronic pelvic pain and sexual dysfunction are more common among women with a history of sexual abuse or assault (25).

Mental Health Consequences of Sexual Assault

In the aftermath of a sexual assault, women worry about being blamed for the

assault, having their name made public, and having their family and friends find out about the assault. The initial reactions to sexual assault may be shock, numbness, withdrawal, and possibly denial. It is difficult to predict how an assaulted individual will react. Despite their recent trauma, women presenting for medical care may appear calm and detached (63).

The *rape trauma syndrome* is a constellation of physical and psychological symptoms, including fear, helplessness, disbelief, shock, guilt, humiliation, embarrassment, anger, and self-blame. The acute, or disorganization, phase of the syndrome lasts from days to weeks. Survivors may experience intrusive memories of the assault, blunting of effect, and hypersensitivity to environmental stimuli. They are anxious, do not feel safe, have difficulty sleeping and eating, and experience nightmares and a variety of somatic symptoms (60,64,65). They may fear that their assailant will return to retaliate or rape them again.

In the weeks to months following the sexual assault, survivors often return to normal activities and routines. They may appear to have dealt successfully with the assault, but they may be repressing strong feelings of anger, fear, guilt, and embarrassment. During this phase of integration and resolution, they begin to accept the assault as part of their life experience, and somatic and emotional symptoms may decrease progressively in severity. However, the sequelae of rape often persist (27). Over the long term, survivors may have difficulty with work and family relationships. Disruption of existing relationships is not uncommon. Nearly half of the survivors lose their jobs or are forced to quit in the year following the rape, and half change their place of residency (23). Counseling can help a woman understand her own and common responses, potentially mitigating the adverse symptoms (64).

Examination

Many health care facilities now have trained sexual assault nurse evaluators (SANE) who provide acute medical examinations and who collect evidentiary materials. **National guidelines for sexual assault forensic examinations describe the role of sexual assault forensic examiners as gathering information for the medical forensic history, collecting and documenting forensic evidence, and documenting pertinent physical finding from patients** (66). These examiners coordinate with advocates to ensure that patients are offered crisis intervention and advocacy before, during, and after the examination process; offer information, treatment, and referrals for STIs, and other nonacute medical concerns; assess pregnancy risk and discuss treatment options with the patient, including reproductive health services; and testify in court if needed (66). **Because of the legal constraints and ramifications, consent must be obtained from the patient before obtaining the history, performing the physical examination, and collecting forensic evidence. Documentation of the handling of specimens is**

especially important, and the chain of evidence for collected material must be carefully maintained. Everyone who handles the evidence must sign for it and hand it directly to the next person in the chain. The chain of evidence extends from the examiner, to the police detective, to the crime laboratory, and finally to the courtroom. If an obstetrician-gynecologist who has not had experience in evidentiary examinations is called upon to perform an examination, they should consider seeking assistance from someone who is familiar with the state and local requirements for evidentiary evidence collection using a sexual assault evidence kit (54). **Coordinated community responses to sexual violence include Sexual Assault Response Teams (SARTs).**

The patient should be interviewed in a quiet and supportive environment by an examiner who is objective and nonjudgmental. Support personnel and patient advocates, such as family, friends, or a counselor from a rape crisis service, should be encouraged to accompany the patient. It is important not to leave the survivor alone and to give her as much control as possible over the examination. To provide useful forensic information, the examination should be performed as soon as possible after the incident occurred. It is important to ascertain whether the survivor bathed, douched, used a tampon, urinated, defecated, used an enema, brushed her teeth or used mouthwash, or changed her clothes after the assault. If a woman communicates with her physician about a sexual assault, she should be encouraged to go directly to an emergency facility without changing, bathing, or otherwise cleaning herself, as these activities can impair the collection of forensic evidence (54).

National guidelines for sexual assault examinations are based on a number of principles, including: (1) providing a coordinated approach to the examination; (2) focusing on victimcentered care; (3) assuring informed consent; (4) being aware of the scope and limitations of confidentiality; (5) informing the victim of the options related to reporting to law enforcement; and (6) informing victims of funding that may be available for the forensic medical examination under the Violence Against Women Act (VAWA) (66). **Except in situations covered by mandatory reporting laws, women may decide whether to report a sexual assault to law enforcement.** A respectful encouragement of forensic evidence collection, even if the patient is undecided about whether to report, can facilitate ultimate investigation and prosecution of the crime.

The national guidelines address sexual assault of adolescents and adults; prepubertal children require a different type of evaluation. Providers in all 50 states are required to report all cases of suspected or known childhood sexual abuse to appropriate authorities.

The forensic examination process addresses a number of considerations (66):

1. **Initial contact:** While some individuals who have been sexually assaulted may

present directly to a medical facility, typically the initial contact is with law enforcement, emergency services, or advocacy agency. The response to this initial contact should be standardized and victim centered.

2. **Triage and intake:** The initial response at the medical site includes evaluation, stabilization, and treatment for serious and life-threatening injuries. The safety of the patient and that of the staff should be considered. Forensic examiners and victim advocates should be contacted.
3. **Documentation of findings by health care personnel:** The examiner will need to document examination findings, the medical forensic history, and evidence collection in a medical forensic report.
4. **Medical forensic history:** The examiner will obtain a history to guide the examination and evidence collection. An advocate should be able to provide support and advocacy during the history taking, if the patient desires.
5. **Photography:** Documentation of injuries or other visible evidence will supplement the history and written documentation. Patient comfort and privacy should be considered and the processes explained.
6. **Examination and evidence collection procedures:** The examiner should recognize the evidentiary purpose of the examination, and attempt to collect as much evidence as possible, documenting evidence and injuries that may be pertinent. The examination and evidence collection should be explained to the patient. An understanding of the testing the evidence will receive will facilitate the appropriate collection and minimize evidence contamination. The general physical and anogenital examination should be thoroughly conducted and findings documented on body diagram forms. Medical specimens should be kept separately from evidentiary specimens.
7. **Alcohol and drug-facilitated sexual assault: The possibility that drugs and/or alcohol may have been** used to facilitate an assault, particularly in adolescents or young adults, should be kept in mind, and toxicology testing may be appropriate (54,67). Routine testing is not recommended; voluntary drug and/or alcohol use may be a factor. The evidence and its chain of custody must be preserved and maintained.
8. **STI evaluation and care:** The need for STI testing should be considered on an individual basis. Prophylaxis against STIs may be indicated, which encompasses follow-up STI examinations, testing, immunizations, counseling, and treatment. Laws in all 50 states limit the use of a survivor's past sexual history including evidence of previously acquired STIs as part of an effort to undermine her credibility (68). **Trichomoniasis, bacterial vaginosis, gonorrhea, and chlamydial infection are the most commonly diagnosed STIs among women who have been sexually assaulted. HBV infection can be prevented through postexposure vaccination;** HPV vaccination is recommended for females through age 25 (68). Testing for STIs

may include Nucleic Acid Amplification (NAAT) testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae,* and serum for evaluation of HIV, hepatitis B, and syphilis. **Because adherence to follow-up examination visits is poor among survivors of sexual assault, presumptive treatment is recommended by the U.S. CDC. This presumptive treatment involves antibiotics for chlamydia, gonorrhea, trichomonas, postexposure hepatitis B vaccination if the hepatitis status of the assailant is unknown and the survivor had not previously been vaccinated, and HPV vaccination for ages 9 to 26 years with follow-up vaccination series (**68). **HIV postexposure prophylaxis (PEP) recommendations should be individualized according to the risk,** if the assailant's HIV status is unknown (54,68). Consultation should be obtained from local HIV specialists of the National Clinicians' Consultation Center Post-Exposure Prophylaxis Hotline (1-888-448-4911) (54,69). Follow-up examinations provide an opportunity to detect infections acquired at the time of the assault, complete hepatitis B and HPV vaccinations if indicated, counsel and treat other STDs, and monitor for medication side effects. The timing of the follow-up examination is dependent on initial testing; repeat testing for HIV can take place at 6 weeks, and at 3 and 6 months (68).

9. **Pregnancy evaluation and care: All victims of sexual assault should be offered prophylaxis for pregnancy** with appropriate informed consent, consistent with guidelines (70). ACOG states that emergency contraception should be immediately available in hospitals and facilities where sexual assault victims are treated (54).
0. **Discharge and follow-up:** Follow-up medical care to address follow up of STD testing and prophylaxis, emergency contraception, and assess for psychological issues should be planned and coordinated with advocates and law enforcement representatives. **Ongoing supportive counseling for the patient should be arranged,** and the patient should be referred to a sexual assault center or a therapist who specializes in the treatment of sexual assault survivors.
1. **Examiner court appearances:** Health care providers who conduct the forensic examination should expect to be called on to testify in court as fact and/or expert witnesses (66).

ELDERLY ABUSE

Elder abuse is defined as a single or repeated act, or lack of appropriate actions, which causes harm, risk of harm, or distress to an individual 60 years or older (71). Elder abuse incorporates a number of issues, including neglect, emotional or psychological abuse, physical abuse, sexual abuse, and financial or material abuse and exploitation. Approximately two-thirds of elder abuse victims are women. Major risk factors for elder abuse include cognitive impairment, depression, anxiety, and having

disabilities or being homebound with its attendant social isolation. ACOG recommends assessing all patients older than 60 years for signs and symptoms of elder abuse, even asking whether they feel safe at home (71). Screening questions for elder abuse can be found online. Depending on state guidelines, elder abuse may be reportable to Adult Protection Services (72).

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SECTION III

Primary Medical Care



CHAPTER 21

Preventive Health Care and Screening

Wing Kay Fok, Paula J. Adams Hillard



CHAPTER 22

Primary Care

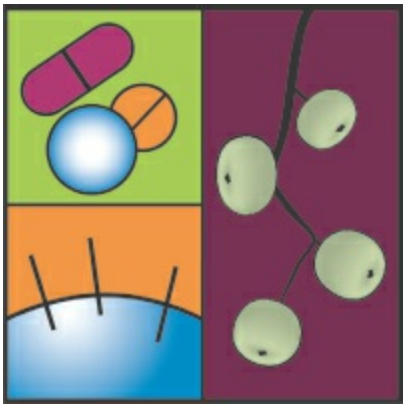
Sharon T. Phelan



CHAPTER 23

Common Psychiatric Problems

Angela Devi Shrestha, Nada Logan Stotland



CHAPTER 24

Complementary and Integrative Health Approaches

Tracy W. Gaudet

CHAPTER 21

Preventive Health Care and Screening



Wing Kay Fok, Paula J. Adams Hillard

Gynecologist as a Primary Care Provider
Approaches to Preventive Care
Guidelines for Primary and Preventive Care
Guide to Clinical Preventive Services
Counseling for Health Maintenance
Nutrition
Alcohol
Exercise
Smoking Cessation

KEY POINTS

1 Preventive health services that encompass screening and counseling for a broad range of health behaviors and risks are important components of general obstetric and gynecologic care.

2 Traditional gynecologic care—including cervical cytology testing, pelvic and breast screening examinations, and the provision of contraceptive services—is considered primary preventive care.

3 Routine health care assessments for healthy women include a medical history, physical examination, routine and indicated laboratory studies, assessment and counseling regarding healthy behaviors, and relevant interventions, taking into account the leading causes of morbidity and mortality within different age groups.

4 Through the Women's Preventive Services Initiative (WPSI), the American College of Obstetricians

and Gynecologists (ACOG) is coordinating with the U.S. Department of Health and Human Services (HHS) to develop and update recommendations for women's preventive health services.

5 Obesity, smoking, and alcohol abuse are preventable problems that have a major impact on long-term health; assessment, counseling, and referral for these health risks is a component of periodic health assessment and primary care.

[1] Although obstetrician-gynecologists are specialists in caring for women during pregnancy and adeptly manage abnormal gynecologic conditions, they also have a traditional role of providing primary and preventive care to women, particularly for women of reproductive age. Preventive health services that encompass screening and counseling for a broad range of health behaviors and risks are important components of general obstetric and gynecologic care. The obstetrician-gynecologist often serves as a woman's point of entry into the health care system, her primary care clinician, and a source of continuity of care (1).

Primary care emphasizes health maintenance, preventive services, early detection of disease, and availability and continuity of care. Women often regard their gynecologist as their primary care provider; indeed, many women of reproductive age have no other physician. Obstetrician-gynecologists estimated that at least one-third of their nonpregnant patients rely on them for primary care (2). **[2] As primary care physicians, obstetrician-gynecologists provide ongoing care for women through all stages of their lives—from the reproductive age to postmenopause. Many services provided as part of traditional gynecologic care, including cervical cytology testing, pelvic and breast screening examinations, and the provision of contraceptive services, are considered primary preventive care.** Some gynecologists include screening for certain medical conditions, such as hypertension, diabetes mellitus, and thyroid disease, and management of those conditions in the absence of complications, as a routine part of their practices.

Some traditional aspects of gynecologic practice, such as family planning and preconception counseling, are recognized as key Healthy People 2020 goals (3). Culturally appropriate evidence- and competency-based clinical guidelines are lacking in the United States, and preventing unintended pregnancies remains an elusive goal (4). Preventive medical services encompass screening and counseling for a broad range of health behaviors and risks, including sexual practices; prevention of sexually transmitted diseases (STDs); the use of tobacco, alcohol, and other drugs; diet; and exercise.

While promoting preventive health care can lead to significant improvements in the overall health, it remains a challenging task for many physicians, as they must prioritize which of the numerous preventive services to recommend and incorporate into everyday practice. Preventive care is often provided in conjunction with an entire team of clinicians, including other specialists, subspecialists, and allied health professionals. In

general, the approach to promoting preventive health care in clinical practice is to tailor services to individual patients based upon the age, lifestyle habits, medical and family history, and other risk factors.

Effectively communicating and explaining the relevant recommendations and the harms of inappropriate screening are equally important and crucial to the provision of preventive health. In a population-based cohort study, the existence of a patient's connection to a physician was more closely associated with the receipt of various levels of preventive care, than race or ethnicity (5). A team approach that extends beyond reliance on the clinician and incorporates all staff of an office system to facilitate reminders and provide patient information can be a very successful strategy for the timely delivery of quality preventive care services.

GYNECOLOGIST AS A PRIMARY CARE PROVIDER

The obstetrician-gynecologist frequently serves as a primary medical resource for women and their families, providing information, [3] guidance, and referrals when appropriate. **Routine health care assessments for healthy women are based on age groups and risk factors. Health guidance takes into account the leading causes of morbidity and mortality within different age groups.** Patient counseling and education require an ability to assess individual needs, assess stages of readiness for change, and use good communication skills, including motivational interviewing to encourage behavioral changes and ongoing care (6). A team approach to care is frequently helpful, utilizing the expertise of medical colleagues, such as nurses; advanced practice nurses, including nurse midwives and nurse practitioners; health educators; other allied health professionals, such as dieticians or physical therapists; relevant social services; and other physician specialists. All clinicians, regardless of the extent of their training, have limitations to their knowledge and skills and should seek consultation at appropriate times for the benefit of their patients in providing reproductive and nonreproductive care.

The National Ambulatory Medical Care Survey (NAMCS), conducted by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics is an annual nationally representative survey of visits to nonfederal office-based patient care physicians. It defines obstetrician-gynecologists among primary care providers, as opposed to medical or surgical subspecialists (7). In 2012, it was estimated that there were 929 million physician office visits. The visit rate for women aged 18 to 64 years (321 visits per 100 women) was 57% higher than the rate for men aged 18 to 64 years (204 per 100 men) (8).

Women's needs for primary care vary across their lifespan. One survey of women's satisfaction with primary care found that women in their early reproductive years (ages 18 to 34) were more satisfied with care coordination and comprehensiveness when

their regular provider was a reproductive health specialist, primarily an obstetrician-gynecologist physician as compared to a generalist, a generalist clinician plus an obstetrician-gynecologist, or no regular provider (9). The scope of services provided by obstetrician-gynecologists varies from one practice or clinician to another and may include more or fewer aspects of well-woman and reproductive health care. It is important to establish with each patient whether she has another primary care clinician, and who will be providing which primary care and preventive health services (1). In 2014, routine prenatal and gynecologic examinations were among the leading principal reasons for care (7).

When asked to characterize the nature of an office or clinic visit, obstetrician-gynecologists may or may not identify themselves as primary care providers, depending on a number of variables (10). Those variables may include the patient's age, pregnancy status, whether it is a new versus a return visit, diagnoses, insurance or referral status, and geographic practice region.

APPROACHES TO PREVENTIVE CARE

In health care, the focus is shifting from disease to prevention. Preventive care—including reproductive life planning, optimization of nutrition and exercise, screening for and management of chronic diseases, immunizations, management of infectious diseases, and attention to psychological and behavioral health—contributes to women's overall health. Efforts are under way to promote effective screening measures that can have a beneficial effect on public and individual health.

To ensure that women of all ages receive appropriate preventive health screenings, health care providers and patients need uniform, established guidelines for recommended preventive services for women.

The Institute of Medicine's July 2011 report noted a perceived lack of transparency in the derivation of certain clinical practice recommendations and in managing conflicts of interest (11). Variations in the guidelines' development processes were felt to be a fundamental cause of the lack of consistent guidelines across specialties and groups, such as the American College of Obstetricians and Gynecologists (ACOG), National Comprehensive Cancer Network (NCCN) and U.S. Preventive Services Task Force (USPSTF). These discrepancies were thought to contribute to provider uncertainty and patient confusion.

In 2016, in response to this concern over inconsistent recommendations, ACOG launched the Women's Preventive Services Initiative (WPSI). **[4] Through a 5-year cooperative agreement with the U.S. Department of Health and Human Services (HHS), Health Resources and Services Administration (HRSA), ACOG will coordinate the WPSI effort to develop, review, update and disseminate recommendations for women's preventive health care services.** WPSI aims to

promote thorough consideration of the best available evidence, ensure transparency and minimize the impact of individual bias, and conflicts of interest.

An advisory panel consisting of representatives from the ACOG, American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), and the National Association of Nurse Practitioners in Women's Health (NPWH) oversees the initiative. Representatives from many medical specialty societies and national health professional organizations listed in Table 21-1 constitute the Multidisciplinary Steering Committee (MSC).

Recommendations presented by the WPSI follow the criteria specified by the National Academies of Sciences, Engineering and Medicine (formerly the Institute of Medicine). Topics considered by the WPSI focus on specific evidence gaps and new recommendations not covered by existing recommendations from the USPSTF, the American Academy of Pediatrics (AAP) Bright Futures Initiatives for infants, children, and adolescents, and the CDC's Advisory Committee on Immunization Practices (ACIP).

Table 21-1 Women's Preventive Services Initiative 2016 Multidisciplinary Steering Committee Participating Organizations

American Academy of Family Physicians	American Osteopathic Association
American College of Obstetricians and Gynecologists	American Psychiatric Association
American College of Physicians	American Geriatrics Society
National Association of Nurse Practitioners in Women's Health	Association of Reproductive Health Professionals
Academy of Women's Health	Association of Women's Health, Obstetric and Neonatal Nurses
American Academy of Pediatrics	National Comprehensive Cancer Network
American Academy of Physician Assistants	National Medical Association
American Cancer Society	Association of Maternal and Child Health Programs
American College of Nurse-Midwives	National Partnership for Women and Families
American College of Preventive Medicine	National Women's Law Center
American College of Radiology	Patient Representative

Source: Women's Preventive Services Initiative. Final recommendations: preventive services for women. In: Recommendations for preventive services for women. Final report to the U.S. Department of Health and Human Services, Health Resources & Services Administration, December 2016. Washington, DC: American College of Obstetricians and Gynecologists; 2017:8.

Reviews and updates of the evidence for each topic under consideration were carefully undertaken. The scope of updates was based on Populations, Interventions, Comparators, Outcomes, Timing and Setting/Study Design (PICOTS) format. Searches were conducted in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and PsycINFO. Studies conducted in settings applicable to the United States were particularly targeted. Recommendations were adopted only if 75% agreement was reached by the Multispecialty Steering Committee. In general, recommendations apply to the general population of women in the United States at average risk for the conditions addressed.

One of the research gaps includes lack of sufficient evidence for tailoring many of the recommendations to the specific needs of racial and ethnic minority women and underserved populations.

Guidelines for Primary and Preventive Care

The initial evaluation of a patient involves a complete history, physical examination, routine and indicated laboratory studies, evaluation and counseling, appropriate immunizations, and relevant interventions. Risk factors should be identified and arrangements should be made for continuing care or referral, as needed.

In its first year, the WPSI updated nine topics (12).

In the subsequent 4 years, various subcommittees will be tasked with developing recommendations on one to two topics each year. The WPSI preventive services recommendations are presented in a single website, http://www.WomensPreventiveHealth.org. Recommendations will be reviewed for currency and accuracy at least every 24 months after submission to and adoption by HRSA.

Guide to Clinical Preventive Services

The USPSTF was commissioned in 1984 as a 20-member nongovernmental panel of experts in primary care medicine, epidemiology, and public health. The USPSTF, comprising primary care providers, now includes nonfederal experts in prevention and evidence-based medicine (such as internists, pediatricians, family physicians, gynecologist-obstetricians, nurses, and health behavior specialists); the task force conducts and publishes scientific evidence reviews on a variety of preventive health services with administrative and research support from the Agency for Health Care Research and Quality (AHRQ). Initial and subsequent reviews and recommendations are being revised and periodically released on the website sponsored by the AHRQ (13). The charge to the panel was to develop recommendations for the appropriate use of preventive interventions based on a systematic review of evidence of clinical effectiveness. The panel was asked to rigorously evaluate clinical research to assess the

merits of preventive measures, including screening tests, counseling, immunizations, and medications.

The task force uses systematic reviews of the evidence on specific topics in clinical prevention that serve as the scientific basis for recommendations. The task force reviews the evidence, estimates the magnitude of benefits and harms, reaches consensus about the net benefit of a given preventive service, and issues a recommendation that is assigned a grade from "A" (recommends; net benefit substantial), to "B" (recommends; net benefit moderate), "C" (recommends; selectively), "D" (recommends; against), "I" (insufficient evidence to recommend for or against) (Table 21-3). The grading system includes suggestions for practice, recommending that the service should be provided, discouraged, or that the uncertainty about the balance of benefits versus harms should be discussed. The task force evaluates services based on age, gender, and risk factors for disease, making recommendations about which preventive services should be included in routine primary care for which populations. *Primary preventive measures* are those that involve intervention before the disease develops, such as quitting smoking, increasing physical activity, eating a healthy diet, quitting alcohol and other drug use, using seat belts and receiving immunizations. *Secondary preventive measures* are those used to identify and treat asymptomatic persons who have risk factors or preclinical disease but in whom the disease itself has not become clinically apparent. Examples of secondary preventive measures are well known in gynecology, such as screening mammography and cervical cytology testing.

Table 21-2 Women's Preventive Services Initiative Clinical Recommendations 2016

Topic	Recommendation
Breast cancer screening for average-risk women	• Initiate mammography screening no earlier than age 40 and no later than age 50. Screening mammography should occur at least biennially and as frequently as annually. Screening should continue through at least age 74 and age alone should not be the basis to discontinue screening.
Breastfeeding services and supplies	• Recommends comprehensive lactation support services (including lactation counseling, education and breastfeeding equipment, and supplies) during the antenatal, perinatal, and postpartum periods. • Access to double electric breast pumps should be based on optimization of breastfeeding, and not predicated on prior failure of a manual pump.
Screening for cervical cancer	• Recommends cervical cancer screening for average-risk women aged 21 to 65 years. • Recommends screening with cytology alone every 3 years for women aged 21 to 29 years. • Recommends screening with cytology and human papillomavirus every 5 years or cytology alone every 3 years for women aged 30 to 65. • Cervical cancer screening is not recommended for women younger than 21 years or those older than 65 with adequate prior screening. Adequate prior negative

	screening is defined as three consecutive negative cytology results or two consecutive negative cotest results within the previous 10 years with the most recent test within the past 5 years.
Contraception	• Recommends the full range of female-controlled U.S. FDA-approved contraceptive methods, effective family planning practices, and sterilization procedures be available as part of contraceptive care. • Recommends timely authorization of contraceptives. • Emphasizes patient-centered decision making and allows for discussion of full range of contraceptive options.
Screening for gestational diabetes mellitus	• Recommends screening pregnant women for gestational diabetes mellitus after 24 weeks of gestation (preferably between 24 and 28 weeks of gestation). • Recommends screening with a 50-g oral glucose challenge test (followed by a 100-g 3-hour glucose tolerance test if results on the initial glucose challenge test are abnormal).
Screening for HIV infection	• Recommends prevention education and risk assessment for HIV infection in adolescents and women at least annually throughout the lifespan. • Recommends all women be tested at least once during their lifetime. • Screening for HIV is recommended for all pregnant women upon initiation of prenatal care. • Rapid HIV testing is recommended for pregnant women who present in active labor with an undocumented HIV status. • Risk factors for HIV infection in women include, but are not limited to: being an active injection drug user; having unprotected vaginal or anal intercourse; having multiple sexual partners; initiating a new sexual relationship; having sexual partners who are HIV-infected, bisexual, or injection drug users; exchanging sex for drugs or money; being a victim of sex trafficking; being incarcerated (currently or previously); and having other sexually transmitted infections (STIs).
Screening for interpersonal and domestic violence	• Recommends screening adolescents and women for interpersonal and domestic violence, at least annually. • Interpersonal and domestic violence includes physical violence, sexual violence, stalking and psychological aggression (including coercion), reproductive coercion, neglect and the threat of violence, abuse, or both. • Risk factors for interpersonal and domestic violence include but are not limited to pregnancy; younger and older age; increased stress; lesbian, gay, bisexual, transgender, and queer (or questioning) status; dependency; drug and alcohol misuse former or current military service; and living in an institutional setting. • Minimum screening intervals are unknown.
Counseling for STIs	• Recommends directed behavioral counseling by a health care provider or other appropriately trained individual for sexually active adolescent and adult women at an increased risk for STIs. • Risk factors include age younger than 25; a recent history of an STI; a new sex partner; multiple partners; a partner with concurrent partners; a partner with an STI; and lack of or inconsistent condom use.
Well-woman	

preventive visits	• Recommends that women receive at least one preventive visit per year beginning in adolescence and continuing across the lifespan.

Source: Women's Preventive Services Initiative. Final recommendations: preventive services for women. In: Recommendations for preventive services for women. Final report to the U.S. Department of Health and Human Services, Health Resources & Services Administration, December 2016. Washington, DC: American College of Obstetricians and Gynecologists; 2017:17–23.

The USPSTF has recognized that for certain issues in medicine, evidence from randomized controlled trials (RCT) are lacking and that it is necessary to consider evidence from other study designs. Nevertheless, even when incorporating evidence from non-RCT studies, insufficient evidence remains a limitation. As clinicians do not have the luxury of waiting for certain evidence, the USPSTF acknowledges the importance of four different "domains" when making clinical decisions about prevention. The four domains pertinent to the decision-making process are the preventable burden of suffering from a particular condition, potential harm of an intervention, monetary and opportunity costs of a particular service, and current practice landscape (15).

Table 21-3 U.S. Preventive Services Task Force Ratings

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of the net benefit (benefits minus harms). The USPSTF changed its grade definitions based on a change in methods in May 2007 and again in July 2012, when it updated the definition of and suggestions for practice for the grade C recommendation (14).

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service
C	The USPSTF recommends selectively offering or providing the service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service
I	The USPSTF concludes that the current	Read the clinical considerations

Statement	evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

International efforts to categorize the effectiveness of treatments include the Cochrane Library, which produces and disseminates high-quality systematic reviews of health care interventions. Their reviews and abstracts are published monthly and are available online and on DVDs by subscription (16). The Cochrane Library provides searchable databases online and through institutional purchase of licenses. Evidence-based guidelines are published in journals available in print and online by discipline (i.e., medicine, mental health, and nursing).

Counseling for Health Maintenance

During periodic assessments, patients should be counseled about preventive care based on their age and risk factors. **[5] Obesity, smoking, and alcohol abuse are associated with preventable problems that can have major long-term impacts on health.** Patients should be counseled about smoking cessation and moderation in alcohol use and directed to appropriate community resources as necessary. Positive health behaviors, such as eating a healthy diet and engaging in regular exercise, should be reinforced. Adjustments may be necessary based on the presence of risk factors and the woman's current lifestyle and condition. Efforts should focus on weight control, cardiovascular fitness, and reduction of risk factors associated with cardiovascular disease and diabetes (6).

Nutrition

Patients should be given general nutritional information and referred to other professionals if they have special needs (6). Assessment of the patient's body mass index (BMI) = weight (in kilograms) divided by height (in meters) squared (kilograms per square meter) will give valuable information about the patient's nutritional status. Tables and apps (applications) to calculate BMI are available in print and electronic resources. Patients who are 20% above or below the normal range require evaluation and counseling and should be assessed for systemic disease or an eating disorder. From 2013 to 2014, the overall age-adjusted prevalence of obesity was 40.4% (95% CI; 37.6%–43.3%) among adult women (17). In 2017, all states had more than 20% of adults with obesity. The South had the highest prevalence of obesity (32.4%), followed by the Midwest (32.3%), the Northeast (27.7%) and the West (26.1%) (18). Overweight and obesity substantially increase the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, and cancers of the endometrium, breast, and colon (19).

Central obesity—measured as the waist-to-hip ratio—is an independent risk factor for disease. Women with a waist circumference greater than 35 in are at higher risk of diabetes, dyslipidemia, hypertension, and cardiovascular disease (20). Metabolic syndrome is a complication of obesity that, while somewhat variably defined, includes a clustering of atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, and abdominal obesity and confers an increased risk for cardiovascular disease and diabetes (21). One-third to one-half of premenopausal women with polycystic ovarian syndrome (PCOS) meet the criteria for metabolic syndrome (22).

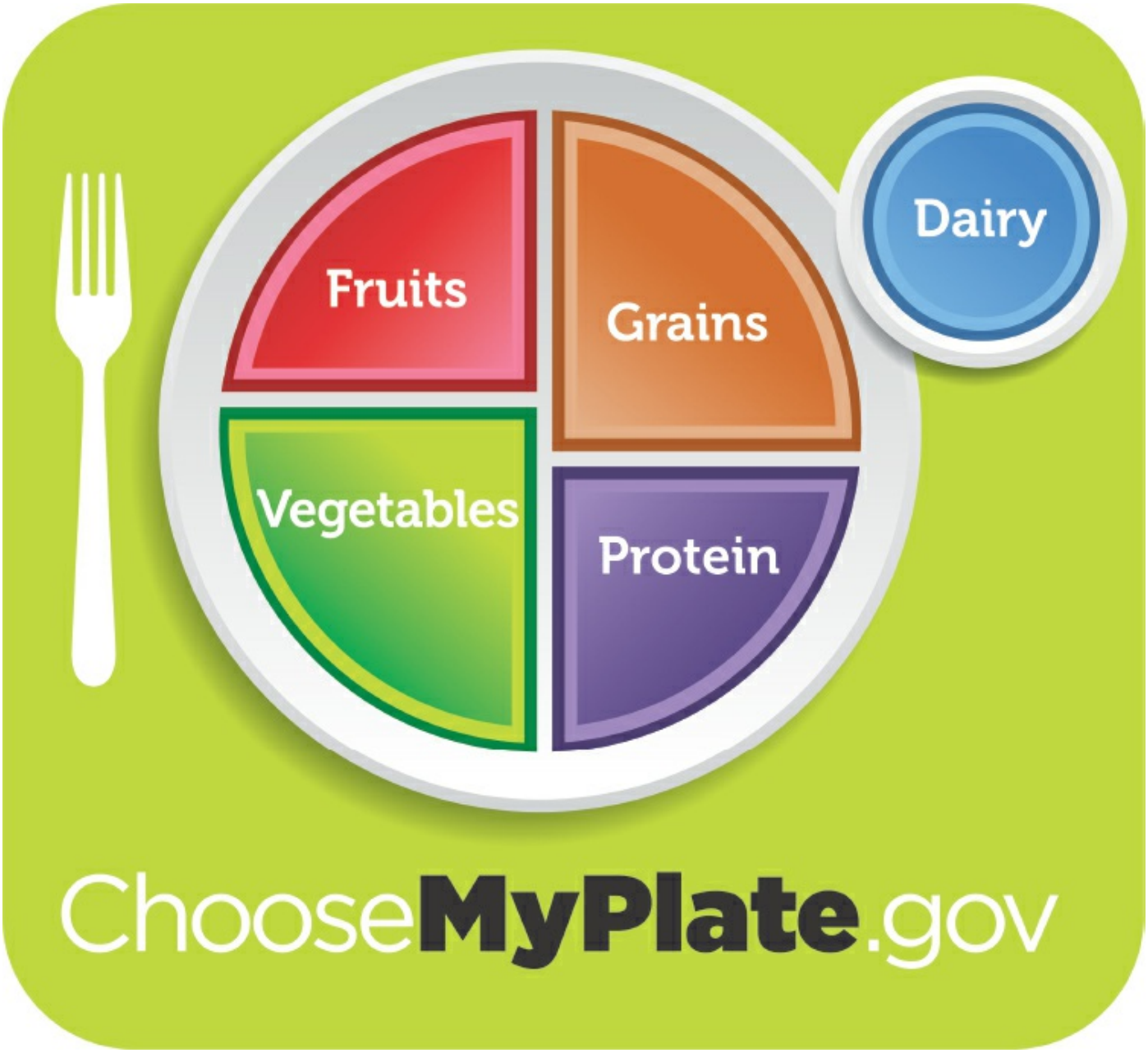


FIGURE 21-1 MyPlate icon. This is a new communications initiative based on the *2010 Dietary Guidelines for Americans,* replacing the Food Pyramid. It is designed to remind Americans to eat healthfully, and illustrates the five food groups using a familiar mealtime visual of a place setting. (From the U.S. Department of Agriculture, http://www.choosemyplate.gov)

Every 5 years, the U.S. Department of Agriculture (USDA) and (HHS) jointly publish a report containing nutritional and dietary information and guidelines for the general public, with the *2015–2020 Dietary Guidelines for Americans* being the most current edition (23). The guidelines provide evidence-based food and beverage recommendations for Americans aged 2 years and older with aims to promote health, prevent chronic disease, and help people reach and maintain a healthy weight. The *Dietary Guidelines* recommend including a variety of vegetables, fruits, grains, fat-free or low-fat dairy, a variety of proteins and oils as part of a healthy eating pattern. The MyPlate symbol is a useful tool to bring together the key elements of healthy eating patterns, translating the *Dietary Guidelines* into key consumer messages that are used in educational materials for the public **(Fig. 21-1)** (23). The guidelines include recommendations to balance food and physical activity and stay within daily calorie requirements.

Fiber content of the diet is being studied for its potential role in the prevention of several disorders, particularly colon cancer. It is recommended that the average diet for adult women contain 22 to 28 g of fiber per day (23). Whole-grain foods and vegetables, citrus fruits, and some legumes, are high in fiber and are emphasized in the guidelines for healthy foods.

Adequate calcium intake is important in the prevention of osteoporosis. A postmenopausal woman should ingest 1,200 mg per day. Adolescents require 1,300 mg per day. Because it may be difficult to ingest an adequate amount of calcium daily in an average diet, supplements may be required.

The U.S. Public Health Service has recommended that women of reproductive age who are capable of becoming pregnant take supplemental folic acid (0.4 mg daily) to help prevent neural tube defects in their infants. Surveys indicate that in 2007, 40% of women of childbearing age consumed a supplement, a percentage that is only half of the *Healthy people 2010* objective of 80% (24). Women who are contemplating pregnancy should be counseled about the risk of fetal neural tube defects and the role of folic acid supplementation in their prevention prior to conception (25).

Alcohol

Alcoholic beverages, if consumed, should be done so in moderation—up to one drink per day for women (23). A simple device called the T-ACE questionnaire (Tolerance; been Annoyed by criticism of drinking; felt need to Cut down; need for Eye-opener) can be used to elicit information about alcohol use and identify problem drinkers (26). Women should be questioned in a nonjudgmental fashion about their alcohol use and directed to counseling services as required.

Exercise

Exercise can help control or prevent hypertension, diabetes mellitus, hypercholesterolemia, and cardiovascular disease and helps to promote the overall

good health, psychological well-being, and a healthy body weight. Moderate exercise along with calcium supplementation can help retard bone loss in postmenopausal women. Physical activity, adequate nutrition, and good health are necessary for bone health (27). Exercise helps promote weight loss, strength and fitness, and stress reduction. Federal exercise guidelines from the HHS note that "regular physical activity reduces the risk of many adverse health outcomes; some physical activity is better than none; for most health outcomes, additional benefits occur as the amount of physical activity increases through higher intensity, greater frequency, and/or longer duration; most health benefits occur with at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity physical activity, such as brisk walking. Additional benefits occur with more physical activity; both aerobic (endurance) and muscle-strengthening (resistance) physical activity are beneficial; health benefits occur for children and adolescents, young and middle-aged adults, older adults, and those in every studied racial and ethnic groups; the health benefits of physical activity occur for people with disabilities; and the benefits of physical activity far outweigh the possibility of adverse outcomes" (28). Cardiovascular conditioning, stretching exercises for flexibility, resistance exercises, or calisthenics for muscle strength and endurance are recommended for most people. Older adults (65 years and older) should do exercises that maintain or improve balance if they are at risk of falling and should determine their level of effort for physical activity relative to their level of fitness (23). Factors that should be considered in establishing an exercise program include medical limitations, such as obesity or arthritis, and careful selection of activities that promote health and enhance compliance (1).

Cardiovascular fitness can be evaluated by measurement of heart rate during exercise. As conditioning improves, the heart rate stabilizes at a fixed level. The heart rate at which conditioning will develop is called the target heart rate (1). The American Heart Association recommends calculation of maximum heart rate using the formula 220 - age. Target heart rate should range from 50% to 70% for moderate exercise and 70% to 85% for strenuous exercise (29). A 2010 study examined the definition of a normal heart rate response to exercise stress testing in women and noted that the traditional male-based calculation of target heart rate may not be appropriate for women (30). The alternative formula for target heart rate, based on this research, is 206 - (patient's age × 0.88).

Smoking Cessation

Smoking is a major cause of preventable illness, and every opportunity should be taken to encourage patients who smoke to quit. Patient education about the benefits of smoking cessation, clear advice to quit smoking, and physician support improve smoking cessation rates, although 95% of smokers who successfully quit do so on their own. Self-help materials are available from the National Cancer Institute, and community-

based support groups and local chapters of the American Cancer Society and the American Lung Association. The combination of counseling and medication (nicotine and non-nicotine options) is more effective than either used alone, and Clinical Practice Guidelines on treating tobacco use, and dependence from the HHS provide recommendations (31).

The "5 As"—*A*sk, *A*dvise, *A*ssess, *A*ssist, and *A*rrange—are designed to be used with smokers who are willing to quit (32). The *Ask* component involves systematically identifying all tobacco users at every visit. It is important that the advice given to urge tobacco users to quit is clear, strong, and personalized. Next, providers should assess a patient's willingness to quit and provide assistance if applicable or provide an intervention to increase future quit attempts. In 2015, the USPSTF released evidence-based recommendations for behavioral and pharmacologic interventions to help people quit smoking. Patient-centered outcomes research strongly supports the use of behavioral interventions alone or in combination with pharmacotherapy. All pregnant women who smoke should receive behavioral interventions (33). Relapse prevention is important, with congratulations for any successes and encouragement to remain abstinent. Patients who use tobacco but are unwilling to quit at the time of the visit should be treated with the "5 Rs" motivational intervention: *R*elevance, *R*isks, *R*ewards, *R*oadblocks, and *R*epetition (31).

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CHAPTER 22

Primary Care



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Respiratory Infections
- Upper Respiratory Infections (URIs)
- Sinusitis
- Otitis Media
- Bronchitis
- Pneumonia
  - *Vaccination*

Cardiovascular Disease
- Hypertension
  - *Epidemiology*
  - *Measurement of Blood Pressure*
  - *Therapy*
  - *Monitoring Therapy*
- Cholesterol
  - *Terms and Definitions*
  - *Metabolism*
  - *Hyperlipoproteinemia*

Diabetes Mellitus
- Classification
  - *Type 1 Diabetes Mellitus*
  - *Type 2 Diabetes Mellitus*
- Diagnosis
- Assessment of Glycemic Control
- Treatment

Lifestyle
Oral Hypoglycemic Agents
Thyroid Diseases
Hypothyroidism
Clinical Features
Diagnosis
Therapy
Hyperthyroidism
Clinical Features
Diagnosis
Therapy
Thyroid Nodules and Cancer
Irritable Bowel Syndrome
Management
Gastroesophageal Reflux Disease
Carpal Tunnel Syndrome
Mitral Valve Prolapse Syndrome, Dysautonomia, and Postural Orthostatic Tachycardia Syndrome (POTS)

KEY POINTS

1 Respiratory infections in adults are commonly viral and do not require antibiotics. For good antibiotic stewardship, one needs to use them only for bacterial infections that require them. If empiric therapy is used, it should be based on the specific patient and the severity of the infection. All patients with possible community-acquired pneumonia should have a chest radiograph to establish the diagnosis and presence of complications.

2 Effective screening for hypertension and hyperlipidemia is critical to reduce the occurrence of cardiac disease (a primary cause of death). When hypertension or significant risks for hypertension are found, active lifestyle intervention needs to be initiated. If this is not adequate, pharmaceutical intervention is used to achieve a goal of less than 140/90. In patients with comorbidities such as diabetes or renal disease, the goal should be less than 130/80.

3 The role of diet in hyperlipidemia is still unclear although a low-fat diet along with weight loss and exercise do reduce lipids. Current recommendations strongly encourage the use of statins as first line pharmaceutical therapy with clear guidelines for use and optimal goals as targets.

4 Type 2 diabetes is increasing as the incidence of obesity increases. Screening high-risk individuals allows early diagnosis and intervention prior to development of complications. Lifestyle modifications including diet, weight loss, and exercise are the first steps in management.

5 Given the frequency of thyroid pathology in women, providers need to understand risk factors that merit screening and the proper physical examination to identify masses. The sensitive thyroid-stimulating hormone (TSH) assay is the single best screening test for hyperthyroidism and hypothyroidism.

As health care providers for women, gynecologists are responsible for providing care that extends beyond diseases of the reproductive organs to include much of the general medical care of their patients. Broadening the spectrum of care requires adjustments in practice, with less emphasis placed on the surgical aspects of the specialty. Early diagnosis and treatment of medical illnesses can have a major impact on a woman's

health. Although timely referral is important for complex and advanced diseases, many conditions can be screened for, recognized, and potentially treated initially by gynecologists.

Respiratory problems are the most common reasons patients seek care from a physician, so gynecologists should be aware of their pathophysiology. Cardiovascular disease has a significant impact on the overall morbidity and is the main cause of death in women. Cardiovascular disease is associated with cigarette smoking, hypertension, hypercholesterolemia, and diabetes mellitus (DM). These conditions are responsive to screening, behavior modification, and control to lower risk factors. Thyroid disease is a major cause of morbidity for women. Because of the interaction of hormones and the overall effect on the endocrine system, thyroid disease can be of special significance in women. The gynecologist should provide screening and initial therapy for these conditions and assess the need for referral.

RESPIRATORY INFECTIONS

Infections of the respiratory system can range from the common cold to life-threatening illness. Those with risk factors should be counseled about preventive measures. Vaccines against flu and pneumonia should be offered as indicated.

Upper Respiratory Infections (URIs)

This term can encompass a number of diagnoses including the "common cold." "Cold" is a term often used for a variety of virus-induced mild URIs that typically have the symptoms of stuffy nose, sore scratchy throat, cough, no or low-grade fever, and fatigue or malaise (1). Ear pain can be part of the cluster. Despite thoughts that "colds" are more common in certain times of the year, there is no seasonal variation in their incidence—only in the virus causing the cold. *Adenovirus, rhinoviruses, coronaviruses,* and *respiratory syncytial viruses* are common etiologies of "colds." Although patients will frequently equate colds and "flu," the viruses that cause influenza tend to have more body aches, fever, and systemic symptoms as well as being seasonal.

Differentiating which virus is causing a cold does not impact treatment, so cultures are not indicated unless there is concern for an influenza virus that might benefit from antiviral medication. The diagnosis of a cold tends to be a process of exclusion. The presence of temperature >100, facial pain, prolonged (>2 weeks) barking cough, exudate on pharynx/tonsils, abnormal breath sounds, or poor oxygen saturation would indicate that other diagnoses need to be considered, such as sinusitis, pertussis, strep throat, bronchitis, monospot, or influenza. In the presence of these findings, strep culture, pertussis screen, viral screen for influenza, or chest x-ray might be indicated.

The treatment of a cold is basically symptomatic. This includes aspirin/NSAID for

any body aches or low-grade temperature, hydration, decongestant (topical or oral), and good hand hygiene. In an otherwise healthy person a cold will last 7 to 10 days and occasionally up to 2 weeks. Spread is by droplets (both small from cough/sneeze and large on hands/environmental) and contact (hands or contaminated surfaces). Antibacterial wipes and cleaners do NOT impact the transmission of cold viruses (2). The use of decongestants such as pseudoephedrine or oxymetazoline HCl should not be used for more than 2 or 3 days because of a risk of a rebound effect.

The risk of acquiring a cold is increased in individuals who are sleep deprived, stressed, have children in day care settings, have chronic diseases, smoke, or have poor nutrition and immune deficiency. The last four situations increase the risk of a more severe "cold" and having it progress into a bacterial complication. Seasonal changes do NOT change the incidence of "colds" but only the virus that caused it.

Sinusitis

A problem frequently encountered in women is self-diagnosed "sinus problems." Many medical problems—headaches, dental pain, postnasal drainage, halitosis, and dyspepsia—may be related to sinus conditions. The sinuses are not an isolated organ, and diseases of the sinuses are often related to conditions that affect other portions of the respiratory system (i.e., the nose, bronchial tree, and lungs). Therefore, during the evaluation of symptoms attributable to sinusitis, the presence of other infections should be investigated.

Multiple infectious and chemical agents or reactions to nervous, physical, emotional, or hormonal stimuli may cause an inflammatory response in the respiratory system (3). Systemic diseases such as connective tissue syndromes and malnutrition may contribute to chronic sinusitis. Environmental factors in the workplace and geographic conditions (e.g., cold and damp weather) may aggravate or accelerate the development of sinusitis. Factors contributing to the development of sinus disease include atmospheric pollutants, allergy, tobacco smoke, skeletal deformities, dental conditions, barotrauma from scuba diving or airline travel, and neoplasms.

[1] Most acute infections (lasting less than 4 weeks) begin with a viral agent (acute viral rhinosinusitis [AVRS]) in the nose or nasopharynx that causes inflammation, blocking the draining ostia (3). The location of the symptoms varies by the anatomic site of infection—maxillary sinus over the cheeks, ethmoid sinus across the nose, frontal sinus in the supraorbital area, and sphenoid sinus to the vertex of the head —and typically last 7 to 10 days, clearing with nothing more than a decongestant. **Viral agents impede the sweeping motion of ciliary function in the sinus and, in combination with edema from inflammation, may occasionally lead to superinfection with bacteria (acute bacterial rhinosinusitis [ABRS]). The most common bacterial agents infecting sinuses are *Streptococcus pneumoniae* and**

Haemophilus influenzae. Gram-negative organisms are usually limited to compromised hosts in intensive care units. **[1]** Although less than 2% of acute sinusitis cases transition from viral to bacterial infections requiring antibiotics, more than 85% of patients receive antibiotic prescriptions. Chronic sinusitis (lasting more than 12 weeks) develops from either inadequate drainage or compromised local defense mechanisms. The flora usually is polymicrobial, consisting of aerobic and anaerobic organisms.

Sinus ailments frequently occur in middle-age individuals. Acute infection is usually located in the maxillary and frontal sinuses. Classically, infection in the maxillary sinus results from obstruction of the ostia found in the medial wall of the nose. Fever, malaise, a vague headache, and pain in the maxillary teeth are early symptoms. Reports of "fullness" in the face or exploding pressure behind the eyes often are elicited as well as increasing pain with bending over. Pressure and percussion over the malar areas can cause severe pain. Purulent exudates in the middle meatus of the nose or in the nasopharynx often are present. To differentiate between a "cold" and sinusitis the following can be helpful. Viral URI typically peak rapidly in 3 to 4 days and they consistently decline in severity of symptoms with full resolution in 7 to 14 days. Sinusitis in contrast will often persistent without improvement for over a week. A pattern of initial improvement with sudden worsening may represent a transition to a bacterial infection. Initial episodes of sinusitis do not require imaging studies; however, when persistent infections occur, studies and referral are indicated. Radiographic changes do not reliably identify sinusitis secondary to bacteria. Unless culture samples are obtained by direct needle drainage, they are contaminated by oropharyngeal flora and are thus of no value. For this reason, therapy usually is empiric.

Systemic decongestants containing *pseudoephedrine* are useful in shrinking the obstructive ostia and promoting sinus drainage and ventilation. Topical decongestants should be used for no longer than 3 days because prolonged use may lead to rebound vasodilation and worsening of symptoms. Mucolytics like *guaifenesin* may help thin sinus secretions and promote drainage. Antihistamines should be avoided in acute sinusitis because of their drying effects, which can lead to thickened secretions and poor drainage of the sinuses. Analgesics are recommended for pain relief. Therapies to relieve symptoms include facial hot packs and analgesics. Topical nasal steroids may accelerate the recovery in patients with viral sinusitis and those with a history of chronic rhinitis or recurrent sinusitis who seek treatment of acute rhinosinusitis (4,5). Improvement should be apparent within 48 hours of treatment, but 10 days may be necessary for complete resolution of symptoms. **If antibiotics are used, broad antibiotic coverage of common aerobes and anaerobes is necessary but should be limited to patients with acute pain, especially unilateral maxillary tooth, facial, or sinus pain, and purulent discharge, particularly if the symptoms initially**

improved and then worsened. This cluster of symptoms is more suggestive of bacterial rather than viral acute sinusitis. It should be noted that the majority of acute bacterial sinusitis cases resolve in 7 to 10 days without antibiotics, similarly to the viral form. [1] For this reason, in an otherwise healthy adult, the use of antibiotics is not recommended. In the setting of comorbidities such as diabetes, chronic respiratory disease, congestive failure or immunodeficiency state, the use of antibiotics for ABRS may be warranted. For acute bacterial sinus infections, *amoxicillin* (1,000 mg three times a day) remains the treatment of choice. *Amoxicillin* is inexpensive, penetrates the sinus tissues well, and can be changed to another antibiotic if symptoms have not improved in 48 to 72 hours. If these give only a minimal or no response after 7 days, consider broader-spectrum antibiotics. If beta-lactam resistance is likely, *amoxicillin/clavulanic acid* (875 mg twice daily) may be used. Other second-line drugs include, *levofloxacin* (500 mg qd), and doxycycline (200 mg qd for 5 to 10 days). The usual treatment course is 5 to 10 days, and patients should be informed that relapses might occur if the full course of treatment is not completed. [1] Trimethoprim/sulfamethoxazole and azithromycin are no longer recommended as a result of high rates of microbial resistance (3).

No clinical criteria can reliably identify those patients who might benefit from treatment with antibiotics. It is reasonable to treat women with presumed bacterial sinusitis if they have high fever, systemic toxicity, immune deficiency, or possible orbital or intracranial involvement (5). Although very rare, untreated sinus infections may have dire consequences, such as orbital cellulitis, leading to orbital abscess, subperiosteal abscess formation of the facial bones, cavernous sinus thrombosis, and acute meningitis. Brain and dural abscesses are rare; when they occur, it usually is the result of direct spread from a sinus. A patient complaining of abnormal vision such as diplopia, changes in mental status, and periorbital edema should prompt a referral to the emergency room for evaluation of intracranial or orbital extension. Computed tomography scanning is the most accurate diagnostic tool. The use of aggressive surgical approaches with broad-spectrum antibiotics is necessary for adequate drainage.

Otitis Media

Otitis media remains primarily a disease of children, but may affect adults, often secondary to a concurrent viral infection of the upper respiratory tract. Diagnosis in most cases reveals fluid behind the tympanic membrane. Treatment is directed to symptoms and involves the use of antihistamines and decongestants, despite few data to support their use for acute serous otitis, as this is typically caused by a blocked eustachian tube. Acute suppurative otitis media is usually a bacterial infection; *S. pneumoniae* and *H. influenzae* are the most common pathogens. [1] Symptoms include acute purulent otorrhea, fever, hearing loss, severe deep throbbing ear pain, and

leukocytosis. Physical examination of the ear reveals a red, bulging, or perforated membrane with possible pre- and postauricular nodes. Indicated treatment is broad-spectrum antibiotics such as *amoxicillin*, *amoxicillin/clavulanic acid, cefuroxime, erythromycin, or azithromycin* (6,7).

Bronchitis

Acute bronchitis is an inflammatory condition of the tracheobronchial tree. Most often it is viral in origin and occurs in winter. It accounts for up to 10% of ambulatory care visits. Common cold viruses (rhinovirus and coronavirus), adenovirus, influenza virus, and *Mycoplasma pneumoniae* (a nonviral pathogen) are the most common pathogens involved. Bacterial infections occur less commonly and may be secondary pathogens. Cough, hoarseness, and mild fever are the usual presenting symptoms. In the initial 3 to 4 days, the symptoms of rhinitis and sore throat are prominent; coughing may last as long as 3 weeks. Presence of tachycardia or tachypnea raises concern for pneumonia (8,9). The prolonged nature of these infections promotes the use of antibiotics to "clear up the infection" (8). Sputum production commonly occurs and may be prolonged in cigarette smokers. **[1]** Most serious bacterial infections occur in cigarette smokers, who have damage to the lining of the upper respiratory tree and changes in the host flora. Differential diagnosis includes the following: postnasal drip, asthma, pneumonia, gastroesophageal reflex disease (GERD), use of angiotensin-converting enzyme (ACE) inhibitors, and heart failure.

Physical examination discloses a variety of upper airway sounds, usually coarse rhonchi. Rales are usually not present on auscultation, and signs of consolidation and alveolar involvement are absent. **During auscultation of the chest, signs of pneumonia such as fine rales, decreased breath sounds, and euphonia ("E to A changes") should be sought.** If the results of the physical examination are uncertain or the patient's condition appears to be in respiratory distress chest radiography should be performed to detect the presence of parenchymal disease. Paradoxically, as the initial acute syndrome subsides, sputum production may become more purulent. Sputum cultures are of limited value because of the polymicrobial nature of infections. In the absence of complications, treatment is directed to relief of symptoms. **[1]** The use of antibiotics is reserved for patients in whom chest radiography findings are consistent with pneumonia (10,11). Cough is usually the most aggravating symptom and may be treated with antitussive preparations containing either *dextromethorphan* or *guaifenesin*. The use of *codeine* as a cough suppressant is discouraged. The efficacy of any expectorant is not proved. If the cough persists longer than 2 weeks the patient may have pertussis. This is treated with *azithromycin* or other macrolides (8).

Chronic bronchitis is defined as a productive cough from excessive secretions for at least 3 months in a year for 2 consecutive years. Prevalence is estimated to be

between 10% and 25% of the adult population who are smokers. Previously the incidence was lower in women than men, but as the prevalence of cigarette smoking in women increased, so too has the incidence of bronchitis in women. Chronic bronchitis is classified as a form of chronic obstructive pulmonary disease (COPD; e.g., "blue bloaters"). Other causes include chronic infections and environmental pathogens found in dust. The cardinal manifestation of disease is an incessant cough, usually in the morning, with expectoration of sputum. Because of frequent exacerbations, the hospitalizations involved and the complexity of medical management, these patients should be referred to an internist.

Pneumonia

Pneumonia is defined as inflammation of the distal lung that includes terminal airways, alveolar spaces, and the interstitium. Pneumonia may have multiple causes, including viral and bacterial infections or aspiration. Aspiration pneumonia is usually the result of depressed awareness commonly associated with the use of drugs and alcohol or anesthesia. Viral pneumonias are caused by multiple infectious agents, including influenza A or B, parainfluenza virus, or respiratory syncytial virus. Most viral syndromes are spread by aerosolization associated with coughing, sneezing, and even conversation. Incubation is short, requiring only 1 to 3 days before the acute onset of fever, chills, headache, fatigue, and myalgias. Symptom intensity is directly related to intensity of the host febrile reaction. Pneumonia develops in only 1% of patients who have a viral syndrome, but mortality rates may reach 30% in immunocompromised individuals and the elderly. An additional risk is the development of secondary bacterial pneumonias after the initial viral insult. These infections are more common in elderly patients and may explain the high fatality in this group (12). *Staphylococcal* pneumonias, which often arise from a previous viral infection, are extremely lethal regardless of patient age. **[1]** The best treatment for viral pneumonia is prevention by immunization. Treatment is supportive and consists mostly of administration of antipyretics and fluids.

Bacterial pneumonia is classified as either community-acquired (CAP) or nosocomial, and in many cases the classification determines prognosis and antibiotic therapy. **[1]** Risk factors that contribute to mortality are chronic cardiopulmonary diseases, alcoholism, diabetes, renal failure, malignancy, and malnutrition. Prognostic features associated with poor outcome include greater than two lobe involvement, respiratory rate greater than 30 breaths per minute on presentation, severe hypoxemia (<60 mm Hg on room air), hypoalbuminemia, and septicemia. Pneumonia is a common cause of adult respiratory distress syndrome (ARDS), with a mortality rate between 50% and 70% (12,13). CAP is the most common cause of severe sepsis and a leading cause of death from infection in the United States.

Signs and symptoms of pneumonia vary depending on the infecting organism and the patient's immune status. In typical **pneumonias, the usual presentation is a patient with high fever, rigors, productive cough, chills, and pleuritic chest pain. Chest radiography often will show infiltrates** (11). The following agents, listed in decreasing order, cause two-thirds of all bacterial pneumonias: *S. pneumoniae, H. influenzae, Klebsiella pneumoniae,* gram-negative organisms, and anaerobic bacteria. Atypical **pneumonias** are more insidious in onset than typical pneumonias. Patients have moderate fever without the characteristic rigors and chills. Additional symptoms include a nonproductive cough, headache, myalgias, and mild leukocytosis. Chest radiography reveals bronchopneumonia with a diffuse interstitial pattern; characteristically, the patient does not appear to be as ill as the x-ray suggests. Common causes of atypical pneumonia include viruses, *M. pneumoniae, Legionella pneumophila, Chlamydia pneumoniae* (also called the TWAR agent), and other rare agents.

A strong index of suspicion is required for diagnosis, especially in the elderly and immunocompromised individuals, who have altered response mechanisms. Subtle clues in the elderly include changes in mentation, confusion, and exacerbation of other illnesses. The febrile response may be entirely absent, and the results of the physical examination are not predictive of pneumonia. In high-risk groups, an increased respiratory rate of greater than 25 breaths per minute remains the most reliable sign of infection. Mortality in these high-risk groups of patients is strongly correlated with the ability of the host to mount normal defenses to the symptoms of fever, chills, and tachycardia.

All women suspected of having pneumonia should undergo chest radiography to establish the diagnosis and to detect alternate diagnoses such as congestive heart failure and tumors. [1] The chest radiograph can detect complications like pleural effusions and multilobar disease. In the setting of CAP in a markedly ill patient, a referral to a pulmonary specialist or to the local emergency room may be indicated because of the high rate of severe complications. The appropriate laboratory studies, including sputum cultures, Gram stains, etc., can be obtained.

The American Thoracic Society updated their original guidelines in 2007 and these are currently in the process of being revised again (12). These clinical recommendations use an evidence-based approach for the diagnosis and management of community-acquired pneumonia. Therapy should be directed at the responsible or most likely pathogen (13), but in many cases of pneumonia, the exact cause cannot be determined, and empiric therapy should be initiated. **[1]** The American Thoracic Society recommends empiric therapy based on four groups of specific patient profiles, the presence of modifying factors, and pneumonia severity **(Table 22-1)**:

- Group I: **Outpatients with no cardiopulmonary disease (congestive heart**

failure or COPD) and no modifying factors. These patients are in the lowest-risk group and are usually infected by pathogens such as *C. pneumoniae, M. pneumoniae,* or *S. pneumoniae.* Patients should be treated with an advanced-generation macrolide such as *azithromycin, clarithromycin,* or *doxycycline.*

- **Group II: Outpatients with cardiopulmonary disease or modifying factors.** Patients in this group usually have some comorbidities and are older than 50 years of age. Aerobic gram-negative bacilli, mixed infections with atypical pathogens, and drug-resistant *S. pneumoniae* (DRSP) should be considered in this patient population. Drug recommendations include *a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) or beta-lactam PLUS macrolide.*
- Group III: **Inpatients who are not in the intensive care unit and have cardiopulmonary or modifying factors.** Drugs for these patients include intravenous fluoroquinolone monotherapy or a combination of an intravenous beta-lactam agent plus either intravenous or oral administration of an advanced *macrolide* or *doxycycline.*
- Group IV: **Inpatients in the intensive care unit.** These patients usually have the most severe pneumonia, and all antibiotics are given intravenously. Immediate consultation with an internist, hospitalist, or infectious disease specialist is recommended.

Table 22-1 Modifying Factors that Increase the Risk of Infection with Specific Pathogens

Penicillin-resistant and Drug-resistant Pneumococci
Age >65 yrs
Beta-lactam therapy within the past 3 mo
Alcoholism
Immune-suppressive illness (including therapy with corticosteroids)
Multiple medical comorbidities
Exposure to a child in a day-care center
Enteric gram-negatives
Residence in a nursing home
Underlying cardiopulmonary disease
Multiple medical comorbidities
Recent antibiotic therapy
Pseudomonas aeruginosa

Structural lung disease (bronchiectasis)
Corticosteroid therapy (>10 mg of prednisone per day)
Broad-spectrum antibiotic therapy for >7 days in the past month
Malnutrition

Adapted from **American Thoracic Society.** Guidelines for the management of adults with community-acquired pneumonia. *Am J Respir Crit Care Med* 2001;163:1730–1754.

Oxygen therapy and hydration should be initiated in addition to antibiotic therapy. Given issues of bacterial resistance and development of severe life-threatening compromise, patients in groups III, IV, and the sicker patients in group II may benefit from consultation with a pulmonary specialist or an internist. Most patients will have an adequate clinical response within 3 days of treatment. Oral antibiotics may be given when patients meet the following criteria: ability to eat and drink, improvement in cough and dyspnea, afebrile (<100°F) on two occasions 8 hours apart, and a decreasing white blood cell count. If other clinical features are favorable, patients may be switched to oral antibiotics even if febrile. They may be discharged on the same day that oral antibiotics are started if other medical and social factors are favorable.

Vaccination

There are numerous vaccines that need to be administered to adults depending on age, comorbidities, and presence of young children. All primary care providers should be familiar with the recommended immunizations and urge their patients to have them. Many are available at pharmacies by prescription if a practice has not undertaken the cost of providing vaccines at the office. The Centers for Disease Control and Prevention (CDC) has a comprehensive chart outlining the vaccines for adults (14). See Figure 22-1. **The *influenza vaccine* should be given every fall to high-risk groups: individuals 50 years of age or older; anyone with serious long-term health problems such as heart disease, lung disease, kidney disease, diabetes, and weak immune systems as with HIV and AIDS; individuals on long-term steroids or receiving cancer treatment; women who are pregnant during the flu season (November through April); and anyone coming in close contact with people at risk of serious influenza like physicians, nurses, and family members.** Vaccination is best given from October to mid-November. Antiviral agents should not be used as a substitute for vaccination but may be a useful adjunct. The four agents approved for use in the United States are *amantadine, rimantadine, zanamivir,* and *oseltamivir.* These drugs should be given within 2 days of the onset of symptoms to shorten the duration of uncomplicated illness caused by influenza (15).

CARDIOVASCULAR DISEASE

The risk factors for coronary artery disease are presented in Table 22-2. Central to treating cardiovascular disease is the control of contributing diseases and risk factors through lifestyle modifications (Table 22-3). Aerobic exercise protects against cardiovascular disease (16). Additional aspects of prevention of myocardial disease, renal disease, and stroke include control of hypertension, identification and control of diabetes and obesity, and control of dietary fats, especially cholesterol, in susceptible individuals **(Fig. 22-2)**.

Table 22-2 Major Risk Factors for Coronary Artery Disease

Age >55 for men and >65 for women
Family history of cardiovascular disease (men <55 yrs; women <65 yrs)
Physical inactivity
Diabetes mellitus
Cigarette smoking
Dyslipidemia
Obesity (body mass index ≥30)
Hypertension
Microalbuminuria or estimated glomerular filtration rate <60 mL/min

Adapted from **Chobanian AV, Bakris GL, Black HR, et al.** The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). *JAMA* 2003;289:2560–2572.

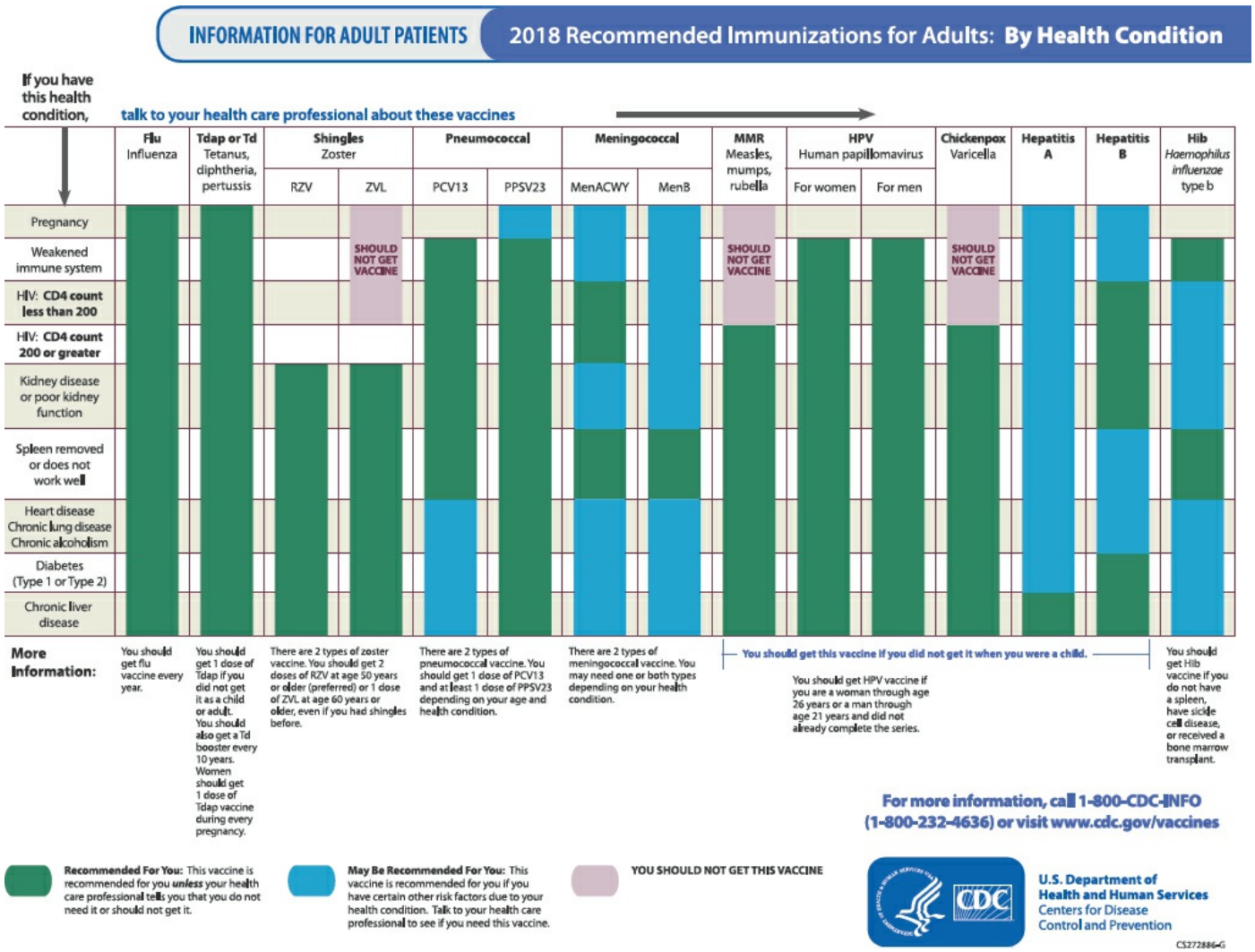


FIGURE 22-1 Recommended immunizations for adults by health condition 2017. (Adapted from U.S. Department of Health and Human Services, Center for Disease Control and Prevention. Recommended immunizations for adults by age. Available online at https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule-easy-read.pdf. Accessed September 28, 2017.)

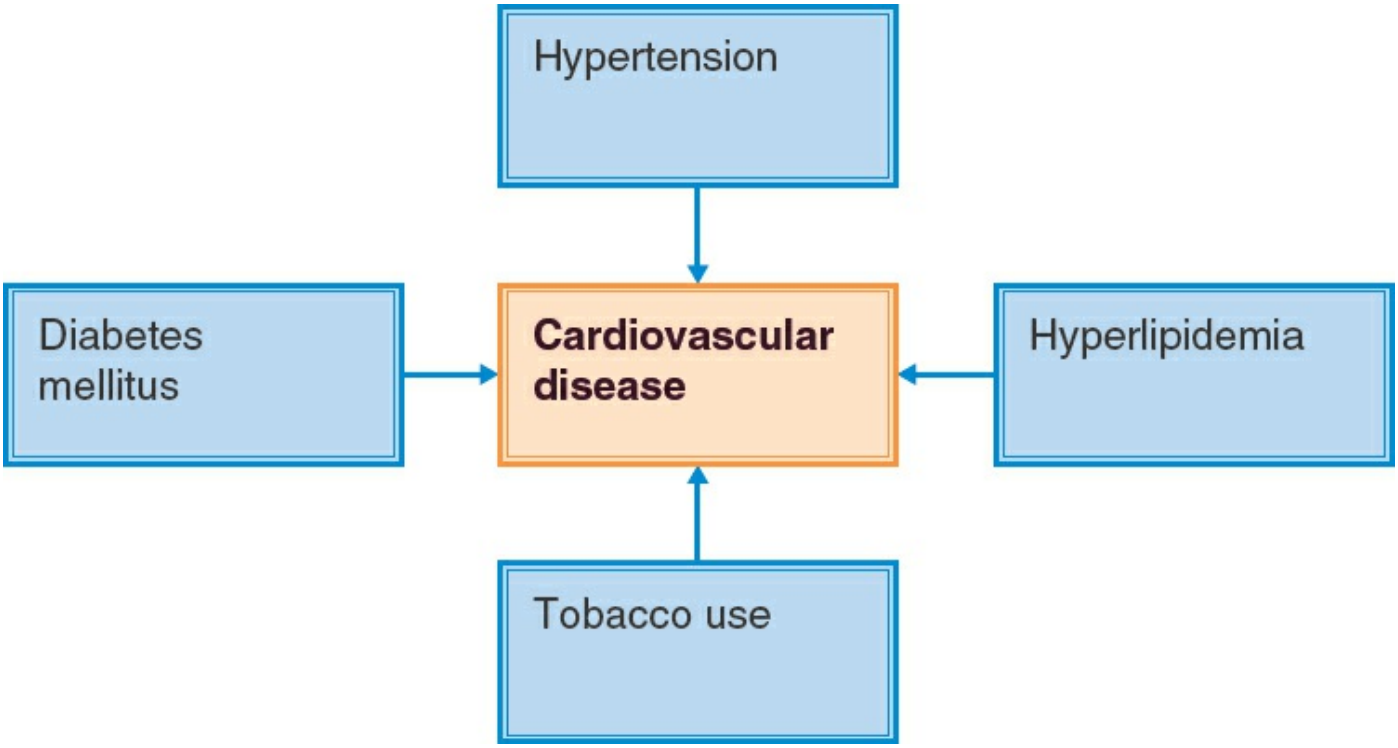


FIGURE 22-2 Disease and risk factors contributing to cardiovascular disease.

Table 22-3 Lifestyle Adjustments to Manage Hypertension

Weight reduction to maintain a body mass index of 18.5–24.9
Limit alcohol use to two drinks per day for men (24 oz beer, 10 oz of wine, 3 oz of 80-proof whiskey) and no more than one drink per day for women and lighter-weight persons
Regular aerobic exercise (at least 30 min per day of brisk walking most days of the week)
Decrease salt intake to less than 2.4 g of sodium or 6 g of sodium chloride per day
Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat

Adapted from **Chobanian AV, Bakris GL, Black HR, et al.** The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). *JAMA* 2003;289:2560–2572.

Hypertension

The relationship between hypertension and cardiovascular events such as stroke, coronary artery disease, congestive heart disease, and renal disease is well known. More than 50 million people in the United States have hypertension. It is found in 15% of the population between the ages of 18 and 74 years; the incidence increases with age and varies with race. Recognition and treatment of hypertension may decrease the development of renal and cardiac disease.

Epidemiology

The incidence of hypertension is twice as high in African Americans than in whites. Geographic variations exist: the southeastern United States has a higher prevalence of hypertension and stroke, regardless of race (17). Preventive measures can be most effective in those at highest risk, such as in African American women and individuals from the lowest socioeconomic level (18). The influence of genetic predisposition is poorly understood. **Classically, hypertension is defined as blood pressure levels higher than 140/90 when measured on two separate occasions.** Life insurance risk tables indicate that when blood pressure is controlled to lower than 140/90, normal survival occurs over a 10- to 20-year follow-up, regardless of gender. Recommendations are based on sustained blood pressures higher than 140/90 (see **Fig. 22-3**) (19).

Table 22-4 Laboratory Tests and Procedures Recommended in the Evaluation of Uncomplicated Hypertension[a]

Urinalysis
Complete blood count
Potassium
Creatinine or estimated glomerular filtration rate
Calcium
Fasting glucose
Lipid profile that includes HDL, LDL, and triglycerides after a 9- to 12-hr fast
12-lead electrocardiogram

[a]If any of the above are abnormal, consultation or referral to an internist is indicated.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Adapted from **Chobanian AV, Bakris GL, Black HR, et al.** The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). *JAMA* 2003;289:2560–2572.

Table 22-5 Blood Pressure (BP) Classification (Adults 18 Yrs and Older)

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	>160	or >100

Modified from **Chobanian AV, Bakris GL, Black HR, et al.** The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). *JAMA* 2003;289:2560–2572.

More than 95% of individuals with hypertension have primary or essential hypertension (cause unknown), whereas fewer than 5% have secondary hypertension resulting from another disorder. [2] Key factors to be determined in the history and physical examination include presence of prior elevated readings including a history of pre-eclampsia, previous use of antihypertensive agents, a family history of cardiovascular death before age 55, use of weight-loss supplements and excessive intake of alcohol or sodium (**Tables 22-2** and **22-3**). Lifestyle modification is considered important in the therapy of hypertension; thus, a detailed history of diet and physical activity should be obtained (16). Baseline laboratory evaluations to rule out reversible causes of hypertension (secondary hypertension) are listed in **Table 22-4**. Diagnosis and management are based on the classification of blood pressure readings, as presented in **Table 22-5**.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) released their seventh report in 2003. The purpose was to provide an evidence-based approach to the prevention and management of hypertension. [2] **Following are some of the key points of this report:**

- **Systolic blood pressure in those older than 50 years is a more important cardiovascular risk factor than diastolic blood pressure.**
- **Beginning at 115/75 mm Hg, the risk of cardiovascular disease doubles for each increment of 20/10 mm Hg.**
- **Individuals who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension.**
- **Patients with prehypertension (systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg) require health-promoting lifestyle modifications to prevent the progressive rise in blood pressure and cardiovascular disease.**
- **For uncomplicated hypertension, thiazide diuretic should be used in most cases for medical treatment, either alone or combined with drugs from other classes.**
- **Other antihypertensive drug classes (ACE inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel blockers) should be used in the presence of specific high-risk conditions (Fig. 22-3).**

These recommendations were supplemented in the 2014 JNC8 meeting with the following (19):

- In the general population aged 60+, initiate pharmacologic treatment at systolic pressures ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg to reach treatment goal of less than 150/90 mm Hg.
- In the general population aged less than 60, initiate pharmacologic treatment to lower blood pressure at a diastolic of 90 mm Hg or greater.
- In the general population aged less than 60, initiate pharmacologic treatment to lower blood pressures at a systolic of 140 mm Hg or greater.
- In population aged 18 or more with chronic kidney disease or diabetes, initiate pharmacologic treatment to lower blood pressure at systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater.
- In the general black population including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker.
- The main objective of hypertensive treatment is to attain and maintain a goal BP. If the goal BP is not reached within a month of treatment, increase the dose of the first drug or add a second agent. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategies or for the management of complicated patients.

[2] Regardless of therapy or care, hypertension will be controlled only if patients are motivated to maintain their treatment plan. If blood pressure control is not easily achieved, if the systolic blood pressure is higher than 180 mm Hg, or if the diastolic reading is higher than 110 mm Hg, referral to an internist is recommended. Referral is indicated if secondary hypertension is suspected or evidence of end-organ damage (renal insufficiency or congestive heart failure) is present.

Measurement of Blood Pressure

Essential variables in the evaluation of hypertension are the acquisition of measurements and the need to standardize measurements (20). **"White coat" or office hypertension (i.e., elevated just by seeing a physician) may occur in up to 30% of patients.** For patients who have repeated normal measures outside of the office, it is reasonable to use ambulatory or home monitoring devices. Given the variation of accuracy and patient interpretation, it is advisable for the patient to bring their blood pressure unit into the office to calibrate it against the office-based measurements.

Blood pressure protocols for measurement should be standardized. The following steps will optimize the accuracy of the reading:

- The patient should rest for 5 minutes in a seated position with legs uncrossed.
- Use the right arm for measurements (for unknown reasons, the right arm has higher readings).

- The cuff should be applied 2 cm above the bend of the elbow.
- The cuff should be inflated to 30 mm Hg above the disappearance of the brachial pulse, or 220 mm Hg.
- The cuff should be deflated slowly. **The cuff size is important, and most cuffs are marked with "normal limits" for the relative size they can accommodate.** The most common clinical problem encountered is small cuffs used with obese patients, resulting in "cuff hypertension."
- Phase-V Korotkoff is when sounds completely disappear. Most experts in hypertension advocate the use of phase-V Korotkoff sounds.

The use of automated devices may help eliminate discrepancies in measurements. Regardless of the method or device used, two measurements should be obtained with less than a 10 mm Hg disparity to be judged adequate. When repeated measures are performed, there should be a 2-minute rest period between readings. Blood pressure has a diurnal pattern, so determinations preferably should be done at the same time.

Therapy

[2] Nonpharmacologic interventions or lifestyle modifications should be attempted before initiation of medication. Drug therapy should be initiated for systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg. An important element in lifestyle modifications is to modify all contributors to cardiovascular disease. In obese patients, weight loss, especially in individuals with truncal and abdominal obesity, can play a significant role in the prevention of atherosclerosis (16). A loss of just 10 lb was reported to lower blood pressure. Enquiries into dietary practices should be made to eliminate excess salt, cholesterol, and fats in the diet. Dietary interventions that use calcium, magnesium, and potassium supplementation did not make a clinically significant reduction in pressure (21). **[2] An exercise program, weight loss, and moderating alcohol intake (to no more than two alcoholic beverages per day) contribute to overall cardiovascular health. Aerobic exercise alone may prevent hypertension in 20% to 50% of normotensive individuals** (16).

[2] The goal of therapy is for the patient to lower blood pressure into the "normal range": a systolic reading less than or equal to 120 mm Hg and a diastolic reading less than or equal to 80 mm Hg. If lifestyle modifications are not sufficient to control blood pressure, then pharmacologic intervention is indicated (Fig. 22-3).

Diuretics

The most commonly used medication for initial blood pressure reduction is a thiazide diuretic. The mechanism of action is to reduce plasma and extracellular fluid

volume. This lowering of volume is thought to decrease peripheral resistance. Cardiac output initially decreases and then normalizes (19). The important long-term effect is a slight decrease in extracellular fluid volume. Potassium-sparing diuretics (*spironolactone, triamterene,* or *amiloride*) are available in fixed doses and should be prescribed to prevent the development of hypokalemia. Potassium supplementation is less effective than the use of potassium-sparing agents. **Thiazide diuretics are best used in patients with creatinine levels less than 2.5 g/L.** Control of hypertension with concurrent renal insufficiency is difficult and is probably best handled by an internist or nephrologist. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) limits the effectiveness of this class of drugs. Other side effects of thiazide diuretics include hyperuricemia, which may contribute to acute gout attacks, glucose intolerance, and hyperlipidemias (19).

Angiotensin-Converting Enzyme Inhibitors

The ACE inhibitors are first-line drugs in the treatment of hypertension. There are relatively few side effects; chronic cough is the most worrisome and is a common reason of discontinuing the use of this group of drugs. Other agents should be considered for patients at risk for pregnancy (a strict contraindication). ACE inhibitors can be used in combination with other agents, including diuretics and calcium channel antagonists. In contrast to beta-blocking agents, these medications can be used in patients with asthma, depression, and peripheral vascular disease. For unknown reasons, they are less effective in African Americans unless a diuretic is used concomitantly. Use with diuretics increases the effectiveness of both drugs, but hypovolemia may result and must be monitored. Any NSAID, including *aspirin,* may decrease the antihypertensive effectiveness. **Creatinine levels should be measured at the start of therapy and 1 week after initiation of any ACE inhibitor.** An increase of up to 35% of the baseline creatinine value is acceptable, and treatment should be continued unless hyperkalemia develops.

Angiotensin-Receptor Blockers

The angiotensin-receptor blockers such as *losartan* and *valsartan* interfere with the binding of angiotensin II to AT_1 receptors. As with ACE inhibitors, they are effective in lowering blood pressure, without causing the side effect of coughing. Angiotensin-receptor blockers have favorable effects on the progression of kidney disease in individuals who have diabetes, and on those without diabetes and congestive heart failure.

Calcium-Channel Blockers

Calcium-channel blockers represent a major therapeutic breakthrough for patients with coronary artery disease. They are effective in patients with hypertension and

peripheral vascular disease. The mechanism of action is to block calcium movement across smooth muscle, therefore promoting vessel wall relaxation. Calcium channel blockers are useful in treating concurrent hypertension and ischemic heart disease. In addition, these drugs are particularly effective in the elderly and African Americans. Side effects noted include headache, dizziness, constipation, gastroesophageal reflux, and peripheral edema. The addition of long-acting calcium-channel blockers made these preparations more amenable for use in hypertension. A relative contraindication for use of these drugs is the presence of congestive heart failure or conduction disturbances.

Adrenergic Inhibitors

Beta blockers were used extensively for years as antihypertensive agents. The mechanism of action is decreasing cardiac output and plasma renin activity, with some increase in total peripheral resistance. As a class, they are an excellent source of first-line therapy, especially for migraine sufferers. Formulations such as *atenolol* are water soluble, $beta_1$ selective, and have fewer side effects than *propranolol.* At higher doses, $beta_2$ effects emerge. An advantage of water-soluble agents is a longer half-life. Reduced dosing schedules improve compliance. Side effects of beta blockers include an increase in triglyceride levels and a decrease in high-density lipoprotein (HDL) cholesterol and blunting of adrenergic release in response to hypoglycemia. NSAIDs may decrease the effectiveness of beta blockers. Contraindications to beta blockers are asthma, sick sinus syndrome, or bradyarrhythmia.

The use of $alpha_1$-adrenergic drugs as single agents decreases total cholesterol and low-density lipoprotein (LDL) cholesterol while increasing HDL cholesterol, in contrast to the metabolic effects of beta-blocking agents. They may contribute to stress urinary incontinence in women because of altered urethral tone. Their mode of action is to promote vascular relaxation by blocking postganglionic norepinephrine vasoconstriction in the peripheral vascular smooth muscle. When $alpha_1$-adrenergic drugs are used in combination with diuretics, hypotension may be further exacerbated. Therapy should begin with small doses taken at bedtime followed by incremental increases. Other side effects that may limit the usefulness of these agents in some patients include tachycardia, weakness, dizziness, and mild fluid retention.

Direct Vasodilators

***Hydralazine* is a potent vasodilator used for years in obstetrics for severe hypertension associated with preeclampsia and eclampsia.** The mechanism of action is direct relaxation of vascular smooth muscle, primarily arterial. Major side effects include headaches, tachycardia, and fluid (sodium) retention that may result in paradoxical hypertension. Several drug combinations are used to counter the side effects and enhance antihypertensive effects of hydralazine. This is not a typical first line medication.

Central-Acting Agents

Central-acting agents (*methyldopa* and *clonidine*) have long been used in obstetrics. The mechanism of action is to inhibit the sympathetics in the central nervous system, resulting in peripheral vascular relaxation. Side effects, including taste disorders, dry mouth, drowsiness, and the need for frequent dosing (except for the transdermal form of *clonidine*), limited the popularity of this group of drugs. **Sudden withdrawal of *clonidine* may precipitate a hypertensive crisis and induce angina.** Compliance is always a major issue, and side-effect profiles contribute significantly to patient nonadherence. With the introduction of new classes of drugs with improved efficacy and reduced side effects, the use of medications in this class is expected to decline.

Monitoring Therapy

Blood pressure readings should be monitored frequently by the patient, or in the office at 1- to 2-week intervals, when initiating intervention. If the patient has other diseases (i.e., cardiovascular, renal), therapy should be initiated earlier and directed to the target organ. If lifestyle modification alone is successful, close monitoring is necessary at 3- to 6-month intervals. When lifestyle modification is unsuccessful, a blood pressure medication should be started to decrease target organ disease. When beginning therapy, concurrent medical conditions treatable with a common agent should be sought. Gender is not an important consideration in choosing an antihypertensive agent. However, presence of diabetes, renal disease, or race can impact preferred initial medication. **Figure 22-3** shows a schematic of how to approach initiating pharmacologic interventions.

After antihypertensive medications are initiated, monitoring should be instituted at approximately monthly intervals to determine blood pressures and to assess side effects. The serum creatinine and potassium levels should be monitored one to two times per year. When blood pressure goals are reached, patients may be seen in the office at 3- to 6-month intervals. Patients capable of home blood-pressure monitoring should be encouraged to measure the blood pressure at the same time twice weekly. **If intolerable side effects develop, a different class of medications should be used and the patient's progress monitored.** Patients whose blood pressure is difficult to control, especially if requiring two agents, should be considered for referral. Patients with evidence of target organ disease should be considered for referral to the appropriate specialist for more intensive diagnostic workup and therapy.

Cholesterol

[3] The dietary influence of cholesterol on atherosclerosis and its relationship to hypertension and cardiovascular events (myocardial infarction and stroke) is

widely debated in the scientific and lay communities. The controversy centers on the effect of dietary cholesterol in assessing the risk and prevention of cardiovascular disease (22). Many assume that all cholesterol and fat in the diet have negative health consequences. Cholesterol metabolism is complex, and some of our knowledge is extrapolated from animal models. The role of cholesterol testing (who, when, and at what age) is hotly debated among health care professionals, and the test itself is fraught with multiple variables that affect results.

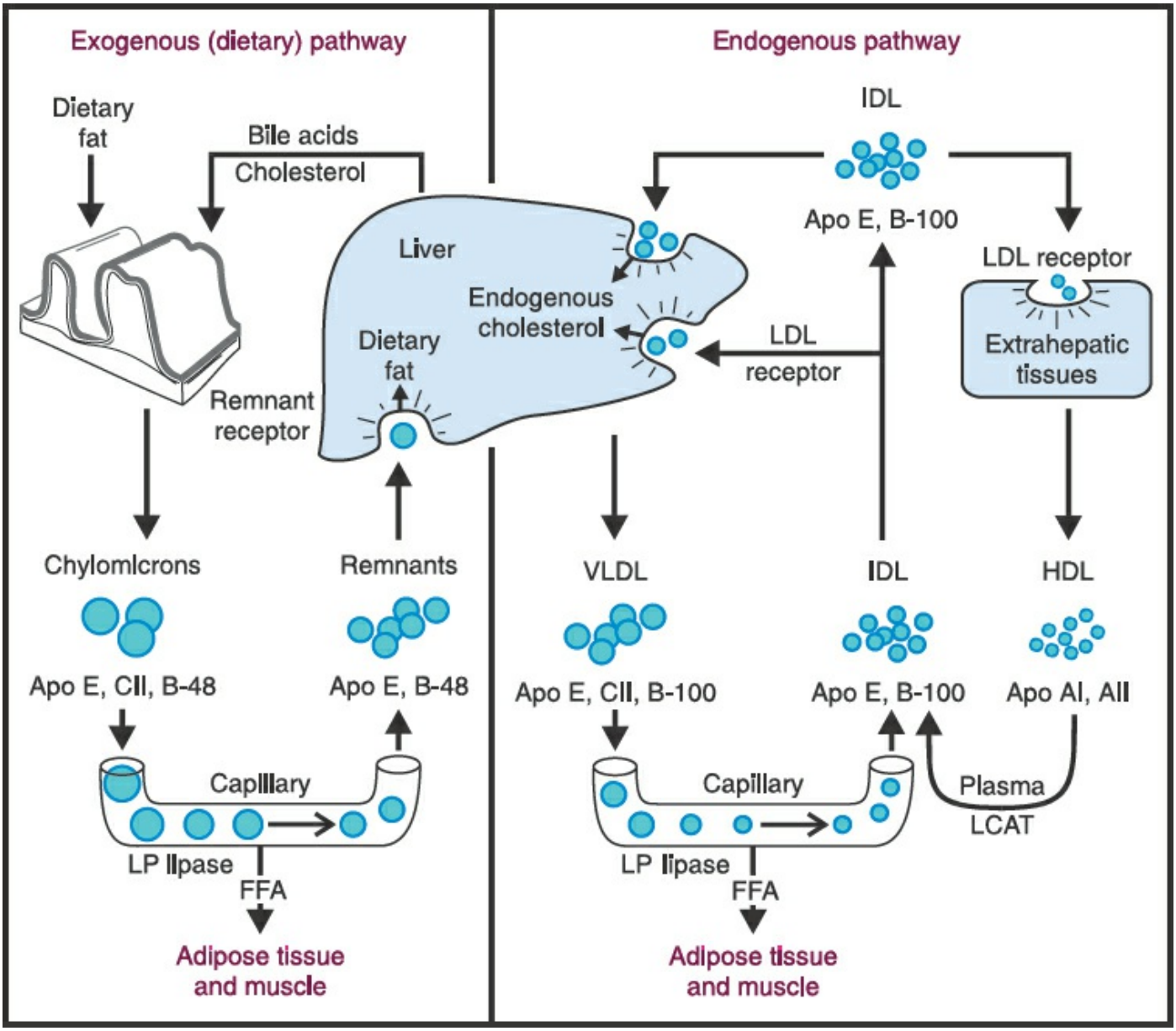


FIGURE 22-4 Metabolic pathways of lipid metabolism. Apo, apoprotein; LP, lipoprotein; FFA, free fatty acid; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very–low-density lipoprotein; HDL, high-density lipoprotein; LCAT, lecithin cholesterol acyltransferase.

Terms and Definitions

Cholesterol is usually found in an esterized form with various proteins and glycerides

that characterize the stage of metabolism. The important lipid particles in cholesterol metabolism are noted in the schematic on Figure 22-4.

Metabolism

Cholesterol metabolism is divided into two pathways: (i) the exogenous pathway derived from dietary sources, and (ii) the endogenous pathway or the lipid transport pathway. Individuals vary in their ability to metabolize cholesterol. Hyporesponders may be given cholesterol-loaded diets with no effect on serum cholesterol measurements. Hyperresponders, in contrast, have high serum cholesterol levels, regardless of dietary intake. Explanations for these differences are well described in animal models, but not in humans.

Despite the negative connotation of LDL in cardiovascular disease, it is a very important cellular metabolite and precursor for adrenocortical cells, lymphocytes, and renal cells. The liver uses LDL for synthesis of bile acids and free cholesterol, which is secreted into the bile. In the normal human, 70% to 80% of LDL is removed from the plasma each day and secreted in the bile by utilization of the LDL receptor pathway.

The final metabolic pathway is the transformation of HDL cholesterol in the extrahepatic tissue. HDL cholesterol carries the plasma enzyme lecithin cholesterol acyltransferase (LCAT). LCAT allows HDL cholesterol to resynthesize lipids to very–low-density lipoprotein (VLDL) cholesterol and recycle the lipid cascade. HDL cholesterol acts as a "scavenger" and therefore reverses the deposit of cholesterol into tissues. There is good evidence that HDL cholesterol is responsible for the reversal of atherosclerotic changes in vessels, hence the term "good cholesterol" (22).

Hyperlipoproteinemia

When cholesterol is measured, various fractions are reported. Plasma cholesterol or total cholesterol consists of cholesterol and unesterified cholesterol fractions. If triglycerides are analyzed in conjunction with cholesterol, then assumptions can be made concerning which metabolic pathway may be abnormal.

Hyperlipoproteinemias are defined by establishing a "normal population" and then setting various limits at the 10th and 90th percentiles. Standards for women set the 80th percentile for cholesterol at 240 mg/dL and the 50th percentile at 200 mg/dL (Table 22-6). A diet low in animal fat and high in vegetable and fiber consumption helps control the level of cholesterol. Plasma elevations of chylomicrons, LDL, VLDL, various remnants of intermediate-density lipoprotein (IDL), and VLDL are classified by the elevated fraction.

Evaluation

There are multiple causes of variation in cholesterol measurements (23). **[3] Major sources of variation within individuals include diet, obesity, smoking, ethanol**

intake, and the effects of exercise. Other clinical conditions that affect cholesterol measurements include hypothyroidism, diabetes, acute or recent myocardial infarction, and recent weight changes. Measurements can be altered by fasting, position of the patient while the sample is drawn, the use and duration of venous occlusion, various anticoagulants, and the storage and shipping conditions.

Table 22-6 Initial Classification Based on the Total Cholesterol, LDL, HDL, and Triglyceride Levels

Initial Classification	
Total cholesterol	
<200 mg/dL	Desirable blood cholesterol
200–239 mg/dL	Borderline high blood cholesterol
≥240 mg/dL	High blood cholesterol
LDL cholesterol	
<100 mg/dL	Optimal cholesterol
100–129 mg/dL	Near or above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
≥190 mg/dL	Very high
HDL cholesterol	
<40 mg/dL	Low HDL cholesterol
≥60 mg/dL	High HDL cholesterol
Triglycerides	
<150 mg/dL	Normal
150–199 mg/dL	Borderline high
200–499 mg/dL	High
>500 mg/dL	Very high

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Adapted from **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486–2497.

- **Age and gender contribute to variations in total cholesterol measurements. [3] Before age 50, women have lower lipid values than men, after which age**

the level in women is higher than in men. This finding may be modified by exogenous oral conjugated estrogens.

- **Seasonal variation also occurs,** with lipid samples in December or January being found to be approximately 2.5% higher than those measured in June or July.
- **The effect of diet and obesity is well established.** [3] Weight reduction in an obese individual affects the triglyceride level, which may decrease as much as 40%. Total cholesterol and LDL decrease less than 10% with diet; however, HDL increases approximately 10%. Weight gain negates any benefit from prior weight loss. Accuracy of lipid measurements depends on the stability of the patient's weight.
- **Alcohol and cigarette smoking are well-known modifiers of cholesterol. Moderate sustained alcohol intake increases HDL and decreases LDL; there is a complementary increase in triglycerides.** [3] **Alcohol has a protective effect when taken in moderation (defined as approximately two alcoholic drinks [2 oz of absolute alcohol] per day), but this effect is negated in higher quantities.** Smoking has the opposite effect, increasing LDL and triglyceride levels and decreasing HDL. HDL_3 decreases with cigarette smoking. The critical number of cigarettes smoked is 15 to 20 per day, regardless of gender, and a variation in the number smoked will affect results. Caffeine has a mixed effect on lipoprotein measurements and should be avoided for 12 hours before blood collection.
- **Exercise is an important variable in the overall risk management of heart disease.** [3] Moderate levels of exercise are as important in the overall cardiovascular health as control of hypertension and cessation of cigarette smoking. Strenuous exercise lowers the concentrations of triglycerides and LDL and increases HDL in the serum. Because of these acute blood changes, vigorous exercise should be avoided within 12 hours of drawing the blood for testing.
- **Patients with hypothyroidism have increased levels of total cholesterol and LDL.**

Testing

Because of the diurnal variation of blood triglycerides, blood samples should be collected in the morning after a 12-hour fast. One of the most important aspects of overall standardization of lipoprotein measurements is the laboratory used. It may be worthwhile to consult a clinical pathologist to determine if the laboratory complies with CDC standards for cholesterol and lipoprotein measurements.

Management

When hyperlipidemia is confirmed on at least two separate occasions, secondary causes should be diagnosed or excluded by taking a detailed medical and drug history, comprehensive physical examination, and appropriate laboratory tests. Causes of secondary dyslipidemia include diabetes, hypothyroidism, obesity, obstructive liver disease, chronic renal failure, pregnancy, and use of medications such as progestins, anabolic steroids, and corticosteroids. **Therapeutic lifestyle changes should be initiated in all patients to reduce their risk of coronary heart disease:**

1. **[3] Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg per day)**
2. **Therapeutic options for enhancing LDL lowering, such as plant stanols/sterols 2 g per day and increased viscous (soluble) fiber 10 to 25 g per day**
3. **Weight reduction**
4. **Increased physical activity**
5. **Smoking cessation and alcohol only in moderation**

The 2013 ACC/AHA Cholesterol Management guidelines changed the management of cholesterol to prevent the occurrence of cardiovascular disease including stroke (24). The recommendations primarily involved patient age, family history of hypercholesterolism, gender, and presence of comorbidities, along with lipid levels. To assist in judging individual risks, an atherosclerotic cardiovascular disease (ASCVD) risk calculator has been developed by the AHA (25). Although many groups challenge the accuracy of the calculations stating they consistently overestimate risks, it is still a useful tool.

[3] The level I recommendations from the 2013 guidelines regarding initiation of medication included:

- High-intensity statin therapy should be initiated (or continued) in patients ≤75 with clinical ASCVD. If not tolerated, moderate-intensity therapy is second line.
- Individuals with LDL ≥190 mg/dL or triglycerides ≥500 need to be evaluated for secondary causes of hyperlipidemia.
- Adults >21 with LDL >190 mg/dL should be treated with statins (high intensity if tolerated).
- Moderate-intensity statin therapy should be initiated (continued) for adults aged 40 to 75 years with diabetes.
- ASCVD calculator should be used to estimate 10-year ASCVD risk for individuals with LDL 70 to 189 mg/dL without clinical ASCVD to guide when statins should be initiated.
- Adults 40 to 75 years of age with LDL 70 to 189 mg/dL without clinical ASCVD or diabetes and an estimated 10-year risk of ASCVD ≥7.5% should be treated

with moderate-intensity statins.

[3] Patients with a family history of cardiovascular disease (history of premature coronary artery problems and strokes) should be tested and started on conservative programs in their 20s. As noted above, if their LDL is greater than 190 mg/dL, they should be started on statins. Otherwise an ASCVD calculation should be done and pharmaceutical therapy started if the 10-year risk is 7.5% or more. Any woman with coronary heart disease or equivalents such as diabetes or other forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease) should initiate lifestyle changes if her LDL is 100 mg/dL or more and drug therapy if her LDL is 190 mg/dL or her 10-year risk calculation is 7.5% or more.

Periodic assessment of cardiovascular risk factors should be done starting at age 40 in patients without prior identified risks. An annual assessment of weight, blood pressure, exercise routine, and smoking status is supported by expert opinion. A true screen requires lipid profile. Recommendations are to do this every 5 years unless there is a significant change in the patient's risk profile, which may merit more frequent screens. The data for routine screening in patients less than age 40 is unclear with no study clearly demonstrating a benefit. For these reasons, USPSTF states it can make no recommendation for or against such screening (26).

Prior to the 2013 ACC/AHA guidelines and confirmed by the U.S. Preventive Service Task Force recommendation, bile acid–binding resins *cholestyramine* and *colestipol* were the mainstay of therapy (26). The significant side effects of nicotinic acid and fibric acid derivatives and poor patient compliance caused by those side effects relegated them to second or third line treatment.

[3] Statins (HMG-CoA [3]-hydroxy-3methyl-glutaryl-coenzyme A reductase inhibitors) have become the mainstay of treatment and prevention. These include *atorvastatin, fluvastatin, lovastatin, pravastatin,* and *simvastatin.* These medicines inhibit HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. **Multiple clinical trials showed that *pravastatin, simvastatin,* and *lovastatin* have a beneficial effect in cardiovascular disease.** Statins are better tolerated than other lipid-lowering drugs, but reported side effects have concerned patients. These include severe myalgias, muscle weakness with increases in creatine phosphokinase, and, rarely, rhabdomyolysis, leading to renal failure. Detailed studies have shown that most of these are mild and resolve with cessation of the medication (24,26,27). The severe side effects of rhabdomyolysis and renal failure are extremely rare. This results in a very favorable benefit to risk ratio for the statins when used in a moderate-risk population (27). As the 10-year risk decreases, the benefit to risk ratio also decreases. For this reason, the USPSTF recommends that patients with less than a 10% risk of an ASCVD event in the next 10 years not start statins without a

physician/patient discussion of risks and benefits of statins.

DIABETES MELLITUS

DM is a chronic disorder of altered carbohydrate, protein, and fat metabolism resulting from a deficiency in the secretion or function of insulin. The disease is defined by the presence of either fasting hyperglycemia or elevated plasma glucose levels based on an oral glucose tolerance testing (OGTT). The major complications of DM are primarily vascular, renal, and metabolic. **[4]** The prevalence of DM is higher in women (especially with a history of gestational diabetes) and certain ethnic groups, although a background rate in the general population is 6.29%, which has increased threefold in 15 years (28).

[4] Risk factors for DM are:

1. **Age greater than 45 years**
2. **Adiposity or obesity**
3. **A family history of diabetes**
4. **Race/ethnicity**
5. **Hypertension (blood pressure 140/90 mm Hg or greater)**
6. **HDL cholesterol less than or equal to 35 mg/dL and/or a triglyceride level greater than or equal to 250 mg/dL**
7. **History of gestational diabetes or delivery of a baby weighing more than 9 lb**

Major complications of DM include blindness, renal disease, gangrene of an extremity, heart disease, and stroke. Diabetes is one of the four major risk factors for cardiovascular disease.

Classification

In 2016, an expert committee was convened by the American Diabetes Association to review the proposed standards for medical care in diabetes. Their findings were reported in 2017 in Diabetes Care. The goal of the revision was to clarify guidelines for nomenclature and testing that might reduce diagnostic confusion and improve patient well-being (Table 22-7). The terms *insulin-dependent diabetes mellitus* (IDDM) and *noninsulin-dependent diabetes mellitus* (NIDDM) were replaced by the terms type 1 and type 2 DM based on insulin levels and function but not on the patient's age.

Type 1 Diabetes Mellitus

With type 1 diabetes, the major metabolic disturbance is the absence of insulin from the destruction of beta cells in the pancreas. Insulin is necessary for glucose metabolism and cellular respiration. When insulin is absent, ketosis results. The cause

of type 1 diabetes is unknown; data suggest an autoimmune association from either a viral infection or toxic components in the environment. Studies in the past decade showed a correlation between many autoimmune diseases and the human leukocyte antigens (HLA).

Table 22-7 Classification of Diabetes Mellitus

1. **Type 1 diabetes** Characterized by pancreatic destruction leading to insulin deficiency typically due to autoimmune beta cell destruction
2. **Type 2 diabetes** A combination of insulin resistance and some degree of inadequate insulin secretion
3. **Gestational diabetes mellitus** Is diabetes diagnosed in the second or third trimester of pregnancy without pre-existing diabetes
4. **Specific types of diabetes due to other causes** A. Endocrinopathies (Cushing, acromegaly, pheochromocytoma, hyperaldosteronism) B. Drug- or chemical-induced (esp. organ transplant medications or glucocorticoids) C. Diseases of the exocrine pancreas (pancreatitis, neoplasia, cystic fibrosis) D. Infections E. Genetic defects of beta-cell function and insulin action

Adapted from **Cefalu W, ed.** Standards of medical care in diabetes—2017. *Diabetes Care* 2017;40(supplement 1).

Insulin-sensitive tissues (muscle, liver, and fat) fail to metabolize glucose efficiently in the absence of insulin. In uncontrolled type 1 diabetes, an excess of counter-regulatory hormones (cortisol, catecholamines, and glucagon) contributes to further metabolic dysfunction. In the absence of adequate amounts of insulin, increasing breakdown products of muscle (amino acid proteolysis), fat (fatty acid lipolysis), and glycogen (glucose glycogenolysis) are recognized. There is an increase in glucose production from noncarbohydrate precursors as a result of gluconeogenesis and ketogenesis in the liver. Without prompt treatment, severe metabolic decompensation (i.e., diabetic ketoacidosis) will occur and may lead to death.

Given the significant complexity and risks involved in the management of type I DM, it is not advised that a generalist be primarily responsible for the management of insulin and the associated comorbidities. These patients should be followed by a provider who specializes in diabetes management.

Type 2 Diabetes Mellitus

[4] Type 2 DM is a heterogeneous form of diabetes that commonly occurs in older age groups (>40 years) and more frequently has a familial tendency than type 1 diabetes. This form of DM accounts for approximately 90% to 95% of those with diabetes. The presence of risk factors strongly influences the development of type 2

diabetes in susceptible populations.

[4] Risk factors for type 2 diabetes include ethnicity, obesity, family history of DM, sedentary lifestyle, impaired glucose tolerance (IGT), upper-body adiposity, and a history of gestational diabetes and hyperinsulinemia.

In contrast to the absence of insulin that occurs with type 1 diabetes, in type 2 diabetes the altered metabolism of insulin results in insulin resistance. **[4]** This condition is characterized by impaired glucose uptake in target tissues. A compensatory increase in insulin secretion results, causing higher-than-normal circulating insulin levels (29). Obesity is present in 85% of affected patients. The cause of type 2 diabetes is unknown, but defects in the secretion and action of insulin are suspected.

Diagnosis

Three methods are available to diagnose DM in nonpregnant women:

1. **A single** fasting **blood glucose greater than or equal to 126 mg/dL on two separate occasions**
2. **An A1c ≥6.5% or random blood glucose equal to or above 200 mg/dL in an individual with classic signs and symptoms of diabetes (polydipsia, polyuria, polyphagia, and weight loss)**

A 2-hour OGTT greater than or equal to 200 mg/dL after a 75-g load of glucose. **[4] The term IGT has been replaced with the term prediabetic state and is not considered diabetes diagnosis. However, it is important to identify these individuals for more frequent screening and intervention. Diagnostic criterion for prediabetes is fasting glucose greater than or equal to 100 mg/dL but less than 126 mg/dL,** or A1c between 5.7% and 6.4%, or a 2-hour value on a 75-g OGTT between 140 and 199 mg/dL (29).

It should be noted that fasting blood glucose, 2-hour OGTT, and A1c screenings perform similarly but interestingly often pick up different patients with positive screens. The 2-hour OGTT will result in the largest number of patients receiving a diagnosis of diabetes. A1c is often the easiest initial screen but the results can be impacted by race/ethnicity and anemia/hemoglobulinopathies.

[4] Patients who should be considered for diabetes testing can be determined by the use of a diabetes risk calculator or using a listing of risk factors. The calculators can be found at the American Diabetes Association website and are available for downloads (30). **Historical risk factors include:**

- **All individuals 45 years of age or older (repeat at a minimum of 3-year intervals)**

- **Persons with classic signs and symptoms of diabetes (i.e., polyuria, polydipsia, polyphagia, and weight loss)**
- **Ethnic groups at high risk (Pacific Islanders, Native Americans, African Americans, Hispanic Americans, and Asian Americans)**
- **Obesity or overweight (body mass index >25 kg/m^2) (or 23 kg/m^2 if Asian American)**
- **History of a first-degree relative with diabetes**
- **Women with gestational diabetes or who have delivered a baby weighing more than 9 lb**
- **Individuals with hypertension (blood pressure >140/90 mm Hg), or on treatment for HBP or have a history of CVD**
- **An HDL cholesterol level less than or equal to 35 mg/dL or triglyceride level greater than or equal to 250 mg/dL**
- **Presence of IGT/prediabetes on previous testing**
- **Women with PCOS or other conditions associated with insulin resistance.**

Table 22-8 Generalist Physician Guidelines in the Therapy of Type II Diabetes Mellitus

• Establish diagnosis and classify the type of diabetes mellitus (DM) (if type I, refer to specialist in diabetes).
• Initiate diabetes education classes to learn blood glucose monitoring and diabetes medications; to learn signs, symptoms, and complications; and to learn how to manage sick days (may be available through local hospital or insurance plan).
• Place patient on ADA diet with appropriate caloric, sodium, and lipid restrictions with aid of nutritionist or diabetologist to help with education and support.
• Establish baseline cardiac and renal risk factors, check feet and toenails at least once a year, and refer to a foot specialist.
• Use finger-stick blood glucose for daily diabetic control.
• Follow chronic glycemic control by HgA_{1c} every 2 to 3 mo in the office.
• Initial general health evaluation should consist of a complete history and physical examination and the following laboratory tests: CBC with differential, chemistry profile, lipid profile, urinalysis, thyroid function tests, urine for microalbuminuria, and ECG (baseline at age 40 or older, repeat yearly).
• Development of vascular, ocular, neurologic, or renal compromise should prompt immediate referral.
• Oral hypoglycemic agents may be considered if fasting blood glucose does not decline or increases despite lifestyle changes. While on oral hypoglycemic agents, check the HgA_{1C} every 3 mo and at least two times a year if stable.

• If the fasting serum glucose is >200 mg/dL consistently or the HgA_{1C} is more than 10%, consider starting insulin and referring the patient to an internist.
• Administer the flu vaccine every fall and the pneumococcal vaccine every 6 yrs.

ADA, American Diabetic Association; HgA_{1c}, hemoglobin A_{1C}; CBC, complete blood count; ECG, electrocardiogram.
Adapted from **Cefalu W, ed.** Standards of medical care in diabetes—2017. *Diabetes Care* 2017;40(supplement 1).

Assessment of Glycemic Control

The only acceptable method for assessment of glycemic control is determination of blood glucose by direct enzyme analysis. Glucometers with memory storage made home glucose monitoring more reliable. Physician treatment guidelines are in Table 22-8.

Treatment

Despite clear treatment recommendations, most diabetic patients have not reached goals regarding A1c, LDL, and BP levels. Many continue to smoke and/or not exercise. The reasons for the lack of success are complex, as is the care for most patients with a chronic disease, especially those with a large behavioral component. If a patient is not reaching goals through lifestyle adjustments and oral medications, referral to a clinic system set up to deal with the multiple facets of care should be made (29).

[4] Patients with prediabetes should be encouraged to implement the lifestyle changes. This group has up to a 25% risk of developing true diabetes within 5 years. If their A1c continues to worsen despite lifestyle intervention, initiation of metformin prior to actual diagnosis of diabetes can be considered.

The purpose of diabetes treatment is to prevent renal, cardiac, and neurologic comorbidities, among others. The purpose of prediabetes treatment is to prevent or at least delay the development of true diabetes. The sooner and more effective the intervention, the better.

Type 2 diabetes is treated by a combination of lifestyle adjustments and medications.

Lifestyle

[4] Diet is the most important component of DM management (both overt diabetes and prediabetics) and usually the hardest way to achieve control. **Three major strategies are used: weight loss, low-fat diet (Ä30% of calories from fat), and physical exercise.** Obese patients should reduce their weight to the ideal body weight. Metabolic advantages of weight reduction are improved lipid profile and improved glucose control secondary to increased insulin sensitivity and decreased insulin resistance. The

greater the weight loss, the greater the improvement in lipid disorders. In the setting of severe obesity (BMI ≥40 or BMI ≥35 with comorbidities), recommendations include consideration of metabolic surgery (formally called bariatric surgery) (29). [4] Physical exercise promotes weight loss and improves insulin sensitivity and dyslipidemia in those people who are in high-risk groups for cardiovascular and microvascular diseases. Treatment with a statin is recommended in the setting of diabetes to decrease LDL.

Oral Hypoglycemic Agents

Oral hypoglycemic agents are recommended for many type 2 diabetic patients. The first oral hypoglycemic agents introduced were sulfonylureas (i.e., glyburide). The mode of action of sulfonylureas is based on two different mechanisms: (i) enhanced insulin secretion from the pancreas, and (ii) an extrapancreatic effect that is poorly understood. Other classes of drugs that have different effects in patients with type 2 diabetes—such as biguanides (metformin), thiazolidinediones, alpha-glucosidase inhibitors, and *insulin* secretagogues—were introduced. Endogenous insulin secretion (as measured by C-peptide) is necessary for oral hypoglycemic agents to work. If the fasting blood glucose on an adequate diabetic diet is greater than 250 mg/dL, there is little effect. Frequent evaluation to monitor control (every 3 to 4 months) is important. If glucose levels cannot be controlled with oral hypoglycemic agents (i.e., *metformin,* a biguanide) or other medicines (i.e., sulfonylureas), insulin therapy should be initiated and referral should be considered because of the increased rate of complications.

THYROID DISEASES

[5] **Thyroid disorders are more common in women and some families, although the exact rate of inheritance is unknown in geriatric populations, the incidence may be as high as 5% (31).** Thyroid hormones act in target tissues by binding to nuclear receptors, which induce change in gene expression. Extrathyroidal conversion of thyroxine (T_4) to triiodothyronine (T_3) takes place in the target tissue. T_3 binds the nuclear receptor with higher affinity than T_4, which makes T_3 more biologically active. Pituitary TSH and hypothalamic thyrotropin-releasing hormone (TRH) regulate hormone production and thyroid growth by normal feedback physiology. Thyroid-stimulating immunoglobulins (TSI), once known as a long-acting thyroid stimulator (LATS), bind to the TSH receptor, which results in the hyperthyroid Graves disease.

More than 99% of circulating T_4 and T_3 concentrations are bound by plasma proteins, predominately to thyroxine-binding globulin (TBG), with the remaining 1% being free. Free levels of thyroid hormones remain constant despite physiologic or pharmacologic alterations. Regardless of total serum protein levels, active thyroid hormone levels remain stable. In healthy women, transitions from puberty to menopause

do not alter free thyroid hormone concentrations. Excess endogenous or exogenous sources of estrogen increase TBG plasma concentration by decreasing hepatic clearance. Androgens (especially testosterone) and corticosteroids have the opposite effect by increasing hepatic TBG clearance.

Thyroid function tests may be misleading in women receiving exogenous sources of estrogen because of these altered binding characteristics. Postmenopausal hormonal therapy and pregnancy alter laboratory findings and complicate interpretation of thyroid function studies. Most laboratories compensate by reporting a free T_4 and T_3 level that mathematically corrects for such physiologic alterations rather than the traditional total T_4, and T_3 resin uptake (32). Another confounder is that hCG can mimic TSH during the first trimester of a pregnancy thereby resulting in a falsely low TSH result raising concerns for hyperthyroidism. If questions arise, a clinical pathologist should be consulted.

Hypothyroidism

[5] Overt hypothyroidism occurs in 2% of women, and at least an additional 5% develop a laboratory diagnosis of subclinical hypothyroidism. Hypothyroidism is another disease that disproportionally impacts women five- to eightfold more commonly than men. The principal cause of hypothyroidism in countries without iodine deficiencies is autoimmune thyroiditis (Hashimoto thyroiditis). A familial predisposition is observed in many cases, but the specific genetic or environmental trigger is unknown. The incidence of autoimmune thyroiditis increases with age, affecting up to 15% of women older than 65 years who commonly have only subtle signs or symptoms. **[5] Many have "subclinical hypothyroidism," which is defined as an elevated serum TSH concentration with a normal serum free T_4 level.** It is uncertain whether treatment will improve the quality of life in otherwise healthy patients who have subclinical hypothyroidism (31,33). In a setting of autoimmune thyroiditis, one has both cellular and antibody-mediated destruction of the thyroid, which can result in either a goiter or atrophic thyroid. Autoimmune thyroiditis may be associated with other endocrine (e.g., type 1 diabetes, primary ovarian failure, adrenal insufficiency, and hypoparathyroidism) and nonendocrine (e.g., vitiligo and pernicious anemia) disorders (33). When any autoimmune disease is diagnosed, there should be a high degree of suspicion for concurrent thyroid disorders. With postpartum thyroiditis, there will be a hyperthyroid phase followed by a hypothyroid phase that can last for months. Iatrogenic causes of hypothyroidism occur after surgical removal or radioactive iodine therapy for hyperthyroidism (Graves) or thyroid cancer. Radiation was used to treat acne and other dermatologic disorders 45 years ago. These patients, now in their 60s or older, have an increased risk of thyroid cancer and require close monitoring. Although worldwide iodine deficiency goiter is the most common form of hypothyroidism, this is uncommon

in North America, given the iodine supplementation in salt and other dietary sources. Hypothyroidism rarely occurs secondary to pituitary or hypothalamic diseases from TSH or TRH deficiency, but this must be considered if symptoms occur after neurosurgical procedures.

Clinical Features

Manifestations of hypothyroidism include a broad range of signs and symptoms: fatigue, lethargy, cold intolerance, nightmares, dry skin, hair loss, constipation, periorbital carotene deposition (causing a yellow discoloration), carpal tunnel syndrome, weight gain (usually less than 5 to 10 kg), depression, irritability, hyperlipidemia, and impaired memory. Menstrual dysfunction is common, either as menorrhagia or amenorrhea. The finding of hyperlipidemia may be the first indication of hypothyroidism, especially the presence of high triglycerides. Hypothyroidism may cause precocious or delayed puberty. Hyperprolactinemia and galactorrhea are unusual manifestations of hypothyroidism; however, assessment of thyroid function should be considered. To distinguish primary hypothyroidism from a prolactin-secreting pituitary adenoma, TSH levels should be assessed in women who have amenorrhea, galactorrhea, and hyperprolactinemia.

Diagnosis

Recommendations for screening asymptomatic women for thyroid disorders in women range from every 5 years starting at age 35 in women (American Thyroid Association), to age 50 (American College of Physicians). Other groups have recommended periodic screening in older women (American Academy of Family Physicians and American Association of Clinical Endocrinologists). The USPSTF stated in their recommendation in 2004 that the evidence is insufficient to recommend for or against screening (31). In 2014, the USPSTF reviewed the data regarding routine screening for asymptomatic women without risk factors and reaffirmed that the evidence is insufficient to recommend for or against screening (34). **[5]** For this reason, screening should be reserved for patients at risk (prior history of thyroiditis or other autoimmune diseases or history of treatment for hyperthyroidism) or women with symptoms or signs that could represent a thyroid dysfunction. **Suspected hypothyroidism should [5] always be confirmed with laboratory studies. Primary hypothyroidism is characterized by the combination of an elevated serum TSH with a low serum free T_4 level.** Autoimmune thyroiditis can be confirmed by the presence of serum antithyroid peroxidase (formerly referred to as antimicrosomal) antibodies. An elevated TSH with a normal free T_4 level implies subclinical hypothyroidism. Central hypothyroidism, although rare, is distinguished by a low or low-normal serum free T_4 level with either a low or inappropriate normal serum TSH concentration.

Therapy

Synthetic L-thyroxine (T_4) is the treatment of choice for hypothyroidism and is available as generic *levothyroxine* (35). There is debate about the value of replacing thyroxine in the subclinical hypothyroidism patient. Such replacement did not result in improved survival, decreased cardiovascular morbidity, or improve the quality of life (36). The mode of action is by conversion of T_4 to T_3 in peripheral tissues. *Levothyroxine* should be taken on an empty stomach. Absorption may be poor when taken in combination with aluminum hydroxide (common in antacids), *cholestyramine,* ferrous sulfate, or fatty meals. The usual T_4 requirement is weight related (approximately 1.6 μg/kg) but decreases for the elderly. Normal daily dosage is 0.1 to 0.15 mg but should be adjusted to maintain TSH levels within the normal range. TSH levels should initially be checked in 6 weeks and whenever dosages or brands are changed. When the dose is stabilized, TSH check once every year or two is adequate unless there is a change in the patient's status (i.e., pregnancy).

A low initial T_4 dose (0.025 mg per day) should be initiated in the elderly or patients with known or suspected coronary artery disease. Rapid replacement may worsen angina and in some cases, induce myocardial infarction.

The use of combined T_3 and T_4 therapy (desiccated thyroid extracts) is not recommended for a number of reasons. The conversion of T_4 to T_3 allows the normal hormonal regulation to control T_3 levels. The use of a combined therapy overrides that and can result in excessive and nonphysiologic levels of T_3 resulting in mild hyperthyroidism. During pregnancy, fetal neurogenesis is dependent on maternal T_4 levels until the estimated gestational age of 16 to 18 weeks (37).

Hyperthyroidism

Hyperthyroidism affects 2% of women during their lifetime, most often during their childbearing years and impacts women fivefold more commonly than men. The Graves disease represents the most common disorder; it is associated with orbital inflammation, causing the classic exophthalmos associated with the disease and a characteristic dermopathy, pretibial myxedema. It is an autoimmune disorder caused by TSH reception antibodies that stimulate gland growth and hormone synthesis. The etiology of the Graves disease in genetically susceptible women is unknown. Autonomously functioning benign thyroid neoplasias are less common causes of hyperthyroidism and are associated with toxic adenomas and toxic multinodular goiter. Transient thyrotoxicosis may be the result of unregulated glandular release of thyroid hormone in postpartum (painless, silent, or lymphocytic) thyroiditis and subacute (painful) thyroiditis. Other rare causes of thyroid overactivity include human chorionic

gonadotropin–secreting choriocarcinoma, TSH-secreting pituitary adenoma, and struma ovarii. Factitious ingestion or iatrogenic overprescribing should be considered in patients with eating disorders as they use this as a weight control strategy.

Clinical Features

Symptoms of thyrotoxicosis include fatigue, diarrhea, heat intolerance, palpitations, dyspnea, nervousness, and weight loss. In young patients, there may be paradoxical weight gain from an increased appetite. Thyrotoxicosis may cause vomiting in pregnant women, which may be confused with hyperemesis gravidarum. Tachycardia, lid lag, tremor, proximal muscle weakness, and warm moist skin are classic physical findings. The most dramatic physical changes are ophthalmologic and include lid retraction, periorbital edema, and proptosis. These eye findings occur in less than one-third of women. In elderly adults, symptoms are often more subtle, with presentations of unexplained weight loss, atrial fibrillation, or new onset angina pectoris. Menstrual abnormalities span from regular menses to light flow to anovulatory menses and associated infertility. Goiter is common in younger women with the Graves disease, but may be absent in older women. Toxic nodular goiter is associated with nonhomogeneous glandular enlargement, whereas in subacute thyroiditis the gland is tender, hard, and enlarged.

Diagnosis

All patients with symptoms of hyperthyroidism should have a complete history and examination done with focus on the thyroid (nodule, tenderness, or goiter), cardiac (hypertension tachycardia), pulmonary (tachypnea), neurologic (peripheral weakness), the eye signs, and presence of peripheral edema or pretibial myxedema (38).

Most thyrotoxic patients have elevated total and free T_4 and T_3 concentrations. In thyrotoxicosis, serum TSH concentrations are virtually undetectable, even with very sensitive assays (sensitivity measured to 0.1 units). Radioiodine uptake scans are useful in the differential diagnosis of established hyperthyroidism. Scans with homogeneous uptake of radioactive iodine are suggestive of the Graves disease, whereas heterogeneous tracer uptake is suggestive of a diagnosis of toxic nodular goiter. Thyroiditis and medication-induced thyrotoxicosis have diminished glandular radioisotope concentration. There is only a modest correlation between the severity of symptoms and the level of thyroid hormones (38).

Therapy

Therapy can be pharmaceutical, thyroid ablation, thyroidectomy, or a combination of the three depending on many variables that include the patient's age, childbearing plans, and response to other therapies (38).

Antithyroid medications, either *methimazole* (10 to 30 mg per day) or

***propylthiouracil* (*PTU;* 50 to 300 mg every 6 to 8 hours) are used for initial therapy.** Both antithyroid drugs block thyroid hormone biosynthesis and may have additional immunosuppressive effects on the gland. The primary difference in oral medications is that *PTU* partially inhibits extrathyroidal T_4-to-T_3 conversion, whereas *methimazole* does not. *Methimazole* has a longer half-life and permits single daily dosing, which may encourage compliance. Except during the first trimester of pregnancy when PTU therapy is preferred, methimazole is the typical first choice in antithyroid medications. Euthyroidism is typically restored in 3 to 10 weeks, and treatment with oral antithyroid agents is continued for 6 to 24 months, unless total ablation with radioiodine or surgical resection is performed. Surgery is less popular because it is invasive and may result in inadvertent parathyroid removal, which commits the patient to lifelong calcium therapy.

Beta-adrenergic blocking agents such as *propranolol* or *atenolol* are useful adjunctive therapy for control of sympathomimetic symptoms such as tachycardia (38). An additional benefit of beta blockers is the blocking of peripheral conversion of T_4 to T_3. If a patient is having symptomatic thyrotoxicosis with heart rate greater than 90 beats per minute or there is a history of pre-existing cardiovascular disease the patient should be referred to an endocrinologist or even an emergency room. In rare cases of thyroid storm, PTU, beta blockers, glucocorticoids, and high-dose iodine preparations (intravenous sodium iodide) should be administered immediately, and referral to an intensive care unit is advisable.

The relapse rate with oral antithyroid medications is 50% over a lifetime. Lifelong follow-up is important when medical therapy is used solely because of the high relapse rate. Both medications have infrequent (5%) minor side effects, which include fever, rash, or arthralgias. Major toxicity (e.g., hepatitis, vasculitis, and agranulocytosis) occurs in less than 1%. PTU appears to be more responsible for major toxicities than methimazole. Patients on either medication should be followed with serial complete blood count (CBC) and liver function tests. However, agranulocytosis cannot be predicted by periodic complete blood counts; therefore, patients who have a sore throat or fever should stop taking the medication and call their physician immediately (38).

Therapy with iodine-131 provides a permanent cure of hyperthyroidism in 90% of patients. The principal drawback to radioactive iodine therapy is the high rate of postablative hypothyroidism, which occurs in at least 50% of patients immediately after therapy, with additional cases developing at a rate of 2% to 3% per year. Based on the assumption that hypothyroidism will develop, these patients should be given lifetime thyroid replacement therapy.

[5] Thyroid nodules are common and are more prevalent in adults aged less than 30 or over 60 years. This is a group that encompasses much of the population seen by an ob-gyn. For this reason, an understanding of the screening and diagnosing is important. The vast majority of nodules when discovered by the patient or the provider, are asymptomatic and benign; however, malignancy (4% to 6% of all nodules) and hyperthyroidism must be excluded (39). The common differential includes multinodular goiter, the Hashimoto thyroiditis, colloid/simple cyst, follicular adenoma, and malignancy. Ultrasound-guided fine-needle aspiration (FNA) is recommended in the presence of the following factors: history of radiation to the head, neck, or upper chest; family history of thyroid cancer; ultrasound findings suggestive of malignancy; or a nodule larger than 1.5 cm in diameter (40).

Thyroid function tests should be performed before FNA and, if results are abnormal, the underlying disease should be treated. A markedly suppressed TSH level implies the nodule is hyperfunctioning and unlikely to be malignant. Because most nodules are "cold" on scanning (especially if TSH is normal), it is more cost effective to proceed with ultrasound rather than radioactive scanning. An ultrasound can determine additional nodules, size of nodule(s), characteristics of the nodules (solid/cystic), thyroid size, and presence of enlarged lymph nodes. Thyroid ultrasound findings of solid hypoechoic nodule **or** features of microcalcifications, irregular margins, rim calcifications, or evidence of extension into the surrounding tissue, raise concerns for malignancy. These should be sampled by FNA irrespective of other findings. The presence of lymphadenopathy should prompt FNA sampling.

Needle biopsy provides a diagnosis in 95% of cases; in the 5% of patients in whom the diagnosis cannot be established, excisional biopsy is necessary. Only 20% of excisional biopsies of an "indeterminate aspiration" are found to be malignant (40). Lesions that are confirmed malignant on biopsy should be treated with extirpative surgery, and benign nodules should be palpated every 6 to 12 months for growth but surgical intervention is not indicated. *Thyroxine* suppressive therapy for benign nodules is not recommended (41).

Papillary thyroid carcinoma is the most common malignancy, found in 75% of thyroid cancers. The majority of cancers are found incidentally during routine examinations. Risk factors include a history of radiation exposure during childhood and family history. Signs include rapid growth of neck mass, new onset hoarseness, or vocal cord paralysis. In the setting of rapid growth, fixed nodule, new onset hoarseness, or the presence of lymphadenopathy, it is important to be sure an FNA is done. Thyroidectomy is the primary treatment with radioactive iodine and TSH suppression with thyroxine. Patients younger than 50 years of age with a primary tumor of less than 4 cm at presentation, even with associated cervical lymph node metastasis, are usually cured. In the elderly, anaplastic tumors have a poor prognosis and progress rapidly despite therapy.

Follicular thyroid cancer is the second most common thyroid cancer, comprising up to 10% of cases. These tend to occur in an older population with peak ages of 40 to 60. It has a threefold greater prevalence in women than men. This form of cancer tends to have vascular invasion, frequently with distant metastases. The prognosis tends to be less favorable with this form of cancer than with papillary cancers, although women do have a better prognosis than men.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a common problem, affecting about 10% to 15% of the population, with women being twice as likely to have the diagnosis (42). Given that its primary symptom is typically crampy chronic abdominal pain, IBS is often in the differential diagnosis for patients with chronic pelvic pain. Stress and certain foods will often trigger the pain, and defecation often will provide some relief from the pain. Other gastrointestinal symptoms include diarrhea and constipation, gastroesophageal reflux disease, nausea, bloating, and flatulence. What makes this a more difficult diagnosis is the spectrum of additional symptoms, including dysmenorrhea, dyspareunia, fibromyalgia complaints, urinary symptoms of frequency and urgency, and even sexual dysfunction.

This spectrum of symptoms renders diagnosis difficult and led to a consensus group that created the Rome criteria in 1992, revised in 2005 (43). The resulting Rome III criteria are: recurrent abdominal pain or discomfort for at least 3 days per month for 3 months associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in the frequency of the stool
- Onset associated with a change in the appearance of the stool—constipation (IBS-C) or diarrhea (IBS-D)

IBS should be a diagnosis of exclusion with consideration initially given to other causes for the dominant symptom. If that is diarrhea, considerations of lactose intolerance, infectious etiology, malabsorption, or celiac disease should be entertained. Symptoms that result in weight loss, rectal bleeding, anemia, or that are noctural or progressive suggests something other than IBS unless proven otherwise.

A basic workup might include complete blood count and chemistries. Evaluation of diarrhea, if that is the dominant symptom, should potentially include stool cultures if infectious etiology is suspected or 24-hour stool collection (if osmotic) if secretory diarrhea is suspected. Initiate dietary reviews for lactose intolerance or gluten sensitivity. Flexible sigmoidoscopy/ colonoscopy is not done routinely unless needed to

rule out inflammatory conditions or malignancy in families with Lynch syndrome or the patient is 50 or older with sudden onset of symptoms.

Management

General management of IBS can be extremely difficult. Often, the first step is to reassure the patient that this is a functional disease and is not related to cancer or malignancy, assuming those were eliminated by history and examination (44). Many individuals have some underlying concerns that diagnostic testing needs to be performed or that something is being missed. Constant reassurance is an important aspect of management. The patient needs to be an active participant in her care and understand the chronic nature of the disease. A symptom diary for several weeks may show a link between various foods and stressors that may be modifiable. Some individuals are able to link various stressors in their lives to symptoms while others will not have identifiable causes. **Common triggers include stress, anxiety, medication (antibiotics, antacids), menstrual cycles, abusive relationships, certain foods (lactose, sorbitol), and travel. Patients should be counseled about dietary interventions, including increasing dietary fiber, decreasing total fat intake, and avoiding foods that trigger symptoms.** Stool softeners are recommended for individuals with (IBS-C) hard stools, and bulk aiding agents may be helpful for those individuals with constipation. The overuse of laxatives is to be discouraged. Good bowel habits should be discussed. Patients with poor habits should set aside a quiet time every day to attempt defecation. Many individuals get into a habit of ignoring stooling symptoms, leading to further problems with lower gastrointestinal disease.

Antidiarrheal agents, specifically *loperamide* or *diphenoxylate,* are often useful in patients with mild disease with diarrhea as a component (IBS-D). The goal is to reduce the number of bowel movements and help to relieve rectal urgency. Anticholinergics including *hyoscyamine* and *dicyclomine hydrochloride* often are helpful. Antispasmodic agents have anticholinergic agents as the primary ingredient, and compliance may be a problem because side effects include dry mouth, visual disturbances, and constipation. These agents can precipitate toxic megacolon, which may result in severe colitis. Toxic megacolon is a medical and potential surgical emergency, in some cases requiring colectomy. **Even though these patients may be extremely difficult to treat, judicious use of symptom-based pharmacologic approaches (because none have clear benefit), reassurance, and patient insight may be helpful. The quality of life for some individuals with IBS is extremely compromised, requiring intense counseling.** It may be difficult to treat them in a busy primary care practice. Those with a concurrent psychiatric disease, such as depression, will often benefit from psychiatric consultation and pharmacologic treatment of the underlying disease in the overall management (45).

Individuals with chronic, debilitating IBS should be referred to a gastroenterologist. Any suspicion of organic disease with systemic changes, including weight loss and bloody diarrhea, should be considered for referral.

GASTROESOPHAGEAL REFLUX DISEASE

The term GERD is a commonly used label for many forms of indigestion and heartburn. The American College of Gastroenterology defines it as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus (46). The term "abnormal" is key because some reflux is physiologic, usually occurring postprandial and typically being asymptomatic. Given the variation in definition, its prevalence is hard to determine, but it is clear that GERD is more common in the Western world.

Symptoms of GERD include heartburn (burning sensation in the retrosternal area) commonly postprandial, regurgitation gastric contents into mouth, dysphagia from esophageal inflammation, and chest pain that can be confused as angina. The definitive diagnosis of GERD is difficult, so empiric treatment with acid suppression is reasonable. **Dysphagia that is progressive is concerning for Barrett metaplasia or adenocarcinoma and merits an endoscopic evaluation** (47). Endoscopy should not be used as the first test to diagnose GERD (48).

Treatment of GERD is multifaceted with lifestyle modification and use of antacids and over-the-counter H_2 receptor antagonists or proton pump inhibitors (PPI) (49). **Lifestyle modifications include smoking cessation, avoidance of eating late in the evening, avoidance of being supine after eating, weight loss, avoidance of tight clothing, and restriction of alcohol use.** Dietary modifications are helpful but should not be draconian, which will ensure noncompliance. Key foods to try to minimize are fatty foods, chocolate, peppermint, and excessive alcohol. The patient can monitor her own symptoms for the foods that are most problematic for her.

Medications that reduce acid secretions are best and include H_2 blockers or PPIs. They do not prevent the reflux but decrease the damage done by the acid when refluxed. Medication needs to be titrated to the severity of the symptoms. H_2 blockers commonly work well for acute pain but in placebo-controlled studies in chronic cases without resolution of heartburn after the common 6-week course, it was found that patients on PPI do better. Maintenance therapy is recommended for patients who have rapid recurrence of symptoms (in less than 2 to 3 months) after they stop their medication. Otherwise patients can be managed with episodic treatments. **The linkage of *Helicobacter pylori* infections and GERD is poorly understood but seems to be mediated through increased gastric acid secretion.** Treatment can initially worsen GERD and may not improve it (50). Benefits and risks should be discussed with the

patient prior to testing and treating for *H. pylori*. The management of GERD during pregnancy is similar to the treatment in the nonpregnant patient.

CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome (CTS) is the cluster of symptoms brought on by compression in the carpal tunnel of the median nerve. These are paresthesia, pain, and weakness. The symptoms are commonly worse at night and may wake the patient from sleep. It is thought women may be more likely to present with complaints of CTS because of their small wrists, repetitive motion injury at work (typing, holding telephone, and reading), and pregnancy with increased edema. The pain and paresthesia can be located in the wrist or hand or can be in the forearm. The weakness may cause a patient to have difficulty opening jars, lifting a plate, turning a doorknob, or holding a glass.

A detailed history is very diagnostic but the use of a couple of simple tests can help to confirm it (51). The most common one is the **Phalen maneuver,** in which the patient flexes her palms at the wrist as close to 90 degrees as possible. Then with the dorsal portion of the hands touching and the arms parallel to the floor, the patient presses the flexed hands against each other for approximately 1 minute. This should reproduce her symptoms along the median nerve. The **Tinel test** involves percussion over the top of the carpal tunnel where the median nerve travels. A positive test is when the percussion reproduces the pain and paresthesia. Additional testing such as nerve conduction studies should be reserved for patients who do not respond to conservative management or have significant muscle weakness.

Treatment involves lifestyle modification to decrease repetitive motion injuries or prolonged marked flexion at the wrist. A carpal tunnel brace can be very helpful in maintaining adequate extension at the wrist, thereby "opening" the tunnel and reducing compression on the medial nerve. Only if these strategies do not work is a surgical intervention indicated.

MITRAL VALVE PROLAPSE SYNDROME, DYSAUTONOMIA, AND POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

The terms mitral valve prolapse syndrome (MVPS), dysautonomia, and postural orthostatic tachycardia syndrome (POTS) all refer to a syndrome in which the patient has problems with palpitations, hypotension, syncope, dyspnea, panic/anxiety disorder, numbness, hyperflexible joints, pectus excavatum, and gastric emptying disorders. Initially patients (typically fivefold times more likely to be women) who presented with these symptoms were thought to be somatizing their anxiety

disorder. It is now accepted that it is a syndrome that appears to involve the autonomic nervous system (52). This often will present first in early adolescence with gradual worsening of the symptoms. The patients are very slender in build and lose weight to a low body mass index over a number of months as the syndrome evolves. This weight loss is the probable cause of the secondary amenorrhea that prompts these women to seek gynecologic care. The symptoms are not clearly explained by the degree of mitral valve prolapse, so many feel MVPS is a marker for individuals at risk for this complex of symptoms. Studies have shown that dysautonomia is an extraarticular manifestation in the joint hypermobility syndrome (53). Increased sympathetic activity is the common pathway for most of the proposed mechanisms for POTS or MVPS. There appears to be a genetic component, with over 10% of patients reporting the diagnosis in family members with orthostatic intolerance (54). It needs to be stressed to the patient that the heart is structurally normal.

A tilt table test is often key to the diagnosis. Treatment focuses on the symptoms and maintaining intravascular volume by encouraging oral intake of water and salts (55). Physical fitness with aerobic exercises to increase muscle mass and reduce dependent pooling of blood; avoidance of smoking, caffeine, and alcohol; and limiting simple carbohydrates will minimize symptoms over time. Additional medications, including adrenoreceptor agonists, acetylcholinesterase inhibitor, mineralocorticoid agonist, beta blockers, and selective serotonin reuptake inhibitors, may be necessary to deal with incompassating symptoms during the acute phase. Because this is a multifaceted disease, it may be best to refer the patient during the acute phase to a physician who is experienced with this syndrome.

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CHAPTER 23

Common Psychiatric Problems



Angela Devi Shrestha, Nada Logan Stotland

Psychiatry in the Gynecology Office
- Psychiatric Assessment
- Approach to the Patient
- Psychiatric Referral
  - *How to Refer*
  - *Which Mental Health Professional?*

Mood Disorders

Depression
- Management

Bipolar Disorder
- Gynecologic Factors
  - *Premenstrual Syndrome and Premenstrual Dysphoric Disorder*
  - *Psychiatric Aspects of Other Reproductive Events*
  - *Induced Abortion*
  - *Peripartum Psychiatric Disorders*
  - *Menopause*
- Suicide

Alcohol and Substance Abuse Disorders

Anxiety Disorders
- Diagnosis
  - *Generalized Anxiety Disorder*
  - *Panic Disorder*
  - *Social Anxiety Disorder*
  - *Agoraphobia*

Specific Phobias
Trauma-Related Disorders
Obsessive–Compulsive Disorder
Somatic Symptom and Related Disorders
Somatic Symptom Disorder
Illness Anxiety Disorder
Management
Conversion, or Functional Neurologic Symptom, Disorder
Factitious Disorder, or Munchausen Syndrome
Referral
Personality Disorders
Diagnosis
Assessment
Management
Adjustment Disorders
Diagnosis
Management
Eating Disorders
Binge-Eating Disorder
Anorexia Nervosa
Bulimia Nervosa
Psychotic Disorders
Gender Identity and Sexual Orientation
Gender Dysphoria
Pharmacologic Treatments
Selective Serotonin Reuptake Inhibitors
Serotonin–Norepinephrine Reuptake Inhibitors
Tricyclic Antidepressants
Monoamine Oxidase Inhibitors
Other Agents
General Management Review
Medication Overview
Resources

KEY POINTS

1 Depression, anxiety, and other psychiatric disorders are common in general gynecologic practice.
2 Referral to mental health specialists can and must be made in a sensitive manner.
3 Suicidal and homicidal behaviors are absolute indications for psychiatric referral.
4 Alcohol and other substance abuse require prompt recognition and intervention.
5 Some women are vulnerable to mood symptoms at times of hormonal change. However, menopausal hormone levels are not correlated with depression and premenstrual syndrome (PMS) should not be diagnosed without 2 months of prospective daily ratings.
6 Personality disorders and somatic symptom disorders rarely can be cured, but informed management can improve outcomes and greatly decrease the suffering of the patient.
7 Withdrawal of successful psychotropic treatment is very likely to lead to relapse.
8 Psychotic disorders should nearly always be managed by psychiatrists.

Psychiatric diagnoses and psychological symptoms are extremely common and account for considerable morbidity and mortality in the general population (1). They are a central or complicating factor in many outpatient visits and in inpatient care. Despite their prevalence, psychiatric disorders are often undiagnosed or misdiagnosed (2). **Clinical depression affects up to one-fourth of women during their lives, but probably more than half of those women are neither diagnosed nor treated** (3,4). Anxiety disorders, alcohol and other substance abuse, and somatic symptom disorders are very common among gynecologic patients. When not detected, these disorders can lead to unnecessary diagnostic and therapeutic interventions, provider frustration, and ongoing patient suffering. More than half of the patients who commit suicide have seen a nonpsychiatric physician during the month prior (5).

PSYCHIATRY IN THE GYNECOLOGY OFFICE

There are several reasons that patients with psychological problems can evoke negative reactions in physicians (Table 23-1). The expression of strong emotions like sadness, rage, or anxiety in patients can provoke those same emotions in physicians and other staff members. Patients who break down in tears, become angry, or embark on a lengthy tale or list of symptoms can disrupt the flow of a busy practice or clinic, inconveniencing others who are waiting for care. Physicians are naturally reluctant to uncover problems for which there seem to be no solutions. Sometimes the necessary social and medical resources are scarce or lacking. Although parity laws forbid discrimination by insurers against mental health care, gynecologists and their patients may have difficulty accessing mental health services. It is sometimes necessary for the physician and family to advocate strongly for mental health care. By incorporating the management strategies in this chapter into their practices, gynecologists can reduce clinical frustration and play a major role in improving the health and well-being of their patients.

Table 23-1 Practitioners' Negative Reactions Toward Patients with Psychiatric Problems

1. Social stigma attached to psychiatric diagnoses, patients, and practitioners.
2. Concern that individuals with psychiatric disorders are weak, unmotivated, manipulative, or defective.
3. Unfamiliarity with the growing scientific basis for psychiatric diagnoses and treatments. Concern that patients with psychiatric problems will demand and consume inordinate and limitless time from a medical practice.
4. Precipitation in others, including doctors, of feelings that are complementary to the strong and unpleasant emotions experienced by patients with psychiatric disorders.
5. Gynecologists' own uncertainty about their skills at psychiatric diagnosis, referral, and treatment.

6. Failure to acknowledge psychiatric problems as legitimate grounds for medical attention.

Psychiatric Assessment

Psychiatric diagnosis, as codified in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), published by the American Psychiatric Association, is based on empirical, valid, and reliable evidence (3). DSM-5 diagnoses strongly correlate with response to treatment. The criteria in DSM-5 are the basis for the diagnostic entities described in this chapter. Accurate diagnosis is critical to successful management, whether care is provided by a gynecologist or through referral to a mental health expert.

Approach to the Patient

Although diagnostic criteria list signs and symptoms, the interaction with a patient should not be reduced to a series of rapid-fire questions and answers. **A wealth of valuable information can be obtained from the patient's spontaneous description of her concerns and from her responses to open-ended questions.** A patient who is encouraged to speak for several minutes before being asked to respond to specific questions will reveal information that is useful, even vital, to her care: a thought disorder, a predominant mood, abnormally high anxiety, a personality style or disorder, and attitudes toward her diagnosis and treatment. Such information may emerge only much later, or not at all, in a question-and-answer format. **As in all medical practice, it is critical that the gynecologist neither jumps to diagnostic conclusions nor proceeds directly to therapeutic interventions.** Allowing a few moments for open-ended discussion does not mean that the physician and the other patients awaiting care are to be held hostage by an overly talkative patient. The clinician can tell the patient with multiple, detailed complaints how much time is available for the current appointment, invite her to focus on her most pressing problem, and offer a future appointment to continue the account.

Diagnosis and treatment recommendations are of no avail unless the patient adheres to the recommendations. One barrier to adherence is a mismatch between the patient's expectations and the proposed diagnostic and treatment regimen. If there is a mismatch, an explanation of the reason will promote ultimate adherence. Sometimes allowing time for the patient to consider the recommendations, confer with friends or relatives, and make a commitment to treatment at a later visit will improve the likelihood of adherence —or of a trusting and genuine doctor–patient collaboration.

Psychiatric Referral

Gynecologists may consider referral to a mental health professional, particularly a psychiatrist, to be a delicate matter. The first question is when to refer, followed by how to refer, and to whom. Most mild psychiatric disorders are treated by nonpsychiatric physicians, who are the main prescribers of antidepressants and anxiolytic medications (6). The factors that determine the decision to refer are:

- The nature and severity of the patient's disorder
- The time available in the gynecologic practice
- The patient's preference
- The gynecologist's degree of comfort with the patient and the disorder
- The availability of mental health professionals

Patients who are acutely suicidal or psychotic should be referred immediately to a psychiatrist (7). The primary provider should refer patients for psychiatric evaluation when the diagnosis is not clear or when the patient fails to respond to initial treatment. The gynecologist can resume responsibility for ongoing care of many patients after their initial or periodic assessment by a psychiatrist.

How to Refer

Some clinicians fear that patients will be insulted or alarmed by a psychiatric referral. Following are techniques that decrease the discomfort of the gynecologist and the patient and enhance the likelihood of success (7). **The referral should be explained on the basis of the patient's own signs, symptoms, and level of distress.** For a patient suffering from clinical depression, for example, this might be difficulty sleeping, loss of appetite, and lack of energy. For a patient with an anxiety disorder, it might be palpitations, shortness of breath, and nervousness. For a patient with mild Alzheimer disease, it might be forgetfulness or frightening episodes in which she finds herself in a neighborhood she does not recognize.

When a somatic symptom disorder is suspected, the gynecologist should emphasize the difficulty of living with symptoms in the absence of a definitive diagnosis and treatment rather than the hypothesis that the symptoms have a psychological basis (7):

1. *"It is very stressful to be suffering while we can't pinpoint the problem. I would like you to see one of our staff who specializes in helping people cope with these difficult situations."*
2. *"It must be difficult to function when you have been so sickly all your life, have seen so many doctors, have had so many diagnostic tests and medical treatments, and still don't have an answer or feel well."*

It is counterproductive to convey the idea that because the diagnostic process has not revealed a specific disorder, the problem must be "in the patient's head." It alienates the patient. It is never possible to rule out an organic cause with absolute certainty; and diseases "in the head" are real diseases (7).

[3] Although suicidal and homicidal behaviors and psychotic symptoms are indications for referral, many physicians fear that questioning patients about these behaviors will precipitate them or offend the patient. That is not the case (8). These questions can be explained as routine and necessary. The asymptomatic patient will quickly dismiss them. An open discussion of impulses to hurt oneself or someone else helps the patient to regain control, recognize the need for mental health care, or agree to emergency interventions such as psychiatric hospitalization, whereas avoiding the subject intensifies the patient's feelings of isolation. The management of suicidal behavior is addressed later in this chapter.

Likewise, the possibility of psychosis need not be avoided. **[8] Most patients with psychotic disorders have had previous experience with psychiatric referral.** They can discuss hallucinations and delusions quite matter-of-factly. The rare patient who comes to a gynecologist in the midst of a first episode of psychosis is likely to be frightened by her symptoms and willing to accept expert consultation.

Despite increasing public sophistication about mental illnesses and psychiatric care, some patients believe that any mention of mental health intervention implies that they are either "crazy" or that the referring physician is convinced that their physical symptoms are imaginary or feigned. It is helpful to state explicitly that this is not the case. Making the reason for the referral clear and founded in signs and symptoms obvious to the patient will nearly always allay anxiety over a psychiatric referral (7).

It is not acceptable to refer a patient to a psychiatrist without informing her in advance and obtaining her consent, unless she is functionally incompetent, or in the throes of a suicidal or homicidal emergency. Even under those circumstances, it is highly preferable to be straightforward. A referral that begins with an unexpected clinical encounter with a psychiatrist is unfair to both the psychiatrist and the patient and is unlikely to result in a satisfactory outcome (7).

[2] To allay any concern a patient may have that a mental health referral is an indication of the gynecologist's disdain or disinterest, and to promote good patient care in general, the referring gynecologist should make it clear to the patient that he or she will remain involved in the patient's care. The mental health professional should be introduced as a member of the health care team, and the gynecologist should ask the patient to call after the mental health appointment to report on how it went. The patient should be given a follow-up appointment with the gynecologist at the time of the referral (7).

Which Mental Health Professional?

Mental disorders are treated by social workers, psychologists, members of the clergy (the first consulted by some patients), and various kinds of counselors as well as by psychiatrists (7). The lay public or even some medical professionals may not understand the distinctions between types of mental health professionals. The criteria for membership in each profession can vary by region and institution. Social workers and psychologists can receive degrees at the bachelor, master, or doctoral level. In some states, licensure is required. Social workers require a master's degree and psychologists receive a doctoral degree, in addition to supervised clinical experience, to qualify for licensure. The category of counselor includes a wide variety of practitioners, such as marriage counselors, pastoral counselors, school counselors, and family counselors. The training of social workers may focus on social policy, institutional care, psychosocial aspects of medical illness, or individual treatment (7).

Practitioners of all these disciplines may or may not be trained in psychotherapy. For a patient whose symptoms do not meet the criteria for a major psychiatric disorder and who is able to eat, sleep, and carry out her regular duties, supportive psychotherapy provided by any trained mental health professional may suffice. Supportive psychotherapy calls on a patient's existing coping mechanisms to combat a stressful situation. Doctoral-level psychologists and neuropsychologists can perform testing that can be helpful in establishing a diagnosis. Such testing is especially useful in identifying and localizing brain pathology and in defining intelligence levels. Undiagnosed cognitive deficits may contribute to noncompliance with gynecologic care and other problems (7).

Trained social workers are often knowledgeable about community resources for patients and their families and about the impact of gynecologic diseases and treatments on patients. Self-help or professionally led therapy groups can be helpful for patients reacting to gynecologic problems such as infertility or malignancy.

Psychiatrists are the only medically trained mental health professionals. They play a particularly important role in resolving diagnostic dilemmas, especially when questions arise about the psychological or behavioral manifestations of medical illness and pharmacologic treatment; when a medical understanding of the gynecologic condition and treatment is essential to the care of the patient; and when such issues as drug–drug interactions must be considered (7). **Psychiatrists are the only mental health professionals trained to prescribe psychoactive medications and other biologic interventions and provide psychotherapy.** The legislatures of several states have conferred prescribing rights on doctoral-level psychologists with additional training but have not defined the limits of the prescribing authority. The gynecologist would have to enquire whether a particular psychologist has completed this training; the numbers are small. It is highly likely that psychiatrists will continue to treat the most seriously ill patients and take ultimate responsibility for psychiatric emergencies (7).

Because psychiatric problems frequently present in gynecologic practice, it is

worthwhile for the gynecologist to develop an ongoing relationship with one or more local mental health professionals. The state psychiatric society may have a list of subspecialists in psychosomatic medicine, formerly known as consultation-liaison psychiatry. This is an official subspecialty for psychiatrists who focus on collaboration with physicians of other specialties. Many psychiatrists without specific fellowship training also offer consultative services. The availability of familiar and trusted resources enhances the likelihood that problems will be identified and addressed. An ongoing relationship with a mental health professional allows the gynecologist to familiarize that professional with relevant developments in gynecology. **It is important to keep up-to-date information on local suicide prevention hotlines, domestic violence agencies, and resources for mothers who may pose a danger to their children.** Local laws may require that physicians report to the authorities their identification of mothers in this situation (7).

Whenever a patient's thinking, emotions, or behaviors cause concern, the gynecologist should first consider a nonpsychiatric medical disorder or a reaction to prescribed or illicit drugs. Psychiatric disorders frequently coexist with these conditions (7). HIV/AIDS infection, some malignancies, hypothyroidism, and other diseases can present with psychiatric symptoms.

Psychiatric conditions are extremely common in gynecologic practice. Some are primary and some are related to reproductive events. **All patients should be screened for depression, anxiety, intimate partner violence, and substance abuse** (7).

Note: Gynecologists generally limit their prescriptions of psychotropic medications to anxiolytics and antidepressants; some of these agents serve both functions. Information about these classes of medications is presented at the end of the chapter; most of the management described in connection with specific disorders is nonpharmacologic.

MOOD DISORDERS

Mood is the emotional coloration of a person's experience. **Mood may be pathologically elevated (mania), lowered (depression), or alternate between the two.** Mood disorders are different from, but frequently confused with, the inevitable ups and downs of everyday life, such as reactions to difficult situations, including gynecologic conditions. In the English language, *depression* is used to describe both a transient mood and a psychiatric disorder. Because of this confusion, patients and their loved ones become frustrated when well-meaning attempts to offer reason, distraction, or thoughtful gestures and interactions in order to affect a self-limited reaction to a difficult situation, fail to influence what are protractedly disturbed moods.

DEPRESSION

[1] Depression is the single most common reason for psychiatric hospitalization in the United States. **As many as 15% of individuals with severe depressive disorders eventually commit suicide** (9). Depression is a significant risk factor for cardiovascular disease and for nonadherence to essential treatments for other diseases, including diabetes. The overall lifetime prevalence of affective disorders is 20.8%; the 12-month prevalence is 9.5% (10–12). **During the reproductive years, depression is two to three times more common in women than in men** (13). The highest incidence of depression is in the age group of 25 to 44 years, but depression occurs in every age group, from toddlers to the aged. Women have a lifetime risk of 10% to 25% and a point prevalence of 5% to 9% (14–16). **[7]** Depression is a recurrent disorder; of those who experience a major depressive episode, 50% have a second one. Of these, 70% have a third, and the incidence continues to increase with each subsequent episode. In the past diagnostic criteria were not standardized, so it is difficult to know whether the incidence of depression has increased over recent years, as has been asserted in the popular press. The Center for Disease Control and Prevention reported that between 2011 and 2014, one in nine Americans had taken at least one antidepressant in the last month (17).

Although public understanding and acceptance of mental illnesses has significantly increased, patients may have difficulty accepting, and telling others, that they are suffering from depression. If the depression occurs under stressful circumstances, they may feel it is inevitable and untreatable. If depression occurs under fortunate circumstances, they may feel guilty because they are not appreciative of their good fortune. While stress can precipitate depression, depression can occur under any circumstances and has a significant genetic contribution. The need to carry out multiple roles in the absence of adequate social support, as is all too common in women's lives, is stressful and can contribute to depression in women (18).

Major depressive disorder, single episode (F32.0) is characterized by the following (3,7):

- **Sad mood or irritability**
- **Hopelessness**
- **Helplessness**
- **Decreased ability to concentrate**
- **Decreased energy**
- **Interference with sleep, generally with early awakening, inability to return to sleep, and failure to feel rested; atypically, with increased sleep**
- **Decreased appetite and weight; atypically, increased food intake**

- **Withdrawal from social relationships**
- **Inability to enjoy previously gratifying activities**
- **Loss of libido**
- **Guilt**
- **Psychomotor retardation or agitation**
- **Thoughts of death or suicide**

The patient who has five or more of the signs and symptoms of depression for most of each day for 2 weeks or more fulfills the criteria for the diagnosis of clinical depression. Depression may be acute or chronic. Like many diseases, it is caused by genetic, neurophysiologic, and environmental factors. Trauma in early life plays a role. **The average duration of a major depressive episode is approximately 9 months** (16). **Patients must be cautioned to continue treatment at least that long, even if symptoms remit; relapse is common.**

Concomitant gynecologic or other medical illness can cause signs and symptoms similar to those of depression—loss of energy, sleep, and appetite—but does not cause guilt, hopelessness, helplessness, or suicidality. These observations are helpful in differentiating depression from the malaise associated with other disease states.

Physical symptoms as an expression of depression are especially common in Asian and Latino cultures and in the elderly (19,20). Some patients with severe depression continue to function and can appear normal and cheerful. They may commit suicide without exhibiting any warning signs to friends, family, or coworkers. **The only way to rule out depression is by asking about symptoms and using the diagnostic criteria.**

Management

Antidepressant medication and psychotherapy are effective treatments for depression. There is evidence that a combination of the two produces the best outcomes (21–23). Reports about the efficacy of alternative treatments, the most common of which is St. John's wort, are conflicting, but mostly negative (24). Patients should be specifically questioned about their use of herbal and other preparations and encouraged to use those whose components are standardized. Transcranial magnetic stimulation is a promising research intervention (25,26).

There are many forms of psychotherapy. Those that were specifically studied for efficacy in the treatment of depression are cognitive-behavioral therapy and interpersonal therapy. These forms of therapy are focused on present thoughts, feelings, relationships, and behaviors. Therapy continues for a set number of sessions, usually no more than 16 weekly sessions, in a prescribed, predetermined progression (27). **There is increasing evidence that supportive and psychodynamic psychotherapies are effective.**

It is especially important for the patient to have the opportunity to work out her feelings about having a psychiatric disorder, understand how it has affected her life, and feel comfortable taking medication or undergoing psychotherapy. Patients often attribute depression to weakness, laziness, or immorality, and they often confuse antidepressants with stimulants, tranquilizers, and other psychoactive drugs. Although written material cannot substitute entirely for verbal instruction, it is useful to provide the patient with written material about depression so that she can review it at her leisure and with her family and friends if they have difficulty understanding her condition. At the same time, clinicians must be aware that there is widespread difficulty understanding written information, especially about medicine. **Many or most antidepressant prescriptions are either not filled or not taken as prescribed** (28).

Depression in one individual has a powerful effect on other members of the family, particularly children. This can be a motivating factor for patients who are reluctant to accept treatment.

BIPOLAR DISORDER (F31.11)

Mania is characterized by the following behaviors (3)**:**

- **Elevated mood, with euphoria or without irritability**
- **Grandiosity**
- **Accelerated speech and physical activity**
- **Increased energy**
- **Decreased sleep**
- **Reckless and potentially damaging behaviors, such as wild expenditures and promiscuity**

Mania can be acute or subacute (hypomania). Hypomania can produce self-confidence, ebullience, energy, and productivity that are pleasurable for the patient and the envy of others, making the patient reluctant to relinquish this mood by undergoing treatment. It can be particularly difficult to arrest the condition before it progresses to full-blown mania. Acute mania is a life-threatening condition; without treatment, patients fail to maintain essential sleep and nutrition levels and literally exhaust themselves with frantic activity. Patients with bipolar illness must be taught and encouraged, and often learn from bitter experience, to recognize the early signs of disturbed mood so that treatment or treatment changes can be initiated. It is important to remember that patients with bipolar disorder have more depressive episodes than manic episodes, and therefore it is important to screen every patient complaining of depression thoroughly for a family history of bipolar disorder and a personal history of manic symptoms. Though depression in those with bipolar disorder may present similarly to

that of unipolar depression, it is important to distinguish, as the treatment consists of mood stabilizers and antipsychotics. **Giving unopposed antidepressants can provoke a manic episode** (29). One potentially helpful screening tool in the diagnosis of bipolar disorder is the Mood Disorder Questionnaire that can be given to patients to fill out (30).

Gynecologic Factors

Connections between female reproductive functions and mood changes have been posited for centuries. When it first became possible to determine circulating hormone levels, researchers expected to find specific relationships between psychological and physiologic changes. These expectations were uniformly discounted. **There is no specific serum hormone level directly associated with premenstrual dysphoria, postpartum depression, or depression at menopause** (31). There is a subgroup of women who are vulnerable, not to absolute circulating hormone levels, but to hormonal changes (32–35). There is a correlation between the degree of hormonal change, pre- and postpartum, and the incidence of postpartum mood disorder. **Women who are vulnerable to hormonal changes may experience severe premenstrual mood symptoms, postpartum depression, and, possibly, depression in association with hormonal influences such as hormonal contraceptive methods, menopause, and hormone treatments** (36).

Premenstrual Syndrome and Premenstrual Dysphoric Disorder

[5] Premenstrual syndrome (PMS), as differentiated from premenstrual dysphoric disorder (PMDD), has been characterized by more than 100 different physical and psychological signs and symptoms, making it difficult to define scientifically. Methodologic problems further complicate the situation; in the United States, the prevalence of attitudes linking the menstrual cycle to adverse mood and behavioral changes is so high that it skews women's perceptions, the way they report symptoms to researchers, and the factors to which they attribute negative feelings.

Premenstrual Dysphoric Disorder (F32.81)

An estimated 3% to 5% of ovulating women appear to suffer from symptoms so marked that they qualify for a diagnosis of PMDD (37,38).

DSM-5 criteria for the diagnosis of PMDD are:

- **In the majority of menstrual cycles, the patient had at least five of the associated symptoms for most of the time during the premenstrual week, with symptoms starting to improve within a few days after the onset of menses, and becoming minimal or absent in the postmenstrual week** (38).

- At least one of the following symptoms must be present: marked affective lability, marked irritability/anger/interpersonal conflict, marked depressed mood/hopelessness/self-deprecating thoughts, marked anxiety/tension.
- Additional symptoms include decreased interest in usual activities; subjective difficulty in concentration; lethargy; marked change in appetite; hypersomnia or insomnia; a sense of being overwhelmed or out of control; and physical symptoms such as bloating or breast tenderness.

The symptoms must markedly interfere with work, family, or academic responsibilities; not be exacerbations of another existing disorder; and must be corroborated by at least 2 months of prospective daily ratings (38).

Records of emotions and behaviors should be kept separate from menstrual records to avoid confounding patients' perceptions. The patient must be screened for domestic abuse and other life circumstances that may contribute to her psychological state (39).

No treatment for PMS has been validated by empirical studies (40 studies of St. John's wort are contradictory) (40). A number of **lifestyle changes and other benign interventions may alleviate symptoms for patients with PMS** (31)**:**

- **Elimination of caffeine from the diet**
- **Smoking cessation**
- **Regular exercise**
- **Regular meals and a nutritious diet, consisting of complex carbohydrates**
- **Adequate sleep**
- **Stress reduction**

Stress reduction can be accomplished by reducing or delegating responsibilities, insofar as that is possible, and devoting part of every day to relaxation techniques such as meditation and yoga. Many women experience stress factors over which they have no control (40).

For PMDD, several selective serotonin reuptake inhibitors (SSRIs) have proven effective in clinical trials. Fluoxetine, sertraline, and paroxetine are FDA approved (42,43). Although SSRIs and all other antidepressants require about 2 weeks of daily administration to achieve therapeutic effect for other depressive disorders, it appears that SSRIs are effective for PMDD when taken in the usual daily doses during the luteal phase, and have even proven efficacious when started at symptom onset. As a result of this quick relief of symptoms, it is thought that the mode of action of SSRIs, when used in this fashion, differs from that which alleviates major depression (31). Other medications for the treatment of PMDD are shown in Table 23-2. There is some interest in the role of oral contraceptives in the management of PMDD, and for patients interested in contraception, trials of oral contraceptives are a reasonable approach (31).

Symptoms must be carefully monitored to determine whether the hormonal intervention improves or exacerbates the problem mood changes.

Table 23-2 Treatment of Premenstrual Dysphoric Disorder

Antidepressants	Fluoxetine 20 mg daily Sertraline 50–150 mg daily Paroxetine CR 12.5–25 mg daily Citalopram 5–20 mg daily Venlafaxine 75 mg daily Clomipramine 25–75 mg daily
Ovulation suppression	Ethinyl 20 mg/drospirenone 3 mg (Yaz) Transdermal estrogen Leuprolide 3.75–7.5mg IM monthly Danazol 200–400 mg daily
Other medications	Alprazolam 0.25 mg twice a day during luteal phase Bromocriptine Spironolactone
Nonpharmacologic	Calcium 600 mg twice daily Chasteberry Cognitive behavioral therapy

From **Lanza di Scalea T, Pearlstein T.** Premenstrual dysphoric disorder. *Psychiatr Clin North Am* 2017;40(2):201–216, with permission.

Psychiatric Aspects of Other Reproductive Events

***Infertility* is described by most women who undergo treatment for it as the most stressful event of their lives.** Each unsuccessful treatment episode is experienced as the loss of a hoped-for pregnancy (44).

***The loss of a fetus or newborn* induces grief, with some of the same symptoms as depression.** Depression is associated with guilt, whereas bereavement is not. However, women who lose pregnancies or infants often do feel guilty, regardless of whether these feelings are logically justified. Patients should not be pressed to "put the loss behind them" or expected to be "over it" within several months. Some feelings of sadness may persist for years. However, their sleep, appetite, and other vital functions and behaviors should begin to improve after a few weeks (44). **Grief that persists and interferes with normal function is characterized as pathologic. Depression can complicate grief and should be treated** (45).

Induced Abortion

Nearly one-third of the women in the United States will have at least one abortion in their lifetimes. The distribution of religious affiliation among patients having abortions parallels that of the United States as a whole; that is, women who report membership in religious faiths opposed to abortions have abortions as often as those without such

affiliations. **There is no convincing evidence that induced abortion causes clinical depression or any other negative psychiatric sequelae.** Studies purporting to demonstrate negative sequelae fail to take into account the circumstances under which women conceive unintended pregnancies and elect to terminate them—abuse, abandonment, poverty, rape, and incest—or the circumstances in which they occur—familial pressure or disapproval, or the presence of clinic demonstrators (46). Nevertheless, scientifically unsupported allegations of physical (breast cancer) and psychological (substance abuse, depression, suicidality) effects have been used to justify restrictive state legislation in many parts of the country. Some state laws require that physicians inform patients of these (nonexistent) risks. Patients may need reassurance, in the form of accurate information, as they make abortion decisions or reflect upon past abortions.

Peripartum Psychiatric Disorders

[5] The incidence of depression in women during their reproductive years is approximately 10%. The incidence of depression does not decrease during pregnancy; most postpartum depression is a continuation of antepartum depression (47–49). Although there are some cross-cultural variations, postpartum depression is found around the globe (50). Risk factors include social isolation, lack of social supports, history of depression, and past or present victimization (51). **It is important to remember that women without risk factors may become depressed.** Postpartum depression must be distinguished from the transitory, self-limited, and very common "baby blues," which are associated with changes in hormone levels and are better characterized as mood intensity and lability rather than depression. Mild depression can be managed with psychotherapy (52). Moderate-to-severe cases often require antidepressant medications (53). Electroconvulsive treatment acts rapidly and effectively, appears to be safe during and after pregnancy, and can be a life-saving option for the most severe cases (54). Treatment with artificial light may alleviate milder symptoms (55). Although no agent can be declared perfectly safe for use during pregnancy and lactation, older SSRI agents are well studied, yielding little evidence of adverse effects on the fetus or nursing infant (56,57). Medication should not be stopped arbitrarily, nor should breastfeeding be prohibited. **The withdrawal of antidepressant medication during pregnancy is very likely to result in recurrent and persistent depression; both antenatal and postnatal depression have demonstrable, long-term ill effects for mother and child** (58–65). There is concern about withdrawal syndromes in neonates whose mothers took SSRIs (66). These concerns arise from anecdotal reports and do not include data about the number of births from which the reports emerged, nor about confounding variables. Some observers recommended that pregnant women be withdrawn from SSRIs some days or weeks before delivery. However, delivery dates are often uncertain; maternal withdrawal might subject the fetus, rather

than the newborn, to withdrawal symptoms; and the likelihood of postpartum depression, with its effects on both the mother and the infant, would be greatly increased. Researchers are exploring ways to prevent postpartum depression, but thus far nothing has proved effective (67,68).

Sertraline appears to be the safest medication for pregnant and lactating women, and *paroxetine* is the cause of most concern. If treatment is begun during pregnancy or lactation, *sertraline* is the reasonable choice. Switching a patient successfully treated with another antidepressant to *sertraline* is not indicated. The fetus would be exposed to a second medication, and the patient may not respond as well to *sertraline* as to the currently effective antidepressant (56,57).

Menopause

[5] Although menopause was assumed for many years to be associated with an increased incidence of depression, empirical studies led to conflicting results and controversy. Menopause appears to have mood effects in some women that can be differentiated from the hormonal effects, such as hot flashes interfering with sleep. Historical theories like "empty nest syndrome" implied that some patients are upset by their loss of fertility or the departure of grown children from the home, but this has not been validated in studies. Many women find menopause liberating (60). For some women the return of adult children to the maternal home, or responsibilities for the care of grandchildren, seems to be a precipitating factor for depression. Patients who suffered PMS or postpartum depression may be vulnerable to a recurrence of depression at this new time of hormonal change. Patients with depression at the time of menopause should be assessed for psychosocial precipitants and domestic abuse. There are conflicting reports on the effectiveness of hormones for treatment of mood symptoms during menopause (70–75). Treatment with SSRIs may ameliorate hot flashes (76).

Depression in elderly patients can cause a *pseudodementia,* characterized by decreased activity and interest and what appears to be forgetfulness. Unlike patients with genuine dementia, these patients report memory loss rather than trying to compensate and cover up for it. The early stages of dementia can precipitate depression as patients react to the loss of cognitive abilities (20).

Suicide

The most acute issue in the assessment and referral of depressed patients is the possibility of suicide (77). **Following are the risk factors for suicide:**

- **Depression**
- **Recent losses**
- **Previous suicide attempts, even if seemingly not serious**

- **Impulsivity**
- **Concurrent alcohol or substance abuse**
- **Current or past physical or sexual abuse**
- **Family history of suicide**
- **A plan to commit suicide**
- **Access to the means to carry out the plan**

Women attempt suicide more frequently than men, but men complete the act more frequently than women (78). This is probably because men use more drastic or irreversible means, such as firearms, whereas women tend to overdose, which can be treated if discovered. It might seem that someone who repeatedly makes suicidal gestures is more interested in the responses of others than in ending her life. However, **past attempts or gestures increase the risk of completed suicide. Patients who made a suicide attempt should be queried about the following risk factors: the intent to die (rather than escape, sleep, or make people understand her distress); increasing numbers or doses of drugs taken in a progression of attempts; and drug or alcohol misuse, especially if it, too, is increasing. Inquiry about suicidal ideation and behavior is an inherent part of every mental status examination and is mandatory for every patient with past or current depression or evidence of self-destructive behavior.** The inquiry can follow from discussion of difficulties in the patient's life or mood or be introduced with a comment that almost everyone has thoughts of death at one time or another. Nonsuicidal patients will immediately volunteer that they have had such thoughts and that they have no intention of acting on them. They will often add reasons: they have too much to look forward to, it is against their religion, or it would hurt their family.

It is important to distinguish among thoughts of death, the wish to be dead, and the intention to kill oneself (77). A patient in a painful life situation—a chronic, painful, or terminal medical condition, the birth of a severely damaged child, or a grievous loss—may express a wish to die, and even refuse recommended medical care but emphatically and honestly disavow any intention of actively harming herself. The patient must be directly asked.

If the patient previously engaged in impulsive self-destructive behavior, without a plan or warning, it is wise to consult a psychiatrist. If a patient is actively contemplating suicide, she must see a psychiatrist immediately (78,79). Other mental health professionals may be helpful but are less likely to have dealt extensively with and assumed responsibility for suicidal patients, be able to determine whether the patient should be hospitalized, and have admitting privileges. Until she is in the physical presence of a psychiatrist, or in a safe environment such as a hospital emergency room, a suicidal patient should be observed and protected at all times—every second—

whether she is in the consulting room or the bathroom. The staff member assigned to remain with her may not leave to make a telephone call, go to the bathroom, or get a cup of coffee. Family members may offer to monitor the patient and can sometimes be effective, but the health care professional is responsible for ensuring that they understand and implement this level of supervision. **It is better to risk inconvenience and possible embarrassment to both the gynecologist and the patient than to risk a fatal outcome. When suicide is an immediate consideration, only a psychiatrist can make the decision that a patient is safe** (79). Psychiatric referral can be useful in less dramatic cases: when the gynecologist lacks experience or is overloaded with patients, when a first trial of treatment is unsuccessful or there is uncertainty about the diagnosis, when domestic violence or substance abuse may be present, and when the depression is recurrent. **Approximately half of suicides are not associated with depression. Suicide can occur in the context of an anxiety disorder, personality disorder, psychotic illnesses, or as an impulsive response to an adverse life event** (79). Suicide is not an inevitable consequence of any of these conditions, including depression. Most people rescued from potentially lethal suicide attempts do not ultimately commit suicide. That is why barriers on bridges, the elimination or safe storage of firearms, the careful management of medications dangerous in overdose, and other approaches to prevent impulsive suicides are necessary.

ALCOHOL AND SUBSTANCE ABUSE DISORDERS

[4] Alcohol and substance abuse are among the most common and most frequently overlooked conditions in medical practice; and are major causes of morbidity and mortality (80). It is important to note that alcohol and substance abuse occur in patients of all ages and socioeconomic categories. A 2013 national survey showed that approximately 13% of women in the United States had used illicit drugs in the past year (81). In the DSM-5, the term "substance" can mean a prescription medication, a toxin, or an illegal drug. **The essential feature of substance dependence, or addiction, is the continued use of the substance despite serious resulting problems.**

Nicotine is included among "substances." Women appear to be more susceptible to nicotine addiction than men. Smoking cessation counseling by the gynecologist is helpful. Withdrawal from alcohol and drugs can be a clinical problem; patients often fail to inform clinicians of their alcohol and substance use before being hospitalized or undergoing procedure (83–85).

Patients frequently use alcohol along with other substances of abuse. The abuse of prescription medication, especially in younger populations, has increased (86), and opioid use has been declared a national emergency. Patients should be advised to take care that their medications are not accessible to others. There are increasing reports of

the deaths of toddlers and young children from the accidental ingestion of opioids left within their reach. Patients concerned about the use of opioids by family members or other people with whom they are in contact may want to obtain opioid antagonists for use in emergencies.

Marijuana can decrease the painful symptoms of some diseases and treatments. For asymptomatic individuals, it has negative effects on cognition and behavior. Nevertheless, among some populations, it is regarded as commonplace. The impact of the recent legalization of marijuana in several states is unknown.

Alcohol is the most frequent substance of abuse. Legal and accepted by the society, it nevertheless causes a high proportion of morbidity, mortality, and life complications. **Women's alcohol abuse is more likely to take place in private than is men's; society frowns more on women who are drunk or create disturbances in public than on men who do the same. Women are more likely than men to use a substance because an intimate partner uses or abuses that substance, and to trade sexual behavior for access to the substance** (87). The most successful treatment for substance abuse disorders is a so-called 12-step program such as Alcoholics Anonymous. M**ost of the programs for the treatment of substance abuse were developed for men. Women are less responsive to the usual confrontational approach** (88,89). Many women with alcohol and substance abuse issues have children. Such women, and women who are pregnant, are often reluctant to enter treatment for fear of prosecution or losing custody. These are realistic fears. **Treatment programs for women with primary responsibility for children must include arrangements for child care—but seldom do.** Recidivism after treatment is very common, but that does not mean that treatment is useless. **On average, patients require three episodes of treatment before achieving sobriety** (82). **The essential obligation of the primary physician is to ask each patient about substance consumption and any problems arising from it** (87). Using the single screening question: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" is proven to be efficacious in detecting substance abuse in primary care settings (85). *Buprenorphine* is a useful adjunct medication for treating opioid addiction; physicians are required to undergo specific training in order to prescribe *buprenorphine* (90).

ANXIETY DISORDERS

Anxiety is a sense of dread without objective cause for fear, accompanied by the usual physical concomitants of fear. Although every human being has anxious feelings from time to time, anxiety disorders are diagnosed when anxiety becomes disabling or so painful as to interfere with an individual's quality of life. **Anxiety disorders place patients at risk for suicide** (91).

Diagnosis

The anxiety disorders include generalized anxiety disorder, panic disorder, social anxiety disorder, agoraphobia, and specific phobias (3).

Generalized Anxiety Disorder (F41.1)

Generalized anxiety disorder is a condition in which anxiety is excessive and persistent, pervading many aspects of a patient's life, and interferes with normal function. Diagnostic criteria include restlessness, easy fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbances. **Whereas depressed patients fall asleep more or less normally and then awaken earlier than intended, anxious patients tend to have difficulty falling asleep** (3).

Panic Disorder (F41.0)

Panic disorder is characterized by panic attacks: sudden, acute periods of intense fear, generally lasting about 15 minutes, with at least four of the following symptoms (3)**:**

- **Diaphoresis**
- **Trembling**
- **Shortness of breath**
- **A choking sensation**
- **Chest discomfort**
- **Gastrointestinal distress**
- **Lightheadedness**
- **A sense of unreality**
- **Fear of going crazy or dying**
- **Paresthesias**
- **Chills or hot flashes**

The attacks can recur with or without specific precipitating events. The patient is preoccupied with them and makes behavioral changes she hopes will avert future attacks: avoiding specific situations, assuring herself there is an escape route from certain situations, or refusing to be alone.

The symptoms of panic attacks are often confused with the symptoms of cardiac or pulmonary disease. They lead to many fruitless trips to the emergency department and to costly, even invasive, medical investigations. A careful history can establish the correct diagnosis in most cases (92).

Social Anxiety Disorder (F40.10)

Social anxiety causes the patient to fear and avoid situations in which the patient

anticipates, without rational cause, that she will be perceived in a humiliating light. Such situations include giving a business-related presentation, making an announcement at a meeting, and having a casual dinner with friends. Patients may alter their lives to avoid these anxieties, interfering with their interpersonal relationships and their ability to carry out their responsibilities, or they may manage to carry on despite considerable psychological pain (93).

Agoraphobia (F40.0)

Agoraphobia is a marked fear of at least two of the following: using public transportation; being in open spaces; being in enclosed spaces; standing in line or in a crowd; being outside of the home alone, leading to avoidance of these situations. She therefore tends more and more to stay at home or limit her sphere of activity to an increasingly short list of venues. Agoraphobia and panic disorder can occur separately or together (94).

Specific Phobias (F40.2)

Specific phobias are irrational fears of certain objects or situations, although the patient recognizes that the object or situation poses no real danger. Of particular concern in gynecology are fear of needles and fear of vomiting. Many patients dread certain aspects of care, sometimes on the basis of past experience or outdated information (95). A simple explanation or alteration in procedure can alleviate the anxiety. For example, a reassuring family member or friend can be allowed to stay with the patient during a diagnostic test, sedation can be administered orally or by inhalation before an intravenous line is inserted, or the patient can be allowed control over her own analgesia.

Behavioral interventions are extremely useful in managing anxiety disorders without problematic side effects. They include hypnosis, desensitization, and relaxation techniques (92–100). These techniques provide a patient with tools to cope with her own anxiety. Specialists in behavioral medicine, usually psychologists, are expert in these techniques. A local medical school department of psychiatry or behavioral medicine is a good source for referrals. Interested gynecologists can master some of the techniques.

Trauma-Related Disorders

Posttraumatic stress disorder (PTSD) (F43.1) is the result of exposure to an event that threatens death or sexual violence of the patient or others. At the time of the trauma, the patient experiences horror, terror, or a sense of helplessness. Afterward, the patient may lose conscious memory of all or part of the event, avoid situations reminiscent of it, and become acutely distressed when she cannot avoid them. She feels numb and detached, without a sense of the future. She is hyperarousable and irritable

and has difficulty sleeping and concentrating. She re-experiences the event in nightmares, flashbacks, and intrusive thoughts (96).

Obsessive–Compulsive Disorder (F42)

Obsessive–compulsive disorder (OCD) is characterized by obsessions: recurrent impulses, images, or thoughts that the patient recognizes as her own, but dislikes and cannot control; or compulsions: intrusive, repetitive behaviors that the patient feels she must perform to prevent some dire consequence (95,98,99). The disorder can be mild or totally crippling; in half of the cases, it becomes chronic. The term OCD has made its way into popular parlance to describe people who focus on details and have trouble making up their minds.

Somatic Symptom and Related Disorders

[6] These disorders are characterized by somatic symptoms associated with significant distress and impairment. The diagnoses are not made on the basis of absent physical or laboratory evidence of a gynecologic or general medical condition; it is never possible to definitively rule out another diagnosis, and our increasing recognition of the powerful intrinsic interactions between the brain and the rest of the body renders the old mind/body distinction obsolete. When dealing with this category of disorders, it is particularly important to ask about, and document, the patient's previous episodes of care; diagnostic procedures performed, opinions rendered, treatments administered.

Somatic Symptom Disorder (F45.1)

This disorder is characterized by somatic symptoms that interfere with normal functioning and are upsetting to the patient. Generally, a patient has several such symptoms, and at least one is present consistently for at least 6 months. She is inordinately concerned about the seriousness of the symptoms; anxious about them; and devotes inordinate time and energy to worrying about them. She may interpret normal bodily sensations as indications of disease, spend considerable energy on careseeking behaviors, and frequently check her body for signs of illness. The disorder is often associated with depressive and anxiety disorders. It should be noted that, in some cultures, depression and anxiety are more often expressed in terms of physical than psychological symptoms (3).

Illness Anxiety Disorder (F45.21)

This disorder is not characterized by complaints about physical symptoms, but by preoccupation with and anxiety about the likelihood of a serious medical condition. The patient checks her body, seeks or avoids medical visits and diagnostic tests.

Management

Somatic symptom disorder and illness anxiety disorder can entirely disrupt the patient's life, and that of her family. On first encounter with the clinician, the patient may express relief that she has finally found the doctor who understands and will diagnose and treat her condition. It is tempting to welcome these accolades, but they are almost always transitory. Given many physicians' fear of missing a serious diagnosis, fear of legal action, and the insistence of these patients, it is difficult to decide when the cost and time of diagnostic procedures and office visits is sufficient. There is no easy way out of this dilemma. It is not worthwhile to inform the patient that there is nothing wrong with her when, in fact, there is something wrong with her. It is best to be proactive. Rather than dreading contacts with the patient and attempting to avoid them, schedule calls and visits at reasonable times and intervals, informing the patient that the clinician feels the visits are necessary for monitoring her condition. Commiserate with her discomfort, but spend the contact focused almost entirely on her progress with getting on with her life despite it. Health-promoting behaviors, and successes, even attempts to carry out her work and family responsibilities and enjoy leisure activities, should be praised and tracked.

Conversion, or Functional Neurologic Symptom, Disorder (F44.4)

This disorder was traditionally called "hysteria." The patient has symptoms of altered voluntary motor or sensory function, in a pattern inconsistent with any known or likely medical causation. There may be weakness or paralysis; seizures; sensory loss (blindness); or difficulties with swallowing or speaking. She may or may not exhibit distress over the symptom or symptoms. The treatment of this disorder generally requires a mental health professional.

Factitious Disorder, or Munchausen Syndrome (F68.1)

This is a poorly understood condition in which the patient actively causes physical damage to herself or feigns somatic symptoms that result in repeated hospital admissions and painful, dangerous, invasive diagnostic, and therapeutic procedures (3). These patients may introduce feces or purulent material into wounds or intravenous lines, inject themselves with insulin, or cause hemorrhages. Given enough diagnostic and therapeutic interventions, significant iatrogenic conditions, such as adhesions from surgery or Cushing syndrome from the administration of steroids, may develop in these patients.

These patients are initially engaging but eventually frustrate the medical staff. Declaring that the patient "only wants attention" is not helpful (101). Most people want attention, but very few are willing to go to these lengths to get it. Confirming the diagnosis is a delicate process. When staff members become suspicious, they will be tempted to validate their suspicions by spying on the patient or sending her out of her hospital room on a pretext and then searching her belongings. The latter is illegal, and

such actions, followed by a confrontation, will end the therapeutic relationship and provoke the patient to flee rather than addressing the problem. Calls for a psychiatric consultation may provoke resentment in the patient and family. Patients soon reappear in another medical facility. As a result, there are few data about the etiology, incidence, and management of this condition. Often these patients are medically sophisticated through some kind of medical training or knowledge gained during previous care episodes or hospitalizations. Mothers may enact this disorder through their children by deliberately making them ill, a condition called **Munchausen by proxy** (3). Munchausen by proxy gained some popular notoriety, and it resulted in accusations and loss of custody for some mothers whose children had serious, chronic diseases requiring multiple medical interventions. Shared electronic records might affect the occurrence of these conditions by making it more difficult for the patient to present to multiple treatment venues.

It is critical to remember that patients whose somatic symptoms result from depression, PTSD and other anxiety disorders, and domestic violence, frequently seek care from gynecologists. These possibilities must be ruled out before care is directed to symptom management. **In the case of domestic violence, the gynecologist is often the only human contact the abuser allows the patient outside the domestic situation** (102). **Several medical associations have drawn attention to the need to screen women for domestic violence and the infrequency with which this is done. It appears that a single screening does not significantly change outcomes. Acknowledging domestic violence, identifying, and accessing resources are part of an often prolonged and incremental process—of which screening can be an important first step** (103). One example of a screening query gynecologists could use is: "Does your partner insult you, threaten you, scream at you, or physically hurt you?" It can be helpful to leave domestic violence resource flyers with tear-off tabs in the restroom for individuals who are not yet comfortable speaking about their abuse with their physician.

Referral

Patients with somatic symptom disorders may resist mental health referral more adamantly than any other single class of patients (101). Focused as they are on physical symptoms, these patients can regard referral as a message that their symptoms are not being taken seriously and as a sign of contempt and rejection by the gynecologist. It is particularly useful with these patients to emphasize that distinctions between the mind and the body are artificial. The brain is part of the body. Our language expresses this synthesis; anxiety causes "butterflies in the stomach," aggravation "gives us a headache," and unwelcome news "gives us a heart attack."

Any referral should be framed as support for the patient's suffering rather than

as a statement that her problems are "all in her head" (104). The mental health professional should be introduced as a member of the medical team. Some medical institutions have dedicated psychiatric consultation, medical psychiatry, or behavioral medicine services offering expertise in the psychological complications of disease and in somatization disorders. Because the so-called somatic and psychological symptoms often coexist and interact, the gynecologist should work in collaboration with the mental health professional. Patients should be given a return appointment with the primary physician, or a request for a telephone contact, at the time of the original mental health referral. This serves to reassure the patient that they are not being dismissed, maintains their contact with the primary physician, and confirms that a line of communication exists to inform the primary physician of the results of the consultation (104).

PERSONALITY DISORDERS

Personality disorders are pervasive, lifelong, maladaptive patterns of perception and behavior (105). They interfere significantly with patients' ability to function in work, family, and other social roles, and cause considerable distress. They are characterized by deficits in a cohesive, persistent sense of identity; interference with standards of behavior, coping skills, and self-reflection. They are associated with a lack of empathy: the ability to understand the feelings of others or the effects of one's behavior on others and the inability to form meaningful, mutual intimate relationships. Patients with personality disorders believe that whatever painful feelings and experiences they have are not the result of their own attitudes and behaviors, but are caused by the attitudes and behaviors of others. They view their own behaviors, which can wreak havoc in the health care setting and in patients' lives, as normal, expectable, inevitable reactions to erroneously perceived circumstances. To make matters worse, their behaviors tend to provoke in others the very responses that confirm their expectations; for example, a patient who is convinced that people always abandon her will cling desperately to others, eventually driving them away.

Diagnosis

Patients often manifest characteristics from several disorders.

Paranoid personality disorder (F60.0) is characterized by pervasive suspicion of the motives and behaviors of others: the belief that others have hostile or exploitative motives with respect to the individual. The patient second-guesses the medical team, expects to be cheated and to see other patients preferentially treated.

Schizoid (F60.1) and schizotypal (F21) personality disorder, as the names indicate, are on a spectrum with schizophrenia, resulting in odd behaviors and

avoidance of others.

Narcissistic personality disorder (F60.81) is characterized by grandiosity, a constant need for admiration, and a lack of concern for others. This patient may insist upon seeing or talking to the clinician, in nonemergent situations, immediately and in preferential treatment in general.

Histrionic personality disorder (F60.4) is manifest in abnormal emotionality and attention-seeking. They may be sexually provocative.

Antisocial personality disorder (F60.2) is associated with a lack of respect, or the absence of social and legal norms. The patient may be skilled at social interactions, inspiring friendship and trust that are exploited for personal gain.

Avoidant personality disorder (F60.6) results in discomfort in social interactions, resulting from a sense of personal inadequacy and fear of negative judgments by others.

Dependent personality disorder (F60.7) leads to a sense that one requires an inordinate amount of care.

Obsessive–compulsive personality disorder (F60.5) is associated with perfectionism and a need to order and control people and circumstances.

Borderline personality disorder (F60.3) is the most likely to cause trouble in gynecologic practice. These patients have difficulty controlling their impulses and maintaining stable moods and relationships (105). They engage in self-destructive behaviors. Their effects are unstable; they get upset or angry easily. They fluctuate between overvaluation and castigation of the same person or direct these feelings alternately between one person and another. When this happens on a gynecology service, office, or clinic, it can precipitate significant tensions among the staff. **Research reveals that many women who were abused are diagnosed as borderline, when PTSD more accurately fits their symptoms** (102,103). **PTSD** is a less stigmatizing and more treatable condition than borderline personality disorder.

Assessment

The impact of personality disorders ranges widely. At one end of the spectrum, the disorder is an exaggerated personality style. At the other end of the spectrum, the individual suffers terrible emotional pain and is unable to function in work roles or relationships, spending significant periods of time in psychiatric hospitals. She characterizes her symptoms of despair as inevitable responses to abandonment or other mistreatment. As the definition implies, the patient will not seek treatment for the signs and symptoms listed in the diagnostic criteria but will have complaints about her treatment by others, their responses to her, and the unfairness and difficulties of life in general. Taking the history, the clinician should frame questions in those same terms: *How long have these troubles gone on, and how much do they interfere with her*

ability to work and relate to others? Personality disorders do not bring patients to gynecologists' offices directly, but they greatly complicate things when patients arrive.

Management

Intense and lengthy psychotherapy is required to effect significant improvement in patients who have personality disorders (102). Expert, targeted therapeutic interventions can be successful and that the long-term prognosis is more hopeful than previously believed. The challenge in the gynecology setting is to minimize contention and drain on medical staff while maximizing the likelihood of effective diagnosis and treatment of the patient's medical problems. **The most helpful single step for the gynecologist is the identification of the personality disorder.** Diagnosis enables the gynecologist to recognize the reasons for a patient's problem behaviors, to avoid becoming entangled in fruitless interactions with the patient, and to set appropriate limits.

There is increasing evidence that psychotropic medications are useful adjuncts in the treatment of personality disorders (103). Treatment should be provided in consultation with a psychiatrist. The patient's ability to use the medication can be compromised by impulsivity, self-destructive tendencies, and unstable relationships. Low doses of major tranquilizers are sometimes helpful, especially when the patient has brief psychotic episodes. Minor tranquilizers or anxiolytics pose significant risk of overdose and physical and psychological habituation (103). They can be prescribed for temporary stresses, but only in a quantity sufficient for several days and with no refill allowed. Some patients' anxiety, demands, and power struggles are eased when they are given control over their own use of medication. Such an approach requires enough familiarity with the patient to ensure her safety and should be managed by an expert. Because the patient with a personality disorder attributes her problems to others, her symptoms cannot be adduced as reasons for psychiatric referral, but her suffering can be. Personality diagnoses are particularly stigmatizing. If a diagnosis of a personality disorder absolutely must be noted in the patient's chart or on insurance forms, it is essential that she be so informed. It is useful to review the diagnostic criteria with her so that she understands the basis for the diagnosis. **All psychiatric diagnoses, but particularly personality disorders, carry a significant stigma.**

ADJUSTMENT DISORDERS

Diagnosis

Adjustment disorders are temporary, self-limited responses to life stressors that are part of the normative range of human experience (unlike those that precipitate PTSD) (106). The patient has mood or anxiety symptoms that are sufficient to lead her to seek medical care but that do not meet criteria of sufficient quantity or quality to

qualify for psychiatric diagnosis. The diagnosis requires an identifiable stressor, onset within 3 months after the stress begins, and spontaneous resolution within 6 months after the stressor ends. Obviously the latter cannot be determined until the symptoms resolve—but they do rule out the disorder if the symptoms persist beyond that time (106).

Adjustment disorders can be distinguished from normal grieving (106). Grieving produces symptoms similar to those of depression, although depression is more likely to cause guilt. Interference with function should not persist beyond several months, but some degree of sadness and preoccupation with the lost loved one often goes on for years. Patients with persistently disabling grief should be referred to a mental health professional.

Management

Patients with adjustment disorders can be treated effectively with brief counseling in the primary care setting (106). The counseling can be provided by the gynecologist or by a nurse clinician, social worker, or psychologist, preferably a member of the office or hospital staff who is familiar with the gynecologist and the practice. The medical setting is sometimes the only place where the patient can vent her feelings and think through her situation. Counseling is aimed at facilitating the patient's coping skills and helping her to make thoughtful decisions about her situation. The gynecologist should follow the patient's progress and facilitate referral to a psychiatrist if symptoms do not resolve.

EATING DISORDERS

Preoccupation with thinness, sometimes to the point of pathology, is a major problem for women in North America (107). Only a small number of women profess to be satisfied with their weights and body shapes. Nearly all admit to current or recent attempts to limit food intake. Physicians have legitimate concerns about the health consequences of obesity and often share social prejudices against overweight patients. However, it is increasingly clear that weight regulation is not simply a matter of caloric intake and energy expenditure. There is evidence for genetic and epigenetic causes of obesity (108). No dietary regimen has proven successful in sustained weight loss. Some patients avoid physician visits altogether because they anticipate being weighed in view of office staff and other patients, or being shamed. Negative comments by the physician or others can precipitate, if not cause, an eating disorder.

The best approach with overweight patients is to acknowledge that being overweight is detrimental to health but that changing one's diet and lifestyle, and losing weight, is very difficult. Primary care physicians should indicate that they are not going to judge the patient, but are available to provide support and

information at the patient's request.

Binge-Eating Disorder (F50.8)

Binge-eating disorder is defined as at least once a week experiencing a sense of loss of control over eating, without feeling physically hungry, and consuming greater than normal amounts of food within a 2-hour period, occurring in private because of embarrassment over the behavior, which results in feelings of depression and humiliation.

Anorexia Nervosa (F50.01)

Anorexia nervosa is characterized by severe restrictions on food intake, often accompanied by excessive physical exercise and the use of diuretics or laxatives. Clinical features include menstrual irregularities or amenorrhea, intense and irrational fear of becoming fat, preoccupation with body weight as an indicator of self-worth, and inability to acknowledge the realities and dangers of the condition. Some patients seek infertility treatment (108). Anorexia poses significant risks of severe metabolic complications and death, often from cardiac consequences of electrolyte abnormalities. Thorough physical and laboratory examination is critical; immediate hospitalization may be necessary (107–110).

Bulimia Nervosa (F50.2)

Bulimia **is characterized by eating binges followed by self-induced vomiting or purging.** Patients' weights may be normal or somewhat higher than normal. Patients have drastically low self-esteem, and the condition frequently coexists with depression (110). Recurrent vomiting can cause erosion of the tooth enamel.

Patients with anorexia or bulimia should be treated by mental health professionals, preferably those with subspecialization in this area. The conditions are highly refractory to treatment; patients can resort to elaborate subterfuges to conceal their failure to eat and gain weight (110,111). Up to 50% of cases will become chronic, and approximately 10% of those will ultimately die of the disease. Amenorrhea patients should not be treated with ovulation induction as it is not protective for bone density, and masks important indicators of disease severity (108).

PSYCHOTIC DISORDERS

The hallmark of psychosis is the presence of delusions or hallucinations. Hallucinations are sensory perceptions in the absence of external sensory stimuli. Delusions are bizarre beliefs about the nature of motivation of external events.

Because there is no reliable definition of "bizarre," a physician working with a patient from an unfamiliar culture must determine whether a given belief is normal in that culture. Delusions and hallucinations are the positive symptoms of schizophrenia. The negative symptoms include apathy and loss of connection to others and to interests. The negative symptoms may be more disabling than the positive. Deficits in cognitive functioning are a core feature of schizophrenia.

Schizophrenia affects approximately 1% of persons worldwide (111). Since the deinstitutionalization of persons with severe and persistent mental illnesses in the United States several decades ago, most affected individuals live in the community. Often health care and other services are inadequate, leaving these women vulnerable to sexual abuse and involuntary impregnation. Overall, the fertility of women with schizophrenia approximates that of matched populations.

It is unclear whether indigent status is a precipitating stress or a result of psychotic illness, but, as extremely few individuals have private or public coverage for adequate treatment, most people with schizophrenia are indigent.

There is wide variability in the functional impact of psychotic disorders. Patients must not be assumed to be incompetent to make medical decisions or lead independent lives, especially if they comply with treatment. Motherhood and child custody are exceedingly sensitive matters for these vulnerable patients.

A relentlessly downhill course is not inevitable; remissions and recovery can occur and, with support, most patients can lead satisfying lives in the community (112). Under the pressures of a busy medical setting, psychotic illnesses can be overlooked, only to erupt in the labor room, operating room, or recovery room. Patients who believe that conspiracies or aliens are responsible for their symptoms can answer yes-or-no medical questions without revealing their delusions. Open-ended questions ("*Tell me about your symptoms*") are more useful (7).

A primary care practitioner can assume responsibility, in consultation with a psychiatrist, for a stable patient who complies with treatment. When a patient expresses delusions, the clinician may indicate that he or she does not share these delusions, but should not debate with the patient. In the process of referral to a mental health professional, the primary clinician should be clear, matter-of-fact, open, and confident of the possibility of successful treatment.

GENDER IDENTITY AND SEXUAL ORIENTATION

Issues of gender identity and sexual orientation continue to be contentious in the society and relevant to gynecology practice. People who identify as lesbian, gay, bisexual, transgender, and queer (LGBTQ) report avoiding essential general and gynecologic care because they are made to feel uncomfortable and misunderstood

by physicians and other staff members, which explains in part, their suboptimal health outcomes. They are at risk of discrimination and bodily harm, and, as a result, at increased risk of anxiety, depression, and suicide.

Attitudes toward gender and sexual orientation are inculcated in everyone throughout their development, including gynecology staff. The practice challenge is to recognize those attitudes and to avoid the assumptions that go with them. The assumption should not be made that a heterosexual woman has exclusively had relationships with men whose birth sex is male, or that a lesbian woman has exclusively had relationships with women whose birth sex is female. **Registration forms and patient histories should allow for the fullest and most accurate account of a patient's legal and preferred names, gender identity, types of sexual partners, relationships, and, all staff must be cautioned not to express or imply negative judgments.**

Gender Dysphoria (F64.1)

Gender dysphoria is defined as a marked incongruence between an individual's assigned gender and the individual's personal experience of gender causes clinically significant distress or functional impairment. Identifying as transgender is not the pathology of this diagnosis, rather it is the distress that accompanies it. Transgender individuals resent implications that they are psychiatrically ill, but medical insurance only covers care for diagnoses, and gender affirming medical and surgical treatment is a financially costly process.

There is evidence that gender dysphoria does not result exclusively from the discomfort with one's primary and secondary sex characteristics, negative impact is derived from the lack of societal acceptance. The largest survey of transgender people showed that more than half of those who identify as transgender have been verbally harassed and not allowed to dress in a way that fits their gender identity and nearly one-quarter have been physically attacked because of being a transgender (113). Unemployment is three times as high in transgender people as compared to the general population, and transgender people are twice as likely to be living in poverty (113). There are many other cultures that acknowledge nonbinary gender identities, and where they have an accepted place in society, gender dysphoria is less common. In the United States, 40% of those who identify as transgender have attempted suicide in their lifetime, nearly nine times the rate of the general population (113). Transgender youth whose parents who are supportive of their identity are three times less likely to have depressive symptoms than transgender youth whose parents are somewhat or not at all supportive (114).

The mainstay of treatment for gender dysphoria is supporting the person's transition to the preferred gender expression through supportive psychotherapy, hormone therapy, and gender affirming surgery if desired. Symptomatic treatment of depressive and

anxiety symptoms is appropriate, though not very effective as monotherapy. As the time of transition is a period of vulnerability to depression, **a gynecologist can be supportive to transmen patients by using less gendered terms such as "chest" rather than "breasts" and "internal canal" rather than "vagina" during a physical examination, and taking special care to screen for suicidal ideation.**

PHARMACOLOGIC TREATMENTS

This section focuses on the conditions most often treated by gynecologists.

The types and characteristics of antidepressants are presented in Table 23-3. **All antidepressants have comparable therapeutic efficacy, and all require up to 2 to 4 weeks to take full effect.** It is not yet possible to identify those patients who will respond best to certain medications, but patients are more likely to respond to a medication successful in family members, and there is early evidence that depression may be related to specific neurotransmitters and respond differentially to medications affecting a given neurotransmitter (115). Patients tend to respond to medications that worked for them in the past and to those that worked for depressed family members. **Many patients require successive trials of two or more antidepressants before the one that is effective for them is identified. It is essential to continue active management through the usual duration of a depressive episode—9 to 12 months for major depression, until the patient has responded sufficiently that she has returned to her previous level of mood and function. If the patient does not recover completely, she should be referred to a psychiatrist** (116).

Selective Serotonin Reuptake Inhibitors

SSRIs pose few risks of medical complications. Side effects include anxiety, tremor, headache, and gastrointestinal upset (either diarrhea or constipation), and usually abate within a few days of the onset of treatment. **A more serious side effect is the loss of libido and interference with orgasm** (117). Patients may be reluctant to report sexual side effects, but they may discontinue treatment because of them. Some women are willing to accept the sexual side effects of SSRIs as an acceptable price to pay for recovery, especially considering that depression already interferes with their sexual functioning. Female patients are frequently concerned about weight gain. In one study, it appeared that a weight gain of 5 to 7 lb might be attributed to an SSRI; the return of normal appetite may lead to weight gain. Concerned patients should be advised to watch their diets carefully while taking the medication. There is some evidence that *bupropion* causes less weight gain than SSRIs. **SSRIs appear to interfere with the efficacy of *tamoxifen*, resulting in excess mortality from breast cancer** (118).

SSRIs are administered in a once-a-day regimen, with little need for dosage

adjustments in most cases. SSRIs have long half-lives, so occasional late or missed doses do not constitute a problem. Withdrawal, especially sudden withdrawal, from SSRIs causes flulike symptoms and sleep problems in a small proportion of patients (119). Patients should be cautioned not to discontinue their medications without consulting the physician, and only then by gradually decreasing the dose. As with most medications, antidepressants were not initially tested in older women, but several are under consideration by the U.S. Food and Drug Administration (FDA) for use in this age group. The FDA mandated the so-called black box warnings on SSRIs when used in adolescents and young adults. This decision is highly controversial. The studies upon which the decision was based included no subject who had committed suicide. Suicidal thoughts, which are extremely common, were conflated with serious attempts, all lumped together as *suicidality*. SSRI prescriptions decreased after the warning was imposed, and there is some evidence that suicides have gone up as a result (120–122).

It is sensible to use a more activating agent (*fluoxetine*) in a lethargic patient and a more sedating agent (*paroxetine*) in an agitated patient (116). Nonetheless, responses vary on an individual basis, even within the same class of medications. The choice of antidepressant is based on side effects, dosage, cost, and the physician's clinical experience **(Table 23-4)**.

Table 23-3 Classes, Side Effects, and Prescribing Considerations for Antidepressant Treatment

Class	Drugs	SE	Considerations
TCA	Imipramine Amitriptyline Doxepin Desipramine Nortriptyline	Weight gain, sedation, dry mouth, nausea, blurred vision, constipation, tachycardia	Generally not first-line therapy due to increased anticholinergic and cardiotoxic SE
MAOI	Isocarboxazid Phenelzine Tranylcypromine Selegiline	Weight gain, fatigue, sexual dysfunction, hypotension	Generally not first-line therapy due to serotonin syndrome and hypertensive crises
SSRI	Fluoxetine Paroxetine Sertraline Citalopram Escitalopram	Headaches, GI distress, insomnia, fatigue, anxiety, sexual dysfunction, weight gain	Often first-line treatment due to safer SE profile. Subtle SE differences must be weighed by the prescriber
SNRI	Venlafaxine Desvenlafaxine Duloxetine Levomilnacipran	Nausea, insomnia, dry mouth, headache, increased blood pressure, sexual dysfunction, weight gain	SEs are similar to but may be slightly more frequent than with SSRI
Atypical	Bupropion	Headache, agitation, insomnia, loss of appetite, weight loss, sweating	Increased seizure risk in eating disorder and epilepsy patients. No sexual dysfunction or weight gain. May also help to quit smoking
	Mirtazapine	Sedation, increased appetite, weight gain	Sedation may be less with higher dose. Much reduced nausea and sexual dysfunction compared with SSRI/SNRI. Some risk of reduced white blood cell count
	Trazodone	Sedation, nausea, priapism (rare)	Lower risk of weight gain and sexual dysfunction, but may cause priapism. Often used to induce sleep as a positive effect
	Vilazodone	Nausea, diarrhea, insomnia	Better SE profile than most ADTs with lower risk of sexual dysfunction or weight gain
	Vortioxetine	Nausea, diarrhea, dizziness	Similar SE profile to the SSRI. May have precognitive benefits in adults with MDD

ADT, antidepressant treatment; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; SE, side effect; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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Serotonin–Norepinephrine Reuptake Inhibitors

Serotonin–norepinephrine reuptake inhibitors (SNRIs) are a class of medications that include venlafaxine, desvenlafaxine, and duloxetine. They are similar to SSRIs in their indications, side effects, and mechanism of action at low doses, but have the pharmacologic property of blocking norepinephrine reuptake at higher doses, making them most similar to TCAs, without the side effect liability. Of the three, duloxetine is the most potent norepinephrine inhibitor, which makes it a first line treatment in patients that have comorbid chronic pain, fibromyalgia or stress incontinence. Venlafaxine and desvenlafaxine have been shown to be effective in the treatment of vasomotor symptoms associated with menopause (123).

One side effect of SNRIs that is unique compared to SSRIs is treatment-emergent hypertension, which may be most likely in venlafaxine and least in duloxetine.

Tricyclic Antidepressants

Tricyclic antidepressants are the oldest antidepressants still in use and are available in generic preparations (116–119). They all have significant anticholinergic side effects that may be problematic in medically ill and elderly patients. They are associated with some slowing of intracardiac conduction; this side effect can be tolerated and managed in all but a few patients, and it can be therapeutic for those with hyperconductibility. **The most important drawback of tricyclic medications is their lethality in overdose, which is especially important because they are used with depressed patients who are already at risk for suicide. In the rare event that they must be used by a potentially suicidal patient, the patient must be given only a few pills at a time** (119).

Table 23-4 Pharmacology of Antidepressant Medications

Antidepressant	Norepinephrine	Serotonin	Dopamine
Amitriptyline	+++	++++	–
Amoxapine	+++	+++	–
Bupropion	0	–	+
Citalopram	–	+++++	0
Clomipramine	+++	++++++	–
Desipramine	+++++	+++	–
Doxepin	+++	+++	0
Duloxetine	++++	++++++	+
Fluoxetine	++	+++++	–
Fluvoxamine	+	+++++	–
Imipramine	+++	+++++	–
Mirtazapine	–	0	0
Nefazodone	++	++	++
Paroxetine	+++	++++++	+
Sertraline	+	++++++	+++
Venlafaxine	+	++++	–

Antidepressant potency for blocking norepinephrine (NE), serotonin (5-hydroxytryptamine [5-HT]), and dopamine (DA) transporters. + to +++++, increasing levels of potency; –, weak; 0, no effect.

Adapted from Richelson E. The clinical relevance of antidepressant interaction with neurotransmitter transporters and receptors. *Psychopharmacol Bull* 2002;36:133–149. In: Kupfer DJ. The pharmacological management of depression. *Dialogues Clin Neurosci* 2005 Sep;7(3):191–205. © Les Laboratoires Servier.

Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors are especially effective for atypical depression, which is associated with abnormally increased, rather than decreased, sleep and appetite. They require dietary restrictions and can be used only in patients who are able to understand and comply with those restrictions to avoid hypertensive crises (115).

Other Agents

Other medications include *bupropion, mirtazapine, trazodone, aripiprazole, lithium* salts, and anticonvulsants, which are effective mood stabilizers used for bipolar disorders (124). *Bupropion* is available in a once-a-day preparation. It lowers the seizure threshold slightly more than other antidepressants and should be avoided or used with caution in patients who have a history of bulimia and head trauma. It is used, under a separate trade name, for smoking cessation, and is particularly useful for smokers who

are depressed. *Bupropion* seems to cause fewer sexual side effects than the SSRIs and may decrease these side effects when added to an SSRI regimen.

Benzodiazepines are most useful in acute situations (123). The use can quickly become chronic, with escalating dosages, diminishing therapeutic effects, and increasing demands on the physician. Women taking benzodiazepines may forget to include them in their medical history. When admitted to the hospital, they may suffer unrecognized withdrawal symptoms, complicating their treatment, or may continue to take medications from a personal supply without informing the medical staff.

There are many patients who could benefit from anxiolytics but who are inordinately worried about becoming dependent or addicted. A patient with no history of addictive behaviors is unlikely to get into trouble with a standard dose of medication (95–98). Given the level of public misinformation about, and stigma against, psychoactive medications, patients may experience their own misgivings, and the negative reactions of friends and family members. It is better to provide written material, or direct the patient to a reputable website, letting her postpone the treatment decision to the next gynecologic visit, than to prescribe medication that will not be taken as the patient is not likely to reveal the nonadherence.

Table 23-5 Compounds Used for Anxiety

Medication	Trade Name	Rate of Absorption[a]	Half-Life[b]	Active Long-Acting Metabolite	Comments
Benzodiazepines					Metabolism of benzodiazepines is inhibited by *cimetidine, disulfiram, isoniazid,* and oral contraceptives. Metabolism of benzodiazepines is enhanced by *rifampin.*
Alprazolam	*Xanax*	Intermediate	Intermediate	No	Preferred in elderly patients or patients with poor hepatic functions.
Chlordiazepoxide	*Librium,* others	Intermediate	Intermediate	Yes	
Clonazepam	Klonopin	Long	Long	No	
Clorazepate	*Tranxene,* others	Short	Short	Yes	
Diazepam	*Valium,* others	Short	Long	Yes	Half-life increased three or four times in elderly patients.
Lorazepam	*Ativan,* others	Intermediate	Intermediate	No	Preferred in elderly patients or patients with poor hepatic function.
Oxazepam	*Serax*	Long	Intermediate	No	Preferred in elderly patients or patients with poor hepatic function.
Prazepam	*Centrax*	Long	Short	Yes	
Atypical agent					
Buspirone	*BuSpar*				Not effective in panic disorder, little sedation, little risk of dependence or tolerance.

[a]Long ≥2 hours; intermediate 1–2 hours; short ≤1 hour.

[b]Long >20 hours; intermediate 6–20 hours; short <6 hours.

Adapted from **Nies AS.** *Principles of Therapeutics.* In Goodman, Louis S., 1906–2000 & Hardman, Joel G & Limbird, Lee E & Gilman, Alfred Goodman, 1941–2015 (2001). *Goodman & Gilman's the pharmacological basis of therapeutics* (10th ed./editors, Joel G. Hardman, Lee E. Limbird). McGraw-Hill, New York.

GENERAL MANAGEMENT REVIEW

Many patients and their families are anxious or resistant because of misinformation or misunderstanding about a medical problem or treatment. Few patients can absorb all the information about significant gynecologic conditions at a single visit, but many feel that asking questions will burden the physician or make the patient appear stupid. Patients suffer anxiety when there is disagreement among family members or medical staff about the diagnosis or recommended treatment **(Table 23-5)**.

It is easy to be trapped into a cat-and-mouse game with an anxious and needy patient who has an anxiety or personality disorder (93). **Faced with an obsessive or anxious, talkative, and needy patient in the midst of bedside rounds, clinic, or office hours, the clinician can develop a pattern of avoidance, sometimes alternating with overindulgence stemming from feelings of guilt. This kind of behavior results in sporadic, unpredictable reinforcement of the patient's symptoms and demands for attention and is very likely to increase them.** Attempting to escape by appearing distracted or yielding with despair to the destruction of the day's schedule and the care of other patients simply heightens the patient's anxiety (94–99).

It is preferable to develop a prospective approach (93). **Gynecologists tend to underrate the power of their personal interactions with patients and their own ability to structure and appropriately limit those interactions. A patient with a long list of symptoms can be informed at the beginning of the visit how much time is available and asked to focus on her most important problem, with other problems to be discussed at future, scheduled appointments.** Instead of scheduling appointments and returning telephone calls grudgingly in response to patient demands, the gynecologist should inform the patient that her condition requires regular, brief scheduled visits. If she is contacting the office more often than visits can reasonably be scheduled, she should be asked to call between visits, at prearranged times, to advise the staff of her progress. There are useful self-help groups for patients with various psychiatric conditions and their families. Although groups focused only on victimization can validate patients' experiences and pain and help them build new lives, they may interfere with their motivation to find other ways to identify themselves and obtain gratification (99). The gynecologist can monitor the patient's responses to the self-help group interaction.

Medication Overview

SSRIs are effective for a variety of anxiety disorders, sometimes in different dosage regimens than those used for depression (123). Benzodiazepines are effective when taken for acute anxiety or during relatively brief, time-limited (several days) stressful situations. The specific agent should be chosen on the basis of onset of action and half-

life. The patient must be admonished to avoid concomitant use of alcohol and to exercise extreme care about driving or engaging in other activities requiring attention, concentration, and coordination. Tolerance and addiction are serious complications from the use of benzodiazepines. There are patients who could benefit from short-term use in particularly stressful situations but who are inordinately and unnecessarily concerned about addiction.

Patients who fail to respond to a trial of office counseling or medication, who are unable to fulfill their responsibilities, exhaust the patience and resources of significant others, pose a diagnostic dilemma, consume inordinate quantities of medical resources, or whose symptoms are becoming increasingly worse should be evaluated by a psychiatrist.

In conclusion: psychiatric issues are ubiquitous in gynecology. This chapter offers the gynecologist the diagnostic and management information that can decrease clinical frustration and increase patient satisfaction.

RESOURCES

American Clinical Social Work Association (ACSWA): http://www.acswa.org/
American Psychiatric Association (APA): http://www.apa.org/
American Psychological Association (APA): https://www.psychiatry.org/
The Complete Mental Health Directory 2018/2019 ed. Gottlieb R, ed., Millerton NY: Grey House Publishing. Contains descriptions of mental health diagnoses, lists of national mental health organizations.
Depression and Bipolar Support Alliance (DBSA): http://www.dbsalliance.org/
International Obsessive Compulsive Disorder Foundation
Mental Health America: http://www.mentalhealthamerica.net/
National Alliance on Mental Illness (NAMI): https://www.nami.org/
World Professional Association for Transgender Health (WPATH): http://www.wpath.org/

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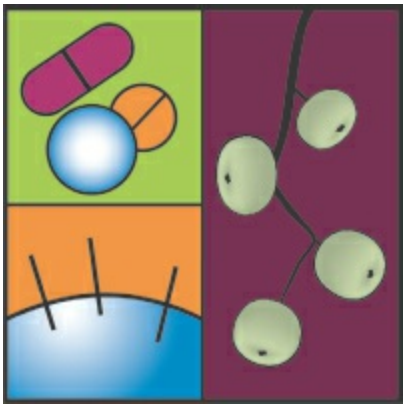
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CHAPTER 24

Complementary and Integrative Health Approaches



Tracy W. Gaudet

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KEY POINTS

1 The spectrum of complementary and integrative approaches is broad and includes methods worthy of integration into our current practice, and ineffective or fraudulent practices that should be avoided.

2 A complete history should include the patient's use of complementary and integrative health approaches (CIH), particularly botanicals and supplements, as these can have actions ranging from estrogenic to anticoagulant.

3 The U.S. Food and Drug Administration (FDA) does not regulate botanicals and supplements, so extra steps must be taken to ensure the quality of such products.

4 The management of many women's health issues can be enhanced by the integration of selected CIH approaches.

5 Perceived congruency of values related to life and health with CIH providers was predictive of use of these approaches; dissatisfaction with conventional medicine is not a predictor of use of CIH.

6 Acupuncture is of benefit in a variety of conditions, including pain, nausea, and vomiting during pregnancy, and secondary to chemotherapy.

7 Mind–body approaches such as stress reduction, visualization, and hypnosis are gaining significance as valuable adjuncts in a spectrum of women's health concerns, from surgery to fertility.

According to the 2012 National Health Interview Survey (NHIS), complementary health approaches are used by an estimated 37% of adult women in the United States (1). **[1]** Although evidence exists to support many of these approaches, some approaches are used in the absence of documented benefit and can be potentially dangerous and fraudulent (2). The primary users of these therapies are women, who are frequently making decisions regarding treatment options without the advice of their physicians. Obstetrician–gynecologists are in an excellent position to help guide patients in their treatment choices, counseling them about potentially dangerous treatments and supporting their use of potentially beneficial ones. The most significant challenge is the lack of training that most obstetrician–gynecologists have in this area; thus, this chapter reviews the domains of CIH as they apply to the practice of gynecology.

DEFINITIONS

The changing use of terms related to this field is indicative of the evolution of the field itself. Of note, the National Institutes of Health (NIH) Center has changed its name from the National Center for Complementary and Alternative Medicine to the National Center for Complementary and Integrative Health (NCCIH). This name change is consistent with national trends, and represents the growing integration of these therapies into mainstream health care. The term complementary health approaches is typically used when referring to health care approaches that are based in traditions outside of mainstream Western, or conventional, medicine. If these approaches are used in place of conventional health care, the term "alternative" is used. Integrative health refers to the incorporation of complementary approaches into mainstream health care (3).

NCCIH organizes complementary health approaches into two groups: natural products and mind body practices. Natural products include herbs or botanicals, vitamins and minerals, and probiotics, often sold as dietary supplements. Mind and body practices include a wide array of approaches that are offered by a trained practitioner or teacher. This group includes acupuncture, yoga, tai chi, qi gong, chiropractic and osteopathic manipulation, meditation, healing touch, clinical hypnosis, massage therapy, relaxation techniques, and movement therapies such as Feldenkrais method and Alexander technique. NCCIH recognizes that some approaches do not fall into either of these categories, such as traditional healers, Ayurvedic medicine, traditional Chinese medicine, homeopathy, and naturopathy (3).

[1] The amount of evidence on the use of these approaches varies widely. A significant number of randomized controlled trials (RCTs), including those with sufficient quantity and quality to allow meta-analyses in some areas, were done to assess the efficacy of acupuncture, botanical medicine, nutritional approaches, manual therapies, and mind–body medicine. Research in the other domains is much more limited. Many culturally based practices such as shamanism and curanderismo have virtually no research basis. A growing number of RCTs are being done in spiritual healing and homeopathy, but these techniques remain controversial based on a lack of understood biophysical mechanisms to justify their efficacy.

Integrative medicine **is a distinct entity separate from the practice of CIH.** Integrative medicine neither blindly advocates CIH nor rejects conventional medicine. Integrative medicine is healing oriented and patient centered and adopts a whole-person approach to the treatment of disease and the maintenance of health. It draws on the best practices of medicine, regardless of system of origin. Typically, **integrative medicine would include, in addition to conventional medicine, CIH techniques that may be of benefit, including nutrition, movement and exercise, mind–body approaches, and spirituality.** In 2013, the American Board of Integrative Medicine (ABOIM) was created. This was a controversial decision, given that the ultimate goal is to have all physicians obtain competencies in integrative medicine. Because of the growth of this field, it was felt that there should be a process to acknowledge expertise in integrative medicine. As the paradigm of conventional medicine broadens to include other therapeutic modalities that previously were considered "integrative," and the system becomes more accepting of health optimization and holistic disease management, there is likely to be greater integration of these philosophies, approaches, and providers. The distinction of "complementary health approaches" may ultimately no longer be useful, nor will integrative medicine. This approach, which is inclusive of effective philosophies and approaches that can improve the health and healing of women and men, will simply become the standard for US health care.

DEMOGRAPHIC DATA

Using data from the 2012 NHIS, it was estimated that 37.2% of adult women used complementary health approaches (1). A study of gynecologic oncology patients revealed that 56% were using CIH, and surveys of menopausal women showed that 80% were using "nonprescriptive therapies" (4). The Study of Women's Health Across the Nation (SWAN) found that approximately one-half of women were actively using herbal, spiritual, or manipulative therapies (4). A study examining the use of CIH by women suffering from nausea and vomiting during pregnancy found that 61% reported using CIH therapies, with the most popular being ginger, vitamin B_6, and acupressure (5). A study evaluating the use of CIH therapies by women with advanced-stage breast

cancer revealed that 73% of patients used CIH, with relaxation or meditation techniques and botanicals being used most often (6). The reason most often given for the use of CIH was immune support, followed by the treatment of cancer. A survey in Washington state exploring use of integrative therapies for menopause revealed that 76% of women were using integrative approaches, with 43% of these women using stress reduction techniques, 37% using over-the-counter integrative approaches, 32% using chiropractic medicine, 30% massage therapy, 23% dietary soy, 10% acupuncture, 9% naturopathy or homeopathy, and 5% herbalists (7). Of these women, 89% to 100% found these approaches to be somewhat or very helpful. Users of hormone therapy (HT) were 50% more likely to use CIH than those who never used HT. **Following the results of the Women's Health Initiative indicating the risks associated with HT, interest in the use of CIH for management of menopausal symptoms increased.**

The Attraction

After the publication of the first national surveys on the use of complementary health approaches stunned the mainstream medical community in the early 1990s, there was much conjecture regarding why so many patients were turning to these approaches. A national survey published in 1998 was the first to explore this question, and its findings remain pertinent (8).

[5] **Dissatisfaction with conventional medicine was *not* predictive of use of complementary health approaches. Patients were using these approaches because they were seeking greater congruency of values regarding life, health, and wellness** (8). The implication is that people are happy to use conventional medicine when they have a diseased or injured body part, but when their goal is to improve their health or manage a chronic condition or lifestyle issue, they turn to integrative care providers. Establishing a partnership with patients can help them explore all of the options for maximizing their health is critical. The Centers for Disease Control and Prevention (CDC) reported that the majority (55%) of people stated that their reason for using CIH therapies was that they thought combining these approaches with conventional ones would help them, and 26% reported they tried these approaches because medical professionals had recommended them (9).

The Challenge

The demographics and trends associated with CIH use create challenges for physicians and patients. A huge market demand creates an opportunity for products and therapies that may be ineffective, dangerous, or fraudulently marketed. The development of high patient demand preceded the incorporation of education regarding CIH for medical students, residents, and practicing physicians. As a result, patients often make decisions

regarding their care without the benefit of medical advice or the coordination of their care by one provider. The best practice of medicine necessitates the integration of all therapies that can benefit the patient and the exclusion of those that can cause harm. Integration of these techniques requires the collaborative, concerted effort of physicians, CIH providers, and patients.

COMPLEMENTARY AND INTEGRATIVE THERAPIES

The many types of CIH techniques can be organized into two categories as outlined by the NIH: natural products and mind body practices. Licensing and certification requirements for practices vary widely from state to state, but most techniques have a formal structure for training and accreditation (Table 24-1).

Natural Products: Botanical Medicine

Botanical or herbal therapies use botanicals singly or in combination for therapeutic value. A botanical is a plant or plant part that contains chemical substances that act on the body. Botanical or herbal medicines were studied extensively in Europe, and large multicenter trials are beginning to provide more robust evidence in this country.

Botanical medicine is the area of CIH most conceptually accessible to patients. Botanicals are the source of the active agents in approximately 25% of prescription drugs and 60% of over-the-counter drugs. **[3]** In the United States, these products are often not perceived as active and are regulated as "dietary supplements" that are not under the direction of the U.S. Food and Drug Administration (FDA). The most popular botanicals used in the United States are listed in Table 24-2.

Complications and Risks

[2] Botanical medicines are being used by an increasing number of patients, and they often do not inform their clinicians of this use. Certain patients are at risk for drug–botanical interactions or adverse reactions, and patients should be questioned about them (Tables 24-3 and 24-4). Mega doses of vitamins and supplements have associated risks and complications.

[3] Because botanicals are regulated as dietary supplements, quality control is challenging. In 1994, the Dietary Supplement Health and Education Act (DSHEA) was enacted (10). This act makes it legal to refer to the supplement's effect on the body's structure or function or to a person's well-being. Products within the jurisdiction of DSHEA are easily recognized by the following statement on their labels: "This product is not intended to diagnose, treat, cure, or prevent any disease." Because the FDA does not regulate these products, the potential for lack of standardization of products, and

adulteration or mislabeling, exists.

It is imperative to review literature. There are several databases that are good resources for clinicians and patients, including the Natural Medicines Comprehensive Database (http://www.naturaldatabase.com) and the Natural Standard (http://www.naturalstandard.com). Numerous drug information databases contain information about natural product interactions, including UptoDate (Lexi-Comp interactions), MicroMedex (AltMedDex), and others. **Botanicals can cause toxicity in one of three ways: (i) the products can be adulterated; (ii) the labels can recommend dosages that exceed appropriate use and cause toxicity even when the product is safe in appropriate dosages; and (iii) even when they are of good quality and taken in the correct dosage, these products can interact with other supplements and pharmaceutical agents.** The Institute of Medicine recommended the following measures: seed-to-shelf quality control, accuracy and comprehensiveness in labeling and other disclosure, enforcement against inaccurate and misleading claims, research into consumer use, incentives for privately funded research, and consumer protection against all potential hazards.

Training and Licensure in Botanical Therapies

There is no national licensure for botanical or herbal medicine, and there is no national or professional organization that regulates or accredits Western and Ayurvedic herbal medicine education. In 1996, the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) developed a national certification written examination, which tests for entry-level capabilities in oriental herbal medicine. Passage of this examination allows practitioners to call themselves Diplomates of Chinese Herbology (Dipl CH). The Commission's Web site contains a searchable directory of certified practitioners (11). Naturopathic physicians are typically trained in botanical medicine as a part of their 4-year curriculum.

CHIROPRACTIC MEDICINE

Chiropractic medicine focuses on the relationship between structure (primarily the spine) and function, and the way that relationship affects the preservation and restoration of health. It uses manipulative therapy as an integral tool. Chiropractors can legally do more than manipulate and align the spine, including taking a medical history, performing a physical examination, and ordering lab tests and x-rays to determine a diagnosis. The spectrum of chiropractors varies in terms of the conditions treated with manipulation. Although some practitioners limit their practice primarily to musculoskeletal problems, others claim to offer effective treatment for virtually any medical condition. They are referred to as doctors, which can be confusing to patients. The chiropractic profession is growing quickly, with approximately 77,000

chiropractors in the United States (12).

Complications and Risks

Chiropractic adjustment is considered safe when performed by a licensed professional. Serious complications are very rare, but may include herniated disk, cauda equina syndrome, or vertebral artery dissection and stroke after cervical manipulation with a rotatory component.

Table 24-1 Training and Licensure in Complementary and Integrative Medicine

Therapy	Training	Licensure
Botanical medicine	None standardized	Written examination developed by the National Certification Commission for Acupuncture and Oriental Medicine tests for entry-level capabilities in oriental herbal medicine. Passage allows practitioners to call themselves Diplomates of Chinese Herbology (Dipl CH).
Chiropractic	Must complete a 4-year chiropractic college program of study accredited by the Council on Chiropractic Education (CCE)	National
Massage therapy and bodywork	There is lack of consistency among licensure laws; requirements range from 500–1,000 hours.	Offered at the state level in 46 states.
Hypnotherapy		The International Medical and Dental Hypnotherapy Association will certify hypnotherapists if they meet the minimum eligibility requirements and provide referrals.
Clinical hypnosis	Basic certification requires a minimum of 40 hours of ASCH-approved workshop training, 20 hours of individualized training, and a minimum of 2 years of independent practice using clinical hypnosis. The advanced level, called approved consultant, requires a minimum of 40 additional hours of ASCH-approved workshop training and 5 years of independent practice using clinical hypnosis.	American Society of Clinical Hypnosis (ASCH) Certification in clinical hypnosis ensures that the certified individual is a bona fide health care professional who is licensed in that state to provide medical, dental, or psychotherapeutic services.
Meditation and stress reduction	None	None

Energy therapies	Given the wide array of energy therapies, the levels of training vary tremendously from modality to modality.	
Acupuncture	Schools provide 3- or 4-year training programs in oriental medicine that consist of about 2,500–3,200 hours.	In most states, the practitioner must provide proof that he/she has attended and graduated from an accredited school or from a school that is in the process of being accredited by the Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM).
		The right to practice exists in 46 states and in the District of Columbia. This right may be designated by licensure, certification, or registration under the state law.
	The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) tests entry-level capabilities with a comprehensive written examination, point location examination, and clean needle technique.	An acupuncturist must pass this examination and meet continuing education requirements every 4 years to retain certification and licensure.
Medical doctors can be certified by the American Board of Medical Acupuncture by taking a minimum 300 hours in training.		
Homeopathy	*Lay homeopaths* have no training standards. Classical Homeopaths (CCH) are credential by the Council on Homeopathic Certification and requires a minimum of 1,000 hours of training. Certified Classical Homeopaths are not licensed as health care professionals. *Registered homeopathic medical assistants* require 300 hours of training and MD or DO supervision. *Licensed health care professionals* can also practice homeopathy, and their training ranges from 200–1,000 hours.	Laws regulating the practice of homeopathy vary from state to state.
Naturopathic medicine	Naturopathic physicians are typically trained in botanical medicine as a part of their 4-year	Currently only 19 states have licensing laws, and licensure

	curriculum.	efforts are underway in at least 12 other states. To be eligible to be licensed/registered as a naturopathic physician, a candidate must graduate from an accredited naturopathic medical school and pass national board examinations. There are seven 4-year naturopathic medical schools accredited by the Council on Naturopathic Medical Education in the United States and Canada.

Table 24-2 Most Used Natural Products

Rank/Herb	% Change From 2002–2012
1. **Fish oil/omega-3 fatty acids**	7.8
2. **Glucosamine and/or chondroitin**	2.6
3. **Probiotics/prebiotics**	1.6
4. **Melatonin**	1.3
5. **Coenzyme Q10**	1.3
6. **Echinacea**	0.9
7. **Cranberry (pills, capsules)**	0.8
8. **Garlic supplements**	0.8
9. **Ginseng**	0.7
10. **Ginkgo biloba**	.07

From **Clarke TC, Black LI, Stussman BJ, et al.** Trends in the use of complementary health approaches among adults: United States, 2002–2012. *Natl Health Stat Reports* 2015;(79):1–16.

Training and Licensure

There is a national process for licensure for chiropractic medicine to which all 50 states adhere. Chiropractors must complete a 4-year chiropractic college program of study accredited by the Council on Chiropractic Education (CCE).

Massage Therapy and Bodywork

Massage therapy involves manipulation of the soft tissues of the body to normalize those tissues. A wide variety of approaches are available that include deep tissue massage, Swedish massage, reflexology, Rolfing, and many others. A number of RCTs documented the value of massage therapy, particularly in pediatric conditions such as childhood asthma. Some studies show an increase in dopamine and serotonin, and an increase in natural killer cells and lymphocytes with regular massage therapy.

Massage therapy and bodywork are used by a wide array of people seeking the benefits of massage, which include physical relaxation, reduced anxiety, increased circulation, and pain relief. Specific indications for massage include treatment of acute low-back pain and lymphatic massage for patients with lymphedema from conditions such as postmastectomy extremity edema. Massage is used by various practitioners, including physicians, physical therapists, osteopathic physicians, chiropractors, acupuncturists, nurses, and massage therapists.

Complications and Risks

Massage should not be used in the presence of bleeding disorders, phlebitis and thrombophlebitis, edema that is caused by heart or kidney failure, fever or infections that can be spread by blood or lymph circulation, and leukemia or lymphoma. Massage should not be performed on or near malignant tumors and bone metastases; over bruises, unhealed scars, or open wounds; on or near recent fracture sites; or over joints or other tissues that are acutely inflamed.

Training and Licensure

There is no national licensure in massage therapy, but 46 states regulate the profession in some form. There is a lack of consistency among licensure laws, with requirements ranging from 500 to 1,000 hours. Depending on the state law, therapists can be referred to as state certified, registered, or licensed (12).

Clinical Hypnosis

Hypnosis involves the induction of trance states and the use of therapeutic suggestions. Hypnosis has documented value for a variety of psychological conditions, pain control, and recovery from surgery.

Complications and Risks

There are occasional reports of unanticipated negative effects during and after hypnosis. The spectrum of reported effects encompassed minor transient symptoms such as headaches, dizziness, or nausea in experimental situations to less frequent symptoms of anxiety or panic, unexpected reactions to an inadvertently given suggestion, and difficulties in awakening from hypnosis. More serious reactions following hypnosis are attributed to the misapplication of hypnotic techniques, failure to prepare the

participant, and pre-existing psychopathology or personality factors. There are no known deaths attributed to the use of hypnosis.

False memories of suggested events that did not occur in reality, particularly when legal and interpersonal battles are involved, can be viewed as an untoward reaction to psychotherapeutic procedures. In hypnotic and nonhypnotic situations, leading and suggestive overtures can produce false memories. Because hypnosis involves direct and indirect suggestions, some of which may be leading in nature, and because hypnosis can increase confidence of recalled events with little or no change in the level of accuracy, therapists must be attentive to the problem of creating false memories.

Training and Licensure

There is no national or state licensure for hypnotherapists. The American Society of Clinical Hypnosis (ASCH) certification in clinical hypnosis is distinct from other certification programs in that it ensures that the certified individual is a health care professional who is licensed in his or her state to provide medical, dental, or psychotherapeutic services. Certification by ASCH distinguishes the professional practitioner from the lay hypnotist. There are two levels of certification; the first is simply called *certification,* which requires, among other things, a minimum of 40 hours of ASCH-approved workshop training, 20 hours of individualized training, and a minimum of 2 years of independent practice using clinical hypnosis. An advanced level, called *approved consultant,* recognizes individuals who obtained advanced training in clinical hypnosis and who have extensive experience in using hypnosis within their professional practices. Certification at this level requires a minimum of 40 additional hours of ASCH-approved workshop training and 5 years of independent practice using clinical hypnosis (13).

Meditation and Stress Reduction

Meditation is a self-directed practice that can relax the body and calm the mind. Most meditative techniques came to the West from religious practices in the East, particularly India, China, and Japan, but it can be found in all cultures of the world. A National Institutes of Health Consensus Panel in 1996 concluded that **mind–body and behavioral techniques were effective in the treatment of stress-related conditions and insomnia, and since then evidence for their effectiveness has continued to grow.** *Mindfulness-based stress reduction* (MBSR), based on *Vipassana meditation* from India, is promoted in this country. This technique is based on the cultivation of mindfulness, an intentional, focused awareness of nonjudgmental attentiveness to experiences in the present moment. Vipassana meditation, one of India's most ancient techniques of meditation, was taught more than 2,500 years ago as a remedy for universal ills.

Table 24-3 Botanicals: Potential for Interactions With Drugs

Drug Class	Herb	Potential Interactions
Anticoagulants	Bilberry	Increased risk of bleeding (high dose)
	Chamomile	Increased risk of bleeding
	Coenzyme Q10	Decreased effectiveness
	Danshen	Increased risk of bleeding
	Dong quai	Increased risk of bleeding
	Feverfew	Increased risk of bleeding
	Garlic	Increased risk of bleeding
	Ginger	Increased risk of bleeding
	Ginkgo	Increased risk of bleeding
	Ginseng	Increased risk of bleeding
	Kava	Increased risk of bleeding
	St. John's wort	Decreased effectiveness
Anticonvulsants	Borage	Decreased seizure threshold
	Comfrey	Increased risk of phenobarbital toxicity
	Evening primrose oil	Decreased seizure threshold
	Valerian	Increased effects of barbiturates
Antidepressants	Ephedra	Increased effect of monoamine oxidase inhibitors
	Ginseng	Increased risk of monoamine oxidase inhibitors
	Kava	Hypertension
	St. John's wort	Monoamine oxidase inhibitors; increased blood pressure level
	Yohimbine	Tricyclics—hypertension; selective serotonin reuptake inhibitors; increased serotonin levels
Diuretics	Aloe	Increased risk of hypokalemia
	Cascara sagrada	Increased risk of hypokalemia

	Licorice	Increased risk of hypokalemia
	Senna	Increased risk of hypokalemia
Hypoglycemic agents	Ginseng	Risk of hypoglycemia
	Stinging nettle	Potential elevation of blood glucose level
Sedatives	Chamomile	Increased drowsiness
	Kava	Increased risk of sedation
	Valerian	Increased risk of sedation

Data from **O'Mathuna DP.** Herb-drug interactions. *Altern Med Alert* 2003;6:37–43.

Transcendental meditation (TM) is a simple method practiced for 15 to 20 minutes in the morning and evening while sitting comfortably with the eyes closed. During this technique, the individual experiences a unique state of restful alertness. TM is useful in the treatment of hypertension.

[7] The relaxation response, which can be elicited by any number of techniques, is a physical state of deep rest that changes the physical and emotional responses to stress (e.g., decrease in heart rate, blood pressure, and muscle tension). If practiced regularly, it can have lasting effects when encountering stress throughout the day.

Table 24-4 Selected Risk Factors for Adverse Reactions or Drug Interactions With Botanicals

• Bleeding disorders or anticoagulation
• Seizure disorders
• Radiation with or without chemotherapy
• Immunosuppression
• Diabetes
• Pregnancy
• Renal insufficiency
• Liver disease
• Heart failure
• Electrolyte imbalances
• Taking sedatives/anxiolytics/central nervous system depressants, oral contraceptives, diuretics,

monoamine oxidase inhibitors, antiretroviral drugs
• Undiagnosed medical conditions

Complications and Risks

Meditation rarely may lead to a "spiritual emergency," defined as a crisis during which the process of growth and change becomes chaotic and overwhelming as individuals enter new realms of spiritual experience. Types of spiritual emergency include but are not limited to loss or change of faith, existential or spiritual crisis, experience of unitive consciousness or altered states, psychic openings, possession, near-death experience, kundalini, shamanic journey, or difficulties with a meditation practice.

Training and Licensure in Meditation and Stress Reduction

There are many systems of meditation, and there is no nationally recognized licensing or certification procedure for teachers of meditation. Many mental health care professionals are trained in a variety of stress reduction techniques.

Energy Therapies

Energy therapies involve the use of energy fields. They are of two categories:

1. *Biofield therapies* are intended to affect energy fields that purportedly surround and penetrate the human body. Some forms of energy therapy attempt to manipulate biofields by applying pressure or manipulating the body by placing the hands in, or through, these fields. Examples include qi gong, Reiki, and therapeutic touch.
2. *Bioelectromagnetic-based therapies* involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating current or direct current fields.

Complications and Risks

Energy-based therapies are the least well researched and the most diverse of all CIH modalities. It is not possible to address potential complications and risks.

Training and Licensure in Energy-Based Therapies

Given the wide array of therapies that fall under this category, the levels of training vary tremendously from modality to modality.

Acupuncture and Oriental Medicine

[6] Acupuncture is a therapeutic intervention that is used in many Asian systems of medicine, with a history extending thousands of years. It has continued to increase in popularity in the United States, and has a growing body of evidence supporting

its effectiveness. It is based on the theory that there are energy channels called meridians that run throughout the body, and that disease results from blockages of this energy. Acupuncture is used as one approach to release these blockages. It involves stimulating specific anatomic points in the body along the meridians by puncturing the skin with a very fine needle (32 gauge or smaller). There are many distinct styles of acupuncture, which include traditional oriental medicine, Japanese Manaka style, Korean hand acupuncture, and the Worsley five-element method.

Given the Western, biomedical model, acupuncture is difficult to comprehend. There is a significant body of research on this technique. In one study involving stimulation of an acupuncture point located on the lateral aspect of the foot that corresponds to the visual cortex, magnetic resonance imaging detected activity of the visual cortex of the brain equivalent to the activity seen when a light is shone in the eye. No activity was seen when an acupuncture needle was placed 1 cm away from the designated acupuncture point (14). Many of the CIH approaches that claim to have an effect and yet seem to be inconsistent with the biomedical model deserve further investigation.

A 1997 National Institutes of Health Consensus Panel established that there was convincing evidence for the use of acupuncture in the treatment of postoperative dental pain, nausea, and vomiting, and promising evidence for headache, low-back pain, stroke, addiction, asthma, premenstrual syndrome (PMS), osteoarthritis, carpal tunnel syndrome, and tennis elbow. This is not yet standard practice, and the body of evidence has continued to grow. There is an extensive body of animal research supporting the neurophysiologic effects of acupuncture on the endorphin system. The available published literature on acupuncture in humans is extensive. PubMed searches in 2013 identified almost 20,000 citations with the term “acupuncture” and almost 1,500 RCTs with “acupuncture” in the title. The Veterans Affairs Evidence-Based Synthesis Program conducted a systematic review of studies that were published from January 2005 to March 2013 and provided an overview of the existing literature on acupuncture, focusing on (1) pain (59 systematic reviews), (2) mental health (20 systematic reviews), and (3) well-being (44 systematic reviews). The investigators examined other clinical areas for which at least three reviews and/or recent large randomized controlled trials (RCTs) exist (48 systematic reviews). The condition with the greatest evidence of effect was chronic pain (15).

Complications and Risks

Bruising and minor bleeding are the most common complications of acupuncture and occur in about 2% of all needles placed (16). They rarely require treatment other than local pressure to the needle site. The most significant risk of acupuncture is infection. The risk of transmissible infection is eliminated by onetime use of disposable needles, which is now standard practice in the United States. Pneumothorax is the second most significant risk of acupuncture. The needles used are 32 gauge or smaller; therefore, a

chest tube usually is not required for treatment.

Training and Licensure

There are approximately 29,000 licensed acupuncturists in the United States. There is no national licensure for acupuncture, and the right to practice exists in 46 states and in the District of Columbia. This right may be designated by licensure, certification, or registration under the state law (12). Educational requirements for state licensure for acupuncture vary. To become licensed in most states, the practitioner must provide proof that he or she has attended and graduated from an accredited school or from a school that is in the process of being accredited by the Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM) (17). These schools provide 3- or 4-year training programs in oriental medicine. The NCCAOM administers a standardized examination to test entry-level capabilities in acupuncture consisting of a comprehensive written examination, point location examination, and demonstration of clean needle technique (11). An acupuncturist must pass this examination and meet continuing education requirements every 4 years to retain certification and licensure. In the United States, many states adopted this examination as the basis for licensure. **Physician acupuncture practitioners may not be as fully trained in the art as nonphysician licensed acupuncturists. To be certified by the American Board of Medical Acupuncture, physicians must take a minimum of 300 hours in training** (18).

Homeopathy

Homeopathic medicine is a CIH alternative medical system based on the work of the German physician and chemist Samuel Hahnemann approximately 200 years ago. **In homeopathic medicine, there is a belief in "the law of infinitesimals" and that "like cures like."** Small, highly diluted quantities of medicinal substances are given to cure symptoms when the same substances given at higher or more concentrated doses would actually cause those symptoms. The number of homeopathic practitioners is estimated at 8,500 (12).

Training and Licensure

There are four subgroups of homeopathic practitioners and standards, regulation, licensure, and educational accreditation vary widely among them. *Lay homeopaths* have no training standards. *Professional homeopaths* can be certified as a Classical Homeopath (CCH) credentialed by the Council on Homeopathic Certification. Certification requires a minimum of 1,000 hours of training, and Certified Classical Homeopaths are not licensed as health care professionals. *Registered homeopathic medical assistants* require 300 hours of training and MD or DO supervision. *Licensed health care professionals* can practice homeopathy, and their training ranges from 200

to 1,000 hours. Laws regulating the practice of homeopathy vary from state to state (12).

Naturopathic Medicine

Naturopathic medicine is a holistic approach to health care that views disease as a manifestation of alterations in the processes by which the body naturally heals itself and emphasizes health restoration rather than disease treatment. Naturopathic physicians employ an array of healing practices, including diet and clinical nutrition; homeopathy; acupuncture; herbal medicine; hydrotherapy (the use of water in a range of temperatures and methods of applications); spinal and soft tissue manipulation; physical therapies involving electric currents, ultrasonography, and light therapy; therapeutic counseling; and pharmacology. It is estimated that there are approximately 5,000 naturopathic physicians practicing in the United States (12).

Training and Licensure

There is no national licensure for naturopathy, and licensure at the state level is inconsistent. Naturopathic medicine is regulated in 19 states, and licensure efforts are underway in at least 12 other states. To be eligible to be licensed/registered as a naturopathic physician, a candidate must graduate from an accredited naturopathic medical school and pass national board examinations. Seven 4-year naturopathic medical schools are accredited by the Council on Naturopathic Medical Education in the United States and Canada. This training focuses on outpatient medicine and does not require a residency. Although the 4-year programs are rigorous, it is possible to get a naturopathic degree online.

PATIENT CARE ISSUES

The Placebo Effect

There is no evidence that the placebo response is more active in CIH than in conventional approaches. Just as with conventional medicine, the effects of certain approaches are more likely than others to be associated with a placebo response. After exposure to a stimulus believed by the patient and the practitioner to be an active intervention, the body responds physiologically in an equivalent manner. **Approximately one-third of patients in placebo-controlled trials of conventional methods experiences a placebo response.** It would be of great value to medicine if the placebo response was better understood and could be activated more reliably in patients. **Clinicians need to understand that the placebo effect is actually an activated healing response, and the ability to achieve an equivalent physiologic response to an intervention, without the risks or costs of an intervention, may be the best possible medicine.**

Potential Misuse

In addition to physical risks, patients and physicians alike should be aware of other areas of potential misuse. Two areas are of particular concern. First, given that the dollars being spent out of pocket are so significant, there are some products and some providers whose primary motivation is monetary. Patients can spend a great deal of money based on false promises or claims. Second, patients can postpone effective or curative therapy or treatment by turning to CIH modalities and excluding conventional approaches. This time can negatively impact the outcome for treatment of many patients' diseases. Factors that should increase suspicion for potential misuse are listed in Table 24-5.

Table 24-5 Factors That Should Increase Suspicion for Potential Misuse

1. Providers or products that make claims that are grandiose and dubious, for example, approaches that claim to cure insulin-dependent diabetes or offer CIH as a cure for cancer.
2. Providers or products who foster dependence, for example, therapists who recommend multiple visits per week or frequent visits for an unlimited period.
3. Providers who recommend products that they sell and from which they profit.
4. Providers or products that support the use of alternative approaches exclusive of conventional medicine or conventional providers.

The Potential Benefits: Therapeutic Opportunities

Given all of the risks and uncertainties, it is appropriate to ask the question: Why should physicians educate themselves regarding CIH? The most basic answer is commitment to the best practice of medicine. [2] If patients are using therapies that are potentially dangerous in their action or interaction, physicians should be aware of this possibility and counsel them accordingly. Physicians have a commitment to offer their patients the best treatment options, regardless of their system of origin. Physicians should be knowledgeable about CIH therapies that can benefit patients and be willing and able to discuss them with patients.

[4] **In addition to these fundamental reasons, there are therapeutic opportunities offered by CIH, as shown by the following examples:**

- Decreased harm of interventions: Chiropractic medicine to treat acute low-back pain and potentially avoid surgery; mind–body approaches to decrease anxiety and need for medical intervention; integrative approaches in the treatment of chronic pain and decrease of opioid use
- Treatment of conditions when conventional approaches fail: Treatment of nausea

and vomiting during pregnancy with acupuncture, vitamin B_6, and ginger
- Prevention: Nutritional approaches to decrease the risk of metabolic and autoimmune disorders
- Improved outcomes: Successful management of menopausal symptoms in patients at risk for breast cancer; integrative therapies pre- and post-op to manage pain and nausea

Doctor–Patient Interaction

One of the greatest barriers regarding issues of CIH is a lack of communication. As multiple studies show, most patients do not tell their physicians about their use of CIH. This can be the case even when the physicians are receptive to the topic. [2] Given the prevalence of use and the potential for interactions with conventional approaches, it is imperative that questions regarding CIH be integrated into the patient history. Many patients simply do not think of sharing this information with their physicians, so direct and specific inquiry is necessary. Many practices incorporate this information in a separate sheet for patients to fill out and for physicians to review and add to the chart. It is useful to know all CIH therapies that patients used in the past or are using presently, particularly anything ingestible. If a patient is seeing a CIH practitioner, it is best to specifically ask if they recommended any supplements or botanicals. Oriental medicine practitioners or acupuncturists, for example, often treat with botanical products or herbal teas. Naturopaths and chiropractors often recommend vitamins and supplements. When patients are asked this history directly in an atmosphere of respect, they usually are very forthcoming, and the most significant barrier is broken.

Three factors contribute to an interesting dynamic that often arises when discussing issues of CIH with patients. This is an area in which (i) most physicians do not receive formal training, (ii) there is little (albeit increasing) research in the mainstream medical journals, and (iii) there is a tremendous amount of information, of variable quality, in the lay press. All of these factors contribute to a circumstance that often is uncomfortable for physicians. This discomfort is important to recognize because it can contribute to avoidance of the topic. The integration of CIH therapies into treatment plans is a relatively new and evolving area. It is appropriate to begin the conversation with a patient by explaining that this is new territory in conventional medicine and that you are not an expert. Most patients have assumed this to be the case, appreciate the honesty, and value the opportunity to discuss these questions. This is a significant step in building a trusting and therapeutic relationship with patients interested in CIH.

It is useful to share the following decision tree with patients when making decisions regarding the use of CIH **(Fig. 24-1)**.

Step One: Assess Potential Harm

Although research regarding CIH approaches is often less than optimal, the potential for any therapy to do harm should be evaluated (to the best of available knowledge). It is necessary to evaluate the potential to cause both direct and indirect harm.

Potential for Direct Harm

This should include any evidence regarding potential harm directly from the therapy or potential interactions. When lacking good evidence, assessment of the invasiveness of the therapy is a strong predictor of risk.

Potential for Indirect Harm

This should include an assessment of potential harm caused by postponing effective treatments, and by financial exploitation. Many CIH approaches are costly, and the patient usually assumes all of the cost. Marketing can prey on vulnerable patients and result in significant and unnecessary expenditures.

Step Two: Assess Potential Benefits

The potential for any approach to be of benefit should be assessed on several levels.

Scientific Evidence

A review of the peer-reviewed literature should certainly be conducted for evidence of the effectiveness of the approach under consideration. There are numerous excellent textbooks on integrative health (19).

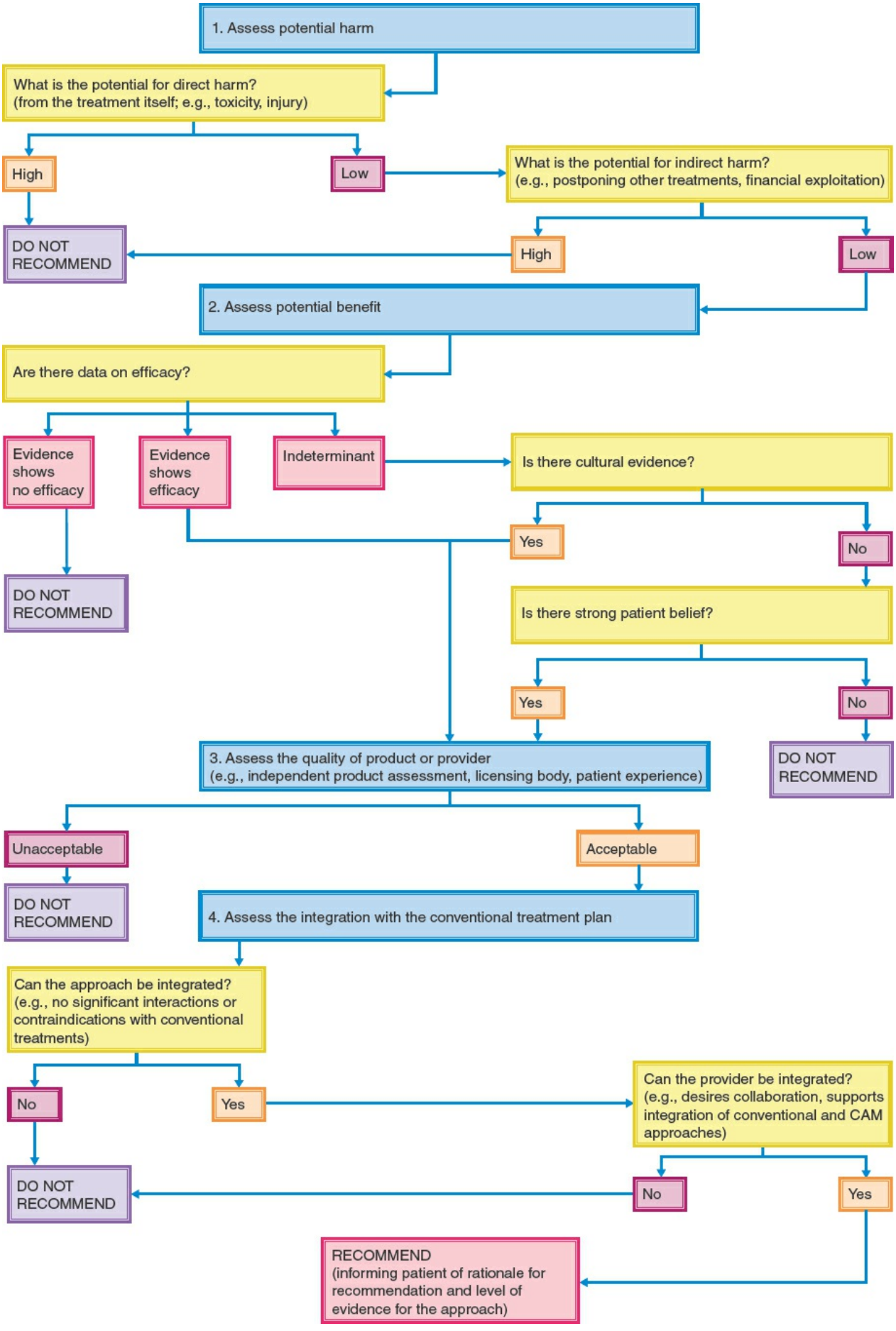

1. Assess potential harm
What is the potential for direct harm?
(from the treatment itself; e.g., toxicity, injury)
High
Low
What is the potential for indirect harm?
(e.g., postponing other treatments, financial exploitation)
DO NOT RECOMMEND
High
Low
2. Assess potential benefit
Are there data on efficacy?
Evidence shows no efficacy
Evidence shows efficacy
Indeterminant
Is there cultural evidence?
DO NOT RECOMMEND
Yes
No
Is there strong patient belief?
Yes
No
DO NOT RECOMMEND
3. Assess the quality of product or provider
(e.g., independent product assessment, licensing body, patient experience)
Unacceptable
Acceptable
DO NOT RECOMMEND
4. Assess the integration with the conventional treatment plan
Can the approach be integrated?
(e.g., no significant interactions or contraindications with conventional treatments)
No
Yes
Can the provider be integrated?
(e.g., desires collaboration, supports integration of conventional and CAM approaches)
DO NOT RECOMMEND
No
Yes
RECOMMEND
(informing patient of rationale for recommendation and level of evidence for the approach)

FIGURE 24-1 Decision tree for integrating complementary and integrative medicine approaches.

Cultural Evidence

Another form of useful information is the historic or cultural use of the approach. For example, it is valuable to consider whether a therapy has a long history of use within a given culture. If, on the other hand, the approach has no historic use, this is important to recognize. Examples include the use of black cohosh for menopausal symptoms, which was used for centuries with reported safety and effectiveness, compared with red clover, which has no historic use or track record. Another example would be acupuncture, with thousands of years of use, compared with photobiomodulation, which has been in use for a relatively short time.

Personal Belief

Another part of the assessment of benefit is to recognize the patient's belief system as it pertains to the approach. If the patient has a strong belief in the approach, and there is no evidence of potential harm, it is often reasonable to support its use. Activating a healing response or a placebo effect can often be very therapeutic.

Step Three: Assess the "Delivery System"

When assessing the delivery system, products and providers must be considered.

Product

Assessing the history of the manufacturing company and understanding its process of quality assurance can be useful. Referral to independent sources for determining the quality of a product and accuracy of labeling may be useful.

Provider

As with conventional clinicians, it can be difficult to assess the skill level of CIH providers. Inquiring about the education of a given provider and his or her licensing status (if there is a licensing body for the field) is an important place to start. It is useful to talk to other patients who used these services. Finally, one's own sense of a provider is extremely important.

Step Four: Assess the Integration

Although the individual CIH therapy may have no evidence of harm and can be of potential benefit, the way in which it is integrated into the patient's overall treatment plan is important. The same is true for CIH providers.

Approaches

The therapy or approach should be integrated into the overall treatment plan. For example, large doses of antioxidant vitamins should not be used in patients undergoing radiation therapy, as they may counteract the action of the radiation. Likewise, patients

with Down syndrome should not undergo chiropractic manipulation.

Providers

Perhaps most importantly, the potential for integration of the providers is essential to assess. If the intention is to offer the patient the best possible care, all providers, conventional and CIH alike, should be assessed for their willingness to integrate their care for the benefit of their patients. If any CIH providers are unsupportive of conventional medicine, it is critical to recognize this and look for a provider who supports integration of care.

It is useful for each physician to recognize his or her own biases about CIH and willingness to learn about the techniques. At a minimum, physicians should know the basics about which CIH approaches may be of benefit to patients and which may be of harm. Familiarity with resources in the community that are more focused on these areas can serve the physician and the patient.

SPECIFIC GYNECOLOGIC ISSUES

Menstrual Disorders

Biologically Based Therapies: Supplements and Botanicals

Premenstrual Symptoms

[4] An integrative approach to PMS can be very valuable. Nutritional changes, exercise, natural products, mind–body approaches, acupuncture, traditional Chinese medicine, and conventional treatments should be considered.

Calcium

Calcium supplementation, 1,200 to 1,600 mg/day in divided doses, has been shown to result in a reduction of luteal phase symptoms. In a review published in the *Annals of Pharmacotherapy*, it was concluded that calcium supplementation should be considered a "sound treatment option in women who experience premenstrual syndrome" (20). Calcium supplements can interfere with the absorption and effectiveness of iron supplements, thyroid hormones, corticosteroids, and tetracycline and therefore should not be taken at the same time of day.

Vitamin B_6

Vitamin B_6 is a water soluble B vitamin that serves as a co-factor in more than 100 enzyme reactions. It has been the subject of many RCTs regarding CIH and PMS. Evidence suggests some benefit over placebo for the symptoms of mastalgia, swollen breasts, pain, and depression. Another review of RCTs indicated that although most of these trials demonstrated some benefit, definite clinical recommendations could not be

made (21). While most controlled studies on vitamin B_6 in the treatment of PMS had limited numbers of patients, which makes the evidence of positive effects fairly weak, this is a benign therapy in doses of 100 mg or less and is reasonable to support. It is important to note that peripheral neuropathies can be seen in doses of 200 mg/day or higher, and interaction with other medications, specifically anti-Parkinson disease drugs.

Magnesium

Magnesium has less evidence for efficacy in treating the symptoms of PMS than calcium, although low magnesium levels were reported in women who have PMS. Two small trials found magnesium in combination with 50 mg of vitamin B_6 was effective in alleviating PMS symptoms (22).

Although more studies are needed to clearly determine effectiveness and which formulation is most efficacious, the use of magnesium is reasonable to support clinically and counteracts the constipating effects of calcium. Magnesium can be taken in 200 to 400 mg/day in divided doses, either cyclically during the luteal phase or continuously. Side effects from magnesium include abdominal cramping and diarrhea. Women with renal insufficiency should be cautious, as magnesium is excreted through the kidneys. Dietary sources of magnesium include green leafy vegetables, nuts, seeds, whole grains, tofu, and legumes.

Omega-3 Fatty Acids

There are two major types of omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids act as anti-inflammatory agents in that they shift arachidonic acid metabolism away from $PGF_{2\alpha}$ and increase levels of the less inflammatory PGE_1. Omega-3 fatty acids are essential foods, and levels are extremely low in the average diet of individuals in the United States. They can be increased through dietary means and supplements. One study looked at essential fatty acids (EFA) and PMS and showed no effect. There are some positive studies looking at the effectiveness of omega-3 fatty acids in treating mild depression with fish oils. This may be a reasonable approach to try if one of the patient's primary symptoms is mood depression (3 g, divided with meals) (23). Side effects are rare, but occasionally patients will experience nausea, diarrhea, belching, or an unpleasant taste in the mouth. Omega-3 fatty acids have an anticoagulant effect and are relatively high in calories.

Chaste Tree

Chaste Tree (*Vitex agnus-castus*) is a botanical with a long history of use for "menstrual disorders." **This botanical is considered one of the primary herbs for reducing PMS among herbalists, and has support in the literature.** Many small studies have shown promising results, and one larger study examined the effectiveness of chasteberry on premenstrual dysphoric disorder (PMDD) (24,25). In this RCT, the

active arm received 20 mg of chasteberry daily. Compared with placebo, the patients receiving chasteberry had a significant improvement in the combined symptom score (25). A multicenter noninterventional trial examined the experience and tolerance of chasteberry in 1,634 patients. After use in three cycles, 93% of women reported a decrease in or cessation of symptoms, and 94% of patients reported good or very good tolerance to this botanical. Adverse drug reactions were suspected by physicians in 1.2% of patients, but there were no serious adverse reactions (26). The primary mechanism of action is not clear, but Chaste Tree is known to reduce prolactin, increase progesterone, and bind opioid receptors. In Germany it has been approved for menstrual irregularities, PMS, and undiagnosed infertility. The typical dose is 20 to 40 mg/day of chaste berry extract. No significant toxicities were reported when used in appropriate dosages.

St. John's Wort

St. John's wort (*Hypericum perforatum*) is generally recognized as an effective antidepressant for the treatment of mild to moderate depression, similar to treatment with standard prescription antidepressants, but the evidence is not definitive. One open trial of 19 women found that this compound, when used at a dose of 300 mg/day of a 0.3% hypericin standardized extract, showed a 51% improvement in mood disturbances in PMS/PMDD (27). This dose is one-third of that typically used for depression. The most recent RCT showed a "non-significant trend for SJW to be superior to placebo." This trial did not use a product that contains both active ingredients, namely hypericin and hyperforin (28). Although adverse reactions occur less frequently than with prescription antidepressants, care must be exercised with the use of this product. Most common side effects include gastrointestinal upset, headache, and agitation. Rare but severe phototoxicity was reported. Because St. John's wort induces the cytochrome P450 complex, significant drug interactions can occur. Specifically, reduced levels of birth control pills, *theophylline, cyclosporine,* and antiretroviral drugs were reported. Interactions were described with *buspirone,* statins, calcium channel blockers, *digoxin,* and *carbamazepine.* There are no apparent significant interactions with *Coumadin.* The mechanism of action for its efficacy in the treatment of PMS is not elucidated. There were two isolated reports of pregnancy occurring in women who were taking oral contraceptives in conjunction with St. John's wort. If patients choose to take St. John's wort, they may want to use a backup method of birth control or change to a different method.

Ginkgo

Ginkgo (*ginkgo biloba*) traditionally was used to relieve breast tenderness and discomfort, improve concentration, and enhance sexual function. Its vascular effects, particularly with regard to dementia and peripheral vascular disease, were studied. One large study examined the effectiveness of ginkgo in the treatment of women with PMS

and found that after two cycles with treatment, breast symptoms were significantly improved in the ginkgo group. The effectiveness in terms of concentration or libido was not examined (29). In doses ranging from 60 to 240 mg of standardized extract per day, ginkgo showed some clinical efficacy in the treatment of breast pain, tenderness, and fluid retention. Ginkgo is promoted as an agent that can increase libido, but the methodology of these studies was criticized, and further studies are required to better define the botanical's role in these areas. Side effects include gastrointestinal upset and headache. High doses can cause nausea, vomiting, diarrhea, restlessness, or insomnia. Ginkgo has anticoagulant activity, and care must be taken when used with anti-inflammatory drugs and with *warfarin.* The underlying mechanism of action is believed to be dilation of vessels and increased blood flow.

Other products that are used, but are not recommended, to treat symptoms of PMS and PMDD are listed in Table 24-6.

Dysmenorrhea

Although dysmenorrhea is managed more effectively than PMS and PMDD with conventional approaches, treatment still has a failure rate of approximately 20% to 25%, and many patients seek alternatives. **The review concluded that vitamin B_1 is effective in the treatment of dysmenorrhea when taken at 100 mg daily, although this finding is based on only one large RCT** (30). The results further suggested that magnesium is a promising treatment, but it is unclear what dose or treatment regimen should be used (30). The addition of fish oils showed promising results. The concentration of omega-6 fatty acid derived eicosanoids such as PGE_2 is elevated during menstruation in women who experience dysmenorrhea. Dysmenorrhea was associated with low dietary intake of omega-3 fatty acids. Several studies showed supplementation to be effective in the management of dysmenorrhea (31). Krill omega-3 phospholipids, which contain phosphatidylcholine with DHA/EPA, outperformed conventional fish oil DHA/EDP in double-blind studies on PMS and dysmenorrhea (32). Given the established benefits of omega-3 fatty acids in other conditions, intake of these compounds can be recommended throughout the menstrual cycle.

Table 24-6 Other Products Often Used to Treat Symptoms of PMS and PMDD (Not Recommended)

• Tryptophan, an amino acid that is a precursor of serotonin, has been shown in several trials to improve the symptoms of PMS and PMDD. Impurities in one product made in Japan have been associated with the development of eosinophilia–myalgia syndrome (EMS), which can be fatal. It is unclear if all the cases were related to impurities or if some were related simply to the active ingredients. Until this is clearly understood, tryptophan should be avoided.
• Dehydroepiandrosterone (DHEA), a hormone secreted by the adrenal glands and often used for depression, has not been shown to be of benefit in PMS/PMDD.
• Melatonin, a hormone that regulates sleep–wake cycles and often used to prevent jet lag, has been

used for the treatment of PMS. There is no evidence of efficacy, and it can worsen depression in some patients.
• Black cohosh (*Cimicifuga racemosa*) has been well studied in the treatment of menopausal symptoms, but it has not been studied in the treatment of PMS/PMDD. Although it may prove to be beneficial, data are needed.
• Evening primrose oil is frequently used for PMS, but with the exception of cyclic mastalgia, research has failed to show benefit beyond placebo.
• Dong quai is an oriental herb often used in combination with other herbs for the treatment of menstrual disorders and menopausal symptoms. Its effectiveness has not been researched.
• Kava has been used to treat anxiety and irritability, and several studies have documented its effectiveness. It has, however, been associated with hepatotoxicity, even necessitating liver transplant. It is unclear whether this effect was related to drug or alcohol interactions, contaminants, or the kava itself.

PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder.

Body-Based Methods

Premenstrual Symptoms

Massage relieves anxiety, sadness, and pain immediately after the therapy, but it does not reduce symptoms of PMS/PMDD overall.

There is no evidence to support the effectiveness of chiropractic manipulation in these conditions. One small (N = 25) placebo-controlled crossover study showed the group receiving chiropractic treatment had a significant improvement in symptoms, but the group that received placebo first improved over baseline with the placebo and experienced no further improvement when they received the active treatment (33).

Dysmenorrhea

A Cochrane review of the use of spinal manipulation for primary and secondary dysmenorrhea concluded that overall there is no evidence to suggest that spinal manipulation is effective in the treatment of primary or secondary dysmenorrhea. In four trials, high-velocity, low-amplitude manipulation was no more effective than sham manipulation, although it was possibly better than no treatment (34). Three of the smaller trials indicated a difference in favor of the manipulation; the one trial with sufficient sample size found no difference. There was no difference in adverse effects between the two groups (34).

Mind–Body Interventions

[7] Relaxation techniques showed some very promising results for women with PMS/PMDD. One study examined the effect of the relaxation response for 15 minutes, twice a day, for 3 months, compared with women who read for the same amount of time, and women who charted their symptoms. Of women in the relaxation response group,

58% experienced improvement in their symptoms, compared with 27% for the reading group, and 17% for the charting group (35). **Given that there are many other health benefits to the relaxation response, with no cost and no risk, it is a good technique to recommend to patients.** Cognitive-behavioral therapy (CBT) and group therapy were of benefit in several small studies. In one study, CBT was effective in reducing psychological and somatic symptoms and impairment of functioning when compared to controls. In two additional studies, the authors found that CBT reduced PMS symptoms compared to the control group (36).

Oriental Medicine and Acupuncture

Oriental medicine and acupuncture have been used for thousands of years for myriad menstrual symptoms. There is a growing body of evidence supporting the effectiveness of acupuncture, particularly in the treatment of pain. A Cochrane review in 2011 found 34 trials on acupuncture or acupressure for dysmenorrhea. Of the 10 trials that were included, 6 were examining acupuncture and 4 on **[6]** acupressure. **Meta-analysis of the acupuncture trials (*n* = 673) showed significant benefit on dysmenorrhea, headache, nausea, and quality of life compared to the control arm, NSAIDs, and Chinese herbs. The meta-analysis on the acupressure studies showed a significant improvement in dysmenorrhea compared to placebo** (37). More research is needed, but this is a promising and safe modality. If a woman is fully informed and interested in pursuing these approaches and has access to a qualified provider, it is very appropriate to support.

Homeopathy

The use of homeopathy in the treatment of PMS and PMDD is not well studied, and neither is its effectiveness in the treatment of related disorders such as depression or anxiety. One study did claim positive results but was fairly weak in design and in showing improvement (36). In one small but well-done study on individualized homeopathic remedies, 90% of patients had at least 30% improvement in their symptoms, compared to 37.5% having that degree of improvement in the placebo arm (36).

Infertility

Mind–Body Interventions

Mind–body approaches are of particular interest in the infertility patient. The treatments for infertility are stress inducing, and increased stress is associated with decreased fertility (and increased risk of such things as gestational diabetes, preterm labor and delivery, and prolonged labor).

In a study of infertility patients, two group psychological interventions were

compared with routine care. The two groups who received group support and CBT had fertility rates of 54% and 55%, respectively, compared with the control group, which had a pregnancy rate of 20%. There were large and disparate dropout rates, which complicate the interpretation of these results (38). In Austria, physicians are required to prescribe psychotherapeutic therapy for every patient undergoing assisted reproductive techniques. These approaches include psychotherapy, hypnotherapy, relaxation, and physical perception exercises. A review of its success associated with pregnancy rates found that of the 1,156 women, the cumulative pregnancy rate of those who utilized the mind–body techniques was 56% and in those who intended to use these approaches it was 41.9%, higher than those who refused (39). In a case control study examining the impact of hypnosis on pregnancy rate in *in vitro* fertilization (IVF), the pregnancy rate in those cycles where hypnosis was used was 53% versus 28% in the controls, and the implantation rate 30% versus 14% (40).

[7] Mind–body therapies, such as relaxation techniques and hypnosis, are appropriate to recommend to relieve a wide variety of issues that can arise with infertility patients, and perhaps improve fertility.

Acupuncture and Oriental Medicine

[6] The use of acupuncture has been studied in the treatment of infertility and overall shows promise. Auricular acupuncture was studied as a therapy for female infertility secondary to oligomenorrhea or luteal insufficiency, and the authors concluded it was a valuable therapy (41). Another study used electroacupuncture in anovulatory women with polycystic ovarian syndrome and found that regular ovulation was induced in more than one-third of the women. After early positive results, there were several recent studies on acupuncture and IVF. In a study of 228 women examining acupuncture and IVF, while the difference did not reach statistical significance, the pregnancy rate in the acupuncture arm was 31% versus 23% in the control arm, and ongoing pregnancy rates at 18 weeks' gestation was 28% versus 18% (42). In an RCT of 225, women undergoing IVF or intracytoplasmic sperm injection (ICSI) with acupuncture had clinical pregnancy rates of 33.6% versus 15.6% in the control group, and ongoing pregnancy rates of 28.4% versus 13.8% (43). In a trial of 182 women comparing usual care versus acupuncture 25 minutes before and after embryo transfer versus acupuncture before and after transfer and 2 days after the transfer, there was again a significant increase in pregnancy rates with acupuncture, but no additional benefit was found in the patients who also received acupuncture 2 days after transfer. The clinical pregnancy rates in the acupuncture group were 39% versus 26% in the controls, and the ongoing pregnancy rate was 36% versus 22% (44).

In an RCT comparing usual care to usual care plus 25 minutes of a standard acupuncture treatment pre- and postembryo transfer, the pregnancy rates were 43% in the intervention arm as opposed to 26% in the control arm (45). In a meta-

analysis including 7 trials and 1,366 women, the authors concluded that the evidence suggests that embryo transfer done with acupuncture improved pregnancy rates and live births among women undergoing IVF (46). At the same time, a meta-analysis including 13 trials and 2,500 women concluded there was not sufficient evidence to conclude that acupuncture improves IVF clinical pregnancy rates (47). The acupuncture protocols are typically designed to promote sedation, uterine relaxation, and increased uterine blood flow. The basis for the effect of acupuncture is hypothesized to be potentially related to modulating neuroendocrinologic factors, increases in uterine and ovarian blood flow, modulating cytokines, and reducing stress, anxiety, or depression. Blood flow impedance in uterine arteries, measured as the pulsatility index, was considered useful in assessing endometrial receptivity to embryo transfer. A study was performed assessing the effect of electroacupuncture on the pulsatility index of infertile women. After treatment twice a week for 4 weeks, the mean pulsatility index was significantly reduced shortly after the last treatment and 10 to 14 days after the treatments. The skin temperature of the forehead was increased significantly, suggesting a central inhibition of sympathetic activity (48). In a study of women undergoing IVF, the women who received acupuncture had increased cortisol levels and increased prolactin levels when compared to the controls, trending toward more normal cycle dynamics (49). A retrospective chart review of 1,069 IVF cycles (fresh, nondonor) compared individualized traditional Chinese medicine to acupuncture at the time of embryo transfer, to routine IVF (50). Live birth rates were found to be 48.3% in the routine group, 50.8% in the acupuncture at time of transfer group, and 61.3% in the traditional Chinese medicine group. More studies are needed in the efficacy of acupuncture and infertility and in the mechanisms of action. Clinically speaking, there is provocative evidence that acupuncture appears safe in early pregnancy, and if patients are interested, it is reasonable to support.

Menopause

Before the release of the results of the Women's Health Initiative, 80% of women in the United States were using "nonprescriptive therapies" to help manage their menopausal symptoms, and many of these therapies were CIH approaches. In a study examining the use of CIH during menopause, a group of 3,302 women were followed across 6 years, and 80% of them used some form of CIH (51). **[4]** In a study examining women's treatment choices after discontinuing HT, 76% of women reported using nonhormonal integrative therapies, and of these 68% found them helpful (52). In a study exploring women's beliefs about "natural hormones," women using compounding pharmacies believed that compared with standard hormones, natural hormones are safer, cause fewer side effects, and are equally or more effective for symptom relief. Many women believed natural HT was equally or more effective for long-term protection of bones

and lipid levels (53). It is reasonable to assume that women are exploring and choosing such therapies in ever increasing numbers, often without being accurately or fully informed. This expanded market generates more products and promotion of alternatives. It is imperative that physicians be informed about these options so they can help patients make medically sound choices. **[4]** It creates an opportunity for clinicians to discuss integrative approaches such as nutrition, stress reduction techniques, exercise and movement, acupuncture and oriental medicine, and massage.

Natural Products

The list of botanicals and supplements promoted and used for the treatment of menopausal symptoms is extensive. Following is a review of the products most commonly used and recommended based on research evidence.

Black Cohosh

Menopause

Black cohosh (*Cimicifuga racemosa*) has traditionally been used for relief of PMS and menopause symptoms. It has been used in the Native American population for centuries and in Germany since 1950. Its most studied form is a brand called *Remifemin,* which is standardized to 1 mg of *deoxyactein* and is administered in a dose of 40 mg two times daily. Most early studies were uncontrolled, but later studies were more methodologically sound. Initially, it was felt that black cohosh decreased luteinizing hormone levels, but it is believed that it may behave like a selective estrogen receptor modulator (SERM), and act at serotonin receptors. It does not contain phytoestrogens and does not have an estrogenic effect on vaginal cytology. There are no changes in hormone levels in women taking black cohosh. In laboratory studies, black cohosh suppresses rather than stimulates breast cells (54).

A 2012 Cochrane review included 16 RCTs studying perimenopausal and menopausal women using black cohosh extract on average 40 mg a day for 23 weeks, compared to placebo, HT, red clover, and fluoxetine (55). The review cited many issues with methodology, and concluded that the evidence is insufficient to support the use of black cohosh for menopausal symptoms. They stated that there is adequate justification for further studies. Traditionally, black cohosh has been used for depressed mood. The authors of a systematic review concluded that black cohosh was effective in reducing depression and anxiety (56). If women are informed of the literature, but would like to do a trial of black cohosh, it is reasonable to support. It should be started at 20 to 40 mg twice daily, standardized to 2.5 triterpenes. The Commission E recommends 40 to 200 mg (57). Patients should be informed that it might take 4 to 8 weeks to feel an effect. Side effects are rare and include gastrointestinal upset, headache, and dizziness. There has been a rare association with liver damage reported, and women with liver disease should avoid black cohosh. While the longest study in the literature lasted 12 months,

there is no indication that longer use is unsafe.

Breast Cancer

Multiple studies showed that black cohosh has an inhibitory effect on estrogen receptor breast cancer cells. In a review of 14 RCTs, the authors concluded that there was no association between black cohosh and an increased risk of breast cancer (58). One study showed augmentation of the antiproliferative effects of *tamoxifen.* In a study that looked at the effectiveness of black cohosh in reducing menopausal symptoms for breast cancer patients, the placebo group and the group receiving black cohosh had a 27% reduction in the number and intensity of hot flashes. Only sweating was significantly more improved in the black cohosh arm (59). In another study, 136 breast cancer survivors were randomized either to *tamoxifen* alone or *tamoxifen* plus black cohosh. At 6 months, there were no significant differences, but at 1 year, 47% of women in the intervention arm versus none in the control group were free of hot flashes. Severe hot flashes were reduced in the intervention arm (24%) compared with the *tamoxifen*-alone arm (74%) (60). In a prospective observational study, 50 women with breast cancer on tamoxifen were treated with an isopropanolic extract of black cohosh for 6 months. Using the Menopause Rating Scale (MRS II) women on tamoxifen had a statistically significant reduction in symptoms, including hot flashes, night sweats, sleep disturbances, and anxiety. There was no improvement in vaginal dryness. No significant side effects were noted (61). Given that black cohosh is not estrogenic, and that promising evidence in women with breast cancer exists, it is reasonable to support a trial of black cohosh in women who are interested.

Ginseng

Many different botanicals use the name *ginseng.* The two most common are Siberian ginseng (*Eleuthero*) and oriental or Korean ginseng (*Panax*). Both of these agents are extracted from the root of their respective plants, and both are traditionally used to combat fatigue or to restore “vital force” for performance enhancement.

Panax ginseng, also known as Asian, Chinese, or Korean ginseng, is a small perennial that grows in northeast Asia and is the most widely used. A systemic review of the evidence for ginseng, which included 10 RCTs, found positive evidence for its impact on sexual function, sexual arousal, and total hot flashes score (62). One study of 12 patients examined its effect on menopausal women, with and without the symptoms of fatigue, insomnia, and depression. At baseline, the patients with symptoms had significantly higher anxiety states. The dehydroepiandrosterone sulfate was one-half that of those in the control group, and the cortisol/dehydroepiandrosterone sulfate ratio was significantly higher in the symptomatic patients. After treatment, the Cornell Medical Index and anxiety state decreased to that of the controls, and the cortisol/dehydroepiandrosterone sulfate ratio decreased significantly, although not to the level of the control group (63).

In terms of the physiologic symptoms, a randomized, multicenter, double-blind parallel group study compared a standard ginseng extract with placebo. Quality of life and physiologic parameters were assessed at baseline and after 16 weeks of treatment. There was no significant difference in symptom relief and the physiologic parameters of follicle-stimulating hormone, estradiol, endometrial thickening, maturity index, or vaginal pH. Patients did experience significant improvement in depression, sense of well-being, and health (64). A second study demonstrated improvement in fatigue, insomnia, mood, and depression (65).

There is no evidence to support the use of ginseng for relief of physiologic symptoms. If patients are suffering from psychological symptoms of menopause, they may benefit from *Panax* ginseng. Although its mechanism of action is not clear, *Panax* ginseng does not appear to be estrogenic. Use of *Panax* ginseng should be avoided with stimulants, and it may cause headaches, breast pain, diarrhea, or bleeding. The recommended dose is 100 mg of a standardized extract two times daily for 3 of 4 weeks.

The estrogenic effect of black cohosh, dong quai, ginseng, and licorice root was evaluated by (i) an examination of the effect on cell proliferation of MCF-7 cells (a human breast cancer cell line), (ii) transient gene expression assay, and (iii) a bioassay in mice. The authors concluded that dong quai and ginseng stimulate growth of MCF-7 cells independent of estrogenic activity, and that black cohosh and licorice root do not have estrogenic activity or stimulate the breast cell line (54).

Red Clover

Red clover (*Trifolium pratense*) is a member of the legume family, with brand names including *Promensil* and *Rimostil.* It contains at least four estrogenic isoflavones and is promoted as a source of phytoestrogens. Red clover is a medicinal herb with no traditional long-term use in menopause. Its estrogenic effects were first discovered by observing its effects on sheep. The term *Clover syndrome* is used to describe the symptoms frequently seen in sheep that consume large amounts of red clover. This syndrome in sheep is characterized by reproductive complications, including infertility. A number of meta-analyses concluded that overall red clover was not clinically better than placebo for relief of vasomotor symptoms (65). In a trial involving 252 women, two red clover supplements were compared with placebo across 12 weeks (*Promensil,* containing 82-mg isoflavones, and *Rimostil,* containing 57-mg isoflavones) (66). Although *Promensil* did reduce hot flashes more quickly than *Rimostil* or placebo, all three groups had the same reduction of hot flashes at the end of 12 weeks. Another large trial of 205 women had similar results. While this does supply some evidence for a biologic effect of *Promensil,* neither of the red clover supplements had a clinically significant effect when compared with placebo. Its effect on the endometrium must be further delineated. In a trial of 109 women looking at the effect of red clover extract on

depression and anxiety, there was a 75% reduction for anxiety and 78% reduction on depression scores, compared to 21% reduction with the placebo (67).

Red clover has unclear demonstrable effects, is believed to be estrogenic, and its effect on the breast and endometrium is not adequately studied. Coumarins are present in some clover species.

Dong Quai

Dong quai (*Angelica sinensis*) has a long history of traditional use in menopause and in the treatment of menstrual problems. In the oriental system of medicine, it is used in combination with other botanicals. Several studies of the effectiveness of dong quai in treating the symptoms of menopause failed to show its effectiveness (68). No evidence exists to support the use of dong quai as a single agent in the treatment of menopausal symptoms. The use of dong quai in combination with other herbs, as is done traditionally, is not well studied. It is important to note that dong quai contains coumarin derivatives.

Kava

Kava (*Piper methysticum*) is native to the South Pacific, and one of its traditional uses is to reduce anxiety. It is often recommended for menopausal symptoms, particularly irritability, insomnia, and anxiety. Studies showed that 100 to 200 mg, three times daily, standardized to 30% kavalactones, decreases irritability and insomnia associated with menopause. It often is used in combination with other components, such as black cohosh and valerian, for the management of menopausal symptoms. One study that examined the use of kava in addition to HT for the treatment of anxiety showed that the combined use resulted in a significant decrease in anxiety when compared with HT alone (69).

Kava has the potential for significant, albeit rare, side effects. Cases of hepatotoxicity severe enough to require transplant were reported (70). Other side effects include dermatitis, and a movement disorder similar to Parkinson disease, but reversible. It was removed from many European markets. The use of kava is not recommended, but if patients are using this botanical (which is available over the counter), they should be informed of the risks, and advised to avoid taking kava in conjunction with other anxiety-reducing agents, with alcohol, or *acetaminophen,* and have liver function tests performed periodically.

St. John's Wort

The leaves and the tips of the flowers of the plant St. John's wort (*Hypericum perforatum*) have been used medicinally, primarily as an antidepressant. It is used for anxiety, and in Germany, it is used to treat menopausal mood swings.

Although its mechanism of action is unclear, St. John's wort does appear to be beneficial in relieving mild to moderate depression, with 60% improvement in mood, energy, and sleep with a dose of 300 mg three times daily. Standardization is

controversial, but it is believed to have at least two active ingredients, namely hypericin and hyperforin. Most research was done on products standardized to 0.3% hypericin. The first trial to examine its use for menopausal symptoms was done in 1999. **[4]** **The authors of a meta-analysis published in 2014 concluded that St. John's wort extract was significantly more effective in the treatment of menopausal symptoms than placebo** (71). In a randomized trial of 301 women using a combination of black cohosh and St. John's wort, the treatment was superior to placebo for both climacteric and psychological symptoms (72). **Given the evidence, and its safety profile, it is very reasonable to support the use of St. John's wort either alone, or in combination with herbs such as black cohosh, for hot flashes, depression, or mood swings.** St. John's wort induces the cytochrome P450 complex. Specifically, lower levels of oral contraceptives, *theophylline, cyclosporine,* and antiretroviral drugs were reported. Interactions were described with *buspirone,* statins, calcium channel blockers, *digoxin,* and *carbamazepine.* There are no apparent significant interactions with *Coumadin.*

Chaste Tree

Chaste Tree (*Vitex agnus-castus*) has a long history of uses by civilizations ranging from Greeks to the monks of medieval times. Among the uses is treatment of menopausal symptoms. Although its use was recommended for this indication, the efficacy of Chaste Tree in menopause is not demonstrated.

Ginkgo Biloba

Ginkgo biloba is often promoted for the improvement of libido in menopausal women. Muira puama plus ginkgo had a significant effect in 65% of the patients in one study (73). Side effects include gastrointestinal upset and headaches, and drug interactions can occur with estrogens, statins, and calcium channel blockers. Ginkgo has an anticoagulant effect.

Phytoestrogens

Phytoestrogens are plant-based compounds that have weak estrogenic activity. They appear to have SERM activity with modest agonist effect at the β-estrogen receptor. Phytoestrogens are categorized as isoflavones, coumestans, lignans, or flavonoids. The most promoted of these groups is isoflavones, which are genistein, daidzein, or glycitein. Soybeans and soy products are a rich source of isoflavones. A 2012 meta-analysis concluded that isoflavones reduced the frequency and the severity of hot flashes by 20.6% and 26.2%, respectively. Supplements containing more than 18.8 mg of genistein were significantly more effective in reducing hot flashes than supplements at lower levels (74). Women who want to consume phytoestrogens should do so through food products rather than supplements, and should aim for 100 mg of isoflavones a day, or 25 g of soy protein. One RCT of 366 women demonstrated endometrial hyperplasia in 3.8% of women who consumed 150 mg/day of isoflavones for 5 years versus 0% in

the placebo arm (75).

Mind–Body Interventions

Mind–body therapies for the treatment of menopausal symptoms have been studied in several domains. **[7]** In a study of clinical hypnosis in breast cancer survivors, hot flash scores were decreased by 68%, and anxiety, depression, and sleep were significantly improved (76). In a study with 187 postmenopausal women with at least seven hot flashes a day, receiving five weekly hypnosis sessions and self-hypnosis, the hypnosis group had a reduction of hot flashes frequency hot flash score, interference, sleep quality, and treatment satisfaction all improved in the treatment arm of 74%, compared to 17% in the control group (77). **[7]** In a study of 110 women with hot flashes randomized to either MBSR or a waitlist control, MBSR significantly improved hot flashes, quality of life, sleep quality, anxiety, and perceived stress. The hot flash score continued to improve after the MBSR intervention (78).

Insomnia, which is another frequent symptom of menopause, is a complex, multifactorial problem. Optimal treatment is described as incorporating the following components: stress management, coping strategies, enhancement of relationships, and lifestyle changes that facilitate sleep (79).

[7] Overall, mind–body techniques are a low- or no-cost, low-risk intervention that can decrease central nervous system adrenergic tone. There is evidence that these approaches are associated with improvement of hot flashes and other menopausal symptoms, and provide general health benefits.

Other Mind and Body Approaches

Oriental medicine was used for more than 2,500 years and includes treatment with acupuncture, herbs, and movement. Although diagnosis and treatment are highly individualized, from the perspective of oriental medicine, menopause is often associated with deficiencies in qi, blood, and jing. Acupuncture is one of the best-studied CIH modalities, and more studies of higher quality are needed regarding its application to the menopausal patient. **[6]** In a meta-analysis of acupuncture in menopausal patients published in 2015, 12 studies were included with 869 patients. Acupuncture was found to reduce the frequency and severity of hot flashes, and improve the psychological, somatic, and urogenital subscale scores (80). In an RCT of 267 women comparing individualized acupuncture plus self-care to self-care alone, the frequency and the intensity of hot flashes significantly decreased in the acupuncture arm. Overall, this group had significant improvement in vasomotor, sleep, and somatic symptoms (81). In a pilot study looking at the use of acupuncture in patients being treated with *tamoxifen,* 15 patients were followed for 6 months (82,94). Patients were evaluated before and after 1, 3, and 6 months of treatment. There was significant improvement in anxiety, depression, and somatic and vasomotor symptoms. Libido was

not affected. A study with 45 women with breast cancer found significantly decreased hot flashes with electroacupuncture (83). This is a promising area for those patients whose options for treatment of these symptoms are limited.

[4] In the hands of a competent practitioner, acupuncture is a safe CIH modality. If menopausal patients are interested in exploring this technique as part of their plan for managing symptoms, it is reasonable to support a trial of acupuncture with a qualified practitioner. Because many of the herbal treatments in oriental medicine can be estrogenic, it is best to avoid them if the patient is taking any form of HT.

"Natural" Hormones

There is a myriad of hormonal options for patients, and many that are touted as "natural alternatives." Because many hormonally active compounds are available over the counter, physician awareness about these issues is essential, especially in light of the findings of the Women's Health Initiative and the large number of women seeking "alternatives."

Natural Versus Bioidentical Hormones

There is a dominant belief in the culture that natural is "good" and synthetic is "bad." A natural product is any product with principal ingredients that are of animal, mineral, or vegetable origins. Natural products may have no resemblance to the ingredients in their natural state. For example, conjugated equine estrogens are natural products. They do not resemble anything natural or native to the human body. It is useful to make this distinction with patients. Very often patients requesting "natural hormones" are uncertain about what they are actually requesting. Most patients, when using this term, are looking for bioidentical hormones, or hormones that are molecularly identical to the hormones their ovaries produce.

The ovaries produce three types of estrogen: 17β-estradiol, estrone, and estriol. Premenopausally, the predominant estrogen produced by the ovary is 17β-estradiol, or E_2. It is converted back and forth to estrone, E_1, which is made in the fat and is the predominant estrogen postmenopausally. All of the patches, and several oral formulations such as *Estrace,* are E_2. When E_2 is taken orally, much of it is converted to E_1 in the gut. E_1 and E_2 essentially are equivalent in their level of estrogenic activity. Estriol, E_3, is the weakest of the three estrogens and is predominantly made in the placenta during pregnancy. It is not conventionally prescribed and is available only through compounding pharmacies. *Estriol* is the predominant form of estrogen in *Tri-est* and *Bi-est. Estriol, Tri-est,* and *Bi-est* are frequently used and recommended by the integrative medicine community.

Conjugated equine estrogens are composed of more than 10 different molecules extracted from the urine of pregnant mares. This is a natural product but is neither

bioidentical nor native. In addition to animal conjugated equine estrogen, a synthetic version, such as *Cenestin,* is available.

It is difficult to draw conclusions regarding options for the use of these hormones. The reasons for this are listed in Table 24-7.

Table 24-7 Reasons for Difficulty in Drawing Conclusions Regarding Use of Hormones

Drawing conclusions regarding options for the use of these hormones is challenging for a variety of reasons:

1. **It is essential to reinforce to patients that all hormones are not created equal.** Different hormones have different effects. For example, *estriol* is often promoted as a hormone that does everything that conjugated equine estrogen does but with none of the risks. Given that it is a significantly weaker estrogen than conjugated equine estrogen, this is dubious and is not based in scientific evidence.
2. **Native or bioidentical hormones are rarely included in research protocols.** The Women's Health Initiative studied only conjugated equine estrogen (*Premarin*) and MPA (*Provera*). The Postmenopausal Estrogen–Progestin Intervention (PEPI) used only conjugated equine estrogen, but did compare it with micronized *progesterone* (and showed micronized *progesterone* to be as effective as *medroxyprogesterone acetate* at protecting the endometrium and better than *medroxyprogesterone acetate* at protecting the lipid benefits of estrogen).
3. **All forms of hormone therapy frequently are clumped together as one entity.** The distinctions between the types of hormones studied are rarely made in the media and often not clear even in the medical literature. The coverage of the Women's Health Initiative is a perfect example, as the media generalized its findings to hormone therapy, and even most information released by and for doctors did not clarify that the findings were regarding one specific form of estrogen combined with one specific form of progestin.

Bioidentical Hormones

Progestogens

Bioidentical *progesterone* is available either through compounding pharmacies or through retail pharmacies as micronized *progesterone,* natural *progesterone,* or *progesterone* USP (brand name *Prometrium*). *Medroxyprogesterone acetate* (MPA) is a nonbioidentical progestin (i.e., its molecular structure is foreign to the body).

Bioidentical Estrogens

E_2, or 17β-estradiol, often is used interchangeably with *conjugated equine estrogen.* It is most bioidentical when delivered in the form of the patch because its oral form is converted to estrone in the gut. No comprehensive long-term data regarding its use are available.

Estriol, or E_3, the weakest of the estrogens that occurs naturally only in high circulating levels during pregnancy, is popular in the integrative community. It is often promoted as the ideal estrogen, a natural alternative providing all of the benefits of HT with none of the risks. This assumption is not supported by the literature, as the research on *estriol* is limited. In one study examining the use of *estriol* over 12 months, 53 women were given 2 mg daily. They reported good symptom relief and satisfaction, and

histologic evaluation of the endometrium revealed no hyperplasia or atypia. Bone mineral density showed no change (84). In another study examining the effect of *estriol,* 64 women were followed for 24 months. There were four treatment arms: 2.0 mg E_3 plus 2.5 mg *MPA,* 0.625 mg of *conjugated estrogen* plus 2.5 mg *MPA,* 1 μg of 1α-hydroxyvitamin D_3, and 1.8 g calcium lactate containing 250 mg of elemental calcium. Outcome measures were taken at baseline, 6, 12, 18, and 24 months, and included the following assessments: bone mineral density at third lumbar vertebrae, serum levels of osteocalcin, total alkaline phosphatase, and urinary ratios of calcium/creatinine and hydroxyproline/creatinine. The findings revealed decreased bone mineral density in the vitamin D and calcium groups and no decrease in the *conjugated estrogen* and E_3 groups. Osteocalcin and alkaline phosphate were decreased or without change in the conjugated estrogen and E_3 groups, and were increased in the vitamin D_3 and calcium groups. Urinary calcium/creatinine ratios were decreased with E_3 and conjugated estrogen, and there was no decrease with the use of vitamin D_3 and calcium. Urinary hydroxyproline/creatinine ratios were decreased in the conjugated estrogen group, unchanged in the E_3 and vitamin D_3 groups, and increased in the calcium group. Uterine bleeding was significantly less in the E_3 group compared with the conjugated estrogen group, with 2.4 days compared with 13 days per person. In conclusion, the study supported the finding that a bone-preserving effect occurred with E_3 when compared with *conjugated estrogen* (85).

It has been proposed that *estriol* might have anticarcinogenic activity. Unlike *estradiol, estriol* is not carcinogenic in rodent models, reduces uterine growth, and enhances phagocytic activity. After one or more pregnancy, *estriol* excretion significantly increases in comparison with nulliparous women. This may or may not be linked to the increased risk of breast and ovarian cancer in nulliparous women. In a study following over 84,000 Finnish women, oral and transdermal estradiol was associated with a slightly increased risk of breast cancer (2 to 3 additional cases per 1,000 women across 10 years), while oral estriol and vaginal estrogens were not associated with an increased risk (86).

Oral *estriol* appears to provide symptom relief and stimulate breast and endometrial tissue less than estradiol. It may prove to have mildly beneficial effects on bone. It appears to exert estrogenic effects on the endometrium and to have no effect or mild effects on lipids. No clinical interventional trials exist on the effect of oral *estriol* use on the breast.

Tri-est and Bi-est

Tri-est and *Bi-est* are formulations in which the predominant *estrogen* is *estriol.* The typical formulations contain 80% *estriol.* Typically *Tri-est* contains 2 mg of *estriol,* 0.25 mg of *estradiol,* and 0.25 mg of *estrone,* and *Bi-est* contains 2 mg of *estriol* and

0.5 mg of *estradiol*. It should be noted that these names refer only to the types of *estrogen* used, and the specific amounts of each can vary. These particular formulations are often marketed as the most "natural" form of estrogen therapy because they contain either two or all three forms of naturally occurring estrogens. The following factors should be noted:

- *Tri-est* and *Bi-est* are not formulated in naturally occurring ratios or quantities.
- Although *Tri-est* and *Bi-est* are only 20% E_2 or E_2 plus E_3, the dose of these more potent estrogens is significant (i.e., 0.5 mg).
- Although a certain combination of $E_1/E_2/E_3$ may prove to have benefits over other forms of HT and should be explored, this research does not exist.

Estriol Vaginal Cream

Vaginal *estriol* looks promising for local effects with very low estrogen exposure. In a prospective, double-blind, placebo-controlled study of 167 postmenopausal women with vaginal atrophy, vaginal dryness and the Global Symptom Score were significantly improved with 0.005% *estriol* vaginal gel (87). *Estriol* vaginal cream was studied in women who had recurrent urinary tract infections. This RCT compared vaginal *estriol* cream with placebo for 8 months of treatment and showed a significant reduction in urinary tract infections (0.5 vs. 5.9 per patient year). In the treatment arm, there was a reduction in vaginal pH from 5.5 to 3.8 compared with no decline in the placebo group (88). In an RCT of 27 women on HT with urogenital atrophy, the addition of vaginal *estriol* shortened the latency period for urinary symptoms (89). In a study of postmenopausal women with urogenital symptoms, 88 were enrolled in this prospective, randomized, placebo-controlled study. The treatment group received intravaginal *estriol* ovules: 1 ovule (1 mg) once daily for 2 weeks and then 2 ovules once weekly for a total of 6 months as maintenance therapy, compared to placebo vaginal suppositories. After therapy, the symptoms and signs of urogenital atrophy significantly improved in the treatment group in comparison with the control group. Significant colposcopic improvements were seen in the treatment arm, and there were statistically significant increases in mean maximum urethral pressure, in mean urethral closure pressure, and in the abdominal pressure transmission ratio to the proximal urethra. In addition, 68% of the treated participants reported subjective improvement in their incontinence, versus 16% in the placebo group (90).

A typical prescription for vaginal *estriol* cream is 1 mg *estriol* per gram; insert 1 gram of cream daily for 2 weeks, then twice a week for maintenance.

Bioidentical Progestins

The Postmenopausal Estrogen–Progestin Intervention (PEPI) trials provided a multicentered RCT that, among other things, compared *conjugated equine estrogen* plus

MPA with *conjugated equine estrogen* plus natural or micronized *progesterone* (91). The trial compared 12 days of 10 mg of *MPA* with 200 mg of micronized *progesterone.* The micronized *progesterone* provided equal protection of the endometrium and was better at protecting the beneficial effects of the *conjugated equine estrogen* on the lipid profile. Patients reported that micronized *progesterone* had significantly fewer side effects than *MPA.* This was the case in several other trials (92,93). Given these data, there is good evidence to prescribe micronized *progesterone.* The arm of the Women's Health Initiative that was prematurely discontinued was the conjugated equine *estrogen/MPA* arm. The *conjugated equine estrogen*–alone arm was continued. The role and the effect of *MPA* should be closely examined. In ovariectomized rhesus monkeys, E_2 plus *MPA* interfered with ovarian estrogen protection against coronary vasospasm. E_2 plus *micronized progesterone* protected against coronary vasospasm. There continues to be increasing evidence that progesterone improves cardiovascular function, and that maintaining a baseline of progesterone may be an effective preventive cardiac measure (94). Given the increased cardiovascular risks in women taking *conjugated equine estrogen* and *MPA,* combined with the positive data from PEPI, micronized *progesterone* is an excellent choice for patients who are taking systemic estrogen and who still have a uterus.

Another area of consideration with bioidentical progesterone is the risk of breast cancer. **While conjugated equine *estrogen/MPA* leads to an increase in the risk of breast cancer after approximately 4 years of use, it is not clear if the same risk is present with micronized progesterone. There are four observational studies that show a mitigation of that risk when micronized progesterone is used** (95).

Natural *progesterone* was used as a single agent in the treatment of menopausal symptoms. The typical dose is 100 mg/day. More research is needed to demonstrate efficacy.

Yam Creams, Progesterone Creams

Yam creams and *progesterone* creams, which are sold over the counter, are distinctly different products. Yam creams should, by definition, not contain *progesterone,* but rather should contain phytoprogesterones, plant products that are *progesterone* like (Table 24-8). *Progesterone* creams, by contrast, should contain progesterone. Part of the challenge is that there is a large media presence asserting that *progesterone* creams can solve all that ails menopausal women. These creams are not regulated by the FDA. Their content is highly variable, ranging from 700 mg *progesterone* per ounce to less than 2 mg per ounce in products whose names imply that they are progesterone creams, not yam creams. The absorption of these products is highly variable.

Table 24-8 Progesterone and Wild Yam Creams

400–700 mg progesterone per ounce	Pro-Gest

	Bio Balance
	Progonol
	OstaDerm
2–15 mg progesterone per ounce	PhytoGest
	Pro-Dermex
	Endocreme
	Yamcon
	Wild Yam Extract
	PMS Formula
	Menopause Formula
	Femarone-Nutri-Gest
Less than 2 mg progesterone per ounce	Wild Yam Cream
	Progesterone-HP

Wild yam creams (which refer to the genus name *Dioscorea villosa,* rather than the fact that they are grown in the wild) are applied topically. They contain steroidal saponins, including diosgenin, and claim to affect estrogen steroidogenesis. Although these are interesting products, studies of their safety and efficacy are needed. In one double-blind, placebo-controlled crossover study, after a 4-week baseline period, patients received 3 months of active treatment and 3 months of placebo. Symptom diaries were maintained at baseline and then for 1 week of each month. Blood and salivary hormone levels and serum lipids were assessed at baseline, 3 months, and 6 months. At 3 months, there were no significant side effects and no change in levels of blood pressure, weight, lipid levels, follicle-stimulating hormone, glucose, estradiol, or progesterone. In terms of symptom relief, the placebo and yam cream had a minor effect on the number and severity of flashes. Wild yam creams appear to be free of side effects, and they appear to have little effect on menopausal symptoms (96).

Table 24-9 Unknown Aspects of Hormone Therapy

• Risks and benefits of bioidentical hormone therapy (i.e., how the results of the Women's Health Initiative translate to bioidentical hormones)
• Role of *medroxyprogesterone acetate* in increasing certain risks
• Long-term risks and benefits of *estriol*

• Effects of different doses of hormones
• Correlation of circulating hormone levels to different doses, and the correlation of different hormone levels to risks and benefits
• Effect of lifelong hormonal exposure
• Risks and benefits of hormone therapy when initiated at the age of menopause

In terms of *progesterone* creams, an RCT of 223 women with severe menopausal symptoms using progesterone cream found the progesterone arm to be no more effective than placebo (97). **Given the data available, *progesterone* or yam creams should not be considered adequate to protect the uterus in a woman taking systemic estrogen. *Progesterone* cream may be useful for symptom relief in women not taking systemic HT, and it may prove to have other benefits and risks.**

Counseling Patients

It's important to communicate to patients what is known regarding HT and what is not known. Some of the unknown aspects of HT are listed in Table 24-9.

Given the present state of medical knowledge, the need to individualize treatment plans in menopausal women cannot be overemphasized. It is essential to clarify patient goals, and individual health risks, history of hormonal exposure (both length and time), family history, and personal preferences. **For women desiring systemic hormone replacement, the bioidentical choice of transdermal estradiol and micronized progesterone is preferred.**

SURGERY AND COMPLEMENTARY AND INTEGRATIVE MEDICINE

Studies showed that most surgical patients use some form of CIH. There are special considerations regarding CIH and the surgical patient. These issues primarily fall into two domains:

1. Supplements that, when used perioperatively, may affect the patient's course
2. CIH approaches that may be of benefit to the surgical patient

When examining what patients are using that may affect their surgical course, the greatest concern and awareness needs to be in the domain of biologically based therapies. A survey of 2,560 surgical patients in 5 California hospitals revealed that 68% of patients were using botanicals, 44% of them did not consult their physician, 56% did not inform their anesthesiologists, and 47% did not stop them before their surgery. Variables that were associated with use included female gender, age 35 to 49

years, higher income, Caucasian race, higher education, and problems with sleep, joints, back, allergies, and addiction (98). A survey based in a tertiary care center examined the use of botanicals and vitamins in patients preoperatively ($N = 3,106$). Of the patients studied, 22% were using botanicals and 51% were using vitamins. The typical users were women in the age range of 40 to 60 years. The most commonly used compounds were echinacea, ginkgo biloba, St. John's wort, garlic, and ginseng (99). In another study based in a university medical center that surveyed patients undergoing outpatient surgery, 64% of patients were using supplements, 90% of them were using vitamins, 43% were using garlic extracts, 32% ginkgo biloba, 30% St. John's wort, 18% ma-huang, 12% echinacea, and others were using aloe, cascara, and licorice (100).

Effects on Surgery

Many of the most commonly used substances have effects of which surgeons and anesthesiologists should be aware. Botanicals used with anesthesia can lead to the following complications:

- Prolongation of anesthetic agents
- Coagulations disorders
- Cardiovascular effects
- Electrolyte disturbances
- Hepatotoxicity
- Endocrine effects

The American Society of Anesthesiologists does not have an official guideline, but it recommends that all natural products be discontinued 2 to 3 weeks before elective surgery.

Prolongation of Anesthetic Agents

Valerian, kava, ginseng, and St. John's wort are among the more commonly used botanicals that may prolong the effects of anesthetic agents. Valerian has sedative effects that are believed to be mediated by *benzodiazepine* and γ-aminobutyric acid (GABA) receptors. For patients who use valerian on a daily basis, it is suggested that it be tapered off over the weeks preceding the surgery. Kava is mediated by GABA receptors and potentiates the sedative effects of anesthetics. The general recommendation is to discontinue its use 24 hours before surgery. St. John's wort induces cytochrome P450 enzymes (*cyclosporin, indinavir,* and *warfarin*). It modulates the GABA receptor and inhibits the reuptake of serotonin, dopamine, and noradrenaline. The recommendation is to discontinue it 5 days preoperatively.

Coagulation Effects

Some of the more commonly used supplements and botanicals that are reported to have anticoagulative properties include fish oil, ginseng (Asian and American), ginkgo, garlic, vitamin E, ginger, feverfew, dong quai, saw palmetto, and chondroitin. Coenzyme Q10, fish oil, and flax seed can have this effect.

Cardiovascular Effects

Licorice root contains glycyrrhizic acid, which has an aldosterone-like effect and can result in hypertension, hyperkalemia, and edema. Glycyrrhizic acid is used in manufactured foods as a sweetener. Ma-huang (ephedra) is associated with arrhythmias and hypertension, and ginseng is associated with hypertension. Fish oil, coenzyme Q10, and garlic are associated with hypotension. There were case reports of reversible episodes of hypertension and palpitations with glucosamine. Occasional occurrences of hypertension, tachycardia, and other cardiac complaints of unknown causality were reported with saw palmetto.

Electrolyte Disturbances

Licorice root was associated with hypernatremia and hypokalemia. Goldenseal can reduce the effect of antihypertensives. Saw palmetto, ginseng, and green tea can cause electrolyte disturbances.

Hepatotoxicity and Endocrine Effects

The following botanicals are associated with hepatotoxicity: kava, red yeast rice (which contains the ingredient in *lovastatin*), chaparral, valerian, and echinacea. In terms of endocrinologic effects, both chromium and ginseng can cause hypoglycemia. Table 24-10 highlights some of the more commonly used botanicals and vitamins and their possible effects in the surgical patient.

Table 24-10 Commonly Used Botanicals and Vitamins and Their Possible Effects in the Surgical Patient

Substance	Potential Negative Effects
Chaparral	Hepatotoxicity
Chondroitin	Anticoagulative properties
Chromium	Hypoglycemia
Coenzyme Q10	Hypotension; cardiac effects; anticoagulative properties
Dong quai	Anticoagulative properties
Echinacea	Hepatotoxicity

Feverfew	Anticoagulative properties
Fish oil	Anticoagulative properties; hypotension
Garlic	Anticoagulative properties
Ginger	Anticoagulative properties
Ginkgo	Anticoagulative properties
Ginseng	Anticoagulative properties Hypertension Hypoglycemia
Glucosamine	Hypoglycemia
Goldenseal	Can reduce effect of antihypertensives
Green tea	Anticoagulative properties; cardiac effects
Flax seed	Anticoagulative properties
Kava	Potentiates the sedative effects of anesthetics Hepatotoxicity
Licorice root	Hypertension Hyperkalemia Hypokalemia Hypernatremia Edema
Ma-huang (ephedra)	Arrhythmias Hypertension
Red yeast rice	Hepatotoxicity
Saw palmetto	Anticoagulative properties; cardiac effects; electrolyte disturbances
St. John's wort	Prolongation of anesthetic effects Inhibits reuptake of serotonin, dopamine, and noradrenaline
Valerian	Prolongation of anesthetic effects Hepatotoxicity
Vitamin E	Anticoagulative properties

Complementary and Integrative Medicine Approaches That May Benefit the Surgical Patient

[4] The two domains in which there is the most research and the most promise with regard to surgical patients are mind–body-based therapies and oriental medicine and acupuncture.

Oriental Medicine and Acupuncture

A review of the use of acupuncture as the sole source of anesthesia for patients undergoing cesarean delivery in China reviewed 12 years of experience with success rates of 92% to 99%. Blood pressure, heart rate, and respiratory rate remained stable throughout the surgery, which is a significant advantage over pharmaceutical anesthesia (101). Although it is unlikely that acupuncture will readily be used as the only source of anesthesia in this country, it demonstrates the effectiveness of this approach and encourages its consideration as an adjunct. In one RCT in patients undergoing upper- and lower-abdominal (gastrointestinal) surgery, acupuncture was given 2.5 cm lateral to the spine before induction. Postoperatively, patients who received the acupuncture had decreased postoperative pain, nausea and vomiting, analgesic requirement, and sympathoadrenal responses. Supplemental morphine use dropped by 50%, and postoperative nausea was reduced by 30%. Cortisol and epinephrine levels were reduced 30% to 50% during the recovery phase and the first postoperative day (102). Several studies specifically looking at nausea and vomiting in women undergoing gynecologic surgeries showed benefit in both acupuncture and acupressure (103–105).

In Germany, auricular electrically stimulated anesthesia is frequently used. Review of one RCT in patients anesthetized with *desflurane* with and without auricular acupuncture revealed significantly reduced anesthetic requirement (the amount of anesthesia required to prevent purposeful movements) (106).

Acupuncture warrants further investigation as an adjunct to anesthesia in gynecologic patients. Even simple adjuncts, such as the use of acupressure bands or electroacupressure bands, are reasonable to support as they are safe and showed some efficacy in decreasing nausea and vomiting postoperatively.

Mind–Body Interventions

[7] Mental preparation for surgery results in psychological, physiologic, and economic benefit. Higher levels of anxiety are associated with a greater risk of complications, depression, and increased need for anesthesia, decreased immune function, and a longer time to heal. Many different physiologic aspects are affected, including decreased chemotaxis and phagocytosis and decreased inflammatory factors such as cytokines. One study examining wound healing took healthy dental students and made a standardized scalpel incision in the palate at two times: one right before examinations and one during summer vacation. The incisions in these healthy students took 3 days (40%) longer to heal during times of stress versus times of decreased stress (107). The power of the spoken word was explored as long ago as 1964, when a study randomized patients to a preoperative visit characterized by sympathetic, caring, and informative communication versus an interchange characterized by cursory remarks. The patients receiving the sympathetic preoperative visit required half the pain medicines and had a two-and-a-half-day decreased hospital stay (108).

A meta-analysis of mind–body interventions and surgery included 191 studies and

more than 8,600 patients. **The use of mind–body approaches, including such interventions as hypnosis, imagery, and relaxation, was associated with reduced blood loss, decreased pain, decreased medication use, increased return of bowel function, decreased psychological stress, and decreased hospital stay by 1.5 days.** In an RCT of 220 women undergoing excisional breast biopsy or lumpectomy, a 15-minute presurgical hypnosis intervention was compared to attention control. In the intervention arm, women required significantly less propofol and lidocaine, and had less pain, nausea, fatigue and emotional upset. In addition, the institution incurred significantly less cost (109). In a study of 241 patients undergoing invasive medical procedures randomized to standard care versus structured attention versus self-hypnosis, the hypnosis had the most pronounced effects on pain and anxiety and improved hemodynamic stability (110).

In a study of ambulatory surgery patients receiving spinal anesthesia, patients who were randomized to listening to soothing music had decreased sedative requirements during the surgery and in the perioperative period (111). In a study of women undergoing hysterectomy, patients received standardized anesthesia and were randomized to music during surgery, music plus positive suggestions, or the sounds of the operating room. On the day of surgery, both the music group and the music-plus-suggestion groups received significantly less rescue anesthesia. On postoperative day 1, the patients who had heard music during surgery had more effective analgesia and early mobilization. At the time of discharge, both intervention groups had less fatigue. There was no change in nausea and vomiting, bowel function, or length of stay (112). In another study with patients undergoing abdominal hysterectomy, patients were randomized to listen intraoperatively to one of four tapes: positive suggestions regarding pain, or nausea and vomiting, or both, or white noise. The positive suggestions had no beneficial effects in reducing nausea and vomiting or the consumption of analgesics or antiemetics (113).

Although the studies and interventions in mind–body approaches in the surgical patient are varied, these interventions are low cost and low risk and may offer very real benefits for the patient, and a greater sense of empowerment.

CONCLUSION

Physicians are driven by a desire and commitment to provide the best possible care, with a responsibility to inform patients of all therapies that can be of benefit, regardless of their system of origin. In practice this is challenging, because there are many unanswered questions in the use of complementary and integrative approaches, and there are often not established standards of care. Each physician, with his or her patient, needs to form his or her own opinions regarding the appropriate integration of CIH therapies for that patient. Many patients will want conclusive evidence of any therapy

before using it. Others, assured of the relative safety of a therapy, may require less conclusive evidence. Illustrating this dilemma, in a systematic review of randomized trials regarding CIH approaches to PMS, the authors concluded that "despite some positive findings, the evidence was not compelling for any of these therapies, with most trials suffering from various methodological limitations. On the basis of current evidence, no complementary or integrative therapy can be recommended as a treatment for premenstrual syndrome" (114). Although this concept is appealing in its simplicity, it may not be in the best interest of patients. It is important to be consistent in requiring evidence, using the same levels of evidence for incorporating approaches from CIH as from conventional interventions. As with many clinical decisions that must be made with incomplete data, many factors must be considered. The potential risks and benefits must be weighed carefully, using *primum non nocere* as the guide.

As more research is done and as medical schools and residency programs continue to incorporate education about these approaches, the gap between patients' desires and standard practices will decrease as appropriate therapies are seamlessly incorporated, and ineffective and fraudulent ones are discarded.

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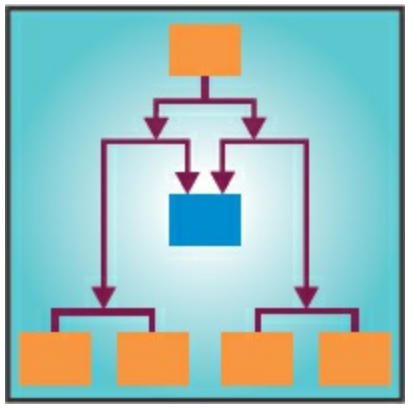
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SECTION IV

Operative Gynecology



CHAPTER 25
Preoperative Evaluation and Postoperative Management
Daniel L. Clarke-Pearson, Stephanie A. Sullivan, Stuart R. Pierce, Lindsay M. West



CHAPTER 26
Gynecologic Endoscopy
Malcolm G. Munro, William H. Parker



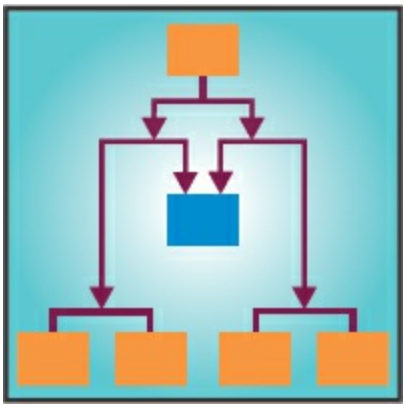
CHAPTER 27
Hysterectomy
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CHAPTER 28
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CHAPTER 25

Preoperative Evaluation and Postoperative Management



Daniel L. Clarke-Pearson, Stephanie A. Sullivan, Stuart R. Pierce, Lindsay M. West

Medical History and Physical Examination
Laboratory Evaluation
Preoperative Discussion and Informed Consent
General Considerations
- Nutrition
- Antimicrobial Prophylaxis in Gynecologic Surgery
- Postoperative Infections
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- Thromboembolism

Enhanced Recovery After Surgery (ERAS)
- Rationale for ERAS
- Perioperative Diet
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- Laxatives
- Outcomes of ERAS Protocols

Management of Medical Problems
- Correction of Existing Fluid and Electrolyte Abnormalities
- Endocrine Disease
- Cardiovascular Diseases
- Hematologic Disorders
- Renal Disease
- Liver Disease

KEY POINTS

1 The preoperative evaluation should be complete and thorough, taking into account the essential aspects of the patient's general medical condition and prior surgical history. The risks, benefits, and potential complications of the surgical procedure should be discussed with the patient, including the most frequent complications of the particular surgical procedure. Alternative management, if any, should be presented.

2 A calculated body mass index (BMI) can be used as a surrogate marker for nutritional status.

3 Careful and meticulous fluid and electrolyte management is essential for all patients undergoing major surgical procedures.

4 Although satisfactory analgesia is easily achievable with available methods, patients continue to suffer unnecessarily from postoperative pain.

5 Prophylactic antibiotics should be employed judiciously. Prompt identification of perioperative infections and their specific treatments are critical to minimize the impact of this common morbidity.

6 Enhanced recovery protocols are comprehensive and include preoperative, intraoperative, and postoperative elements. Adherence to these protocols has reduced hospital length of stay, postoperative complications, and health care costs.

7 Early in the clinical course, a postoperative small bowel obstruction may exhibit signs and symptoms similar to those of an ileus. Initial conservative management as outlined for the treatment of ileus is appropriate.

8 Because pulmonary embolism is the leading cause of death following gynecologic surgical procedures, the use of prophylactic venous thromboembolism regimens is an essential part of management. In patients at moderate risk, intermittent pneumatic compression (IPC) during and after gynecologic surgery reduces the incidence of deep venous thrombosis (DVT) on a level similar to that of low-dose or low–molecular-weight *heparin*. A combination of mechanical (IPC) and pharmacologic prophylaxis is recommended for high-risk patients.

9 Patients who are predisposed to cardiovascular, respiratory, and endocrine illnesses must be thoroughly evaluated preoperatively. Coronary artery disease and chronic obstructive pulmonary disease (COPD) are major risk factors for patients undergoing abdominal surgery. Patients with hypertension should receive medication to control their blood pressure before surgery. Perioperative management of medical complications must be prompt and meticulous.

The successful outcome of gynecologic surgery is based on thorough evaluation, careful preoperative preparation, and attentive postoperative care. This chapter discusses the general perioperative management of patients undergoing major gynecologic surgery and addresses specific medical problems that could complicate the surgical outcome.

MEDICAL HISTORY AND PHYSICAL EXAMINATION

[1] Gynecologic surgery should be undertaken only after gaining a thorough understanding of a patient's medical history and performing a complete physical examination.

1. **The medical history should include detailed questions to identify any medical illnesses that might be aggravated by surgery or anesthesia.** Coronary artery

disease, diabetes, pulmonary diseases, and obesity are the most common causes of postoperative complications.

2. **Medications currently being taken (including nonprescription drugs) and those discontinued within the month before surgery should be recorded.** Information about the use of "alternative therapies," herbs, and vitamins should be elicited (1,2). Specific instructions must be given to the patient regarding the need to discontinue any medication before surgery (e.g., *aspirin,* antiplatelet agents, diuretics, hormone replacement, or oral contraceptives), and those medications that should be continued (e.g., β-blockers, α_2-agonists, statins, H_2 blockers, and proton pump inhibitors). Collaboration with the anesthesiologist in making decisions about continuing preoperative medications is essential. In the case of herbal medications, there is no evidence that herbal medications improve surgical outcomes and many may increase complications **(Table 25-1)** (3). It is recommended that all herbal medications be discontinued at least a week before surgery.
3. **The patient should be questioned regarding known allergies to medications (e.g., sulfa and *penicillin*), foods, or environmental agents (latex).**
4. **Previous surgical procedures, and the patient's course following those surgical procedures, should be reviewed to identify and protect against potential complications.** The patient should be asked about specific complications, such as excessive bleeding, wound infection, venous thromboembolism, peritonitis, or bowel obstruction. Prior pelvic surgery should alert the gynecologist to the possibility of distorted surgical anatomy such as adhesions or ureteral stricture. In such cases, it may be prudent to identify any pre-existing abnormality by performing computed tomography (CT) or other imaging. Many patients may not be entirely clear about the extent of the previous surgical procedure or the details of intraoperative findings. Therefore, operative notes from previous procedures should be obtained and reviewed.
5. **Family history may identify familial traits that might complicate planned surgery.** A family history of excessive intra- or postoperative bleeding, venous thromboembolism, malignant hyperthermia, and other potentially inherited conditions should be sought.
6. **The review of systems should be detailed to identify any coexisting medical or surgical conditions.** Inquiry about gastrointestinal and urologic function is particularly important before undertaking pelvic surgery because many gynecologic diseases involve adjacent nongynecologic viscera. The patient may have less serious symptoms, which could be corrected along with performing the primary surgery (e.g., stress urinary incontinence, fecal soiling, symptomatic cystocele).
7. **Although many women undergoing gynecologic surgical procedures are otherwise healthy, with pathology identified only on pelvic examination, other**

major organ systems should not be neglected in the physical examination. Identification of abnormalities, such as a heart murmur, pulmonary compromise, hernia, or osteoarthritis of hips or knees should lead the surgeon to obtain additional testing and consultation to minimize intra- and postoperative complications.

Table 25-1 Potential Effects of Common Herbal and Dietary Supplements

Herb/Dietary Supplement	Potential Perioperative Effect
Aconite	Potential ventricular arrhythmias
Aloe	May potentiate thiazides
Black cohosh	May potentiate hypotensive effects
Danshen	May cause bleeding
Dong quai	May cause bleeding
Echinacea	Allergic reactions; decreased effectiveness of immunosuppressants
Ephedra/ma huang	Risk of myocardial ischemia and stroke from tachycardia and hypertension; ventricular arrhythmias with halothane; long-term use may cause intraoperative hemodynamic instability; life-threatening interaction with monoamine oxidase inhibitors, anesthesia, potential for withdrawal
Garlic	May increase bleeding risk
Ginkgo	May increase bleeding risk
Ginseng	Lowers blood sugar and may increase bleeding risk
Kava	May increase the sedative effect of anesthetics (an association between kava use and fatal hepatotoxicity has been reported)
Licorice	May cause hypertension and hypokalemia
Senna	May cause electrolyte imbalance
St. John's wort	Induction of cytochrome p450 enzyme; excessive sedation and delayed emergence from general anesthesia; potential serotonin syndrome if used in combination with other serotonergic agents
Valerian	Excessive sedation and delayed emergence from general anesthesia; benzodiazepine-like acute withdrawal
Yerba mate	May cause hypertension or hypotension and excess sympathetic nervous system stimulation

LABORATORY EVALUATION

"Routine" preoperative laboratory testing of healthy women is to be discouraged as abnormal results are infrequent and are rarely of consequence in the surgical or anesthetic management of the patient (4). Despite well-established guidelines, approximately 90% of patients undergo unnecessary testing in a major university medical center (5). The selection of appropriate preoperative laboratory studies should depend on the type of the anticipated surgical procedure and the patient's medical status. The Revised Cardiac Risk Index (RCRI) can be used to predict the risk of cardiac complications after noncardiac surgery. These clinical risk factors include cerebrovascular disease, congestive heart failure (CHF), creatinine level >2 mg/dL, and insulin-dependent diabetes.

Chest x-ray:

- **New or unstable cardiovascular or pulmonary signs or symptoms**
- **At risk for pulmonary complications**

Electrocardiogram:

- **Signs or symptoms of cardiovascular disease**
- **High-risk surgery (risk of perioperative cardiac event >5%)**
- **Intermediate-risk surgery (risk of perioperative cardiac event 1% to 5% and one RCRI clinical risk factor)**

Complete blood count:

- **Major surgery**
- **Patients with conditions with an increased risk for anemia**

Renal function:

- **Recognized renal or cardiovascular disease**

Coagulation studies (activated partial thromboplastin time [APTT], prothrombin time [PT], platelet count):

- **Not recommended routinely**
- **Patients with a history of bleeding or liver disease**
- **Patients taking anticoagulants**
- **History or examination concerning for an underlying coagulation disorder**

Urinalysis:

- **Not recommended routinely; may be considered, given symptoms or history**
- **Consider for invasive urologic procedures** (6)

Tumor markers:

- **In general, tumor markers are used to follow patients with known ovarian cancers. They are not considered "diagnostic." However, an elevated tumor marker in a patient with a "suspicious" pelvic mass may be helpful in determining whether the patient should be referred to a gynecologic oncologist** (7).

Imaging of adjacent organ systems should be undertaken in individual cases as

follows:

1. CT urography is helpful to delineate ureteral patency and course, especially in the presence of a pelvic mass, gynecologic cancer, or congenital müllerian anomaly. A CT urogram is not of value in the evaluation of most patients undergoing pelvic surgery.
2. Upper endoscopy, colonoscopy, barium enema, or upper gastrointestinal studies with small bowel assessment may be of value in evaluating some patients before undergoing pelvic surgery. Because of the proximity of the female genital tract to the lower gastrointestinal tract, the rectum and sigmoid colon may be involved with benign (endometriosis or pelvic inflammatory disease) or malignant gynecologic conditions. Conversely, a pelvic mass could have a gastrointestinal origin such as a diverticular abscess or a mass of inflamed small intestines (Crohn disease) or, rarely, a gastric or pancreatic carcinoma. Any patient with gastrointestinal symptoms should be further evaluated.
3. Other imaging studies, including ultrasonography, CT scanning, or magnetic resonance imaging (MRI), may be useful in selected patients, for example, to evaluate a pelvic mass. There are several scoring systems that can be used in the evaluation of a pelvic ultrasound that may suggest the increased likelihood of ovarian cancer (8).

PREOPERATIVE DISCUSSION AND INFORMED CONSENT

[1] The preoperative discussion should include a description of the surgical procedure, its expected outcome, and risks and is the basis for obtaining signed informed consent (9,10). Informed consent is an educational process for the patient and her family and fulfills the need to convey information in understandable terms. The items listed in Table 25-2 should be discussed, and, after each item, the patient and family should be invited to ask questions. Documentation of the discussion is an important component of the patient's record that the physician should always include with the preprinted surgical consent form.

Following are components of the informed consent process:

1. **A discussion of the nature and the extent of the disease process should include an explanation in lay terms of the significance of the disease or condition.** Printed materials, computer-based learning programs, and videos may assist in this process. The patient's competency to understand the discussion and written consent should be assessed. If the patient speaks a different language, a qualified interpreter should be present and the presence of the interpreter documented.
2. **The goals of proposed surgery should be discussed in detail.** Some gynecologic

surgical procedures are performed purely for diagnostic purposes (e.g., dilation and curettage, cold knife conization, diagnostic laparoscopy), whereas most are aimed at correcting a specific problem. The extent of the surgery should be outlined, including which organs will be removed. Most patients like to be informed regarding the type of surgical incision and the estimated duration of anesthesia.

3. **The expected outcome of the surgical procedure should be explained.** If the procedure is being performed for diagnostic purposes, the outcome will depend on surgical or pathologic findings that are not known before surgery. When treating an anatomic deformity or disease, the expected success of the operation should be discussed, and the potential for failure of the operation (e.g., failure of tubal sterilization or the possibility that stress urinary incontinence may not be alleviated, or may recur). When treating cancer, the possibility of finding advanced disease and the potential need for adjunctive therapy (e.g., postoperative radiation therapy or chemotherapy) should be mentioned. Other issues of importance to the patient include discussion of loss of fertility or loss of ovarian function. These issues should be raised by the physician to ensure that the patient adequately understands the pathophysiology that may result from the surgery and to allow her to express her feelings regarding these issues. Unanticipated findings at the time of surgery should be mentioned. For example, if the ovaries are unexpectedly found to be diseased, the best surgical judgment may be that they should be removed.
4. **The risks and potential complications of the surgical procedure should be discussed, including the most frequent complications of the particular surgical procedure.** For most major gynecologic surgeries, the risks include intra- and postoperative hemorrhage, postoperative infection, venous thromboembolism, injury to adjacent viscera, and wound complications. The patient should understand that minimally invasive surgery, despite small skin incisions, may have many of the same risks of injury or complications as does “open” surgery. Given the potential for transfusion of blood products, it should be clarified whether the patient would object to receiving a transfusion. Pre-existing medical problems (e.g., diabetes, obesity, chronic obstructive pulmonary disease [COPD], coronary artery disease) result in additional risks and should be reviewed with the patient. Measures that will be taken to reduce the risk of complications should be described (e.g., prophylactic antibiotics, bowel preparation, venous thromboembolism prophylaxis).
5. **The usual postoperative course should be discussed in enough detail to allow the patient to understand what to expect in the days following surgery.** Information regarding the need for a suprapubic catheter, prolonged central venous monitoring, or an intensive care stay helps the patient accept her postoperative course and avoids surprises that may be disconcerting to the patient and her family. The expected duration of the recovery period, in and out of the hospital, should be outlined.

6. **The surgeon should describe others who will be involved with the surgical procedure (residents, assistants) and their roles in the patient's care.** Any conflict of interest should be disclosed.
7. **Alternative methods of therapy should be discussed, including medical management or other surgical approaches.** The potential risks and benefits of alternative treatments should be discussed.
8. The patient should have an understanding of the outcome of the disease.

Table 25-2 Outline of Key Points of the Preoperative Informed Consent Discussion

1. The nature and extent of the disease process
2. The extent of the actual operation proposed and the potential modifications of the operation, depending on intraoperative findings
3. The anticipated benefits of the operation, with a conservative estimate of successful outcome
4. The risks and potential complications of the surgery
5. Alternative methods of therapy and the risks and results of those alternative methods of therapy
6. The results likely, if the patient is not treated

GENERAL CONSIDERATIONS

Nutrition

Young patients undergoing elective gynecologic surgery have adequate nutritional stores and, for the most part, do not require nutritional support. **All patients should have a nutritional assessment, especially elderly patients and those undergoing gynecologic cancer surgery or other major gynecologic procedures in which a prolonged postoperative recovery is expected.** Nutritional status should be reassessed at regular intervals postoperatively until the patient successfully returns to a regular diet.

A nutritional assessment includes a careful history and physical examination, which are the most useful, reliable, and cost-effective methods of determining a patient's nutritional status. In particular, information about recent weight loss, dietary history, fad diets, extreme exercise, or anorexia or bulimia should be elucidated. Physical evidence of malnutrition, including temporal wasting, muscle wasting, ascites, and edema, should be noted. Accurate height and weight measurements should be obtained and an ideal body weight, percentage ideal body weight, and percentage usual body weight may be calculated. A variety of techniques were developed to determine a patient's nutritional state; however, many methods lack clinical utility outside of a research setting. Anthropometric measurements of skin-fold thickness and arm-muscle circumference

provide an estimate of total body fat and lean muscle mass. Nutritional screening assessments, such as the Mini Nutritional Assessment and the Prognostic Nutritional Index, have been described to evaluate a patient's nutritional status (11).

[2] The calculated body mass index (BMI) can be used as a surrogate marker for nutritional status. **BMI is calculated as body weight in kilograms divided by the height in square meters. A BMI less than 22 increases the risk of malnutrition, and a BMI less than 19 gives clear evidence of malnutrition** (12). The degree of malnutrition can in part be determined by serum concentrations of albumin, transferrin, and prealbumin. The levels of these serum proteins are greatly influenced by the patient's level of hydration. Prealbumin has the shortest half-life, at 2 to 3 days, and levels of this protein are depressed very early in comparison with serum transferrin and albumin, which have half-lives of 8 and 20 days, respectively (14). Serum albumin is a substitute for the Prognostic Nutritional Index, which is a time-consuming calculation, in assessing malnutrition in women with gynecologic malignancies (15). **Hypoalbuminemia, characterized by an albumin of less than 3.5 g/dL, is correlated with morbidity, mortality, and increased postoperative complication rates in data from the National Surgical Quality Improvement Program** (13). Protein-energy malnutrition, as characterized by hypoalbuminemia, can result in poor wound healing, increased risk for infection, functional decline, increased morbidity and mortality.

Decisions regarding the need for nutritional support should be based on several individualized factors. These factors include the patient's prior nutritional state, the anticipated length of time in which the patient will not be able to eat, the extent of surgery, and the likelihood of complications. The nutritional assessment should determine whether the cause of the malnutrition is increased enteral loss (malabsorption, intestinal fistula), decreased oral intake, increased nutritional requirements as a result of hypermetabolism (sepsis, malignancy), or a combination of these factors. Severe malnutrition, if not corrected, can further complicate the postoperative problem by causing altered immune function, chronic anemia, impaired wound healing, and eventually multiple organ system failure and death.

There is evidence that preoperative nutritional support may improve postoperative outcomes in patients with significant pre-existing malnutrition (16,17). **According to the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, evidence-based medicine supports the use of preoperative nutritional support for 7 to 14 days in severely malnourished patients undergoing major nonemergent gastrointestinal surgery** (14). Preoperative oral supplementation may reduce infectious complications and shorten hospital stays, however the effect on mortality is unclear (18). ASPEN guidelines do not support the routine use of parenteral nutritional support in the immediate postoperative period for patients undergoing major gastrointestinal surgery; however, the guidelines do indicate a role for nutritional

support postoperatively in patients in whom oral intake will be inadequate for 7 to 10 days (14).

Antimicrobial Prophylaxis in Gynecologic Surgery

Gynecologic procedures often involve breaching the reproductive and gastrointestinal tracts, which harbor endogenous bacteria capable of causing polymicrobial infections in the postoperative period (Table 25-3). **Despite great advances in aseptic technique and drug development, bacterial contamination of the operative site and postoperative infections are a frequent part of the practice of gynecologic surgery.** Prevention of these surgical complications includes using proper aseptic technique, minimizing tissue trauma, minimizing the amount of foreign material in the surgical site, controlling diabetes, avoiding immunologic suppression, maximizing tissue oxygenation, draining blood and serum from the surgical site, and using prophylactic antibiotics. **[5]** Antibiotic prophylaxis is given with the belief that antibiotics enhance the immune mechanisms in host tissues that resist infections by killing the bacteria that inoculate the surgical site during surgery (19).

Table 25-3 Bacteria Indigenous to the Lower Genital Tract

Lactobacillus	*Enterobacter agglomerans*
Diphtheroids	*Klebsiella pneumoniae*
Staphylococcus aureus	*Proteus mirabilis*
Staphylococcus epidermidis	*Proteus vulgaris*
Streptococcus agalactiae	*Morganella morganii*
Streptococcus faecalis	*Citrobacter diversus*
α-Hemolytic streptococci	*Bacteroides* species *B. disiens* *B. fragilis* *B. melaninogenicus*
Group D streptococci	
Peptostreptococci	
Peptococcus	
Clostridium	
Gaffkya anaerobia	
Escherichia coli	
Fusobacterium	
Enterobacter cloacae	

Infections in the skin or pelvis that result from gynecologic surgery (e.g., parametritis, cuff cellulitis, pelvic abscess) typically are polymicrobial in nature. These infections are complex and often involve gram-negative rods, gram-positive cocci, and anaerobes. Antibiotic prophylaxis should be sufficiently broad to cover these potential pathogens (Table 25-4) (20).

The timing of antimicrobial prophylaxis is important. There is a relatively narrow window of opportunity for affecting outcomes (21). In the United States, it is customary to give antimicrobial prophylaxis shortly before or during the induction of anesthesia. **Data revealed that a delay of 3 hours or more between the time of bacterial inoculation (i.e., skin incision) and administration of antibiotics may result in ineffective prophylaxis. Evidence indicates that for prophylaxis, one dose of antibiotic is appropriate. When the surgical procedure proceeds longer than 1 to 2 times the half-life of the drug or blood loss is greater than 1.5 L, additional intraoperative doses of antibiotics should be administered to maintain adequate levels of medication in serum and tissues** (22). There are no data to support the continuation of prophylactic antimicrobial agents into the postoperative period for routine gynecologic procedures.

***Cephalosporins* emerged as the most important class of antimicrobial agents for prophylaxis.** These drugs have a broad spectrum and relatively low incidence of adverse reactions. *Cefazolin* (1 g) appears to be widely used in the United States by gynecologic surgeons because of its relatively low cost and long half-life (1.8 hours). Other *cephalosporins* such as *cefoxitin, cefotaxime,* and *cefotetan* are commonly used for prophylaxis. These agents appear to have a broader spectrum of activity against anaerobic bacteria and are appropriate selections when colorectal resections are possible, such as during a debulking surgery for ovarian cancer. For the majority of gynecologic procedures, there is little evidence that a clinically relevant distinction exists between *cefazolin* and the other agents. Obese patients, defined as having a BMI greater than 35 or weight greater than 100 kg, should receive 2 g of *cefazolin* to achieve appropriate blood and tissue antibiotic concentrations (20).

Table 25-4 Antibiotic Prophylaxis Regimens by Procedure

Procedure	Antibiotic	Dose
Hysterectomy Urogynecology procedures, including those involving mesh	*Cefazolin*[a] *Clindamycin*[c] plus *gentamicin* or *quinolone*[d] or *aztreonam* *Metronidazole*[c] plus *gentamycin* or *quinolone*[d]	1 g or 2 g IV[b] 600 mg IV 1.5 mg/kg IV 400 mg IV 1 g IV 500 mg IV 1.5 mg/kg IV 400 mg IV 1 g IV
Hysterosalpingogram or	*Doxycycline*[e]	100 mg orally, twice daily for 5 days

Chromotubation		
Induced abortion/dilation and evacuation	*Doxycycline* *Metronidazole*	100 mg orally 1 hr before procedure and 200 mg orally after procedure 500 mg orally twice daily for 5 days

[a]Alternatives include *cefotetan, cefoxitin, cefuroxime,* or *ampicillin–sulbactam*.

[b]A 2-g dose is recommended in women with a body mass index greater than 35 or weight greater than 100 kg or 220 lb.

[c]Antimicrobial agents of choice in women with a history of immediate hypersensitivity to *penicillin*.

[d]*Ciprofloxacin* or *levofloxacin* or *moxifloxacin*.

[e]If patient has a history of pelvic inflammatory disease or procedure demonstrates dilated fallopian tubes. No prophylaxis is indicated for a study without dilated tubes.

IV, intravenously.

Adapted from Antibiotic prophylaxis for gynecologic procedures. *American College of Obstetricians and Gynecologists Practice Bulletin* No. 104, May 2009.

Antimicrobial prophylaxis, although usually beneficial, is not without risk. Anaphylaxis is the most life-threatening complication from antibiotic use. Allergic reactions to *penicillins* are reported in 0.7% to 8% courses of treatment (23). While first-generation *cephalosporins* have cross-reactivity to *penicillins*, data indicate that it is safe to administer second- or third-generation *cephalosporins* to women who report a history of adverse reactions to *penicillins* as the cross-allergy is negligible (24).

A single dose of broad-spectrum antibiotics can result in pseudomembranous colitis, caused by *Clostridium difficile.* Diarrhea may develop in as many as 15% of hospitalized patients treated with β-lactam antibiotics (25). These gastrointestinal complications from antibiotics may cause serious morbidity in the surgical patient, and the surgeon should be able to recognize and manage these problems.

Not all gynecologic surgery patients need to receive prophylactic antibiotics. The surgeon should choose agents to cover procedures based on available data, thereby avoiding the potential for adverse reactions and minimizing the unnecessary use of antibiotics, which may contribute to increased rates of antimicrobial resistance. In patients with *cephalosporin* allergies or anaphylaxis to *penicillin,* other drugs or combinations should be chosen to provide adequate prophylactic coverage. Antimicrobial prophylaxis options for common gynecologic procedures are presented in Table 25-3. Antibiotic prophylaxis is not indicated for diagnostic or operative laparoscopy, exploratory laparotomy, or diagnostic or operative hysteroscopy, including endometrial ablation, intrauterine device insertions, endometrial biopsy, or urodynamics (20).

Subacute Bacterial Endocarditis Prophylaxis

It was thought that women who had severe valvular disease or other cardiac conditions

required antibiotic prophylaxis prior to genitourinary (GU) or gastrointestinal (GI) procedures in order to prevent bacterial endocarditis as a result of the transient bacteremia provoked by the surgery. After reviewing the pertinent evidence-based literature, the American Heart Association (AHA) issued revised guidelines in 2007 stating that antibiotic prophylaxis was not necessary solely to prevent endocarditis in patients undergoing GI or GU procedures, including hysterectomy (26). For those at highest risk of infective endocarditis undergoing high-risk procedure, antibiotics should still be considered (Table 25-5).

Postoperative Infections

Infections are a major source of morbidity in the postoperative period. Risk factors for infectious morbidity include the absence of perioperative antibiotic prophylaxis, contamination of the surgical field from infected tissues or from spillage of large bowel contents, an immunocompromised host, poor nutrition, chronic and debilitating severe illness, poor surgical technique, and pre-existing focal or systemic infection. Sources of postoperative infection can include the lung, urinary tract, surgical site, pelvic sidewall, vaginal cuff, abdominal wound, and sites of indwelling intravenous catheters. Early identification and treatment of infection will result in the best outcome for these potentially serious complications.

Table 25-5 Recommendations for Prophylaxis of Bacterial Endocarditis

Highest-Risk Patients	Agents	Regimen (Within 30–60 min of Starting Procedure)
Standard regimen	*Amoxicillin*	2 g PO
	Ampicillin	2 g IM or IV
	or	
	Cefazolin or *ceftriaxone*	1 g IM or IV
	Cephalexin	2 g
Penicillin-allergic (oral)	*Cephalexin*	2 g
	Clindamycin	600 mg
	Azithromycin or *clarithromycin*	500 mg
Penicillin-allergic (non-oral)	*Cefazolin* or *ceftriaxone*	1 g IM or IV
	Clindamycin	600 mg IM or IV

IM, intramuscularly; IV, intravenously.

Derived from **Wilson W, Taubert KA, Gewitz M, et al.** Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007;116:1736–1754.

Although infectious morbidity is a frequent complication of surgery, the incidence of infections can be decreased by the appropriate use of simple preventive measures. Systemic antibiotic prophylaxis and meticulous surgical technique will help decrease the incidence of postoperative pelvic and abdominal infections in these patients. Blood and necrotic tissue are excellent media for the growth of aerobic and anaerobic organisms. Care should be taken to obtain hemostasis to prevent postoperative hematomas. Antibiotic therapy, rather than prophylaxis, should be initiated during surgery in patients who have frank intra-abdominal infection or pus. Elective surgical procedures should be postponed in patients who have preoperative infections. In an epidemiologic study conducted by the Centers for Disease Control and Prevention (CDC), the incidence of nosocomial surgical infections ranged from 4.3% in community hospitals to 7% in municipal hospitals (27). Data confirmed this, with an incidence of 2% to 5% (28). Urinary tract infections accounted for approximately 40% of these nosocomial infections. Infections of the skin and wound accounted for approximately one-third of the infections, and respiratory tract infections accounted for approximately 16%. In patients who had any type of infection before surgery, the risk of infection at the surgical wound site increased fourfold. Rates of infection were higher in older patients, in patients with increased length of surgery, and in those with increased length of hospital stay before surgery. The relative risk was three times higher in patients with a community-acquired infection before surgery. These community-acquired infections included infections of the urinary and respiratory tracts.

Historically, the standard definition of febrile morbidity for surgical patients was the presence of a temperature higher than or equal to 100.4°F (38°C) on two occasions at least 4 hours apart during the postoperative period, excluding the first 24 hours. Other sources defined fever as two consecutive temperature elevations greater than 101.0°F (38.3°C) (29,30). Febrile morbidity is estimated to occur in as many as one-half of patients; it is often self-limited, resolves without therapy, and is usually noninfectious in origin (31). Overzealous evaluations of postoperative fever, especially during the early postoperative period, are time consuming, expensive, and sometimes uncomfortable for the patient (31). **The value of 101.0°F is more discriminatory than 100.4°F to distinguish an infectious cause from an inconsequential postoperative fever in the benign gynecologic patient.**

The assessment of a febrile surgical patient should include a review of the patient's history with regard to risk factors. The history and the physical examination should focus on the potential sites of infection **(Table 25-6)**. The examination should include

inspection of the pharynx, a thorough pulmonary examination, percussion of the kidneys to assess for costovertebral angle tenderness, inspection and palpation of the abdominal incision, examination of sites of intravenous catheters, and an examination of the extremities for evidence of deep venous thrombosis (DVT) or thrombophlebitis. In gynecologic patients, an appropriate workup may include inspection and palpation of the vaginal cuff for signs of induration, tenderness, or purulent drainage. A pelvic examination should be performed to identify a mass consistent with a pelvic hematoma or abscess and to look for signs of pelvic cellulitis.

Patients with fever in the early postoperative period should have an aggressive pulmonary toilet, including incentive spirometry (30). **[5]** Fever within the first 48 hours of surgery is likely to be cytokine related; thus if fever persists beyond 48 hours postoperatively, additional laboratory and radiologic data may be obtained. The evaluation may include complete and differential white blood cell counts and a urinalysis. In one study, results from fever workups included positive blood cultures in 9.7% of patients, a positive urine culture in 18.8%, and a positive chest x-ray in 14%. These data support the need for a tailored workup based on the patient's clinical picture (32). Blood cultures can be obtained but will most likely be of little yield unless the patient has fever at the time of collection. In patients with costovertebral angle tenderness, renal ultrasound or CT urogram may be indicated to rule out the presence of ureteral damage or obstruction from surgery, particularly in the absence of laboratory evidence of urinary tract infection. Patients who have persistent fevers without a clear localizing source should undergo CT scanning of the abdomen and pelvis to rule out the presence of an intra-abdominal abscess. If fever persists in patients who had gastrointestinal surgery, a barium enema or upper gastrointestinal studies with small bowel assessment may be indicated late in the course of the first postoperative week to rule out an anastomotic leak or fistula.

Table 25-6 Posthysterectomy Infections

Operative Site	Nonoperative Site
Vaginal cuff	Urinary tract
Pelvic cellulitis	Asymptomatic bacteriuria
Pelvic abscess	Cystitis
Intraperitoneal	Respiratory
Adnexa	Atelectasis
Cellulitis	Pneumonia
Abscess	Vascular
Abdominal incision	Phlebitis

Cellulitis	Septic pelvic thrombophlebitis
Simple	Pyelonephritis
Progressive bacterial synergistic	
Necrotizing fasciitis	
Myonecrosis	

Urinary Tract Infections

Historically, the urinary tract was the most common site of infection in surgical patients (33). A significant decrease in urinary tract infections was noted after the institution of perioperative use of prophylactic antibiotics. The incidence of postoperative urinary tract infection in gynecologic surgical patients not receiving prophylactic antibiotics is thought to be as high as 40%, and **even a single dose of perioperative prophylactic antibiotic decreases the incidence of postoperative urinary tract infection to as low as 4%** (34,35).

Symptoms of a urinary tract infection may include urinary frequency, urgency, and dysuria. In patients with pyelonephritis, patients may exhibit systemic symptoms such as headache, malaise, nausea, and vomiting. A urinary tract infection is diagnosed on the basis of microbiology and is defined as the growth of 10^5 organisms cultured per milliliter of a voided specimen urine. Most infections are caused by coliform bacteria, with *Escherichia coli* being the most frequent pathogen. Other pathogens include *Klebsiella, Proteus,* and *Enterobacter* species. *Staphylococcus* organisms are the causative bacteria in fewer than 10% of cases.

Despite the high incidence of urinary tract infections in the postoperative period, few of these infections are serious. Most are confined to the lower urinary tract, and pyelonephritis is a rare complication (36). Catheterization of the urinary tract, either intermittently or continuously with the use of an indwelling catheter, is implicated as a main cause of urinary tract contamination (37). More than 1 million catheter-associated urinary tract infections occur yearly in the United States, and **catheter-associated bacteria remain the most common etiology of gram-negative bacteremia in hospitalized patients.** Bacteria adhere to the surface of urinary catheters and grow within bile films, which appear to protect embedded bacteria from antibiotics, making treatment less effective. The use of urinary tract catheters should be minimized. An indwelling catheter should be removed or replaced in a patient undergoing treatment for catheter-related infections.

The treatment of urinary tract infection includes hydration and antibiotic therapy. Infections may be considered complicated or uncomplicated which helps providers dictate the type and length of therapy. Infections are considered complicated

if they occur in patients with poorly controlled diabetes, immunosuppression, pregnancy, kidney disease, urinary obstruction, anatomic abnormality of the genitourinary tract, recent hospitalization, or those with an indwelling catheter, stent, or nephrostomy tube (38). Commonly prescribed and effective antibiotics include *penicillin, sulfonamides, cephalosporins, fluoroquinolones,* and *nitrofurantoin* (39). The choice of antibiotic should be based on knowledge of the susceptibility of organisms cultured at a particular institution. In some institutions, for example, more than 40% of *E. coli* strains are resistant to *ampicillin.* For uncomplicated urinary tract infections, an antibiotic that has good activity against *E. coli* should be given in the interim while awaiting results of the urine culture and sensitivity data.

Patients who have a history of recurrent urinary tract infections, those with chronic indwelling catheters (Foley catheters or ureteral stents), and those who have urinary conduits should be treated with antibiotics that will be effective against the less common urinary pathogens such as *Klebsiella* and *Pseudomonas.* **Chronic use of *fluoroquinolones* for prophylaxis is not advised because these agents are notorious for inducing antibiotic-resistant strains of bacteria.**

Pulmonary Infections

The respiratory tract is an uncommon site for infectious complications in gynecologic surgical patients. This low incidence is probably a reflection of the young age and good health status of gynecologic patients in general. In acute care facilities, pneumonia is a frequent hospital-acquired infection, particularly in elderly patients (40). Risk factors include extensive or prolonged atelectasis, preexistent COPD, severe or debilitating illness, central neurologic disease causing an inability to clear oropharyngeal secretions effectively, nasogastric suction, and a prior history of pneumonia (40,41). In surgical patients, early ambulation and aggressive management of atelectasis are the most important preventive measures.

A significant percentage (40% to 50%) of cases of hospital-acquired pneumonia is caused by gram-negative organisms (33). These organisms gain access to the respiratory tract from the oral pharynx. Gram-negative colonization of the oral pharynx is increased in patients in acute care facilities and is associated with the presence of nasogastric tubes, pre-existing respiratory disease, mechanical ventilation, and tracheal intubation (42). The use of antimicrobial drugs seems to significantly increase the frequency of colonization of the oral pharynx with gram-negative bacteria.

A thorough lung examination should be included in the assessment of all febrile surgical patients. In the absence of significant lung findings, chest radiography is probably of little benefit in patients at low risk for postoperative pulmonary complications. In patients with pulmonary findings or with risk factors for pulmonary complications, chest radiography should be performed. A sputum sample should be obtained for Gram stain and culture. The treatment should include postural drainage,

aggressive pulmonary toilet, and antibiotics. The antibiotic chosen should be effective against gram-positive and gram-negative organisms. In patients who are receiving assisted ventilation, the antibiotic spectrum should include drugs that are active against *Pseudomonas* organisms.

Phlebitis

Historically, intravenous catheter–related infections were common; the reported incidence is 25% to 35% in the 1980s (43). Because the incidence of catheter-related phlebitis increases significantly after 72 hours, intravenous catheters should be changed after 72 to 96 hours with special care to examine the site and dressing daily (44).

The catheter should be removed if there is any associated pain, redness, or induration. Phlebitis can occur even with close surveillance of the intravenous site. In one study, more than 50% of the cases of phlebitis became evident more than 12 hours after discontinuation of intravenous catheters (45). Less than one-third of patients had symptoms related to the intravenous catheter site 24 hours before the diagnosis of phlebitis.

Phlebitis can be diagnosed based on the presence of fever, pain, redness, induration, or a palpable venous cord. Occasionally, suppuration will be present. Phlebitis is usually self-limited and resolves within 3 to 4 days. The treatment includes application of warm, moist compresses and prompt removal of any catheters from the infected vein. Antibiotic therapy with antistaphylococcal agents should be instituted for catheter-related sepsis. Excision or drainage of an infected vein rarely is necessary.

Wound Infections

The results of a prospective study of more than 62,000 wounds were revealing in regard to the epidemiology of wound infections (46). The wound infection rate varied markedly, depending on the extent of contamination of the surgical field. The wound infection rate for clean surgical cases (infection not present in the surgical field, no break in aseptic technique, no viscus entered) was lower than 2%, whereas the incidence of wound infections with dirty, infected cases was 40% or higher. Preoperative showers with *hexachlorophene* slightly lowered the infection rate for clean wounds, whereas preoperative shaving of the wound site with a razor increased the infection rate. The wound infection rate increased with the duration of preoperative hospital stay and with the duration of surgery. Incidental appendectomy increased the risk of wound infection in patients undergoing clean surgical procedures. The study concluded that the **incidence of wound infections could be decreased by short preoperative hospital stays, hexachlorophene showers before surgery, minimizing shaving of the wound site, use of meticulous surgical technique, decreasing operative time as much as possible, bringing drains out through sites other than the wound, and dissemination of information to surgeons regarding their wound**

infection rates. A program instituting these conclusions led to a decrease in the clean wound infection rate from 2.5% to 0.6% over an 8-year period. The wound infection rate in most gynecologic services is lower than 5%, reflective of the clean nature of most gynecologic operations.

The symptoms of wound infection often occur late in the postoperative period, usually after the fourth postoperative day, and may include fever, erythema, tenderness, induration, and purulent drainage. Wound infections that occur on postoperative days 1 through 3 are generally caused by streptococcal and *Clostridia* infections. The management of wound infections is mostly mechanical and involves opening the infected portion of the wound above the fascia, with cleansing and debridement of the wound edges as necessary. Wound care, consisting of debridement and dressing changes two to three times daily, will promote growth of granulation tissue, with gradual filling in of the wound defect by secondary intention. Clean, granulating wounds can often be secondarily closed with good success, shortening the time required for complete wound healing.

Pelvic Cellulitis

Vaginal cuff cellulitis is present in most patients who undergo hysterectomy. It is characterized by erythema, induration, and tenderness at the vaginal cuff. A purulent discharge from the apex of the vagina may be present. The cellulitis is often self-limited and does not require any treatment. Fever, leukocytosis, and pain localized to the pelvis may accompany severe cuff cellulitis and most often signifies extension of the cellulitis to adjacent pelvic tissues. In such cases, broad-spectrum antibiotic therapy should be instituted with coverage for gram-negative, gram-positive, and anaerobic organisms. If purulence at the vaginal cuff is excessive or if there is a fluctuant mass noted at the vaginal cuff, the vaginal cuff should be gently probed and opened with a blunt instrument. The cuff can be left open for dependent drainage or, alternatively, a drain can be placed into the lower pelvis through the cuff and removed when drainage, fever, and symptoms in the lower pelvic region have resolved.

Intra-Abdominal and Pelvic Abscess

The development of an abscess in the surgical field or elsewhere in the abdominal cavity is an uncommon complication after a gynecologic surgery. It is likely to occur in contaminated cases in which the surgical site is not adequately drained or as a secondary complication of hematomas. **The causative pathogens in patients who have intra-abdominal abscesses are usually polymicrobial in nature.** The aerobes most commonly identified include *E. coli, Klebsiella, Streptococcus, Proteus,* and *Enterobacter.* Anaerobic isolates are common, usually from the *Bacteroides* group. These pathogens arise mainly from the vaginal tract but can be derived from the gastrointestinal tract, particularly when the colon was entered at the time of surgery.

Intra-abdominal abscess may be difficult to diagnose. The evolving clinical picture is often one of persistent febrile episodes with a rising white blood cell count. Findings on abdominal examination may be equivocal. If an abscess is located deep in the pelvis, it may be palpable by pelvic or rectal examination. **CT scanning is more sensitive and specific than ultrasonography for diagnosing intra-abdominal abscesses and often is the radiologic procedure of choice.**

Standard therapy for intra-abdominal abscess is evacuation and drainage combined with appropriate administration of antibiotics. Abscesses located low in the pelvis, particularly in the area of the vaginal cuff, can be reached through a vaginal approach. In many patients, the ability to drain an abscess by placement of a drain percutaneously under CT guidance obviated the need for surgical exploration. With CT guidance, a pigtail catheter is placed into an abscess cavity via transabdominal, transperineal, transrectal, or transvaginal approaches. The catheter is left in place until drainage output decreases. Transperineal and transrectal drainage of deep pelvic abscesses are successful in 90% to 93% of patients, obviating the need for surgical management (47,48). **For those patients in whom radiologic drainage is not successful, surgical exploration and evacuation are indicated.** The standard approach to initial antibiotic therapy is to employ broad-spectrum parenteral antibiotic therapy with both aerobic and anaerobic coverage (49). There are several acceptable regimens including piperacillin–tazobactam, or clindamycin with ceftriaxone, or metronidazole with ceftriaxone, or ertapenem, or ticarcillin–clavulanate, or aztreonam with clindamycin (for those who have a penicillin allergy) (49). Parenteral antibiotics can be transitioned to oral therapy when clinical improvement is noted (WBC improving, afebrile for 48 hours, and abscess is shrinking). Oral antibiotics should be tailored to culture results.

Necrotizing Fasciitis

Necrotizing fasciitis is an uncommon infectious disorder, affecting roughly 1,000 patients per year (50). This disease process is characterized by a rapidly progressive bacterial infection that involves the subcutaneous tissues and fascia while characteristically sparing underlying muscle. Systemic toxicity is a frequent feature of this disease, as manifested by the presence of dehydration, septic shock, disseminated intravascular coagulation, and multiple organ system failure.

There are two forms of necrotizing fasciitis, type I and type II. Type I infections are caused by mixed aerobic and anaerobic bacteria and occur in patients with risk factors such as recent surgery, diabetes, or immune compromise. Type II infections are a result of β-hemolytic streptococci and can occur in healthy patients who have a predisposing injury, such as a skin laceration (51). Bacterial enzymes such as hyaluronidase and lipase released in the subcutaneous space destroy the fascia and adipose tissue and induce a liquefactive necrosis. Noninflammatory intravascular coagulation or

thrombosis subsequently occurs. Intravascular coagulation results in ischemia and necrosis of the subcutaneous tissues and skin. Subcutaneous spread of up to 1 inch per hour can be seen, often with little effect on the overlying skin (52). Late in the course of the infection, destruction of the superficial nerves produces anesthesia in the involved skin. The release of bacteria and bacterial toxins into the systemic circulation can cause septic shock, acid–base disturbances, and multiple organ impairment.

The diagnosis is often difficult to make early in the disease course. **Most patients with necrotizing fasciitis develop erythema, edema, and pain, which in the early stages of the disease are disproportionately greater than that expected from the degree of cellulitis present and characteristically extend beyond the border of erythema** (51). Late in the course of the infection, the involved skin may be anesthetized secondary to necrosis of superficial nerves. Temperature abnormalities, both hyperthermia and hypothermia, are concomitant with the release of bacterial toxins and with bacterial sepsis (52). The involved skin is initially tender, erythematous, and warm. Edema develops, and the erythema spreads diffusely, fading into normal skin, characteristically without distinct margins or induration. Subcutaneous microvascular thrombosis induces ischemia in the skin, which becomes cyanotic and blistered. As necrosis develops, the skin becomes gangrenous and may slough spontaneously (52). Most patients will have leukocytosis and acid–base abnormalities. Subcutaneous gas may develop, which can be identified by palpation and radiography. The finding of subcutaneous gas by radiography is often indicative of clostridial infection, although it is not a specific finding and may be caused by other organisms. These organisms include *Enterobacter, Pseudomonas,* anaerobic streptococci, and *Bacteroides,* which, unlike clostridial infections, spare the muscles underlying the affected area.

Successful management of necrotizing fasciitis involves early recognition, immediate initiation of resuscitative measures (including correction of fluid, acid–base, electrolyte, and hematologic abnormalities), aggressive surgical debridement and redebridement as necessary, and broad-spectrum intravenous antibiotic therapy (52). During surgery, the incision should be made through the infected tissue down to the fascia. An ability to undermine the skin and subcutaneous tissues with digital palpation often will confirm the diagnosis. Excision of infected, necrotic tissue should extend toward the periphery of the affected tissue until well-vascularized, healthy, resistant tissue is reached at all margins. The remaining affected tissue must be excised. The wound can be packed and sequentially debrided as necessary until healthy tissue is displayed at all margins. **Hyperbaric oxygen therapy may be of some benefit, particularly in patients for whom culture results are positive for anaerobic organisms** (53). Retrospective nonrandomized studies demonstrated that the addition of hyperbaric oxygen therapy to surgical debridement and antimicrobial therapy appear to significantly decrease wound morbidity and overall mortality in patients with

necrotizing fasciitis (53). After the initial resuscitative efforts and surgical debridement, the primary concern is the management of the open wound. Allograft and xenograft skin can be used to cover open wounds, thus decreasing heat and evaporative water loss.

Significant improvement in wound healing may be aided by a vacuum-assisted closure (VAC) method that uses a subatmospheric pressure technique (54). In situations in which spontaneous closure is not likely, the VAC device may permit the development of a suitable granulation bed and prepare the tissue for graft placement, thereby increasing the probability of graft survival. Skin flaps can be mobilized to help cover open wounds when the infection resolves and granulation begins.

Postoperative Gastrointestinal Complications

Ileus

Following open abdominal or pelvic surgery, most patients experience some degree of intestinal ileus. The exact mechanism by which this arrest and disorganization of gastrointestinal motility occurs is unknown, but it appears to be associated with the opening of the peritoneal cavity and is aggravated by manipulation of the intestinal tract, intestinal resection, and prolonged surgical procedures. Infection, peritonitis, opioids, and electrolyte disturbances may result in ileus. For most patients undergoing common gynecologic operations, the degree of ileus is minimal, and gastrointestinal function returns relatively rapidly, allowing the resumption of oral intake within 12 hours of surgery. Ileus is reported in 3% of patients undergoing total abdominal hysterectomy (55). Patients who have intolerance for oral intake, persistently diminished bowel sounds, abdominal distension, absence of flatus, nausea, or vomiting require further evaluation. **Patients with symptoms of ileus or small bowel obstruction who underwent minimally invasive surgery are a different matter. Minimally invasive surgery should result in a daily improvement in GI function. An "ileus" in the case of minimally invasive surgery more likely represents GI injury, which should be evaluated immediately with a CT scan using GI contrast.**

Ileus is usually manifested by abdominal distension with nausea and/or vomiting and should be evaluated by physical examination. Pertinent points of the abdominal examination include assessment of the quality of bowel sounds and palpation in search of distension, tympany, masses, diffuse tenderness, or rebound. The possibility that the patient's signs and symptoms may be associated with a more serious intestinal obstruction or intestinal complication (such as a perforation) must be considered. Pelvic examination should be performed to evaluate the possibility of a pelvic abscess or hematoma that may contribute to the ileus. **Abdominal radiography to evaluate the abdomen in the flat (supine) position and in the upright position will aid in the diagnosis of an ileus. The most common radiographic findings include dilated loops**

of small and large bowel and air–fluid levels while the patient is in the upright position. Air should be present in the colon or rectum. In the postoperative gynecology patient, especially in the upright position, the abdominal x-ray may show free air. This common finding following surgery lasts 7 to 10 days in some instances and is not necessarily indicative of a perforated viscus in most patients.

The initial management of a postoperative ileus is aimed at gastrointestinal tract decompression and maintenance of appropriate intravenous replacement fluids and electrolytes.

1. **The patient should be made NPO status (nothing by mouth) with intravenous (IV) fluids and electrolytes.** If nausea and vomiting persist, **a nasogastric tube should be used to evacuate the stomach of its fluid and gaseous contents.** Continued nasogastric suction removes swallowed air, which is the most common source of gas in the small bowel.
2. **Laboratory evaluation should include** CBC, serum electrolytes, creatinine and blood urea nitrogen (BUN), and liver functions.
3. **Fluid and electrolyte replacement must be adequate to keep the patient well hydrated and in metabolic balance.** Significant amounts of third-space fluid loss occur in the bowel wall, the bowel lumen, and the peritoneal cavity during the acute episode. Gastrointestinal fluid losses from the stomach may lead to metabolic alkalosis and depletion of other electrolytes. Careful monitoring of serum chemistry levels and appropriate replacement are necessary.
4. **Most cases of severe ileus begin to improve over a period of several days.** This improvement is recognizable by a reduction in the abdominal distension, return of normal bowel sounds, and passage of flatus or stool. Repeat abdominal radiographs should be obtained as necessary for further monitoring.
5. **When the gastrointestinal tract function appears to have returned to normal, the nasogastric tube may be removed and a liquid diet instituted.**

If a patient shows no evidence of improvement during the first 48 to 72 hours of medical management, other causes of ileus should be sought. Such cases may include ureteral injury, peritonitis from pelvic infection, unrecognized gastrointestinal tract injury with peritoneal spill, or fluid and electrolyte abnormalities such as hypokalemia. With persistent ileus, the use of water-soluble upper gastrointestinal contrast studies (CT scan with oral contrast) may assist in distinguishing an ileus from a small bowel obstruction. In the latter case, a “transition point” is usually identified.

Small Bowel Obstruction

Obstruction of the small bowel following major, open gynecologic surgery occurs in approximately 1% to 2% of patients (56,57). **The most common cause of small**

bowel obstruction is adhesions to the operative site. If the small bowel becomes adherent in a twisted position, partial or complete obstruction may result. Less common causes of postoperative small bowel obstruction include entrapment of the small bowel into an incisional hernia or an unrecognized defect in the small bowel or large bowel mesentery (internal hernia). [7] **Early in its clinical course, a postoperative small bowel obstruction may exhibit signs and symptoms similar to those of ileus. Initial conservative management as outlined for the treatment of ileus is appropriate.** Because of the potential for mesenteric vascular occlusion and resulting ischemia or perforation, worsening symptoms of abdominal pain, progressive distension, fever, leukocytosis, or acidosis should be evaluated carefully because immediate surgery may be required.

In most cases of small bowel obstructions following gynecologic surgery, the obstruction is only partial and the symptoms usually resolve with conservative management.

1. **Further evaluation after several days of conservative management may be necessary.** Evaluation of the small intestines with an upper gastrointestinal study, or a CT scan with small bowel assessment is appropriate. In most cases, complete obstruction is not documented, although a narrowing ("transition point") or tethering of the segment of small bowel may indicate the site of the problem.
2. **Laboratory evaluation should include** CBC, serum electrolytes, and serum lactate.
3. **Further conservative management with nasogastric decompression and intravenous fluid and electrolyte replacement may allow time for bowel wall edema or torsion of the mesentery to resolve.**
4. **Serial and radiographic examinations should be performed to exclude possible bowel ischemia or perforation.**
5. **If resolution is prolonged and the patient's nutritional status is marginal, the use of TPN may be necessary.**
6. **Conservative medical management of postoperative small bowel obstruction usually results in complete resolution.** If persistent evidence of small bowel obstruction remains after full evaluation and an adequate trial of medical management, exploratory laparotomy may be necessary to manage the obstruction. Risk factors for operative management include persistent abdominal pain, distension, fever at 48 hours, and CT findings of high-grade obstruction (58). In most cases, lysis of adhesions is all that is required, although a segment of small bowel that is badly damaged or extensively sclerosed from adhesions may require resection and reanastomosis.

Colonic Obstruction

Postoperative colonic obstruction following surgery for most gynecologic conditions is exceedingly rare. It is usually associated with a pelvic malignancy, which in most cases was known at the time of the initial operation. Advanced ovarian carcinoma is the most common cause of colonic obstruction in postoperative gynecologic surgery patients, and it is caused by extrinsic impingement on the colon by the pelvic malignancy. Intrinsic colonic lesions may be undetected, especially in a patient with some other benign gynecologic condition. When colonic obstruction is manifested by abdominal distension and abdominal radiography reveals a dilated colon and enlarging cecum, further evaluation of the large bowel is required by water-soluble enema or colonoscopy. **Dilation of the cecum to more than 10 to 12 cm in diameter as viewed by abdominal radiography requires immediate evaluation and surgical decompression by performing colectomy or colostomy.** Surgery should be performed as soon as the obstruction is documented. Conservative management of colonic obstruction is not appropriate because the complication of colonic perforation has an exceedingly high mortality rate. In patients who are too ill to undergo surgery, the interventional radiologist may be able to place a cecostomy tube or the gastroenterologist may place a colonic stent (59).

Diarrhea

Episodes of diarrhea often occur following abdominal and pelvic surgery as the gastrointestinal tract returns to its normal function and motility. Prolonged and multiple episodes may represent a pathologic process such as impending small bowel obstruction, colonic obstruction, or pseudomembranous colitis. Excessive amounts of diarrhea should be evaluated by abdominal radiography and stool samples tested for the presence of ova and parasites, bacterial culture, and *C. difficile* toxin. Proctoscopy and colonoscopy may be advisable in severe cases. Evidence of intestinal obstruction should be managed as outlined. Infectious causes of diarrhea should be managed with the appropriate antibiotics and fluid and electrolyte replacement. *C. difficile*–associated pseudomembranous colitis may result from exposure to any antibiotic. Discontinuation of these antibiotics (unless they are needed to treat another severe infection) is advisable, along with the institution of appropriate therapy. Oral *vancomycin* is the preferred initial treatment for severe *C. difficile* colitis (oral *metronidazole* is an alternative treatment for moderate cases) (60).

Therapy should be continued until the diarrhea abates, and several weeks of oral therapy may be required to obtain complete resolution of the pseudomembranous colitis.

Fistula

Gastrointestinal fistulas are rare complications of gynecologic surgery. They are most often associated with malignancy, prior radiation therapy, intestinal resection with anastomosis, or surgical injury to the large or small bowel that was improperly repaired

or unrecognized. Signs and symptoms of gastrointestinal fistula are often similar to those of small bowel obstruction or ileus, except that fever is usually a more prominent component of the patient's symptoms. When fever is associated with gastrointestinal dysfunction postoperatively, evaluation should include early assessment of the gastrointestinal tract to confirm its continuity. **When fistula is suspected, the use of water-soluble gastrointestinal contrast material is advised to avoid the complication of barium peritonitis.** Evaluation with abdominal pelvic CT scan may assist in identification of a fistula and associated abscess. **Recognition of an intraperitoneal gastrointestinal leak or fistula formation usually requires immediate surgery, unless the fistula has drained spontaneously through the abdominal wall or vaginal cuff.**

An *enterocutaneous fistula* arising from the small bowel and draining spontaneously through the abdominal incision (with no evidence of intraperitoneal infection) may be managed successfully with medical therapy. Therapy should include nasogastric decompression, replacement of intravenous fluids, TPN, and appropriate antibiotics to treat an associated mixed bacterial infection. If the infection is under control and there are no other signs of peritonitis, the surgeon may consider allowing potential resolution of the fistula over a period of up to 2 weeks. Some authors suggested the use of *somatostatin* to decrease intestinal tract secretion and allow earlier healing of the fistula. In some cases, the fistula will close spontaneously with this mode of management. If the enterocutaneous fistula does not close with conservative medical management, surgical correction with resection, bypass, or reanastomosis will be necessary.

A *rectovaginal fistula* that occurs following gynecologic surgery is usually the result of surgical trauma that may have been predisposed by the presence of extensive adhesions and scarring in the rectovaginal septum associated with endometriosis, pelvic inflammatory disease, or pelvic malignancy. **A small rectovaginal fistula may be managed with a conservative medical approach, in the hope that decreasing the fecal stream will allow closure of the fistula.** A small fistula that allows continence except for an occasional leak of flatus may be managed conservatively until the inflammatory process in the pelvis resolves. At that point, usually several months later, correction of the fistula is appropriate. Large rectovaginal fistulas for which there is no hope of spontaneous closure are best managed by performing a diverting colostomy followed by repair of the fistula after inflammation resolves. After the fistula closure is healed and deemed successful, the colostomy may be reversed.

Thromboembolism

Risk Factors

[8] DVT and pulmonary embolism are largely preventable, yet significant, complications in postoperative patients. The magnitude of this problem is relevant to the gynecologist, because **40% of all deaths following gynecologic surgery are directly attributed to pulmonary emboli,** and it is the most frequent cause of postoperative death in patients with uterine or cervical carcinoma (61,62).

The causal factors of venous thrombosis were first proposed by Virchow in 1858 and include a hypercoagulable state, venous stasis, and vessel endothelial injury. Risk factors include major surgery; advanced age; nonwhite race; malignancy; history of DVT, lower extremity edema, or venous stasis changes; presence of varicose veins; being overweight; a history of radiation therapy; and hypercoagulable states, such as factor V Leiden, pregnancy, and use of oral contraceptives, estrogens, or *tamoxifen.* Intraoperative factors associated with postoperative DVT include increased anesthesia time, increased blood loss, and the need for transfusion in the operating room. It is important to recognize these risk factors and to provide the appropriate level of venous thrombosis prophylaxis (63–66). Caprini has created a scoring system that attributes different "points" for each risk factor that when totaled define a level of risk (67). The American College of Chest Physicians (ACCP) has embraced the Caprini Risk Score to define the recommended intensity of prophylaxis for an individual patient (68). The levels of thromboembolism risk are listed in Table 25-7.

Prophylactic Methods

A number of prophylactic methods significantly reduced the incidence of DVT, and a few studies included a large enough patient population to show a reduction in fatal pulmonary emboli (69). The ideal prophylactic method would be effective, free of significant side effects, well accepted by the patient and nursing staff, widely applicable to most patients, and inexpensive.

Low-Dose Heparin

The use of small doses of subcutaneously administered *heparin* for the prevention of DVT and pulmonary embolism is the most widely studied of all prophylactic methods. **More than 25 controlled trials demonstrated that *heparin* given subcutaneously 2 hours preoperatively and every 8 to 12 hours postoperatively is effective in reducing the incidence of DVT. The value of low-dose *heparin* in preventing fatal pulmonary emboli was established by a randomized, controlled multicenter international trial, which demonstrated a significant reduction in fatal postoperative pulmonary emboli in general surgery patients receiving low-dose *heparin* every 8 hours postoperatively** (69). Trials of low-dose *heparin* in gynecologic surgery patients showed a significant reduction in postoperative DVT.

Although low-dose *heparin* is considered to have no measurable effect on coagulation, most large series noted an increase in the bleeding complication rate,

especially a higher incidence of wound hematoma (70). Although relatively rare, thrombocytopenia is associated with low-dose *heparin* use and was found in 6% of patients after gynecologic surgery (70). If patients remain on low-dose *heparin* for more than 4 days, it is reasonable to check their platelet count to assess the possibility of *heparin*-induced thrombocytopenia.

Low–Molecular-Weight Heparin

Low–molecular-weight heparins (LMWH) are fragments of *heparin* that vary in size from 4,500 to 6,500 Da. When compared with unfractionated *heparin, LMWH* have more anti-Xa and less antithrombin activity, leading to less effect on partial thromboplastin time and possibly leading to fewer bleeding complications (71). An increased half-life of 4 hours results in increased bioavailability when compared with unfractionated *heparin.* The increase in half-life of *LMWH* allows the convenience of once-a-day dosing.

Table 25-7 Thromboembolism Risk Stratification (Caprini Risk Score)

1 Point
Age 41–60 yrs Minor surgery BMI >25 kg/m^2 Swollen legs Varicose veins Pregnancy or postpartum state History of unexplained or recurrent abortions (>3) Oral contraceptive use or hormone replacement Sepsis (<1 mo) Serious lung disease, including pneumonia (<1 mo) Abnormal pulmonary function Congestive heart failure History of inflammatory bowel disease Medical patient at bed rest
2 Points
Age 61–74 yrs Major open surgery (>45 min) Laparoscopic surgery (>45 min) Malignancy Confined to bed (>72 hrs) Immobilizing cast Central venous access
3 Points
Age >74 yrs History of VTE Family history of VTE Congenital or acquired thrombophilias (i.e., Factor V Leiden, anticardiolipin antibodies, elevated serum

homocysteine, prothrombin 20210A) Heparin-induced thrombocytopenia
5 Points
Stroke (<1 mo) Elective arthroplasty Hip, pelvis, or leg fracture Acute spinal cord injury (<1 mo)

Randomized controlled trials have compared *LMWH* with *unfractionated heparin* in patients undergoing gynecologic surgery. In all studies, there was a similar incidence of DVT. Bleeding complications were similar between the *unfractionated heparin* and *LMWH* groups (72). **A meta-analysis of general surgery and gynecologic surgery patients from 32 trials indicated that daily *LMWH* administration is as effective as *unfractionated heparin* in DVT prophylaxis without any difference in hemorrhagic complications** (73).

Mechanical Methods

Stasis in the veins of the legs occurs while the patient is undergoing surgery and continues postoperatively for varying lengths of time. Stasis occurring in the capacitance veins of the calf during surgery, plus the hypercoagulable state induced by surgery, are the prime factors contributing to the development of acute postoperative DVT. Prospective studies of the natural history of postoperative DVT showed that the calf veins are the predominant site of thrombi and that most thrombi develop within 24 hours of surgery (74).

Although probably of only modest benefit, reduction of stasis by short preoperative hospital stays and early postoperative ambulation should be encouraged for all patients. Elevation of the foot of the bed, raising the calf above heart level, allows gravity to drain the calf veins and should further reduce stasis.

Graduated Compression Stockings

Controlled studies of graduated compression stockings are limited but do suggest modest benefit when they are carefully fitted (75,76). Poorly fitted stockings may be hazardous to some patients who develop a tourniquet effect at the knee or mid-thigh (62). Variations in human anatomy do not allow perfect fit of all patients to available stocking sizes. The simplicity of graduated compression stockings and the absence of significant side effects are probably the two most important reasons that they are often included in routine postoperative care. Compared to thigh length stockings, calf-high stockings appear to offer the same degree of venous thromboembolism protection (77).

Intermittent Pneumatic Compression

The largest body of literature dealing with the reduction of postoperative venous stasis deals with intermittent compression of the leg by pneumatically inflated sleeves placed

around the calf or leg during intra- and postoperative periods. [8] Various pneumatic compression devices and leg sleeve designs are available, and the literature has not demonstrated superiority of one system over another. **Calf compression, during and after gynecologic surgery, significantly reduces the incidence of DVT on a level similar to that of low-dose *heparin*.** In addition to increasing venous flow and pulsatile emptying of the calf veins, intermittent pneumatic compression (IPC) appears to augment endogenous fibrinolysis, which may result in lysis of very early thrombi before they become clinically significant (78).

The duration of postoperative external pneumatic compression differed in various trials. External pneumatic compression may be effective when used in the operating room and for the first 24 hours postoperatively in patients at moderate risk who will ambulate on the first postoperative day (78,79).

External pneumatic compression used in patients undergoing major surgery for gynecologic malignancy reduced the incidence of postoperative venous thromboembolic complications by nearly threefold, but only if calf compression was applied intraoperatively and for the first 5 postoperative days (80,81). Patients with gynecologic malignancies may remain at risk for a longer period than general surgical patients because of stasis and hypercoagulable states; therefore, these patients appear to benefit from longer use of IPC.

Table 25-8 VTE Prophylactic Regimens Based on an Individual's Caprini Risk Score

Score
0: Early ambulation.
1–2: Low risk: Graded compression stockings and/or intermittent pneumatic compression.
3–4: Moderate risk: Intermittent pneumatic compression or low-dose heparin or low–molecular-weight heparin.
>4: High risk: Intermittent pneumatic compression and low-dose heparin or low–molecular-weight heparin. Consider prolonged prophylaxis for 28 days.

Intermittent pneumatic leg compression has no significant side effects or risks and is considered slightly more cost-effective when compared with pharmacologic methods of prophylaxis (82). Compliance in wearing the leg compression while in bed is of utmost importance, and the patient and nursing staff should be educated to the proper regimen for maximum benefit (83).

[8] Using the Caprini Risk Score, the ACCP guidelines recommend different prophylactic regimens based on an individual patient's risk score (**Table 25-8**).

Continued prophylaxis for 28 days with low–molecular-weight heparin has been shown to significantly reduce the incidence of VTE at 30 and 90 days postoperatively in

patients undergoing "open" abdominal procedures for malignancy (84). There have been no trials specific to gynecologic surgery that have evaluated prolonged prophylaxis, although this strategy seems reasonable, especially for gynecologic cancer patients undergoing "open" procedures.

Guidelines do not distinguish the risks of minimally invasive gynecologic surgery (MIGS) from "open surgery." Some have argued that MIGSs are much lower-risk surgical procedures and no prophylaxis is necessary (85). Others have shown that despite the use of IPC, there remains approximately 2% incidence of VTE in patients undergoing more complex gynecologic surgery (86).

Management of Postoperative Deep Venous Thrombosis and Pulmonary Embolism

Because pulmonary embolism is the leading cause of death following gynecologic surgical procedures, identification of high-risk patients and the use of prophylactic venous thromboembolism regimens are essential parts of management (61,62,87).

The early recognition of DVT and pulmonary embolism and immediate treatment are critical. Most pulmonary emboli arise from the deep venous system of the leg following gynecologic surgery; the pelvic veins are also a known source of fatal pulmonary emboli.

The signs and symptoms of DVT of the lower extremities include pain, edema, erythema, and prominent vascular pattern of the superficial veins. These signs and symptoms are relatively nonspecific; 50% to 80% of patients with these symptoms will not have DVT (88). Conversely, approximately 80% of patients with symptomatic pulmonary emboli have no signs or symptoms of thrombosis in the lower extremities (89). Because of the lack of specificity when signs and symptoms are recognized, additional tests should be performed to establish the diagnosis of DVT.

Diagnosis

Doppler Ultrasound

B-mode duplex Doppler imaging is the most common technique for the diagnosis of symptomatic venous thrombosis, especially when it arises in the proximal lower extremity. With duplex Doppler imaging, the femoral vein can be visualized and clots may be seen directly (90). Compression of the vein with the ultrasound probe tip allows assessment of venous collapsibility; the presence of a thrombus diminishes vein wall collapsibility. Doppler imaging is less accurate when evaluating the calf and the pelvic veins.

Venography

Although venography is considered the "gold standard" technique for diagnosis of DVT, other diagnostic studies are accurate when performed by a skilled technologist and, in nearly all patients, may replace the need for contrast venography. Venography is moderately uncomfortable, requires the intravenous injection of a contrast material that

may cause allergic reaction or renal injury, and may result in phelebitis in approximately 1% of patients (91). If the results of noninvasive imaging are normal or inconclusive and the clinician remains concerned given clinical symptoms, venography should be performed to obtain a definitive answer.

Magnetic Resonance Venography

In addition to having a sensitivity and specificity comparable to venography, magnetic resonance venography (MRV) may detect thrombi in pelvic veins that are not imaged by venography (92). The primary drawback to MRV is the time involved in examining the lower extremity and pelvis and the expense of this technology.

Treatment

Deep Venous Thrombosis

The treatment of postoperative DVT requires the immediate institution of anticoagulant therapy. Treatment may be with either *unfractionated heparin* or *LMWH*, followed by 3 to 6 months of oral anticoagulant therapy with *warfarin (Coumadin). The new oral antithrombins and factor Xa inhibitors are options for secondary prophylaxis.*

Unfractionated Heparin

After venous thromboembolism is diagnosed, *unfractionated heparin* (or low–molecular-weight heparins, see below) should be initiated to prevent proximal propagation of the thrombus and allow physiologic thrombolytic pathways to dissolve the clot. An initial bolus of 80 U/kg is given intravenously, followed by a continuous infusion of 1,000 to 2,000 U/hr (18 U/kg/hr). ***Heparin* dosage is adjusted to maintain APTT levels at a therapeutic level 1.5 to 2.5 times the control value.** Initial APTT should be measured after 6 hours of *heparin* administration and the dose adjusted as necessary. Patients having subtherapeutic APTT levels in the first 24 hours have a 15-fold increased risk of recurrent VTE when compared to patients who are adequately anticoagulated. Patients should be managed aggressively using intravenous *heparin* to achieve prompt anticoagulation. A weight-based nomogram is helpful in achieving a therapeutic APTT level (93).

Low–Molecular-Weight Heparin

Two *LMWH* preparations (*enoxaparin* and *dalteparin*) were effective in the treatment of venous thromboembolism and have a cost-effective advantage over intravenous *heparin* in that they may be administered in the outpatient setting. The dosages used in treatment of thromboembolism are unique and weight adjusted according to each *LMWH* preparation. Because *LMWH* has a minimal effect on APTT, serial laboratory monitoring of these levels is not necessary. Similarly, monitoring of anti-Xa activity (except in difficult cases or those with renal impairment) is not of

significant benefit in a dose adjustment of *LMWH.* The increased bioavailability associated with *LMWH* allows for twice-a-day dosing, potentially making outpatient management an option for a subset of patients. **A meta-analysis involving more than 4,000 patients from 22 trials suggests that *LMWH* is more effective, safer, and less costly when compared with *unfractionated heparin* in preventing recurrent thromboembolism** (94).

Following initial treatment with either unfractionated heparin (UFH) or LMWH, continued secondary prophylaxis/treatment is usually achieved by an oral agent. In patients with active cancer, continued treatment with LMWH has been found to be superior (95).

Oral anticoagulant (*warfarin*) administration may be started on the first day of *heparin* infusion. The international normalized ration (INR) should be monitored daily until a therapeutic level is achieved (2 to 3 times normal value). The change in the INR resulting from *warfarin* administration often precedes the anticoagulant effect by approximately 2 days, during which time low-protein C levels are associated with a transient hypercoagulable state. Therefore, *heparin* should be administered until the INR is maintained in a therapeutic range for at least 2 days, confirming proper *warfarin* dose. Intravenous *heparin* may be discontinued in 5 days if an adequate INR level is established.

Oral inhibitors of thrombin or factor Xa may be used in place of warfarin (96). Advantages of these agents include faster uptake and there is no need for ongoing monitoring. Disadvantages include the fact that there is no agent to "reverse" the anticoagulant effect (in the case of urgent surgery or bleeding), cost, and the inconvenience of twice-a-day dosing (patient compliance). Safety and efficacy in pregnancy have not been established. Therapeutic dosing of these different agents is shown in Table 25-9.

Pulmonary Embolism

Many of the signs and symptoms of pulmonary embolism are associated with other, more commonly occurring pulmonary complications following surgery. **The classic findings of pleuritic chest pain, hemoptysis, shortness of breath, tachycardia, and tachypnea should alert the physician to the possibility of a pulmonary embolism.** Many times the signs are subtle and may be demonstrated only by a persistent tachycardia or a slight elevation in the respiratory rate. Patients suspected of pulmonary embolism should be evaluated initially by chest x-ray, electrocardiography (ECG), and arterial blood gas assessment. Any evidence of abnormality should be further evaluated by a spiral CT scan of the chest or a ventilation–perfusion lung scan. A high percentage of lung scans may be interpreted as "indeterminate." In this setting, careful clinical evaluation and judgment are required to decide whether pulmonary arteriography should be performed to document or exclude the presence of a pulmonary embolism.

Table 25-9 Therapeutic Dosing of Non–Vitamin K Antagonist Oral Anticoagulants

Dosing—Typical initial doses in those with normal renal function are:
• *Rivaroxaban,* 15 mg twice daily (for the first 3 weeks)
• *Apixaban,* 10 mg twice daily (for first 7 days)
• *Edoxaban,* 60 mg once daily (and 30 mg once daily in patients with a creatinine 30–50 mL/min or a body weight below 60 kg)
• *Dabigatran,* 150 mg twice daily

The treatment of pulmonary embolism is as follows:

1. Immediate anticoagulant therapy, identical to that outlined for the treatment of DVT, should be initiated.
2. Respiratory support, including oxygen and bronchodilators, and an intensive care setting, if necessary.
3. Although massive pulmonary emboli are usually quickly fatal, rarely pulmonary embolectomy is successful.
4. Pulmonary artery catheterization (PAC) with the administration of thrombolytic agents bears further evaluation and may be important in patients with massive pulmonary embolism.
5. Vena cava interruption (filter) may be necessary in situations in which anticoagulant therapy is ineffective in the prevention of rethrombosis and repeated embolization from the lower extremities or pelvis. A vena cava filter may be inserted percutaneously above the level of the thrombus and caudad to the renal veins. In most cases, anticoagulant therapy is sufficient to prevent repeat thrombosis and embolism and to allow the patient's own endogenous thrombolytic mechanisms to lyse the pulmonary embolus.

ENHANCED RECOVERY AFTER SURGERY (ERAS)

Rationale for ERAS

As surgical technology has been evolving, so have concepts for perioperative care. Traditional perioperative management has included nothing by mouth (nil per os, NPO) after midnight, liberal intraoperative fluids, and dependence on opioid pain medications for postoperative pain. However, in the 1990s, European physicians began to better understand the association between perioperative physiologic stress and postoperative morbidity (97). Stress increases immunosuppression, hypoxia, insulin resistance, and catabolism (98). An optimal perioperative management strategy would target each of these factors to minimize morbidity, and in the early 2000s, the initial enhanced

recovery protocol was crafted (99). ERAS was first embraced by colorectal physicians but has been spreading throughout disciplines (100).

[6] Enhanced recovery protocols are comprehensive and address elements from the patient's initial arrival in the office with her chief complaint until she leaves the hospital following surgery. Preoperatively, its components include preoperative counseling, carbohydrate loading, the use of liberal antiemetics (including preoperative steroids), and avoidance of prolonged fasting. Intraoperatively, there is a focus on normothermia, balanced fluids, avoidance of drains, a minimally invasive approach, multimodal pain medications, including regional anesthesia when able. Following surgery, the aims include early mobilization and feeding, prompt discontinuation of intravenous fluids, multimodal pain medications, timely discontinuation of urinary catheters, and regional anesthesia (99–101). Some important components of an ERAS protocol will be highlighted below.

Perioperative Diet

With respect to perioperative nutrition, there are important considerations for an ERAS protocol. There is no evidence regarding prolonged preoperative fasting and aspiration risk (102), and fasting is known to increase insulin resistance which increases perioperative morbidity. Given the paucity of data regarding "NPO after midnight," eating ad lib until 6 hours preoperatively followed by consumption of clear liquids until 2 hours preoperatively is recommended by the American Society of Anesthesiology (103). Another unique feature of an ERAS protocol is preoperative carbohydrate loading. Drinks containing 12.5% maltodextrin given 2 to 3 hours preoperatively have been shown to improve insulin resistance and decrease hospital stay (104,105). Practically, the recommendation is for the patient to ingest a 12-oz Gatorade 2 to 3 hours preoperatively. Postoperatively the aim is early feeding, including for patients who have undergone colorectal surgery, as there has not been an association in increased anastomotic leak (106). With respect to postoperative fluids, the goal is to discontinue as soon as possible or at the latest, on postoperative day 1.

Bowel Preparation

While some surgeons may recommend a bowel preparation preoperatively, there has not been definitive evidence of benefit but there are areas of concern with their use (107). Bowel preparations are implicated in patient dissatisfaction, electrolyte disturbances, and dehydration. Therefore, ERAS protocols recommend avoidance of bowel preparation.

Management of Nausea and Vomiting

Postoperative nausea and vomiting are unfortunately common in patients. A multimodal, prophylactic approach utilizing medications in at least two antiemetic classes has been employed. Available agents include NK-1 antagonists, corticosteroids, 5-HT_3 antagonists, butyrophenones, antihistamines, phenothiazines, and anticholinergics (108). If nausea is present postoperatively, an antiemetic of a different class should be used. A scopolamine patch can be considered as it has been shown to improve postoperative nausea and vomiting (109).

Perioperative Fluids

General Principles

Fluid and Electrolyte Maintenance Requirements

The body adjusts to higher and lower volumes of intake by changes in plasma tonicity. Alterations in plasma tonicity induce adjustments in circulating antidiuretic hormone (ADH) levels, which ultimately regulate the amount of water retained in the distal tubule of the kidney. In the preoperative and the early postoperative periods, it is usually necessary to replace only sodium and potassium. Chloride is automatically replaced, concomitant with sodium and potassium, because chloride is the usual anion used to balance sodium and potassium in electrolyte solutions. There are various commercially available solutions containing 40 mmol of sodium chloride, with smaller amounts of potassium, calcium, and magnesium, designed to meet the requirements of a patient who is receiving 3 L of intravenous fluids per day. **The daily requirement can be met by any combination of intravenous fluids. For example, 2 L of D5 (5% dextrose)/0.45 normal saline (7 mEq sodium chloride each), supplemented with 20 mEq of potassium chloride, followed by 1 L of D5W (5% dextrose in water) with 20 mEq of potassium chloride, would suffice.**

Fluid and Electrolyte Replacement

Fluid and electrolyte losses beyond the daily average must be replaced by appropriate solutions. The choice of solutions for replacement depends on the composition of the fluids lost. Often, it is difficult to measure free water loss, particularly in patients who have high losses from the lungs, skin, or the gastrointestinal tract. Weighing these patients daily can be very useful. Up to 300 g of weight loss daily can be attributable to weight loss from catabolism of protein and fat in the patient who is taking nothing by mouth (110). Any loss beyond this level represents fluid loss, which should be replaced accordingly.

Patients with a high fever can have increased pulmonary and skin loss of free water, sometimes in excess of 2 to 3 L per day. These losses should be replaced with free water in the form of D5W. Perspiration typically has one-third the osmolarity of plasma and can be replaced with D5W or, if the loss is excessive, with D5/0.25 normal

saline.

Patients with acute blood loss need replacement with appropriate isotonic fluid or blood or both. There is a wide range of plasma volume expanders, including albumin, dextran, and hetastarch solutions, that contain large molecular-weight particles (<50 kDa molecular weight). These particles are slow to exit the intravascular space, and about one-half of the particles remain after 24 hours. Controversy exists over the ideal strategy for intravascular volume replacement (111). A systematic review of 25 randomized clinical trials demonstrated preserved renal function and reduced intestinal edema in surgical patients receiving hyperoncotic albumin solutions, as compared with control fluids (112). Meta-analyses on the use of human albumin and crystalloids versus colloids in fluid resuscitation did not show a benefit in mortality rates (113,114). Caution is required in interpreting results from these pooled controlled trials because mortality outcome was not the end point of most of the studies, and publication bias is a limitation. Possible side effects with synthetic colloid solutions include adverse effects on hemostasis, severe anaphylactic reactions, and impairment of renal function (111). These solutions are expensive and **for most cases, simple replacement with 0.9 normal saline or lactated Ringer solution will suffice.** One-third of the volume of lactated Ringer solution or normal saline typically will remain in the intravascular space and the remainder goes to the interstitium.

Appropriate replacement of gastrointestinal fluid loss depends on the source of fluid loss in the gastrointestinal tract. Gastrointestinal secretions beyond the stomach and up to the colon are typically isotonic with plasma, with similar amounts of sodium, slightly lower amounts of chloride, slightly alkaline pH, and more potassium (in the range of 10 to 20 mEq/L). Under normal conditions, stool is hypotonic. However, under conditions of increased flow (i.e., severe diarrhea), stool contents are isotonic with a composition similar to that of the small bowel contents. Gastric contents are typically hypotonic, with one-third the sodium of plasma, increased amounts of hydrogen ion, and low pH.

Postoperative Fluid and Electrolyte Management

Several hormonal and physiologic alterations in the postoperative period may complicate fluid and electrolyte management. The stress of surgery induces an inappropriately high level of circulating ADH. Circulating aldosterone levels are increased, especially if sustained episodes of hypotension occurred either intra- or postoperatively. The elevated levels of circulating ADH and aldosterone make postoperative patients prone to sodium and water retention.

Total body fluid postoperative volume may be altered significantly. First, 1 mL of free water is released for each gram of fat or tissue that is catabolized and, in the postoperative period, several hundred milliliters of free water are released daily from tissue breakdown, particularly in the patient who has undergone extensive intra-

abdominal dissection and who is restricted from ingesting food and fluids by mouth. This free water is often retained in response to the altered levels of ADH and aldosterone. Second, fluid retention is further enhanced by third spacing, or sequestration of fluid in the surgical field. **The development of an ileus may result in an additional 1 to 3 L of fluid per day being sequestered in the bowel lumen, bowel wall, and peritoneal cavity.**

In contrast to renal sodium homeostasis, the kidney lacks the capacity for retention of potassium. **In the postoperative period, the kidneys continue to excrete a minimum of 30 to 60 mEq/L of potassium daily, irrespective of the serum potassium level and total body potassium stores** (115). If this potassium is not replaced, hypokalemia may develop. Tissue damage and catabolism during the first postoperative day usually result in the release of sufficient intracellular potassium to meet the daily requirements. Beyond the first postoperative day, potassium supplementation is necessary.

Correct maintenance of fluid and electrolyte balance in the postoperative period starts with the preoperative assessment, with emphasis on establishing normal fluid and electrolyte parameters before surgery. Postoperatively, close monitoring of daily weight, urine output, serum hematocrit, serum electrolytes, and hemodynamic parameters will yield the necessary information to make correct adjustments in crystalloid replacement. The normal daily fluid and electrolyte requirements must be met and any unusual fluid and electrolyte losses, including those from the gastrointestinal tract, lungs, or skin, must be compensated. After the first few postoperative days, third-space fluid begins to return to the intravascular space, and ADH and aldosterone levels revert to normal. The excess fluid retained perioperatively is mobilized and excreted through the kidneys, and exogenous fluid requirements decrease. Patients with inadequate cardiovascular or renal reserve are prone to fluid overload during this time of third-space reabsorption, especially if intravenous fluids are not appropriately reduced.

The most common fluid and electrolyte disorder in the postoperative period is fluid overload. Fluid excess can occur concomitantly with normal or decreased serum sodium. Large amounts of isotonic fluids are usually infused intraoperatively and postoperatively to maintain blood pressure and urine output. Because the infused fluid is often isotonic with plasma, it will remain in the extracellular space. Under such conditions, serum sodium will remain within normal levels. Fluid excess with hypotonicity (decreased serum sodium) can occur if large amounts of isotonic fluid losses (e.g., blood and gastrointestinal tract) are inappropriately replaced with hypotonic fluids. The predisposition toward retention of free water in the immediate postoperative period compounds the problem. An increase in body weight occurs concomitantly with the fluid expansion. In the patient who is not allowed anything by mouth, catabolism should induce a daily weight loss as great as 300 g per day. The

patient who is gaining weight in excess of 150 g per day is in a state of fluid expansion. Simple fluid restriction will correct the abnormality. When necessary, diuretics can be used to increase urinary excretion.

States of fluid dehydration are uncommon but will occur in patients who have large daily losses of fluid that are not replaced. **Gastrointestinal losses should be replaced with the appropriate fluids. Patients with high fevers should be given appropriate free water replacement, because up to 2 L per day of free water can be lost through perspiration and hyperventilation.** Although these increased losses are difficult to monitor, a reliable estimate can be obtained by monitoring body weight.

Tenets of Fluid Management in ERAS

[3] The ideal fluid management for a perioperative patient is euvolemia. In order to achieve this, ERAS protocols consist of minimizing crystalloids and prioritizing the use of colloids and vasopressors when needed. When crystalloids are used, balanced fluids (such as lactated Ringers) are preferred. Many times this approach is goal-oriented, utilizing measurements of stroke volume to guide resuscitation. There is evidence that patients have improved postoperative outcomes when utilizing either hypovolemic or goal-oriented fluid paradigms (116).

Postoperative Pain Management

General Principles

[4] **Although satisfactory analgesia is easily achievable with available methods, patients continue to suffer unnecessarily from postoperative pain. Studies consistently show that 25% to 50% of patients suffer moderate to severe pain in the postoperative period** (117,118). There are several reasons for the existing inadequacies in pain management. First, patient expectations of pain relief are low and they are not aware of the extent of analgesia that they should expect. Second, there is a lack of formal physician training in pain management. Third, attitudes continue to be influenced by the common misconception that the use of narcotics in the postoperative period results in opioid dependence.

Many effective pain control paradigms exist. The *patient-controlled analgesia* (PCA) technique, which allows patients to self-administer small doses of narcotic on demand, allows titration of measured boluses of narcotic as needed to relieve pain. This technique can provide a more thorough analgesia with maintenance of steady-state drug concentrations. These devices eliminate the delay between the onset of pain and the administration of analgesic agents, a common problem inherent with on-demand analgesic orders in busy hospital wards. PCA has excellent patient acceptance. Compared with conventional intramuscular injections, serum

narcotic levels have significantly lower variability in patients using PCA (119). Patients using PCA have improved analgesia, a lower incidence of postoperative pulmonary complications, and less confusion than those given intramuscular narcotics (120). The total dose of narcotic used is lower with PCA than with conventional intramuscular depot injection.

The use of PCA does not eliminate the adverse side effects of narcotics. Potentially life-threatening respiratory depression is seen in as many as 0.5% of patients using PCA. The use of a continuous narcotic infusion in addition to demand dosing is associated with a fourfold increase in respiratory depression. Elderly patients and those with pre-existing respiratory compromise are at risk for respiratory depression (119).

In summary, use of PCA shortens the time between the onset of pain and the administration of pain medication, provides more continuous access to analgesics, and permits an overall steadier state of pain control.

Epidural and Spinal Analgesia

Anesthetics and narcotics administered either in the epidural space or intrathecally are among the most potent analgesic agents available; the efficacy of these agents is greater than that provided by intravenous PCA techniques. These drugs can be administered in several ways, including a single-shot dose given by epidural or intrathecal injection, intermittent injection given either on schedule or on demand, and continuous infusion.

Because of the risk of central nervous system infections and headaches, intrathecal administration is usually limited to a single dose of narcotic, local anesthetic, or both. In comparison with epidural administration, duration of action for a single dose is increased via the intrathecal route as a result of the high concentrations of drug attained in the cerebrospinal fluid. The risk of central nervous system and respiratory depression, and systemic hypotension, is increased. The low doses of opioids required for intrathecal analgesia are sufficient to be associated with an increased risk of respiratory depression (121). Some investigators warn against the use of intrathecal spinal analgesia outside the intensive care setting.

Epidural administration is the preferred approach and provides extended (>24 hours) pain control during the postoperative period. Relative contraindications are the presence of coagulopathy, sepsis, and hypotension. Both anesthetic and narcotic agents are used with excellent efficacy. Among the anesthetic agents, *bupivacaine* is the most popular, providing excellent analgesia with minimal toxicity. Epidural analgesia is most suited for pain control in the lower abdomen and extremities. Potential adverse effects of epidural anesthetic agents include urinary retention, motor weakness, hypotension, and central nervous system and cardiac depression. In contrast to anesthetic agents, opioids offer excellent analgesia without accompanying sympathetic blockade. Epidural opioids tend to have a much longer duration of action, and hypotension is a rare complication. Compared with epidural anesthetics, there is a

higher incidence of nausea and vomiting, respiratory depression, and pruritus (122).

Compared with analgesics administered intramuscularly or intravenously, epidural analgesia is associated with improved postoperative pulmonary function, a lower incidence of pulmonary complications, a decrease in postoperative venous thromboembolic complications (most likely secondary to earlier ambulation), fewer gastrointestinal side effects, a lower incidence of central nervous system depression, and shorter convalescence (122). **A systematic review concluded that continuous epidural anesthesia is more effective than intravenous opioid PCA in reducing postoperative pain for up to 72 hours after abdominal surgery** (123). Severe respiratory depression, which occurs in less than 1% of patients, is the most serious potential complication. A lower incidence of respiratory depression occurs with the more lipophilic drugs such as *fentanyl,* which is quickly absorbed within the spinal cord and is less likely to diffuse to the central nervous system respiratory control centers. Pruritus, nausea, and urinary retention are common but can be managed easily and usually are of little clinical significance. Cost is perhaps the main and most limiting drawback of epidural analgesia.

Close monitoring by nursing staff is required for safe administration of epidural analgesia. An intensive care setting is not necessary. Epidural analgesics can be administered safely in a hospital ward setting under close nursing supervision, using respiratory monitoring with hourly ventilatory checks during the first 8 hours of epidural analgesia.

Nonsteroidal Anti-Inflammatory Drugs

Current therapeutic strategies for perioperative pain control are largely dependent on multimodal therapy with opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). The nonselective NSAID *ketorolac* is a potent drug that can be given orally or parenterally. ***Ketorolac* has a slightly slower onset of activity than *fentanyl* but has an analgesic potency comparable to *morphine.*** The theoretical advantages of NSAIDs over opioids include absence of respiratory depression, lack of abuse potential, decreased sedative effects, decreased nausea, early return of bowel function, and faster recovery. In clinical studies, *ketorolac* is found to have analgesic effects similar to those of morphine in postoperative orthopedic patients and, when used in conjunction with PCA, significantly reduced opioid requirements (124,125). Depending on the type of surgery, *ketorolac* has an opioid dose-sparing effect of a mean of 36% and improves analgesic control of moderate to severe pain 24 hours postoperatively (126). In the obstetric population, intravenous *ketorolac* is effective in reducing postoperative narcotic use after cesarean delivery (127). Although the U.S. Food and Drug Administration has not approved *ketorolac* for use during lactation, it was quantified in breast milk and has lower levels than *ibuprofen* (128).

Potential adverse effects associated with the use of NSAIDs include an increased risk

of renal compromise (particularly in patients suffering from acute hypovolemia), gastrointestinal side effects, hypersensitivity reactions, and bleeding. The effects of *ketorolac* on bleeding are inconsistent. Studies of *ketorolac* on healthy volunteers showed transient increases in bleeding time and decreases in platelet aggregation, but these changes were not clinically significant (129). A retrospective cohort study showed increased risk of gastrointestinal and operative site bleeding in elderly patients receiving high doses of *ketorolac,* between 105 and 120 mg per day. Increased risk for all gastrointestinal bleeding was associated with the use of *ketorolac* for more than 5 days (130). Controlled prospective studies did not show a significant increase in blood loss in patients who receive NSAIDs perioperatively. *Ketorolac* may be associated with elevated rates of acute renal failure when therapy exceeds 5 days (131). A meta-analysis of the use of postoperative NSAIDs in patients with normal preoperative renal function showed a clinically insignificant reduction in renal function (132). These agents should be used with extreme care, if at all, in patients with asthma, because 5% to 10% of adult patients with asthma are sensitive to *aspirin* and other NSAID preparations.

With the advantages of less gastrointestinal toxicity and a lack of antiplatelet effects, selective cyclooxygenase-2 (COX-2) inhibitors are a valuable option in perioperative pain management (133). Although evidence exists showing an increased risk of serious cardiovascular events associated with COX-2 inhibitors, short-term use of these agents in the perioperative setting can be considered in low-risk patients without existing cardiovascular disease (134–139).

In addition to NSAIDs, other adjuvant analgesics are being explored to minimize opioid use and the accompanying side effects, which can delay recovery. *Capsaicin* is a nonnarcotic that promotes release of substance P, a neurotransmitter for pain and heat, which initially results in a burning sensation, but eventually leads to substance P depletion and a reduction in pain. It is available in topical and injectable preparations. *Ketamine* blocks centrally located *N*-methyl-d-aspartate pain receptors, and at low subanesthetic doses can reduce central sensitization caused by surgery and prevent opioid-induced hyperalgesia. At higher doses, *ketamine* is associated with hallucinations, dizziness, nausea, and vomiting. *Gabapentin* and *pregabalin* are nonnarcotics that prevent the release of excitatory neurotransmitters that relay pain signals. They reduce opioid requirements and are effective antihyperalgesic agents (139).

Tenets of Pain Control in ERAS

Postoperative pain control is an important focus of ERAS protocols. Opioids are implicated in slowing gastrointestinal function, increasing nausea and vomiting, and at times creating patient confusion. All of these factors directly inhibit postoperative progress. Therefore, a successful pain medication approach needs to be multimodal and

not primarily rely on opioids. ERAS protocols include preoperative medications which often include NSAIDs, GABA agonists, and/or muscle relaxants. Many protocols include the use of regional anesthesia for pain control, especially in the context of a laparotomy. With the use of an epidural, postoperative pain control and gastrointestinal function have been found to be improved versus the use of an opioid PCA (140). The use of epidural analgesia has been associated with difficulty ambulating and urinary retention, which goes against the goals of an ERAS protocol (141). After incision closure, use of local bupivacaine is encouraged. Other important postoperative pain medications include the use of NSAIDs (i.e., *ketorolac*).

Drains

Prophylactic drains have been used since the 1800s in an effort to reduce perioperative fluid collections or identify bleeding or anastomotic leaks. Studies have found that drains provide low sensitivity in detecting a leak (142). There is limited data regarding prophylactic drain use in pelvic surgery and data is inconsistent. Routine use of prophylactic drains is not recommended, but can be considered in the setting of patient risk factors.

Similarly, nasogastric tubes had commonly been utilized in the postoperative period in order to protect anastomoses. Studies have found no clear benefit of prophylactic nasogastric tube use. A meta-analysis of approximately 5,000 patients revealed that patients without nasogastric tubes demonstrated less time to bowel function and a shorter hospital stay. The rate of anastomotic leak was no different between the two groups (143). Routine nasogastric tube use is discouraged.

Laxatives

To encourage expeditious return of bowel function, laxatives are often used. While available data does not demonstrate a clear benefit, there are few if any adverse effects with their use. Therefore, laxatives may be used in the postoperative period.

Outcomes of ERAS Protocols

[5] Given the purposeful design of enhanced recovery protocols, outcomes have demonstrated significant improvement in many areas of perioperative care. In meta-analyses, ERAS protocols have been associated with an average decrease in length of hospital stay of 1.14 days without a concomitant increase in readmission (144). Similarly, complication rates were decreased by half (145). Studies have shown that as compliance to a protocol increases, mortality decreases (146). Fitting with decreased perioperative complications and reduced readmissions, Canadian ERAS protocols have been associated with health care cost savings up to $7,000 per patient (147). Another

benefit of an ERAS protocol is that patients report improved quality of life and decreased pain scores (148,149).

A challenge of enhanced recovery protocols is the need for a highly dynamic and cooperative atmosphere as teamwork and standardization are crucial to the success of such a protocol (141). This includes the patient herself, the surgeon, the anesthesiologist, and the nurses, dietitians, trainees, and hospital administrators. While this is not an easy undertaking, it is of utmost importance, given the broad benefits seen in perioperative care with initiation of and adherence to an enhanced recovery protocol.

MANAGEMENT OF MEDICAL PROBLEMS

Correction of Existing Fluid and Electrolyte Abnormalities

Correct maintenance of fluid and electrolyte balance in the postoperative period starts with the preoperative assessment, with emphasis on establishing normal fluid and electrolyte parameters before surgery. Preoperative electrolyte abnormalities can pose a diagnostic challenge. The correct diagnosis and therapy are contingent on a correct assessment of total body fluid and electrolyte status. After taking a detailed history, initial evaluation should include an assessment of hemodynamic, clinical, and urinary parameters to determine the overall level of hydration and the fluid status of the extracellular fluid compartment. The patient with good skin turgor, moist mucosa, stable vital signs, and good urinary output is well hydrated. The patient with orthostasis, sunken eyes, parched mouth, and decreased skin turgor has extracellular volume contraction.

The laboratory workup for patients with pre-existing fluid problems should include assessment of blood hematocrit, serum chemistry, glucose, BUN and creatinine, urine osmolarity, and urine electrolyte levels. Serum osmolarity is calculated by the following equation:

$$2[Na^+] + \text{glucose (mg/dL)}/18 + \text{BUN (mg/dL)}/2.8$$

Normal serum osmolarity is typically 290 to 300 mOsm. The BUN:creatinine ratio is typically 10:1 but will rise to a ratio of greater than 20:1 under conditions of extracellular fluid contraction. Under conditions of extracellular fluid deficit, urine osmolarity will typically be high (>400 mOsm), whereas urine sodium concentration is low (<15 mEq/L), indicative of an attempt by the kidney to conserve sodium. Under conditions of extracellular fluid excess or in cases of renal disease, in which the kidney has impaired ability to retain sodium and water, urine osmolarity will be low and urine sodium will be high (>30 mEq/L).

Specific Electrolyte Disorders

Hyponatremia

Because sodium is the major extracellular cation, shifts in serum sodium levels are usually inversely correlated with the hydration state of the extracellular fluid compartment. The pathophysiology of hyponatremia is usually expansion of body fluids leading to excess total body water (115,150). Symptomatic hyponatremia usually does not occur until the serum sodium is below 120 to 125 mEq/L. The severity of the symptoms (nausea, vomiting, lethargy, seizures) is related more to the *rate* of change of serum sodium than to the actual serum sodium level.

Hyponatremia secondary to inappropriate secretion of ADH can occur with head trauma, pulmonary or cerebral tumors, and states of stress. The abnormally elevated ADH results in excess water retention. Treatment includes water restriction and, if possible, correction of the underlying cause. Hyponatremia in the form of extracellular fluid excess can be seen in patients with renal or cardiac failure and in conditions such as nephrotic syndrome, in which total body salt and water are increased, with a relatively greater increase in the latter. Administration of hypertonic saline to correct the hyponatremia would be inappropriate in this setting. In addition to correcting the underlying disease process, treatment should include, water restriction with diuretic therapy.

Inappropriate replacement of body salt losses with water alone will result in hyponatremia. This situation will typically occur in patients who lose large amounts of electrolytes secondary to vomiting, nasogastric suction, diarrhea, or gastrointestinal fistulas, and who received replacement with hypotonic solutions. Simple replacement with isotonic fluids and potassium will usually correct the abnormality. Rarely, rapid correction of the hyponatremia is necessary, in which case hypertonic saline (3%) can be administered. Hypertonic saline should be administered very cautiously to avoid a rapid shift in serum sodium, which will induce central nervous system dysfunction.

Hypernatremia

Hypernatremia is an uncommon condition that can be life-threatening if severe (serum sodium greater than 160 mEq/L). Extracellular fluid deficit results in a hyperosmolar state, which can cause disorientation, seizures, intracranial bleeding, and death. The causes include excessive extrarenal water loss, which can occur in patients who have a high fever, who have diabetes insipidus, either central or nephrogenic, and who have iatrogenic salt loading. The treatment involves correction of the underlying cause and replacement with free water either by the oral route or intravenously with D5W. As with severe hyponatremia, marked hypernatremia should be corrected slowly, no faster than 10 mEq per day, unless the patient is symptomatic from severe acute hypernatremia (151).

Hypokalemia

Hypokalemia may be encountered preoperatively in patients with significant

gastrointestinal fluid loss (prolonged emesis, diarrhea, nasogastric suction, intestinal fistulas) or marked urinary potassium loss secondary to renal tubular disorders (renal tubular acidosis, acute tubular necrosis, hyperaldosteronism, prolonged diuretic use). The symptoms associated with hypokalemia include neuromuscular disturbances, ranging from muscle weakness to flaccid paralysis, and cardiovascular abnormalities, including hypotension, bradycardia, arrhythmias, and enhancement of digitalis toxicity. These symptoms rarely occur unless the serum potassium level is less than 3 mEq/L. The treatment is potassium replacement. Oral therapy is preferable in patients who are on an oral diet. If necessary, potassium replacement can be given intravenously in doses that should not exceed 10 mEq per hour.

Hyperkalemia

Hyperkalemia is encountered infrequently in preoperative patients. It is usually associated with renal impairment, adrenal insufficiency, or potassium-sparing diuretic use. Marked hyperkalemia (potassium >7 mEq/L) can result in bradycardia, ventricular fibrillation, and cardiac arrest. The treatment chosen depends on the severity of the hyperkalemia and whether there are associated cardiac abnormalities detected with ECG. *Calcium gluconate* (10 mL of a 10% solution), given intravenously, can quickly offset the toxic effects of hyperkalemia on the heart. One ampule each of sodium bicarbonate and D5W, with or without insulin, will cause a rapid shift of potassium into cells. Over the longer term, cation exchange resins such as *sodium polystyrene sulfate* (*Kayexalate*), taken orally or by enema, will bind and decrease total body potassium. Hemodialysis is reserved for emergent conditions in which other measures are not sufficient or have failed (151).

Postoperative Fluid and Electrolyte Management

Several hormonal and physiologic alterations in the postoperative period may complicate fluid and electrolyte management. The stress of surgery induces an inappropriately high level of circulating ADH and aldosterone levels, making postoperative patients prone to sodium and water retention.

Total body fluid postoperative volume may be altered significantly. First, free water is released from tissues postoperatively, particularly in the patient who has undergone extensive intra-abdominal dissection and who is restricted from oral hydration. This free water is often retained in response to the elevated levels of ADH and aldosterone. Second, fluid retention is further enhanced by third spacing of fluid in the surgical field. **The development of an ileus may result in an additional 1 to 3 L of fluid per day being sequestered in the bowel lumen, bowel wall, and peritoneal cavity.** After the first few postoperative days, third-space fluid begins to return to the intravascular space, and ADH and aldosterone levels revert to normal. The excess fluid

retained perioperatively is mobilized and excreted through the kidneys, and exogenous fluid requirements decrease.

In contrast to renal sodium homeostasis, the kidney lacks the capacity for retention of potassium. **In the postoperative period, the kidneys continue to excrete a minimum of 30 to 60 mEq/L of potassium daily, irrespective of the serum potassium level and total body potassium stores** (115). If this potassium is not replaced, hypokalemia may develop. Tissue damage and catabolism during the first postoperative day usually result in the release of sufficient intracellular potassium to meet the daily requirements. Beyond the first postoperative day, potassium supplementation is necessary.

Patients with inadequate cardiovascular or renal reserve are prone to fluid overload during this time of third-space reabsorption, especially if intravenous fluids are not appropriately reduced.

The most common fluid and electrolyte disorder in the postoperative period is fluid overload. An increase in body weight occurs concomitantly with the fluid expansion. The patient who is gaining weight in excess of 150 g per day is in a state of fluid expansion. Simple fluid restriction will correct the abnormality. Diuretics can be used to increase urinary excretion, where appropriate.

States of fluid dehydration are uncommon but will occur in patients who have large daily losses of fluid that are not replaced. **Gastrointestinal losses should be replaced with the appropriate fluids. Patients with high fevers should be given appropriate free water replacement, because up to 2 L per day of free water can be lost through perspiration and hyperventilation.** Although these increased losses are difficult to monitor, a reliable estimate can be obtained by monitoring body weight.

Postoperative Acid–Base Disorders

A variety of metabolic, respiratory, and electrolyte abnormalities in the postoperative period can result in an imbalance in normal acid–base homeostasis, leading to alkalosis or acidosis. Proper fluid and electrolyte replacement and maintenance of adequate tissue perfusion will help prevent or correct most acid–base disorders that occur during the postoperative period.

Alkalosis

The most common acid–base disorder encountered in the postoperative period is alkalosis (115). Alkalosis is usually of no clinical significance and resolves spontaneously. While *respiratory alkalosis* usually results from hyperventilation caused by excitation of the central nervous system, numerous metabolic derangements can result in *metabolic alkalosis,* including posttraumatic transient hyperaldosteronism, nasogastric suction, infusion of bicarbonate during blood transfusions in the form of citrate, and use of diuretics. Alkalosis can be corrected with removal of the inciting cause and the correction of extracellular fluid and potassium deficits **(Table 25-10)**.

Full correction usually can be safely achieved over 1 to 2 days.

Marked alkalosis (serum pH >7.55) can result in serious cardiac arrhythmias or central nervous system seizures. Myocardial excitability is particularly pronounced with concurrent hypokalemia. Under such conditions, fluid and electrolyte replacement may not be sufficient to rapidly correct the alkalosis, requiring treatment with *acetazolamide* or an acidifying agent.

Table 25-10 Causes of Metabolic Alkalosis

Disorder	Source of Alkali	Cause of Renal HCO Retention
Gastric alkalosis		
Nasogastric suction	Gastric mucosa	↓↓ ECF, ↓ K
Vomiting		
Renal alkalosis		
Diuretics	Renal epithelium	↓ ECF, ↓ K
Respiratory acidosis and diuretics		↓ ECF, ↓ K, ↑ PCO_2
Exogenous base	$NaHCO_3$, Na citrate, Na lactate	Coexisting disorder of ECF, K, $PaCO_2$

↓ ECF, extracellular fluid depletion; ↓ K, potassium depletion; ↑↑ PCO_2, carbon dioxide retention; $NaHCO_3$, sodium bicarbonate; $PaCO_2$, partial pressure of carbon dioxide, arterial.

Acidosis

***Respiratory acidosis* results from carbon dioxide retention in patients who have hypoventilation. *Metabolic acidosis* is less common during the postoperative period but can be serious because of its effect on the cardiovascular system,** including decreased myocardial contractility, a propensity for hypotension, and refractoriness of the fibrillating heart to defibrillation (115).

Metabolic acidosis results from a decrease in serum bicarbonate levels. **The proper workup includes a measurement of the anion gap:**

$$\text{Anion gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-) = 10 \text{ to } 14 \text{ mEq/L (normal)}$$

The anion gap is composed of circulating protein, sulfate, phosphate, citrate, and lactate.

With metabolic acidosis, the anion gap can be increased or normal. An increase in circulating acids will consume and replace bicarbonate ion, increasing the anion gap. Postoperatively, conditions of poor tissue perfusion will increase circulating lactic acid, severe diabetes or starvation will increase ketoacids, and renal dysfunction will

increase circulating sulfates and phosphates (152). The diagnosis can be established via a thorough history and measurement of serum lactate (normal <2 mmol/L), serum glucose, and renal function parameters. Metabolic acidosis in the face of a normal anion gap is usually the result of excess chloride and decreased bicarbonate that can be seen in patients who underwent saline loading, those with severe diarrhea or renal tubular acidosis. A summary of the various causes of metabolic acidosis is shown in Table 25-11.

The treatment of metabolic acidosis depends on the cause. In patients with lactic acidosis, restoration of tissue perfusion is imperative. This state can be accomplished through cardiovascular and pulmonary support as needed, oxygen therapy, and aggressive treatment of systemic infection wherever appropriate. Ketosis from diabetes can be corrected gradually with *insulin* therapy. Ketosis resulting from chronic starvation or from lack of caloric support postoperatively can be corrected with nutrition. In patients with normal anion gap acidosis, bicarbonate lost from the gastrointestinal tract should be replaced, excess chloride administration can be curtailed, and, where necessary, a loop diuretic can be used to induce renal clearance of chloride. Dilutional acidosis can be corrected with mild fluid restriction.

Table 25-11 Causes of Metabolic Acidosis

High Anion Gap	Normal Anion Gap	
	Hyperkalemic	**Hypokalemic**
Uremia	Hyporeninism	Diarrhea
Ketoacidosis	Primary adrenal failure	Renal tubular acidosis
Lactic acidosis	NH_2Cl	Ileal and sigmoid bladders
Aspirin	Sulfur poisoning	Hyperalimentation
Paraldehyde	Early chronic renal failure	
Methanol	Obstructive uropathy	
Ethylene glycol		
Methylmalonic aciduria		
NH_2Cl (chloramine)		

Adapted from **Narins RG, Lazarus MJ.** Renal system. In: Vandam LD, ed. *To Make the Patient Ready for Anesthesia: Medical Care of the Surgical Patient*. 2nd ed. Menlo Park, CA: Addison Wesley; 1984:67–114.

Bicarbonates should not be given unless serum pH is lower than 7.2 or severe cardiac complications secondary to acidosis are present. Close monitoring of serum

potassium levels is mandatory. Under states of acidosis, potassium will exit the cell and enter the circulation. The patient with a normal potassium concentration and metabolic acidosis is actually depleted of intracellular potassium. Treatment of the acidosis without potassium replacement will result in severe hypokalemia with its associated risks.

Endocrine Disease

The three most frequent endocrine disorders that occur in patients undergoing gynecologic surgery are diabetes mellitus (DM), thyroid disease, and adrenal abnormalities. The pathophysiology of these disorders aids in understanding the effects of surgery on patients with these problems.

Diabetes Mellitus

DM is a complicated medical disorder of glucose metabolism that is related to a lack of production of, or resistance to, insulin. According to the American Diabetes Association, 14.9 million American women, or 11.7% of all women older than 18 years, suffer from diabetes (153). Approximately 50% of individuals with DM will require surgery during their lives (154). The direct effect of DM on the end organs determines the risk of surgery, rather than the type or duration of surgery or the management of the condition itself. The current criteria for diagnosis of diabetes include (155):

1. Polyuria, polydipsia, or unexplained weight loss with a random nonfasting glucose of ≥200 mg/dL, *or*
2. Fasting glucose ≥126 mg/dL (in which fasting is defined as no food intake for 8 hours), *or*
3. Two-hour oral glucose tolerance test of 75 g, with serum glucose ≥200 mg/dL, *or*
4. Hemoglobin A_{1c} ≥6.5%.

Confirmation of the diagnosis requires repeating the same test on a different day or concordant results of two different tests simultaneously.

Patients with DM have elevated risk of coronary artery disease and experience exaggerated hyperglycemia perioperatively. With this in mind, goals of the preoperative assessment and perioperative management are to ensure glycemic control and metabolic homeostasis and to anticipate complications related to DM.

Preoperative Risk Assessment

Preoperative risk assessment for diabetes should begin with a review of systems. Nocturia, polyuria, polydipsia, glucosuria, obesity, previous gestational diabetes, ethnicity, and family history are relevant aspects of the history.

Type 1 (insulin-dependent) diabetes, or type 2 diabetes (noninsulin-dependent), should be established because the preoperative risk and perioperative management of each differs. The patient's routine glucose management strategies, glucose levels, medications, and baseline hemoglobin A_{1c} should be assessed (156). The presence of end-organ complications of diabetes should be documented.

Cardiovascular risk resulting from large- and small-vessel arterial occlusive disease should be a focus in the preoperative setting. A careful history and physical examination should be performed to determine the presence or absence of coronary artery or cerebral vascular disease (154). Diabetic patients are less likely to have symptoms of coronary disease compared to their nondiabetic counterparts. For patients with inducible ischemia, coronary artery disease, or multiple clinical risk factors for heart disease, perioperative β-blockade should be considered, with initiation and careful titration of medication several weeks prior to surgery (157,158). Further evidence of end-organ disease can manifest as retinal or renal dysfunction. If diabetic nephropathy is present, imaging studies using contrast dye should be avoided. If a contrast study must be performed, adequate hydration before and after the procedure is essential, and oral *metformin* should be withheld for 24 to 48 hours after the procedure.

Diabetes is associated with increased perioperative infections (159). Preoperative evaluation should include examination of the skin and urine sediment to detect asymptomatic infection. Wound infections, skin infections, pneumonia, and urinary tract infections account for two-thirds of the postoperative complications in patients with diabetes (160). There is a known predisposition for patients with DM to have increased colonization by methicillin-resistant *Staphylococcus aureus,* increased infections by gram-negative and staphylococcal bacteria, and an increased incidence of gram-negative and group B streptococcal sepsis (161,162). Seven percent of individuals with diabetes will have postoperative gram-negative sepsis, a rate approximately seven times higher than that of the nondiabetic population. These complications occur more often in patients with poor glucose control, probably caused by impaired leukocyte function in the presence of hyperglycemia (163,164). Individuals with DM have an increased risk of wound dehiscence and wound infection, possibly related to an impaired immune function, with changes in phagocytosis, cell-mediated immunity, and intracellular bactericidal activity (165).

The traditional goal for glucose control perioperatively is to maintain the glucose level below 200 mg/dL (156,160). **Significant debate continues regarding whether strict glycemic control below 110 mg/dL may be beneficial in critically ill patients** (166,167). **Perioperative hyperglycemia (>250 mg/dL) is associated with increased susceptibility to infection and poor wound healing.** The American Diabetes Association endorses a perioperative glucose target range of 80 to 180 mg/dL (168).

For patients with diabetes controlled with diet alone or oral medications, oral

hypoglycemic agents should be discontinued when the patient ceases oral intake of food, and hyperglycemic episodes in the perioperative period are treated with sliding-scale regular *insulin* if blood sugar levels exceed 200 mg/dL (156,160).

Insulin-dependent and type 1 diabetes pose more difficult problems. These patients require a basal rate of insulin and a baseline intake of glucose. Type 1 diabetics are at risk of developing diabetic ketoacidosis whether or not they are eating (156). **Preoperatively, the goals include avoiding ketoacidosis and hypoglycemia, and, to a lesser extent, hyperglycemia. Traditionally, approximately one-third to one-half of the patient's usual daily dose of intermediate-acting *insulin* is given subcutaneously the morning of surgery. Omit any short-acting *insulin* without oral intake. An infusion of 5% dextrose should be given while being restricted from oral intake. Additional regular *insulin* can be administered in the operating room as needed** (154,156). If patients are normally on a continuous *insulin* infusion, they may continue at their usual infusion rate. There is no single regimen that is superior for the intraoperative management of type 1 diabetic patients and consultation with endocrine and anesthesia colleagues can be helpful in managing these complex regimens.

Postoperative Management

Postoperative monitoring of patients with DM includes careful monitoring of serum glucose levels to avoid severe hypoglycemia or hyperglycemia. **If an intravenous *insulin* regimen is used, blood glucose levels must be checked every 1 to 2 hours. If a sliding-scale *insulin* administration is used, blood glucose should be checked and documented approximately every 6 hours until the patient is eating and stable on her preoperative regimen. The serum glucose level should be maintained at less than 250 mg/dL, and ideally below 140 mg/dL when fasting and below 180 mg/dL with random draws** (169). For type 2 diabetics, oral hypoglycemics can be restarted when the patient resumes eating, except with *metformin,* which requires normal renal and liver function (156).

Thyroid Syndromes

Thyroid dysfunction should be suspected in any patient with a history of hyperthyroidism, use of thyroid replacement medication or antithyroid medication, prior thyroid surgery, or radioactive iodine therapy.

Hyperthyroidism

Diffuse toxic goiter (Graves disease) is the most common cause of hyperthyroidism and results from abnormal stimulation of the thyroid gland by antithyroid antibodies. Other causes of hyperthyroidism include multinodular goiter, excess thyroid hormone, or thyroiditis. Any signs or symptoms suggestive of weight loss, tachycardia, atrial

fibrillation, goiter, or proptosis should initiate a more extensive laboratory evaluation of thyroid function. Total thyroxin, free triiodothyronine (T_3), free thyroxin (T_4), and thyroid-stimulating hormone (TSH) tests are useful in diagnosis. **In hyperthyroidism, the free T_4 level will be elevated, and the TSH level will be suppressed** (170). A new diagnosis of hyperthyroidism necessitates postponement of elective surgery until adequate treatment with antithyroid medication is received because of the risk of thyroid storm. Thyroid storm is associated with mortality of up to 40% (171). Stable thyroid conditions do not require any special preoperative treatments or tests. **Ideally, a euthyroid state should be maintained for 3 months before elective surgery.** In emergent situations, β-blockers can be used to counter sympathomimetic drive such as palpitations, diaphoresis, and anxiety. Antithyroid medications such as *propylthiouracil* (*PTU*) or *radioactive iodine* do not render patients euthyroid quickly enough for urgent surgery. *Radioactive iodine* requires 6 to 18 weeks to establish a euthyroid state (170). When thyroid dysfunction is corrected and maintained for several months, elective surgery can proceed without additional perioperative monitoring. Antithyroid medications should be resumed with return of bowel function. If a prolonged delay in resumption of oral intake is encountered, *PTU* and *methimazole* can be administered rectally (172). **When time does not permit establishment of a euthyroid state preoperatively, oral administration of *PTU* and a** b-***blocker* can be implemented for 2 weeks before surgery, and with careful monitoring, optimal results can be achieved** (173). Alternatively, oral b-*blockers, glucocorticoids,* and *sodium iopanoate* can be used for 5 days, followed by surgery on day 6 (172). In the emergent setting, close monitoring of the patient for tachycardia, arrhythmias, and hypertension is necessary. b-*Blockers* can control these symptoms until definitive therapy can be initiated after recovery from surgery.

Any signs suggestive of the development of thyroid storm—including hemodynamic instability, tachycardia, arrhythmias, hyperreflexia, diarrhea, fever, delirium, or CHF—mandate transfer to an intensive care setting for optimal monitoring and management in consultation with a medical endocrinologist. Such thyroid instability can be triggered by underlying infection, which requires diagnosis and treatment to facilitate management of this medical emergency. The mortality rate from thyroid storm is reportedly between 10% and 75% (172). Treatment of thyroid storm consists of b-*blockers, thioamides, iodine, iodinated contrast agents,* and *corticosteroids* (160). *Aspirin* should not be given for fever in the patient with thyroid storm because it may interfere with the protein binding of T_4 and T_3, resulting in increased free serum concentrations (160).

Hypothyroidism

The incidence of hypothyroidism is approximately 1% in the adult population, and 5% in adults older than 50 years (170). **In women older than 60 years, the incidence of**

hypothyroidism may approach 6% (171). **Hypothyroidism is 10 times more common in women than in men** (170). Many such cases are secondary to previous antithyroid therapy (*radioactive iodine* or thyroidectomy) for hyperthyroidism. The most common primary cause of hypothyroidism is Hashimoto thyroiditis, an autoimmune condition (170). A history of lethargy, cold intolerance, lassitude, weight gain, fluid retention, constipation, dry skin, hoarseness, periorbital edema, and brittle hair can be indicative of inadequate thyroid function. In this setting, physical findings of increased relaxation phase of deep tendon reflexes, cardiomegaly, pleural or pericardial effusions, or peripheral edema should stimulate further investigation of thyroid function by assessment of TSH and free T_4 levels. Hypothyroidism decreases cardiac output by 30% to 50% as a result of decreased stroke volume and heart rate (174). Hyponatremia may be associated with hypothyroidism because of the inability of the kidneys to excrete water (174). When elective surgery is planned for severely hypothyroid patients, surgery should be postponed until thyroid replacement therapy is initiated (170). In patients with mild or moderate hypothyroidism, the delay of surgery is controversial (170).

For young patients with mild to moderate hypothyroidism, a starting dose of 1.6 µg/kg of thyroid hormone replacement can be given. In elderly patients, *thyroxin* dosage (0.025 mg once a day) should be given with interval dose increases every 4 to 6 weeks until the patient is euthyroid (171). **Dosage levels can ultimately be titrated against TSH levels.** In severely hypothyroid patients requiring urgent or emergent surgery, intravenous T_3 or T_4 may be given, along with intravenous *corticosteroids* to avoid consequences of unrecognized adrenal insufficiency (160,170).

In the immediate postoperative setting, T_4 therapy can be held for 5 to 7 days while waiting for return of bowel function because the half-life of circulating T_4 is approximately 5 to 9 days (173). If more than 5 to 7 days of decreased bowel function are expected, T_4 can be given by the intramuscular or intravenous route at approximately 80% of the oral dose (174).

Adrenal Insufficiency

Adrenal insufficiency may result in catastrophic postoperative complications, including death. The most common cause of adrenal insufficiency in the surgical patient is secondary to the exogenous use of *corticosteroids*. The physician should ascertain whether a patient used exogenous steroids for asthma (including inhaled steroids), malignant conditions, arthritis, or irritable bowel syndrome. The type of steroid use, the route, the dose, the duration, and the temporal relationship to the timing of the surgical procedure must be determined. The type of surgical procedure and its associated stress should be taken into consideration. The use of high doses of exogenous steroids for prolonged periods can cause circulatory collapse, and they have adverse effects on

wound healing and immunocompetence.

The daily replacement dose of cortisol is approximately 5 to 7.5 mg of *prednisone*. Suppression of the hypothalamic–pituitary–adrenal (HPA) axis by exogenous steroids for more than a few weeks may produce relative adrenal insufficiency. When systemic steroids are used for longer periods, adrenal insufficiency may persist for up to 1 year. Short courses of low-dose oral steroids (<5 mg of *prednisone* in a single morning dose for any duration of time, alternate-day dosing of short-acting glucocorticoids, and any dose of corticosteroids given for less than 3 weeks) are not thought to cause clinically significant suppression of the HPA axis (160). More than 1,500 mcg daily for inhaled corticosteroids (or 750 mcg daily of fluticasone) or more than 2 g per day of class I topical glucocorticoids may cause suppression (175). If either the dose or duration of glucocorticoid administration exceeds the preceding regimen, biochemical tests are recommended to preoperatively evaluate the function of the adrenal gland. The easiest and safest test to assess HPA function is the *cosyntropin* stimulation test. *Cosyntropin,* a synthetic analog of adrenocorticotropic hormone, is given in a dose of 250 µg intravenously, and a blood sample is collected 30 minutes after the injection and assayed for plasma cortisol. A plasma cortisol value of greater than 18 to 20 µg/dL indicates adequate adrenal function (160,170). If the history regarding exogenous steroid use is unclear, the *cosyntropin* stimulation test should be considered as a preoperative test to determine whether the patient will need perioperative glucocorticoid coverage. The amount of glucocorticoid replacement should be equivalent to the normal physiologic response to surgical stress **(Table 25-12)** (176).

For minor surgical stress, such as colonoscopy, the glucocorticoid target is approximately 25 mg of *hydrocortisone* equivalent on the day of the procedure (176). For moderate surgical stress, for example, open cholecystectomy, the glucocorticoid target is 50 to 75 mg of *hydrocortisone* equivalent on the day of the procedure and tapered quickly for 1 to 2 days. The patient should receive her normal daily dose preoperatively, followed by 50 mg of *hydrocortisone* intravenously administered intraoperatively. For major surgical stress, such as liver resection, the glucocorticoid target range is 100 to 150 mg *hydrocortisone* equivalent on the day of the procedure, tapering rapidly over the next 1 to 2 days to the usual dosage (176). The patient should receive her normal daily dose preoperatively.

Administration of high-dose steroids should be stopped as soon as possible postoperatively because they can inhibit wound healing and promote infection. Hypertension and glucose intolerance can develop. When a prolonged or involved procedure is performed and longer steroid use is necessary, careful tapering may be required. The previously recommended approach was to halve the dose of *hydrocortisone* on a daily basis until a dose of 25 mg is reached. Eliminating one daily dose each day until the drug is stopped was considered the safest method of withdrawal;

no consensus on the timing or duration of steroid tapering exists. Addison disease is uncommon but should be considered in the differential diagnosis if the patient develops perioperative hypotension after steroids are withdrawn. In addition to blood and isotonic fluid replacement, a "stress" dose of steroids should be given if adrenal insufficiency is suspected and sepsis and hypovolemia are excluded.

Cardiovascular Diseases

The incidence of perioperative cardiovascular complications decreased markedly as a result of improvements in preoperative detection of high-risk patients, preoperative preparation, and surgical and anesthetic techniques (177).

Preoperative Evaluation

Cardiovascular outcomes are related to baseline cardiovascular risk. Thus, the goal of a preoperative cardiac evaluation is to determine the presence of heart disease, its severity, and the potential risk to the patient during the perioperative period. Every patient should be questioned about symptoms of cardiac disease including chest pain, dyspnea on exertion, peripheral edema, wheezing, syncope, claudication, or palpitations. Prescriptions for antihypertensive, anticoagulant, antiarrhythmic, antilipid, or antianginal medications may be the only indication of cardiac problems.

On physical examination, the presence of findings such as hypertension, jugular venous distension, laterally displaced point of maximum impulse, irregular pulse, third heart sound, pulmonary rales, heart murmurs, peripheral edema, or vascular bruits should prompt a more thorough evaluation. Laboratory evaluation of patients with known or suspected heart disease should include a blood count and serum chemistry analysis. Patients with heart disease tolerate anemia poorly. Serum sodium and potassium levels are particularly important in patients taking diuretics and digitalis. BUN and creatinine values provide information on renal function and hydration status. Assessment of blood glucose levels may detect undiagnosed DM.

Coronary Artery Disease

[9] Coronary artery disease is a major risk factor for patients undergoing abdominal surgery. In an adult population without a prior history of myocardial infarction, the incidence of myocardial infarction following surgery is 0.1% to 0.7% (178).

Because of the high mortality and morbidity associated with perioperative myocardial infarction, considerable effort is made to predict perioperative cardiac risk. Risk assessment is stratified into three major categories: (i) clinical predictors, (ii) functional capacity, and (iii) surgery-specific risk (179). Clinical predictors of increased perioperative cardiac risk include high-risk surgical procedures, history of ischemic heart disease, history of CHF, history of transient ischemic attack or stroke,

preoperative insulin therapy, and preoperative serum creatinine levels greater than 2.0 mg/dL. These factors are incorporated into the RCRI (Table 25-13) (180), a prospectively validated tool that places patients into one of four risk classes. Depending on the number of risk factors, the risk of major cardiac events (myocardial infarction, cardiac arrest, pulmonary edema, and complete heart block) ranges from 0.5% to 9.1% (Table 25-14).

Table 25-13 Major Cardiac Event Rates by the Revised Cardiac Risk Index

Class	(Number of Risk Factors)	Events/Patients	Event Rate% (95% CI)
I	(0)	2/488	0.4 (0.05, 1.5)
II	(1)	5/567	0.9 (0.3, 2.1)
III	(2)	17/258	6.6 (3.9, 10.3)
IV	(3)	12/109	11.0 (5.8, 18.4)

CI, confidence interval.

Adapted from **Lee TH, Marcantonio ER, Mangione CM, et al.** Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043–1049.

The patient's functional status is assessed by a thorough history (Table 25-15), and self-reported exercise tolerance can be used to predict perioperative risk, based on a system of metabolic equivalents (METS) (181). Surgery-specific risk is subdivided into high-risk procedures (emergent major operations, aortic and vascular procedures, and prolonged surgical procedures associated with large fluid shifts or blood loss), intermediate-risk procedures (intraperitoneal and intrathoracic), and low-risk procedures (endoscopic, breast surgery, and ambulatory procedures). **Patients with any clinical risk factor and poor functional capacity (METS <4) undergoing more than low-risk nonemergent surgery should undergo preoperative testing, based on the AHA guidelines** (182).

Table 25-14 Clinical Predictors of Increased Perioperative Cardiovascular Risk

Major
Unstable coronary syndromes: acute (≤7 days) or recent (7 days–30 days) MI, unstable or severe angina
Decompensated congestive heart failure
Significant arrhythmias (high-grade AV block, symptomatic ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate)
Severe valvular disease
Intermediate

History of cerebrovascular disease
Prior ischemic cardiac disease
Compensated or prior congestive heart failure
Diabetes mellitus
Renal insufficiency
Minor
Advanced age
Abnormal ECG (LVH, LBBB, ST–T abnormalities)
Rhythm other than sinus
Uncontrolled systemic hypertension

MI, myocardial infarction; AV, atrioventricular; ECG, electrocardiogram; LVH, left ventricular hypertrophy; LBBB, left bundle branch block.

Adapted from **Fleisher LA, Beckman JA, Brown KA, et al.** 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2009;120:e169–e276.

Table 25-15 Functional Capacity Assessment From Clinical History

Excellent
Carry 24 lb up eight steps
Carry objects that weigh 80 lb
Outdoor work (shovel snow, spade soil)
Recreation (ski, basketball, squash, handball, jog, or walk 5 mph)
Moderate
Have sexual intercourse without stopping
Walk at 4 mph on ground level
Outdoor work (garden, rake, weed)
Recreation (roller skate, dance)
Poor
Shower and dress without stopping
Basic housework

Walk 2.5 mph on level ground
Recreation (golf, bowl)

Adapted from **Mehta RH, Bossone E, Eagle KA.** Perioperative cardiac risk assessment for noncardiac surgery. *Cardiologia* 1999;44:409–418.

Extent of preoperative testing depends on the level of perioperative cardiac risk. Patients who have dyspnea of unknown origin, current or past heart failure, prior cardiomyopathy, or with any of the above factors and no cardiac assessment in the past 12 months should consider echocardiogram testing preoperatively (182). ***Exercise stress testing*** **before surgery can identify patients who have ischemic heart disease not apparent at rest but are at high risk for perioperative myocardial infarction and cardiac mortality, up to 25% and 18.5%, respectively** (183). The exercise stress test must be selectively applied to a high-risk population because its predictive value depends on the prevalence of the disease.

Exercise stress testing is limited in some patients who cannot exercise because of musculoskeletal disease, pulmonary disease, or severe cardiac disease. *Dipyridamole-thallium scanning* may be used to overcome the limitations of exercise stress testing. This study has a high degree of sensitivity and specificity but a low positive predictive value (182,184).

Dobutamine stress echocardiography is another test to evaluate cardiac risk in patients who are unable to exercise. This method identifies regional cardiac wall motion abnormalities after *dobutamine* infusion. Positive and negative predictive values are similar to those of *dipyridamole-thallium* testing for a perioperative event (185). Coronary angiography should be considered only in patients who have an indication for angiography independent of the planned surgery, such as patients with acute coronary syndromes, unstable angina, angina refractory to medical therapy, or high-risk results on noninvasive testing.

Preoperative testing should be used discriminately in intermediate-risk patients. Controversy exists regarding the accuracy of these tests to provide prognostic information beyond what is obtained from clinical risk stratification for nonvascular procedures. Diagnostic testing should not lead to unnecessary additional testing or harmful delays in surgery. **The American College of Cardiology and the AHA present a detailed algorithm that incorporates risk factor stratification to guide clinicians to proceed directly to surgery, to delay surgery and obtain preoperative noninvasive testing, or to attempt risk factor modification** (182).

Nearly two-thirds of postoperative myocardial infarctions occur during the first 3 days postoperatively (189). Prevention, early recognition, and treatment are important because myocardial infarctions that occur in the postoperative period have mortality rates of up to 25% and are associated with increased rates of cardiovascular

death in the 6 months following surgery (186). Postoperative tachycardia and increased preload are the most important causes of ischemia because both conditions decrease oxygen supply to the myocardium while simultaneously increasing myocardial oxygen demand. Tachycardia limits the diastolic time, when the coronary arteries are perfused, which decreases the volume of oxygen available to the myocardium. Increased preload increases the pressure exerted by the myocardial wall on the arterioles within it, thus decreasing myocardial blood flow.

Other factors associated with perioperative myocardial ischemia include physiologic responses to the stress of intubation, intravenous or arterial line placement, emergence from anesthesia, pain, and anxiety. These stresses result in catecholamine stimulation of the cardiovascular system, resulting in increased heart rate, blood pressure, and contractility, which may induce or worsen myocardial ischemia. Loss of intravascular volume because of third spacing of fluids or postoperative hemorrhage can induce ischemia (187).

Postoperative myocardial infarction is often difficult to diagnose. Chest pain, which is present in 90% of nonsurgical patients with myocardial infarction, may be present in only 50% of patients with postoperative infarction because myocardial pain may be masked by coexisting surgical pain and the use of analgesics (178). The presence of arrhythmia, CHF, or hypotension may indicate infarction and should prompt a thorough cardiac investigation and electrocardiographic monitoring. **Measurement of creatinine kinase (CK-MB) isoenzyme and troponin T levels are the most sensitive and specific indicators of myocardial infarction, and assessments should be obtained for all patients suspected of myocardial infarction** (186).

Despite the high incidence of silent myocardial infarction, routine use of postoperative ECG for all patients with cardiovascular disease is controversial. Many patients will exhibit P-wave changes that spontaneously resolve and do not represent ischemia or infarction. Conversely, patients with proven myocardial infarctions may show few, if any, ECG abnormalities. The American College of Cardiology and the AHA advise consideration of postoperative surveillance via ST-segment monitoring for myocardial infarction in patients with known or suspected coronary artery disease (179). In a review of over 2,400 patients, the sensitivity of predicting postoperative cardiac events was 55% to 100%, specificity 37% to 85%, positive predictive value 7% to 57%, and negative predictive value 89% to 100% (188). If routine screening of asymptomatic patients is desired, ECG should be performed 24 hours following surgery because significant ECG changes that occur immediately postoperatively will persist for 24 hours. It is prudent to continue serial ECG assessments for at least 3 days postoperatively.

Postoperative management of patients with coronary artery disease is based on maximizing delivery of oxygen to the myocardium and decreasing myocardial oxygen utilization. Most patients benefit from supplemental oxygen in the postoperative

period, although special care should be exercised in patients with COPD. Oxygenation can easily be monitored by pulse oximetry. Anemia is detrimental because of loss of oxygen-carrying capacity and resultant tachycardia and should, therefore, be carefully corrected in high-risk patients. Although transfusion criteria are not absolute, all patients with a hemoglobin less than 6 mg/dL, and hemoglobin of 6 to 10 mg/dL with significant cardiac risk factors should be offered blood transfusion (189).

Patients with coronary artery disease may benefit from pharmacologic control of hyperadrenergic states that result from increased postoperative catecholamine production. β-Blockers decrease heart rate, myocardial contractility, and systemic blood pressure, all of which are increased by adrenergic stimulation. The Perioperative Ischemic Evaluation (POISE) trial, a randomized controlled trial of *metoprolol* versus placebo, enrolling 8,000 patients undergoing noncardiac surgery, revealed a reduction in cardiovascular death, myocardial infarction, and cardiac arrest. There was an increased risk of stroke and total mortality (190). The AHA provides the following guidelines: Continue β-blocker therapy in patients on baseline β-blockers for treatment of cardiac disease. Consider initiating and titrating β-blockers in patients with coronary artery disease or high cardiac risk (as defined by the presence of more than one clinical risk factor) who are undergoing intermediate-risk surgery (158). Therapy should be initiated at least 1 week before surgery to allow for proper titration. The timing and optimal duration of β-blocker therapy remain an area of uncertainty. Nevertheless, for patients already on β-blocker therapy, they should continue it perioperatively because abrupt withdrawal results in a rebound hyperadrenergic state.

Prophylactic use of other agents such as *nitroglycerin* and calcium channel blockers remains controversial, as data did not show a consistent benefit toward reducing risk of ischemic cardiac events. *Nitroglycerin* may cause hypotension, which may worsen cardiac status (158).

Congestive Heart Failure

Patients with CHF face a substantially increased risk of myocardial infarction during and after surgery (191). The postoperative development of pulmonary edema may be associated with a high mortality rate, especially if it occurs in the setting of cardiac ischemia (192,193). **To prevent severe postoperative complications, CHF must be corrected preoperatively.** The signs and symptoms of CHF are listed in Table 25-16 and should be assessed based on preoperative history and physical examination. Patients who are able to perform usual daily activities without developing CHF are at limited risk of perioperative heart failure.

Table 25-16 Signs and Symptoms of Congestive Heart Failure

1. Presence of an S_3 gallop

2. Jugular venous distension
3. Lateral shift of the point of maximal impulse
4. Lower extremity edema
5. Basilar rales
6. Increased voltage on electrocardiogram
7. Evidence of pulmonary edema or cardiac enlargement on chest radiograph
8. Tachycardia

Treatment usually relies on aggressive diuretic therapy, although care must be taken to avoid dehydration, which may result in hypotension during the induction of anesthesia. Hypokalemia can result from diuretic therapy and is especially deleterious to patients who are taking *digitalis*. In addition to diuretics and *digitalis*, treatment often includes the use of preload- and afterload-reducing agents. Optimal use of these drugs and correction of CHF may be aided by consultation with a cardiologist. It is preferable to continue the usual regimen of cardioactive drugs throughout the perioperative period.

Postoperative CHF frequently results from excessive administration of intravenous fluids and blood products. Other common postoperative causes are myocardial infarction, systemic infection, pulmonary embolism, and cardiac arrhythmias. The cause of postoperative heart failure must be diagnosed because, to be successful, treatment should be directed simultaneously to the underlying cause. The most reliable method of detecting CHF is chest radiography, in which the presence of cardiomegaly or evidence of pulmonary edema is a helpful diagnostic feature.

Acute postoperative CHF frequently manifests as pulmonary edema. Treatment of pulmonary edema may include the use of intravenous *furosemide,* supplemental oxygen, *morphine sulfate,* and elevation of the head of the bed. ECG, arterial blood gas, serum electrolytes, and renal function chemistry measurements should be obtained expediently. If the patient's condition does not improve rapidly, she should be transferred to an intensive care unit.

Arrhythmias

Nearly all arrhythmias found in otherwise healthy patients are asymptomatic and of limited consequence. In patients with underlying cardiac disease, however, even brief episodes of arrhythmias may result in significant cardiac morbidity and mortality.

Preoperative evaluation of arrhythmias by a cardiologist and anesthesiologist is important because many anesthetic agents and surgical stress contribute to the development or worsening of arrhythmias. **Patients with heart disease have an increased risk of arrhythmias, most commonly ventricular arrhythmias.** Patients

taking antiarrhythmic medications before surgery should continue taking those drugs during the perioperative period.

Patients with first-degree atrioventricular (AV) block or asymptomatic Mobitz I (Wenckebach) second-degree AV block require no preoperative therapy. A pacemaker is appropriate in patients with symptomatic Mobitz II second- or third-degree AV block before elective surgery (194). In emergency situations, a pacing pulmonary artery catheter can be used. **When performing gynecologic surgery on patients with pacemakers, it is preferable to place the electrocautery unit ground plate on the leg to minimize interference by preventing the pacemaker generator from sitting within the electrocautery circuit and to maximize distance from the pacemaker device. If possible, use of bipolar cautery devices is recommended rather than monopolar devices. In patients with a demand pacemaker in place, the pacemaker should be converted preoperatively to the fixed-rate (or asynchronous) mode. Patients should be monitored continuously intraoperatively with both telemetry and continuous pulse oximeter. Close coordination with anesthesia and cardiology is imperative. Patients with an implantable cardioverter defibrillator device should have their device programmed off prior to surgery and reprogrammed postoperatively** (158).

Surgery is not contraindicated in patients with bundle branch blocks or hemiblocks (195). Perioperative mortality rates are not increased by bundle branch block. Complete heart block rarely develops during noncardiac surgical procedures in patients with conduction system disease. The presence of a left bundle branch block may indicate the presence of aortic stenosis, which can increase surgical mortality if it is severe.

Valvular Heart Disease

Although there are many forms of valvular heart disease, two types—aortic and mitral stenosis—primarily are associated with significantly increased operative risk. Patients with significant aortic stenosis appear to be at greatest risk, which is increased in the presence of atrial fibrillation, CHF, or coronary artery disease. Significant stenosis of aortic or mitral valves should be repaired before elective gynecologic surgery.

Severe valvular heart disease usually is evident during physical exertion. Common findings in such patients are listed in Table 25-17. The classic history presented by patients with severe aortic stenosis includes exercise dyspnea, angina, and syncope, whereas symptoms of mitral stenosis are paroxysmal and effort dyspnea, hemoptysis, and orthopnea. Most patients have a remote history of rheumatic fever. Severe stenosis of either valve is considered to be a valvular area of less than 1 cm^2, and diagnosis can be confirmed by echocardiography or cardiac catheterization.

Table 25-17 Signs and Symptoms of Valvular Heart Disease

Aortic Stenosis
1. Systolic murmur at right sternal border, which radiates into carotids
2. Decreased systolic blood pressure
3. Apical heave
4. Chest radiograph with calcified aortic ring, left ventricular enlargement
5. Electrocardiogram with high R waves, depressed T waves in lead I, and precordial leads
Mitral Stenosis
1. Precordial heave
2. Diastolic murmur at apex
3. Mitral opening snap
4. Suffused face and lips
5. Chest radiograph with left atrial dilation
6. Electrocardiogram with large P waves and right-axis deviation

Patients with valvular abnormalities are subdivided by the AHA into risk groups for the development of subacute bacterial endocarditis following surgery. **Patients in the highest-risk groups should receive prophylactic antibiotics immediately preoperatively to prevent subacute bacterial endocarditis** (Table 25-5). As defined by the AHA, only patients with prosthetic cardiac valves, congenital heart disease, and cardiac transplantation who develop cardiac valvulopathy should receive perioperative endocarditis prophylaxis (26). All other patients do not require antibiotics for subacute bacterial endocarditis prophylaxis. Routine prophylaxis for GI or GU procedures is not recommended. Only in cases of a known infection of the GI or GU tract should antibiotics coverage for enterococcus with *amoxicillin* or *ampicillin* or *vancomycin* be provided.

Patients with aortic and mitral stenosis tolerate sinus tachycardia and other tachyarrhythmias poorly. In patients with aortic stenosis, sufficient levels of *digitalis* should be provided to correct preoperative tachyarrhythmias, and *propranolol* may be used to control sinus tachycardia. Patients with mitral valve stenosis often have atrial fibrillation and, if present, *digitalis* should be used to reduce rapid ventricular response.

Patients with mechanical heart valves usually tolerate surgery well (196). These patients should receive antibiotic prophylaxis (Table 25-5). If the patient is taking *aspirin* therapy, it should be discontinued 1 week before the procedure and restarted as soon as it is considered safe by the surgeon. Patients with a bileaflet aortic valve with

no risk factors (atrial fibrillation, previous thromboembolism, left ventricular dysfunction, a hypercoagulable state, older-generation thrombogenic valve) generally do not require anticoagulation bridging. *Warfarin* should be stopped 72 hours prior to the procedure and resumed 24 hours after the procedure. In contrast, patients with a mechanical aortic valve and any above-mentioned risk factor, or a mechanical mitral valve, should be bridged with intravenous unfractionated *heparin* or subcutaneous low–molecular-weight *heparin* when the INR falls below 2. Anticoagulation should be stopped 6 to 8 hours (if using *heparin* drip) or 12 hours (if using low–molecular-weight heparin) before the surgery. Bridging anticoagulation should be restarted postoperatively when the patient's bleeding risk is low and can be stopped when the INR reaches therapeutic levels (197).

In the postoperative period, patients with mitral stenosis should be carefully monitored for pulmonary edema because they may not be able to compensate for the amount of intravenous fluid administered during surgery. Prevention of tachycardia is important, as it may lead to pulmonary edema. Patients with mitral stenosis frequently have pulmonary hypertension and decreased airway compliance. They may require more pulmonary support and therapy postoperatively, including prolonged mechanical ventilation.

For patients with significant aortic stenosis, it is imperative that a sinus rhythm be maintained during the postoperative period. Even sinus tachycardia can be deleterious because it shortens the diastolic time. Bradycardia less than 45 beats per minute should be treated with *atropine*. Supraventricular dysrhythmias may be controlled with *verapamil* or direct-current cardioversion. Particular attention should be provided to the maintenance of proper fluid status, digoxin levels, electrolyte levels, and blood replacement.

Hypertension

Patients with controlled essential hypertension have no increased risk of perioperative cardiac morbidity or mortality. Patients with concomitant heart disease are at elevated risk and should be completely evaluated by a cardiologist preoperatively. Laboratory studies should include an ECG, chest radiography, blood count, urinalysis, and serum electrolytes and creatinine measurement. Antihypertensive medications should be continued perioperatively. β-Blockers should be continued, parenterally if necessary, to avoid rebound tachycardia, hypercontractility, and hypertension. *Clonidine* may cause significant rebound hypertension, if withdrawn acutely. Angiotensin-converting enzyme inhibitor agents and angiotensin II receptor antagonists are associated with increased intraoperative hypotension and perioperative renal dysfunction possibly resulting from a hypovolemic state. It may be prudent to withhold these agents on the morning of surgery and resume them postoperatively when good renal function and euvolemia are confirmed (158).

[9] Patients with diastolic pressures higher than 110 mm Hg or systolic pressures higher than 180 mm Hg should receive medication to control their hypertension before surgery. β-Blockers may be particularly effective agents for treatment of preoperative hypertension (179).

Postoperative hypertension is usually treated parenterally because gastrointestinal absorption may be diminished, and transdermal absorption can be erratic in patients who are cold and rewarming. Commonly used parenteral antihypertensives are listed in Table 25-18.

Table 25-18 Common Parenteral Antihypertensives

Drug	Route	Initial Dose	Onset	Duration	Side Effects
Nitroprusside	IV infusion	0.5 μg/min	Immediate	2–5 min	Tachycardia, nausea
Labetalol	IV infusion	20 mg	5–10 min	4 hrs	Bronchospasm, dizziness, nausea
Esmolol	IV infusion	50 μg/min	2 hrs	9 min	Headache, somnolence, dizziness, hypotension
Nifedipine	Sublingual	10 mg	5 min	2 min	Hypotension, headache, dizziness, nausea, peripheral edema
Verapamil	IV infusion	5–10 mg	3–5 min	2–5 hrs	Nausea, headache, hypotension, dizziness, pulmonary edema

IV, intravenous.

Perioperative Antiplatelet Agents

Increasing numbers of patients undergo coronary revascularization procedures, otherwise known as coronary artery bypass grafting, or percutaneous coronary intervention, typically stent placement. With the evolution of bare-metal and drug-eluting stents, perioperative management of cardiovascular thrombotic risk versus perioperative bleeding and mortality is challenged. Given that drug-eluting stents generally require 12 months' treatment with dual agent *aspirin* and thienopyridine (i.e., clopidogrel), the American College of Cardiology and American Heart Association (ACC/AHA) guidelines recommend avoiding elective surgery within 12 months of drug-eluting stent placement. When surgery cannot wait, the ACC/AHA recommends continuation of *aspirin* perioperatively, discontinuation of *thienopyridine* 5 days prior to surgery, and resuming it as soon as possible postoperatively. Ultimately the risk of perioperative morbidity secondary to bleeding must be weighed against the risk of repeat thrombosis and cardiovascular morbidity and mortality. If a patient requires new placement of a cardiac stent and noncardiac surgery in the following 12 months, placement of a bare-metal stent is recommended rather than a drug-eluting stent, as these require only 4 to 6 weeks of dual-antiplatelet therapy. Again, *aspirin* should be continued perioperatively. Following a newly placed bare-metal stent, noncardiac surgery should be scheduled at least 30 to 45 days after the stent placement to decrease cardiac morbidity (179).

Hemodynamic Monitoring

Hemodynamic monitoring is integral to the perioperative management of patients with

cardiovascular and pulmonary diseases. The desire for the quantitative estimate of cardiac function resulted in the development of bedside PAC.

Before the development of the pulmonary artery catheter, central venous pressure (CVP) measurement was used to assess intravascular volume status and cardiac function. To measure the CVP, a catheter is placed in the central venous system, most frequently the superior vena cava, allowing an estimation of right atrial pressure. If the pulmonary vascularity and left ventricular function are normal, the CVP accurately reflects the left ventricular end-diastolic pressure (LVEDP). The LVEDP reflects cardiac output or systemic perfusion and was considered the standard estimator of left ventricular pump function. If right ventricular function is normal, the CVP accurately reflects intravascular volume.

When left or right ventricular dysfunction is present, measurement of pulmonary artery occlusion pressure can be used to accurately assess volume status and cardiovascular function. A baloon-tipped PAC, known as a Swan-Ganz catheter, is an invasive tool used to improve detection in cardiovascular function changes over clinical observation (198).

The distal lumen of the catheter, which is beyond the balloon occluding the pulmonary artery, measures left atrial pressure (LAP) and, in the absence of mitral valvular disease, LAP approximates LVEDP. Pulmonary–capillary wedge pressure (PCWP) equals the LAP, which equals LVEDP and is normal at 8 to 12 mm Hg. Because the standard pulmonary artery catheter has an incorporated thermistor, thermodilution studies can be performed to determine cardiac output. Knowledge of the cardiac output is helpful in establishing cardiovascular diagnoses. For example, a patient with hypotension, low-to-normal wedge pressure, and a cardiac output of 3 L per minute is most likely hypovolemic. The same patient with a cardiac output of 8 L per minute is probably septic with resultant low systemic vascular resistance.

The effect of PAC use on patient outcome is controversial. Several large trials did not confer a definite benefit to PAC use. A randomized controlled trial of 1,994 high-risk (American Society of Anesthesiologists class III or IV risk) patients aged 60 or older undergoing urgent or elective major noncardiac surgery compared outcomes of those who underwent PAC placement versus standard care. Results analyzed by a blinded assessor revealed no benefit of PAC over standard care with central venous catheters (199). Another randomized controlled trial enrolling 65 intensive care units in the United Kingdom found no difference in mortality among critically ill patients managed with or without a PAC (200). A meta-analysis of 13 randomized controlled trials of PAC use found no significant difference in mortality rates and an increased use of inotropes and intravenous vasodilators (201). **Routine preoperative use of PAC in noncardiac surgery patients is no longer indicated. Use of PAC in critically ill patients postoperatively remains controversial.**

Hematologic Disorders

The presence of hematologic disorders, although uncommon in gynecologic patients, significantly affects operative morbidity and mortality and should be considered routinely in preoperative evaluation. Preoperative assessment should include consideration of anemia, platelet and coagulation disorders, white blood cell function, and immunity.

Anemia

Moderate anemia is not in itself a contraindication to surgery because it can be corrected by transfusion. If possible, surgery should be postponed until the cause of the anemia can be identified and the anemia corrected without resorting to transfusion. By tradition, anesthetic and surgical practice recommended a hemoglobin level of greater than 10 g/dL or a hematocrit of greater than 30%. Data suggest a lower tolerance for pre- and intraoperative transfusion threshold to improve intra- and postoperative morbidity and mortality (202). It remains that no universal "transfusion threshold" is agreed upon, but that a hematocrit of less than 24% should prompt strong consideration (203). The circulating blood volume provides oxygen-carrying capacity and tissue oxygenation. Individual tolerance of anemia depends on overall physical fitness and cardiovascular reserve. Maintenance of adequate tissue perfusion requires an increase in cardiac output as hemoglobin concentration falls (189). In the healthy patient, oxygen delivery is unchanged when it falls below 7 g/dL (204). In contrast, a patient with ischemic heart disease will not tolerate anemia as well (205). The presence of cardiac, pulmonary, or other serious illness justifies a more conservative approach to the management of anemia. Patients with long-standing anemia may have normal blood volume levels and tolerate surgical procedures well. There is no evidence that mild to moderate anemia increases perioperative morbidity or mortality (205).

Autologous blood donation is advocated as a safer alternative for the patient; however, the use of preoperative autologous blood donation has come under scrutiny (206). **Preoperative autologous blood may lead to more liberal blood transfusion, iatrogenic anemia, volume overload, and bacterial contamination** (207). Preoperative autologous blood donation is poorly cost effective (208). The National Heart, Lung, and Blood Institute does not recommend collection of autologous blood for procedures with a likelihood of transfusion less than 10%, such as uncomplicated abdominal and vaginal hysterectomies (209).

Platelet and Coagulation Disorders

Surgical hemostasis is provided by platelet adhesion to injured vessels, which plugs the opening as the coagulation cascade is activated, resulting in the formation of fibrin clots. Functional platelets and coagulation pathways are necessary to prevent excessive

surgical bleeding. Platelet dysfunction is encountered preoperatively more frequently than coagulation disorders.

Platelets may be deficient in both number and function. The normal peripheral blood count is 150,000 to 400,000 per mm^3, and the normal life span of a platelet is approximately 10 days. Although there is no clear-cut correlation between the degree of thrombocytopenia and the presence or amount of bleeding, several generalizations can be made. If the platelet count is higher than 100,000/mm^3 and the platelets are functioning normally, there is little chance of excessive bleeding during surgical procedures. Patients with a platelet count higher than 75,000/mm^3 almost always have normal bleeding times, and a platelet count higher than 50,000/mm^3 is probably adequate. **A platelet count lower than 20,000/mm^3 often will be associated with severe and spontaneous bleeding.** Platelet counts higher than 1,000,000/mm^3 are often, paradoxically, associated with bleeding.

In patients with immune destruction of platelets, human leukocyte antigen (HLA)–matched donor-specific platelets may be required to prevent rapid destruction of transfused platelets. If surgery can be postponed, a hematology consultation should be obtained to identify and treat the cause of the platelet abnormality.

Abnormally low platelet counts result from either decreased production or increased consumption of platelets. Although there are numerous causes of thrombocytopenia, most are exceedingly uncommon. Decreased platelet production may be drug induced and is associated with the use of sulfonamides, cinchona alkaloids, *thiazide* diuretics, NSAIDs, gold salts, *penicillamine,* anticonvulsants, and *heparins* (210). Decreased platelet count is a feature of several diseases, including vitamin B_{12} and folate deficiency, aplastic anemia, myeloproliferative disorders, renal failure, and viral infections. Inherited congenital thrombocytopenia is extremely rare. More commonly, thrombocytopenia results from immune destruction of platelets by diseases such as idiopathic thrombocytopenia purpura and collagen vascular disorders. **Consumptive thrombocytopenia is a feature of disseminated intravascular coagulation, which is encountered most frequently in conjunction with sepsis or malignancy in the preoperative population.**

Platelet dysfunction most often is acquired, but may be inherited. Occasionally, a patient with von Willebrand disease, the second most common inherited disorder of coagulation, may be encountered in the preoperative setting. Platelet dysfunction is more difficult to diagnose than abnormalities of platelet count. A history of easy bruising, petechiae, bleeding from mucous membranes, or prolonged bleeding from minor wounds may signify an underlying abnormality of platelet function. Such dysfunction can be identified with the help of a bleeding time, but full characterization of the underlying etiology should be carried out with hematologic consultation. If at all possible, surgery should be postponed until therapy is instituted.

Disorders of the coagulation cascade often are diagnosed through a personal or family history of excessive bleeding during minor surgery, childbirth, or menses. Many women with menorrhagia are referred for surgical intervention and require a thorough preoperative evaluation for possible inherited disorders of hemostasis, such as factor VIII (hemophilia), factor IX (Christmas disease), factor XI deficiencies, and von Willebrand disease. Von Willebrand disease is the most common hereditary bleeding disorder, with prevalence in the general population of roughly 1%. Seventy percent to 90% of women with von Willebrand disease have menorrhagia (211). Identified women can be treated effectively with *desmopressin* nasal spray, avoiding unanticipated or excessive bleeding during surgery (212). In the absence of a genetic diagnosis, the diagnosis of von Willebrand disease is difficult and involves a combination of clinical and laboratory assessments, including von Willebrand factor antigen and von Willebrand factor functional activity or ristocetin cofactor assay (212). Physiologic fluctuations occur with von Willebrand factor levels, requiring repeat testing and consultation or referral to a hematologist. It is recommended that women presenting with menorrhagia without obvious pelvic abnormalities should be routinely screened for inherited bleeding disorders before undergoing invasive procedures.

There are few commonly prescribed drugs that affect coagulation factors, the exceptions being *warfarin* and *heparin.* Disease states that may be associated with decreased coagulation factor levels are primarily liver disease, vitamin K deficiency (secondary to obstructive biliary disease, intestinal malabsorption, or antibiotic reduction of bowel flora), and disseminated intravascular coagulation.

Preoperative laboratory screening for coagulation deficiencies is controversial. Routine screening is not warranted in patients who do not have historical evidence of a bleeding problem (213). Patients who are seriously ill or who will be undergoing extensive surgical procedures should undergo testing preoperatively to determine PT, partial thromboplastin time, fibrinogen level, and platelet count.

Blood Component Replacement

Packed red blood cells (PRBCs), which may be stored for several weeks, are used for most postoperative transfusions. Most clotting factors are stable for long periods. The exceptions are factors V and VIII, which decrease to 15% and 50% of normal, respectively. Most hematologic problems observed in the postoperative period are related to perioperative bleeding and blood component replacement. Although the primary cause of the bleeding is usually lack of surgical hemostasis, other factors, including deranged coagulation, may compound the problem. Such coagulopathy can result from massive transfusion (less than one blood volume) and is thought to be caused by dilution of platelets and labile coagulation factors by platelet- and factor-poor PRBCs, fibrinolysis, and disseminated intravascular coagulation.

A review in *Transfusion* questioned the traditional practice of limiting blood

component replacement in massive transfusion. Summarizing 14 articles and encompassing nearly 4,600 patients, the conclusions note a decrease in all-cause mortality with more liberal transfusion of platelets and fresh frozen plasma (FFP) (214).

A task force for the American Society of Anesthesiologists **recommended critical values for replacement in patients with massive transfusion and microvascular bleeding** (189):

1. **Platelet transfusion usually is indicated for counts less than 50,000/mm^3 (with intermediate platelet counts, i.e., 50,000/mm^3 to 100,000/mm^3, the transfusion of platelet concentrates should be based on the risk of more significant bleeding).**
2. **FFP therapy is indicated if the prothrombin or APTT values exceed 1.5 times the normal value.**
3. **Cryoprecipitate transfusion is indicated if fibrinogen concentrations decrease to less than 80 to 100 mg/dL.**

Cryoprecipitate transfusions are recommended for prophylaxis in nonbleeding perioperative patients with fibrinogen deficiencies or von Willebrand disease refractory to *desmopressin acetate* and bleeding patients with von Willebrand disease (212).

Donor blood is stored in the presence of citrate, which chelates calcium to prevent clotting, increasing the theoretical risk of hypocalcemia following massive transfusion. Citrate is metabolized at a rate equivalent to 20 U of blood transfused per hour; thus, routine supplementation of calcium is unnecessary. Close monitoring of calcium levels is required in patients with hypothermia, liver disease, or hyperventilation because citrate metabolism may be slowed. Hepatic metabolism of citrate to bicarbonate can result in metabolic alkalosis following transfusion, resulting in subsequent hypokalemia, despite the high level of extracellular potassium in stored blood.

Pulmonary Disease

In patients undergoing abdominal surgery, anesthesia-related airway irritation, splinting of breathing related to pain, and immobilization lead to several pulmonary physiologic changes, including a decrease in the functional residual capacity (FRC), an increase in ventilation–perfusion mismatching, and impaired mucociliary clearance of secretions from the tracheobronchial tree (215). **Risk factors for postoperative pulmonary complications include the following (Table 25-19) (216):**

- **Upper abdominal or thoracic, or abdominal aortic aneurysm surgery**
- **Surgical procedure time longer than 3 hours**
- **COPD**

- **Smoking within 2 months of surgery**
- **Use of *pancuronium* for general anesthesia**
- **New York Heart Association Class II pulmonary hypertension**
- **General anesthesia**
- **Emergency surgery**
- **Poor nutrition (serum albumin <3.5 mg/dL or BUN <8)**

Healthy, asymptomatic patients do not require preoperative pulmonary function testing, arterial blood gas measurements, or chest x-rays. Most patients with abnormal chest x-rays have history or physical examination findings suggestive of pulmonary disease.

Table 25-19 Predictors of Postoperative Pulmonary Complications[a]

Parameter	Value
Maximal breathing capacity	<50% predicted
FEV_1	<1 L
FVC	<70% predicted
FEV_1/FVC	<65% predicted
Pao_2	<60 mm Hg
$PaCO_2$	>45 mm Hg

[a]*Complication* defined as atelectasis or pneumonia.
FEV, forced expiration volume; FVC, forced vital capacity; Pao_2, partial pressure of oxygen, arterial; $PaCO_2$, partial pressure of carbon dioxide, arterial.
Adapted from **Blosser SA, Rock P.** Asthma and chronic obstructive lung disease. In: Breslow MJ, Miller CJ, Rogers MC, eds. *Perioperative Management*. St. Louis, MO: Mosby; 1990:259–280.

Asthma

Asthma affects approximately 22 million individuals in the United States, including 6% of children (217). It is characterized by a history of episodic wheezing, physiologic evidence of reversible obstruction of the airways either spontaneously or following bronchodilator therapy, and pathologic evidence of chronic inflammatory changes in the bronchial submucosa.

Multiple stimuli are noted to precipitate or exacerbate asthma, including environmental allergens or pollutants, respiratory tract infections, exercise, cold air, emotional stress, nonselective β-adrenergic blockers, and NSAIDs. Management of asthma includes removal of the inciting stimuli and use of appropriate pharmacologic

therapy to relax the airways and alleviate inflammation (217). The optimal therapy for asthma involves managing the acute symptoms and long-term management of the inflammatory component of the disease.

Pharmacotherapy of Asthma

The treatment of asthma is divided into long-term control modalities and short-term modalities. **Recognizing the underlying pathophysiology in asthma as an inflammatory condition, inhaled corticosteroids are the cornerstone for maintenance therapy.** Onset of action is slow (several hours), and up to 3 months of steroid therapy may be required for optimal improvement of bronchial hyperresponsiveness. Even with acute bronchospasm, steroid treatment can enhance the beneficial effect of β-adrenergic treatment. During acute exacerbations of asthma, a short course of oral steroids, in addition to inhaled steroids, may be necessary. For adults with chronic asthma, only a minority will require chronic oral steroid therapy. Patients taking oral steroids should receive intravenous steroid support in the form of 100 mg of hydrocortisone IV every 8 hours perioperatively, sharply tapering within 24 hours of surgery to avoid adrenal insufficiency. Other long-term control therapies include (217):

1. Leukotriene modifiers (i.e., *montelukast*): These agents interfere with leukotrienes, substances released from mast cells, eosinophils, and basophils important in the inflammatory response.
2. *Cromolyn sodium:* Highly active in the treatment of seasonal allergic asthma in children and young adults. It is usually not as effective in older patients or in patients in whom asthma is not allergic in nature.
3. *Immunomodulators:* Omalizumab, a monoclonal antibody to immunoglobulin E (IgE), has gained support for prevention and may be an important adjunct in symptomatic suppression.
4. Long-term β_2-adrenergic agonists (i.e., *salmeterol*): Although not appropriate for single-agent management or use in mild disease, they are an important adjunct in the suppression of symptoms in patients with significant disease.
5. Methylxanthines (i.e., *theophylline*): These were relegated to third-line status in the management of asthma. *Theophylline* toxicity can develop when other drugs such as *ciprofloxacin, erythromycin, allopurinol, Inderal,* or *cimetidine* are concomitantly administered. Therapeutic serum levels must be monitored closely.

β_2-Adrenergic agonists remain the first-line drugs for acute asthma attacks. These drugs, inhaled four to six times daily, rapidly relax smooth muscle in the airways and are effective for up to 6 hours. Studies of β_2-agonists in chronic asthma failed to show any influence of these agents on the inflammatory component of asthma. β_2-

Agonists are recommended for short-term relief of bronchospasm ("rescue inhalers") or as first-line treatment for patients with very infrequent symptoms or symptoms provoked solely by exercise (217).

Anticholinergic agents are weak bronchodilators that work via inhibition of muscarinic receptors in the smooth muscle of the airways. The quaternary derivatives, such as *ipratropium bromide* (*Atrovent*), are available in an inhaled form that is not absorbed systemically. Anticholinergic drugs may provide additional benefit in conjunction with standard steroid and bronchodilator therapy but should not be used as single-agent therapy because they do not inhibit mast cell degranulation, do not have any effect on the late response to allergens, and do not have an anti-inflammatory effect (217).

Perioperative Management of Asthma

In patients with asthma, elective surgery should be postponed whenever possible until pulmonary function and pharmacotherapeutic management are optimized. Recent guidelines of the American Academy of Allergy, Asthma and Immunology recommend three interventions to reduce perioperative pulmonary complications related to asthma (217):

1. Review the patient's asthmatic control, including the need for oral steroids.
2. Optimize the patient's symptomatic control through the use of long-acting pharmacotherapy, including oral steroids if needed.
3. For patients on oral steroid therapy within 6 months of therapy or for patients using large doses of inhaled corticosteroids, consider perioperative stress dose steroids.

For mild asthma, the use of inhaled β-adrenergic agonists preoperatively may be all that is required. For chronic asthma, optimization of steroid therapy will greatly decrease alveolar inflammation and bronchiolar hyperresponsiveness. Inhaled β_2-agonists should be added to therapy as needed for further control of asthma. Each drug prescribed should be used in maximal dosage before adding an additional agent. Preoperative treatment with combined corticosteroids and an inhaled β_2-adrenergic agonist for a 5-day period may decrease the risk of postoperative bronchospasm in patients with asthma (218). For patients undergoing emergent surgery who have significant bronchoconstriction, a multimodal approach should be instituted, including aggressive bronchodilator inhalation therapy and intravenous steroid therapy. The role of spirometry, outside of cardiothoracic procedures, has limited value in predicting postoperative pulmonary complications and should be limited to the confirmation of undiagnosed obstructive pulmonary disease (219).

Chronic Obstructive Pulmonary Disease

[9] COPD is the greatest risk factor for the development of postoperative pulmonary complications. COPD encompasses both chronic bronchitis and emphysema, disease entities that often occur in tandem. Cigarette smoke is implicated in the pathogenesis of both, and any treatment plan must include cessation of smoking (220). Chronic bronchitis is defined as the presence of productive cough on most days for at least 3 months per year and for at least 2 successive years (221). It is characterized by chronic airway inflammation and excessive mucus production. The histologic changes of emphysema include destruction of alveolar septa and distension of airspaces distal to terminal alveoli. The destruction of alveoli results in air trapping, loss of pulmonary elastic recoil, collapse of the airways in expiration, increased work of breathing, and significant ventilation–perfusion mismatching (221). The impaired ability to cough effectively and clear secretions predisposes patients with COPD to atelectasis and pneumonia in the postoperative period.

Patients with COPD and a history of heavy smoking account for most postoperative pulmonary complications in gynecologic surgical patients. The severity of COPD can be determined preoperatively via a thorough history and physical examination. According to recommendations regarding the use of preoperative pulmonary function tests by the American College of Physicians, these should be reserved for individuals in whom COPD is suspected, but unconfirmed (219,222). Typically, patients with COPD demonstrate impaired expiratory air flow, manifested by diminished FEV_1, forced vital capacity (FVC).

The preoperative preparation for patients at risk for postoperative pulmonary complications should include cessation of smoking for as long as possible preoperatively. One to 2 weeks of cessation decreases sputum volume. Two months of smoking abstinence is required to significantly lower the risk of postoperative pulmonary complications (215). Longer periods of abstinence can be counseled in patients undergoing elective surgery.

In patients with severe COPD, maximum improvement in airflow limitation can be achieved with a therapeutic trial of high-dose oral corticosteroids followed by a 2-week trial of high-dose inhaled steroid (*beclomethasone* 1.5 mg per day or the equivalent) in addition to inhaled bronchodilator therapy. Ideally, oral and inhaled steroid therapy should be initiated 1 to 2 weeks preoperatively. Inhaled steroids, in particular, address the inflammatory component of COPD. Oral steroid therapy initiated preoperatively should be maintained throughout the perioperative period and then tapered postoperatively. β-Adrenergic agonist therapy can be initiated at least 72 hours preoperatively and is beneficial in patients who demonstrate either clinical or spirometric improvement on bronchodilators.

Patients with COPD and an active bacterial infection suggested by purulent sputum should undergo a full course of antibiotic therapy before surgery. The

antibiotic used should cover the most likely etiologic organisms, *Streptococcus pneumoniae* and *Haemophilus influenzae.* In any patient with acute upper respiratory infection, surgery should be delayed if possible. The use of antibiotics to sterilize the sputum in the absence of evidence of an acute infection should be avoided because this practice may lead to bacterial resistance.

Aggressive pulmonary toilet, including incentive spirometry, chest physical therapy, and continuous positive airway pressure devices, reduced the risk of perioperative pulmonary complications in patients undergoing upper abdominal surgery, many of which can be instituted preoperatively (222).

Postoperative Pulmonary Management

Atelectasis

Atelectasis accounts for more than 90% of all postoperative pulmonary complications. The pathophysiology involves a collapse of the alveoli, resulting in ventilation–perfusion mismatching, intrapulmonary venous shunting, and a subsequent drop in the PaO_2. Collapsed alveoli are susceptible to superimposed infection, and if managed improperly, atelectasis will progress to pneumonia. Despite the decrease in PaO_2, the partial pressure of carbon dioxide (PCO_2) remains unaffected unless atelectatic changes progress to large volumes of the lung or pre-existing lung disease is present.

Auscultation of the chest may reveal decreased breath sounds at the bases or dry rales upon inspiration. Percussion of the posterior thorax may suggest elevation of the diaphragm. Radiologic findings include the presence of horizontal lines or plates on posteroanterior chest x-rays, occasionally with adjacent areas containing hyperinflation. These changes are most pronounced during the first 3 postoperative days.

Therapy for atelectasis should be aimed at expanding the alveoli and increasing the FRC. The most important maneuvers are those that promote maximal inspiratory pressure, which is maintained for as long as possible. It can be achieved with aggressive supervised use of incentive spirometry, deep breathing exercises, coughing, and in some cases, the use of positive expiratory pressure with a mask (continuous positive airway pressure). Oversedation should be avoided, and patients should be encouraged to ambulate and change positions frequently.

Cardiogenic (High-Pressure) Pulmonary Edema

Cardiogenic pulmonary edema can result from myocardial ischemia, myocardial infarction, or from intravascular volume overload, particularly in patients who have low cardiac reserve or renal failure. The process usually begins with an increase in the fluid in the alveolar septa and bronchial vascular cuffs, ultimately seeping into the alveoli. Complete filling of the alveoli impairs secretion and production of surfactant. Concomitant with alveolar flooding, there is a decrease in lung compliance, impairment

of the oxygen diffusion capacity, and an increase in the arteriolar–alveolar oxygen gradient. Ventilation–perfusion mismatching in the lung results in a decrease in the PaO_2, resulting eventually in decreased oxygenation of the tissues and impairment of cardiac contractility.

Symptoms may include tachypnea, dyspnea, wheezing, and use of the accessory muscles of respiration. Clinical signs may include distension of the jugular veins, peripheral edema, rales upon auscultation of the lungs, and an enlarged heart. Radiographic findings may include the presence of bronchiolar cuffing and increased interstitial fluid markings extending to the periphery of the lung. The diagnosis can be confirmed with the use of central hemodynamic monitoring, which will denote an elevated CVP and, more specifically, an elevation in the PCWP.

The patient's volume status should be evaluated thoroughly. In addition, myocardial ischemia or infarction should be ruled out by performing ECG and analyzing cardiac enzyme levels. The management of cardiogenic pulmonary edema includes oxygen support, aggressive diuresis, and afterload reduction to increase the cardiac output. In the absence of myocardial infarction, an inotropic agent may be used. Mechanical ventilation should be reserved for cases of acute respiratory failure.

Noncardiogenic Pulmonary Edema (Adult Respiratory Distress Syndrome)

In contrast with cardiogenic pulmonary edema, in which alveolar flooding is a result of an increase in the hydrostatic pressure of the pulmonary capillaries, alveolar flooding in patients with adult respiratory distress syndrome (ARDS) is the result of an increase in pulmonary capillary permeability. The primary pathophysiologic process is one of damage to the capillary side of the alveolar–capillary membrane. This damage results in rapid movement of fluid containing high concentrations of protein from the capillaries to the pulmonary parenchyma and alveoli. Lung compliance decreases and oxygen diffusion capacity is impaired, resulting in hypoxemia. If not managed aggressively, respiratory failure may result. **The causes of ARDS include shock, sepsis, multiple red blood cell transfusions, aspiration injury, inhalation injury, pneumonia, pancreatitis, disseminated intravascular coagulation, and fat emboli** (244). Twenty-eight-day mortality is reported between 25% and 40%, with overall mortality as high as 70% (223). Irrespective of the cause, which should be identified and treated if possible, the evolving clinical picture and management are very similar.

Clinically, ARDS passes through several stages. Initially, patients develop tachypnea and dyspnea with no remarkable findings on clinical evaluation or on chest x-ray. Chest x-rays eventually reveal bilateral diffuse pulmonary infiltrates. As lung compliance becomes impaired, FRC, tidal volume, and vital capacity decrease. The PaO_2 decreases and, characteristically, increases only marginally with oxygen supplementation. An attempt should be made to maintain the arterial oxygen level above 90%. This may be

achievable initially by administering oxygen by mask. For patients with severe hypoxemia, endotracheal intubation with positive-pressure ventilation should be instituted.

Hemodynamic monitoring is invaluable and should be initiated early in the course of the disease process in the appropriate intensive care unit setting. Patients with any evidence of fluid overload should receive aggressive diuresis, whereas others may require fluid resuscitation for maintenance of tissue perfusion while the PCWP is maintained below 15 mm Hg. Pulmonary wedge pressure may be falsely elevated when PEEP is being applied. **The goal of management is to maintain the lowest PCWP, with acceptable cardiac output and blood pressure.** In the setting of hypotension and oliguria, inotropic support with *dopamine* or *dobutamine* or both is helpful.

With aggressive management, particularly if the inciting cause is identified and treated, ARDS can be reversed during the first 48 hours with few sequelae. After the first 48 hours, progression of the ARDS will cause lung damage that may leave residual pulmonary fibrosis. The long-term outcome is usually apparent within the first 10 days, at which time approximately half of patients are weaned from ventilatory support or have died (223).

Renal Disease

The need for surgical intervention in patients with renal impairment resulted in the development of a very specialized medical approach to their care. Precautions are necessary to compensate for the kidneys' impaired ability to regulate fluids and electrolytes and excrete metabolic waste products. Equally important are the unique problems that develop in patients with chronic renal impairment, including an increased risk of sepsis, coagulation defects, impaired immune function and wound healing, and a propensity to develop specific acid–base abnormalities. Special consideration must be given to a variety of different medications, anesthetic agents, and numerous hematologic and nutritional factors that are important in the successful surgical care of patients with renal insufficiency.

Management of fluid levels and cardiovascular hemodynamics in patients with acute or chronic renal impairment is paramount. Intravascular fluid volume changes that lead to hypertension or hypotension are very common in these patients and often are difficult to manage secondary to autonomic dysfunction, acidosis, and other problems that are inherent to the underlying kidney disease. Dialysis-dependent patients are especially susceptible to postoperative complications, and invasive monitoring should be considered to help guide fluid replacement and avoid volume overload.

Co-management of dialysis-dependent patients with their nephrologists is imperative to reduce morbidity and mortality in the perioperative period. For those patients with end-stage renal disease (ESRD) on hemodialysis, dialysis is frequently recommended

the day prior to surgery to allow patients to be as euvolemic as possible prior to their procedure. Patients who perform peritoneal dialysis may increase their regimen during the week preceding surgery to offset potential delays in resumption of peritoneal dialysis postoperatively. Dialysis should be resumed according to the patient's normal schedule postoperatively. A short-lived but rather significant fall in the number of platelets occurs during dialysis; in addition, *heparin* is used in hemodialysis equipment to prevent clotting. Because of these factors and concerns about postoperative bleeding, dialysis is usually avoided during the first 12 to 24 hours following surgery. If patients require significant intraoperative volume repletion or blood transfusion, they are at an increased risk for volume overload and earlier dialysis may be necessary to prevent significant volume overload.

The major hematologic concern in patients with chronic renal insufficiency is the increased incidence of bleeding. These bleeding problems are secondary to abnormal bleeding times and, in particular, disorders of platelet secretion, platelet aggregation, and decreased von Willebrand factor activity (224). Anemia, which is common in patients with renal insufficiency, should be treated preoperatively with erythropoiesis-stimulating agents to allow patients to enter surgery at their target hemoglobin concentration. Checking a bleeding time is no longer recommended prior to surgery in patients with ESRD as a normal bleeding time does not predict the safety of surgical procedures. Optimizing preoperative hemoglobin, appropriate dialysis timing, and the use of desmopressin, cryoprecipitate, or conjugated estrogens can reduce uremic bleeding (225,226).

Impaired kidney function causes phosphate retention by the kidney and impaired vitamin D metabolism. Therefore, hypocalcemia is common in patients with renal insufficiency, but tetany and other signs of hypocalcemia are relatively uncommon because metabolic acidosis increases the level of ionized calcium. Oral phosphate binders, such as *aluminum hydroxide* (1 to 2 g per meal), and dietary phosphate restriction (1 g per day) is the usual treatment for hypocalcemia–hyperphosphatemia in patients with renal insufficiency. In chronic situations, because of central nervous system toxicity associated with elevated aluminum levels, it is preferable to treat hypocalcemia–hyperphosphatemia with large doses of *calcium carbonate* (6 to 12 g per day) rather than with the standard aluminum-containing antacids (227).

Approximately 20% of patients with renal insufficiency exhibit clinical evidence of protein-calorie malnutrition. Vitamin deficiencies, most notably with water-soluble vitamins, occur with dialysis. Nutritional disturbances in patients with chronic renal insufficiency arise secondary to deficiencies in protein intake, and studies show that, in patients with chronic renal insufficiency, their kidneys are hyperfiltrating (228). Postoperatively, both protein and caloric intake may need to be increased dramatically to meet catabolic demands in surgical patients. As much as 1.5 g/kg of protein and 45 kcal/kg of calories may be needed (228). Cardiovascular disease is very common in

patients with chronic kidney disease and complications are the leading cause of mortality in patients with ESRD (229). Careful preoperative cardiovascular risk assessment should be done for patients with ESRD with a focus on optimization preoperatively to reduce cardiovascular events in the perioperative period.

Patients with chronic renal disease have an altered ability to excrete drugs and are prone to significant metabolic derangements secondary to the altered bioavailability of many commonly used medications. Because of this, and the effect of dialysis on drug pharmacokinetics, the gynecologic surgeon and nephrologist must be aware of the lowered metabolism and bioavailability of narcotics, barbiturates, muscle relaxants, antibiotics, and other drugs that require renal clearance. Pain control in the perioperative period can be achieved with a variety of agents including acetaminophen, tramadol, and certain opiates. Non-opioids are always preferred, and acetaminophen can be used without dose adjustment (230). Morphine should be avoided in patients with renal dysfunction while fentanyl or hydromorphone can be used if opiates are necessary (230,231).

Liver Disease

Management of perioperative problems in gynecologic patients with liver disease requires a comprehensive understanding of normal liver physiology and the pathophysiology underlying diseases of the liver that may complicate surgery or recovery. **Patients with liver disease often have numerous complicated problems involving nutrition, coagulation, wound healing, encephalopathy, and infection.**

Table 25-20 Child's Classification of Liver Dysfunction

Parameter	Child Classification		
	A	B	C
Bilirubin	<2.0	2.0–3.0	>3.0
Albumin	>3.5	3.0–3.5	<3.0
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Mild	Advanced
Nutritional status	Excellent	Good	Poor

History and Physical Examination

Patients with a history of alcohol abuse, drug use, hepatitis, jaundice, blood product exposure, or a family member with liver disease should undergo biochemical evaluation. During the physical examination, note should be made of any jaundice, signs of muscle wastage, ascites, right upper quadrant tenderness, palmar erythema, or hepatomegaly.

Laboratory Testing

The biochemical profile (alkaline phosphatase, calcium, lactate dehydrogenase, bilirubin, serum glutamic–oxaloacetic transaminase, cholesterol, uric acid, phosphorous, albumin, total protein, and glucose) is not useful for routine preoperative evaluation. Mild abnormalities can result in further extensive testing that requires consultation, delays in surgery, and increased cost without net benefit. A possible exception is selected use of biochemical testing when the history or physical examination reveals abnormalities. Patients with known liver disease should undergo albumin and bilirubin testing using the Child's risk classification (Table 25-20). This system was originally designed to predict mortality following portosystemic shunt surgery. It divides patients into three classes of severity based on five easily assessed clinical parameters. Measurement of PT may be helpful in patients with significant histories of liver disease. If a history of hepatitis is ascertained, the patient should be tested for serum aminotransferase, alkaline phosphatase, bilirubin, albumin levels, and PT. Serologic documentation of hepatitis is important.

Drug Metabolism

Patients with altered liver function should be carefully monitored because of the prolonged action of many medications used during surgery. In addition to impaired metabolism, hypoalbuminemia decreases drug binding, which alters serum levels and biliary clearance rates. The degree of hepatic metabolism varies greatly, depending on the type of medication considered.

Determination of Operative Risk

Although it is well known that acute hepatobiliary damage results in increased morbidity and mortality in the surgical patient, estimating the operative risk in patients with hepatic dysfunction is difficult based on the history and physical examination. **The most accurate method for risk assessment of surgery in patients with hepatic dysfunction is Child's classification** (Table 25-20). Using this system, accurate assessment of morbidity and mortality can be directly related to the degree of liver dysfunction (232). The Child's classification is useful for patients undergoing a variety of different types of abdominal surgery. Data show operative mortalities of 10%, 30%, and 82% for each of the three Child's classifications, respectively, while other data called this into question with operative mortality of 2%, 12%, and 12% (233,234). The major cause of perioperative death was often sepsis. This classification correlated significantly with postoperative complications such as bleeding, renal failure, wound dehiscence, and sepsis. Another method for determining operative risk in patients with cirrhosis is the Model for End-Stage Liver Disease (MELD), which takes into account the patient's PT, bilirubin, and creatinine with various iterations used to better predict perioperative morbidity and mortality (235). Originally designed to predict outcomes in

cirrhotic patients undergoing the transjugular intrahepatic portosystemic shunt (TIPS) procedure, it was further studied to include patients undergoing other surgical procedures. In patients with a MELD score greater than 15, elective surgery should be deferred (236).

Acute Viral Hepatitis

Acute viral hepatitis poses an increased risk of operative complications and perioperative mortality and is a contraindication for elective surgery (237). Elective surgery should be delayed for approximately 1 month after the results of all biochemical tests have returned to normal (238). In patients with ectopic pregnancy, hemorrhage, or bowel obstruction secondary to malignancy, surgical intervention must take place before normalization of serum transaminase levels (237). In these situations, the perioperative morbidity (12%) and mortality (9.5%) rates are much higher than when they are performed under ideal situations (239).

Chronic Hepatitis

Chronic hepatitis is a group of disorders characterized by inflammation of the liver for at least 6 months. The disease is divided by morphologic and clinical criteria into chronic persistent hepatitis and chronic active hepatitis. A liver biopsy is usually required to establish the extent and type of injury. The surgical risk in these patients correlates most closely with the severity of disease. The risk of surgery in patients with asymptomatic or mild disease is minimal in contrast to a significant risk for those patients who have symptomatic chronic active hepatitis. Elective surgery is contraindicated in symptomatic patients, and nonelective surgery is associated with significant morbidity (238). **Asymptomatic carriers of the hepatitis B virus (HBV; individuals who test positive for the HBV surface antigen) are not at increased risk for postoperative complications in the absence of elevated aminotransferase levels and liver inflammation.**

Alcoholic Liver Disease

Alcoholic liver disease encompasses a spectrum of diseases including fatty liver, acute alcoholic hepatitis, and cirrhosis. Elective surgery is not contraindicated in patients with fatty liver because liver function is preserved. **If nutritional deficiencies are discovered, they should be corrected before elective surgery.** Acute alcoholic hepatitis is characterized on biopsy by hepatocyte edema, polymorphonuclear leukocyte infiltration, necrosis, and the presence of Mallory bodies. Elective surgery in these patients is contraindicated (240). Abstinence from alcohol for approximately 6 to 12 weeks along with clinical resolution of the biochemical abnormalities are recommended before surgery is considered. Severe alcoholic hepatitis may persist for several months despite abstinence and, if any question of continued activity exists, a liver biopsy should

be repeated (241). In cases of urgent or emergent surgery on patients with alcohol dependence, administration of tapered doses of *benzodiazepine* is appropriate as prophylaxis against alcohol withdrawal.

Cirrhosis

Cirrhosis is an irreversible liver lesion characterized histologically by parenchymal necrosis, nodular degeneration, fibrosis, and a disorganization of hepatic lobular architecture. The most serious complication of cirrhosis is portal venous hypertension, which ultimately leads to bleeding from esophageal varices, ascites, and hepatic encephalopathy. Conventional liver biochemical test results correlate poorly with the degree of liver impairment in patients with cirrhosis. Hepatic dysfunction may be somewhat quantified by low albumin levels and prolonged PTs.

Surgical risk is increased in patients with advanced liver disease, although it is substantially greater in emergency surgery than in elective surgery. Perioperative mortality correlates with the severity of cirrhosis and can be estimated through the use of the Child's classification (Table 25-20) and the Model for End-Stage Liver Disease (MELD) score. In patients with Child's class A cirrhosis, surgery can usually be performed without significant risk, whereas in patients with Child's class B or C, surgery poses a major risk and requires careful preoperative consideration. Preoperative preparation should include the following measures: (i) optimizing nutritional status by enteral and parenteral nutrition and supplementation with vitamin B_1, (ii) correcting coagulopathy with administration of FFP or cryoprecipitate or both, (iii) minimizing pre-existing encephalopathy, (iv) preventing sepsis from spontaneous bacterial peritonitis by administering prophylactic antibiotic therapy, and (v) optimizing renal function and carefully correcting electrolyte abnormalities (242). Meticulous preoperative preparation focused on correcting abnormalities associated with advanced liver disease may improve surgical outcomes (243).

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CHAPTER 26

Gynecologic Endoscopy



Malcolm G. Munro, William H. Parker

Laparoscopy
- Diagnostic Laparoscopy
- Therapeutic (Operative) Laparoscopy
- Patient Preparation and Communication
- Equipment and Technique
- Complications

Hysteroscopy
- Diagnostic Hysteroscopy
- Operative Hysteroscopy
- Endometrial Ablation
- Patient Preparation and Communication
- Equipment and Technique
- Complications

KEY POINTS

1 In gynecology, endoscopes are used most often to diagnose conditions and/or direct surgical procedures by direct visualization of the peritoneal cavity (laparoscopy) or the inside of the uterus (hysteroscopy).

2 When used appropriately, endoscopic surgery offers the benefits of reduced procedure-related pain, improved cosmetic result, lower cost, and faster recovery.

3 Endoscopic surgery is a highly technical process. Consequently, surgeons must thoroughly understand the function and limitations of endoscopic and related equipment, as well as troubleshooting technical adversity.

4 At the present time, there is no evidence that "robotic" assistance to laparoscopic surgery has any clinical, cost, or cosmetic advantages over laparoscopic surgery. Available evidence is that cost is increased while cosmetic results are not as good based on the location and length of incisions.

5 Laparoscopic gynecologic surgeons should be prepared for the spectrum of pathologic and anatomical situations that may be encountered, considering bowel, bladder, ureter, and vascular structures that may be involved.

6 The patient considering laparoscopic surgery should be properly counseled regarding the potential outcomes, including adverse outcomes, and the risk of conversion to laparotomy.

7 The initial entry into the abdominal/peritoneal cavity must be considered carefully, as it can be associated with a large number of the complications encountered during laparoscopic surgery. The main entry strategies are "open laparoscopy," often referred to as the Hasson entry, and "closed" entry, which includes preinsufflation using a hollow needle, and "direct entry" techniques where the port is passed through the abdominal wall without prior inflation of the peritoneal cavity.

8 Proper patient selection and intraoperative management are critical for laparoscopic surgery for ovarian cysts. If malignancy is strongly suspected, laparotomy may be preferable.

9 Laparoscopic myomectomy usually requires laparoscopic suturing; thus, more technical skills are needed than with many other endoscopic procedures.

10 Laparoscopic total hysterectomy comprises any removal of the uterus where at least part of the dissection is accomplished laparoscopically, while the remainder, if any, is finished vaginally.

11 Dehiscence and hernia risk appear to significantly increase when the fascial incision created for laparoscopic instrumentation is larger than 10 mm in diameter.

12 The incidence of unintended injuries associated with the use of radiofrequency (RF) electricity can be reduced with a good understanding of electrosurgical principles. Surgeons should always be in direct control of electrode activation and all electrosurgical hand instruments should be removed from the peritoneal cavity when not in use.

13 Patients recovering from laparoscopic surgery usually feel better every day. Pain diminishes, gastrointestinal function improves rapidly, and fever is extremely unusual. Therefore, if a patient's condition is not improving, possible complications of anesthesia or surgery should be considered.

14 Hysteroscopy is useful as a diagnostic aid by allowing direct evaluation of the endometrial cavity. Diagnostic hysteroscopy is superior to hysterosalpingography in the evaluation of the endometrial cavity, but the diagnostic accuracy of transvaginal ultrasonography is similar, especially when sonographic contrast is injected into the endometrial cavity.

15 A number of intrauterine procedures can be performed under hysteroscopic direction, including adhesiolysis, sterilization, transection of a uterine septum, resection of leiomyomas and polyps, removal of retained products of conception, and endometrial destruction, usually with RF resection, desiccation, or vaporization.

16 Most diagnostic and operative hysteroscopic procedures can be performed in an office or procedure room setting with minimal discomfort and at a much lower cost than in a surgical center or a traditional operating room.

17 The two major risks of hysteroscopic surgery are perforation, with the potential for damage to surrounding structures such as bowel, bladder, and blood vessels; and the fluid and electrolyte consequences of systemic overload of the fluid distension needed to create an operative field.

18 The risks of perforation can be mitigated by careful attention to access technique and the careful and informed use of intrauterine energy-based systems.

19 Risks of systemic overload of distension media can be minimized with the use of normal saline as the distending medium, and by careful attention to measurement of systemic absorption, a process that is best accomplished using automated fluid management systems.

Endoscopic procedures use a narrow telescope, an "endoscope" to view the interior of a viscus or preformed space. Although the first medical endoscopic procedures were

performed more than 100 years ago, the potential of this method has been extended to perform a variety of operations. [1] In gynecology, endoscopes are used most often to diagnose conditions or direct the performance of surgical procedures in the peritoneal cavity (laparoscopy) or the inside of the uterus (hysteroscopy).

[2] **When used appropriately, endoscopic surgery offers the benefits of reduced pain, improved cosmesis, lower cost, and faster recovery.** The indications for endoscopic surgery are outlined here, including the technology, potential uses, and complications of laparoscopy and hysteroscopy.

[3] Because endoscopic surgery relies so much on technology—distension, lighting, imaging, energy, mechanical instrumentation—surgeons must thoroughly understand the function and limitations of endoscopic and related equipment, and be prepared for troubleshooting technical activity.

LAPAROSCOPY

The past five decades have witnessed rapid progress and technologic advances in gynecologic laparoscopy. Operative laparoscopy was largely developed in the 1970s, and in the early 1980s, laparoscopy was first used to direct the application of laser or radiofrequency (RF) electrical energy for the treatment of advanced stages of endometriosis. The use of high-resolution (1), and high definition (HD) video cameras (2) in operative laparoscopy has made it easier to view the pelvis during the performance of complex procedures. **Most procedures that were previously performed using traditional laparotomy techniques became feasible with the laparoscope including adnexal procedures such as ovarian cystectomy and removal of ectopic pregnancy; uterine surgery, such as myomectomy and hysterectomy; and pelvic floor reconstructive procedures such as sacral colposuspension.** The endoscopic approach may have drawbacks for some patients. Although many laparoscopic procedures reduce the cost and morbidity associated with surgery, others have been replaced by even less invasive procedures, and a few have not been shown to be effective replacements for more traditional operations.

[4] The use of microprocessor-assisted laparoscopy permits the surgeon to operate remote from the operative field, in a sitting position, with the so-called "robot" allowing translation of natural hand manipulations to the peritoneal cavity with the specially designed instruments. **Evidence suggests that clinical outcomes with and without microprocessor-assisted ("robotic") laparoscopy are similar, but that the costs associated with the use of this device are greater** (3). There is evidence that the cosmetic result—the sum of incision number, length, and location—is less acceptable to patients than standard laparoscopy or even small laparotomies (4–6). As a result, for competent laparoscopic surgeons, use of this device adds nothing to the performance of laparoscopic gynecologic surgery except cost.

Diagnostic Laparoscopy

The objective lens of a laparoscope can be positioned to allow wide-angle or magnified views of the peritoneal cavity. The clarity and illumination of the optics facilitate greater appreciation of fine details than is possible with the naked eye. For example, laparoscopy is the standard method for the surgical diagnosis of endometriosis and pelvic adhesions because no other imaging technique provides the same degree of sensitivity and specificity.

There are limitations to diagnostic laparoscopy. The view of the operative field may be restricted, and if tissue or fluid becomes attached to the lens, vision may be obscured. Soft tissues, intramural myomas, or the inside of a hollow viscus such as the uterus or urinary bladder cannot be visualized or palpated. For assessment of these tissues, an imaging modality, such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), is superior. Because of its ability to view soft tissue, ultrasonography is more accurate than laparoscopy for the evaluation of the inside of adnexal masses. The intraluminal contour of the uterus can be shown only by hysteroscopy or contrast imaging such as contrast hysterosonography, hysterosalpingography (HSG), or MRI. Transvaginal ultrasonography (TVUS), in combination with serum assays of β-human chorionic gonadotropin (β-hCG) and progesterone, can be used to diagnose ectopic pregnancy, usually allowing medical therapy to be given without laparoscopic confirmation (7). As a result of the advances in laboratory testing and imaging technology, laparoscopy is more often used to confirm a clinical impression than for initial diagnosis.

Laparoscopy may disclose abnormalities that are not necessarily related to the patient's problem. Although endometriosis, adhesions, leiomyomas, and small cysts in the ovaries are common, they are frequently asymptomatic. Thus, diagnostic laparoscopy must be performed prudently, interpreting findings in the context of the clinical problem and other diagnoses.

Therapeutic (Operative) Laparoscopy

The role of laparoscopy in the operative management of gynecologic conditions has evolved from a curiosity to the recognized standard of care. Many procedures previously performed as traditional laparotomic and vaginal operations are readily performed under laparoscopic direction. **Operative laparoscopy has the benefit of shorter hospital stays, less postoperative pain, and faster return to normal activity when compared with procedures performed via laparotomy.** These features contribute to a reduction in the "indirect costs" of surgical care including less time away from work, and a diminished need for post discharge supportive care in the home (8). In addition to the general benefits of endoscopic procedures, adhesions are less likely to form with laparoscopic surgery than with laparotomy. Because sponges are not

used, the amount of direct peritoneal trauma is reduced substantially, and contamination of the peritoneal cavity is minimized. The reduced exposure to the drying effect of room air allows the peritoneal surface to remain relatively moist and, therefore, less susceptible to injury and subsequent adhesion formation.

Despite these advantages, there are potential limitations: exposure of the operative field can be reduced, small instruments are required that must be used through fixed ports, and the ability to manipulate the pelvic viscera is often limited. In some cases, the cost of hospitalization increases, despite a shortened stay, because of prolonged operating room time and the use of more expensive surgical equipment and supplies. Efficacy may be reduced if a surgeon cannot adequately replicate the abdominal operation. In some patients, there is an increased risk of complications, which can be attributed to the innate limitations of laparoscopy, the level of surgical expertise, or both. **[5]** Laparoscopic gynecologic surgeons should be prepared for the spectrum of pathologic and anatomic situations that may be encountered, considering the bowel, bladder, ureter, and vascular structures that may be involved. With an adequate combination of ability, training, and experience, operative time is comparable to that of traditional abdominal surgical procedures and complications may be reduced.

Tubal Surgery

Sterilization

Laparoscopic sterilization has been extensively used since the late 1960s and while it can be performed with local anesthetics, it is usually accomplished under general anesthesia. **The fallopian tubes can be removed (salpingectomy) or occluded by suture, clips, silastic rings or with RF electrocoagulation, most commonly with a bipolar electrocoagulation instrument (see Chapter 14).** When an "operative laparoscope" is used, only one incision is required because the sheath in such a system contains an instrument channel. Otherwise, a second port is needed for the introduction of the occluding instrument. Should bilateral salpingectomy be chosen, up to three ports are needed—one for visualization, and two for manipulation and transection of tissue.

Patients generally remain in the hospital only for a few hours; even when general anesthesia is used. Postoperative pain is usually minor and related to gas that remains in the peritoneal cavity (shoulder pain, dyspnea), and in the case of occlusive devices, pain at the surgical site. These effects normally disappear within a few days. The failure rate varies by technique but is about 5.4 per 1,000 woman-years (9,10). **Bilateral resection of the fallopian tubes has become a more prevalent technique as a result of some evidence that many malignancies that were categorized as ovarian cancers arise in the fallopian tube, and that salpingectomy can reduce the risk of these malignancies** (11). Failure and complication rates are being studied in these patients. The use of laparoscopic tubal sterilization has been impacted by the availability of office vasectomy, effective intrauterine contraception, and the development of office-

based hysteroscopic sterilization techniques.

Ectopic Gestation

Medical therapy with *methotrexate* is considered first-line therapy for tubal pregnancies that, in addition to contraindications to methotrexate use, meet criteria that may include the following: hemodynamic stability, no cardiac activity, tubal mass smaller than 4 cm as determined by ultrasonography, and an acceptably low β-hCG level (12–14). **When surgical therapy is required, ectopic gestation can usually be managed successfully by using laparoscopic salpingotomy, salpingectomy, or segmental resection of a portion of the oviduct (see Chapter 32)** (15,16). Salpingotomy is typically performed with scissors or a RF needle electrode after carefully injecting the mesosalpinx with a dilute *vasopressin*-containing solution (e.g., 20 international units in 100 mL of normal saline) **(Fig. 26-1)**. For salpingectomy, the vascular pedicles are usually secured with electrosurgical desiccation/coagulation, but it is also possible using ligatures or clips. Tissue is usually removed from the peritoneal cavity through one of the laparoscopic cannulas.

When salpingotomy is performed, regardless of the route, there is approximately a 5% chance that trophoblastic tissue remains. In such instances, medical treatment with *methotrexate* is considered appropriate (see Chapter 32). Consequently, a-hCG levels should be measured weekly until there is confidence that complete excision has occurred (17–19).

Ovarian Surgery

Ovarian Masses

Laparoscopic removal of selected ovarian masses is a well-established technique supported by high-quality evidence (20–22). **[8]** Proper patient selection is critical for laparoscopic management of adnexal masses because of the possible adverse effect of laparoscopic approaches on prognosis with malignant tumors (23,24). Preoperative ultrasonography is mandatory. Sonolucent lesions with thin walls and no solid components are at very low risk for malignancy and, therefore, are suitable for laparoscopic removal. For postmenopausal women, the measurement of CA125 levels is useful in identifying candidates for laparoscopic management (25,26). Combining age, menopausal status, an ultrasound score, and the serum CA125 level into a "Risk of Malignancy Index" may offer an effective means to identify cysts at high risk for epithelial malignancy (27–29). **Lesions with ultrasonographic findings suggestive of mature teratoma (dermoid), endometrioma, hemorrhagic, or other cysts presenting with torsion or other causes of acute pain may be suitable for endoscopic management** (30–33). Ovarian tumors should be assessed by frozen histologic section, and any frank malignancy should be managed expeditiously by laparotomy (20,24,26).

The technique for performing laparoscopy for oophorectomy and cystectomy is

similar to that used for laparotomy (19). Pelvic washings should always be collected immediately after entry into the peritoneal cavity and prior to any surgical dissection. For cystectomy, scissors are used to incise the ovarian capsule, and blunt dissection or pressurized fluid (aquadissection) are used to separate the cyst from the ovary. Surgeons should use energy-based techniques with caution as there is evidence that related damage to the adjacent ovarian cortex could compromise the patient's "ovarian reserve" (34,35). If oophorectomy is performed, the vascular pedicles are occluded and transected, usually with RF electrosurgical coagulation and cutting systems, but in some instances with sutures, clips, or linear cutting and stapling devices. This is ideally done by isolating the infundibulopelvic ligament. **The ureter should be identified and should be clear of the pedicle to be transected.** Cysts that appear to be benign may be drained before extraction through a laparoscopic cannula or, less commonly, a posterior culdotomy. **If there is concern about the impact of spilled cyst contents, the specimen should be removed in a retrieval bag inserted into the peritoneal cavity through a laparoscopic port.** Some authors describe a minilaparotomy technique, or enlarging one port site incision, to exteriorize the mass, drain it externally without intraperitoneal spill, remove the cyst or ovary, and replace the adnexa into the peritoneal cavity (36).

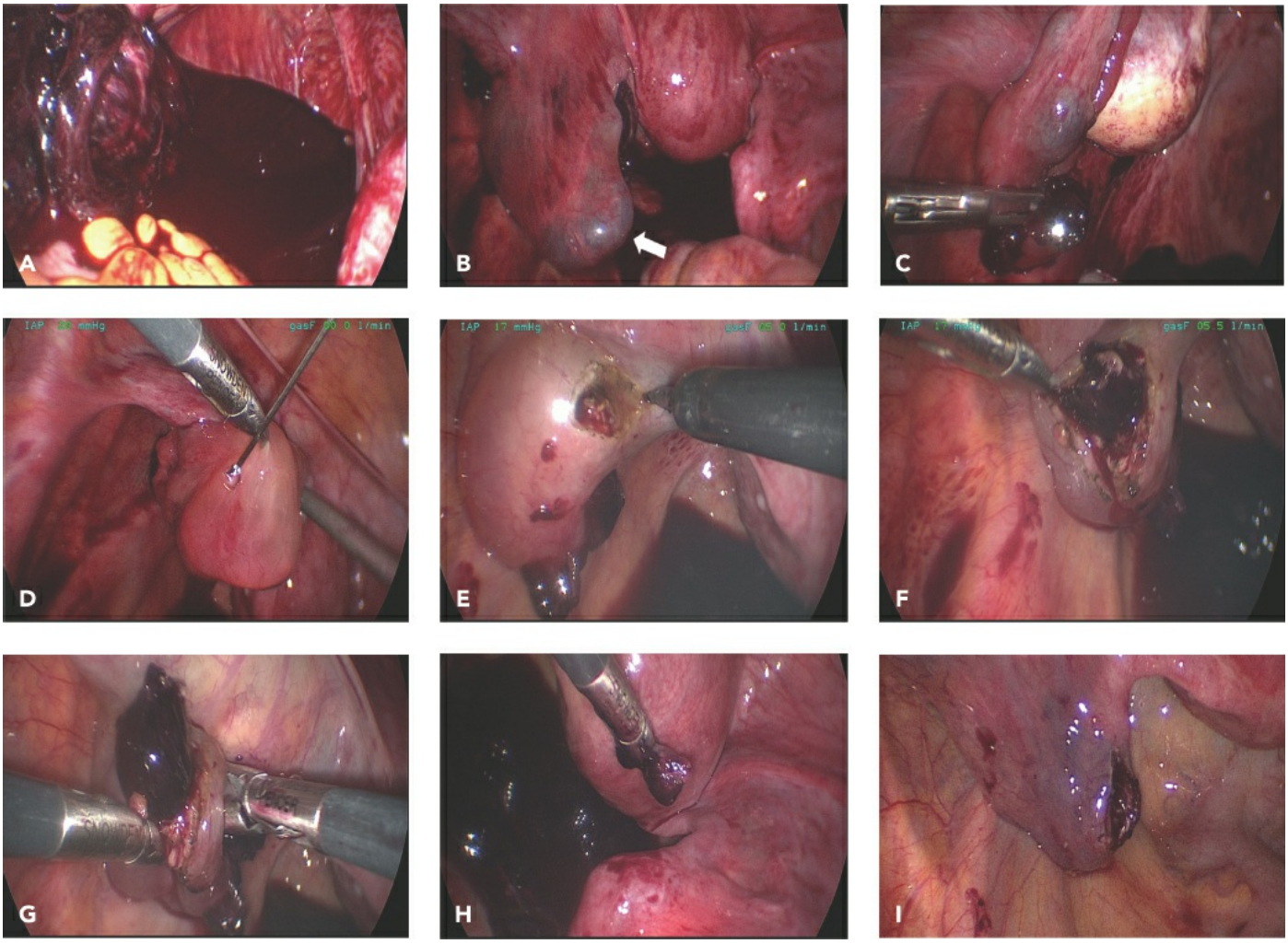


FIGURE 26-1 Laparoscopic salpingotomy for unruptured tubal ectopic pregnancy. A: Bleeding through the fimbriated end results in a hemoperitoneum; (**B**) after removing clot, the left tube is seen distended with blood and gestational tissue (*arrow*); (**C**) the left tube is suspended over the left ovary; (**D**) dilute vasopressin (20 units in 100 mL of normal saline) is injected between the leaves of the mesosalpinx. A salpingotomy incision is made in the proximal portion of the distended tube (**E**) using a radiofrequency needle electrode. The ectopic pregnancy is carefully expressed and removed from the fallopian tube (**F, G**, and **H**). The post evacuation appearance of the tube is shown (**I**). The small incision will heal without the need for sutures.

Although previously the ovary was routinely closed after cystectomy, this practice is controversial. Some evidence suggests that suture closure could contribute to the formation of adhesions (37). Other studies, including a RCT, suggest that suture-based closure of the ovary is associated with fewer adhesions than using electrodesiccation alone (38).

Other Ovarian Surgeries

Ovarian torsion, previously treated by laparotomy and oophorectomy, more often can be managed laparoscopically (39,40). Even if there is apparent necrosis, the adnexa can be untwisted, usually with preservation of normal ovarian function (32,41).

If an ovarian cyst is present, as is typically the case, cystectomy may be performed after "detorsion" or, if appropriate, deferred to a later time. Rarely is adnexectomy indicated.

Polycystic ovarian syndrome should be treated medically. In rare instances, surgical therapy is indicated to reduce ovarian cortical volume, a technique that can be performed laparoscopically using electrosurgery or laser vaporization to perform ovarian "drilling." This procedure reduces the volume of ovarian stromal tissue and may lead to a temporary return to normal ovulation (42–44). Although such procedures have been shown to be successful in a number of randomized trials (45), postoperative adhesions form in 15% to 20% of patients, underscoring the need to first exhaust medical treatment options (46,47).

Uterine Surgery

Myomectomy

[9] Laparoscopic myomectomy, requires laparoscopically-directed suturing and, thus, requires more technical skills than many other endoscopic procedures (Fig. 26-2). In addition the procedure requires the performance of morcellation so that the fragments of leiomyoma can be removed through the laparoscopic ports or a small incision. **There is high-quality evidence suggesting that, compared to laparotomy, the laparoscopic approach is associated with reduced postoperative pain and fever and a shorter institutional stay** (48). While it is possible that microprocessor-assisted ("robotic") laparoscopic myomectomy may allow more surgeons to suture effectively under laparoscopic guidance, in expert hands there appears to be no benefit to robotic surgery in any measurable perioperative outcome (49,50).

Some controversies regarding the appropriateness of laparoscopic myomectomy remain, given concerns about the perceived risks associated with intraperitoneal morcellation. There have been questions related to the efficacy of the approach, especially as it relates to the treatment of infertility and the symptom of heavy menstrual bleeding (HMB), each of which is thought to be secondary to submucous myomas.

Morcellation of leiomyomas following removal from the uterus can be performed via laparotomy or under laparoscopic direction using either hand-held cutting instruments, or, in the instance of laparoscopic technique, with an electrosurgical or electromechanical morcellating system that cuts and extracts the tissue (see **Fig. 26-27**). Much of the controversy around this technique relates to the potential impact of morcellation in general, and electromechanical morcellation in particular, on the prognosis for patients who have unsuspected leiomyosarcomas. There is no convincing evidence that morcellation adversely impacts the prognosis for these very malignant tumors (51). **However, for women undergoing myomectomy, the risk of leiomyosarcoma is extremely low, with a reported incidence ranging from approximately 4/10,000** (52), **to 2/1,000** (53) **and for myomectomy there is no**

evidence that one method of morcellation is better than the other with respect to impact on oncologic prognosis (54,55). There is evidence that leiomyoma cells are already present in the peritoneal cavity prior to morcellation (56), a finding that would suggest that the disease has already disseminated prior to myomectomy by any technique (57).

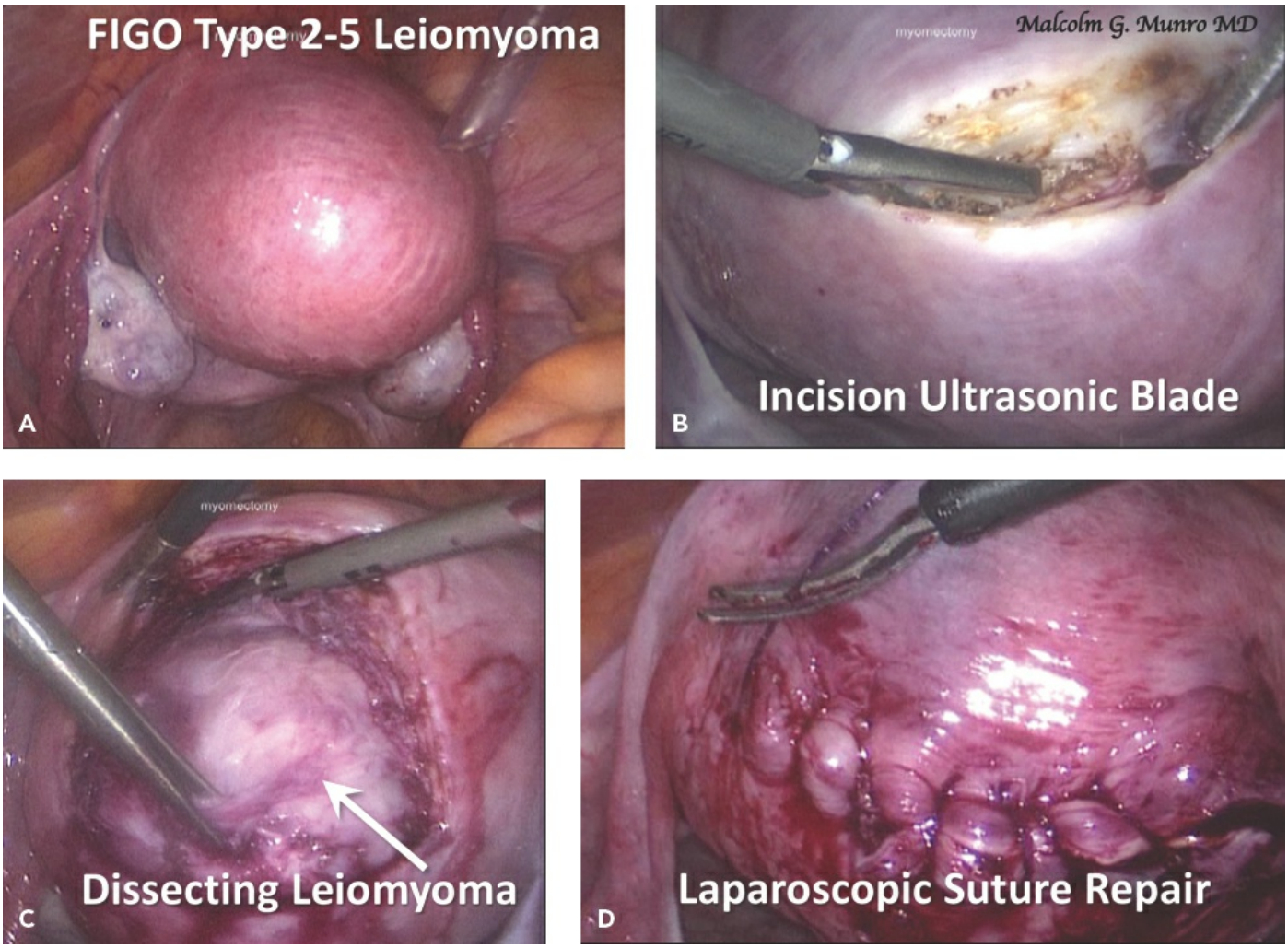


FIGURE 26-2 Laparoscopic myomectomy. This patient has a FIGO type 2–5 leiomyoma (**A**), and has the symptoms of heavy menstrual bleeding and infertility. An ultrasonic cutting blade is used to make a transverse incision in the fundus (**B**), and then the leiomyoma is dissected out from the myometrium (**C**). **D:** Laparoscopic technique is used to create multiple layers of running suture to close the defect. The leiomyoma is removed from the peritoneal cavity through a laparoscopic port after morcellation.

Although there are some well-designed studies evaluating infertility outcomes (Class-1, randomized clinical trials) comparing laparoscopic myomectomy with laparotomy, the sample sizes are relatively small, and the cases are highly selected limiting the size and number of the lesions to be removed (58,59). Nevertheless, **fertility outcomes have been shown to be similar with laparoscopy and laparotomy** (59–61). These and other trials evaluating perioperative outcomes such as duration of admission, surgical

pain, and operative complications demonstrated the laparoscopic approach to be superior (62).

Proper patient selection for myomectomy, regardless of route, is extremely important, particularly because, by age 50, the prevalence of leiomyomas may be as high as 70% in Caucasians and over 80% in women of African ancestry (63). It is relatively easy to mistakenly ascribe symptoms to the presence of leiomyomas. Unless the myoma is adjacent to the endometrium, it is unlikely to contribute to HMB or infertility. The impact of intramural myomas on infertility is not well understood (64). Leiomyomas that cause pressure are often large and may be located so close to vital vascular structures, that their location may preclude the laparoscopic approach even in expert hands. Many women will do well with expectant or medical management, or with procedural alternatives such as uterine artery embolization. The surgeon should freely select a laparotomic approach, either at the outset, or during the procedure if technical limitations put the patient at risk or otherwise compromise the potential relevant clinical outcomes (65). **Patients who have pedunculated or subserosal leiomyomas that cause bothersome discomfort or pain in association with torsion are especially good candidates for laparoscopic excision** (19,66).

Hysterectomy

[10] Laparoscopic hysterectomy (LH) encompasses a variety of procedures, including the facilitation of vaginal hysterectomy (VH) with variable extents of endoscopic dissection, supracervical hysterectomy (SCH) by dissection, amputation and mechanical removal of the fundus, and the removal of the entire uterus under laparoscopic direction (67). In most environments, the procedure is performed with a combination of electrosurgical vessel sealing devices and mechanical cutting systems, often incorporated into a single instrument. In some instances, sutures, clips, and linear cutting and stapling devices are employed in the process of dissecting or occluding vascular pedicles.

When LH was introduced, complications, while lower than for AH, were higher than in comparison with VH (68). With time, training and experience, this outcome has changed with complication rates of LH and VH becoming similar, while remaining lower than for AH (69–71). One study has demonstrated that hospital readmission rates are even lower with LH compared with all other techniques, including instances where the da Vinci microprocessor device is used to assist the laparoscopic procedure (71,72). The procedural costs of LH are generally greater than either VH or AH (8,73), but it is evident that patients can be safely discharged within hours of surgery for both VH and LH, an approach that further reduces the cost of care (74,75). The surgical costs can be substantially reduced when reusable instruments are employed (76). In addition to reduced institutional stay, most studies show less postoperative pain, and faster postoperative recovery with LH than when hysterectomy is performed via laparotomy

(68,77,78). There is evidence that pain scores and quality-of-life measures, including sexual activity and physical and mental functioning, were significantly better for women who underwent hysterectomy via laparoscopy versus laparotomy (79). These differences were present at 6 weeks following surgery and remained at the 12-month follow-up visit. When the societal benefits of faster return to work or family are considered, the cost of laparoscopic surgery is less (80).

Selection of the route of hysterectomy must be done considering the anatomy, the disorder or disease state, the patient's wishes, and the training and experience of the surgeon. LH offers no advantage for women in whom VH is possible, because the endoscopic approach is more expensive and probably has a higher risk for perioperative morbidity (77). **The ideal place for LH is as a replacement for laparotomy** (68,81,82).

There are relatively few remaining indications for laparotomy-based hysterectomy, an approach, which should be reserved for the minority of women for whom a laparoscopic or vaginal approach is not appropriate. These include: (a) patients with medical conditions, such as cardiopulmonary disease, where the risks of either general anesthesia, or the increased intraperitoneal pressure associated with laparoscopy are deemed unacceptable; (b) where morcellation is known to be or likely to be required and uterine malignancy or hyperplasia is either known or suspected. In instances where a minimally invasive approach such as LH or VH may be considered, hysterectomy via laparotomy may be performed for the following reasons: (a) hysterectomy is indicated but there is no access to the surgeons or facilities required for VH or LH and referral is not feasible; (b) circumstances where anatomy is so distorted by uterine disease or adhesions that a vaginal or laparoscopic approach is not deemed safe or reasonable by individuals with recognized expertise in either VH or LH techniques (76,79,82). For surgeons without the skill and training to perform minimally invasive hysterectomy (either vaginal or laparoscopic), and for benign indications, consideration should be given for referral to a gynecologist with such training (82).

Infertility Operations

The use of assisted reproductive technology, and, in particular, in vitro fertilization (IVF) and embryo transfer (ET) have, at least for those with financial means, replaced the performance of tubal surgery. However, for many, when infertility occurs secondary to disruption of the normal anatomy or anatomic relationships by an inflammatory process, **laparoscopically directed operations used to restore anatomy can be successful and include fimbrioplasty, adhesiolysis, and salpingostomy for distal obstruction** (83). Fimbrioplasty is distinguished from salpingostomy because it is performed in the absence of pre-existing complete distal obstruction. Endometriosis associated with adnexal distortion can be treated by laparoscopic adhesiolysis or resection. Whereas there is no known additional benefit for medical treatment of

coexistent active endometriosis, the evidence relating to ablation of minimal and mild endometriosis is mixed (84,85) although when subjected to meta-analytic technique, there is a slight fecundity benefit for those undergoing laparoscopic ablation (86).

Adhesiolysis may be accomplished by blunt or sharp dissection with scissors, ultrasonic shears, or an RF electrosurgical electrode. While laser-based instruments have been used, there is no evidence that they provide any additional value over less expensive techniques such as electrosurgery (87–89). The dissecting instruments are usually passed through an ancillary port; when laser energy is used, the channel of the operating laparoscope may be used for this purpose. Although there has been controversy regarding the most appropriate modality for adhesiolysis, these methods are probably equally effective in appropriately trained hands.

Laparoscopic operations for the treatment of mechanical infertility are probably equally effective to similar procedures performed by laparotomy. In patients with extensive adhesions, successful outcomes are unlikely regardless of the approach. Consequently, assisted reproductive technologies such as IVF and ET are necessary in these situations (see Chapter 36) (19,83).

Endometriosis

Endometriosis is an enigmatic disorder whereupon the extent of visible disease frequently is unrelated to the severity of symptoms; frequently it is asymptomatic with other disorders responsible for the patient's pain or infertility. The endometriosis-related inflammation that can occur may create dense adhesions in the pelvis that involve the uterus, fallopian tubes, ovaries, bladder, ureters (90), bowel, and in particular the rectum and sigmoid colon (91). As a result, the incidence of postoperative complications such as fistula are relatively high (90,92). Consequently, when extensive disease exists, and if removal or reconstruction is indicated, endometriosis becomes a surgical challenge requiring surgeons with a training in retroperitoneal dissection to preserve the integrity of the ureters and bowel, particularly in the cul-de-sac between the rectum and vagina. In many instances, optimal surgical management involves a multidisciplinary approach including urologic and colorectal surgeons.

The laparoscopic management of endometriomas parallels that of adnexal masses, although the complex ultrasonographic features of many endometriomas sometimes make it difficult to distinguish them preoperatively from a neoplasm (93). The close attachment of the endometrioma to the ovarian cortex and stroma may make it difficult to find surgical dissection planes, and incomplete removal increases the risk of recurrence. In such instances, there may be a tendency either to compromise the function of the remaining ovary by attempting complete removal or risk recurrence by leaving part of the endometrioma in place. **It is common to find the endometrioma adherent to the posterior uterus, the cul-de-sac, or the pelvic sidewall (Fig. 26-3). In such cases, the surgeon must dissect carefully, protecting the ureter and bowel.**

A Cochrane review found good evidence that excisional surgery for endometriomas decreases the recurrence rate of the endometrioma, decreases the risk for return of pain symptoms, and in women who were previously subfertile, increases the rate of subsequent spontaneous pregnancy (94). Consequently, where possible, an excisional approach should be the goal.

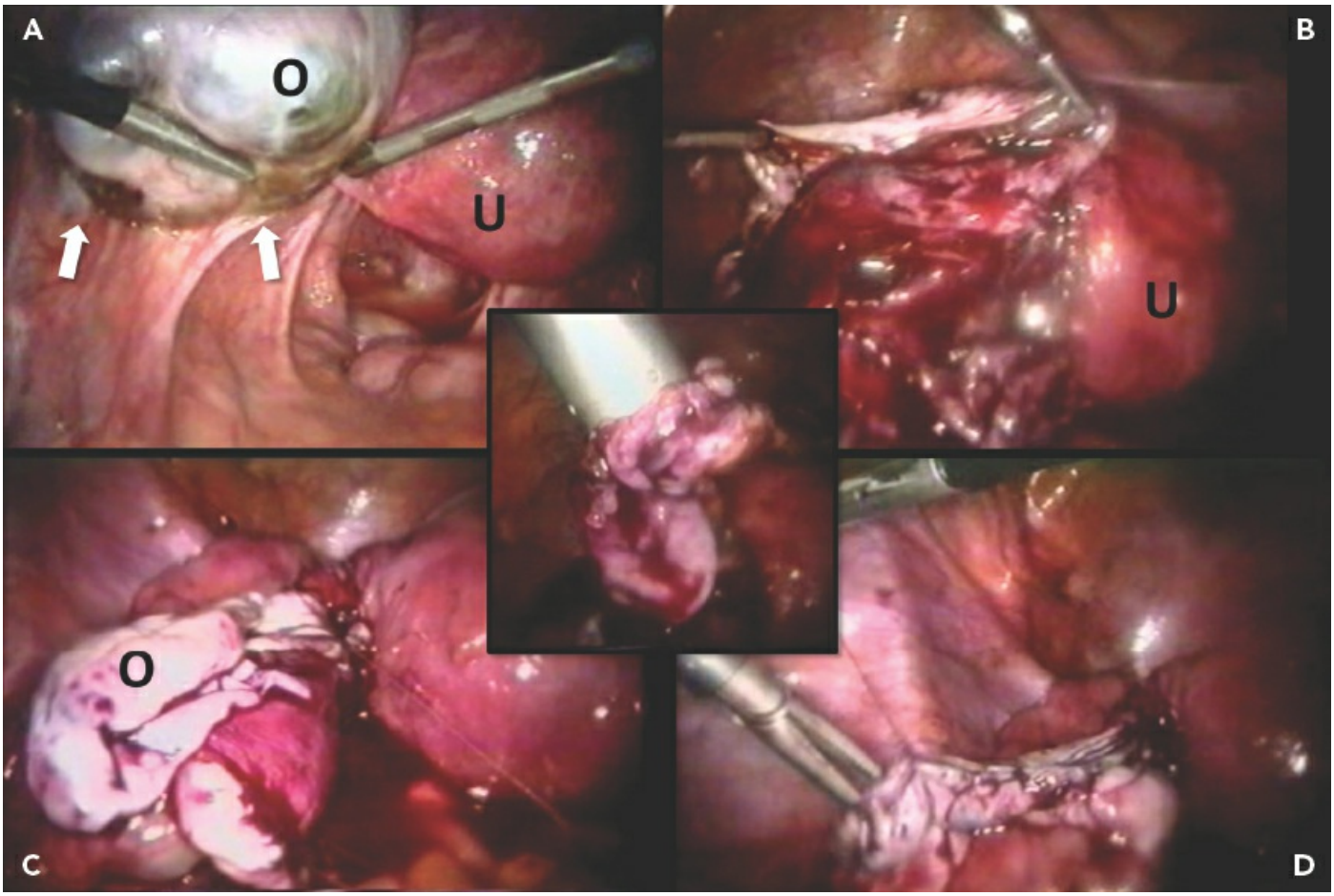


FIGURE 26-3 Removal of left ovarian endometrioma. (**A**) The endometrioma in the ovary (O), lateral to the uterus (U) is attached to the pelvic sidewall (*arrows*) over the left ureter. (**B** and **C**) After careful drainage and careful dissection the remaining ovary is like a shell. In **D** the ovary has been sutured closed and the endometrioma removed via a laparoscopic port (*inset*).

Multifocal endometriosis may be treated by mechanical excision or ablation, the latter using coagulation or vaporization with either electrical or laser energy. With proper use, each energy source creates approximately the same amount of thermal injury (87–89). Endometriosis frequently is deeper than appreciated initially, making excisional techniques valuable in many instances (19,83,95–97). Excisional techniques have been demonstrated superior with respect to postoperative spontaneous pregnancy rates (94) although systematic reviews of randomized trials are somewhat inconsistent (98).

Endometriosis cases should be performed by a surgeon skilled in the treatment of

endometriosis, whenever possible, in order to adequately treat ovarian and extraovarian disease thereby minimizing the need for further surgery.

Pelvic Floor Disorders

Laparoscopy can be used to guide procedures to treat pelvic support defects, including culdoplasty, enterocele repair, vaginal vault suspension, paravaginal repair, and retropubic cystourethropexy for urinary stress incontinence.

Retropubic cystourethropexy comprises the use of either suture or mesh to attach the anterior vagina to Cooper ligaments, located on the posterior aspect of the symphysis, thereby suspending the proximal urethra in a fashion that treats urinary stress incontinence. In the last decade, the advent of mesh-based midurethral slings placed transvaginally largely superseded laparoscopic retropubic cystourethropexy in the treatment of urinary stress incontinence because of reduced morbidity and cost, with at least equal or superior results (99–101). There was published evidence supporting the notion that the laparoscopic approach is effective when compared with laparotomy, most commonly the Burch colposuspension (102,103). There has been increased interest in the performance of laparoscopic retropubic cystourethropexy because of concerns related to the use of vaginal mesh. Consequently, the laparoscopic Burch colposuspension has, to some degree, experienced a rebirth (104).

For vaginal vault prolapse, particularly that which occurs following hysterectomy, the surgical approaches have included a spectrum of techniques applied either vaginally or abdominally. **The laparoscopic technique most commonly performed is sacrocolpopexy, where the vaginal apex is loosely attached to the anterior aspect of the sacrum, usually with mesh secured with suture at either end.** There is evidence that the abdominal approaches are superior to those performed vaginally (105–108) and that the laparoscopic technique is associated with equivalent anatomic and functional outcomes at 12 months (109), equivalent "cures" at about 3 years (110), with reduced complications and hospital stay (109,111).

Although apical and anterior compartment defects can be successfully corrected via laparoscopy, posterior and perineal defects are best visualized and repaired using vaginal techniques. The laparoscopic treatment of enterocele and vault prolapse may be useful in patients who require abdominal approaches after failure of a previous vaginal procedure. Because of the anatomical proximity of the pelvic ureter to the uterosacral ligament and anterolateral vagina, bilateral ureteral patency should be confirmed cystoscopically after laparoscopic vaginal vault suspension, enterocele repair, culdoplasty, cystourethropexy, or paravaginal repair.

Gynecologic Malignancies

For some gynecologic cancers, the role of laparoscopic techniques has been clearly established, while for others, the precise place for endoscopy in surgical management

is unclear. High-quality evidence was published in the late 20th and early 21st century supporting the notion that, for endometrial (112–114) and cervical cancer (115,116) clinical outcomes were preserved while cost and morbidity were reduced with the use of laparoscopic technique. Because the value of LH had already been determined, the fundamental issue was the utility of laparoscopic technique for pelvic lymph node sampling, or pelvic lymphadenectomy. Later and larger scale studies suggested that women whose surgeries were facilitated by laparoscopy did as well as those whose surgeries were via laparotomy (117,118). The literature reports the use of microprocessor-assisted laparoscopic surgery, compared with standard laparoscopy, adds to cost and cosmetic impact without improving clinical outcomes for endometrial (119,120) or cervical cancer (121–124).

Laparoscopy has been used for "second-look" procedures for ovarian cancer (125), and is being investigated for the staging and treatment of early ovarian malignancy (126–129) and for identifying the resectability of ovarian cancer (130). Microprocessor-based devices that assist the performance of laparoscopy (e.g., da Vinci system) have been employed to facilitate radical hysterectomy for cervical cancer and cytoreduction of ovarian cancer (see Chapter 39) (131,132). Laparoscopy in gynecologic oncology surgery has value without apparent prognostic compromise in properly selected patients.

Patient Preparation and Communication

[6] The rationale, alternatives, risks, and potential benefits of the selected procedure, compared with alternative medical and surgical management, should be explained to the prospective patient. She should know the likely outcome of expectant management if the procedure was not performed.

The expectations and risks of the laparoscopic procedure, and those of any other procedures that may be needed, must be explained. It may be helpful to compare risks and recovery with the same procedure performed via laparotomy. The risks of laparoscopy include those associated with anesthesia, infection, bleeding, and injury to the abdominal and pelvic viscera. The possibility of conversion to laparotomy, if a complication should occur, or if the procedure cannot be completed via laparoscopy, should be discussed. Infection is uncommon with laparoscopic surgery. For procedures involving extensive dissection, there is a higher risk for visceral injury than if such dissection is not necessary. These risks should be clearly presented in a fashion that includes the possibilities of immediate and delayed recognition of complications, such as ureter or bowel injury. The patient should be given realistic expectations regarding postoperative disability. Because pain and visceral dysfunction normally continue to improve after uncomplicated laparoscopy, the patient should be instructed to communicate immediately any regression in her recovery. For most gynecologic

laparoscopic surgical procedures, patients can be discharged on the day of surgery, but the time absent from work or school will depend upon a number of factors including the nature of the surgery, the postoperative response of the patient, and the nature of her work. If there is extensive dissection, or if the surgery lasts longer than 4 hours, hospital admission may be necessary, and the period of disability may be extended. The university professor undergoing adnexectomy for an ovarian mass may be back on the job within a few days; the kindergarten teacher may require 6 weeks or more after a laparoscopic pelvic floor reconstruction, because lifting may compromise the integrity of the repair.

It has long been the perception that preoperative mechanical bowel preparation reduces the morbidity of colonic surgery should an injury occur, and improves visualization and exposure of the operative field at laparoscopy. There is now an abundance of high-quality evidence demonstrating that preoperative mechanical bowel preparation does not reduce the morbidity of colonic surgery (133). There exists high-quality evidence from randomized trials demonstrating that mechanical bowel preparation does not improve visualization at gynecologic laparoscopy and may have a number of adverse effects (134–136). Therefore, gynecologic surgeons should abandon routine preoperative bowel preparation to improve visualization. In selected instances, such as in severe endometriosis when cul-de-sac dissection is anticipated, mechanical bowel preparation should be considered.

Communication with the family or other designated individuals should be arranged prior to the procedure. The patient should arrange for a friend or family member to be present to discuss the results of the procedure with the physician and to drive her home if she is discharged the same day.

Equipment and Technique

To facilitate the discussion of laparoscopic equipment, supplies, and techniques, it is useful to divide procedures into "core competencies," which are as follows:

1. Patient positioning
2. Operating room organization
3. Peritoneal access
4. Visualization
5. Manipulation of tissue and fluid
6. Cutting, hemostasis, and tissue fastening
7. Tissue extraction
8. Incision management

Patient Positioning

Proper positioning of the patient is essential for patient safety, operator comfort, and optimal visualization of the pelvic organs. There may be advantages to positioning the patient while awake to reduce the frequency of positioning-related complications.

Laparoscopy is performed on an operating table that can be tipped to create a steep, head-down (Trendelenburg) position that allows the bowel to move out of the pelvis to facilitate visualization after the cannulas have been placed. The footrest can be removed or dropped to allow access to the perineum. The patient is placed in the low lithotomy position, with the legs appropriately supported in stirrups and the buttocks protruding slightly from the lower edge of the table **(Fig. 26-4)**. **The thighs are usually kept in the neutral position to preserve the sacroiliac angle, reducing the tendency of bowel to slide into the peritoneal cavity. The feet should rest flat, and the lateral aspect of the knee should be protected with padding or a special stirrup to avoid peroneal nerve injury.** The knees should be kept in at least slight flexion to minimize stretching of the sciatic nerve and to provide more stability in the Trendelenburg position. The arms are positioned at the patient's side by adduction and pronation to allow freedom of movement for the surgeon and to lower the risk for brachial plexus injury **(Fig. 26-5)**. Care must be exercised to protect the patient's fingers and hands from injury when the foot of the table is raised or lowered. After the patient is properly positioned, the bladder should be emptied with an indwelling catheter and a uterine manipulator positioned in the endometrial cavity and secured by an intracavitary balloon or attached to the cervix as appropriate.

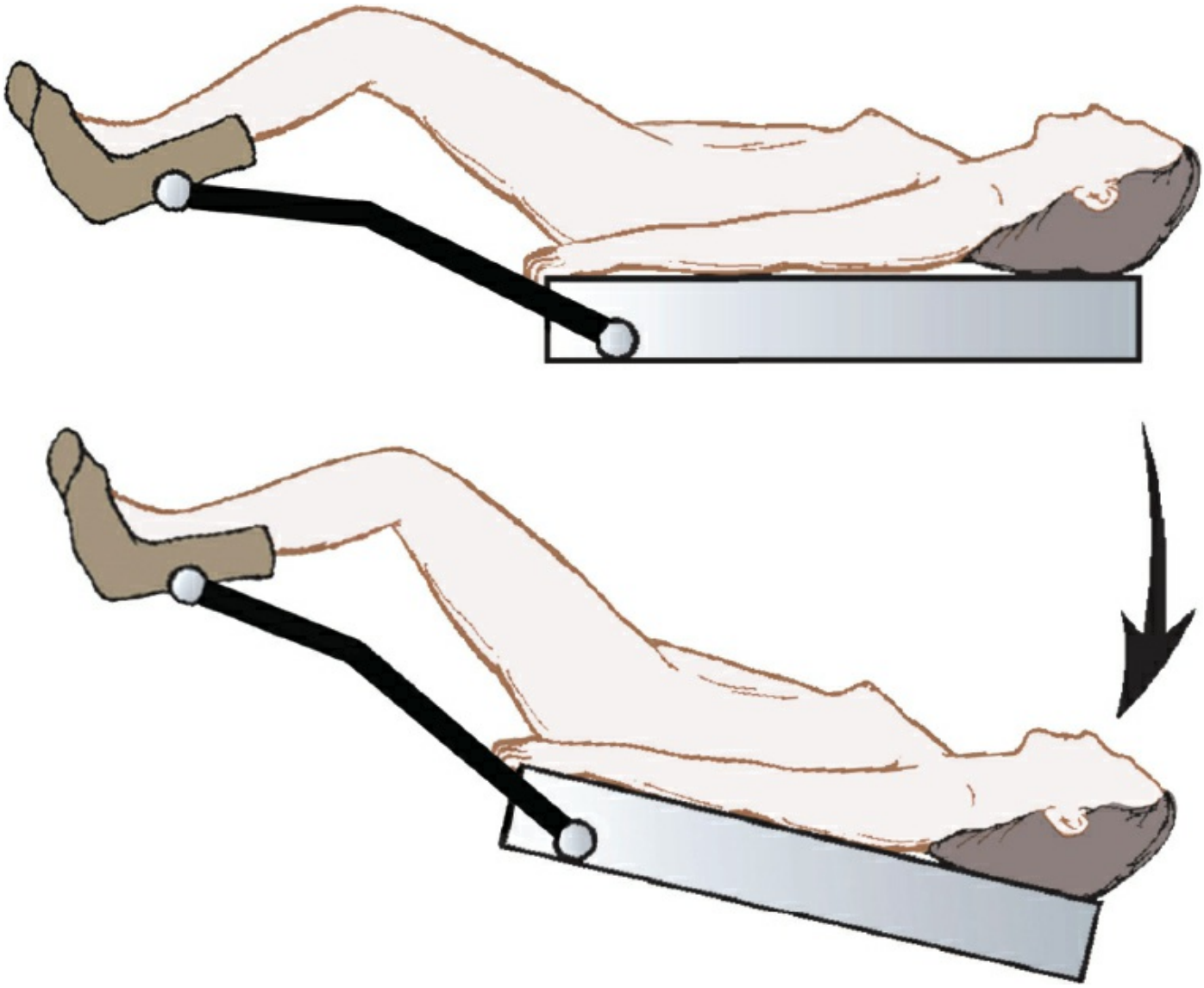


FIGURE 26-4 Patient positioning: the low lithotomy position. The patient's buttocks are positioned so that the perineum is at the edge of the table. The legs are well supported with stirrups, with the thighs in slight flexion. Too much thigh flexion may impede the manipulation of laparoscopic instruments while in the Trendelenburg (head-down) position.

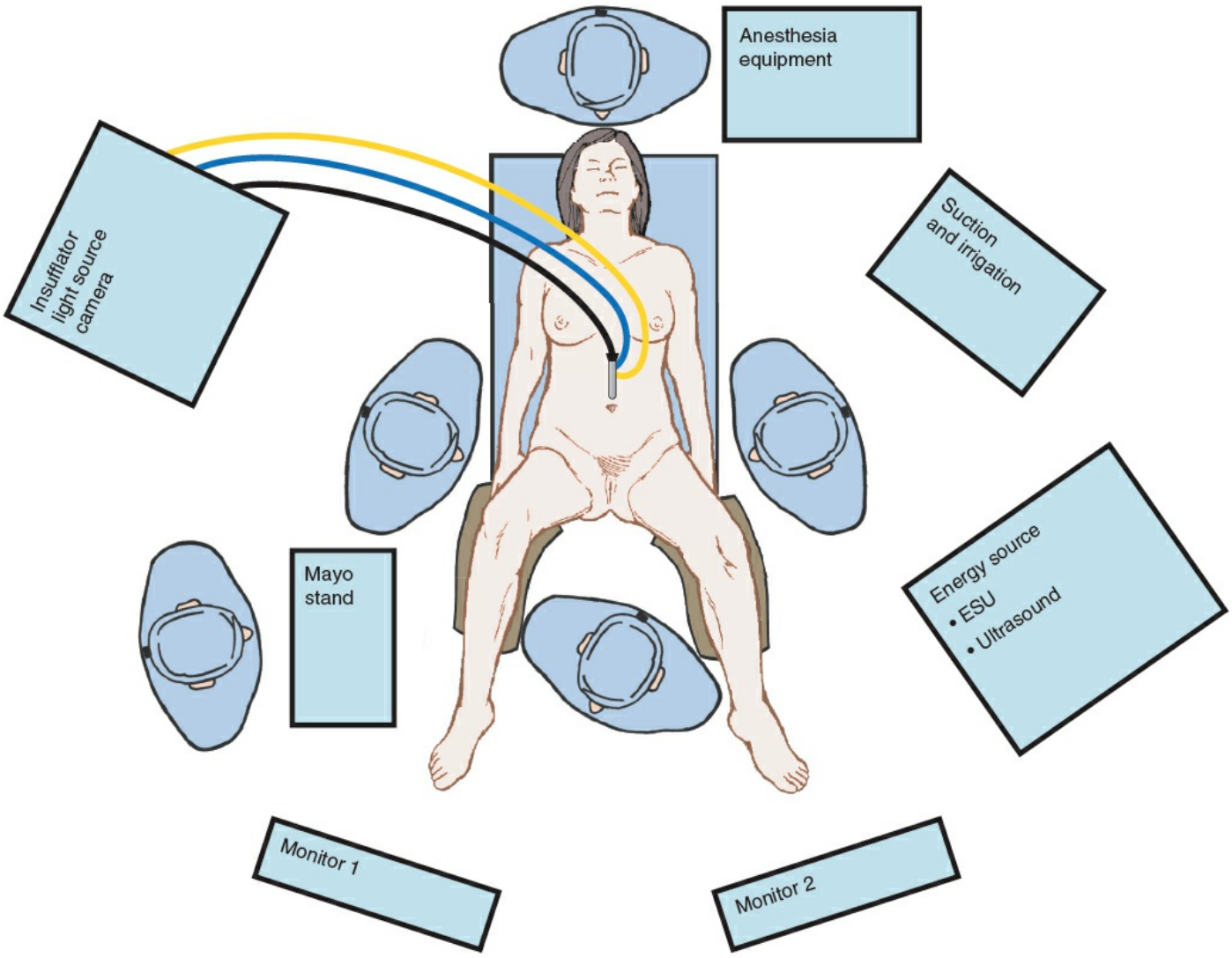


FIGURE 26-5 Operating room organization, stylized view. The patient's arms are at the sides. The right-handed surgeon stands on the patient's left. Instruments and equipment are distributed around the patient within view of the surgeon. For pelvic surgery, the monitor should be located between the patient's legs.

Operating Room Organization

The arrangement of instruments and equipment is important for safety and efficiency. The orientation depends on the operation, the instruments used, and whether the surgeon is right- or left-handed. An orientation for a right-handed operator is shown in **Figures 26-5** and **26-6**.

For pelvic surgery, the ideal circumstance is to have two television monitors, one positioned above each foot of the patient allowing the surgeon and the primary assistant the opportunity to view the surgical field without having to turn their heads **(Fig. 26-6)**. If only one monitor is available, it is typically placed at or over the foot of the table within the angle formed by the patient's legs.

The right-handed surgeon usually stands by the patient's left side, but at an angle facing the patient's contralateral foot. The first assistant is in a mirror image position on

the right side, and an additional assistant for uterine manipulation, if present, sits between the patient's legs. The nurse or technician and instrument table are typically positioned beside one leg of the patient in a fashion that avoids obscuring the video monitor(s) on the left or right, depending on surgeon preference. The insufflator may be placed on the opposite side of the patient, in front of the surgeon, to allow continuous monitoring of the inflation rate and intra-abdominal pressure. The energy source (e.g., electrosurgical or ultrasonic generator) may be placed on the same side as the surgeon to facilitate positioning of the power cords and foot pedals, although increasingly, foot pedals are not used, and with battery-powered instruments, cables and remote control units are unnecessary.

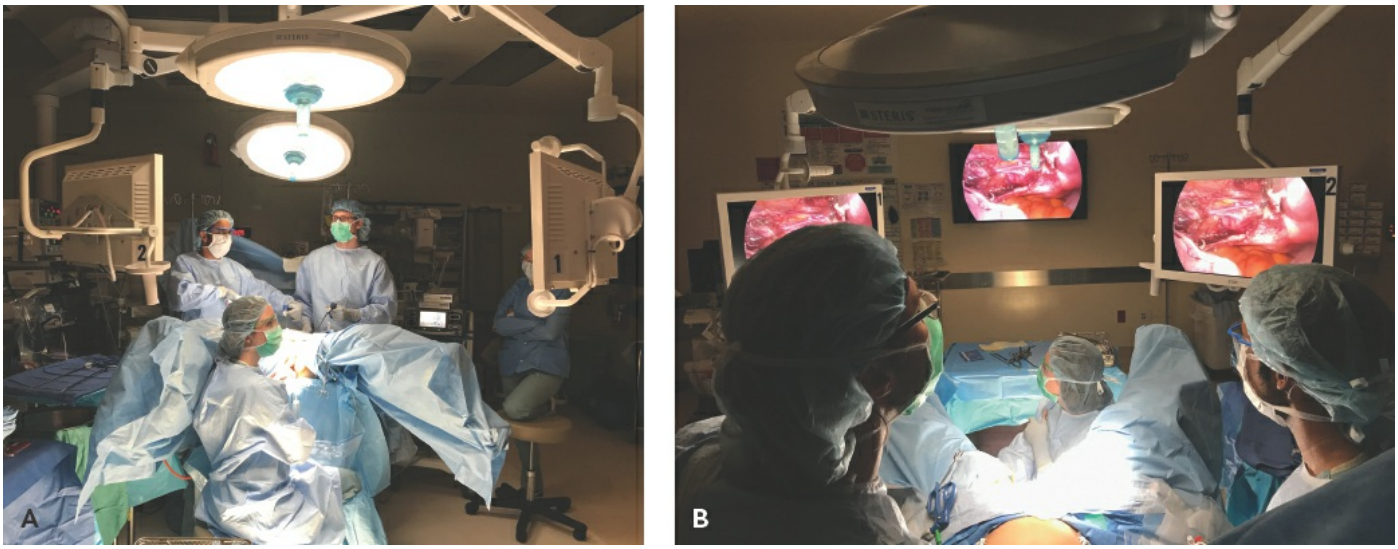


FIGURE 26-6 Operating room organization, photographic view. A: View from the foot of the table. Note the second assistant positioned between the legs of the patient for uterine manipulation. **B:** View from the head of the table.

Peritoneal Access

[7] Before any laparoscopic procedure can be performed, the surgeon must successfully access the peritoneal cavity. A pneumoperitoneum must be created, and a primary cannula must be placed to allow introduction of the laparoscope. **This initial entry into the abdominal cavity must be considered carefully, as it can be associated with a large number of the complications encountered during laparoscopic surgery** (137). Various points on the abdominal wall can be chosen for the initial entry, although the umbilicus is the most common **(Fig. 26-7)**.

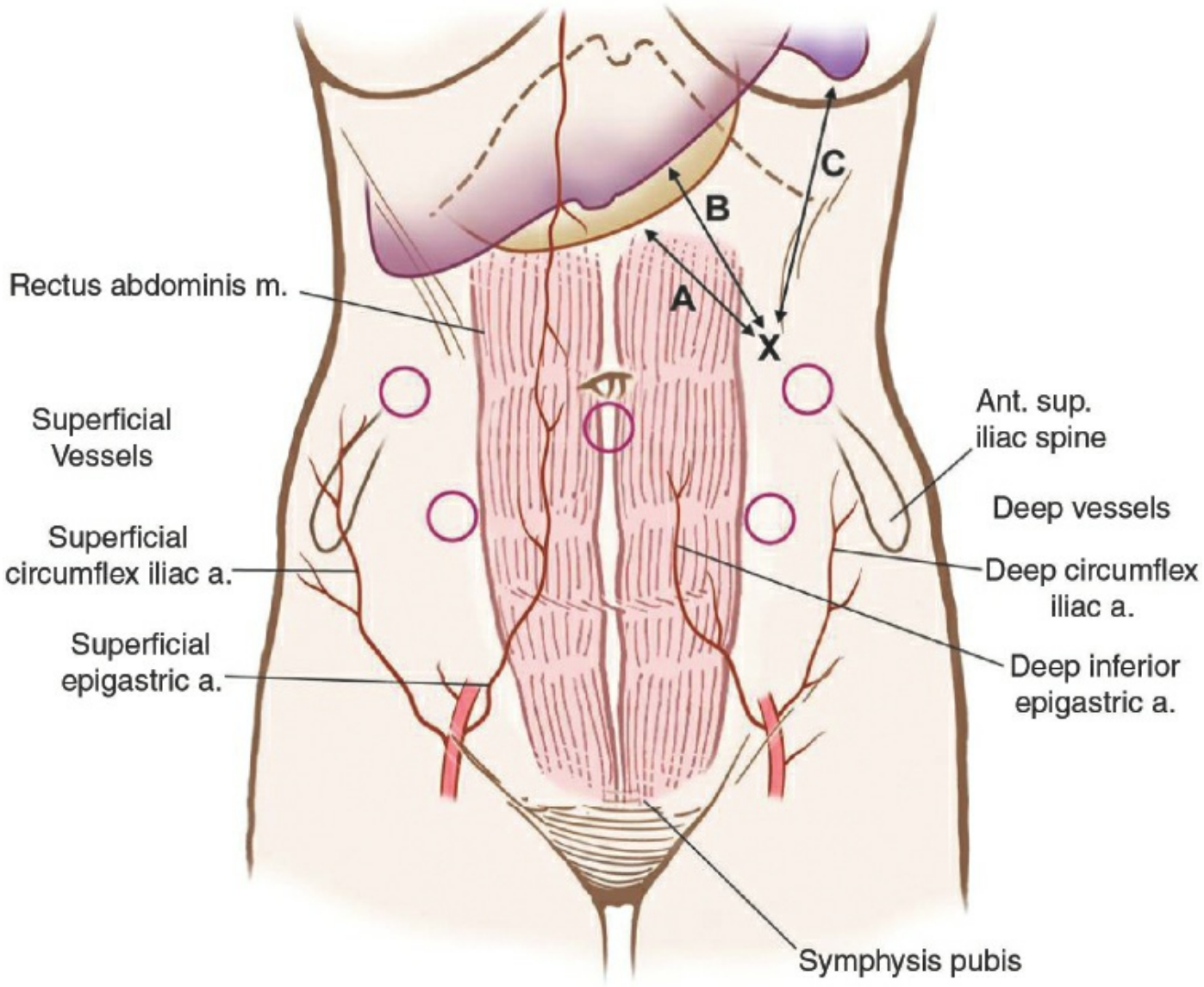


FIGURE 26-7 Laparoscope access sites and vascular anatomy of the anterior abdominal wall. Location of the vessels that can be traumatized when inserting trocars into the anterior abdominal wall.

The main entry strategies are "open laparoscopy," often referred to as Hasson entry, and "closed" entry, which includes "preinsufflation" using a hollow needle to inflate the peritoneal cavity prior to positioning of the initial cannula or port, and "direct entry" techniques where the port is passed through the abdominal wall without prior inflation of the peritoneal cavity.

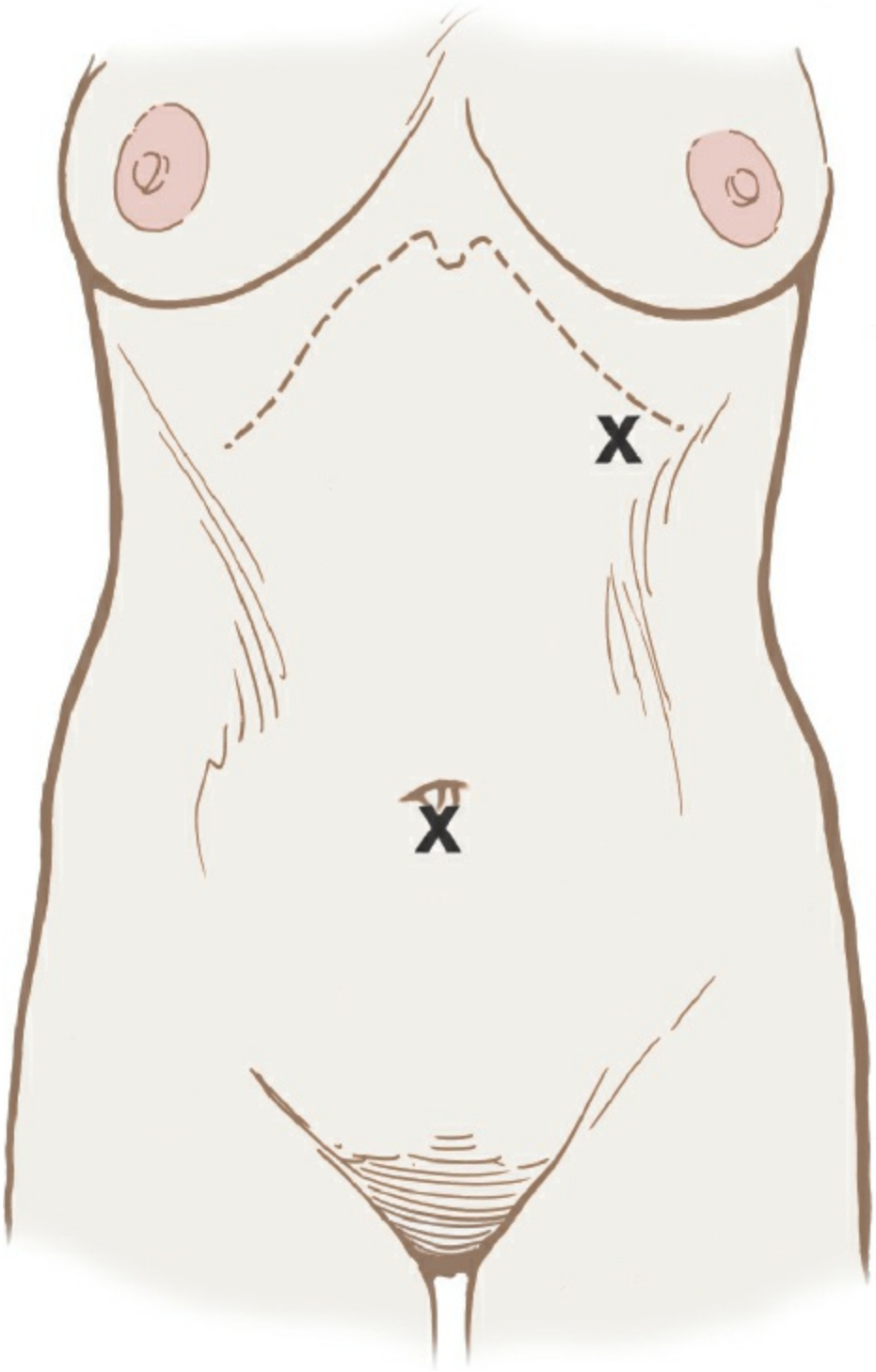


FIGURE 26-8 Typical insertion sites. In most instances, both the insufflation needle, if used, and the primary cannula are inserted through the umbilicus. When subumbilical adhesions are known or suspected, the insufflation needle may be placed through the pouch of Douglas or in the left upper quadrant after evacuation of the gastric contents with an orogastric tube. Some systems allow the insufflation needle to function to position a cannula for a 2 mm laparoscope (Figure 26-16).

1. Access sites

The site of initial or primary access is generally through the umbilicus. However, there are a number of circumstances where this may not be appropriate or even

safe. Such circumstances include pregnancy, the presence of a very large pelvic mass, or when previous surgery has been performed in the lower or mid abdomen. In such instances alternate sites such as the left upper quadrant may be more appropriate (Fig. 26-8).

2. Access techniques

After the location for the initial entry has been determined, the surgeon must choose the technique with which to enter the abdomen. Laparoscopic entry can be achieved with the open (Hasson), or closed techniques. While each technique has its advantages and disadvantages, surgeon training and experience probably plays a role in minimizing complications and available evidence suggests that, with respect to risk, there is no overall advantage of one technique over another (137). Surgeons should be familiar with all techniques but should likely adhere to the method with which they have the most experience.

The open entry technique, first described by Dr. Harrith Hasson, involves gaining entry into the peritoneal cavity via a small "minilaparotomy" skin incision that is typically about 1.5 cm in length (138). Using careful blunt dissection, the incision is carried down to the fascia which is visualized, grasped, tented-up using surgical instruments, and sharply incised; the peritoneum, if identified separately, is carefully opened to enter the peritoneal cavity. The edges of the fascial incision are tagged with stay sutures, and a cannula of appropriate diameter, fitted with a conical occluder and a blunt obturator (Hasson system) is inserted through the facial incision and fixed in position, using either the stay sutures or an integrated balloon system **(Fig. 26-9)**. After removing the obturator, the laparoscope can be inserted through the cannula, and when proper intra-abdominal placement is visually confirmed, the abdomen can be insufflated. The Hasson entry is most often performed at the umbilicus, but this technique can be used at any appropriate location on the abdominal wall.

The closed access approaches comprise the one-stage "direct insertion" technique, and the two-stage approach consists of preinsufflation with a specially designed hollow needle, which **(Fig. 26-10)** is followed by insertion of the trocar– cannula system.

Safe insertion of the insufflation needle (the Veress needle is the reusable version) mandates that the instrument be maintained in a midline, sagittal plane while the operator directs the tip between the iliac vessels, anterior to the sacrum but inferior to the bifurcation of the aorta and the proximal aspect of the vena cava. Because the sacral promontory is commonly covered in part by the left common iliac vein, vascular injury may still occur in the midline below the bifurcation (139).

To reduce the risk of retroperitoneal vascular injury while minimizing the chance of inadvertent preperitoneal insufflation, in women of average or lower weight, the insufflation needle is directed to the patient's spine at a 45-degree angle. In heavy

to obese individuals, this angle may be increased incrementally to nearly 90 degrees, accounting for the increasing thickness of the abdominal wall and the tendency of the umbilicus to gravitate caudad with increasing abdominal girth **(Fig. 26-11)** (140,141). With one hand used to lift the anterior abdominal wall, the needle's shaft is held by the tips of the fingers of the dominant hand and then steadily but purposefully guided into position only far enough to allow the tip's entry into the peritoneal cavity.

The tactile and/or auditory feedback created when the needle passes through the facial and peritoneal layers of the abdominal wall may provide guidance and help prevent overaggressive insertion attempts. This proprioceptive feedback is less apparent with disposable needles than with the classic Veress needle. With the former, the surgeon must listen to the "clicks" as the needle obturator retracts when it passes through the rectus fascia and the peritoneum. The needle should never be forced. Regardless of technique, the underlying retroperitoneal vessels are protected ultimately by limiting the depth of insertion of the insufflation needle.

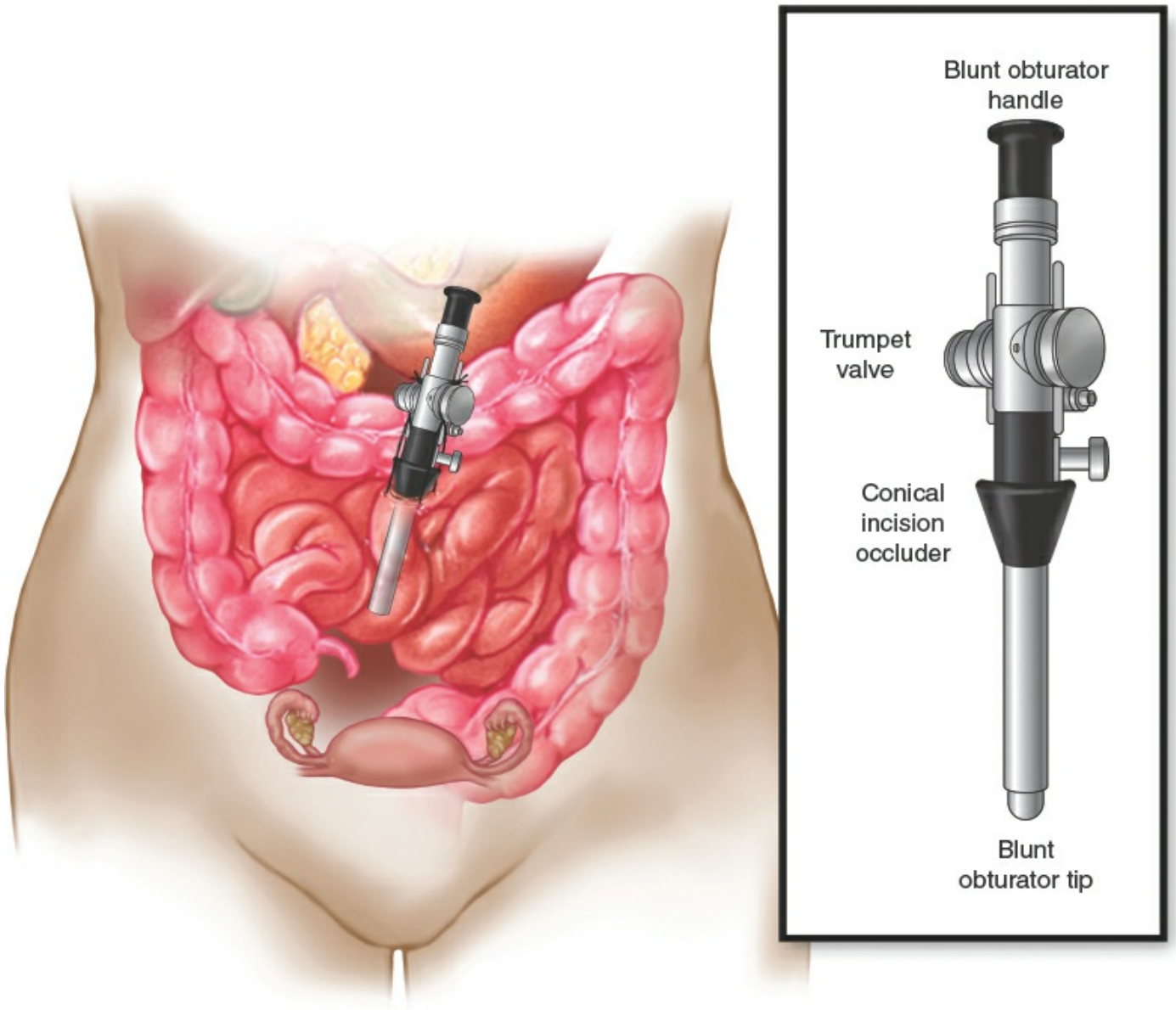


FIGURE 26-9 Open or minilaparotomic (Hasson) access. This technique requires that a minilaparotomy be made in or just below the umbilicus. The Hasson system including the blunt obturator is positioned in the peritoneal cavity using sutures attached to the fascia to hold the device in place. Alternatively, a balloon around the distal tip of the device can be used along with the conical occluder to preserve the pneumoperitoneum.

After the needle has been inserted, but before insufflation, the operator should try to detect whether the insufflation needle has been malpositioned in the omentum, mesentery, blood vessels, or hollow organs such as the stomach or bowel. The most direct approach is to use a specially designed insufflation needle that has an integrated cannula through which a small-diameter (e.g., 2 mm) laparoscope can be passed to visualize the point of entry (see Fig. 26-16). Otherwise, indirect methods are necessary. **The most accurate test of appropriate needle position is an initial intraperitoneal pressure of less than 8 to 10 mm Hg as measured by the insufflator** (142–144). Traditionally, the use of a syringe attached to the insufflation needle has

been used to aspirate potential blood or gastrointestinal contents and there is evidence that this technique has value in determining visceral or blood vessel placement (143). To facilitate this examination, a small amount of saline may be injected via the syringe. Tests that are designed to create negative pressure, such as lifting the abdominal wall to attempt aspiration of a drop of saline placed over the open, proximal end of the needle have been demonstrated ineffective (143).

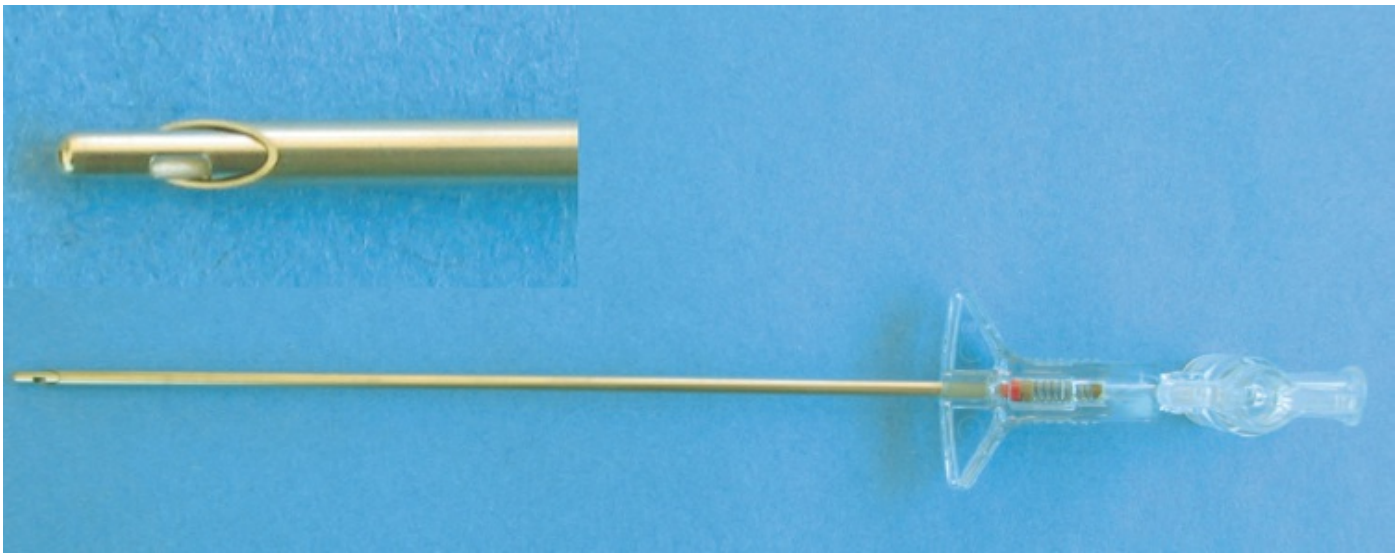


FIGURE 26-10 Insufflation needle. When pressed against tissue such as fascia or peritoneum, the spring-loaded blunt obturator (*inset*) is pushed back into the hollow needle, revealing its sharpened end. When the needle enters the peritoneal cavity, the obturator springs back into position, reducing the risk of injury to the intra-abdominal contents. The handle of the hollow needle allows the attachment of a syringe or tubing for insufflation of the distention gas.

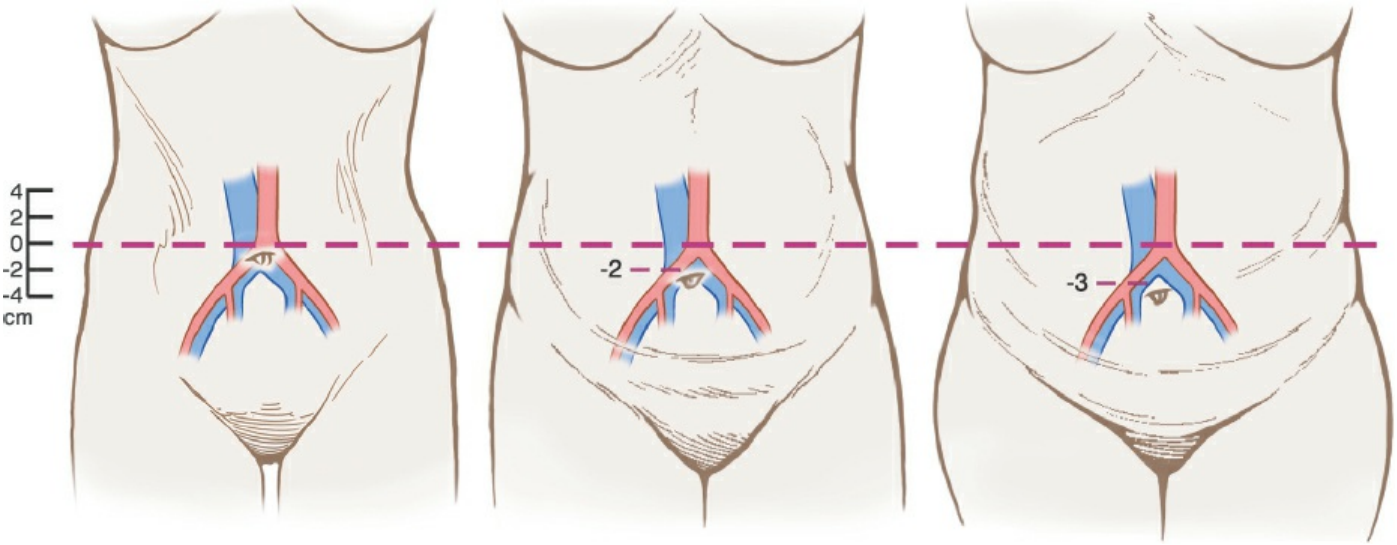


FIGURE 26-11 Umbilicus and weight. Location of the great vessels and their changing relationship to the umbilicus with increasing patient weight (from **left** to **right**). The location of the umbilicus tends to migrate caudally with increasing weight, however, there is considerable variation—the great vessels may, in some instances lie directly below the umbilicus.

Intraperitoneal pressure varies with respiration and is slightly higher in obese patients. Another reassuring sign that has not had adequate evaluation is the loss of liver "dullness" over the lateral aspect of the right costal margin. However, this sign may be absent if there are dense adhesions in the area, usually the result of previous surgery. Symmetric distention is unlikely to occur when the needle is positioned extraperitoneally. Proper positioning can be shown by lightly compressing the xiphoid process, which increases the pressure measured by the insufflator.

The amount of gas transmitted into the peritoneal cavity should depend on the measured intraperitoneal pressure, not the volume of gas inflated. Intraperitoneal volume capacity varies significantly between individuals. Many surgeons prefer to insufflate to 25 to 30 mm Hg for positioning of the cannulas and there is a body of evidence supporting this approach (142,145). This level usually provides extra volume and enough counterpressure against the peritoneum to facilitate introduction of the cannula, potentially reducing the chance of bowel or posterior abdominal wall and vessel trauma. **After placement of the cannulas, the pressure should be dropped to 10 to 15 mm Hg, which reduces the risk of subcutaneous insufflation leading to crepitus and essentially eliminates hypercarbia or decreased venous return of blood to the heart** (142,145,146).

There is little evidence that it is necessary to create a pneumoperitoneum prior to the insertion of the trocar–cannula system in the absence of pre-existing abdominal wall adhesions. Therefore, in women with no previous surgery, the primary puncture can be performed with a trocar–cannula system, which reduces operating time. This technique is referred to as "direct entry," which involves the blind insertion of the primary cannula before insufflating the abdomen. Regardless of the technique, preinsufflation or direct entry, the first, or primary, cannula must be of sufficient caliber to permit passage of the laparoscope. The patient should be in an unaltered supine position during placement of the primary cannula. After creating an intraumbilical incision, the abdominal wall is elevated wither using intraperitoneal pressure (20–30 mm Hg), or by affixing Kocher clamps to the fascia. Both hands can be positioned on the device, using one to provide counter pressure and control to prevent "overshoot" and resultant injury to bowel or vessels. The angle of insertion is the same as for the insufflation needle; adjustments are made according to the patient's weight and body habitus (141). The laparoscope should be inserted to confirm proper intraperitoneal placement and then the insufflation gas is allowed to flow.

Access Cannulas

Laparoscopic cannulas (or ports) allow the insertion of laparoscopic instruments into the peritoneal cavity while maintaining the pressure created by the distending gas (**Figs. 26-12** and **26-13**). Cannulas are hollow tubes with a valve or sealing mechanism at or near the proximal end. The cannula may be fitted with a Luer-type port that allows

attachment to hollow tubing connected with the CO_2 insufflator. Larger-diameter cannulas (8 to 15 mm) may be fitted with adapters or specialized valves that allow the insertion of smaller-diameter instruments without loss of intraperitoneal pressure.

The obturator is a longer instrument of slightly smaller diameter that is passed through the cannula, exposing its tip. Most obturators are called "trocars" because their tip is designed to penetrate the abdominal wall after the creation of an appropriately sized skin incision. Many disposable trocar–cannula systems are designed with a "safety mechanism"—usually a pressure-sensitive spring that either retracts the trocar or deploys a protective sheath around its tip after passage through the abdominal wall. None of these protective devices has been shown to make insertion safer and they all increase the cost of the equipment. Round-tipped obturators are not designed to penetrate the abdominal wall; they serve to facilitate passage of a Hasson cannula into the peritoneal cavity **(Fig. 26-9)**. Some access cannulas require no obturator, relying on a wood-screw design to penetrate the abdominal wall **(Fig. 26-13)**.

After the initial cannula (either the Hasson or the closed entry cannula) is successfully placed and the abdomen is insufflated, the surgeon should survey the peritoneal cavity and place additional cannulas under direct vision as necessary. If there are adhesions to the anterior abdominal wall in an area where the surgeon wishes to place a laparoscopic port, adhesiolysis can be performed to allow safe placement of the cannula.

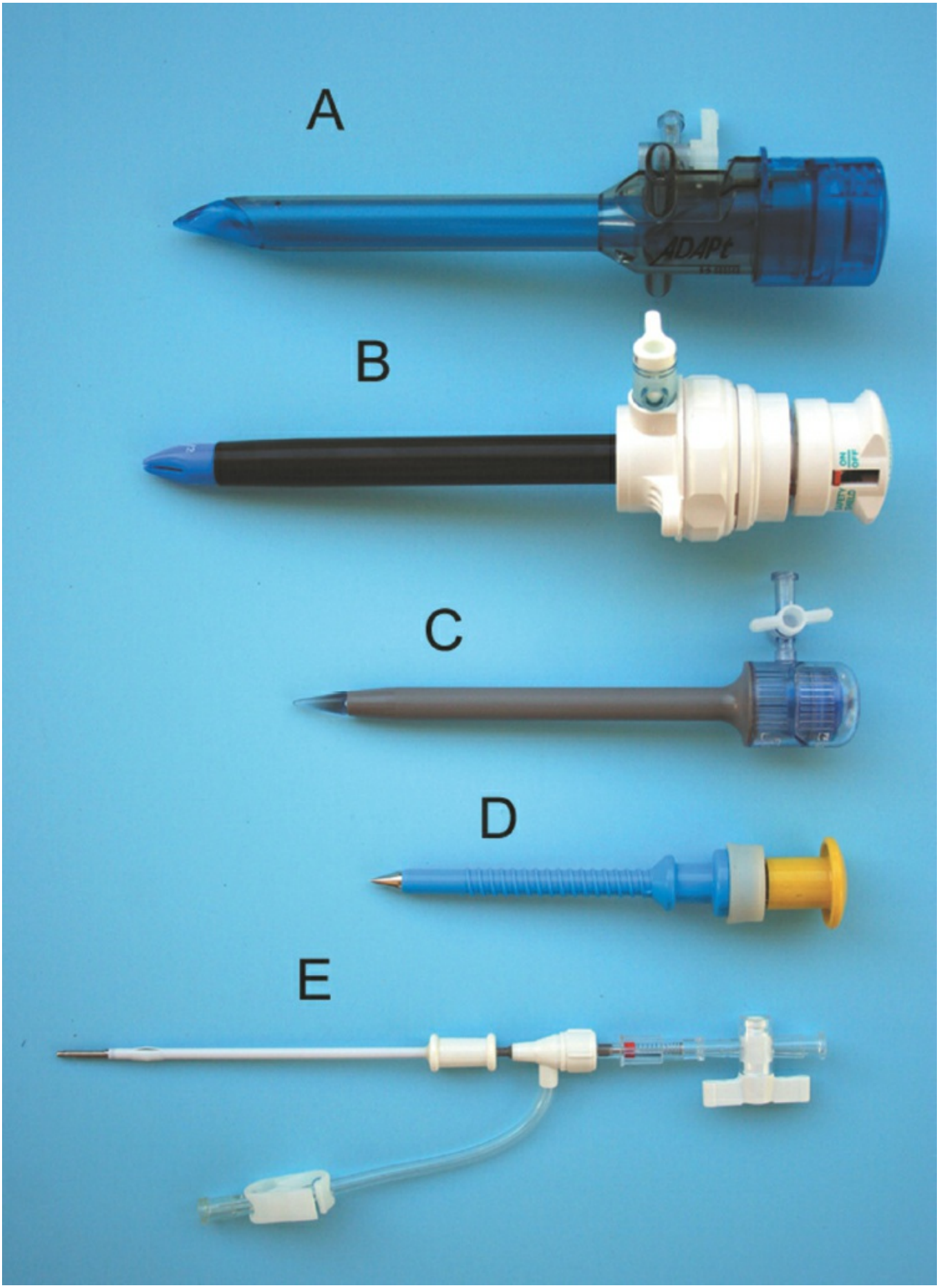

A
ADAPt
B
C
D
E

FIGURE 26-12 Disposable access systems. These instruments are designed for single use. A 12-mm internal diameter blunt access system is shown in **A**. The next device (**B**) also has a 12-mm internal diameter, but has a deployable blade that is used to cut through the abdominal wall. A smaller-diameter blunt conical device is shown in **C** while a sharp conical access system is presented in **D.** Both **C** and **D** have a 5.5 mm in inside diameter. A narrow, 2.7-mm diameter cannula is shown in **E.** The trocar for this system is a long insufflation needle with a spring deployable obturator.

Ancillary cannulas are necessary to perform most diagnostic and operative laparoscopic procedures, as they allow the insertion and use of laparoscopic hand instruments such as scissors, probes, and other manipulating devices. Most disposable ancillary cannulas are identical to those designed for insertion of the primary cannula; however, simple cannulas without the so-called "safety mechanisms" and insufflation ports are generally sufficient (Figs. 26-12 and 26-13).

Proper positioning of ancillary cannulas depends on the planned procedure, the nature of the pathologic and associated processes, and a sound knowledge of the abdominal wall vascular anatomy. For the secondary puncture, the patient may be tipped head down (Trendelenburg), allowing the abdominal contents to move away from beneath the incision sites, thus making it unnecessary to lift the abdominal wall during secondary cannula insertion. Alternatively, the intraperitoneal pressure may be maintained at 25 to 30 mm Hg to allow insertion of the secondary cannulas prior to placing the patient in Trendelenburg position.

Ancillary cannulas should always be inserted under direct vision because injury to bowel or major vessels can occur. Before insertion, the bladder should be drained with a urethral catheter. The insertion sites depend on the procedure, the disease, the patient's body habitus, and the surgeon's preference. For diagnostic laparoscopy, the most useful and cosmetically acceptable site for insertion of an ancillary cannula is in the midline of the lower abdomen, about 2 to 4 cm above the symphysis. The ancillary cannula should not be inserted too close to the symphysis because it limits the mobility of the ancillary instruments and access to the cul-de-sac. Laparoscopic cannulas can become dislodged and slip out of the incision during a procedure. There are a variety of cannulas designed to reduce slippage that include those with threaded exteriors and anchoring systems with balloon tips. The surgeon can prevent slippage by ensuring that the skin incisions are not too large for the cannula.

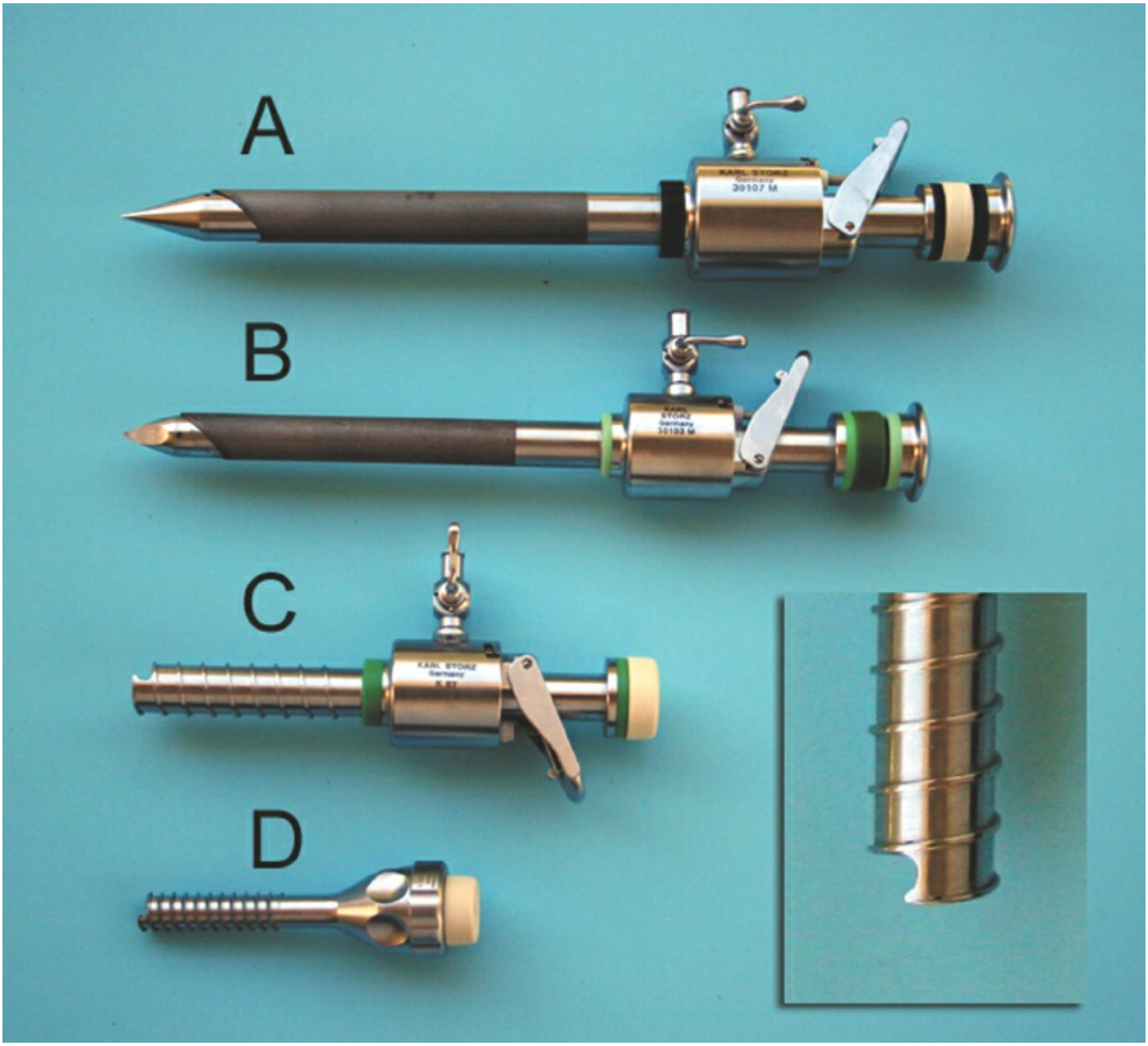


FIGURE 26-13 Reusable access systems. A: A sharp conical device while **B** represents a pyramidal-tipped design. **C** and **D** (and *inset*) are images of the so-called EndoTip device that can be positioned in the abdominal wall by simply twisting or screwing it in without the requirement of a trocar.

In addition to the suprapubic cannula, placement of bilateral lower–quadrant cannulas is useful for operative laparoscopy, but the superficial and inferior epigastric vessels must be located to avoid injury (Fig. 26-7). Transillumination of the abdominal wall from within permits the identification of the superficial inferior epigastric vessels in most thin women. The deep inferior epigastric vessels cannot be identified by this mechanism because of their location deep to the rectus sheath. The most consistent landmarks are the medial umbilical ligaments (obliterated umbilical arteries) and the exit point of the round ligament into the inguinal canal. At the pubic crest, the deep inferior epigastric vessels can often be visualized between the medially

located umbilical ligament and the laterally positioned exit point of the round ligament. The cannula should be inserted lateral to the vessels if they are visualized. If the vessels cannot be seen and it is necessary to position the cannula laterally, the device should be placed 3 to 4 cm lateral to the medial umbilical ligament or lateral to the lateral margin of the rectus abdominis muscle. If the incision is placed too far laterally, it will endanger the deep circumflex epigastric artery. The risk of injury can be minimized by placing a 22-gauge spinal needle through the skin at the desired location, directly observing the entry through the laparoscope. This provides reassurance that a safe location has been identified and allows visualization of the peritoneal needle hole, which provides a precise target for inserting the cannula.

Cannulas should be placed at an angle that is perpendicular to the contour of the abdomen, to ensure that the distance traveled from the skin to the parietal peritoneum is as short as possible. This will reduce the risk of injuries associated with insertion, such as those caused by trocars sliding medially during placement and injuring abdominal wall vessels. A properly angled port will ensure ease of operation when instruments are being introduced through the cannula. Large-diameter devices are more likely to cause injury; therefore, the smallest cannulas necessary to perform the procedure should be used. Ancillary cannulas should not be placed too close together because this hinders optimal mobility of the hand instruments, which compromises access and maneuverability.

The incision must be the appropriate size for the cannula that is being placed. It must be of adequate length to allow easy insertion of the device through the skin—a 1-cm long incision is inadequate to allow passage of a 1-cm diameter device. The outside diameter of a cannula is larger than the inside diameter; allowance must be made for the thickness of the material used to create the port. In some instances, this can add two or more millimeters to the device's outside diameter, and, therefore, increase the required length of the incision. Conversely, if the incision made is too large, in addition to the cosmetic impact, the cannula may slip out during the case, or there may be continuous leakage of the pneumoperitoneum around the cannula.



FIGURE 26-14 Single port access system. Demonstrated is a three-port access system from Medtronic (*inset*) and a similar device being used intraoperatively through the umbilicus with multiple instruments, including the laparoscope.

Single incision laparoscopic surgery refers to a technique where only one multi-instrument laparoscopic port is used to perform the procedure. The single incision is usually made at the umbilicus and about 2.5 to 3 cm in length. The specially designed port is placed in the incision which allows insufflation, introduction of the laparoscope and two or more additional instruments to permit completion of the procedure without additional incisions **(Fig. 26-14)**. Pelosi et al. published the first single incision multiport laparoscopic procedure (147). This technique has certain limitations, given the limited number of access channels and the fact that that the laparoscope and operative instruments are introduced parallel to each other. These issues have been partially addressed with improved instrumentation, such as steerable laparoscopes and hand instruments. With specialized training, surgeons have been able to perform certain types of cases safely and successfully using the single incision technique (148). One drawback to this method may be an increased risk of postoperative umbilical hernia,

likely a result of the larger umbilical incision (149).

Visualization

During endoscopy, the image must be transferred through an optical system to the eye of the surgeon. Historically, surgeons looked directly through the laparoscope to view the intra-abdominal contents. Virtually all modern laparoscopy is performed using video guidance.

Endoscopes

Laparoscopes are more than simple telescopes as they serve a dual purpose—transmission of light into a dark and closed cavity and obtaining an image of the operative field. The light is generally transmitted from a cold light source via a fiberoptic cable to an attachment on the endoscope that passes the light to the distal end of the telescope via a peripherally arranged array of fiberoptic bundles. The image is generally obtained by a distally positioned lens and transmitted to the eyepiece via a series of rod-shaped lenses. The eyepiece can be used to directly view the peritoneal contents or can serve as a point of attachment for a digital video camera. Some endoscopes transmit the image by a collection of densely packed fiberoptic bundles. This approach generally diminishes resolution, but allows flexibility of the endoscope, which is of great value for small-caliber telescopes or if the device is designed to be "steerable" with an articulated distal end. Another concept is to position a digital "chip" on the end of the system, which functions as a camera, obviating the need to have any lenses or fibers for transmission of an image. This design is colloquially called "chip-on-a-stick."

A laparoscope with an integrated straight channel, parallel to the optical axis, is called an "operating laparoscope" because the channel permits the introduction of operating instruments. This provides an additional port for the insertion of instruments and the application of laser energy. However, operative endoscopes are of relatively larger caliber than standard laparoscopes. They may have smaller fields of view, thereby presenting increased risks associated with the use of monopolar electrosurgical instruments. Standard, "viewing only" laparoscopes permit better visualization at a given diameter.

In general, the wider the diameter of the laparoscope the brighter the image, because increased light- or wider-diameter lenses result in an improved viewing experience for the surgeon. Narrow-diameter laparoscopes are associated with reduced transfer of light into and out of the peritoneal cavity; therefore, they require a more sensitive camera or a more powerful light source for adequate illumination. Previously, ideal illumination was provided by 10-mm diagnostic laparoscopes, but improvements in optics has allowed the 5-mm diameter laparoscope to become the standard in many operating rooms **(Fig. 26-15)**. Very narrow diameter laparoscopes, 2 mm or less, can provide adequate illumination for many procedures, and with a reduced cosmetic

impact (Fig. 26-16).

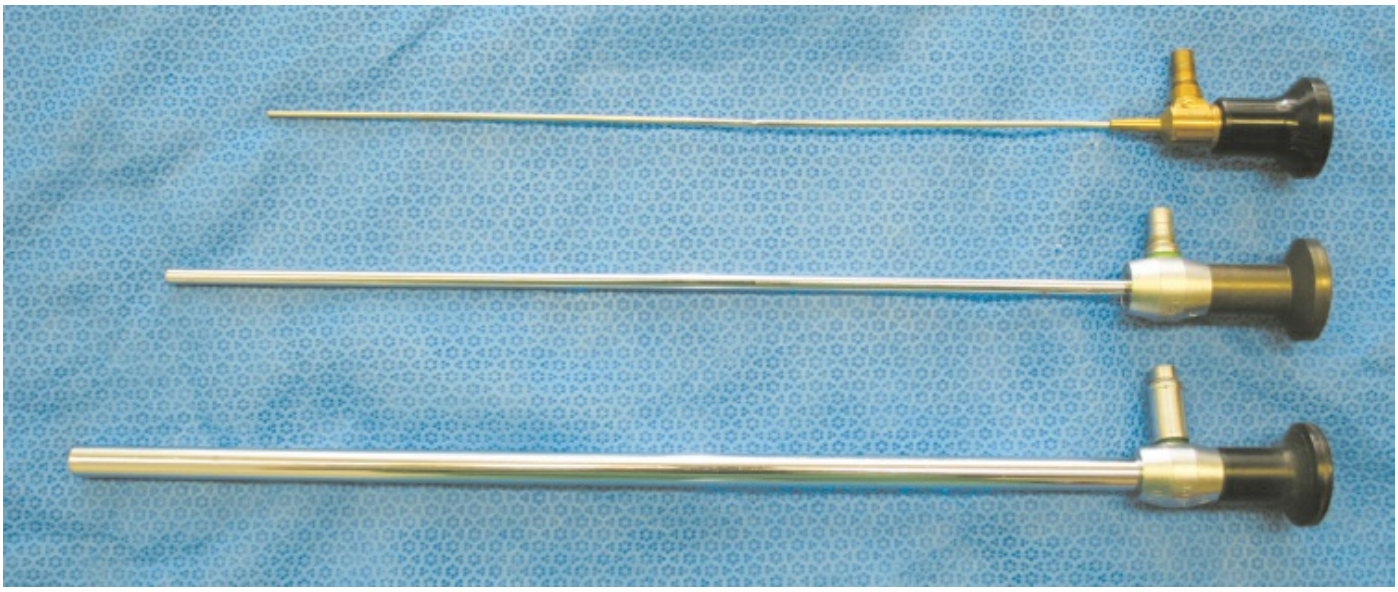


FIGURE 26-15 Laparoscopes. Three 0-degree laparoscopes are shown. From **top** to **bottom**, 2-mm, 5-mm and 10-mm diameter.

The viewing angle depicts the relationship of the visual field to the axis of the endoscope and typically ranges from 0 to 45 degrees to the horizontal (see Fig. 26-50). The zero-degree scope is the standard for gynecologic surgery. However, the 30-degree angle is invaluable in difficult situations, such as the performance of laparoscopic sacrocolpopexy, some myomectomies, and hysterectomy in the presence of large myomas.

Imaging Systems

The video camera is usually attached to the eyepiece of the endoscope where it captures the image and transmits it to the camera located outside the operative field, where it is processed, sent to a monitor and, potentially, a recording device (Fig. 26-17). Laparoscopes without an optical path have been introduced, with the sensor located on the distal tip of the endoscope, a design that still requires a remote camera location.

The resolution capability of the monitor should be equal to that provided by the camera. Most monitors can display at least 800 horizontal lines of resolution, while HD systems generally possess 1,080 lines and "4-K" devices can resolve up to 2,160 lines.

The more light transmitted through the endoscope, the better the visualization. The best available output is achieved from 250 to 300 watts, usually using xenon or metal halide bulbs. Most camera systems are integrated with the light source to vary light output automatically, depending on the amount of exposure required. Light guides or cables transmit light from the source to the endoscope via a bundle of densely packed optical fibers (fiberoptic). Fiberoptic cables lose function over time, particularly if mishandling breaks the fibers.

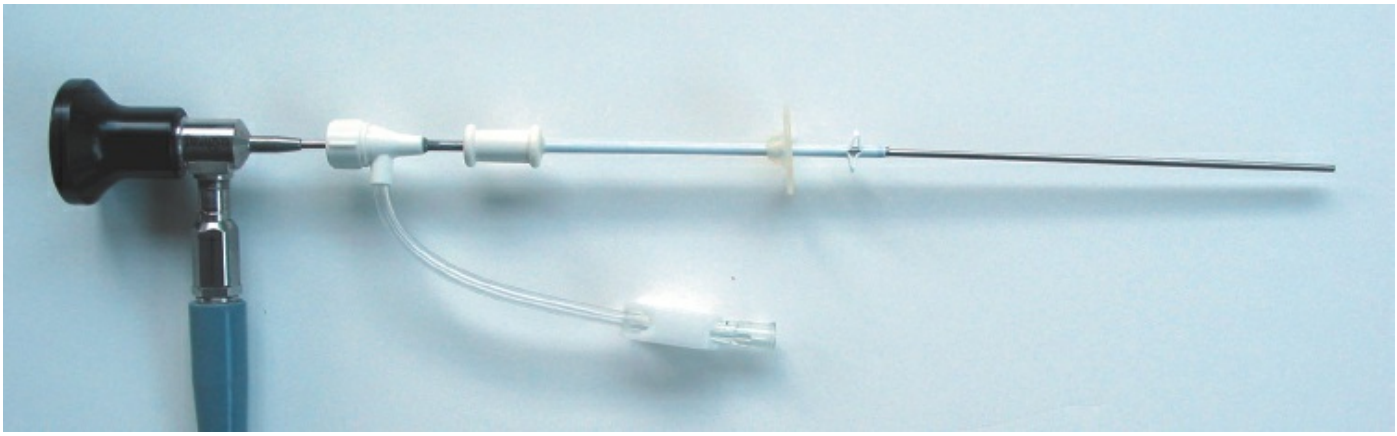


FIGURE 26-16 "Scout" laparoscope. The 2-mm laparoscope is passed through the 2.7-mm access system from **Figure 26-12E**. The tubing is connected to inflow gas, usually carbon dioxide.

Creation of a Working Space

The peritoneal cavity is a potential space, making it necessary to fill it with a gas, typically CO_2, to create a working environment. Other approaches are being explored using mechanical lifting systems that allow room air into the peritoneal cavity (150,151), a process called "gasless" laparoscopy.

To create a pneumoperitoneum, CO_2 is instilled into the peritoneal cavity under pressure by a machine called an insufflator. The insufflator delivers the CO_2 from a gas cylinder to the patient through tubing connected to a Luer adaptor on one of the laparoscopic cannulas. Most insufflators can be set to maintain a predetermined intra-abdominal pressure. High flow rates (9 to 20 L/min) are especially useful for maintaining exposure when suction of smoke or fluid depletes the volume of intraperitoneal gas.

Intraperitoneal retractors attached to a pneumatic or mechanical lifting system can be used to create an intraperitoneal space much like a tent (150). This "gasless" or "isobaric" technique may have some advantages over pneumoperitoneum, particularly in patients with cardiopulmonary disease (152) or with a potential malignancy. Airtight cannulas are not necessary, and instruments do not need to have a uniform, narrow, cylindrical shape. Consequently, some conventional instruments may be used directly through the incisions. Despite being introduced more than 20 years ago, and with evidence of efficacy (153), gasless laparoscopy has not experienced much of an uptake in gynecology, possibly because of perceived difficulties attaining adequate exposure.



FIGURE 26-17 Laparoscopic "tower" and camera. While many operating rooms now integrate their controllers, light sources, suction irrigation systems, and video monitors into floating platforms, for others the "tower" remains a useful method for positioning and storing the equipment. Here the monitor is on the top, the camera base next, then the light source and image printer. A camera sensor and coupler are shown; the coupler attaches the camera to the eyepiece of the endoscope.

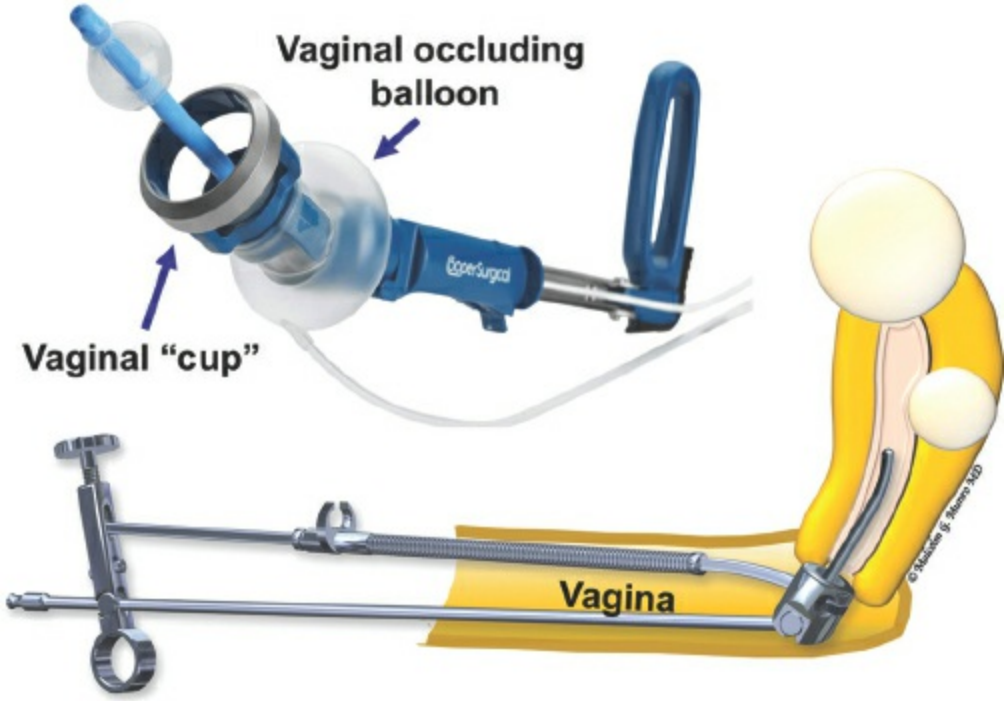


FIGURE 26-18 Uterine manipulators. The manipulator is useful not only to provide access to different aspects of the uterus, but for exposing the adnexa and the cul-de-sac. The manipulator at the top is called the Rumi® (CooperSurgical, Trumbull, CT, USA). It has a vaginal "cup" to help delineate the vagina, particularly useful for hysterectomy, and an occluding balloon that allows maintenance of pneumoperitoneum when a culdotomy is created. The manipulator on the bottom is the Valtchev® (Conkin Surgical Instruments Ltd, Vancouver, BC, Canada), and is entirely reusable. Note the articulation point that, in this case, is creating maximal anteversion of the uterus.

Manipulation of Tissue and Fluid

Uterine Manipulators

Uterine manipulation is an important component of the exposure strategy for most pelvic procedures, especially for myomectomy and hysterectomy. A properly designed uterine manipulator should have an intrauterine component, or obturator, and a method for fixation of the device to the uterus. Articulation of the instrument permits acute anteversion or retroversion, both of which are extremely useful maneuvers. If the uterus is large, longer and wider obturators are used so that the manipulations can be performed more effectively. Two types of uterine manipulators are shown in Figure 26-18. A hollow channel attached to a port allows intraoperative instillation of liquid dye to aid in the identification of the endometrial cavity (during myomectomy) or to demonstrate tubal patency.

Grasping Forceps

The forceps used during laparoscopy should, to the extent possible, replicate those used in open surgery. Disposable instruments generally do not have the quality, strength, and precision of reusable forceps (Fig. 26-19). Instruments with teeth (toothed forceps) are

necessary to securely grasp the peritoneum or the edge of an ovary for removal of an ovarian cyst. Minimally traumatic instruments designed like Babcock clamps are needed to safely retract the fallopian tube. Tenaculum-like instruments are desirable to retract leiomyomas or the uterus. A ratchet is useful to hold tissue without arduous hand pressure. Graspers should be insulated if unipolar RF instruments are being used to attain hemostasis.

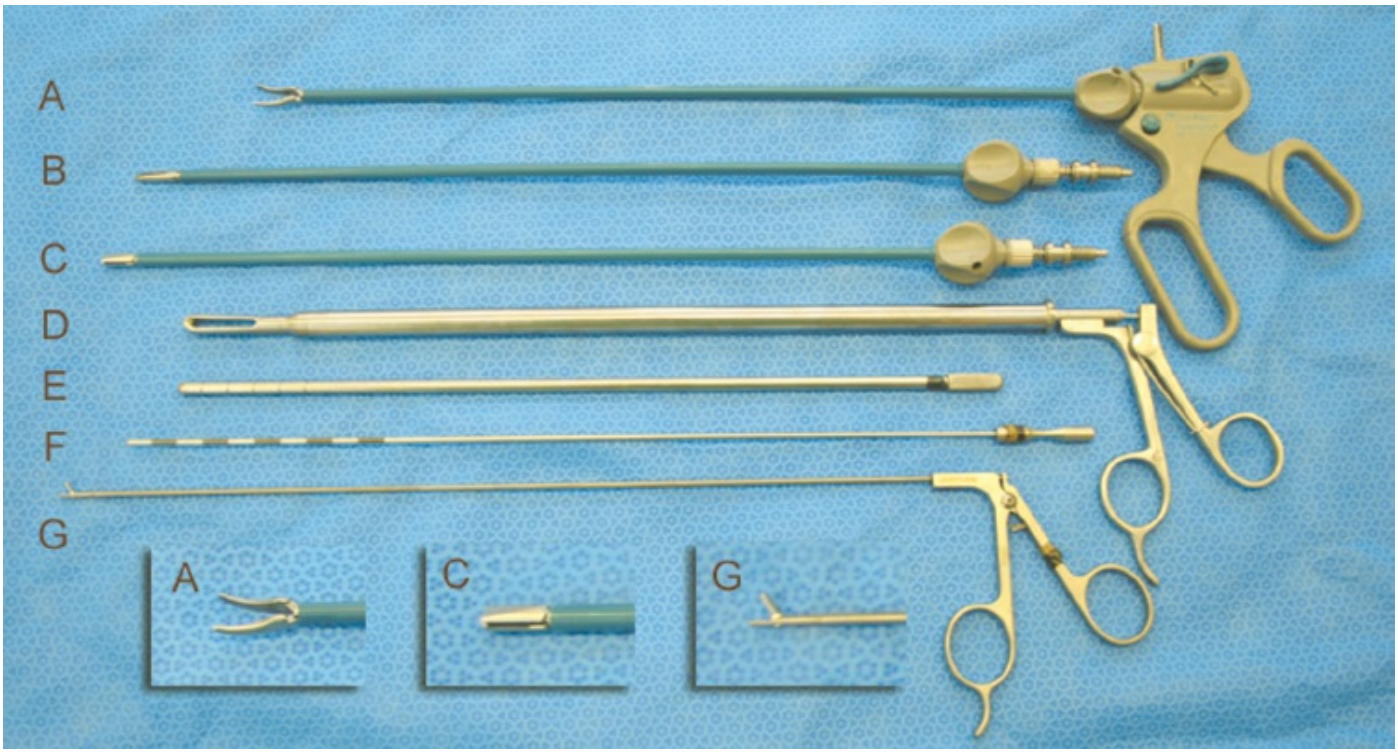


FIGURE 26-19 Laparoscopic instruments for grasping and manipulating tissue. A: (**top** and *inset*) are 5-mm diameter graspers with a curved tip, often called "Maryland" graspers. Other reusable tips (**B**) and (**C**) may be positioned in the same handle as is shown for **A**. **D:** is a 10-mm claw grasper while (**E**) and (**F**) are 5- and 2-mm manipulating probes respectively. **G:** is a 2-mm grasping forceps.

Suction and Irrigation

Devices called "suction-irrigators" can be used to introduce irrigation fluid into the abdomen, and suction it away as needed. A high-pressure mechanical pump allows the fluid to be introduced for irrigation, or for hydro- or "aquadissection." The device is attached to a wall suction and can be used to clear away any fluid as needed. The cannulas used for suction and irrigation depend on the irrigation fluid used and the fluid being removed. For ruptured ectopic gestations or other procedures in which there is a large amount of blood and clots, large-diameter cannulas (7 to 10 mm) are preferred. Cannulas with narrow tips are more effective in generating the high pressure needed for hydrodissection. Isotonic fluids should generally be used to minimize the risk of fluid overload and electrolyte imbalance. There is evidence that normal saline is more likely to induce oxidative stress and reduce fibrinolytic activity (154,155), and, perhaps,

increase the risk of adhesion formation (156), a circumstance that makes Ringer's lactate a more appropriate solution (157).

Hemostasis, Cutting, and Tissue Fixation

Hemostasis can be achieved during laparoscopic surgery using energy sources, sutures, clips, linear staplers, and topical or injectable substances. Cutting can be managed by mechanical means or by using electrical, ultrasonic, laser, or RF energy. Secure apposition or tissue fixation may be accomplished with sutures, clips, or staples. With appropriate training, a skilled surgeon can obtain good results with any combination of these techniques for cutting, hemostasis, and tissue fixation. Studies in animals have not demonstrated any difference in injury characteristics when cutting is performed with either laser or RF energy (87–89) and randomized controlled studies have shown no differences in fertility outcomes (158). Differences in results are more likely to be caused by other factors, such as patient selection, extent of disease, and degree of surgical expertise. Consequently, it is difficult to justify the costs associated with using lasers during laparoscopic gynecologic surgery.

Hemostasis

Because of the visual, tactile, and mechanical limitations of laparoscopy, prevention of bleeding is important for the conduct of efficient, effective, and safe procedures. RF electricity is the least expensive and most versatile method for achieving hemostasis during laparoscopy and can be applied with either monopolar or bipolar instruments.

The current for performing electrosurgical techniques is provided by a device that converts the alternating polarity circuit from a wall source from a frequency of 60 Hz to one in the RF spectrum typically from 300 to 500 KHz (300–500,000 Hz). These devices, some of which are proprietary, can be simple or complex, providing power for monopolar and bipolar instrument **(Fig. 26-20)**.

Regardless of the type of system, **the process of electrical desiccation and coagulation is best achieved by contacting the tissue and activating the electrode using continuous low-voltage or "cutting" current.** With adequate power, typically 30 to 50 watts (depending, in part on the surface area of the electrode[s]), tissue will be heated, desiccated, and coagulated. **Blood vessels should be compressed with the blades of the forceps before the electrode is activated so that the "heat sink" effect of flowing blood is eliminated. This allows the opposing walls of the vessel to bond, forming a strong tissue seal in a process called *coaptive coagulation***. Bipolar devices can be fitted with a serial ammeter that measures the current flowing through the system. When the tissue between the blades of the forceps is completely desiccated, the device is no longer able to conduct electricity, which can trigger a visual or auditory cue for the surgeon. With generic devices, the surgeon can reduce lateral thermal spread of RF energy by manually pulsing delivery or by simultaneously running irrigation fluid

over the pedicle.



FIGURE 26-20 RF Electrosurgical generator. Displayed is the Medtronic Valleylab™ FT10 Energy Platform (Medtronic Inc., Minneapolis, MN, USA), a radiofrequency electrosurgical generator designed to be used with a spectrum of monopolar, bipolar, and proprietary bipolar instruments. The device is capable of outputting high-voltage ("coagulation") and low-voltage ("cut") waveforms for monopolar instruments as well as a low-voltage waveform for bipolar instruments.



FIGURE 26-21 Reusable bipolar system. The Karl Storz RoBi™ (Karl Storz Endoscopy Americas, Culver City, CA, USA), system comprises a reusable device with changeable cutting and dissecting/coagulating tips displayed on the right. A coagulating tip is seen in the *inset*.

Generic bipolar devices are generally reusable, and some have changeable tips to use in different situations (Fig. 26-21). Automated RF systems comprise proprietary generators that pulse energy and generally proprietary bipolar forceps, often with included mechanical blades designed to cut tissues following coagulation of the tissue (Fig. 26-22). These systems are usually designed such that the generator stops automatically when current is no longer being conducted by the tissue between the blades of the forceps or when the tissue uniformly reaches a temperature predetermined to indicate tissue desiccation and coagulation.

Control of superficial bleeding can be achieved with *fulguration*, the near-contact spraying of tissue with modulated, high-voltage RF waveforms from the "coagulation" side of the electrosurgical generator using a monopolar instrument. Care must be taken to perform laparoscopic fulguration safely, ensuring that the entire shaft of the laparoscopic instrument is well away from bowel.

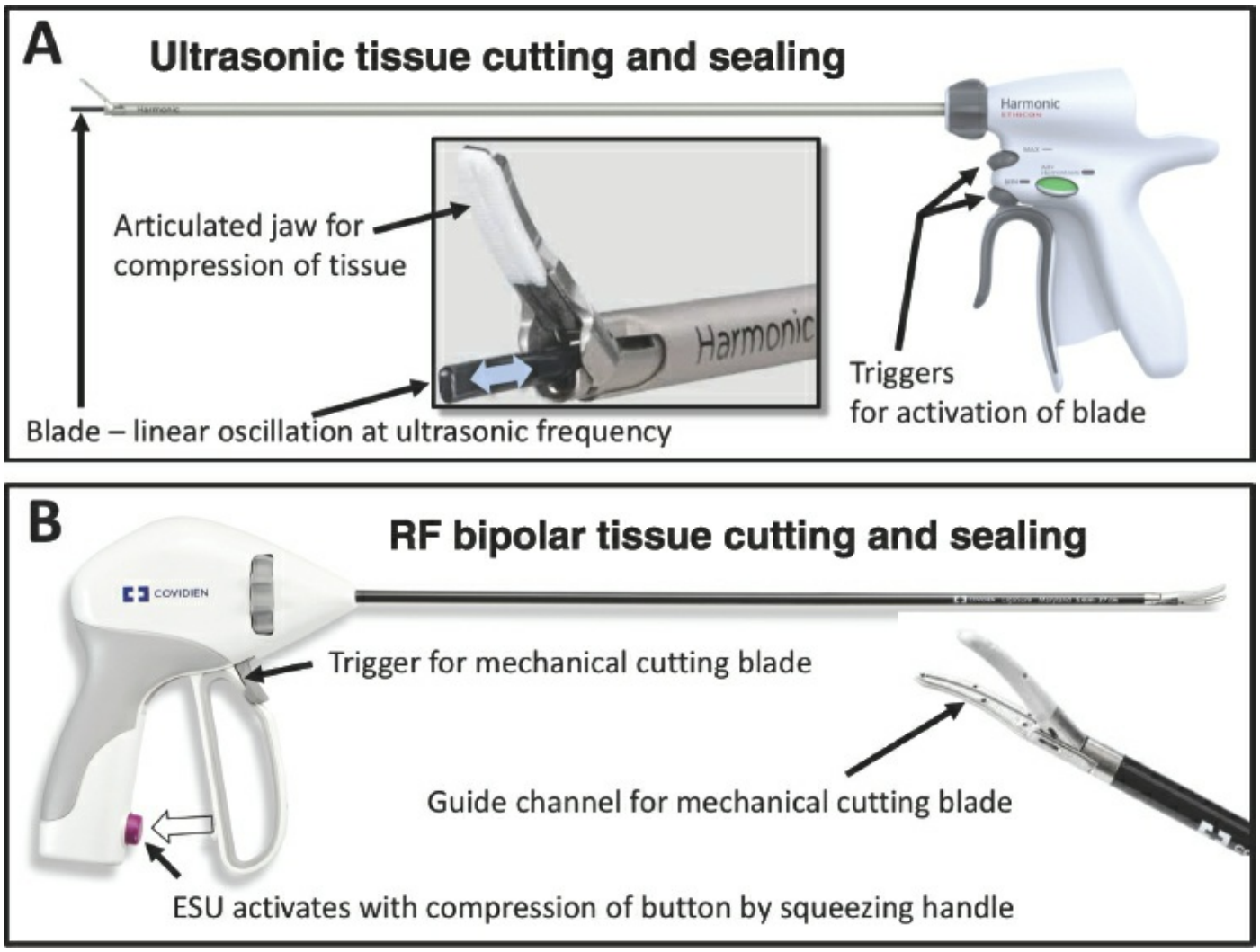


FIGURE 26-22 Laparoscopic hybrid cutting and sealing devices. (**A**) Ethicon Endosurgery's Harmonic Ace®+7 (Ethicon Endosurgery Inc, Cincinnati, OH, USA) LCS and (**B**) the Medtronic LigaSure™ Maryland. These two devices both cut and coagulate or seal tissue. The ligating cutting shears (LCS) are based on ultrasound technology. The bottom blade oscillates while the top jaw is opened to grasp the tissue and then used by the surgeon to slowly transect and seal the blood vessels in the tissue being transected. The RF bipolar radiofrequency device (**B**) is the Medtronic 1737 Maryland device that, using electrical impedance, tells the surgeon when the tissue is coagulated. Tissue is transected using a mechanical blade activated by a hand-controlled trigger.

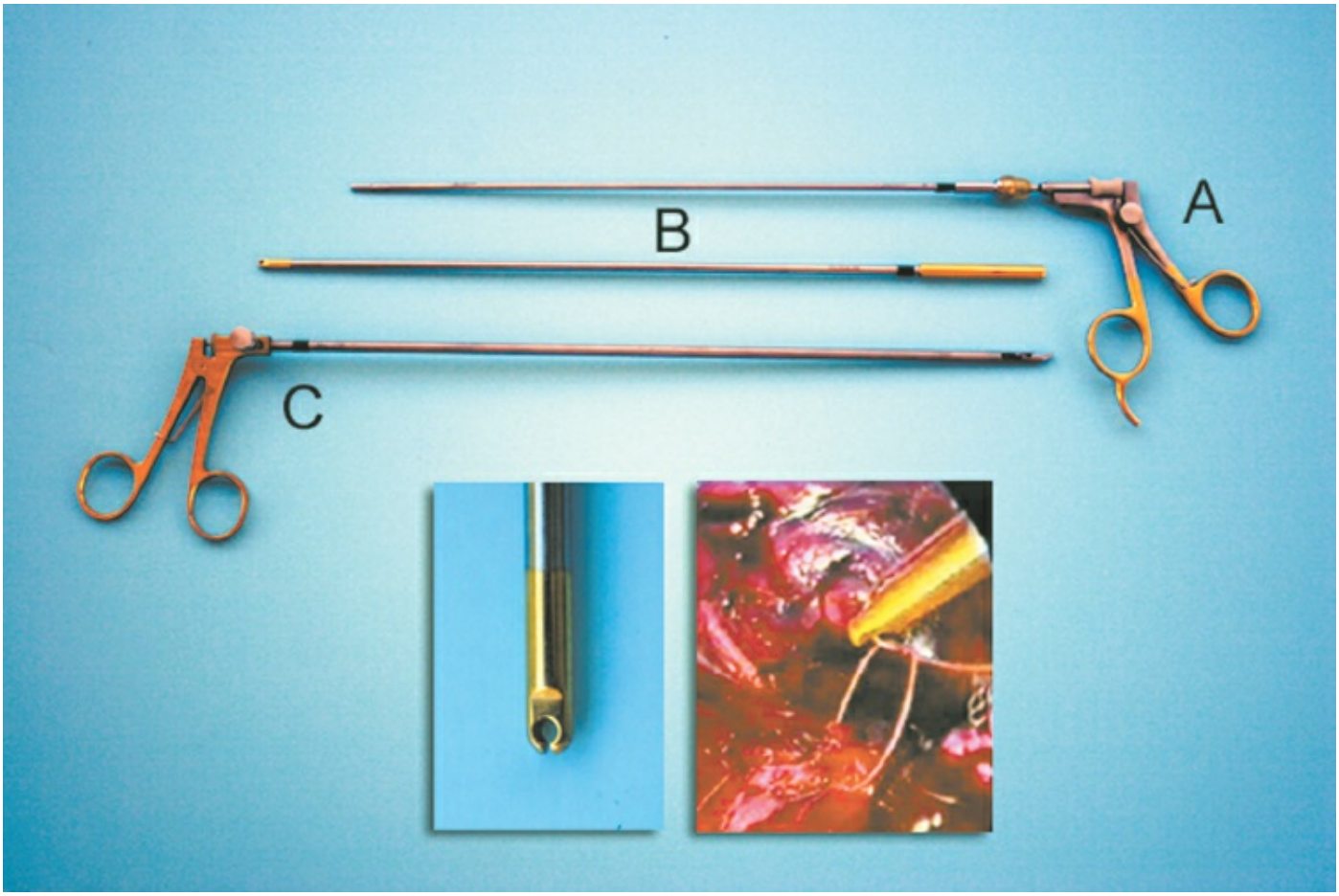


FIGURE 26-23 Laparoscopic suturing instruments. 3-mm and 5-mm diameter laparoscopic needle drivers are displayed in **A** and **C** while a knot manipulator is shown in **B** and *inset left*. The device is shown transferring a knot into the peritoneal cavity (*inset right*).

Ultrasonic instruments can be used for hemostasis. Those with a forceps-like end effector disperse the mechanical energy in a way that allows the tissue to be heated and coagulated. These so called "ligating-cutting" shears also cut when high pressure is exerted in the handle by the surgeon (Fig. 26-22).

Hemostatic clips may be applied with specially designed laparoscopic instruments. Nonabsorbable clips made of titanium are useful for relatively narrow vessels, and longer, delayed absorbable, self-retaining clips are generally preferred for larger vessels, 3 to 4 mm or more. Clips may be of particular value when securing relatively large vessels near an important structure such as the ureter.

Laparoscopic suturing is a method of maintaining hemostasis (159–161). Compared with clips or linear staplers, suturing has a relatively low cost of materials, although operating time may be longer. The two basic methods for securing a ligature around a blood vessel are the creation of intracorporeal and extracorporeal knots, depending on where the knot is formed. Intracorporeal knots replicate the standard instrument-tied knot and are formed within the peritoneal cavity. Extracorporeal knots are created outside the abdomen under direct vision and transferred into the peritoneal cavity by

knot manipulators (see Fig. 26-23). Pretied knotted suture loops attached to long introducers, called "Endoloops®," may be used to secure vascular pedicles. However, care should be taken to make sure that they are tightly secured and that no other tissue is incorporated in the loop. A number of devices that facilitate the formation and tying of knots are available. Various barbed sutures that facilitate laparoscopic suturing by eliminating the need to tie knots are commercially available. The suture contains small barbs along its length that fix the suture in place within the tissue. This is particularly helpful in procedures that require a great deal of suturing, such as laparoscopic myomectomy.

Small areas of low-volume bleeding can be treated with topical hemostatic agents. Topical agents such as microfibrillar collagen are available in 5-mm and 10-mm diameter laparoscopic applicators. Fibrin sealants (e.g., Tisseel®) and bovine thrombin and gelatin (Floseal®) can be used. A solution of dilute vasopressin may be injected locally to maintain hemostasis for myomectomy or removal of ectopic pregnancy.

Cutting

The most useful cutting instruments are scissors (Fig. 26-24). Because it is difficult to sharpen laparoscopic scissors, most surgeons prefer disposable instruments that can be used until dull and then discarded. Scissors are ideal for cutting avascular tissue, or in situations such as adhesiolysis near vital structures where thermal energy must be avoided.

Often surgeons need to coagulate a vascular pedicle by sealing the blood vessels, and separate the pedicle by cutting the coagulated area. In this situation, the target tissue can be coagulated using a bipolar instrument, and divided using scissors. Devices that initially coagulate the tissue, then mechanically divide it, have become prevalent, and provide a more efficient option to achieve the same goal.

Another mechanical cutting tool is the linear stapler–cutter that can simultaneously cut and hemostatically staple the edges of the incision. These devices are of limited utility in gynecologic laparoscopy because of their high cost, the large dimensions of the instruments, and inability of the staples to secure the large pedicles that exist in the pelvis.

Laser and electrical sources of energy manifest their effect by conversion of electromagnetic energy to mechanical energy, which is transformed to thermal energy. Highly focused RF electrical current (high-power or current density), generated by a specially designed electrosurgical generator produces vaporization or cutting, by raising the intracellular temperature above 100°C resulting in the rapid conversion of water to steam and a massive increase in intracellular volume. This expansion ruptures the already damaged cell membrane resulting in cellular and tissue vaporization into a cloud of steam, ions, and protein particles. If the instrument used to focus the energy is moved in a linear fashion, the result is tissue transection or cutting. Less focused RF

energy (moderate current or power density) elevates intracellular temperature, causing desiccation, rupture of hydrogen bonds, and resulting tissue coagulation, but vaporization does not occur.

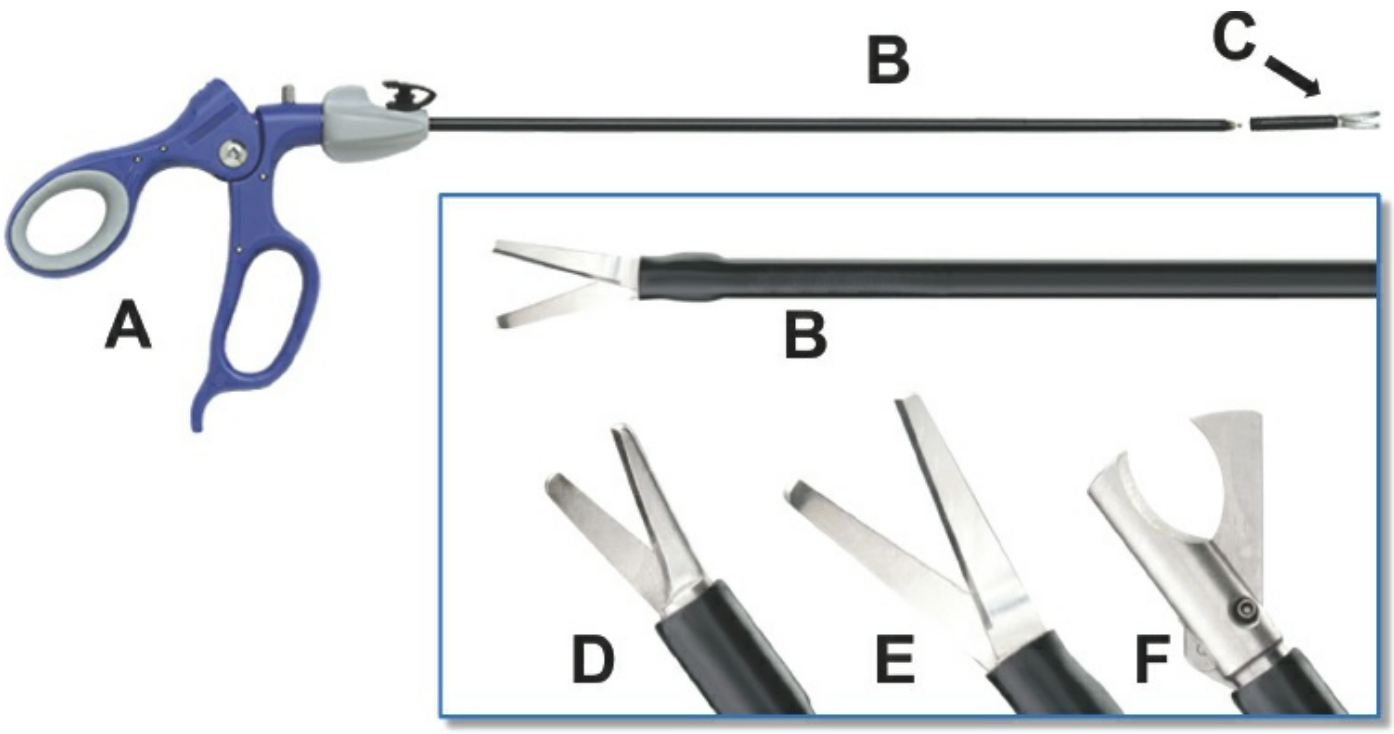


FIGURE 26-24 Laparoscopic mechanical cutting instruments. Demonstrated is a laparoscopic hand instrument with a handle (**A**), shaft (**B**), and detachable tips (**C**). The scissor tips are demonstrated in short straight (**D**), long curved (**E**), and hooked (**F**) designs.

Monopolar electrosurgical instruments that are narrow or pointed are capable of generating the high-power densities necessary to vaporize or cut tissue (Fig. 26-25). Continuous or modulated and relatively low-voltage outputs are generally the most effective; for example, 60 watts of 'pure cutting' current. For optimal results, the instrument should be used in a noncontact fashion, following (not leading) the energy through the tissue. Laparoscopic scissors are generally of monopolar instruments and are designed to cut mechanically; energy may be applied simultaneously for desiccation and hemostasis when cutting tissue that contains small blood vessels (Fig. 26-23).

Laser energy can be focused to vaporize and cut tissue. The most efficient laser-based cutting instrument is the CO_2 laser, which has the drawback of requiring linear transmission because light cannot be conducted effectively along bendable fibers. The potassium-titanyl-phosphate (KTP) and neodymium:yttrium, aluminum, garnet (Nd:YAG) lasers are effective cutting tools. They are capable of propagating energy along bendable quartz fibers but have a slightly greater degree of collateral thermal injury than RF electrical or CO_2 laser energy. Because of such limitations and their additional expense, these lasers are of limited value.

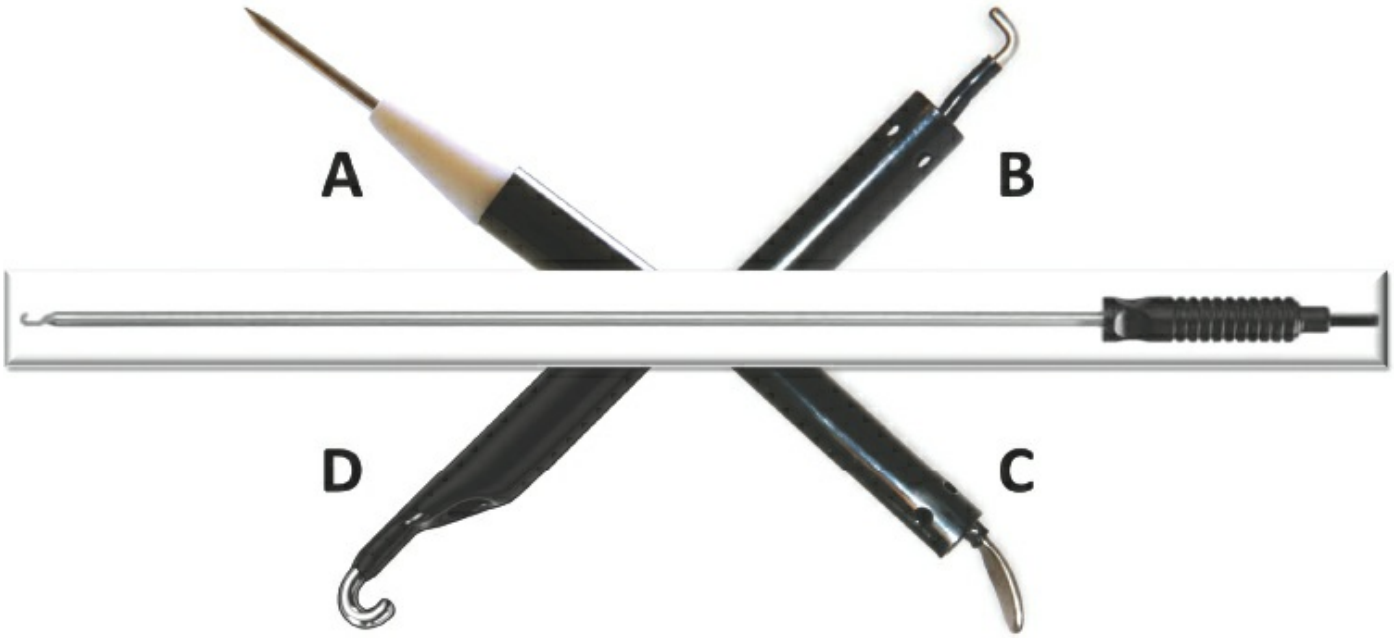


FIGURE 26-25 Laparoscopic monopolar RF cutting instruments. Shown are a monopolar laparoscopic probe with a hook electrode and four electrodes designed to focally vaporize and/or transect tissue. The needle electrode is seen in **A**, an L electrode in **B**, a spatula in **C** and a hook electrode is demonstrated by **D**.

Ultrasonic cutting is largely accomplished mechanically using a blade that oscillates back and forth in a linear fashion (Fig. 26-22). The oscillation is achieved using a vibrating element located in a handle that oscillates the blade, hook, or one arm of the clamp 55,000 times per second (55 kHz). The distance of the oscillation can be varied and determines the efficiency of the cutting process. The tip of the device cuts mechanically, but there is a degree of collateral thermal tissue coagulation injury that can be used for hemostasis. In low-density tissue, the process of mechanical cutting is augmented by the process of cavitation, in which reduction of local atmospheric pressure allows vaporization of intracellular water at body temperature.

Tissue Extraction

After excising tissue, it is necessary to remove it from the peritoneal cavity. Small samples can be pulled through an appropriate-sized cannula with grasping forceps; however, larger specimens may not fit. If the specimen is cystic, it may be drained by a needle or incised, shrinking it to a size suitable for removal through the cannula or one of the small laparoscopic incisions. It is often helpful to place specimens in endoscopic retrieval bags for removal, which help contain the specimen and facilitate its removal from the abdominal cavity in its entirety (Fig. 26-26). **If there is any concern for malignancy in an ovarian cyst, all attempts should be made to keep the cyst intact during dissection, and to place the specimen in an appropriately sized bag before**

drainage and removal, thus preventing spillage of the cyst contents within the abdomen.



FIGURE 26-26 Specimen removal bag. This 10-mm diameter system is positioned in the peritoneal cavity. Then, the bag is deployed (*insets*), allowing the surgeon to place specimens for removal, generally through the port or cannula.

More solid tissue, such as leiomyomas or the entire uterus, may be broken up or "morcellated" into smaller pieces for removal. This may be achieved manually or laparoscopically and can be performed with or without containment in a specimen bag.

Manual morcellation refers to the simple process of bringing the excised intra-abdominal specimen up to any opening where it can be reached by the surgeon, and cut into small pieces using scissors or a scalpel, to allow it to be removed. When performing total LH for a large uterus, the vaginal opening can be used to access the specimen for manual morcellation. Some surgeons opt to perform this procedure after placing the uterus into a large specimen bag in order to contain it. In cases of

laparoscopic SCH and myomectomy, there is no vaginal incision. Therefore, manual morcellation can be performed using a minilaparotomy, often created by enlarging the umbilical laparoscopic incision to about 3 cm. Alternatively, an incision can be made in the posterior cul-de-sac (posterior colpotomy) to provide access, an approach that has the advantage of being more cosmetically acceptable.

Laparoscopic morcellation can be achieved with scissors, ultrasonic equipment, or electrosurgery, but the most efficient technique for laparoscopic morcellation of large solid specimens is the use of electromechanical morcellators. Often referred to as "power morcellators," these devices utilize a rapidly rotating blade that can quickly core and remove large solid specimens from the abdomen **(Fig. 26-27)**.

Concerns have been raised about electromechanical morcellators, based upon the notion that their use may disseminate tumor cells in cases where an undiagnosed uterine malignancy is present. Studies show that among women undergoing hysterectomy or myomectomy for presumed benign leiomyomas, the prevalence of occult malignancy, or undiagnosed uterine sarcoma, is approximately 1 in 500 to 2,500 (162–164). Morcellation of a uterine sarcoma may worsen the patient's prognosis, although data supporting this notion are limited. Consequently, the FDA issued a warning statement regarding the use of electromechanical morcellation (165). This led many surgeons to limit their use of these devices. Most experts in the field believe that electromechanical morcellation still has a role in gynecologic surgery, allowing us to provide minimally invasive surgical options to women with large benign tumors (166).

Various products have been developed to allow electromechanical morcellation to be performed within a contained system using a large specimen bag positioned in the abdomen. These techniques are still being refined, and it is not yet clear if this approach will improve the prognosis for a patient with an inadvertently morcellated malignancy.

Although our ability to preoperatively distinguish benign myomas from malignant sarcomas is limited, surgeons must evaluate each patient based on risk factors and appropriately select low-risk patients as candidates for morcellation. With appropriate patient selection and a thorough informed consent process, women at low risk for cancer can continue to benefit from electromechanical morcellation.

Incision Management

[11] Dehiscence and hernia risk appear to significantly increase when the fascial incision is larger than 10 mm in diameter (167,168). Closure of the fascia can be performed using special ligature carriers used to position suture under direct laparoscopic vision to prevent the accidental incorporation of bowel into the incisions. An alternative is the use of 5/8 round needles and standard needle drivers. In either instance, the peritoneum should be closed to reduce the risk of Richter hernia.

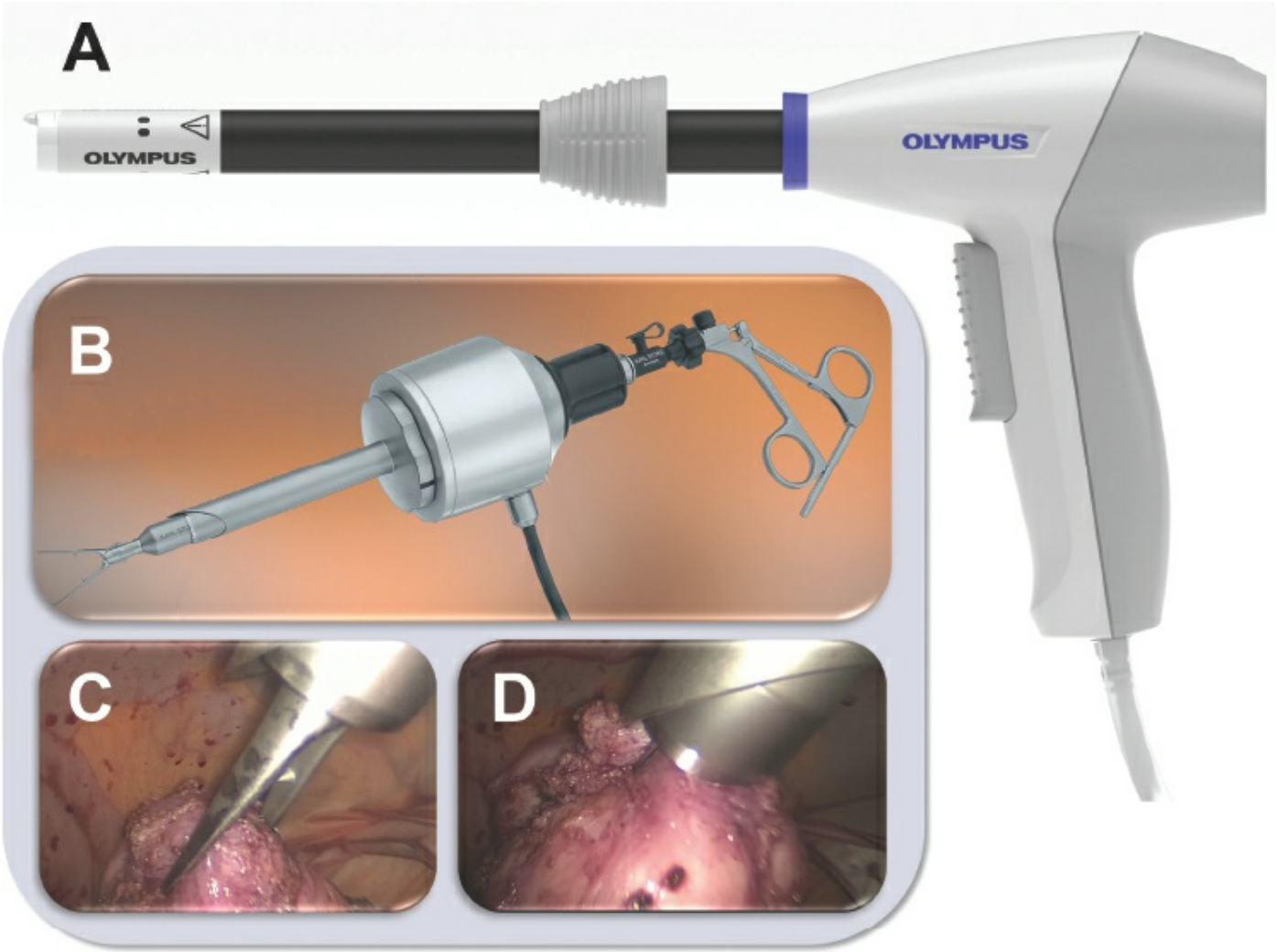


FIGURE 26-27 Solid tissue morcellators. RF based (**A**) and electromechanical (**B**). These devices are positioned in the peritoneal cavity and attached to a power generator. The blunt obturator is removed; a grasping instrument inserted through the lumen is used to withdraw the tissue, which is cut by a cylindrical blade (**C** and **D**).

Complications

[13] Patients recovering from laparoscopic surgery usually feel better every postoperative day. Pain diminishes, gastrointestinal function improves rapidly, and fever is extremely unusual. Therefore, if a patient's condition is not improving, possible complications of anesthesia or surgery should be considered. Laparoscopic procedures can be complicated by infections, trauma, hemorrhage, or by problems associated with anesthetic use. The incidence of infection is lower than with procedures performed by laparotomy. Conversely, problems associated with visualization in conjunction with the change in anatomic perspective may increase the risk of damage to blood vessels or vital structures such as the bowel, ureter, or bladder.

Anesthetic and Cardiopulmonary Complications

Laparoscopic surgery is generally safe. A review of laparoscopic tubal sterilization in 9,475 women found no deaths from complications of anesthesia (169,170). However, the potential risks of general anesthesia include hypoventilation, esophageal intubation, gastroesophageal reflux, bronchospasm, hypotension, narcotic overdose, cardiac arrhythmias, and cardiac arrest.

These risks can be enhanced by some of the inherent features of gynecologic laparoscopy. For example, the Trendelenburg position, in combination with the increased intraperitoneal pressure provided by pneumoperitoneum, places greater pressure on the diaphragm, increasing the risk of hypoventilation, hypercarbia, and metabolic acidosis. This position, combined with anesthetic agents that relax the esophageal sphincter, promotes regurgitation of gastric content, which can lead to aspiration, bronchospasm, pneumonitis, and pneumonia. Parameters of cardiopulmonary function associated with CO_2 and N_2O insufflation include reduced PO_2, O_2 saturation, tidal volume, and minute ventilation and increased respiratory rate. The use of intraperitoneal CO_2 as a distention medium is associated with an increase in PCO_2 and a decrease in pH. Elevation of the diaphragm may be associated with basilar atelectasis, resulting in right-to-left shunt and ventilation–perfusion mismatch (171). All of these effects are manageable and reversible, with contemporary anesthetic techniques (172).

Carbon Dioxide Embolus

Carbon dioxide is the most widely used peritoneal distention medium, largely because the rapid absorption of CO_2 in blood reduces the significance of gas emboli. However, if large amounts of CO_2 gain access to the central venous circulation, if peripheral vasoconstriction occurs, or if the splanchnic blood flow is decreased by excessively high intraperitoneal pressure, severe cardiorespiratory compromise may result.

The signs of CO_2 embolus include sudden and otherwise unexplained hypotension, cardiac arrhythmia, cyanosis, and heart murmurs. The end-tidal CO_2 level may increase, and findings consistent with pulmonary edema may manifest (173). Accelerating pulmonary hypertension may occur, resulting in right-sided heart failure.

Because gas embolism may result from direct intravascular injection through an insufflation needle, the proper placement of the insufflation needle, if used, must be ensured. Although the initial intraperitoneal pressure may be set at 20 to 30 mm Hg for port placement, it should be maintained at 8 to 12 mm for the rest of the case (174). The risk of CO_2 embolus is reduced by careful hemostasis because open venous channels are the portal of entry for gas into the systemic circulation. The anesthesiologist should continuously monitor the patient's color, blood pressure, heart sounds, heartbeat, and end-tidal CO_2 to allow early recognition of the signs of CO_2 embolus.

If CO_2 embolus is suspected or diagnosed, the surgeon must evacuate the CO_2

from the peritoneal cavity and place the patient in the left lateral decubitus position, with the head below the level of the right atrium. A large-bore central venous line should be inserted immediately to allow aspiration of gas from the heart. Because the findings are nonspecific, the patient should be evaluated for other causes of cardiovascular collapse.

Cardiovascular Complications

Cardiac arrhythmias occur relatively frequently during laparoscopic surgery and are related to a number of factors, the most significant of which are hypercarbia and acidemia. Early reports of laparoscopy-associated arrhythmia were associated with spontaneous respiration; therefore, most anesthesiologists have adopted the practice of mechanical ventilation during laparoscopic surgery. **The incidence of hypercarbia is reduced by operating with intraperitoneal pressures at levels less than 12 mm Hg** (175).

The risk of cardiac arrhythmia may be reduced by using NO_2 as a distending medium. Although NO_2 is associated with a decreased incidence of arrhythmia, it is insoluble in blood and, therefore, its use may increase the risk of gas embolus. External lifting systems (gasless laparoscopy) avoid the complication of hypercarbia and can provide protection against cardiac arrhythmia (176).

Hypotension can occur because of decreased venous return secondary to very high intraperitoneal pressure, and this condition may be potentiated by volume depletion. Vagal discharge may occur in response to increased intraperitoneal pressure, which can cause hypotension secondary to cardiac arrhythmias (176). All of these side effects should be considered when performing surgery on patients with pre-existing cardiovascular disease.

Gastric Reflux

Gastric regurgitation and aspiration can occur during laparoscopic surgery, especially in patients with obesity, gastroparesis, hiatal hernia, or gastric outlet obstruction. In these patients, the airway must be maintained with a cuffed endotracheal tube, and the stomach must be decompressed (e.g., with a nasogastric tube). The lowest necessary intraperitoneal pressure should be used to minimize the risk of aspiration. Patients should be moved out of the Trendelenburg position before being extubated. Routine preoperative administration of *metoclopramide*, H2-blocking agents, and nonparticulate antacids reduces the risk of aspiration.

Extraperitoneal Insufflation

The most common causes of extraperitoneal insufflation are preperitoneal placement of the insufflating needle and leakage of CO_2 around the cannula sites. Although this condition is usually mild and limited to the abdominal wall, subcutaneous emphysema

can become extensive, involving the extremities, the neck, and the mediastinum. Another relatively common site for emphysema is the omentum or mesentery, a circumstance that may be mistaken for preperitoneal insufflation.

Subcutaneous emphysema may be identified by the palpation of crepitus, usually in the abdominal wall. Emphysema can extend along contiguous fascial plains to the neck, where it can be visualized directly. Such a finding may reflect mediastinal emphysema, which may indicate impending cardiovascular collapse (177–180).

The risk of subcutaneous emphysema is reduced by the proper positioning of the insufflation needle and by maintaining a low intraperitoneal pressure after placement of the desired cannulas. Other approaches that reduce the chance of subcutaneous emphysema include open laparoscopy and the use of abdominal wall lifting systems that make gas unnecessary.

If the insufflation has occurred extraperitoneally, the laparoscope can be removed and the procedure can be repeated. Difficulty may ensue because of the altered anterior peritoneum. Open laparoscopy or the use of an alternate site, such as the left upper quadrant, should be considered. One approach is to leave the laparoscope in the expanded preperitoneal space while the insufflation needle is reinserted under direct vision through the peritoneal membrane caudad to the tip of the laparoscope (181).

In mild cases of subcutaneous emphysema, the findings quickly resolve after evacuation of the pneumoperitoneum, and no specific intraoperative or postoperative therapy is required. When the extravasation extends to the neck, it is usually preferable to terminate the procedure because pneumomediastinum, pneumothorax, hypercarbia, and cardiovascular collapse may result. Following termination of the procedure, it is prudent to obtain a chest x-ray. The patient's condition should be managed expectantly unless a tension pneumothorax results, in which case immediate evacuation must be performed using a chest tube or a wide-bore needle (14 to 16 gauge) inserted in the second intercostal space in the midclavicular line.

Electrosurgical Complications

The incidence of unintended injuries associated with the use of RF electricity can be reduced with a good understanding of electrosurgical principles.

RF electrosurgery is performed using two electrodes, connected to an electrosurgical generator. With monopolar instrumentation, one of the electrodes is used to focus the energy and create one of the electrosurgical effects (vaporization/cutting or desiccation/coagulation), while the other is a large area device attached to the patient remotely to diffuse the current (see **Fig. 26-29**). Complications of RF electrosurgery occur secondary to thermal injury from unintended or inappropriate use of the active electrode(s) or, for monopolar instrumentation, current diversion to an undesirable path, or injury at the site of the dispersive electrode. Such complications may occur with the use of these instruments during laparoscopic, laparotomic, or vaginal surgery. Active

electrode injury can occur with either unipolar or bipolar instruments, whereas trauma secondary to current diversion and dispersive electrode accidents occur only with unipolar devices. Complications of electrosurgery are reduced by adherence to safety protocols coupled with a sound understanding of the principles of electrosurgery and the circumstances that can lead to injury (182). An excellent source of information regarding the principles and safe use of RF electricity and other energy sources called Fundamental Use of Surgical Energy (FUSE), created by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) is available free of charge (183).

Active Electrode Trauma

If a button or foot pedal is accidentally depressed, tissue adjacent to the electrode of a monopolar instrument will be traumatized. Potential sites of injury include the bowel, ureter, and other intraperitoneal structures, or, if the electrode lies on the abdomen, the skin. Injury from direct extension of thermal effect can occur when the zone of vaporization or coagulation extends to large blood vessels or vital structures such as the bladder, ureter, or bowel. Bipolar instruments, even those with advanced impedance sensing systems, reduce but do not eliminate the risk of thermal injury to adjacent tissue (184,185). Therefore, blood vessels should be isolated before electrosurgical coagulation, especially when they are near vital structures, and appropriate amounts of energy must be applied to allow an adequate margin of noncoagulated tissue.

The diagnosis of direct thermal visceral injury may be difficult. If unintended activation of the electrode occurs, nearby intraperitoneal structures should be evaluated carefully. The appearance can be affected by several factors, including the output of the generator, the type of electrode, its proximity to tissue, and the duration of activation. The diagnosis of visceral thermal injury is often delayed until signs and symptoms of fistula or peritonitis appear. Because these complications may not manifest until 2 to 10 days after surgery, patients should be advised to report any postoperative fever or increasing abdominal pain.

Thermal injury to the bowel, bladder, or ureter that is recognized at the time of laparoscopy should be managed immediately, taking into consideration the potential extent of the zone of coagulative necrosis (186,187). Incisions made with the focused energy from a pointed electrode are associated with a minimal amount of surrounding thermal injury. Prolonged or even transient contact with a relatively large-caliber electrode may produce a zone of thermal necrosis that may be much larger than visually apparent. In such cases, wide excision or, for example, resection of up to several centimeters of bowel may be necessary. The choice of route of access for any required surgical repairs depends in part on the nature of the injury and on the skills and training of the surgeon.

[12] The incidence of unintended activation injuries can be reduced if the surgeon is always in direct control of electrode activation and if all electrosurgical hand

instruments are removed from the peritoneal cavity when not in use. When removed from the peritoneal cavity, the instruments should be detached from the electrosurgical generator, or they should be stored in an insulated pouch near the operative field. These measures prevent damage to the patient's skin if the electrode is accidentally activated.

Current Diversion

Current diversion occurs during the use of monopolar instrumentation when the RF circuit follows an unintended path between the active electrode and the electrosurgical generator. This may occur with insulation defects, direct coupling, or capacitative coupling. In older, grounded systems, unlikely to be in use in operating rooms today, current can be diverted if any part of the patient's body touches a conductive and grounded object. In any of these situations, if the power density becomes high enough, unintended and severe thermal injury can result.

Insulation Defects

If the insulation coating the shaft of a monopolar electrosurgical instrument becomes defective, it can allow current diversion to adjacent tissue, that is most often bowel, potentially resulting in significant injury, in part because such defects create a zone of high-current density **(Fig. 26-28)**. Therefore, the instruments should be examined before each procedure to detect worn or obviously defective insulation. When using monopolar laparoscopic instruments, the shaft of the device should be kept away from vital structures and, if possible, totally visible in the operative field.

Direct Coupling

Direct coupling occurs when the activated electrode of a monopolar instrument touches and energizes another uninsulated metal conductor such as a laparoscope, cannula, or other instrument. Direct coupling has value for creating hemostasis by using a grasping instrument to occlude a blood vessel while a separate activated electrode is placed in contact with the grasping instrument to provide the energy for desiccation and coagulation. However, unintentional direct coupling can be disastrous, if an activated electrode touches another noninsulated device that rests against structures such as bowel or the urinary tract **(Fig. 26-29)**. The risk of direct coupling can be reduced by eliminating the simultaneous use of noninsulated instruments and monopolar instruments. Furthermore, the surgeon should visually confirm that there is no contact with other conductive instruments before activating a monopolar instrument.

Capacitive Coupling

Capacitance is the ability of a conductor to establish an electrical current in an unconnected but nearby circuit. An electrical field is established around the shaft of any activated unipolar instrument (including the cord), a circumstance that makes the electrode, and the cord, a potential capacitor. This field is harmless if the circuit is

completed through a dispersive, low-power density pathway, however, if the nearby circuit focuses the energy on tissue, thermal injury can occur **(Fig. 26-30)**. The figure demonstrates two mechanisms for capacitative coupling, the cord wrapped around the towel clip results in coupling that can focus the energy on the skin, and the activated needle electrode by being in close proximity to the laparoscope can induce current that is focused on the nearby bowel. This latter mechanism occurs with operative laparoscopes, where the electrode capacitively couples with the metal casing (188), and with the somewhat similar "single port" systems where the laparoscope and hand instruments, including monopolar instruments are passed through the same concentrated array of ports (189).

The risk of capacitive coupling-related complications can be reduced in a number of ways. First, it is important to avoid the use of hybrid laparoscope–cannula systems that contain a mixture of conductive and nonconductive elements. Instead, the use of all-plastic or all-metal cannula systems is preferred. It may be best to avoid the use of monopolar instruments using operating laparoscopes or multiport, single site access systems. If a multiport access cannula or an operating laparoscope is to be used, only bipolar RF instruments should be used in the operating channel. The surgical team should ensure that towel clips, potentially in contact with the patient's skin, are not used to secure monopolar cables. Surgeons should be careful to avoid juxtaposing instruments between an activated electrode and tissue. Finally, minimizing the use of high-voltage, modulated current ("coagulation" current) will reduce the risk of capacitative coupling.

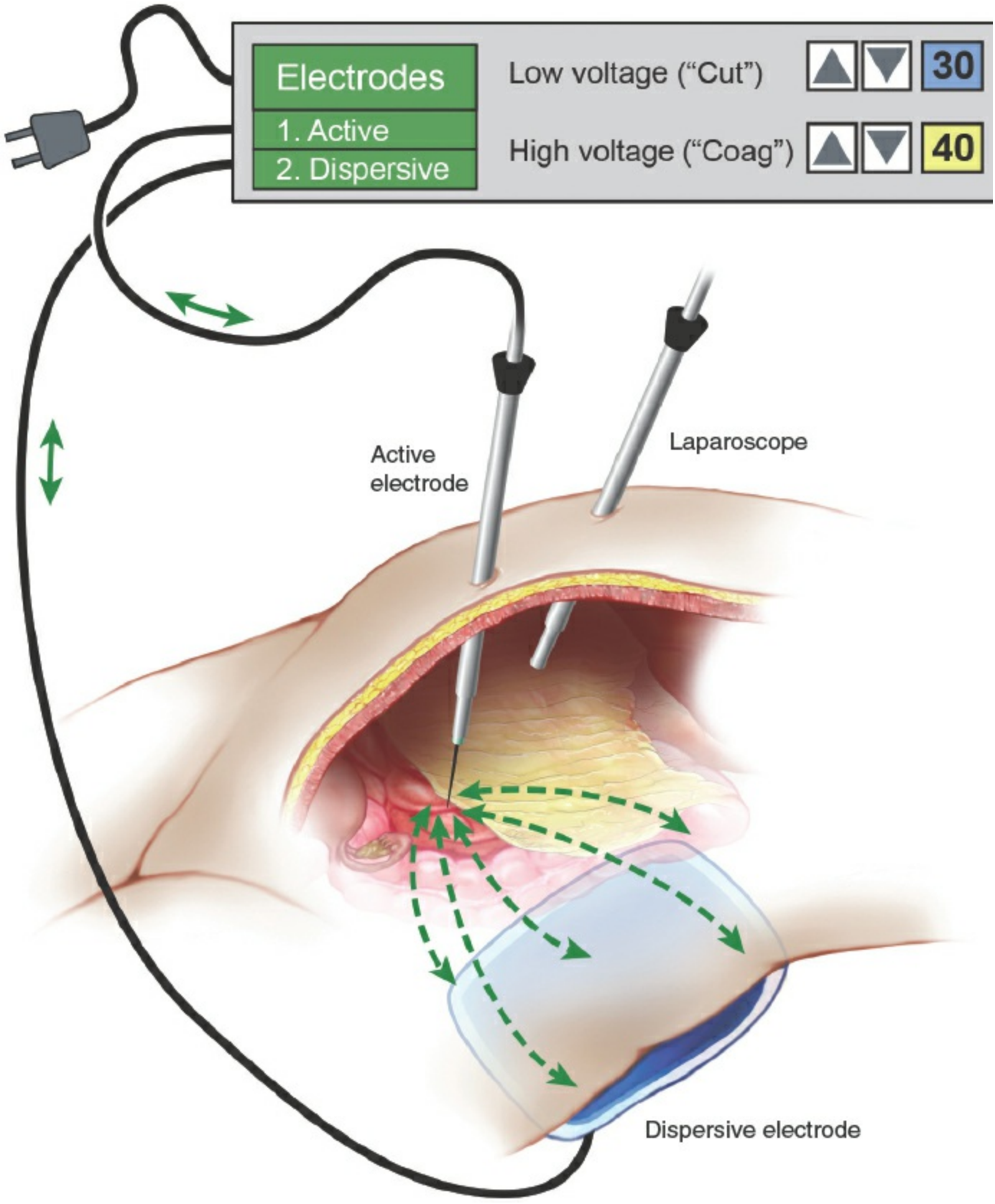


FIGURE 26-28 RF monopolar instrumentation. The electrosurgical generator converts wall output at about 60 Hz, to radiofrequency waveforms—typically between 300 and 500 KHz. The dispersive electrode defocuses the current, while the "active electrode", actually a current focusing electrode, is used to create a tissue effect. The current oscillates between the two electrodes through the patient.

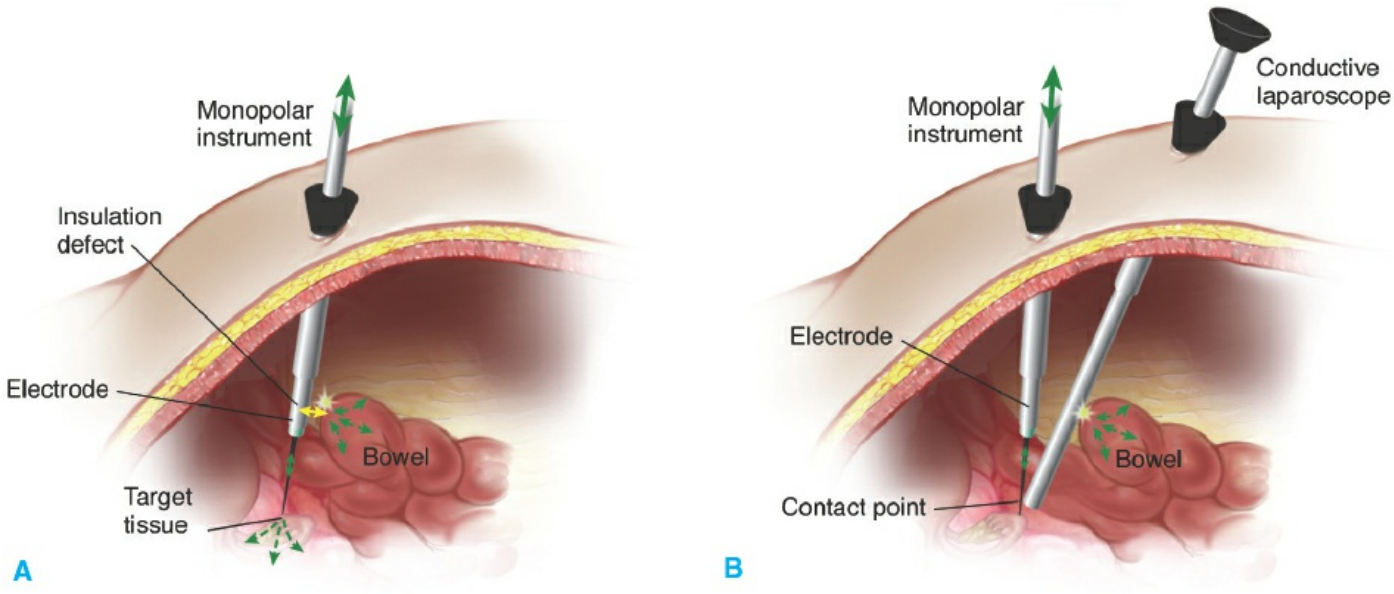


FIGURE 26-29 Current diversion secondary to insulation defects and direct coupling. These events may occur with the use of monopolar instrumentation when there is a defect in the insulation (**A**) or, classically, to contact a conductive instrument that, in turn, touches other intraperitoneal structures (**B**). In the example depicted (**B**), the activated electrode is touching the laparoscope, and current is transferred to bowel through a small enough contact point that thermal injury results. Another common target of such coupling is to noninsulated hand instruments.

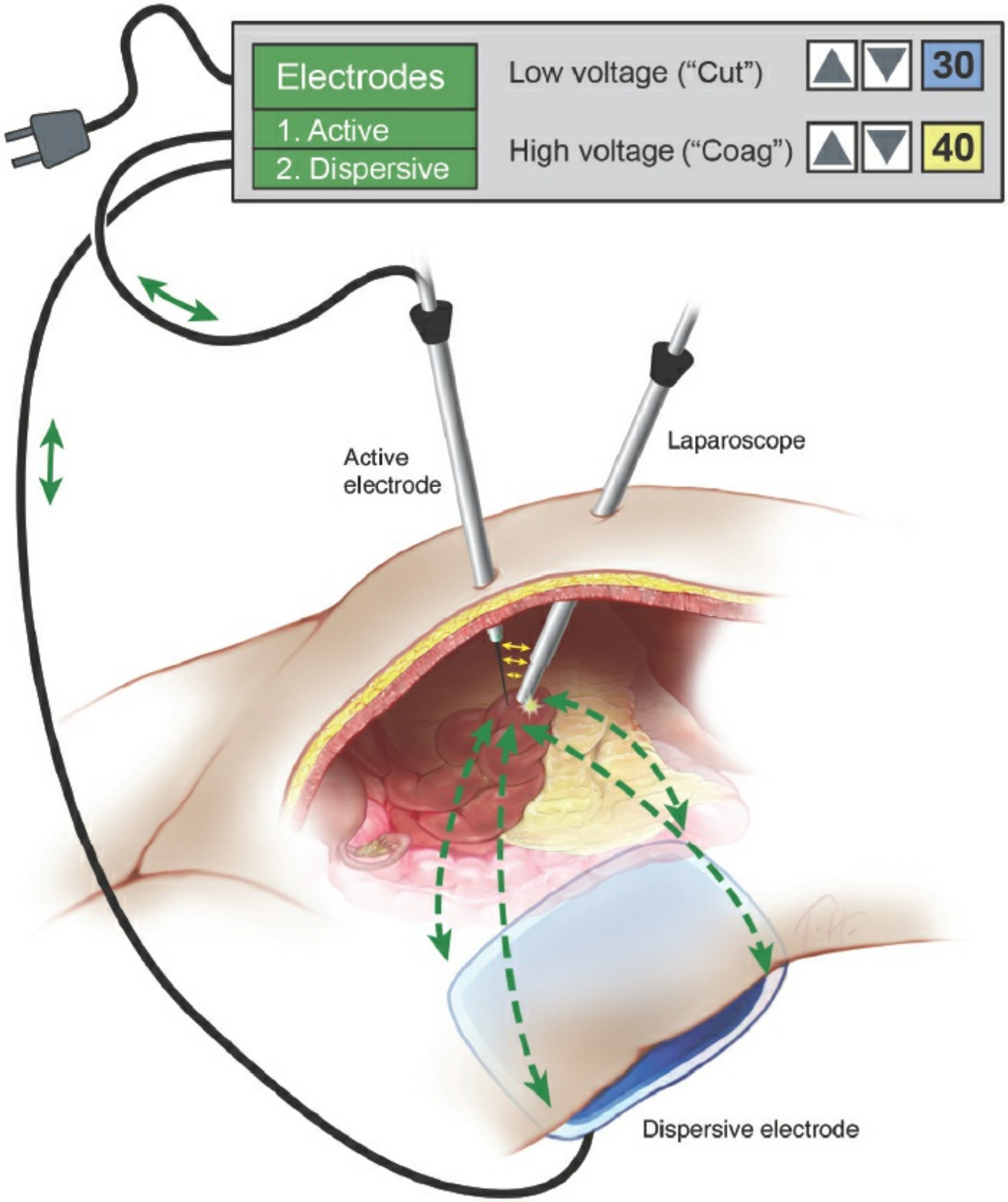


FIGURE 26-30 Capacitative coupling. All activated RF electrodes emit a surrounding charge, proportional to the voltage of the current. This makes the electrode as well as the connecting cables potential capacitors. In general, as long as the charge is allowed to disperse through the abdominal wall, no sequelae will result. However, if the path between the active and dispersive electrodes is interrupted, for example by

non-contact or “open” activation, and especially with high voltage current (shown), the current can couple to nearby structures such as a laparoscope conductive cannula or directly to which could be in contact with bowel.

Dispersive Electrode Burns

Modern electrosurgical units are designed with isolated circuits and impedance monitoring systems that shut down the machine if dispersive electrode (“patient pad”) detachment occurs. The use of isolated circuit electrosurgical generators with dispersive electrode monitors has virtually eliminated dispersive electrode–related thermal injury. Dispersive electrode monitoring is actually accomplished by measuring the impedance in the dispersive electrode, which should always be low because of the large surface area. Without such devices, partial detachment of the dispersive electrode could result in a thermal injury because reducing the surface area of the electrode in contact with the skin raises the current density **(Fig. 26-31)**.

Because a few ground-referenced machines without such safeguards may still be in use, it is important to know the type of electrosurgical unit used in the operating room. If the electrosurgical generator is ground referenced and if the dispersive electrode becomes detached, unplugged, or otherwise ineffective, the current seeks any grounded conductor, such as electrocardiograph patch electrodes or the conductive metal components of the operating table. If the conductor has a small surface area, the current or power density may become high enough to cause thermal injury.

Hemorrhagic Complications

Great Vessel Injury

The most dangerous hemorrhagic complications are injuries to the great vessels, including the aorta and the vena cava, the common iliac vessels and their branches, and the internal and external iliac arteries and veins. The most catastrophic injuries occur secondary to insertion of an insufflation needle or the tip of the obturator (trocar) used to position the primary or ancillary cannulas. The vessels most frequently damaged are the aorta and the right common iliac artery as it branches from the aorta in the midline. The anatomically more posterior location of the vena cava and the iliac veins provides relative protection, but not immunity, from injury (190). **After vascular injury, patients usually develop profound hypotension with or without hemoperitoneum. In some cases, blood is aspirated through the insufflation needle before the introduction of the distending gas. In such instances, the needle should be left in place while immediate preparations are made to obtain blood products and perform laparotomy. The bleeding frequently will be contained in the retroperitoneal space, which usually delays the diagnosis; consequently, hypovolemic shock may develop.** To avoid late recognition, the course of each great vessel must be identified before completing the procedure. Because it is difficult to

assess the volume of blood filling the retroperitoneal space, **immediate laparotomy is indicated if retroperitoneal bleeding is suspected**. A midline incision should be made to allow access to the great vessels. Upon entry into the peritoneal cavity, the aorta and vena cava should immediately be compressed just below the level of the renal vessels to gain at least temporary control of blood loss. The most appropriate course of action depends on the site and extent of injury. Vascular or general surgery consultation may be necessary to evaluate and repair significant vascular injuries. Although most of these injuries are small and amenable to repair with suture, some are larger and require the insertion of a vascular graft. Deaths have occurred as a result of these injuries.

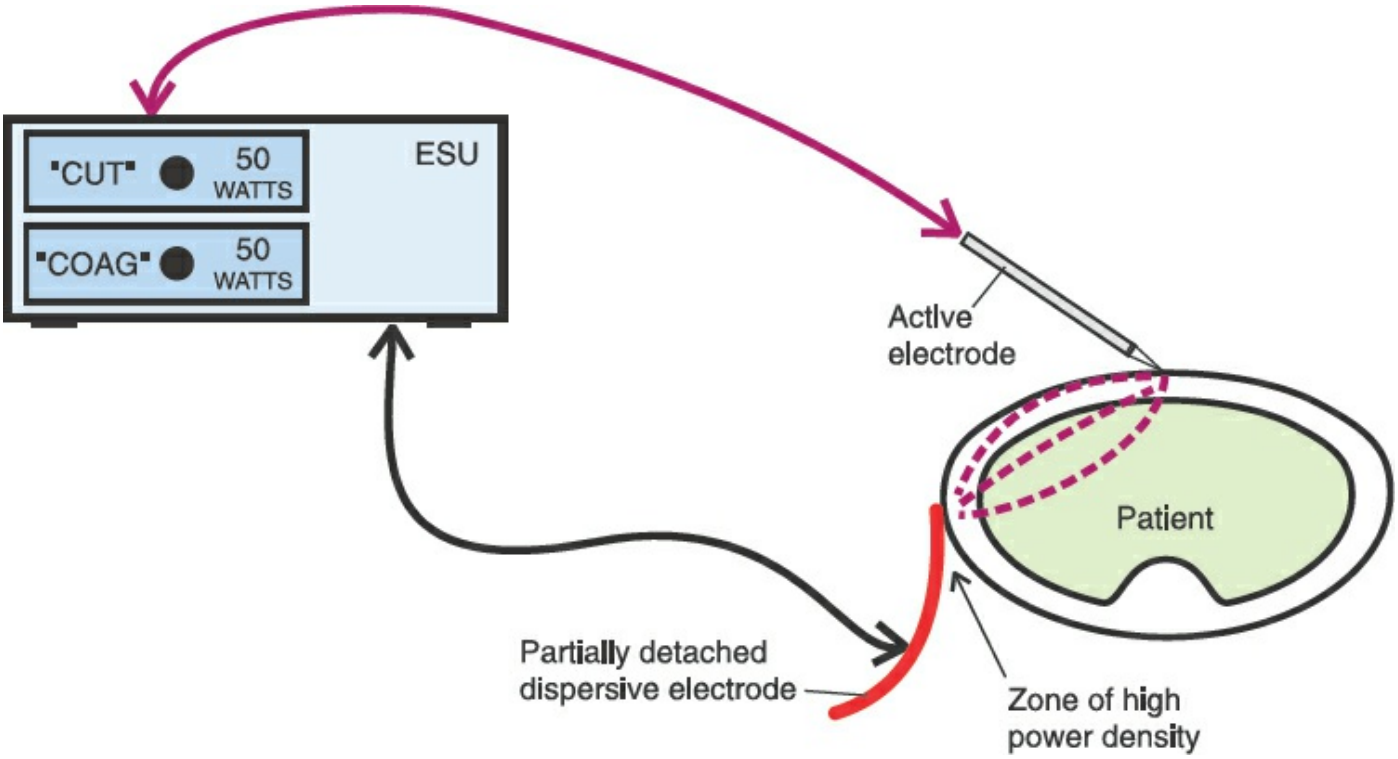


FIGURE 26-31 Dispersive electrode burns. If the dispersive electrode becomes partially detached, the current density may increase to the point that a skin burn results.

Abdominal Wall Vessel Injury

The abdominal wall vessels most commonly injured during laparoscopy are the superficial inferior epigastric vessels as they branch from the femoral artery and vein and course cephalad in each lower quadrant. They are invariably damaged by the initial passage of an ancillary trocar–cannula system or by the introduction of a wider device later in the procedure. The problem may be recognized immediately by the observation of blood dripping along the cannula or out through the incision. However, the bleeding may be obstructed by the cannula until it is withdrawn at the end of the operation.

The more serious injuries are those to the deep inferior epigastric vessels, which

are branches of the external iliac artery and vein that course cephalad but are deep to the rectus fascia and often deep to the muscles. More laterally located are the deep circumflex iliac vessels, which are not often encountered in laparoscopic surgery. Laceration of these vessels may cause profound blood loss, particularly when the trauma is unrecognized and causes extraperitoneal bleeding.

Signs of injury, in addition to blood dripping down the cannula, include the postoperative appearance of shock and abdominal wall discolorization or hematoma located near the incision. In some instances, the blood may track to a more distant site, presenting as a pararectal or vulvar mass. Delayed diagnosis may be prevented by laparoscopic evaluation of each peritoneal incision after removal of the cannula.

Superficial inferior epigastric vessel trauma usually stops bleeding spontaneously; therefore, expectant management is appropriate. A straight ligature carrier can be used to repair lacerated deep inferior epigastric vessels. Alternatively, a Foley catheter may be inserted through the cannula, inflated, put on traction, and held in place with a clamp for 24 hours. If a postoperative hematoma develops, local compression should be used initially. Open removal or aspiration of the hematoma should not be undertaken because it may inhibit the tamponade effect and increase the risk of abscess. However, if the mass continues to enlarge or if signs of hypovolemia develop, the wound must be explored.

Intraperitoneal Vessel Injury

Hemorrhage may result from inadvertent entry into a vessel or failure of a specific occlusive technique. In addition to delayed hemorrhage, there may be a further delay in diagnosis at laparoscopy as a result of the restricted visual field and the temporary occlusive pressure exerted by CO_2 in the peritoneal cavity.

Inadvertent division of an artery or vein is usually evident immediately. Transected arteries may go into spasm and bleed minutes to hours later, going unnoticed temporarily because of the limited visual field of the laparoscope. Therefore, at the end of the procedure, all areas of dissection must be carefully examined. Carbon dioxide should be vented, which decreases the intraperitoneal pressure so that blood vessels temporarily occluded by higher pressure can be recognized.

Gastrointestinal Complications

The stomach, the small bowel, and the colon can be injured during laparoscopy. Mechanical entry into the large or small bowel can occur 10 times more often when laparoscopy is performed in patients who have had prior intraperitoneal inflammation or abdominal surgery. Loops of intestine can adhere to the abdominal wall under the insertion site and be injured (191,192).

Insufflation Needle Injuries

Needle entry into the gastrointestinal tract may be more common than reported because it may occur unnoticed and without further complication. Gastric entry may be identified by the increased filling pressure, asymmetric distention of the peritoneal cavity, or aspiration of gastric particulate matter through the lumen of the needle. Initially, the hollow, capacious stomach may allow the insufflation pressure to remain normal. Signs of bowel entry are the same as those for gastric injury, with the addition of feculent odor.

If particulate debris is identified, the needle should be left in place, and an alternate insertion site should be identified, such as the left upper quadrant. Immediately after successful entry into the peritoneal cavity, the site of injury can be identified. Defects must be repaired immediately by laparoscopy or laparotomy.

Trocar/Obturator Injuries

Damage caused by a sharp-tipped obturator or trocar is usually more serious than needle injury. Inadvertent gastric entry usually is associated with stomach distention because of aerophagia, difficult or improper intubation, or mask induction with inhalation anesthetic. Most often, the injury is created by the trocar–cannula system used for primary access. Ancillary cannulas may result in visceral injury, although placement of these cannulas under direct vision helps to reduce the risk of injury. **The risk of gastric perforation can be minimized with the selective use of preoperative nasogastric or oral gastric suction when left upper–quadrant entries are used or when the intubation was difficult.** Open laparoscopy likely has little impact on the risk for gastrointestinal complications, particularly those related to adhesions to the anterior abdominal wall from previous surgery. For high-risk patients, left upper–quadrant needle and trocar–cannula insertion with a properly decompressed stomach are preferable (193–196).

If the trocar of a primary cannula penetrates the bowel, the condition is usually diagnosed when the mucosal lining of the gastrointestinal tract is visualized. If the large bowel is entered, a feculent odor may be noted. However, the injury may not be immediately recognized because the cannula may not stay within the bowel or may pass through the lumen. Such injuries usually occur when a single loop of bowel is adherent to the anterior abdominal wall. The injury may not be recognized until peritonitis, abscess, enterocutaneous fistula, or death occurs (197,198). Therefore, **at the end of the procedure, the removal of the primary cannula must be viewed either through the cannula or an ancillary port, a process facilitated by routine direct visualization of closure of the incision of the primary port.**

Trocar-related injuries to the stomach and bowel require repair as soon as they are recognized. If the injury is small, a trained operator can repair the defect under laparoscopic direction using a double layer of running 2-0 or 3-0 absorbable sutures. Extensive lesions may require resection and reanastomosis, which in most instances

requires at least a small laparotomy. The preoperative use of mechanical bowel preparation in selected high-risk cases minimizes the need for laparotomy or colostomy, but evidence suggests that bowel surgery, if necessary, may be safely performed in unprepared bowel (199).

Dissection and Thermal Injury

When mechanical bowel trauma is recognized during the dissection, treatment is the same as that described for trocar injury. Should the injury involve RF electrical energy, it is important to recognize that the zone of desiccation and coagulation may exceed the visual area of damage. This is especially true if the exact mechanism of the thermal injury is unknown or if injury results from contact with a relatively large surface area electrode that would be more likely to create a large coagulation injury. Conversely, bowel injury created under direct vision with a RF needle or blade electrode is associated with little collateral coagulation effect and, therefore, can be managed similar to a mechanically induced lesion. Consequently, surgical repair should be implemented considering these factors, and should include, if necessary, resection of ample margins around the injury. Thermal injury may be handled expectantly if the lesion seems superficial and confined, such as is the case when fulguration (noncontact arcing of high-voltage current) involves bowel. In such instances, the depth of injury is generally less than half a millimeter. In a study of 33 women with such injuries who were managed expectantly in the hospital, only 2 required laparotomy for repair of perforation (200).

Urologic Injury

Damage to the bladder or ureter may occur secondary to mechanical or thermal trauma incurred during laparoscopic procedures. Ideally, such injury should be prevented; otherwise, as is the case for most complications, it is preferable to identify the trauma intraoperatively.

Bladder Injury

Bladder injury can result from the perforation of the undrained bladder by an insufflation needle or trocar, or it may occur while the bladder is being dissected from adherent structures or from the anterior uterus (201,202). The frequency of injury is difficult to estimate and varies with procedure. Estimates of the frequency of unintentional cystotomy associated with LH ranges from 0.4% to 3.2% and appears to be more frequent in the context of a previous cesarean section (203,204). The injury may be readily apparent by direct visualization. If an indwelling catheter is in place, hematuria or pneumaturia (CO_2 in the catheter drainage system) may be noticed. A bladder laceration can be confirmed by injecting sterile milk or a diluted methylene blue solution through a transurethral catheter. Thermal injury to the bladder, however, may not be apparent initially and, if missed, can present as peritonitis or a fistula.

Routine preoperative bladder drainage usually prevents trocar-related cystotomies. Separation of the bladder from the uterus or other adherent structures requires good visualization, appropriate retraction, and excellent surgical technique. Sharp mechanical dissection is preferred, particularly when relatively dense adhesions are present.

Very small-caliber injuries to the bladder (1 to 2 mm) may be treated with bladder catheterization for 3 to 7 days. If repair is undertaken immediately, catheterization is unnecessary. When a larger injury is identified, it can be repaired laparoscopically (201,202,205). If the laceration is near the trigone or involves the trigone, however, an open procedure should be used. The mechanism of injury should be taken into consideration in making this evaluation because electrical injuries often extend beyond the visible limits of the apparent defect. If a coagulation-induced thermal injury occurred, the coagulated portion should be excised.

For small lesions, closure may be performed with layers of absorbable 2-0 to 3-0 sutures. Postoperative catheterization with either a transurethral or suprapubic catheter should be maintained for 2 to 5 days for small fundal lacerations and for 10 to 14 days for injuries to the trigone. Cystography should be considered before the urinary catheter is removed.

Ureteral Injury

One of the most common causes of ureteral injury during laparoscopy is electrosurgical trauma (184,206,207) although ureteral injury can occur after mechanical dissection, including linear cutting and stapling devices infrequently used in contemporary gynecologic laparoscopic surgery (207–209). Although intraoperative recognition of ureteral injury is possible, the diagnosis is frequently delayed (207,210). Intraoperative diagnosis of ureteral injury may be confirmed intraoperatively by visual inspection or demonstration of leakage following the intravenous injection of indigo carmine. Alternatively, cystoscopy following the intravenous injection of indigo carmine, or a similar dye, will generally show bilateral patency if there is no ureteric injury. Because there is adequate evidence that this approach may identify the majority of ureteral injuries, contemporary guidelines recommend routine performance of cystoscopy following LH (211).

Unrecognized ureteral obstruction may present a few days to 2 weeks after surgery with flank pain and fever with or without signs of peritonitis and leukocytosis (212). Abdominal ultrasound may be helpful, but a CT urogram can more precisely identify the site and degree of the obstruction.

Discharge or continuous incontinence is a delayed sign of ureterovaginal or vesicovaginal fistula. A vesicovaginal fistula can be confirmed by filling the bladder with methylene blue and detecting dye on a tampon previously placed in the vagina. With a ureterovaginal fistula, the methylene blue will not pass into the vagina, but it can be detected with the intravenous injection of indigo carmine.

Knowledge of the course of the ureter through the pelvis is a prerequisite to reducing the risk of injury. The ureter can usually be seen through the peritoneum of the pelvic sidewall between the pelvic brim and the attachment of the broad ligament. Because of variation from one patient to another or the presence of disease, the location of the

ureter can become obscured, making it necessary to enter the retroperitoneal space. The techniques used for retroperitoneal dissection are important factors in reducing the risk of ureteric injury. Blunt and sharp dissection with scissors is preferred, although hydrodissection can be used (213). The selective placement of ureteral stents may be helpful in reducing the risk of injury.

Ureteral injury can be treated immediately if it is diagnosed intraoperatively. Although limited damage may heal over a ureteral stent left in place for 10 to 21 days, repair is indicated in most patients. Laparoscopic repair of ureteric lacerations and transections has been performed, but most injuries require laparotomy (206,214).

Incomplete or small obstructions or lacerations may be treated successfully with a stent placed either using a retrograde or anterograde technique. Urinomas may be drained percutaneously. If a stent cannot be placed successfully, a percutaneous nephrostomy should be performed before operative repair is undertaken. Repair may be accomplished by excision and reanastamosis, or, more commonly, ureteric reimplantation with or without facilitating procedures such as a psoas hitch or a Boari flap.

Neurologic Injury

Peripheral nerve injury is usually related to poor positioning of the patient, excessive pressure exerted by the surgeons, or to port placement (215,216). Positioning the patient in lithotomy while she is awake may decrease this risk because the woman can determine if any undue pressure or discomfort is experienced (217). Nerve injury may occur as a result of the surgical dissection.

In the extremities, the trauma may be direct, such as when the common peroneal nerve is compressed against a stirrup. The femoral nerve or the sciatic nerve or its branches may be overstretched and damaged by excessive flexion or external rotation of the hips. The peroneal nerve may be injured by compression if the lateral head of the fibula rests against the stirrup (217–219). Brachial plexus injuries may occur secondary to the surgeon or assistants leaning against an abducted arm during the procedure. If the patient is placed in a steep Trendelenburg position, the brachial plexus may be damaged because of the pressure exerted on the shoulder joint. In most cases, sensory or motor deficits are found as the patient emerges from anesthesia. The likelihood of brachial plexus injury can be reduced with adequate padding and support of the arms and shoulders or by placing the patient's arms in an adducted position (220).

Most injuries to peripheral nerves resolve spontaneously. The time to recovery depends on the site and severity of the lesion. For most peripheral injuries, full sensory nerve recovery occurs in 3 to 6 months. Recovery may be hastened by the use of physical therapy, appropriate braces, and electrical stimulation of the affected muscles. Open microsurgery should be performed for transection of major intrapelvic nerves.

Incisional Hernia and Wound Dehiscence

Incisional hernia after laparoscopy has been reported in more than 900 cases (167,168). The most common defect is dehiscence that develops in the immediate postoperative period. Hernias may be asymptomatic or may cause pain, fever, periumbilical mass, obvious evisceration, and the symptoms and signs of mechanical bowel obstruction. Although no incision is immune to the risk, defects that are larger than 10 mm in diameter are particularly vulnerable (168,221,222).

Richter hernias contain only a portion of the diameter of intestine in the defect, and the diagnosis is often delayed because the typical symptoms and findings of mechanical bowel obstruction may be absent (223). The initial symptom is usually pain. These hernias most often occur in incisions that are lateral to the midline where there is a greater amount of preperitoneal fat creating a potential space for incarceration. Fever can be present if incarceration occurs, and peritonitis may result from subsequent perforation. The condition is difficult to diagnose, requires a high index of suspicion, and may be confirmed with ultrasonography or CT (224).

In most cases, these occurrences can be prevented by using small-caliber cannulas, where possible, and with routine fascial and peritoneal closure of defects made by peritoneal access. The risk of inadvertent incorporation of the intestine into the wound can be reduced by viewing the closure with a smaller-caliber laparoscope passed through a narrow-caliber ancillary port. All ancillary cannulas should be removed under direct vision to ensure that bowel is not drawn into the incision and that there is an absence of active incisional bleeding.

The management of laparoscopic incisional defects depends on the time of presentation and the presence and condition of entrapped bowel. Evisceration always requires surgical intervention. If the condition is diagnosed immediately, the intestine is replaced into the peritoneal cavity (if there is no evidence of necrosis or intestinal defect), and the incision is repaired, usually with laparoscopic guidance. If the diagnosis is delayed or the bowel is incarcerated or at risk of perforation, laparotomy is necessary to repair or resect the intestine.

Infection

Wound infections after laparoscopic surgery are uncommon; most are minor skin infections that can be treated successfully with expectant management, drainage, or antibiotics (225). Severe necrotizing fasciitis can occur rarely. Bladder infection, pelvic cellulitis, and pelvic abscess have been reported (226).

Laparoscopy is associated with a much lower risk of infection than with laparotomy or vaginal surgery. Prophylactic antibiotics should be offered to selected patients (e.g., those with enhanced risk for bacterial endocarditis and those for whom total hysterectomy is planned). Patients should be instructed to monitor their body temperature after discharge and to report immediately a temperature higher than 38°C.

HYSTEROSCOPY

The hysteroscope is an endoluminal endoscope, adapted from the urologic cystoscope that can be used to directly evaluate the internal topography of the cervical canal and endometrial cavity **(Fig. 26-32)** to aid diagnosis or to direct the performance of a variety of intrauterine procedures. Although the first published description of a hysteroscopic procedure was in 1869, a polypectomy (227), the use of hysteroscopy didn't become common until the last half of the 20th century. Hysteroscopic lysis of intrauterine adhesions (IUAs) was first described in 1973 (228). The technique of endoscopically guided electrosurgical resection was adapted from urology to gynecology, initially for the removal of uterine leiomyomas (229). Hysteroscopic division of uterine septa was originally developed using a mechanical technique with specially designed scissors (230). Hysteroscopic destruction of the endometrium, generally termed endometrial ablation (EA), was originally reported using Nd:YAG laser vaporization, but subsequent innovators used the urologic resectoscope to ablate the endometrium using electrosurgical coagulation, resection, or vaporization (231–233). Hysteroscopically guided thermal ablation with heated fluid is a procedure that has been used since 2002, the only endoscopically guided technique for "nonresectoscopic" EA (NREA). Developments in the design of endoscopes have resulted in smaller-diameter instruments that retain the ability to provide a high-quality image. Such developments further facilitate the use of hysteroscopy in an office or procedure room setting using no or local anesthesia.

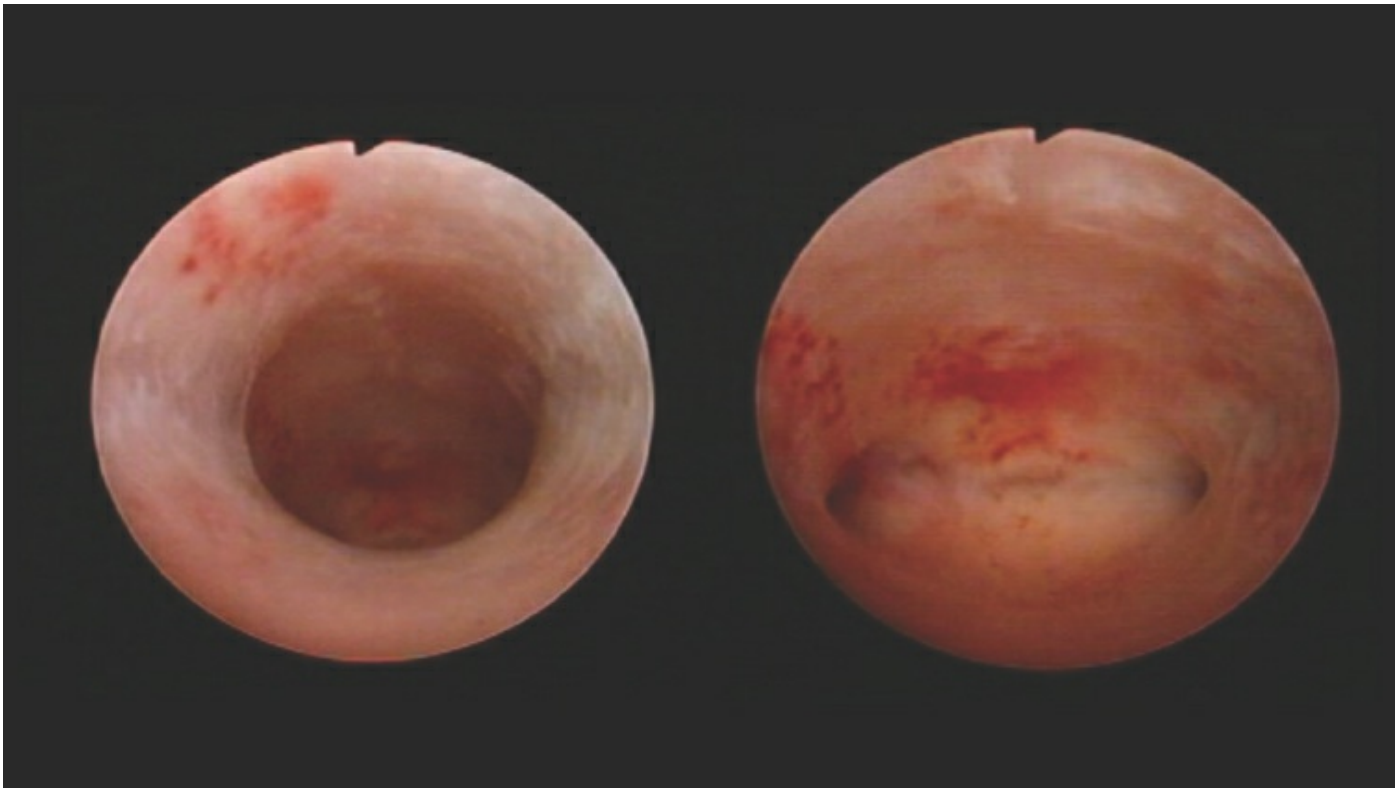


FIGURE 26-32 Hysteroscopic view of a normal cervical canal (**left**) and endometrial cavity (**right**). On the **right**, an image of a postmenopausal uterus, the right and left cornual areas are easily seen. The ecchymosis posteriorly may be due to trauma from positioning the hysteroscope.

Diagnostic Hysteroscopy

The goal of evaluation of the uterine cavity is either to obtain a sample of the endometrium, usually for the detection of hyperplasia or neoplasia, or to identify structural abnormalities; typically, a uterine septum or focal lesions such as adhesions, polyps, or submucous leiomyomas. Blind endometrial sampling has been the diagnostic mainstay for the detection of endometrial hyperplasia, whereas hysteroscopy, HSG, TVUS, contrast sonohysterography (gel or saline infusion sonography), and MRI are options in the detection and characterization of structural anomalies. **[14]** Hysteroscopic examination is superior to HSG in the evaluation of the endometrial cavity (234,235). The diagnostic accuracy of TVUS is similar, especially when sonographic contrast is injected into the endometrial cavity, usually intrauterine saline or gel, a procedure called sonohysterography that, when normal saline is used, is termed saline infusion sonography (SIS) (236–238). MRI and ultrasound-based techniques have the advantage of allowing evaluation of the myometrium, whereas office-based hysteroscopy allows simultaneous division of adhesions, or removal of small polyps and even some leiomyomas. Diagnostic hysteroscopy provides information not obtained by blind endometrial sampling (239–244), such as detection of endometrial polyps or submucous leiomyomas (239,241,244,245) and can allow for the performance of directed endometrial biopsy **(Fig. 26-33)**. Malignant or hyperplastic polyps or other localized lesions can be identified with hysteroscopy and removed via directed excision (242). However, blind curettage remains an effective approach for the identification of global endometrial histopathology (239,244,246).

The following are potential indications for diagnostic hysteroscopy:

1. **Unexplained abnormal uterine bleeding (AUB)**
   - **Premenopausal**
   - **Postmenopausal**
2. **Selected infertility cases**
   - **Abnormal hysterography or TVUS**
   - **Unexplained infertility**
   - **Routine assessment prior to ET**
   - **“Second look” evaluation following selected uterine surgery cases**
3. **Recurrent pregnancy loss (RPL)**



FIGURE 26-33 Hysteroscopically-guided endometrial biopsy. These 5-Fr biopsy forceps are opened wide just prior to capture of a focal endometrial lesion, likely a polyp. **[16] For many patients, diagnostic hysteroscopy can be performed in an office or procedure room setting with minimal discomfort and at a much lower cost than in a surgical center or a traditional operating room (Fig. 26-34).** For some, concerns about patient comfort or a pre-existing medical condition may preclude office hysteroscopy. Although hysteroscopy can, in many patients, provide more information than blind curettage, it should be used prudently. For most patients, other diagnostic or therapeutic measures can be undertaken before, or instead of, diagnostic hysteroscopy. For example, in women in the late reproductive years with AUB, or for those with postmenopausal bleeding, transvaginal sonography, and/or office endometrial biopsy or curettage typically are adequate to evaluate for neoplasia and to provide enough information to support an initial management strategy. If a satisfactory diagnosis cannot be established, or if bleeding continues without explanation or response to treatment, further investigation with one or a combination of ultrasound, endometrial sampling, contrast sonohysterography, or office hysteroscopy is appropriate. For women in their earlier reproductive years who have AUB, medical or expectant management may be used initially, depending on the severity and inconvenience of the bleeding. For those who do not respond to medical treatments such as oral contraceptives, the performance of TVUS, contrast sonohysterography, or hysteroscopy with biopsy **(Fig. 26-33)**, can be used for diagnosis (247).

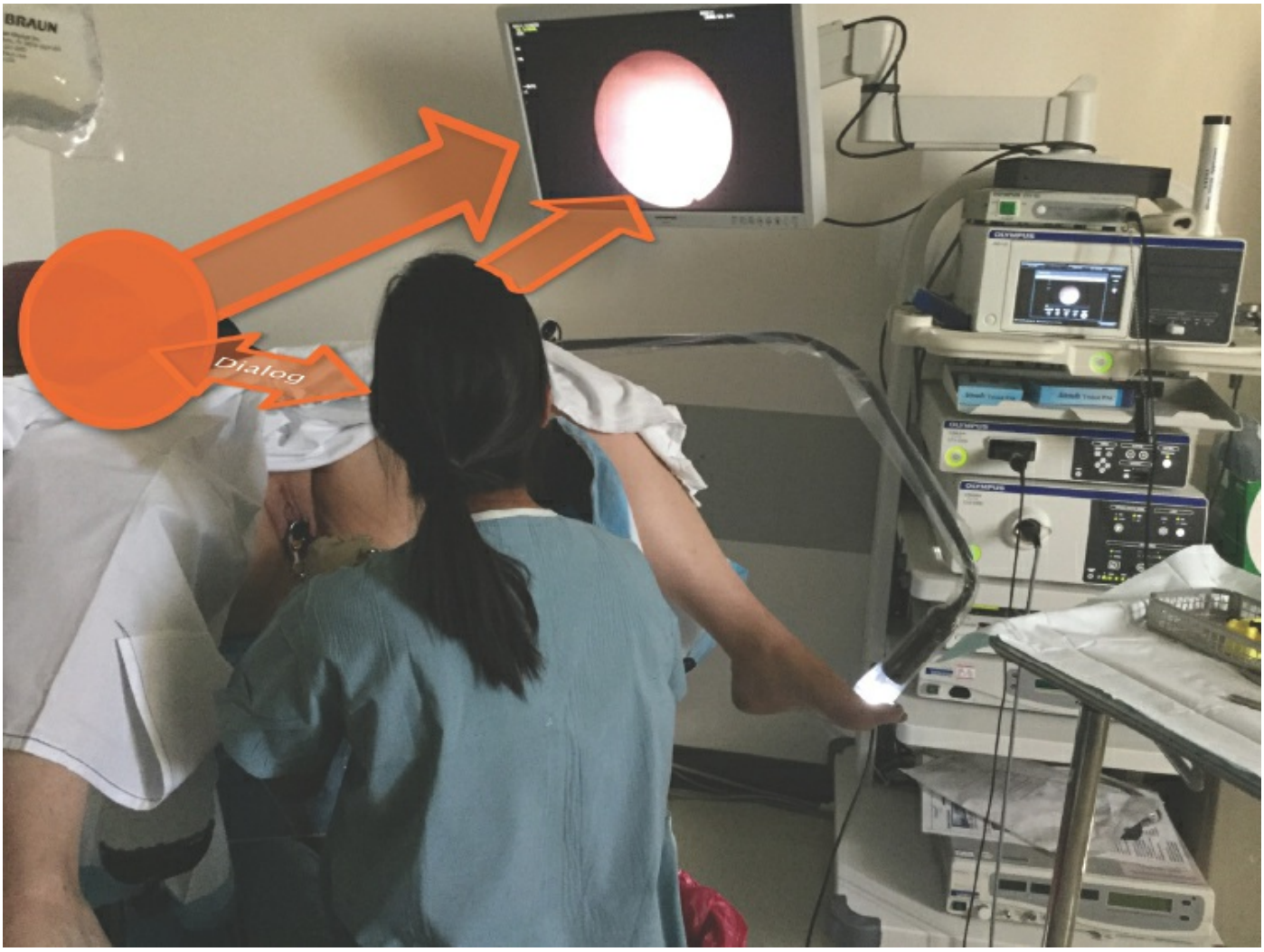


FIGURE 26-34 Office-based hysteroscopy under local anesthesia. Here both the surgeon and the patient can view the image of the endometrial cavity, and the patient can ask questions in real time. Patient's typically require no narcotic systemic analgesics, even if operative procedures are performed.

For women with infertility, HSG is generally the best initial imaging step because it provides information about the patency of the oviducts. In the presence of a suspicious or identified abnormality in the endometrial cavity, hysteroscopy or contrast sonohysterography can be performed to confirm the diagnosis, better define the abnormality, and perhaps direct the removal of a lesion—if hysteroscopy is performed. Some experts consider hysteroscopy or contrast sonohysterography mandatory for such patients because of the frequent occurrence of false-negative radiologic images in those with intrauterine anomalies (248). In women with previous IVF failure, there is evidence that hysteroscopic identification and treatment of these "missed" anomalies improves pregnancy rates (249). Confirmation of patency of the oviduct is unnecessary in women who have recurrent abortions; therefore, these patients can be evaluated primarily with hysteroscopy.

Operative Hysteroscopy

A number of intrauterine procedures can be performed under endoscopic direction, including adhesiolysis, sterilization, transection of a uterine septum, resection of leiomyomas and polyps, removal of retained products of conception, and endometrial destruction through Nd:YAG laser vaporization or RF resection, desiccation, or vaporization. Hysteroscopy may be used to direct the removal of foreign bodies including embedded intrauterine contraceptive devices (IUDs). **[16]** With proper use of local anesthesia, most of these procedures can be performed in an office setting (250).

Foreign Body

If the string of an IUD is absent, the device often can be removed with a specially designed hook or a toothed curette (e.g., Novak). When removal is difficult or impossible, after sonographic confirmation that the device is in the endometrial cavity, hysteroscopy can be performed using a sheath with an operating channel, thereby allowing removal with grasping forceps **(Fig. 26-35)**. If the device is not seen, or if only a portion is visible hysteroscopically, the remainder imbedded in the myometrium, individualized management is recommended, usually following additional imaging studies to more precisely identify the location of the device.

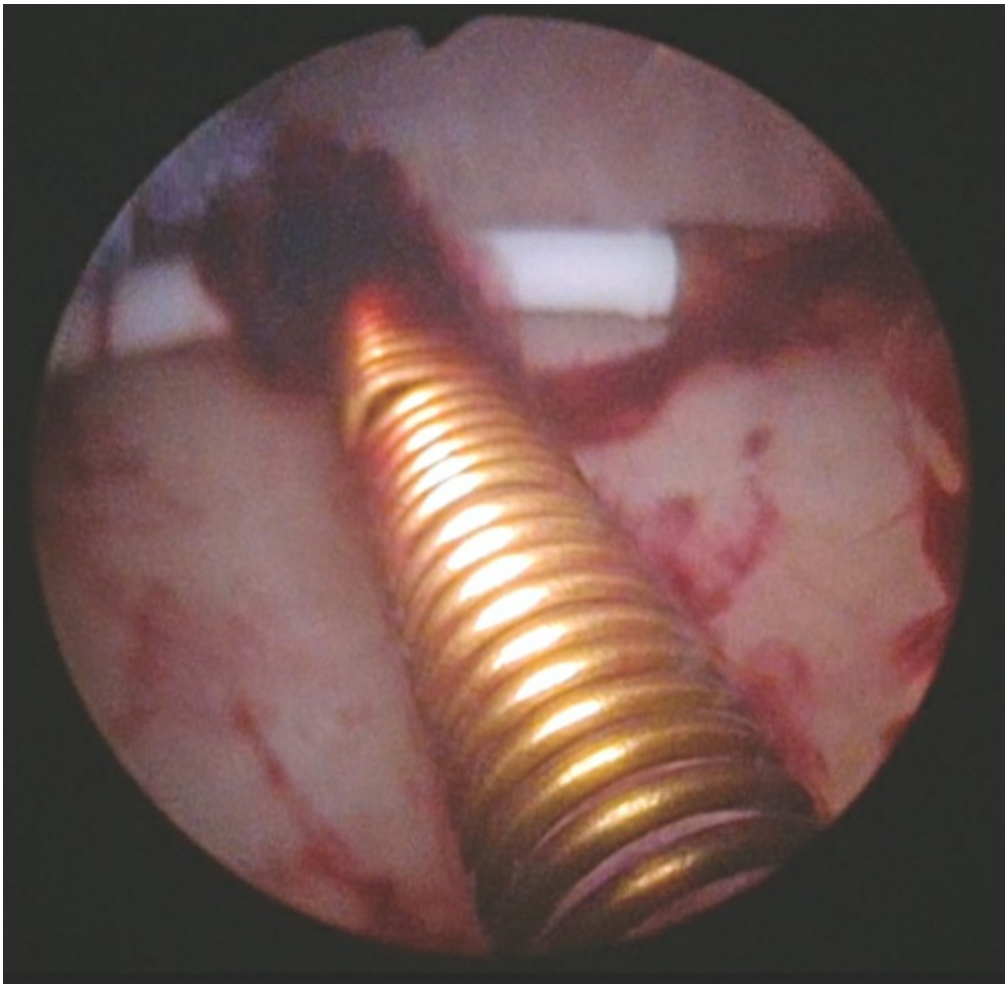


FIGURE 26-35 IUD in endometrial cavity. This Cu-T-380A copper-based intrauterine system is easily seen hysteroscopically; if strings are not seen emanating from the cervix, the hysteroscope can be used to remove the device with 5-Fr grasping forceps.

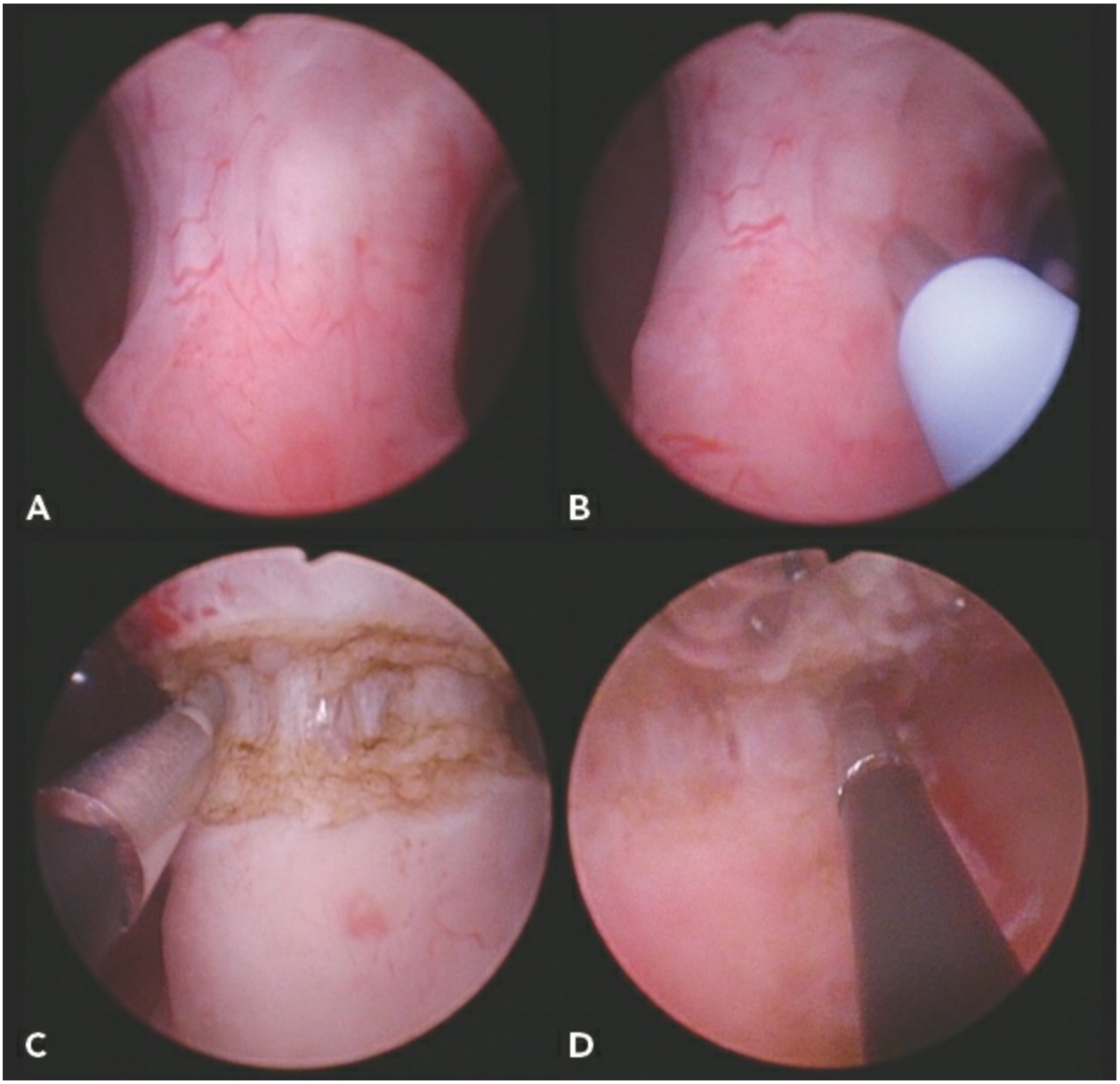


FIGURE 26-36 Transection of a uterine septum (rAFS Class 5A). The leading edge of the septum is seen close to the internal os (**A**). Additional anesthesia is injected via a 5-Fr needle passed through the 5-Fr channel in the operating sheath (**B**). A bipolar radiofrequency (RF) needle is used to start the transection (**C**) that is nearly complete in **D**. This procedure was done completely under local anesthesia in an office environment.

Septum

When RPL is associated with a single corpus containing a uterine septum (rAFS Class V or CONUTA U2), hysteroscopic division of the septum improves reproductive outcome at a rate comparable to abdominal metroplasty, with reduced morbidity and cost (see Chapter 33) (251–256). There are fewer data regarding infertility but there is some

evidence that metroplasty does improve fecundity (257). Confirmation of the external architecture of the corpus is important and can be achieved using either MRI or three-dimensional ultrasound. One group has described an office method of "see and treat" where dissection is continued until attainment of two of three criteria (pain, bleeding, the visualization of myometrial fibers) determine the end-point of septal transection (258). This procedure can be successfully performed in the office setting using local anesthesia protocols, with additional ½% lidocaine with 1/200,000 epinephrine directly injected into the septum or into each cornu to capture innervation from T10 coursing into the corpus alongside the utero-ovarian ligament. The procedure may be performed mechanically with scissors or with energy-based techniques such as an electrosurgical knife, needle, or loop **(Fig. 26-36)**. Because most septa have few vessels, scissors can be used easily, and the minimal risk for thermal damage is avoided. Properly applied, monopolar, and, especially bipolar instrumentation is associated with minimal thermal injury.

Endometrial Polyps

Endometrial polyps have been associated with AUB and infertility. Although such polyps can be removed with blind curettage, many are missed (239,241,244,245). Therefore, known or suspected endometrial polyps are more successfully treated with hysteroscopic guidance, which can usually be performed as an office procedure. For relatively small polyps, hysteroscopy should be used to direct the use of small-caliber scissors to transect the polyp at the base and grasping forceps to remove the lesions from the endometrial cavity **(Fig. 26-37)**. For larger polyps, special polyp snares, electrosurgical needles, a uterine resectoscope, or an electromechanical tissue removal system, may be used to sever the stalk and morcellate the lesion. For patients with infertility and endometrial polyps, it is not clear whether or not polyp number and size are related to outcome (259). Consequently, removal of all accessible polyps should be attempted if the process can be completed with minimal trauma.

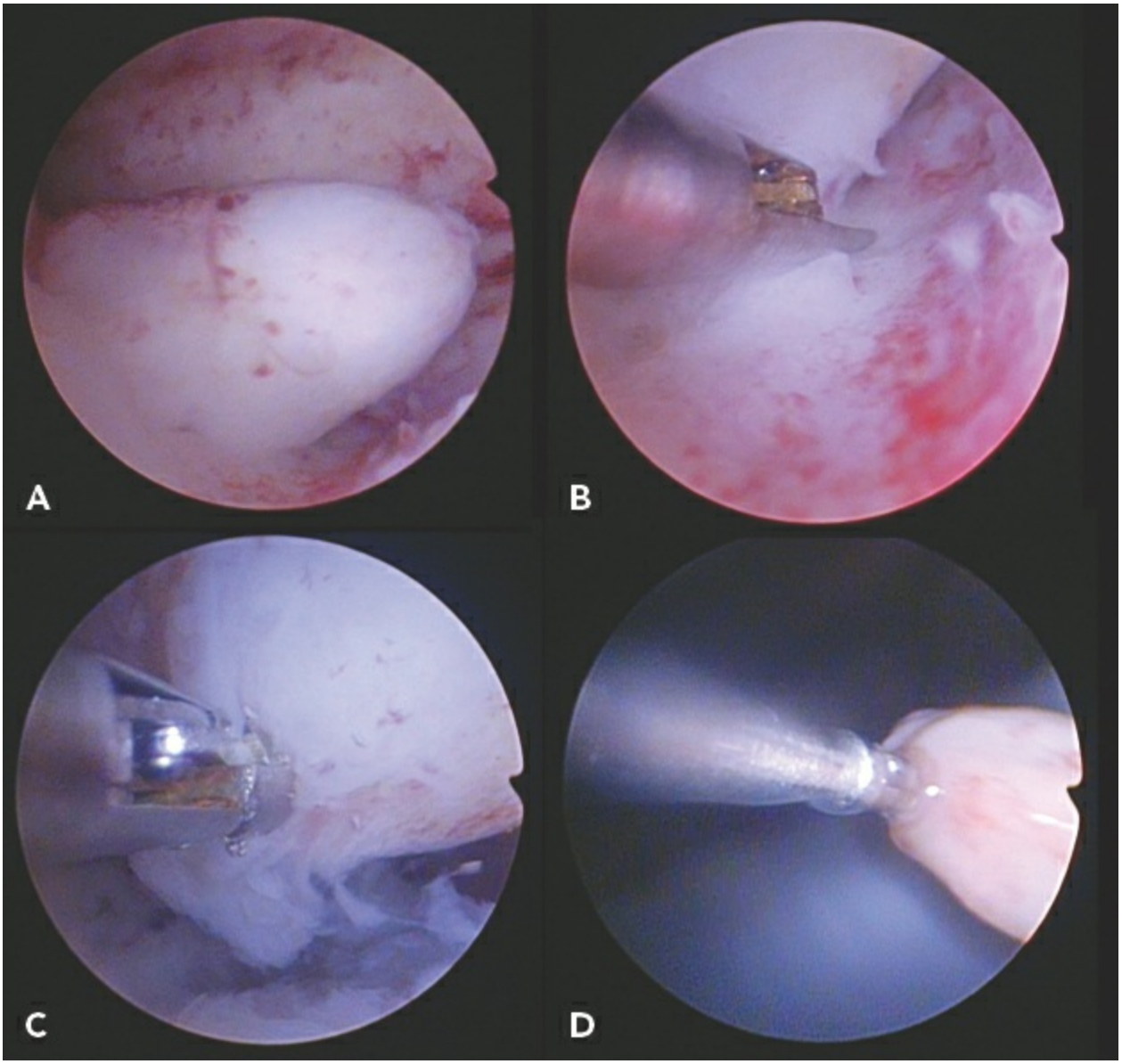


FIGURE 26-37 Endometrial polypectomy. A: The polyp is seen in mid cavity on the right posterior endometrium. The lesion is transected as close as possible to the endometrium to minimize the risk of recurrence, but leaving a tiny attachment (**B**). Forceps are used to grasp the polyp at the attachment, then twisting it until it detaches from the endometrium (**C**). The lesion is pulled through the cervical canal, removing the hysteroscopic system in the process (**D**).

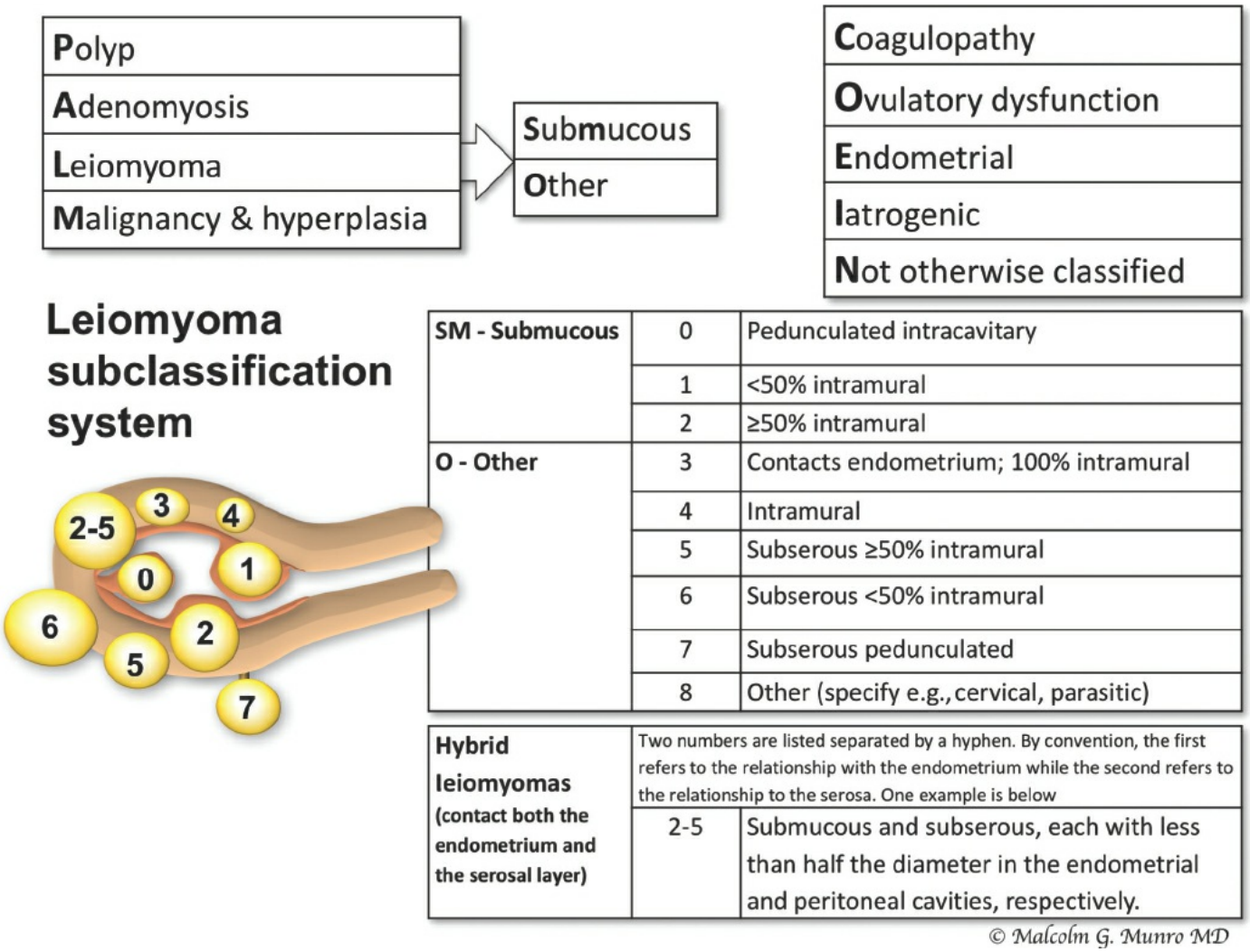


FIGURE 26-38 FIGO leiomyoma classification system. Seen here in the context of FIGO's System 2, the PALM-COEIN system, the leiomyoma system is a subclassification. For the hysteroscopic surgeon type 0 and 1 lesions are usually removable as long as the size is reasonable (generally not more than 5-cm diameter); many type 2 tumors can be removed, but there are limitations and risks. The surgeon must distinguish type 2 from type 2–5 tumors as the latter cannot be removed hysteroscopically.

Leiomyomas

Hysteroscopy may be used to direct the removal of selected submucous leiomyomas in women with HMB, infertility, or recurrent first trimester spontaneous pregnancy loss (236,260–266). This approach is limited based on the location, size, and number of lesions. Preoperative administration of gonadotropin-releasing hormone (GnRH) agonists may help shrink submucous myomas, facilitating their complete removal, and may reduce operating time and systemic absorption of distension media (267–269).

To facilitate evaluation and documentation of the investigation of women with fibroids, a classification system has been developed that categorizes the location of leiomyomas in the uterus, including submucous tumors, based on the proportion of the myoma that is in the uterine cavity (Fig. 26-38) (270). In patients with myomas that are 3 cm or less in diameter and entirely intracavitary (type 0), excision is

relatively easily accomplished, with minimal endometrial trauma. Type 2–5 lesions require an abdominal approach with laparoscopy or laparotomy, with suture-based repair of the defect. Small type 0 leiomyomas may be removed following transection of the stalk with scissors or an electrode attached to a uterine resectoscope. For larger type 0 lesions, or for type 1 leiomyomas, some combination of dissection of the tumor from the myometrium and either electrosurgical or mechanical morcellation **(Fig. 26-39)** will be necessary to effect removal. For selected type 2 myomas, careful dissection into the avascular plane interposed between the tumor and the myometrial pseudocapsule may be attempted, provided that satisfactory ultrasonography or MRI has demonstrated an adequate margin of myometrium between the deepest aspect of the lesion and the uterine serosa. In some instances, it may be preferable to undertake such procedures with laparoscopic monitoring to ensure that the bowel is not adjacent to the zone of dissection. Increasingly, this type of guidance can be provided using transabdominal ultrasonography. In some centers, the vast majority of type 2 tumors are removed under hysteroscopic direction, in an office setting, using local anesthesia, an incision into the pseudocapsule, careful dissection, and electromechanical morcellation **(Fig. 26-40)** (271). Patients should be counseled that for some type 1 and many type 2 myomas, it may take more than one procedure to complete excision (261,272). Hysteroscopic myomectomy of type 1 and 2 tumors should be performed using an accurate fluid management system, to minimize the risk of fluid overload. The use of intrauterine prostaglandin $F_{2\alpha}$ has been described to facilitate extrusion of type 2 myomas (273).

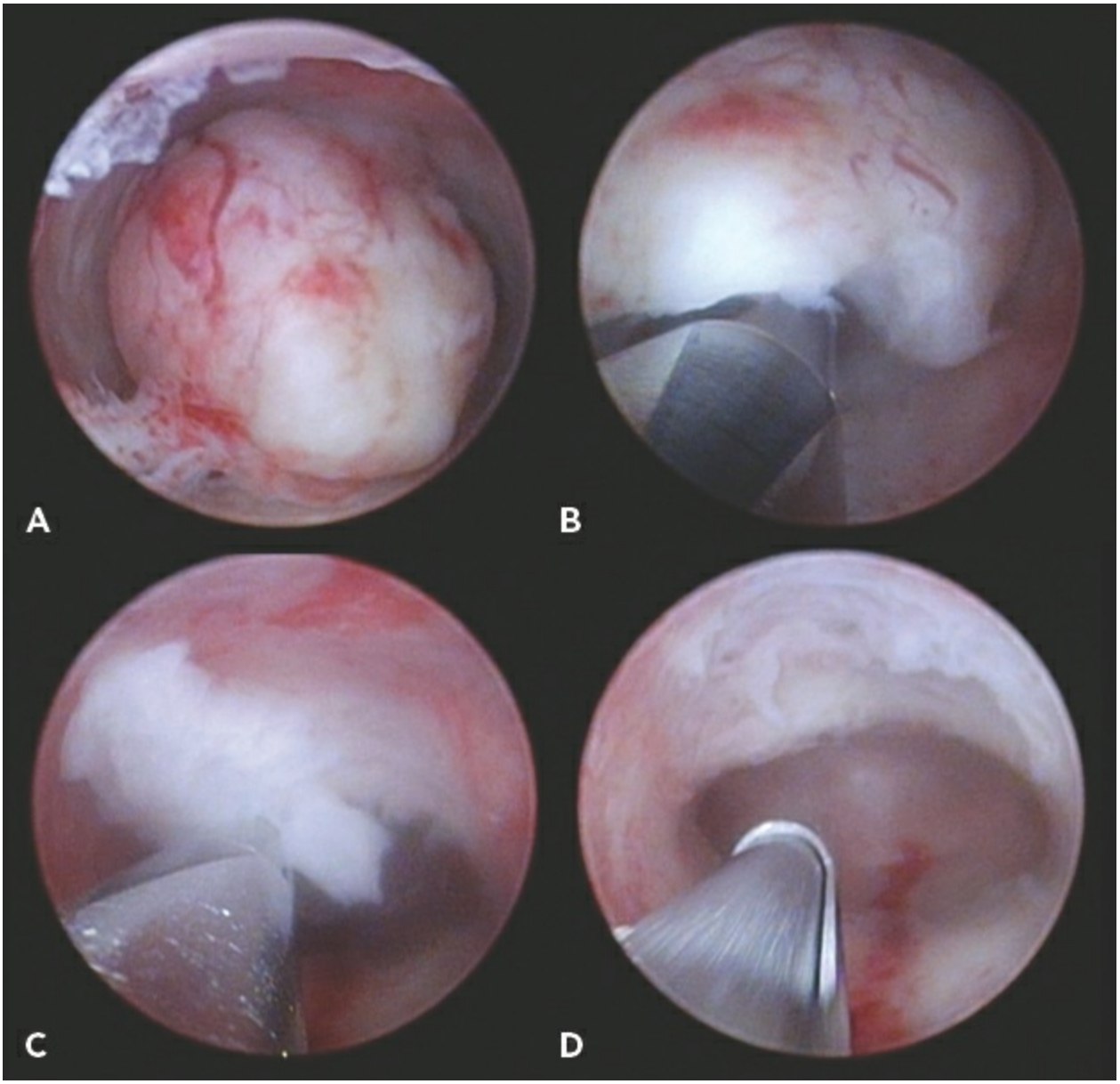


FIGURE 26-39 Myomectomy—FIGO type 0 leiomyoma. A: Note that the leiomyoma is entirely intracavitary and attached to the endometrium/myometrium by a narrow stalk. An electromechanical morcellator (Myosure®, Hologic Inc Marlborough, MA, USA) has been introduced and a portion of the tumor has been removed (**B**); it is almost totally gone in **C. D:** The tumor has been totally removed from the anterior wall.

Endometrial Ablation

The symptom of HMB caused by primary endometrial dysfunction (AUB-E) or ovulatory disorders (AUB-O) (270) that does not respond to oral medical therapy may be managed by EA using coagulation, resection, or vaporization, provided the patient is willing to forego future fertility (77). If future fertility is desired, a levonorgestrel-releasing IUD can provide virtually equal clinical outcomes (274–276). Ablation may be performed with a Nd:YAG laser (232), or RF electrosurgical desiccation, resection,

or vaporization using a uterine resectoscope **(Fig. 26-41)** (233,272) or by any of a number of nonresectoscopic techniques, including those employing thermal balloons, cryotherapy, heated free fluid or vapor, or RF electrical energy delivered by a bipolar probe (277–281). Many of these EA devices can be used in the office setting with local anesthetic protocols.

Endometrial resection is an EA technique performed with an electrosurgical loop electrode to shave the endometrium and superficial myometrium (231,282,283). Vaporization utilizes specially designed electrodes that are attached to standard resectoscopes that are capable of destroying large volumes of tissue without morcellation (272). Endometrial coagulation is achieved with ball- or barrel-shaped electrodes that are used to coagulate and desiccate the endometrial surface to an appropriate depth of about 4 mm (77,233). Complications of these procedures include fluid overload, electrolyte imbalances (if nonelectrolytic or even isosmotic media are used), uterine perforation, bleeding, and intestinal and urinary tract injury (284,285). The risk of uterine perforation may be reduced by using a combination of resection or vaporization and electrosurgical ablation; the latter is most suitable for the thinner areas of the myometrium in the cornu. The preoperative use of GnRH analogs or *danazol* may reduce operating time, and GnRH agonists may reduce bleeding and the amount of fluid absorbed into the systemic circulation (260,286).

For many women, these procedures are successful in reducing or eliminating menses without hysterectomy or long-term medical therapy (77,287). Success rates vary and depend on the duration of follow-up and the definition of success. For many patients, amenorrhea is the goal, whereas for others, it is normalization of menses. About 75% to 95% of patients are satisfied with the surgical procedure after 1 year. Reports of amenorrhea rates range from approximately 30% to 90%. Forty to 50% (depending in part upon the technique) is a useful number to quote to patients considering the likelihood of postprocedure amenorrhea. The nonresectoscopic techniques have similar clinical outcomes (288), thus reducing the need for resectoscopic ablation. The nonresectoscopic approaches all have limitations defined by the size or configuration of the endometrial cavity. For those women with HMB who are not suitable for nonresectoscopic techniques because of large uteri (>12 cm sounded length), resectoscopic EA remains a viable option (289).

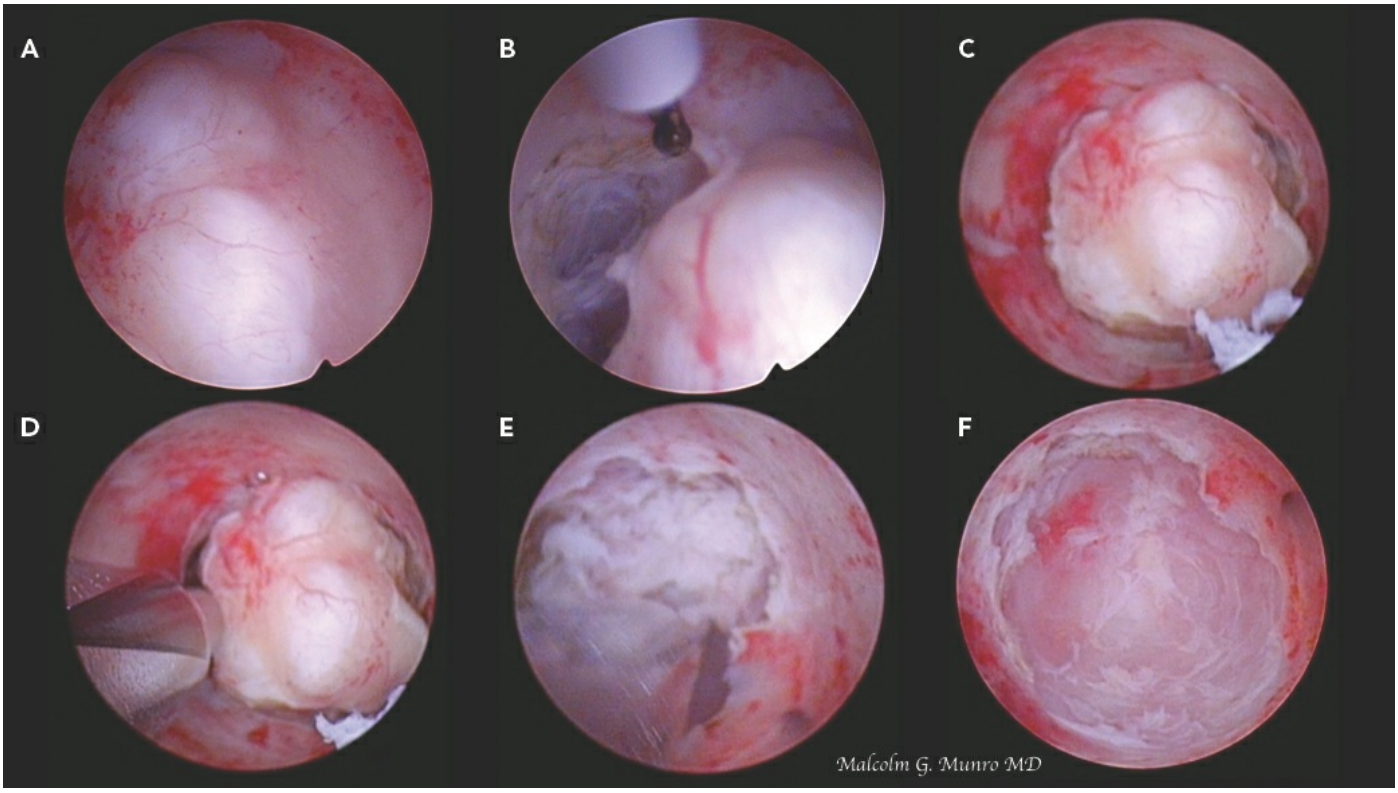


FIGURE 26-40 Myomectomy—FIGO type 2 leiomyoma. A: The deep FIGO type 2 leiomyoma can be seen at the uterine fundus. **B:** A bipolar RF needle is used to circumscribe the leiomyoma, incising into the pseudocapsule, which "releases" the fibroid as the myometrium pushes it into the endometrial cavity (**C**). Either a RF resectoscope, or here, an electromechanical morcellator is placed into the pseudocapsule (**D**) and the leiomyoma is resected (**E**). The final result (**F**). This cavity will fill in as the myometrium expands and as endometrial epithelialization occurs over the next 12 weeks or so. Anesthesia—local.

The long-term efficacy and impact of ablation or resection on women with adenomyosis is unknown. Because ectopic endometrium located in the myometrium inevitably cannot be ablated, there is potential for persisting or augmented bleeding and pain. There is evidence that EA failures may be more common in women with AUB-A (290,291). Another factor associated with post EA pain is a previous tubal occlusion procedure, a circumstance that should be considered when counseling women about the possible long-term risks of EA (290,292).

Sterilization

Sterilization can be performed under hysteroscopic guidance, an approach that eliminates the disadvantages and risks associated with abdominal or laparoscopic techniques (293). Until recently the only product available, was Essure®, a system that comprises a nickel-titanium coil with a Dacron filament that could be inserted relatively quickly in an office or procedure room setting (see Chapter 14). Tubal occlusion resulted from ingrowth of fibrous tissue across the coils, a process that takes approximately 3 months to complete. Various protocols were in place, depending on the country, to determine device placement prior to use. In 2018 the product was withdrawn

by the manufacturer, the result of patient concerns about side effects of the procedure.

Synechiae

Asherman syndrome is the presence of adhesions in the endometrial cavity (IUAs) resulting in infertility or recurrent spontaneous abortion with or without amenorrhea. If IUA do not occlude the upper cervical canal or lower uterine segment, these synechiae may be detected on a hysterogram or contrast sonohysterogram but are best shown with diagnostic hysteroscopy **(Fig. 26-42)**. Relatively thin, fragile synechiae may be divided with the tip of a rigid diagnostic hysteroscope (294). Thicker lesions will require division by semi-rigid or rigid scissors. Because the endometrium has often been substantially damaged, and difficult to identify, the use of RF energy–based instruments should be minimized or avoided. Reproductive outcome depends on the extent of the preoperative endometrial damage (295,296). This is another hysteroscopic procedure that is amenable to performance in the office, in selected cases, but the surgeon must be careful to maintain orientation within the endometrial cavity. Simultaneous intraoperative imaging with transabdominal ultrasound, or, in some institutions, intraoperative fluoroscopy, is desirable and often necessary in moderate and severe cases.

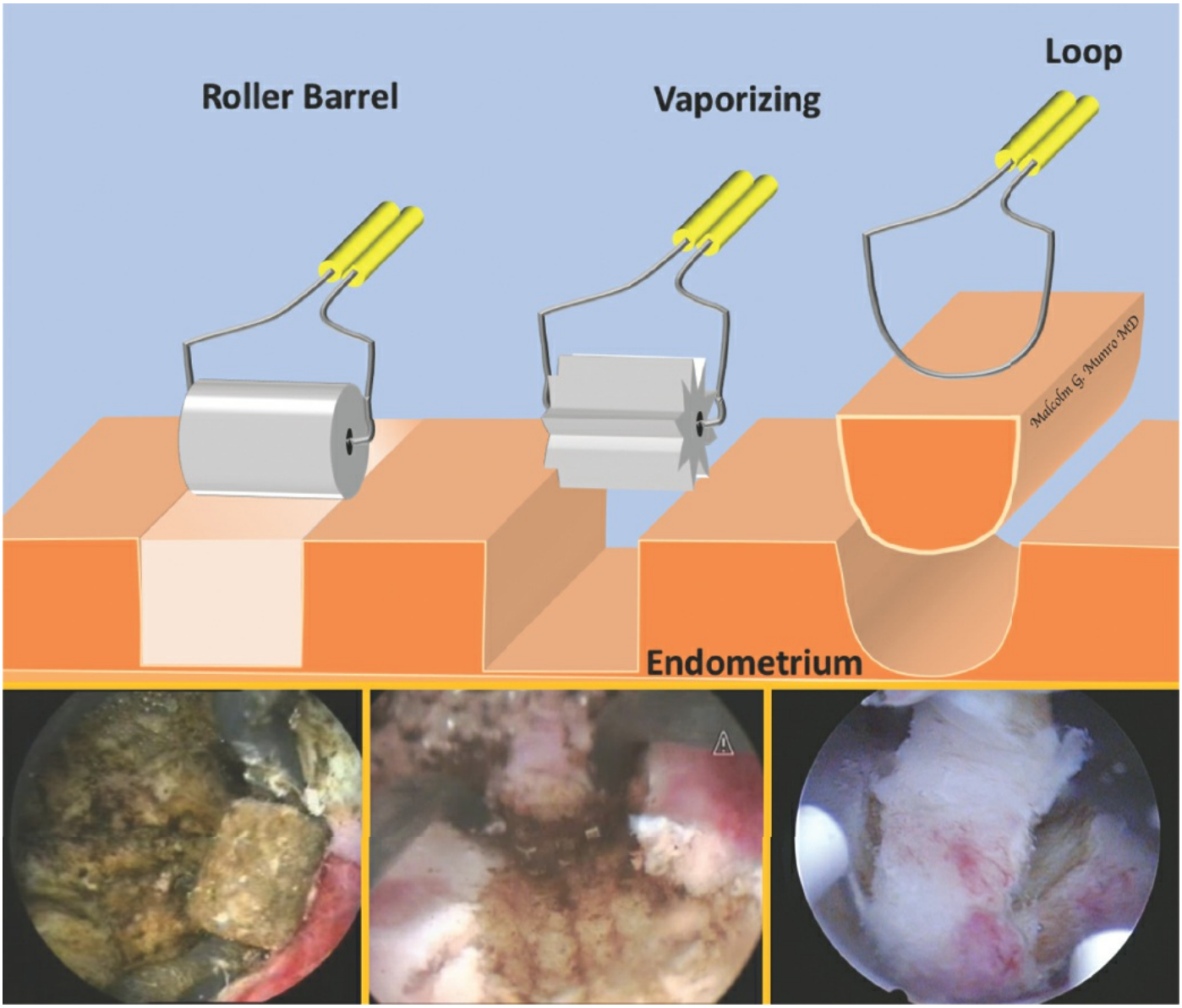


FIGURE 26-41 Resectoscopic endometrial ablation (REA) techniques. REA can be accomplished with coagulation using a rolling ball or barrel (shown) and either low or modulated high-voltage RF outputs; by vaporization using a suitably designed electrode and high Wattage low-voltage RF waveforms; or using a resection loop and low-voltage current. In each case, the surgeon's goal is to treat the entire endometrium —if medically prepared, the depth should be about 4 mm.

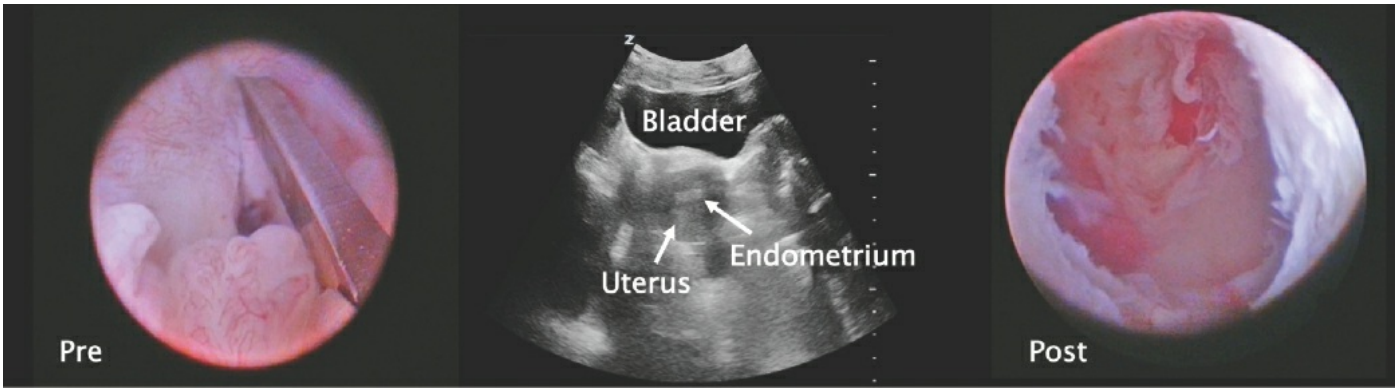


FIGURE 26-42 Asherman Syndrome—Isthmical Adhesions. This patient has amenorrhea associated with localized adhesions at the level of the isthmus. She is operated upon in the office procedure room using both hysteroscopic and transabdominal sonographic guidance. On the **left**, the scissors are seen dividing the adhesions while also viewed from the ultrasound perspective (**center**). The endometrial cavity is entered (**right**) and the procedure is completed. Some use a stent; we perform a second-look procedure in 4 to 8 weeks.

Patient Preparation and Communication

Diagnostic hysteroscopy procedures traditionally have been performed in the office or clinic settings. Operative hysteroscopy has usually been performed in an operating room or hospital outpatient surgical center. In a number of medical centers, 90% of the operative hysteroscopies are performed in an office procedure room setting using local anesthesia assisted by ensuring that the environment is comfortable, even including the use of music (297). The patient should understand the rationale for the planned procedure, the anticipated discomfort, potential risks, and the expectant, medical, and surgical alternatives. The nature of the procedure and the chance of therapeutic success should be explained, and she should be given a realistic estimate of success based on the operator's experience.

Diagnostic Hysteroscopy: Risks

The risks of diagnostic hysteroscopy are few, and those complications that occur rarely have severe consequences (298). The uncommon adverse events that should be discussed with the patient include perforation, bleeding, and those related to anesthesia and the distention media. After diagnostic hysteroscopy, most patients have slight vaginal bleeding, and occasionally, lower abdominal cramps. Severe cramps, dyspnea, and upper abdominal and right shoulder pain can develop when CO_2 is used as the distension media as it passes through the fallopian tubes into the peritoneal cavity. Even in an office environment, the patient should be encouraged to have a friend or relative escort her home.

Operative Hysteroscopy: Risks

Counseling before operative hysteroscopy varies depending on the planned procedure, type of anesthesia, and procedure location—office or operating/procedure room. Overall, the risks of operative hysteroscopy are higher than those of diagnostic hysteroscopy. These increased risks are largely confined to procedures such as adhesiolysis of severe intrauterine synechiae or resection of leiomyomas that are either large or extend deeply into the myometrium. These risks include those associated with anesthesia, intrinsic to all hysteroscopic procedures, and related to the specific surgical procedure to be performed (298). With any hysteroscopic procedure, air embolus is a possibility, as are complications associated with the gaseous or fluid distention media used. Hypotonic distension media may not be tolerated in some patients if there is

significant intravascular absorption, especially in patients with underlying cardiovascular disease. The patient must be aware of the risks associated with uterine perforation, which range from failure to complete the procedure to hemorrhage or damage to the intestines or to the urinary tract. If such complications occur, laparotomy may be necessary to repair the injury.

Equipment and Technique

The equipment required for hysteroscopy depends on the reason for the procedure. The surgeon must be knowledgeable about the equipment, its mechanisms, and the technical specifications to facilitate efficiency, optimal clinical outcome, and decrease the probability of complications. A typical hysteroscopy setup for both diagnostic and operative procedures is shown in **Figures 26-43** and **26-44**.

Core competencies required for hysteroscopy are as follows:

1. **Patient positioning and cervical exposure**
2. **Anesthesia**
3. **Cervical dilation**
4. **Uterine distention**
5. **Visualization and imaging**
6. **Intrauterine cutting and hemostasis**
7. **Other instrumentation**

Patient Positioning and Cervical Exposure

Hysteroscopy is performed in a modified dorsal lithotomy position; the patient is supine, and the legs are held in stirrups. For hysteroscopic procedures performed while the patient is conscious, comfort must be considered in conjunction with the need to gain good exposure of the perineum. Stirrups that hold and support the knees, calves, and ankles permit prolonged procedures. “Candy cane” stirrups should be avoided for hysteroscopic surgery, especially for conscious patients.

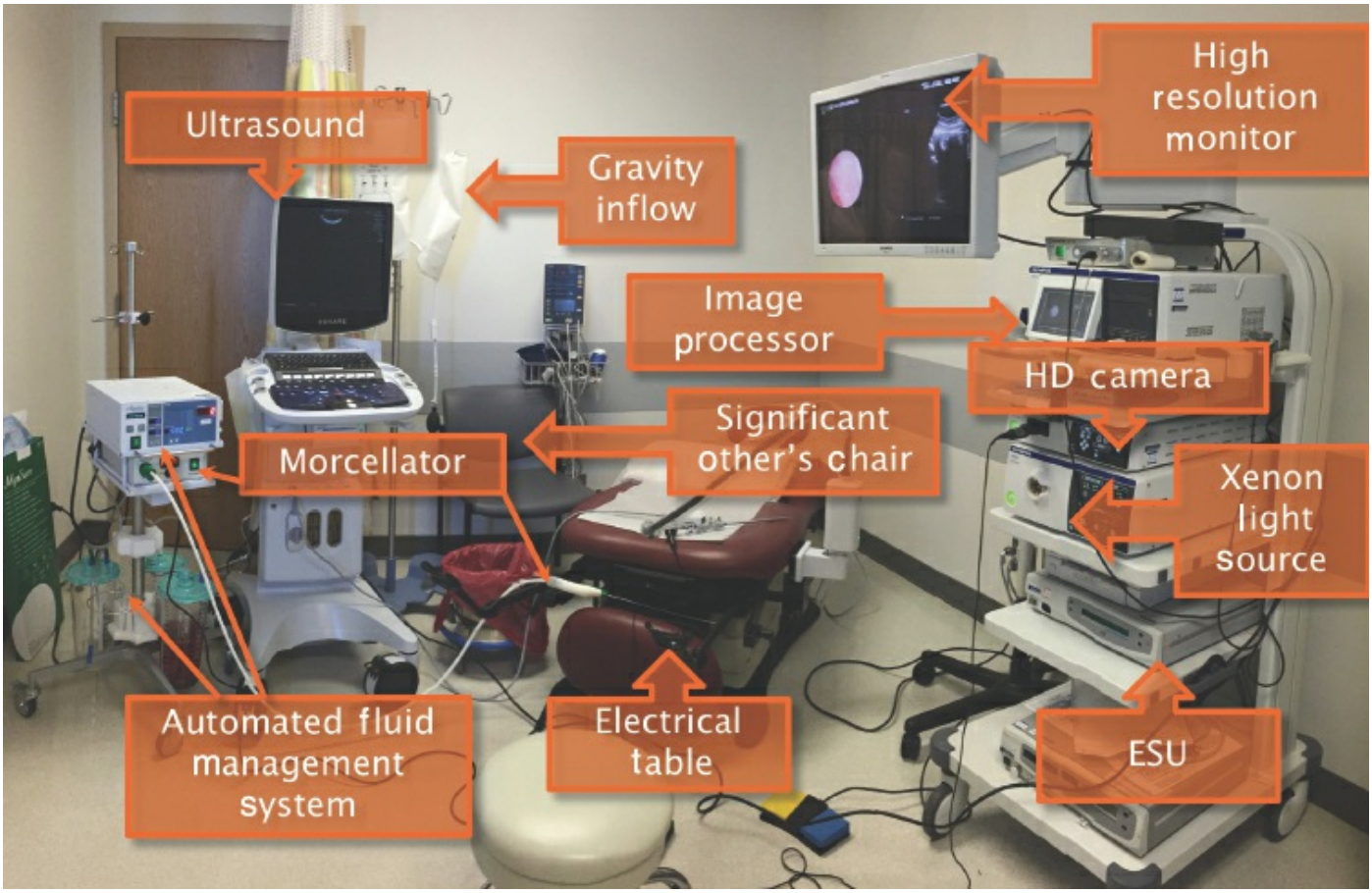


FIGURE 26-43 Office hysteroscopy setup. Hysteroscopic procedures are facilitated with an electric examination table designed to adjust the patient's position. Distension media may be positioned on an IV pole, but wide, cystoscopy tubing allows maintenance of higher intrauterine pressures suitable for viewing and performing simple procedures such as polypectomy or transcervical sterilization. A light source is necessary and a camera desirable. The camera is attached to the monitor and may be connected to a printer and/or video recorder. The camera head is attached to a flexible hysteroscope.

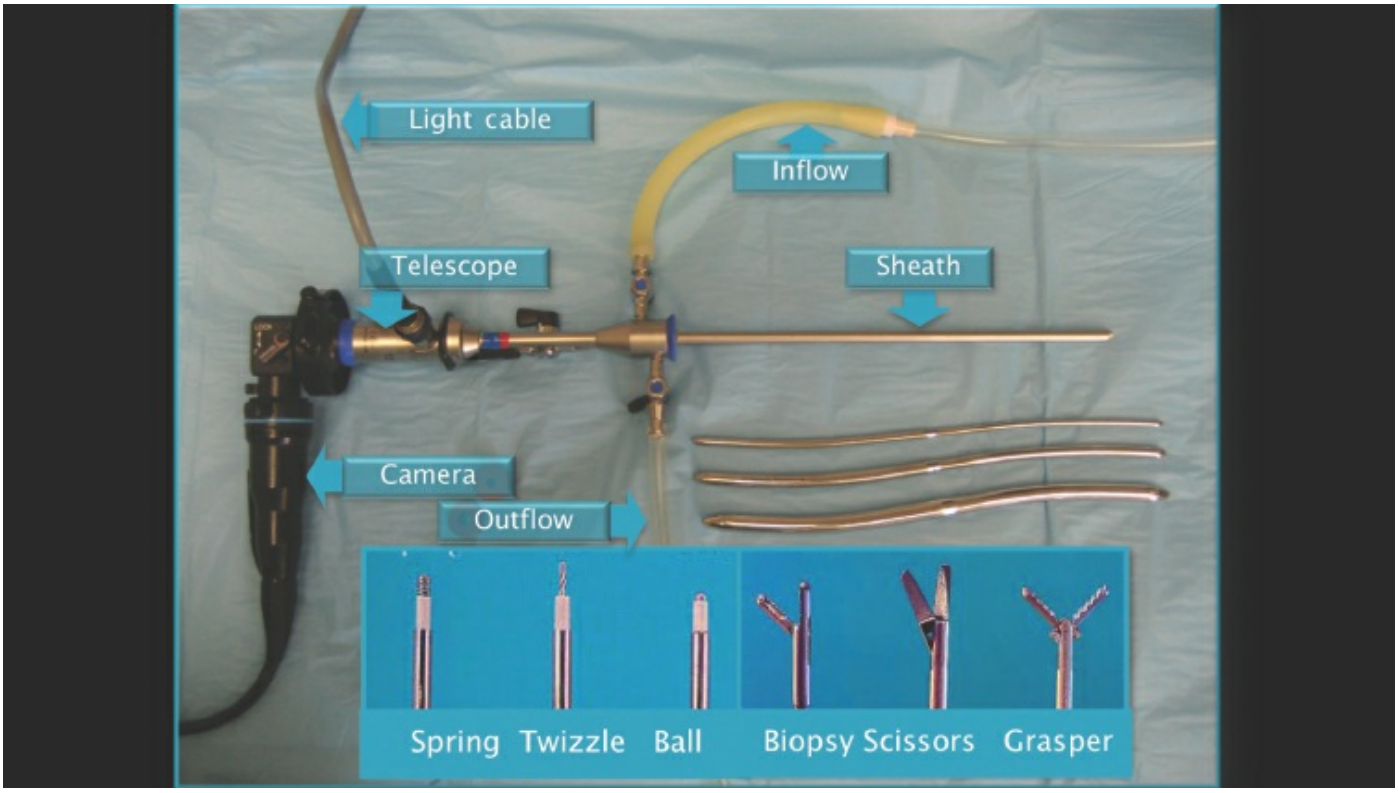


FIGURE 26-44 Office hysteroscopy instruments. An assembled continuous flow operating hysteroscope with a 5.5-mm diameter external sheath is shown connected to inflow and outflow tubing and an attached medical video camera and light cable. In the *lower right inset* are three 5-Fr instruments that can be passed through the operating channel into the endometrial cavity. From **left** to **right** these are biopsy forceps, semi-rigid scissors, and grasping forceps. In the *left inset* are bipolar RF instruments. From **left** to **right** these include a "spring tip" for tissue vaporization; a "twizzle tip" for tissue transection; and a "ball tip" for vessel coagulation.

There are a number of methods whereby the cervix may be accessed. Historically, a speculum is used, but "vaginoscopic" and occasionally digital access are additional options applicable to many patients.

When the traditional speculum-based exposure is used for cervical exposure, the operator should select the smallest speculum possible, particularly when the procedure is performed under no or local anesthesia. A bivalve speculum hinged on only one side allows its removal without disturbing the position of the tenaculum and hysteroscope. Typically, a tenaculum is attached to the cervix; clinicians can minimize the pain associated with this process by injecting a small amount of local anesthetic (such as xylocaine 1%) using a spinal needle prior to grasping the cervix. The use of weighted specula should be avoided in conscious patients because of the discomfort involved (Fig. 26-45). Dilation may or may not be required depending on the status of the cervix and the outside diameter of the hysteroscopic system.

The "vaginoscopic" technique (Fig. 26-45) avoids the speculum, using the hysteroscope to deliver distending media to the vagina, usually allowing visual access to the external os. Absent cervical stenosis and provided a narrow enough

hysteroscopic system, access to the endometrial cavity can usually be accomplished with overall comfort greater than that associated with the traditional technique (299). Such an approach can be additionally useful—even essential—for virginal women, or others for whom a speculum is inappropriate or uncomfortable.

Anesthesia

The anesthetic requirements for hysteroscopy vary greatly, depending on the patient's level of anxiety, the status of her cervical canal, the procedure, and the outside diameter of the hysteroscope or sheath. In some patients, diagnostic hysteroscopy is possible without anesthesia, especially if the patient is parous or if narrow-caliber (<3 mm in outside diameter) hysteroscopes and sheaths are used (299). For large-diameter hysteroscopic systems, pain caused by cervical dilation may be reduced with the preprocedural use of oral or vaginal *misoprostol*, or by inserting a laminaria "tent," in the cervix 3 to 8 hours before the procedure. Laminaria are thin rods of natural ("slippery elm") or synthetic construction that, when passed through the internal os, expand over several hours thereby dilating the cervix. If laminaria are left in place too long (e.g., longer than 24 hours), the cervix may overdilate, which is counterproductive for CO_2 insufflation.

For most diagnostic and many operative procedures, effective uterine anesthesia is obtained using local anesthetic techniques, permitting the hysteroscopy to be done in an office procedure room. Paracervical block may be the most effective (300). Following exposure of the cervix with a vaginal speculum, a spinal needle can be used to instill about 3 mL of 0.5% to 1% lidocaine into the anterior lip of the cervix to allow attachment of a tenaculum to allow manipulation of the exocervix. While the exact location and depth of the injection varies with providers and studies, the uterosacral ligament location (about 4-mm deep at approximately at the 4- and 8-o'clock positions as one looks at the cervix) has been demonstrated successful (301). Care must be taken to avoid intravascular injection. An alternative technique is the use of an intracervical block where the anesthetic agent is injected evenly around the circumference of the cervix, attempting to reach the level of the internal os. The efficacy of this approach is unclear (300). Recognizing the complex innervation of the uterus, alternative or additional topical anesthesia may be applied to the cervical canal or to the endometrium, or both, using anesthetic spray, gel, or cream. It is unclear how effective these approaches are, because many of the study protocols seemed to allow inadequate time between application and initiation of the procedure (302). A number of options have been published including instillation of 5 mL of 2% *mepivacaine* into the endometrial cavity with a syringe or the application of similar amounts of 2% lidocaine gel. Many operative procedures can be performed with these techniques combined, if deemed necessary, with the oral or intravenous use of anxiolytics or analgesics. The use of such systemic agents mandates continuous monitoring of blood pressure and

oxygenation, and the availability of appropriate resuscitative staff and equipment. An important component of the optimal use of local anesthesia is to allow sufficient time between injection or application of the agents and the commencement of the procedure. While injectable local anesthetic agents such as *lidocaine* and *mepivacaine* may have an onset of action of 2 to 3 minutes, it may take up to 15 to 20 minutes to obtain a maximal effect. If local anesthesia is not deemed appropriate, regional or general anesthesia may be used in the context of a surgical center or operating room.

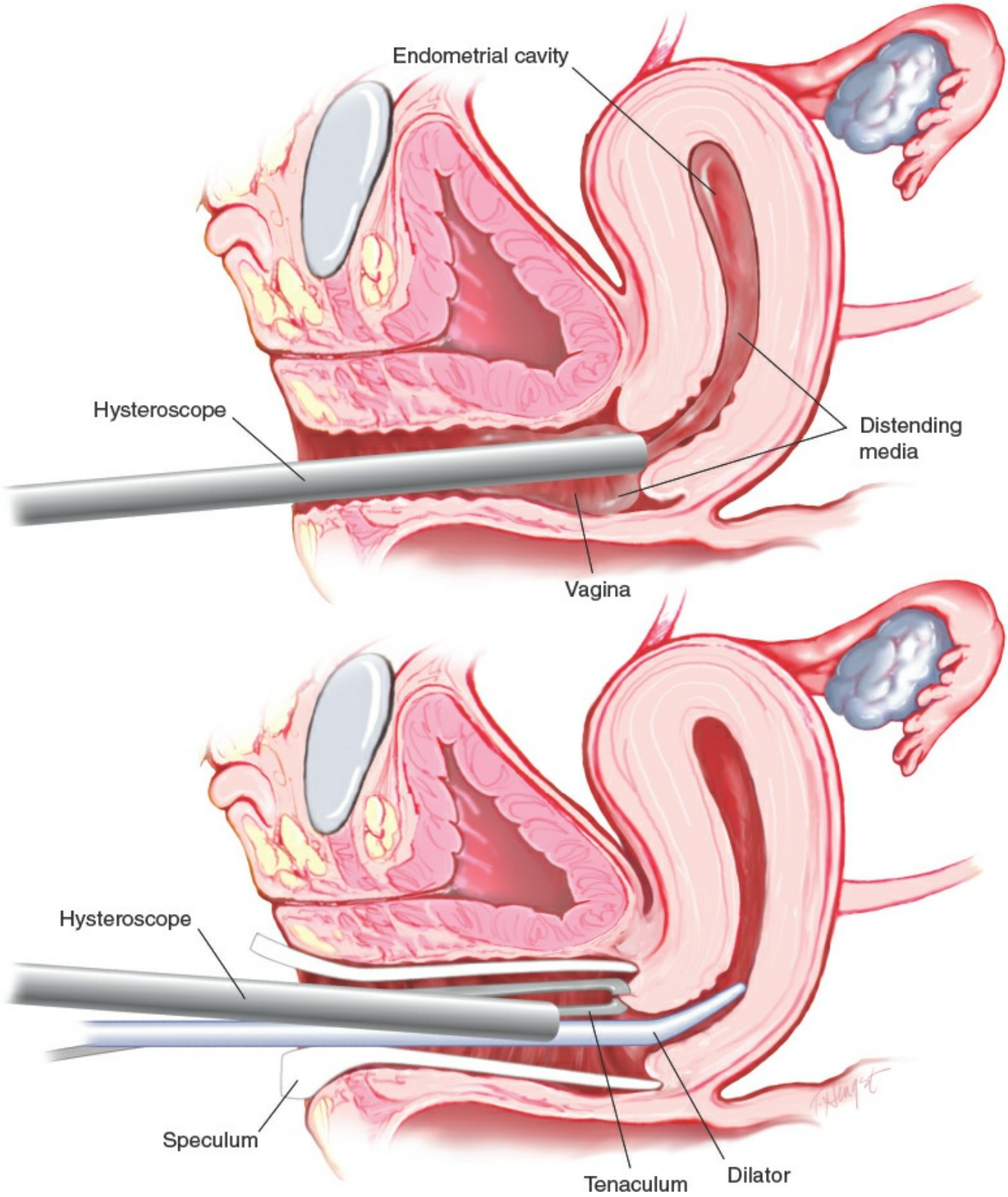


FIGURE 26-45 Hysteroscopic access. In many instances, the hysteroscopic system can be passed into the vagina (vaginoscopic access, *top panel*), the external os visualized endoscopically, and then advanced into the endometrial cavity without a tenaculum or cervical dilation. The more traditional approach of tenaculum and cervical dilation is necessary if the cervical canal is stenotic or substantially narrower than the outside diameter of the hysteroscopic system.

Cervical Dilation

In many instances, and particularly in vaginally parous women, dilation of the cervix will be unnecessary, especially if narrow-caliber hysteroscopic systems are used. Sometimes dilation will be necessary. Although a seemingly simple process, cervical stenosis, or suboptimal technique can result in perforation that compromises the entire procedure. If the objective lens of the endoscope cannot be placed in the endometrial cavity, the hysteroscopy cannot be done. The process of dilation should be undertaken carefully, respecting the orientation of the cervix to the axis of the vaginal canal (version) and that of the corpus to the cervix (flexion). In difficult circumstances, simultaneous ultrasound may be valuable, and difficult dilation may be facilitated directly with the hysteroscope.

There are a number of options available to facilitate cervical dilation. There is high-quality evidence that prostaglandin E_1 (*misoprostol*) administered 400 μg orally or 200–400 μg vaginally, approximately 3 to 24 hours before the procedure facilitates cervical dilation (303–306). This may have more utility for postmenopausal women (307) who require estrogenization, with a vaginal preparation, administered daily for 2 weeks before the procedure (308). Intraoperatively administered intracervical *vasopressin* (0.05 U/mL, 4 cc at 4 and 8 o'clock) substantially reduces the force required for cervical dilation (309). Regardless of the circumstance, the cervix should be dilated as atraumatically as possible. It is best to avoid using a uterine sound because it can traumatize the canal or the endometrium, causing unnecessary bleeding and uterine perforation. The best approach may be to use the hysteroscope, not a dilator or sound, to explore the cervical canal, a circumstance that generally facilitates visually guided entry into the endometrial cavity. Should actual obstruction be encountered, the use of scissors to divide adhesions, or transabdominal ultrasound to guide advancement of the hysteroscopic is generally successful.

Uterine Distention

Distention of the endometrial cavity is necessary to create a viewing space. The choices include CO_2 gas, high-viscosity 32% *dextran* 70, and several low-viscosity, electrolyte free fluids, including 1.5% glycine, 3% sorbitol, 5% mannitol and dextrose in water, and 0.9% normal saline. A pressure of 45 mm Hg or higher is generally required for adequate distention of the endometrial cavity and to visualize the tubal ostia. To minimize extravasation, the pressure used should be the lowest possible to provide adequate exposure, and to stay below the mean arterial pressure (310). For each of the fluids, there are several methods used to create this pressure by infusion into the endometrial cavity.

Sheaths

Rigid hysteroscopes are fitted to an external sheath before they are passed into the endometrial cavity through the cervical canal. The design and diameter of the sheath

reflect the dimensions of the endoscope and the purpose of the instrument. Typical diagnostic combinations have a sheath slightly wider than the telescope, allowing infusion of the distention media. Operative sheaths have additional channels, to permit the passage—introduction and removal—of distention media, and the insertion of surgical instruments, such as RF electrodes or semi-rigid scissors, biopsy devices, or grasping forceps. These sheaths are usually 5 to 8 mm in diameter, and some allow continuous flow of distention media in and out of the endometrial cavity (Fig. 26-46).

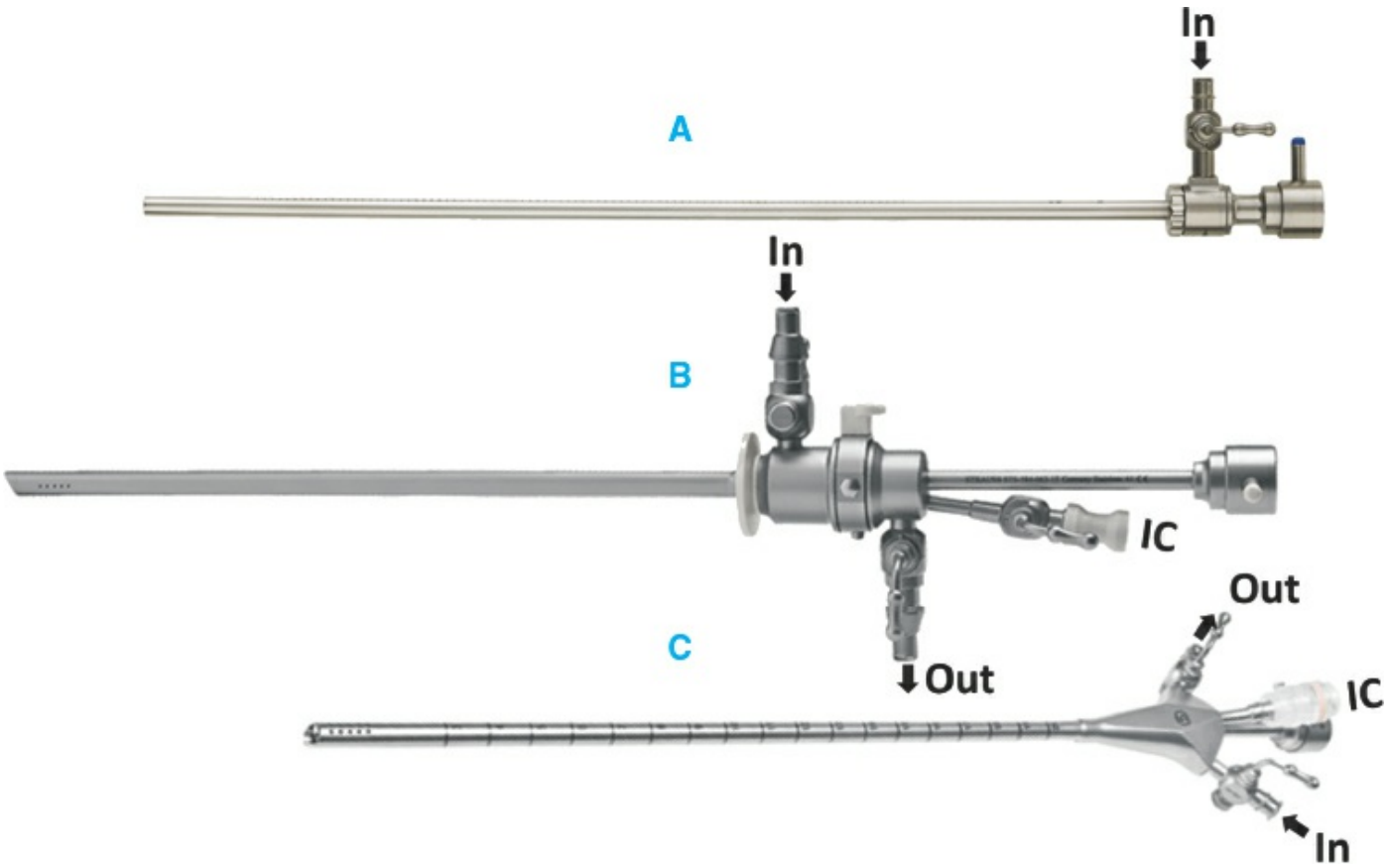


FIGURE 26-46 Hysteroscopic sheaths. A: A simple "diagnostic" sheath, with only one inflow channel (*In*), but no outflow and no instrument channel. **B:** A continuous flow system with two separate sheaths connected together. One sheath is responsible for inflow (*In*) and one for outflow (*Out*), a circumstance that does much to maintain a clear field, particularly if there is blood or debris. There is a separate instrument channel (*IC*). **C:** A single piece continuous flow sheath with integrated inflow and outflow channel, and an instrument channel (*IC*).

Media

CO_2 provides an excellent view for diagnostic purposes, but it is unsuitable for operative hysteroscopy and for diagnostic procedures when the patient is bleeding because there is no effective way to remove blood and other debris from the endometrial cavity. To prevent CO_2 embolus, the gas must be instilled by an insufflator that is specially designed for the procedure—the intrauterine pressure is kept below 100 mm Hg, and the flow rate is maintained at less than 100 mL/min.

Normal saline is a useful and safe medium for RF-based procedures that do not require monopolar RF resectoscopes. Even if there is absorption of a substantial volume of solution, saline typically does not cause electrolyte imbalance. Therefore, saline is a good fluid for minor procedures performed in the office. The development of bipolar RF instrumentation for hysteroscopic surgery has allowed the application of saline as a distending medium in even more advanced and complex procedures.

Viscous solutions of 32% dextran 70 are useful for patients who are bleeding, because they do not mix with blood. However, dextran solutions are expensive, of limited availability and tend to "caramelize" on instruments, which must be disassembled and thoroughly cleaned in warm water immediately after each use. Anaphylactic reactions, fluid overload, and electrolyte disturbances can occur.

For standard operative hysteroscopy with monopolar RF resectoscopes, low-viscosity, nonconductive fluids such as 1.5% glycine, 3% sorbitol, and 5.0% *mannitol* are used most often. These solutions can be used with standard, monopolar RF instrumentation because there are no electrolytes to disperse the current and impede the electrosurgical effect. Each of these media is inexpensive and readily available, usually in 3-L bags suitable for continuous-flow hysteroscopy. Because each fluid is electrolyte-free, extravasation into the systemic circulation can be associated with electrolyte disturbances. Compared with 1.5% glycine or 3.0% sorbitol, 5% mannitol is iso-osmolar, and it functions as a diuretic, an advantage when performing resectoscopic surgery. **Regardless of the electrolyte content of the fluid distending media, systemic "absorption" must be monitored continuously, or frequently (every 5 minutes), by collecting outflow from the sheath and subtracting it from the total infused volume.** Frequently the manufacturer fills the bags with more than the 3 L, which makes accurate calculation of absorbed volume especially difficult (311). There exist a number of machines designed to provide continuous feedback to the surgeon regarding the degree of negative fluid balance **(Fig. 26-47)**. **Absorbed volumes of electrolyte free solutions that are greater than 1 L mandate the intraoperative measurement of electrolyte levels.** The risk of fluid overload is reduced by the judicious restriction of intravenous fluid by the anesthesiologist. The administration of an appropriate dose of *furosemide* should be considered, and the surgeon should plan for the expeditious completion of the procedure. **If there is more than a preset limit (1.0 to 1.5 L of electrolyte free extravasated fluid, or 2.0 to 2.5 L of normal saline), the procedure should be stopped**. Excessive circulating *sorbitol* may cause hyperglycemia, and large volumes of glycine may elevate levels of ammonia in the blood (312).

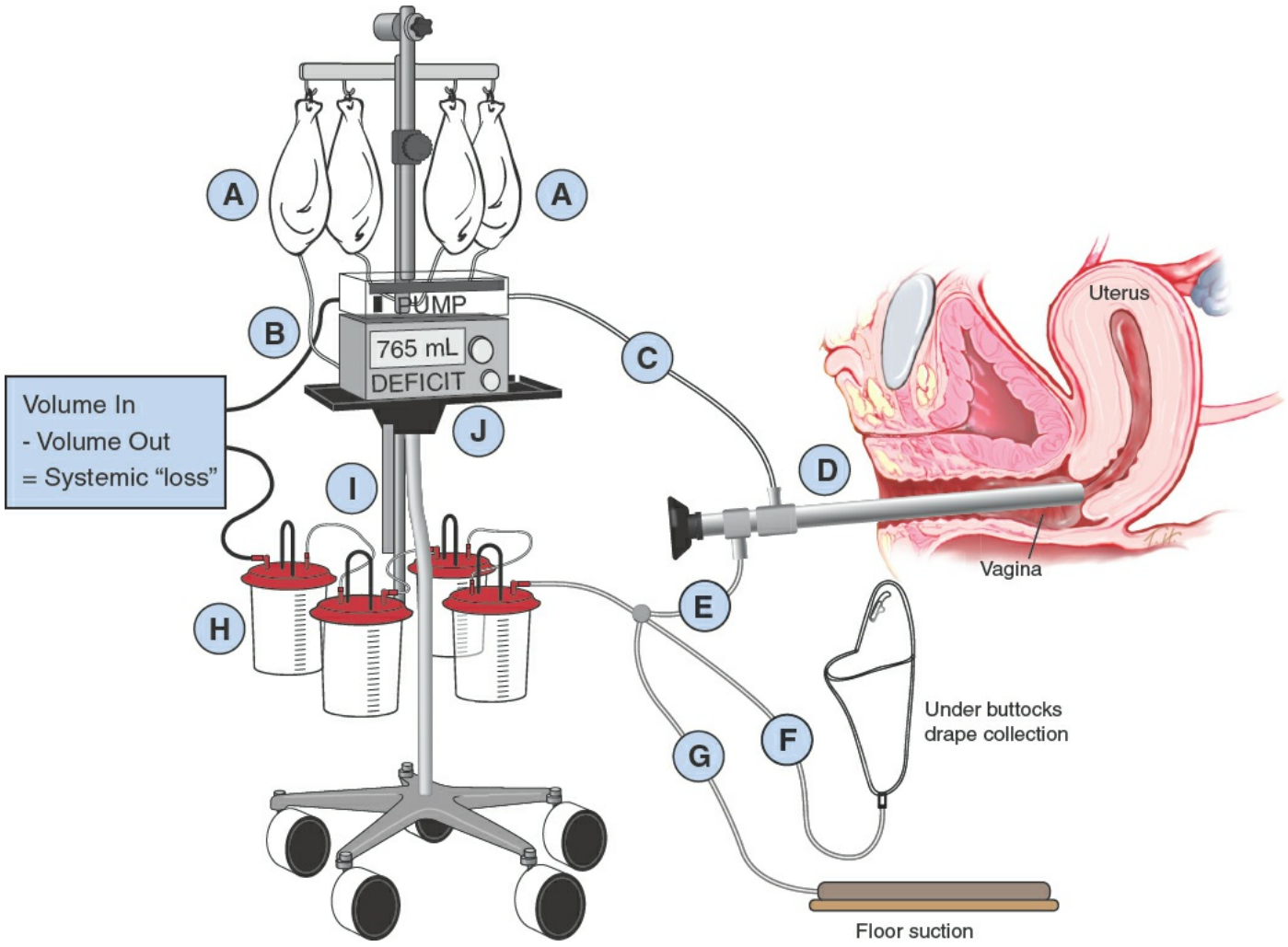


FIGURE 26-47 Fluid management system. Hysteroscopic fluid management systems combine a pump that delivers fluid to the endometrial cavity with a system for calculating the amount of fluid that is absorbed systemically—the deficit. The bags of fluid are hung (*A*) and connected to the pump (*B*) that delivers the media via tubing (*C*) to the inflow channel of the hysteroscopic system (*D*). Then, the fluid is either systemically absorbed through blood vessels or the peritoneal cavity via fallopian tubes, or collected from the outflow channel of the hysteroscope (*E*), the underbuttocks drape (*F*) and, if available, floor suction (*G*), into containers at the base of the system (*H*).The collected fluid is weighed by an electronic scale (*I*) and the microprocessor system converts this weight to volume that, when subtracted from the measured infused volume by the microprocessor, allows the "deficit" to be displayed on the screen in mL (*J*).

Media Delivery Systems

Syringes can be used for office diagnostic procedures and are especially good for infusing *dextran* solution. The syringe can be operated by the surgeon and is either connected directly to the sheath or attached by connecting tubing. Because this technique can be tedious, it is suited only for diagnostic hysteroscopy and simple operations such as polypectomy or IUD retrieval.

For low-viscosity fluids such as normal saline, continuous hydrostatic pressure is effectively achieved by elevating the vehicle containing the distention media above the level of the patient's uterus. The achieved pressure is the product of the width of the

connecting tubing and the elevation—for operative hysteroscopy with 10-mm tubing, intrauterine pressure ranges from 70 to 100 mm Hg when the bag is between 1 to 1.5 m above the uterine cavity.

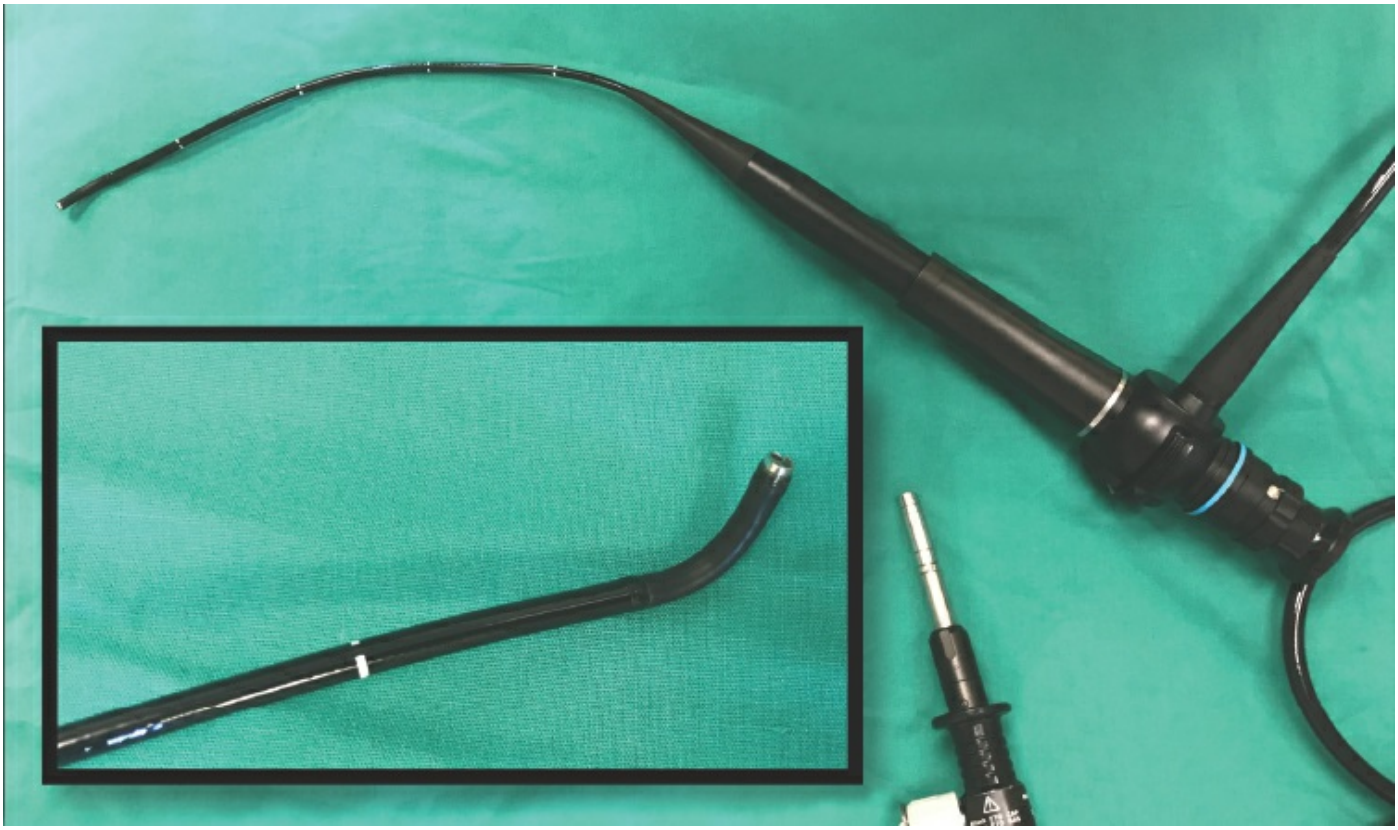


FIGURE 26-48 Flexible hysteroscope. This flexible hysteroscope uses optical fibers for both light and optical transmission has an integrated fluid channel for delivery of media and a 3.5-mm outer diameter and can be articulated (*inset*) to provide a better view in the cornua or for the uterine sidewalls. The "post" to connect the system to the remote "cold" light source is in the *lower right*. These hysteroscopes are not suitable for surgical procedures because they both lack an operating channel and the continuous flow system needed to keep the field clear.

A pressure cuff may be placed around the infusion bag to elevate the pressure in the system. Caution must be exercised, because this technique causes increasing extravasation if intrauterine pressure rises above the mean arterial pressure.

A variety of infusion pumps are available, ranging from simple devices to instruments that maintain a preset intrauterine pressure. Simple pump devices continue to press fluid into the uterine cavity regardless of resistance, whereas the pressure-sensitive pumps reduce the flow rate when the preset level is reached, thereby impeding the efflux of blood and debris and compromising the view. Virtually all media management systems designed for hysteroscopic use allow the surgeon to preset an intrauterine pressure. Such pressure management is usually based on measurements in the remote machine, so data may be delayed and somewhat inaccurate. The development of more sensitive and accurate pressure management systems is a remaining need.

Imaging

Endoscopes

Hysteroscopes are available in two basic types—flexible and rigid. Flexible hysteroscopes **(Fig. 26-48)** are self-contained in that they do not require a sheath—the single integrated channel is used to transmit gas or fluid to the endometrial cavity for distention. As a result, these instruments are generally of smaller diameter than rigid systems. They can be designed to be "steerable" allowing angled viewing. Flexible hysteroscopes utilize fiberoptic bundles rather than lenses to transmit the image to the observer, have lower resolution than rigid instruments of a similar diameter and typically do not have a channel with a caliber suitable for most hand instruments. For other uses, rigid hysteroscopes are more durable and provide a superior image. The most commonly used hysteroscopes are 3 to 4 mm in outside diameter, although those using fibers can be made smaller than 2 mm in diameter.

Rigid endoscopes require an angled (foreoblique) lens to provide a field of view useful for operative hysteroscopy. In addition to 0-degree versions, they are commonly used in 12- to 15-degree, and 25- to 30-degree models **(Fig. 26-49)**. The surgeon must be aware of the difference between the viewing angle and the long axis of the endoscope to facilitate passage through the cervical canal **(Fig. 26-50)**. The 0-degree telescope provides a panoramic view and is best for diagnostic procedures, although it is the standard lens used for the hysteroscopic electromechanical and similar systems. Hysteroscopes with 25- to 30-degree angles are most often used for cannulation of the fallopian tubes or placement of sterilization devices. Twelve- to 15-degree designs are a suitable compromise useful for diagnosis and most operative procedures. The utility of endoscopes with more extreme foreoblique views may be offset by the tendency of instruments to leave the visual field on full extension.

Light Sources and Cables

Adequate illumination of the endometrial cavity is essential. Because it runs from a standard 110- or 220-volt wall outlet, the light source requires no special electrical connections. For most cameras and endoscopes, the element must have at least 150 watts of power for direct viewing and preferably 250 watts or more for video and operative procedures (313).

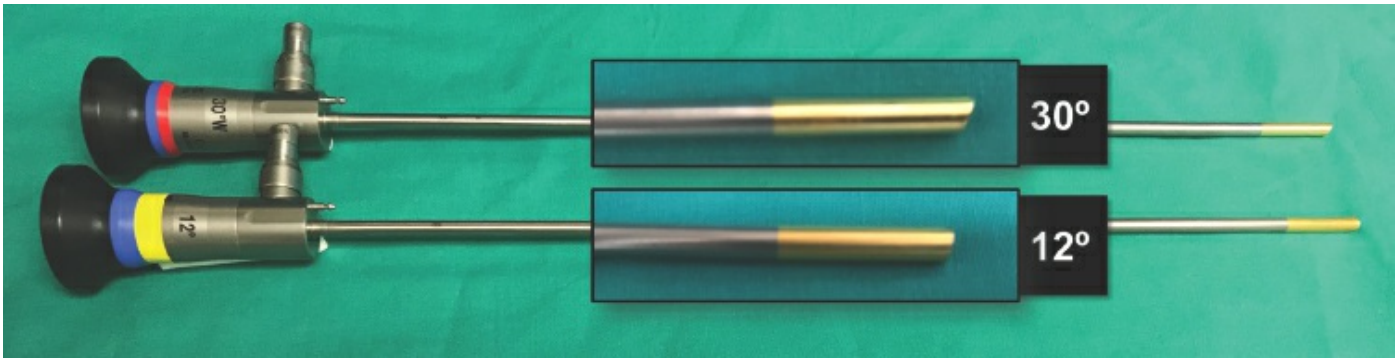


FIGURE 26-49 Rigid hysteroscopes. Demonstrated are a 12-degree (**bottom**) and a 30-degree (**top**) foreoblique variety.

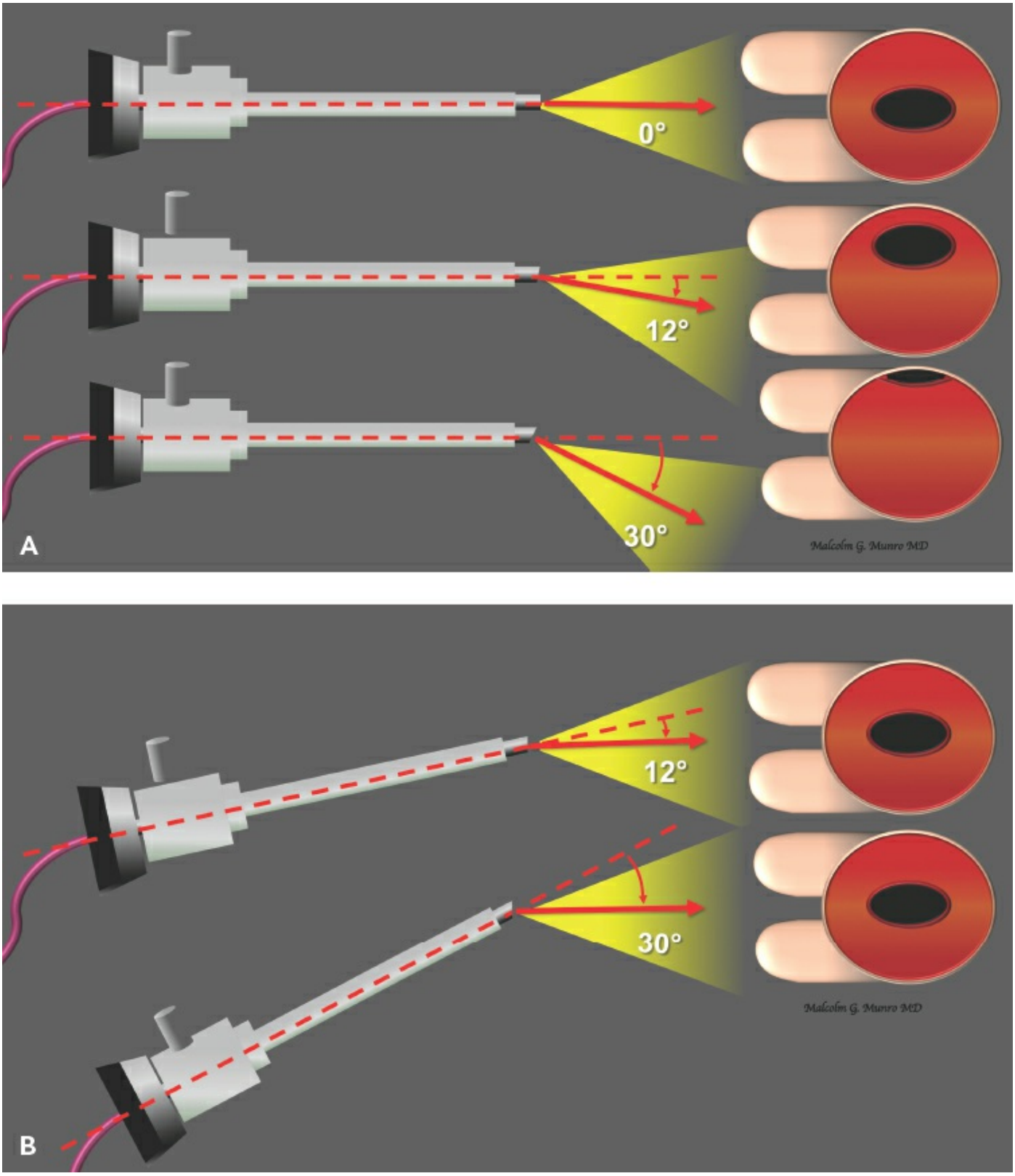


FIGURE 26-50 Rigid endoscope optics. A: When the 0 degrees hysteroscope is inserted into the cervix the cervical canal is generally central (**top**) and the direction of insertion is aligned with the viewing angle. When a 12-degree lens is inserted with the axis of the endoscope aligned with that of the cervix, the canal will be seen to be anterior (**middle**), a circumstance that becomes more extreme with a 30-degree viewing angle to the point that only the cervical sidewall is seen (**bottom**). **B.** Adjusting the viewing angle to see the

cervical canal for the 12-degree and the 30-degree lenses is shown. This maneuver demonstrates the location of the canal, but for insertion the axis must be oriented as in **A**.

Imaging

Although diagnostic hysteroscopy may be performed with direct visualization, it is best to use video guidance for prolonged operations. Video imaging is important for teaching and recording pathology and procedures. The camera must be sensitive because of the narrow diameter of the endoscope and the frequently relatively dark background of the endometrial cavity, particularly when it is enlarged. For procedures at increased risk for perforation, such as lysis of adhesions or when dissection deeply invades the myometrium, simultaneous transabdominal ultrasound imaging can be used **(Fig. 26-51)**.

Image Documentation

A small video camera can be used to coordinate the procedure with the operating room team and to teach or monitor the performance of trainees. Video imaging has utility for the patient when hysteroscopic surgery is performed without sedation, facilitating their understanding of the pathology, if present, and the procedure performed. It allows the acquisition of still or video images for future reference or teaching, although it is important to preserve patient anonymity, or privacy, depending on the nature and purpose of the recorded material. Several video recording formats are available, each with inherent advantages and disadvantages. High-definition digital cameras provide high-quality video still images and high-resolution digital video, suitable for publication or teaching.

Intrauterine Cutting and Hemostasis

The instruments available for use through operative hysteroscopes include electrosurgical instruments, mechanically operated biopsy, grasping, cutting, and punch-biopsy devices. These tools are narrow and flexible enough to navigate the 1- to 2.3-mm diameter operating channel **(Fig. 26-44)**. The value of mechanical devices is often limited by their small size and relatively flimsy construction. The biopsy forceps can be used to sample targeted lesions, the scissors to divide adhesions, dissect myomas and transect polyps, and the grasping forceps to remove small polyps or intrauterine devices. Some operative hysteroscopes are designed to allow passage of fibers for the conduction of Nd:YAG laser energy, although this modality has generally been superseded by electrodes that provide similar or superior functionality at reduced cost.

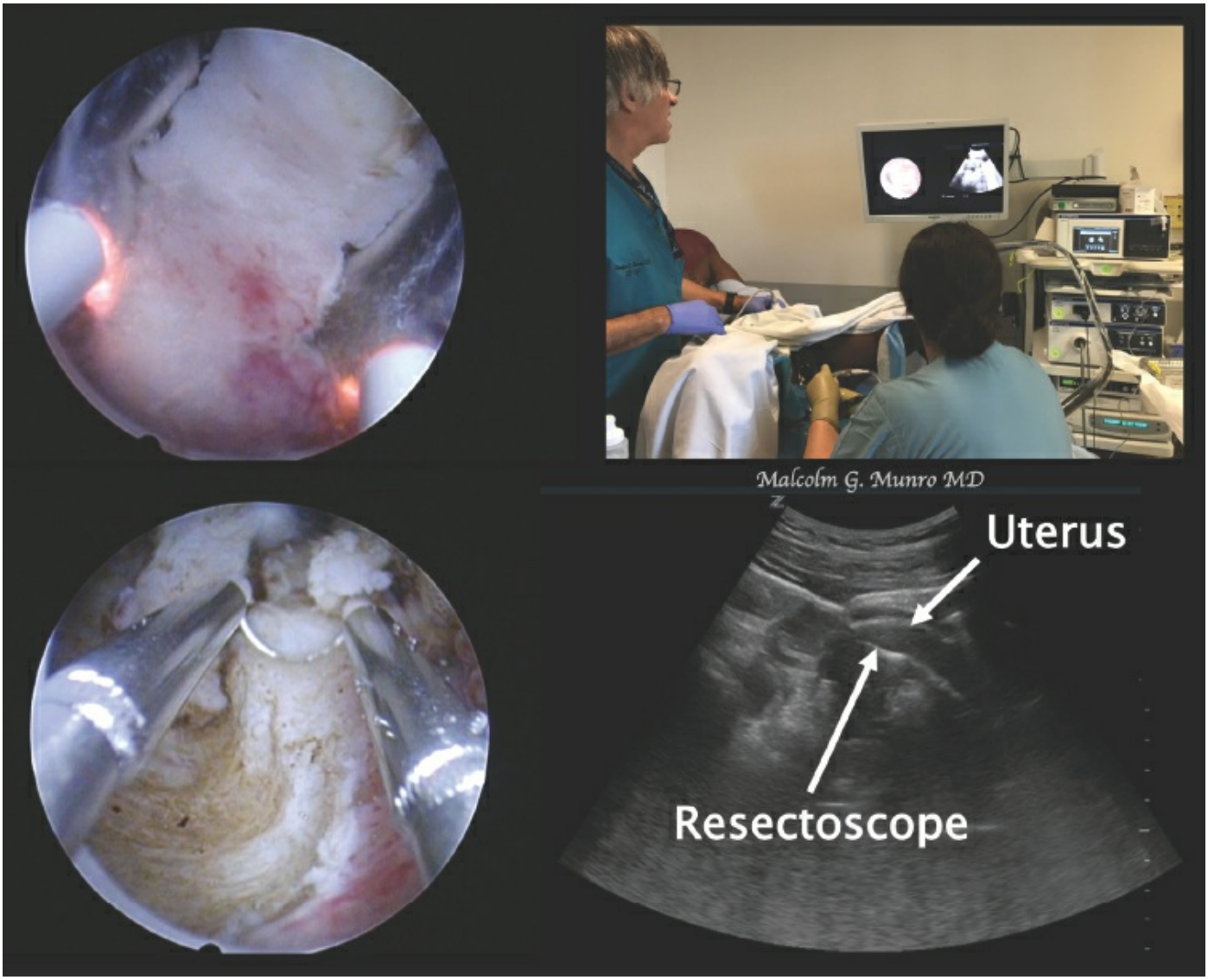


FIGURE 26-51 Simultaneous hysteroscopic and transabdominal ultrasound imaging. For procedures at enhanced risk for uterine perforation, the use of transabdominal ultrasound can provide the surgeon with a view of both the endometrial cavity and the myometrium and serosa. The fluid in the endometrial cavity provides a contrast medium that facilitates sonographic identification of the intrauterine instruments.

The uterine resectoscope is like the one used in urology and is designed to apply RF electrical energy in the endometrial cavity (Fig. 26-52). An understanding of the principles of electrosurgery is mandatory for safe and effective use of this instrument. By sliding the "working element," one of a variety of electrode tips can be manipulated back and forth within the cavity. Tissue can be divided with a pointed electrode, excised with a loop, or desiccated with a rolling ball or bar. An electrode with multiple tips or edges can be used to vaporize tissue, provided high-power generator outputs are used. For monopolar resectoscopes clear operative field is maintained by the continuous flow of nonconductive distending media in and out of the cavity. Although basic design modifications have made the resectoscope more useful in gynecology, extraction of resected fragments is time-consuming. The most effective

approaches include “trapping” of fragments between the electrode and the distal tip of the endoscope, or the periodic use of a uterine curette, or polyp forceps, inserted after removal of the resectoscope. One company has introduced a system that aspirates the fragments as they are made. Alternatively, much of the myoma or endometrium can be vaporized, thereby minimizing the need for periodic but time-consuming removal of tissue “chips.” If vaporization is used, it is important to obtain representative samples of the endometrium or myoma for pathologic analysis. Resectoscopes are available in both monopolar and bipolar designs. The advantages of bipolar systems—decreased electrosurgical injuries, and, because saline can be used, reduced risk of fluid and electrolyte complications, and increased tolerance for systemic media absorption—are increasingly making them the best choice for surgeons and patients.

The problem of tissue removal has been partially addressed by using an alternative design to the resectoscope. These hysteroscopic morcellation, or “tissue removal” devices are based on the design of an orthopedic endoscopic “shaver.” They comprise a hollow cannula and a distal fenestration or “window” that is repeatedly opened and closed with a reciprocating blade that “chops” the target tissue as it is aspirated through the window into the suction channel **(Fig. 26-53)**. These devices are particularly useful for large polyps and FIGO type 0 and many type 1 leiomyomas, but require additional dissecting techniques for many deeper type 1 and type 2 fibroid resection (271) **(Fig. 26-40)**.

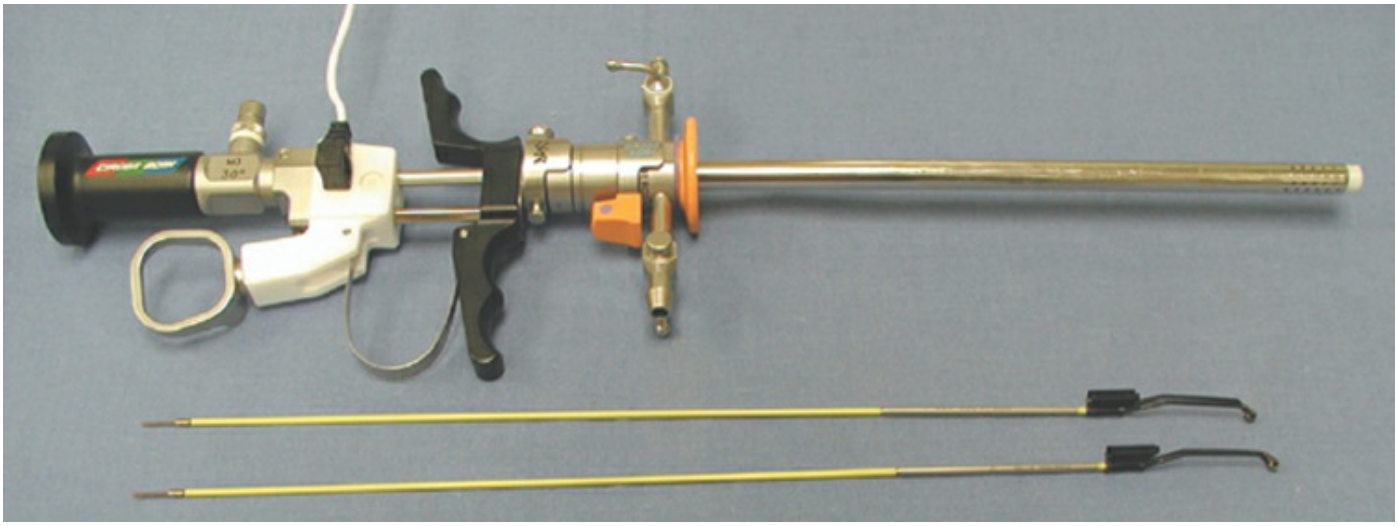


FIGURE 26-52 Resectoscope. The assembled resectoscope is shown, with two electrodes in the foreground. Manipulation of the electrode is via the white handle in the proximal portion of the device.



FIGURE 26-53 Electromechanical morcellator. These systems have their own proprietary hysteroscope system with an offset eyepiece (**right**) to allow for one of the rigid hollow probes (**bottom**) to be inserted. The probe is connected to a motor drive (**center**) that is activated by depressing a footpedal (**upper left**) that activates both an oscillating blade and suction. The blade transects the tissue, and the suction transports it to a collecting sac in the fluid management system.

Other Instrumentations

For any hysteroscopic procedure, it is necessary to have available a cervical tenaculum, dilators, uterine curette, and appropriate-sized vaginal specula. When using the resectoscope, it is helpful to have a modern, solid-state, isolated circuit electrosurgical generator capable of delivering modulated and nonmodulated RF current. The simultaneous use of transabdominal ultrasound is often necessary to aid in difficult uterine access situations, or to assist in guiding the performance of adhesiolysis or myomectomy of type 2 leiomyomas. Laparoscopy or laparotomy may be necessary for emergencies secondary to uterine perforation.

Complications

The primary potential risks of positioning a hysteroscopic system in the endometrial cavity solely for viewing ("diagnostic hysteroscopy") are limited to cervical trauma and uterine perforation. Other adverse events such as infection, excessive bleeding, and complications related to the distention media are extremely uncommon when the procedure is short, and does not involve instrumentation of the myometrium (0%–1%) (298). **The risks of operative hysteroscopy are related to one of five aspects of the procedure performed: (a) anesthesia; (b) distention media; (c) perforation; (d) bleeding; and (e) the use of energy** (284,298).

Anesthesia

Local anesthetic protocols typically include the intracervical or paracervical injection of 0.5% to 2% *lidocaine* or *mepivacaine* solution, with or without a local vasoconstrictor such as adrenaline. The risk of overdosage is minimized by ensuring that intravascular injection is avoided and by not exceeding the maximum recommended doses (*lidocaine,* 4 mg/kg; *mepivacaine,* 3 mg/kg). The use of a dilute vasoconstrictor such as epinephrine 1/200,000 reduces the amount of systemic absorption of the agent, virtually doubling the maximum dose that can be used and facilitates the onset of action of local anesthetic agents (314).

Complications of intravascular injection or anesthetic overdose include allergy, neurologic effects, and impaired myocardial conduction. Allergy is characterized by the typical symptoms of agitation, palpitations, pruritus, coughing, shortness of breath, urticaria, bronchospasm, shock, and convulsions. Treatment measures include administration of oxygen, isotonic intravenous fluids, intramuscular or subcutaneous adrenaline, and intravenous prednisolone and aminophylline. Cardiac effects related to impaired myocardial conduction include bradycardia, cardiac arrest, shock, and convulsions. Emergency treatment measures include the administration of oxygen, intravenous *atropine* (0.5 mg), intravenous *adrenaline,* and the initiation of appropriate cardiac resuscitation. The most common central nervous system manifestations are paresthesia of the tongue, drowsiness, tremor, and convulsions. Options for therapy include intravenous *diazepam* and respiratory support.

Distention Media

[17] The other major complication associated with hysteroscopic procedures is excessive absorption of media, a risk that can be minimized with careful attention to technique.

Carbon Dioxide

Because carbon dioxide is highly soluble in blood emboli that occur are usually

clinically insignificant. However, in rare instances, CO_2 emboli may result in serious intraoperative morbidity and even death (315–317). These risks can be eliminated by avoiding the use of CO_2 with operative procedures, or minimized by ensuring that the insufflation pressure is always lower than 100 mm Hg, and that the flow rate is lower than 100 mL/min. The insufflator used must be especially designed for hysteroscopy; it is difficult to set laparoscopic insufflator flow rates below 1,000 mL/min.

Dextran 70

Dextran 70 is a hyperosmolar medium that, albeit rarely, can induce an allergic response, or coagulopathy (318,319). Similar to other types of distention media if sufficient volumes are infused, there is a risk of vascular overload and heart failure (320,321). Because dextran is hydrophilic, it can draw 6 times its own volume into the systemic circulation. Consequently, the volume of this agent should be limited to less than 300 mL. There is little use of dextran 70 because of the limited supply of the solution.

Low-Viscosity Fluids

The low-viscosity fluids—1.5% glycine, 3% sorbitol, and 5.0% mannitol—are commonly used, largely because of their low cost, compatibility with monopolar electrosurgical instruments, and availability in large-volume bags. Should these electrolyte-free, and usually hypotonic, media be absorbed to excess in the systemic circulation, they can create serious fluid and electrolyte disturbances a potentially dangerous complication which can result in pulmonary edema, hyponatremia, heart failure, cerebral edema, and death. These issues combine to support the notion that, where possible, it is best to use systems that can function in normal saline or similar solutions. While the risk of fluid overload remains, patients will tolerate a larger volume of systemic absorption without the risk of electrolyte imbalance and related complications. There exist a number of published guidelines describing the steps required to reduce the risk of fluid overload at the time of hysteroscopy, but those from the AAGL are the most current (322).

1. Before undertaking anything but simple operative procedures using these agents, baseline serum electrolyte levels should be measured. Women with cardiopulmonary disease should be evaluated carefully. While high-quality studies have suggested that the selective preoperative use of agents such as GnRH agonists may reduce operating time and media absorption (323,324), another, equally well-designed trial, did not reach the same conclusions (325). Intracervical injection of 8-mL dilute intracervical vasopressin (0.01 U/mL) immediately prior to surgery has been shown effective at reducing the amount of systemic absorption of distending media (326).

The duration of this effect may be limited to approximately 20 to 30 minutes so repeat dosing at suitable intervals may be useful.

2. In the operating room, media infusion and collection should take place in a closed system to allow accurate measurement of the "absorbed" volume. **[19]** The volume should be measured continuously with a device specifically designed for the purpose. If such a system is not available, volume should be calculated every 10 minutes by support staff who are trained in these calculations and unencumbered by duties that may interfere with this task. If such "manual" methodology is used, it is important to understand that available evidence suggests that there is a great deal of variability and inaccuracy with such techniques (327).
3. The lowest intrauterine pressure necessary for adequate distention should be used to complete the operation, if possible at a level that is below the mean arterial pressure. A good range is 70 to 80 mm Hg, which can be achieved with a specially designed pump or by maintaining the meniscus of the infusion bag 1 m above the level of the patient's uterus.
4. **When using electrolyte free media, deficits of more than 1 L require repeat measurement of serum electrolyte levels and consideration of the dose of intravenous *furosemide* appropriate to the patient's renal function. When such a deficit exists, the procedure should be completed expeditiously**. If the deficit reaches a preset limit (no more than 1.5 L), the procedure should be terminated, and a diuretic such as *mannitol* or *furosemide* should be used as needed. The maximum deficit allowed when normal saline is used, is approximately 2.5 L. Regardless of the media, small patients, or those with cardiovascular compromise will typically have a lower tolerance for fluid deficits, a circumstance that mandates setting a lower limit for systemic absorption and, consequently, termination of the procedure (328).

Perforation

Perforation may occur during dilation of the cervix, positioning of the hysteroscope, or because of the intrauterine procedure itself. **[18]** The risks of perforation can be reduced by careful attention to the techniques used to access the endometrial cavity, and by careful use of energy-based systems.

With complete perforation, the endometrial cavity typically does not distend, and the visual field is generally lost. When perforation occurs during dilation of the cervix, the procedure must be terminated, but, because of the blunt nature of the dilators, usually there are no other injuries. **If the uterus is perforated by the activated tip of a laser, electrode, or an activated electromechanical tissue removal device, there is a risk for bleeding or injury to the adjacent viscera. Therefore, the operation must be stopped, and laparoscopy or laparotomy should be performed**. Injury to the uterus is

relatively easy to detect with a laparoscope. However, mechanical or thermal injury to the bowel, ureter, or bladder is more difficult to the extent that laparoscopy is frequently inadequate to make a complete evaluation. If the patient's condition is managed expectantly, she should be advised of the situation and asked to report any symptoms of bleeding or visceral trauma such as fever, increasing pain, nausea, and vomiting.

Bleeding

Bleeding that occurs during or after hysteroscopy results from trauma to the vessels in the myometrium or injury to other vessels in the pelvis. Myometrial vessels are more susceptible to laceration during resectoscopic procedures that require myometrial dissection for procedures such as endometrial resection or FIGO type 1 or type 2 myomectomy.

In planning operations that involve deep resection, anemic patients should be treated medically, if possible, with agents such as ulipristal acetate or a GnRH agonist, if necessary, while oral or intravenous iron is used to replenish iron stores. An alternative approach, perhaps suitable for nonanemic patients is obtaining and storing autologous blood before surgery.

The risk of bleeding may be reduced by the preoperative injection of diluted *vasopressin* into the cervical stroma (326). The risk of injury to the branches of the uterine artery can be lowered by limiting the depth of resection in the lateral endometrial cavity near the uterine isthmus, where ablative techniques should be considered. When performing myomectomy, identification and dissection of the pseudocapsule, totally or largely eliminates myometrial injury and related bleeding. When bleeding is encountered during resectoscopic procedures, the ball electrode can be used to desiccate the vessel electrosurgically. Intractable bleeding may respond to the injection of diluted vasopressin or to the inflation of a 30-mL Foley catheter balloon or similar device in the endometrial cavity (260).

Thermal Trauma

Thermal injury to the intestine or ureter may be difficult to diagnose, and symptoms may not occur for several days to 2 weeks. Therefore, the patient should be advised of the symptoms that could indicate peritonitis.

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CHAPTER 27

Hysterectomy



Tommaso Falcone, Beri Ridgeway

Indications
- Leiomyomas
- Abnormal Uterine Bleeding
- Intractable Dysmenorrhea
- Pelvic Pain
- Cervical Intraepithelial Neoplasia
- Obstetric Emergency
- Pelvic Inflammatory Disease
- Endometriosis
- Pelvic Mass or Benign Ovarian Tumor
- Pelvic Organ Prolapse

Preoperative Considerations
- Health Assessment
- Hysterectomy Versus Supracervical Hysterectomy
- Prophylactic Salpingo-Oophorectomy
- Concurrent Surgical Procedures
  - *Pelvic Support Procedures*
  - *Appendectomy*
  - *Cholecystectomy*
  - *Abdominoplasty*
  - *Tissue Extraction Techniques*
- Choice of Surgical Access: Vaginal, Abdominal, or Laparoscopic Hysterectomy

Perioperative Checklist

Technique
- Abdominal Hysterectomy
  - *General Preparation*
  - *Surgical Technique*
  - *Intraoperative Complications*

Postoperative Management
Postoperative Pain Management
Vaginal Hysterectomy
Preoperative Evaluation
Perioperative Considerations
Procedure
McCall Culdoplasty
Surgical Techniques for Selected Patients
Schuchardt Incision
Intraoperative Complications
Perioperative Care
Laparoscopic Hysterectomy
Preoperative Preparation
Surgical Technique of Laparoscopic Hysterectomy
Robotic-Assisted Laparoscopic Hysterectomy
Laparoendoscopic Single-Site Surgery
Intraoperative Complications: Laparoscopic Hysterectomy
Postoperative Complications of Hysterectomy
Incisional Pain and Infections
Hemorrhage
Urinary Tract Complications
Urinary Retention
Ureteral Injury
Vesicovaginal Fistula
Prolapse of the Fallopian Tube
Vaginal Cuff Dehiscence
Discharge Instructions
Readmission and Emergency Department Visits After Discharge
General Pelvic Symptoms and Quality of Life
Sexual Function

KEY POINTS

1 Hysterectomy is one of the most commonly performed surgical procedures in the United States.
2 Vaginal hysterectomy is the procedure of choice unless this route is contraindicated.
3 Randomized clinical trials do not demonstrate an advantage of robotic or single-port hysterectomy over conventional laparoscopic hysterectomy.
4 There appears to be no advantage to the routine use of supracervical hysterectomy when compared with total hysterectomy.
5 Salpingo-oophorectomy at the time of hysterectomy for benign disease in premenopausal women at average risk for ovarian malignancy is associated with an increase in long-term patient mortality from cardiovascular disease, and ovarian conservation should be strongly considered in these patients.

[1] Hysterectomy is one of the most common surgical procedures performed. According to the National Hospital Discharge survey, the rate of inpatient hysterectomy between 1998 and 2010 decreased, with 36% fewer hysterectomies performed in 2010 compared with 2002 (Table 27-1) (1). These data do not represent hysterectomies performed in ambulatory settings and recent data of outpatient hysterectomy volume in

nonhospital ambulatory settings indicate that a shift in the location of the hysterectomy explains in part the observed drop in hysterectomy. Data from the US Healthcare Cost and Utilization Project State Ambulatory Surgery and Services Database (SASD) suggest that approximately 100,000 to 200,000 hysterectomies are performed in ambulatory settings (2). These procedures are overwhelmingly laparoscopic or robotic. **Therefore laparoscopic, including robotic hysterectomies, accounts for the majority of hysterectomies performed, followed by abdominal and then vaginal.** The decline in abdominal and hospital-based hysterectomies have important cost and training implications. Hysterectomy rates are higher for black women (3). Bilateral salpingo-oophorectomy decreased significantly, while bilateral salpingectomy increased significantly between 1998 and 2011 (4).

Table 27-1 Indications for Inpatient Hysterectomy Based on National Hospital Discharge Survey United States 2010 (1)

	Number of Hysterectomies
Uterine leiomyoma	195,000
Abnormal uterine bleeding	195,000
Endometriosis	83,000
Benign ovarian neoplasms	70,000
Pelvic organ prolapse	74,000
Gynecologic cancer	53,000

Numbers are rounded.

INDICATIONS

Leiomyomas

The number of hysterectomies performed for leiomyomas, abnormal uterine bleeding, endometriosis, benign ovarian masses and prolapse have decreased over time (1,5) (see Chapter 11). Fertility-preserving surgical management (myomectomy) is possible in most patients with leiomyomas. The decision to perform a hysterectomy for leiomyomas is usually based on the need to treat symptoms—abnormal uterine bleeding, pelvic pain, or pelvic pressure. Other indications for intervention have included “rapid” uterine enlargement, ureteral compression, or uterine growth after menopause. There is no clearly reproducible definition of rapid growth. The concept of rapid growth was challenged because these patients did not demonstrate clearly malignant conditions (6). Refuted reasons for hysterectomy in patients with leiomyomas are size greater than 12

weeks of gestation without symptoms, inability to palpate the ovaries on bimanual examination, and increased morbidity at hysterectomy with increased uterine size. If the procedures are performed abdominally, there is no difference in surgical morbidity between patients with a 12-week–sized uterus and those with a 20-week–sized uterus (7). **Hysterectomy for leiomyomas should be considered only in symptomatic patients who do not desire future fertility** (7).

To reduce uterine size before hysterectomy, patients with large leiomyomas may be pretreated with a gonadotropin-releasing hormone (GnRH) agonist (8,9). In many cases, the reduction of uterine size is sufficient to permit vaginal hysterectomy when an abdominal hysterectomy would otherwise be necessary. In one prospective trial, premenopausal patients with leiomyomas the size of 14 to 18 weeks' gestation were randomized to receive either 2 months of preoperative depot GnRH agonist or no GnRH agonist (9). Treatment with a short course (8 weeks) of *leuprolide acetate* before surgery enabled the procedures to be converted safely from an abdominal hysterectomy to a vaginal hysterectomy (9). This preoperative regimen was associated with a rise in hematocrit before surgery and a shorter hospital stay and convalescent period because patients were more likely to have a vaginal rather than an abdominal hysterectomy.

Abnormal Uterine Bleeding

Abnormal uterine bleeding requires an extensive investigation to rule out reversible causes of bleeding (see Chapter 10). Anovulatory uterine bleeding is typically associated with polycystic ovary syndrome (PCOS), a condition in which anovulatory cycles are common. The bleeding can be controlled by medical intervention with *progestin* or a combination of *progestin* and *estrogen* given as oral contraceptives. **Ovulatory abnormal uterine bleeding can be controlled by nonsteroidal anti-inflammatory agents, hormonal intervention, *tranexamic acid,* or the *levonorgestrel* intrauterine device. In patients with abnormal uterine bleeding, endometrial sampling should be performed before hysterectomy** (10). Dilation and curettage is not an effective means of controlling bleeding and is not necessary before hysterectomy. Hysterectomy should be reserved for patients who do not respond to or cannot tolerate medical therapy. Alternatives to hysterectomy (e.g., endometrial ablation or uterine artery embolization) should be considered in selected patients because these operations may be cost-effective and have a lower morbidity rate. However, in a clinical trial that randomized endometrial ablation to hysterectomy, 29% of patients assigned to the ablation underwent hysterectomy by 60 months (11). In a follow-up of another randomized clinical trial comparing uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids, 31% of those randomized to uterine artery embolization ultimately underwent a hysterectomy (12).

Intractable Dysmenorrhea

About 10% of adult women are incapacitated for as many as 3 days per month as a result of dysmenorrhea (see Chapter 12). Dysmenorrhea can be treated with nonsteroidal anti-inflammatory agents used alone or in combination with oral contraceptives or other hormone agents. The *levonorgestrel* intrauterine device effectively reduces dysmenorrhea symptoms. **Hysterectomy is rarely required for the treatment of primary dysmenorrhea.** In patients with secondary dysmenorrhea, the underlying condition (e.g., leiomyomas, endometriosis) should be treated primarily. Hysterectomy should be considered only if medical therapy fails and if the patient does not want to preserve fertility.

Pelvic Pain

In a review of 418 women in whom hysterectomy was performed for a variety of nonmalignant conditions, 18% had chronic pelvic pain. Preoperative laparoscopy was performed in only 66% of these patients. After hysterectomy, there was a significant reduction in pain and an improvement in quality of life (13). In a review of 104 patients who underwent hysterectomy for chronic pelvic pain that was believed to be of uterine origin, 78% experienced improvement in their pain after follow-up for a mean of 21.6 months (14). However, 22% of patients had no improvement in or exacerbation of their pain. **Hysterectomy should be performed only in those patients whose pain is of gynecologic origin and does not respond to nonsurgical treatments** (see Chapter 12).

Cervical Intraepithelial Neoplasia

In the past, hysterectomy was performed as primary treatment of cervical intraepithelial neoplasia. More conservative treatments, such as laser or loop electrosurgical excision procedure (LEEP), can be effective in treating the disease, making hysterectomy unnecessary in most women with these conditions (see Chapter 16). For patients with recurrent high-grade dysplasia who do not desire to preserve fertility, hysterectomy may be an appropriate treatment option. After hysterectomy, these patients are at increased risk for vaginal intraepithelial neoplasia.

Obstetric Emergency

Most emergency hysterectomies are performed because of postpartum hemorrhage resulting from uterine atony. Other indications include uterine rupture that cannot be repaired or a pelvic abscess that does not respond to medical therapy. Hysterectomy may be required for patients with placenta accreta or placenta increta.

Pelvic Inflammatory Disease

Pelvic inflammatory disease can be treated successfully with antibiotics. **The uterus, tubes, and ovaries rarely need to be removed in a patient with pelvic inflammatory disease that is refractory to intravenous antibiotic therapy** (see Chapter 15). Whether one proceeds with conservative surgical management, abscess drainage, or organ removal is a subjective decision that must be based on the individual. If accessible, some pelvic abscesses may be drained successfully by percutaneous catheter drainage guided by ultrasonography or computed tomography (CT) scanning. **Surgical intervention is necessary if the patient has acute abdominal findings associated with peritonitis and signs of sepsis in the presence of a ruptured tubo-ovarian abscess.** For the patient who desires future fertility, consideration should be given to unilateral salpingectomy or salpingo-oophorectomy or bilateral salpingo-oophorectomy without hysterectomy. For the patient in whom bilateral salpingo-oophorectomy is required, the uterus can be left in place for possible ovum donation and *in vitro* fertilization.

Endometriosis

Medical and conservative surgical procedures are successful for treatment of endometriosis (15). **Bilateral salpingo-oophorectomy, with or without hysterectomy, should be performed only in patients who do not respond to conservative surgical (resection or ablation of endometriotic implants) or medical therapy** (see Chapter 13). Most patients with endometriosis who require hysterectomy have unrelenting pelvic pain or dysmenorrhea. Other less common situations include patients who do not desire future fertility and who have endometriosis involving other pelvic organs, such as the ureter or colon. **Hysterectomy with or without salpingo-oophorectomy provides significant pain relief to the majority of patients. At the time of hysterectomy for endometriosis, consideration should be given to conserving normal-appearing ovaries** (16).

Pelvic Mass or Benign Ovarian Tumor

If a pelvic mass is palpated on pelvic examination, a transvaginal ultrasound should be performed (see Chapter 10). If the mass is suspicious, appropriate consultation with a gynecologic oncologist is recommended. Benign-appearing ovarian tumors that are persistent or symptomatic require surgical treatment. If the patient desires fertility, the uterus should be conserved. If fertility is not an issue or if the patient is perimenopausal or postmenopausal, a decision must be made regarding whether the uterus should be removed. In one study, 100 patients who underwent bilateral salpingo-oophorectomy plus hysterectomy for benign adnexal disease were compared with a group of risk-

matched women who underwent bilateral salpingo-oophorectomy without hysterectomy for the same indication (17). There was a significant increase in operative morbidity, estimated blood loss, and the length of hospital stay for patients in whom hysterectomy was performed.

Pelvic Organ Prolapse

Hysterectomy is often performed for symptomatic pelvic organ prolapse at the time of pelvic floor reconstruction. Unless there is an associated condition requiring an abdominal incision, vaginal or laparoscopic hysterectomy is the preferred approach for pelvic organ prolapse. Following hysterectomy for prolapse, the vaginal apex must be suspended or the patient will likely have posthysterectomy prolapse. **Uterine prolapse typically is not an isolated event and most often is associated with a variety of pelvic support defects. Each defect must be corrected to optimize the surgical outcome and decrease the risk of developing future pelvic support defects.** Uterine-sparing approaches to pelvic organ prolapse have been studied (18,19).

PREOPERATIVE CONSIDERATIONS

The preoperative discussion should include an informed consent that documents the options, risks, benefits, alternatives, expected outcomes, and personnel involved with the procedure. The medical record should reflect the completion of childbearing and that adequate trial of medical or nonsurgical management was offered, attempted, or declined. Specific sterilization consent forms are required in most states.

Health Assessment

An assessment of a patient's health status is important in order to obtain an optimal outcome after hysterectomy for benign disease. There are no routinely recommended tests, although individual hospitals may have their own requirements. The patient should be evaluated for risk factors associated with venous thromboembolic events (20). Age, medical history, such as inherited or acquired thrombophilias, obesity, smoking, and hormonal medication, including contraceptives or hormone therapy, may increase the risk.

It is important to assess and correct underlying anemias before surgery. Blood product use can be minimized with preoperative iron supplementation or the use of GnRH agonists.

Hysterectomy Versus Supracervical Hysterectomy

There is a trend toward retention of the cervix at hysterectomy because of the perception that several outcome parameters, including sexual function and pelvic support, are better after a supracervical hysterectomy. Three prospective randomized clinical trials as summarized in a Cochrane review challenge this perception (21). **[4]** **There is no evidence to support the concept that leaving the cervix improves sexual function or lower rates of incontinence or constipation.** All of these studies included hysterectomies that were performed by laparotomy.

The Cochrane review did find that surgical time was decreased by approximately 11 minutes. This decreased surgical time may be more significant for laparoscopic cases, as the most difficult part of the surgery is the detachment of the cervix from the lateral ligaments and from the vagina. This is where most ureteral injuries occur during laparoscopic hysterectomy. This advantage should be balanced with the potential risk of ongoing cyclic bleeding from the cervix that is reportedly between 5% and 20% from the randomized clinical trials and 19% from a prospective observational laparoscopic trial (22). With conservation of the cervix, the patient should be told there is a potential 1% to 2% risk for reoperation to remove the cervix and that trachelectomy is associated with a risk of intraoperative complications. Patients with suspected gynecologic cancers, endometrial hyperplasia, or cervical dysplasia are not candidates for supracervical hysterectomy.

Prophylactic Salpingo-Oophorectomy

The decision to remove the ovaries and tubes should be based on assessment of risk and not the route of hysterectomy (23). Premenopausal women who are at average risk of ovarian cancer (approximate lifetime risk of 1.4%) should have their ovaries preserved when they are undergoing hysterectomy for benign conditions where the ovaries and fallopian tubes are healthy (23). Elective removal of the ovaries at the time of hysterectomy has declined with 53% having no adnexal surgery (4). Elective salpingectomy at the time of hysterectomy has increased (4).

Salpingo-oophorectomy can be performed prophylactically to reduce the risk of ovarian cancer and to eliminate the potential for further surgery for either benign or malignant disease. Arguments against prophylactic salpingo-oophorectomy center on the need for earlier and more prolonged hormone therapy, the potential increased risk of cardiovascular disease and bone loss and poor compliance with long-term estrogen replacement therapy (24). **[5]** There is no overall survival benefit of prophylactic salpingo-oophorectomy in women at average risk for ovarian cancer. In premenopausal women younger than 50 years at average risk for ovarian cancer who underwent bilateral salpingo-oophorectomy, there was a significant increase in mortality from cardiovascular disease compared to women who had ovarian preservation (24). A Markov decision analysis model was used to estimate the best strategy for maximizing a

woman's survival when salpingo-oophorectomy is considered in women at average risk for ovarian cancer who are undergoing hysterectomy for benign disease, and in the women who had salpingo-oophorectomy before age 55 years, there was an 8.58% excess mortality by age 80 (25). The American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists recommend carefully assessing risk, and considering ovarian conservation in premenopausal women who are at average risk of ovarian cancer (23,26).

Because salpingo-oophorectomy is associated with a reduced risk of ovarian and breast cancer, women with a strong family history of ovarian and breast cancer and those who carry germline mutations, *BRCA1* or *BRCA2,* should consider risk-reducing salpingo-oophorectomy as their lifetime risk of ovarian cancer is between 10% and 50% (23,26–28). **A genetic counselor or gynecologic oncologist can provide an individual risk assessment.**

Based on the finding that many serous carcinomas arise in the fallopian tube rather than in the ovary, it was proposed that bilateral salpingectomy with ovarian conservation should be performed in patients with these high penetrance germline mutations while awaiting more definitive surgical intervention (29). **Opportunistic bilateral salpingectomy in average-risk women has been associated with decreased rates of ovarian cancer in population-based cohort data** (30). This potential benefit of salpingectomy should be discussed with patients prior to hysterectomy for benign disease.

Although salpingo-oophorectomy and salpingectomy can be accomplished by laparoscopy or laparotomy in nearly 100% of cases, the success rate for vaginal hysterectomy ranges from 65% to 95% for experienced vaginal surgeons (31,32).

Concurrent Surgical Procedures

Pelvic Support Procedures

Patients with pelvic organ prolapse should be offered surgical repair of prolapse at the time of hysterectomy. Typically pelvic support procedures are performed after the completion of the hysterectomy. Patients with pelvic organ prolapse must have a thorough preoperative evaluation that details bladder and bowel function and an examination that describes all pelvic floor defects. Procedures to treat pelvic organ prolapse or incontinence should be performed by a surgeon who regularly performs these operations (33).

Appendectomy

Appendectomy may be performed concurrently with hysterectomy to prevent appendicitis and to remove disease that may be present. The former use is of limited value because the peak incidence of appendicitis is between 20 and 40 years of age,

whereas the peak age for hysterectomy is 10 to 20 years later. However, there is no increase in morbidity associated with appendectomy performed at the time of hysterectomy.

Cholecystectomy

Gallbladder disease is about four times more common in women than men, and its highest incidence occurs between 50 and 70 years of age, when hysterectomy is most often performed. Women may require both procedures and a combined procedure does not appear to result in increased febrile morbidity or length of hospital stay.

Abdominoplasty

Abdominoplasty performed at the time of hysterectomy is associated with a shorter hospital stay, a shorter operating time, and a lower intraoperative blood loss than when the two operations are performed separately. Liposuction can be performed safely at the time of hysterectomy.

Tissue Extraction Techniques

Morcellation of the enlarged uterus has allowed minimally invasive approaches to hysterectomy. This can be accomplished by simple scalpel or with a power morcellator. The U.S. Food and Drug Administration (FDA) has discouraged the use of a power morcellator because of concerns of prognosis if the tissue contains uterine sarcomas (34). Following FDA communications, utilization of minimally invasive approaches has decreased in patients that have a large uterus that cannot be easily delivered vaginally. The frequency of supracervical hysterectomy has also decreased (35,36). However, based on many reports, including a large analysis of over 30,000 women by Pritts et al. (37), **the Agency for Healthcare Research and Quality (AHRQ) Report on the Management of Uterine Fibroids** (38) **concluded that an unexpected leiomyosarcoma will be identified in fewer than 1 and up to 13 of every 10,000 surgeries performed for symptomatic fibroids, and that it is unclear whether the type of morcellation impacts the survival of women with this poor prognosis malignancy.** Contained tissue extraction techniques have been introduced in the belief that this could reduce the risk of power morcellation of the large uterus (39). Uterine morcellation is still widely used with vaginal extraction (40).

Choice of Surgical Access: Vaginal, Abdominal, or Laparoscopic Hysterectomy

Increased utilization of the minimally invasive approach to hysterectomy by laparoscopy or robotic assistance has decreased hysterectomy rates by laparotomy. Vaginal hysterectomy rates have been stable. There are no specific criteria that can be used to determine the route of hysterectomy. **The route chosen should be based on the**

individual patient, but the vaginal approach is preferred, when feasible. Characteristics that make the vaginal approach more challenging include a narrow pubic arch (less than 90 degrees), a narrow vagina (narrower than two fingerbreadths, especially at the apex), and uterine immobility. The presence of an adnexal mass, cul-de-sac disease, pelvic adhesions, or the assessment of chronic pain may require the addition of laparoscopy for assessment. A previous cesarean section or nulliparity does not contraindicate a vaginal approach (Table 27-2) (41).

Table 27-2 General Factors Influencing the Route of Hysterectomy for Benign Disease

• Vaginal shape and accessibility to the uterus
• Uterine size and shape
• Extent of extrauterine disease and need for concurrent procedures
• Other clinical factors[a]
• Surgeon competence and available support facilities
• Preference of the informed patient

[a]Examples include accessibility of laparoscopy or laparotomy as with prior abdominoplasty or hernia repair, hip disease limiting leg abduction, anesthesia issues, morbid obesity, other factors.

Table 27-3 Comparison of Three Approaches to Hysterectomy for Benign Gynecologic Disease

Vaginal hysterectomy compared with abdominal hysterectomy Shorter return to normal activities (mean difference –9.5 days, 95% CI –12.6 to –6.4)
Laparoscopic hysterectomy compared with abdominal hysterectomy Shorter return to normal activities (mean difference –13.6 days, 95% CI –15.4 to –11.8) More urinary tract injuries (odds ratio [OR] 2.4, 95% CI 1.2 to 4.8)
Laparoscopic hysterectomy compared with vaginal hysterectomy No evidence of a difference between the groups for any primary outcomes
Robotic-assisted laparoscopic hysterectomy compared with laparoscopic hysterectomy No evidence of a difference between the groups for any primary outcomes

Data from **Aarts JWM, Nieboer TE, Johnson M, et al.** Surgical approach to hysterectomy for benign gynecological disease. *Cochrane Database Syst Rev* 2015;(8):CD003677.

[2] A systematic review validated the perception that vaginal hysterectomy is the surgical route of choice for hysterectomy (42). There were 24 manuscripts comparing laparoscopic with vaginal hysterectomy. Outcomes and complications were similar with vaginal hysterectomy, which is a less expensive approach. Vaginal hysterectomy has fewer perioperative complications compared with laparoscopic or robotic approaches, with laparotomy having the highest (43). **Cost-analysis trials demonstrate that**

laparoscopic hysterectomy can be cost-effective relative to the abdominal approach but not compared with vaginal hysterectomy (44). **[3] Robotic surgery has shown no advantage over the conventional laparoscopic approach for hysterectomy (Table 27-3) 45).**

The practice style and personal preferences of surgeons probably play a significant role in selection of hysterectomy type. With appropriate evidence-based treatment guidelines and adequate surgical education and skill, the proportion of hysterectomies performed vaginally can be increased (46,47). Adopting published guidelines for choosing the route of hysterectomy increased the proportion of hysterectomies performed vaginally to over 90% and reduced the ratio of abdominal to vaginal hysterectomy from 3:1 to 1:11 (48).

PERIOPERATIVE CHECKLIST

It is important to systematically perform a checklist of perioperative measures to effectively reduce potential complications (Table 27-4). If excessive blood loss is expected, intraoperative blood salvage techniques should be considered. All patients undergoing hysterectomy for benign disorders are at (at least) moderate risk for venous thromboembolism and require prophylaxis (20). Mechanoprophylaxis (intermittent pneumatic compression devices) or chemoprophylaxis (unfractionated *heparin* or low–molecular-weight *heparin*) or a combination of chemoprophylaxis and mechanoprophylaxis are indicated, depending on the patient's risk. Patients on oral contraceptives up to the time of hysterectomy should be considered for chemoprophylaxis. Minimally invasive hysterectomy is associated with a decreased incidence of venous thromboembolism. However, prolonged operative time may dampen the benefit (49). Mechanical bowel preparation for prevention of infection complications from bowel injury is not recommended (50).

Table 27-4 Perioperative Checklist

1. Is the informed consent signed specifically stating the disposition of the ovaries?
2. Is cervical cancer screening up to date?
3. Documentation that future fertility is not desired
4. Documentation of laboratory results indicating that the patient is not pregnant
5. Are blood products available if needed?
6. Appropriate antibiotic selected according to American College of Obstetricians and Gynecologists guidelines
7. Was the appropriate prophylaxis for venous thromboembolic events chosen?

8. Document that prophylactic antibiotics will be discontinued within 24 hrs after surgery
9. Documentation of discontinuing the Foley catheter within 24 hrs

TECHNIQUE

Abdominal Hysterectomy

General Preparation

Surgical site infections occur in 2% of hysterectomies. Obesity, diabetes, smoking, steroid use, poor nutrition and prior surgery all increase the risk (51). Excellent glycemic control in diabetics can lower the frequency of infection in this population. To reduce the colony count of skin bacteria, the patient is asked to wash or bathe with chlorhexidine preoperatively (51). Although treating all patients with bacterial vaginosis may decrease vaginal cuff cellulitis, universal screening preoperatively awaits further clinical trials (51). Hair surrounding the incision area may be removed at the time of surgery with a hair clipper. The area should not be shaved.

Preoperative antibiotics are given, typically a single dose 30 to 60 minutes before skin incision. Cefazolin 1 to 2 g and increased to 3 g for obese patients is recommended. Alternatives should be given for patients with severe penicillin allergies. Redosing is recommended after 3 hours of surgery and with excessive bleeding (52).

Skin Preparation

Chlorhexidine-alcohol–based skin preparations have a lower odds of surgical site infection compared with povidone-iodine preparations. Concentrations of 4% or less can be used in the vagina (51).

Patient Positioning

For most abdominal cases, the patient is placed in the dorsal supine position for the operation. After the patient is anesthetized adequately, her legs are placed in the stirrups and a pelvic examination is performed to validate the in-office pelvic examination findings. A Foley catheter is placed in the bladder, and the vagina is cleansed with a chlorhexidine alcohol or iodine solution. The patient's legs are straightened.

Surgical Technique

Incision

The choice of incision should be determined by the following considerations:

1. Simplicity of the incision

2. Need for exposure
3. Potential need for enlarging the incision
4. Strength of the healed wound
5. Cosmetics of the healed incision
6. Location of previous surgical scars

The skin is opened with a scalpel, and the incision is carried down through the subcutaneous tissue and fascia. With traction applied to the lateral edges of the incision, the fascia is divided. The peritoneum is opened similarly. This technique minimizes the possibility of inadvertent enterotomy while entering the abdominal cavity.

Abdominal Exploration

Cytologic sampling of the peritoneal cavity, if needed, should be performed before abdominal exploration. The upper abdomen and the pelvis are explored systematically. The liver, gallbladder, stomach, kidneys, para-aortic lymph nodes, and large and small bowel should be examined and palpated.

Retractor Choice and Placement

A variety of retractors were designed for pelvic surgery. The Balfour and the O'Connor–O'Sullivan retractors are used most often. The Bookwalter retractor has a variety of adjustable blades that can be helpful, particularly in obese patients. **Figure 27-1** demonstrates pertinent anatomy.

Elevation of the Uterus

The uterus is elevated by placing broad ligament clamps at each cornu so that it crosses the round ligament **(Fig. 27-2 inset)**.

Round Ligament Ligation or Transection

The uterus is deviated to the patient's left side, stretching the right round ligament. With the proximal portion held by the broad ligament clamp, **the distal portion of the round ligament is ligated with a suture ligature or simply transected with an electrosurgical device (Fig. 27-2)**. The distal portion can be grasped with forceps, and the round ligament is cut to separate the anterior and posterior leaves of the broad ligament. **The anterior leaf of the broad ligament is incised with Metzenbaum scissors or electrosurgery along the vesicouterine fold, separating the peritoneal reflection of the bladder from the lower uterine segment (Fig. 27-2).**

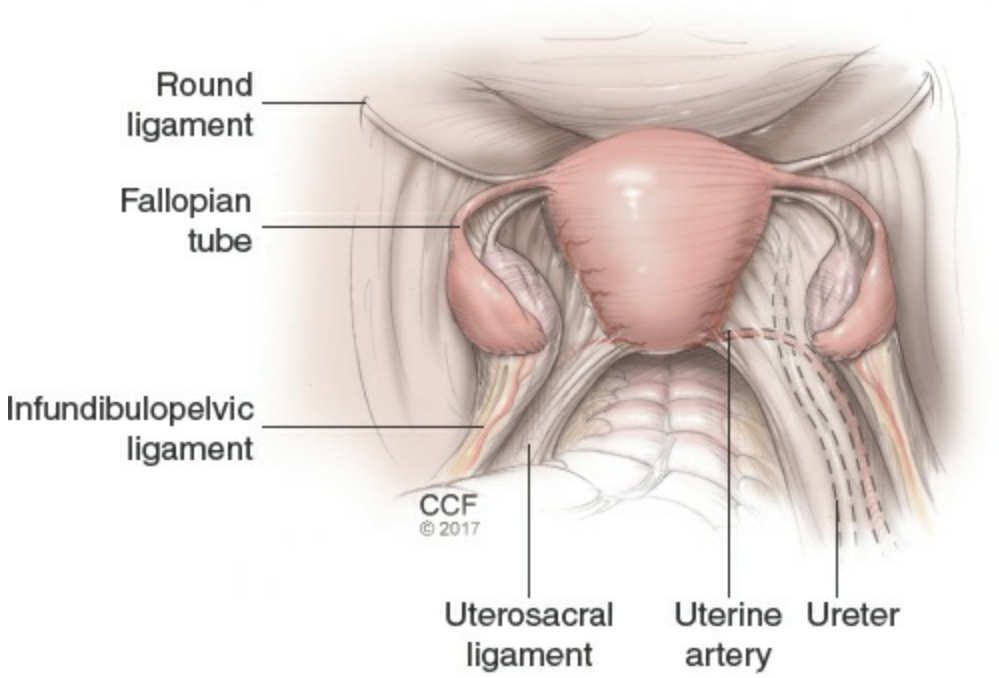


FIGURE 27-1 Surgical view of pertinent anatomy in abdominal and laparoscopic hysterectomy.

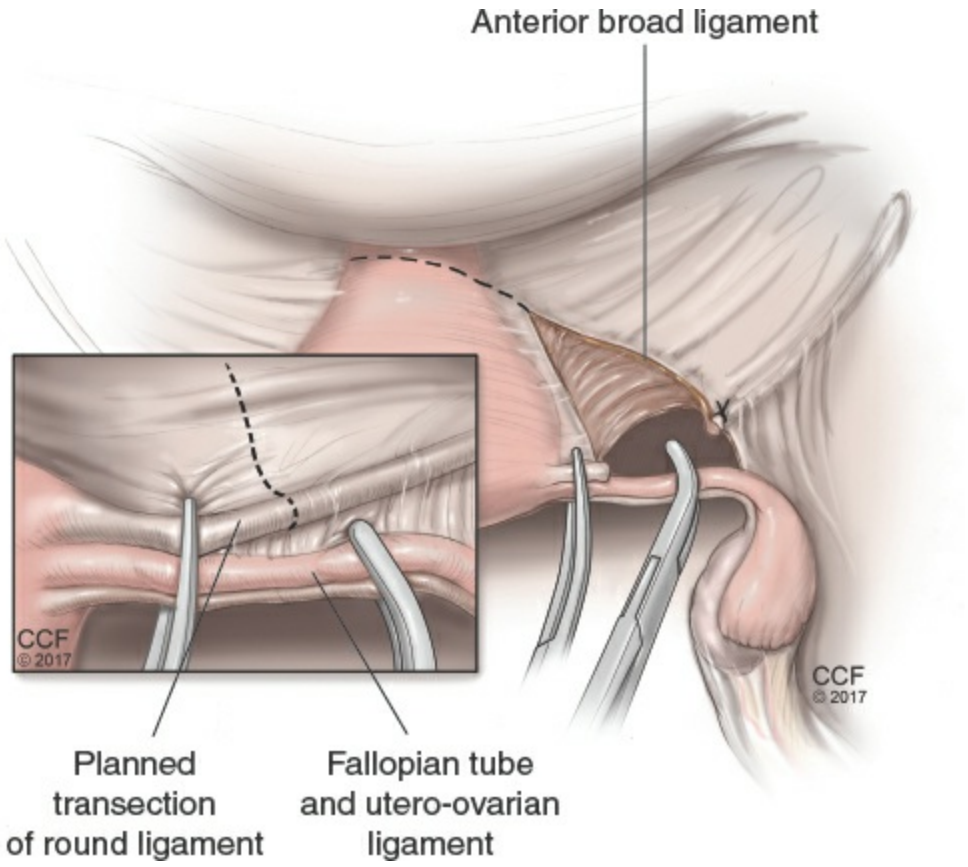


FIGURE 27-2 The uterus is elevated by placement of clamps across the round and utero-ovarian ligaments. The round ligament is transected and the anterior broad ligament is incised and opened (*inset*).

Ureter Identification

The retroperitoneum is entered by extending the incision cephalad on the posterior leaf of the broad ligament. Care must be taken to remain lateral to the infundibulopelvic ligament and iliac vessels. The external iliac artery courses along the medial aspect of the psoas muscle and is identified by bluntly dissecting the loose alveolar tissue overlying it. **By following the artery cephalad to the bifurcation of the common iliac artery, the ureter is identified crossing the common iliac artery. The ureter should be left attached to the medial leaf of the broad ligament to protect its blood supply (Fig. 27-3).**

Utero-Ovarian Vessel and Ovarian Vessel (Infundibulopelvic Ligament) Ligation

If the ovaries are to be preserved, the uterus is retracted toward the pubic symphysis and deviated to one side, placing tension on the contralateral ovarian vessels (also called infundibulopelvic ligament), the tube, and the ovary. **If the fallopian tube is taken, the mesosalpinx is incised with progressive clamping, cutting, and ligating.** The tube is left attached to the uterus. With the ureter under direct visualization, the utero-ovarian ligaments are clamped on each side with a curved Heaney or Ballantine clamp, cut, and ligated with a free-tie and a suture ligature. The medial clamp at the uterine cornua should control back bleeding; if it does not, the clamp should be repositioned to do so **(Fig. 27-3A)**.

If the ovaries are to be removed, the peritoneal opening is enlarged and extended cephalad to the ovarian vessels (infundibulopelvic ligament) and caudad to the uterine artery. This opening allows proper exposure of the uterine artery, the ovarian vessels, and the ureter. In this manner, the ureter is released from its proximity to the uterine vessels and ovarian vessels. A curved Heaney or Ballantine clamp is placed lateral to the ovary **(Fig. 27-3B)**; care is taken to ensure that the entire ovary is included in the surgical specimen.

Bladder Mobilization

Using Metzenbaum scissors or an electrosurgical device, the bladder is dissected from the lower uterine segment and cervix. An avascular plane, which exists between the lower uterine segment and the bladder, allows for this mobilization. Tonsil clamps may be placed on the bladder edge to provide counter traction and easier dissection.

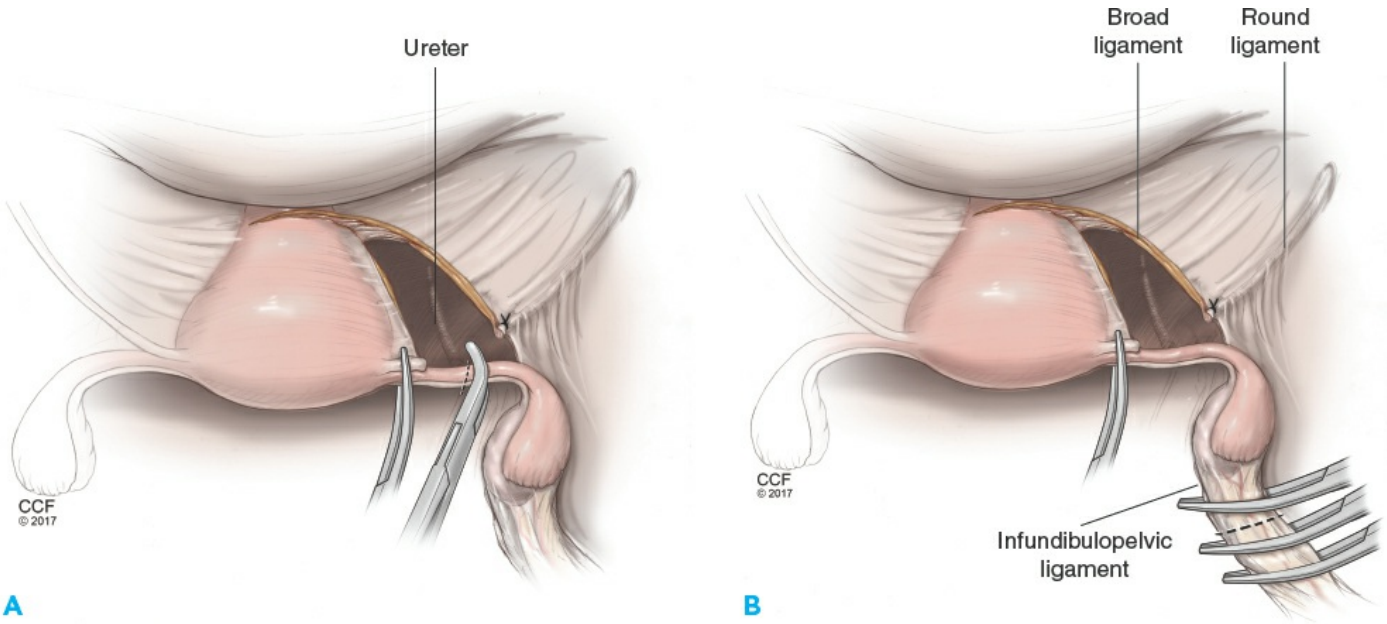


FIGURE 27-3 The incision in the anterior broad ligament is extended along the vesicouterine peritoneal fold. When an ovarian-sparing hysterectomy is planned, the utero-ovarian ligament is cross-clamped (**A**). When bilateral salpingo-ophorectomy is planned, the infundibuloligament is cross-clamped (**B**).

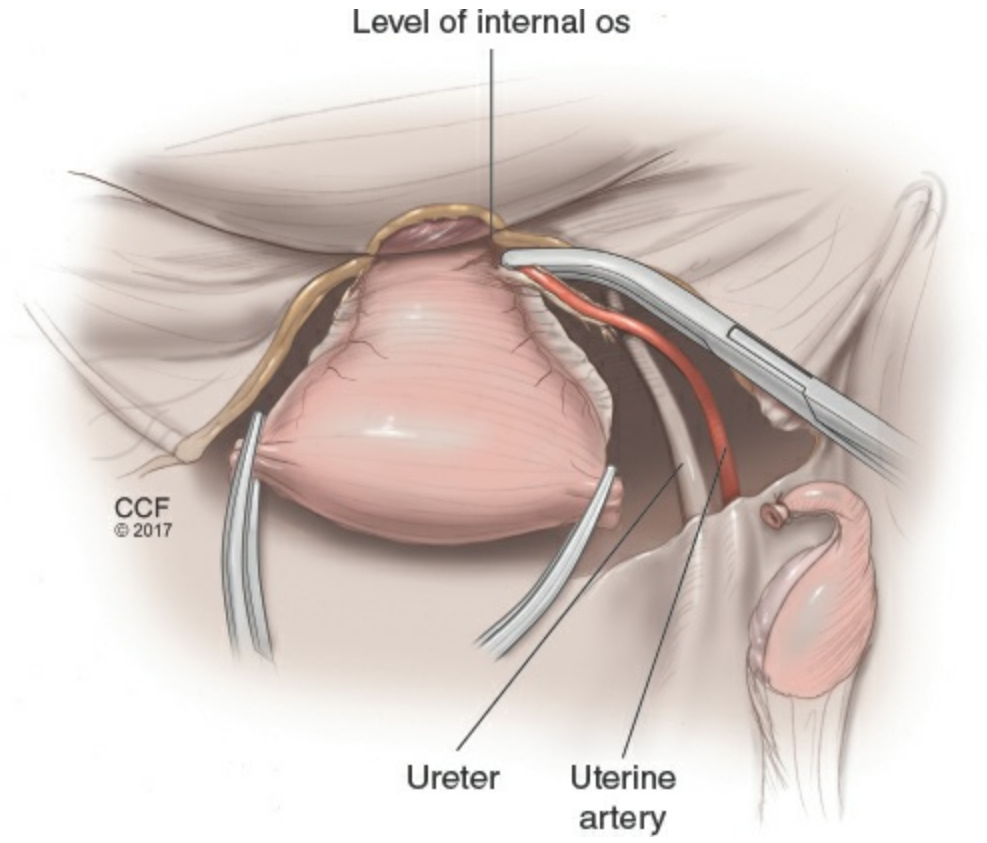


FIGURE 27-4 Identification of the ureter in the retroperitoneal space on the medial leaf of the broad ligament. The course of the ureter is traced and the uterine vessels are skeletonized prior to ligating the uterine vessels.

Uterine Vessel Ligation

The uterus is retracted cephalad and deviated to one side of the pelvis, stretching the lower ligaments. **The uterine vasculature is dissected or "skeletonized" from any remaining areolar tissue, and a curved Zeppelin or Heaney clamp is placed perpendicular to the uterine artery at the junction of the cervix and body of the uterus.** Care is taken to place the tip of the clamp adjacent to the uterus at this anatomic narrowing (Fig 27-4). The vessels are cut, and the pedicle is ligated.

The same procedure, beginning with the round ligament is repeated on the contralateral side.

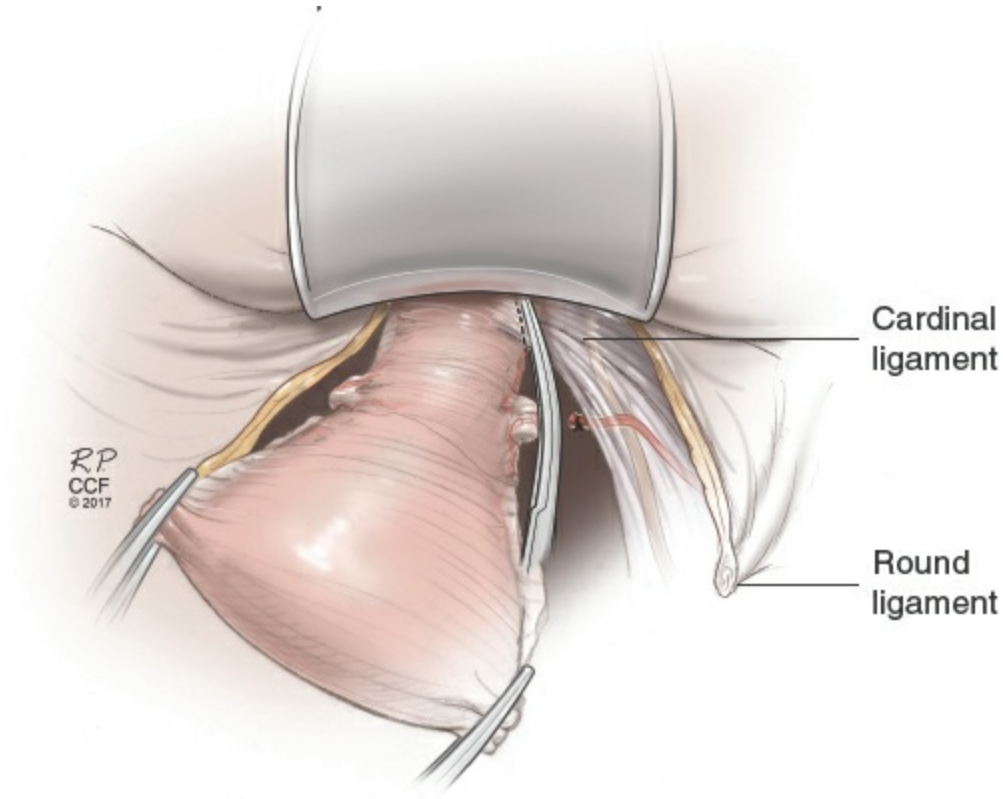


FIGURE 27-5 Ligation of the cardinal and uterosacral ligaments.

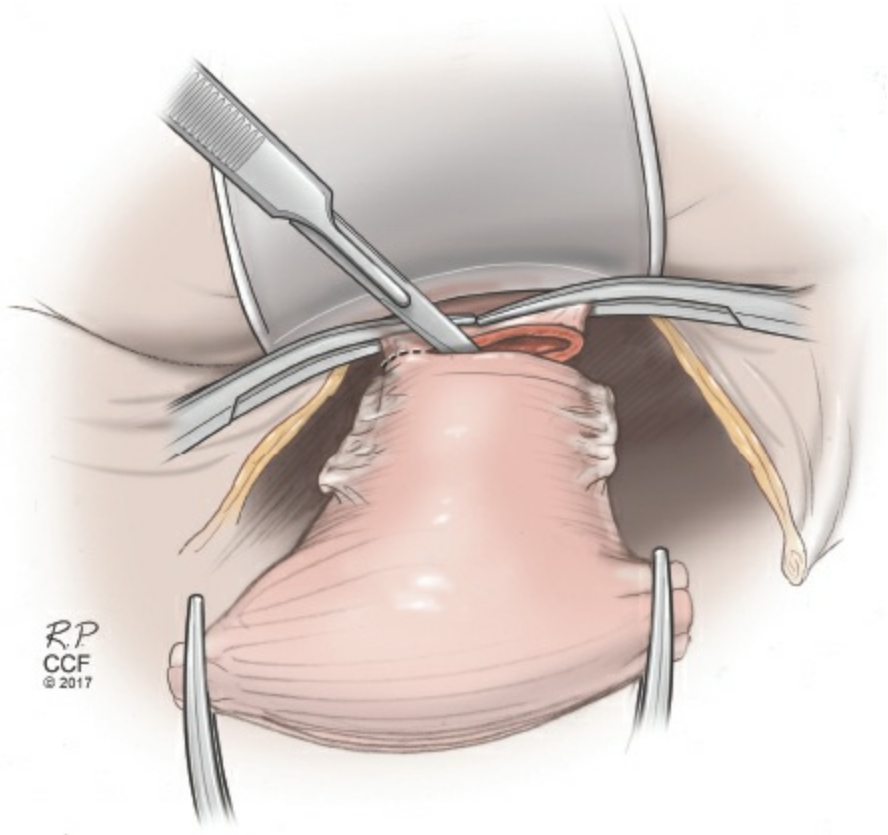


FIGURE 27-6 Removal of the uterus by transection of the vagina.

Incision of Posterior Peritoneum

If the rectum is to be mobilized from the posterior cervix, the posterior peritoneum between the uterosacral ligaments just beneath the cervix and rectum may be incised. A relatively avascular tissue plane exists in this area, allowing mobilization of the rectum inferiorly out of the operative field.

Cardinal Ligament Ligation

The cardinal ligament is divided by placing a straight Zeppelin or Heaney clamp medial to the uterine vessel pedicle for a distance of 2- to 3-cm parallel to the uterus. The ligament is cut, and the pedicle is suture ligated. This step is repeated on each side until the junction of the cervix and vagina is reached **(Fig. 27-5)**.

Removal of the Uterus

The uterus is placed on traction cephalad, and the tip of the cervix is palpated. Curved Heaney clamps are placed bilaterally, incorporating the uterosacral ligament and upper vagina just below the cervix. Care should be taken to avoid foreshortening the vagina. The uterus is removed with scalpel or curved scissors **(Fig. 27-6)**.

Vaginal Cuff Closure

A figure-of-eight suture of 0 braided absorbable material is placed at the angle of the vagina for traction and hemostasis. **The pedicles are sutured with a Heaney stitch, incorporating the uterosacral and cardinal ligament at the angle of the vagina (Fig. 27-7).** A running-locked or figure-of-eight sutures can be used for hemostasis along the cuff edge **(Fig. 27-7)**.

Irrigation and Hemostasis

The pelvis is thoroughly irrigated with saline. Meticulous hemostasis in the pelvis, particularly of the vascular pedicles, should be ensured. Ureteral position and integrity are checked to ensure that they are intact and do not appear dilated.

Peritoneal Closure and Fascia Closure

The pelvic peritoneum is not reapproximated. The parietal peritoneum is not reapproximated as a separate layer. **Fascia can be closed with an interrupted or continuous 0 or 1 monofilament absorbable suture.** A prospective randomized trial did not show any advantage of interrupted versus continuous fascial closure (53). Bites should be taken about 1 cm from the cut edge of the fascia and about 1 cm apart to prevent wound dehiscence.

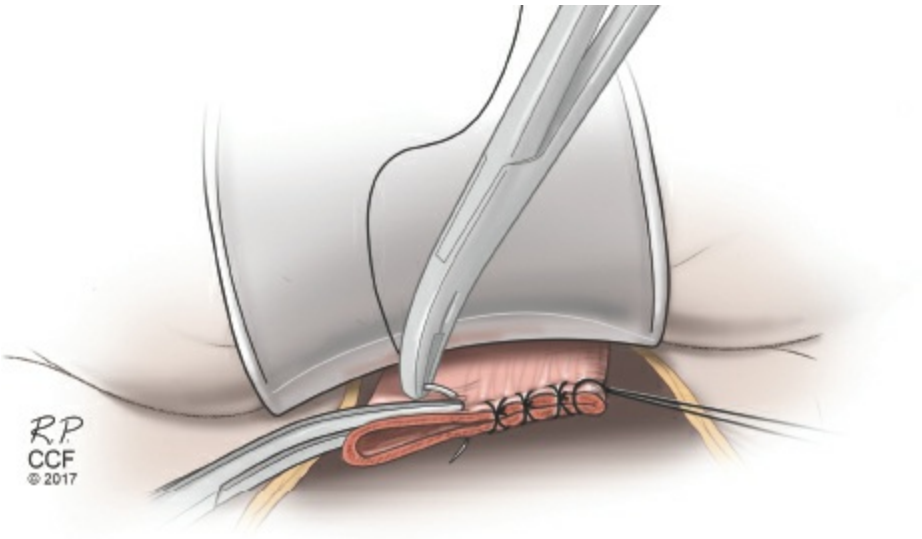


FIGURE 27-7 Vaginal cuff closure incorporating the uterosacral and cardinal ligaments.

Skin Closure

The subcutaneous tissue should be irrigated, with careful hemostasis. Wound disruption seems to be decreased with closure of the subcutaneous fat layer in women with 2 cm or more fat (54). Skin staples or subcuticular sutures are used to reapproximate the skin edges. A dressing is applied and left in place for about 24 hours.

Intraoperative Complications

Every surgeon must be prepared to recognize and repair operative injuries, because

despite a high level of attention to detail, injuries and complications, recognized and unrecognized, can still occur.

Ureteral Injuries

Ureter injuries usually occur at three separate areas: at the pelvic brim as it crosses over the common iliac vessels, in the midpelvis as the uterine artery crosses over it, and near the cervix at the internal os. Most ureteral injuries can be avoided by opening the retroperitoneum and directly identifying the ureter. The use of ureteral catheters as a substitute for direct visualization is often of little help in patients with extensive fibrosis or scarring resulting from endometriosis, pelvic inflammatory disease, or ovarian cancer. In these instances, a false sense of security may increase an already high risk for ureteral injury. The use of ureteral catheters is associated with hematuria and acute urinary retention, although their complications are usually temporary in nature.

Direct visualization is accomplished by opening the retroperitoneum lateral to the external iliac artery. Blunt dissection of the loose areolar tissue is performed to visualize the artery directly. The artery may be traced cephalad to the bifurcation of the internal and external iliac arteries. The ureter crosses the common iliac artery at its bifurcation and may be followed throughout its course in the pelvis.

Despite these precautions, ureteral injuries may occur. Prompt consultation is necessary if the surgeon is not trained in ureteral repair. If a ureteral obstruction is suspected, confirmation may be obtained by intravenous injection of sodium fluorescein or indigo carmine followed by cystoscopy to demonstrate a brilliant colored ureteral jet minutes after injection. The integrity of the ureters should be confirmed by the presence or absence of bilateral spill of tinted urine. Thermal injury is not usually detected with this test and may present days after the hysterectomy.

Bladder Injury

Because of the close anatomic relationship of the bladder, uterus, and upper vagina, the bladder is the segment of the lower urinary tract that is most vulnerable to injury. Bladder injury may occur on opening the peritoneum or, more frequently, during the dissection of the bladder off the cervix and upper vagina. **Unless there is involvement of the bladder trigone, a bladder laceration is easily repaired.** In the nonirradiated bladder, a one- or two-layer closure with a small-caliber braided absorbable suture such as a 3-0 polyglycolic acid is adequate. The bladder should be drained postoperatively. The length of time that drainage is required is controversial. If the bladder is not compromised, drainage should be continued at least until gross hematuria clears, which may occur as soon as 48 hours postoperatively. A more conservative practice is to continue drainage for 3 to 14 days, depending on the type of injury.

The use of routine cystoscopy to diagnose an unsuspected ureter or bladder injury has

been proposed by several groups. In low-risk patients that do not undergo pelvic floor procedures the probability of identifying an unsuspected injury is small (55).

Bowel Injury

Small bowel injuries are the most common intestinal injuries in gynecologic surgery. **Small defects of the serosa or muscularis may be repaired using a single layer of continuous or interrupted 3-0 braided absorbable suture.** Although single-layer closure of the small bowel has proved adequate, it is safer to close defects involving the lumen in two layers using a 3-0 braided absorbable suture. The defect should be closed in a direction perpendicular to the intestinal lumen. If a large area is injured, resection with reanastomosis may be necessary. The transverse colon rarely is injured in normal gynecologic procedures because it is well outside the operative field. However, the descending colon and the rectosigmoid colon are intimately involved with the pelvic structures and are at significant risk for injury during gynecologic surgery. Injuries not involving the mucosa may be repaired with a single running layer of 2-0 or 3-0 braided absorbable suture. If the laceration involves the mucosa, it may be closed as with small bowel injuries.

Hemorrhage

Significant arterial bleeding usually arises from the uterine arteries or the ovarian vessels near the insertion of the infundibulopelvic ligaments. Blind clamping of these vessels presents a risk for ureteral injury; therefore, the ureters should be identified in the retroperitoneal space and traced to the area of bleeding to avoid inadvertent ligation. It is best to apply a pressure pack to tamponade the bleeding and slowly remove the pack in an effort to visualize, isolate, and individually clamp the bleeding vessels. Mass ligatures should be avoided. The use of surgical clips may be helpful. Venous bleeding is less dramatic but often is more difficult to manage, particularly in the presence of extensive adhesions and fibroids. This type of bleeding can be controlled with pressure alone or with suture ligation. Bleeding from peritoneal edges or denuded surfaces may be controlled with pressure, application of topical agents such as thrombin or collagen, or electrosurgery.

Postoperative Management

Bladder Drainage

Overdistention of the bladder resulting from bladder trauma or the patient's reluctance to initiate the voluntary phase of voiding is one of the most common complications after abdominal hysterectomy. **An indwelling bladder catheter can be used for the first few postoperative hours until the patient is able to ambulate and urinate but should be removed within 24 hours.** If urogynecologic procedures such as a retropubic urethropexy are performed, a catheter may be needed for a longer period of time. This

catheter may be removed when satisfactory postvoid residual levels of less than 100 mL are obtained.

Postoperative Pain Management

Postoperative pain control is a critical part of a satisfactory surgical outcome. Ideally, it starts perioperatively and is initiated at any time before the hysterectomy is completed as surgical length and intraoperative blood loss are not affected (56). Although hospital length of stay is not affected by the use of preemptive analgesia, it decreases the use of postoperative opioid analgesics and improves pain assessment. The recommended medications for preemptive use are gabapentin, acetaminophen, and COX-2 inhibitors. Preemptive opioids such as fentanyl resulted in lower postoperative pain scores and use of opioids. In patients with a higher risk of nausea and vomiting preemptive antiemetics such as promethazine should be administered.

Diet

As soon as the patient is alert, diet is resumed, offering solid foods as tolerated with return of appetite. **Early postoperative feeding was shown to be safe and to speed return of bowel function and recovery.**

Activity

Early ambulation decreases the incidence of thrombophlebitis and pneumonia. Patients are encouraged to begin ambulation on their first postoperative day if possible and to increase their time out of bed progressively as their strength improves. On discharge, the patient is instructed to avoid lifting more than 20 pounds for 6 weeks, thereby minimizing stress on the fascia to allow full healing. **Sexual intercourse is not recommended until at least 6 weeks after surgery, when the vaginal cuff is fully healed.** Patients are instructed to avoid driving until full mobility returns because postoperative pain and tenderness may hinder sudden braking or steering maneuvers in emergency situations. With these exceptions, the patient is encouraged to return to normal activities as soon as she feels comfortable doing so.

Wound Care

The abdominal incision normally requires little attention, except for ordinary hygienic measures. The wound is kept covered with a sterile dressing for the first 24 hours after surgery, by which time the incision has sealed. After the dressing is removed, the incision should be cleaned daily with mild soap and water and kept dry.

Vaginal Hysterectomy

Preoperative Evaluation

Evaluation of Uterine Descent, Uterine Size and Shape, and Bony Structure

The vaginal approach to hysterectomy is appropriate for many hysterectomy indications. The one disadvantage is that the vaginal approach precludes visual evaluation of the abdominal cavity. When considering vaginal hysterectomy, it is critical to determine if vaginal hysterectomy is feasible. Though the best evaluation occurs under anesthesia immediately prior to hysterectomy, office evaluation suffices in most cases. Office evaluation includes bimanual examination to assess uterine mobility, evaluation of the bony pelvis, and review of available imaging. Of these components, uterine mobility is the most important factor in determining the feasibility of a vaginal hysterectomy. Often at the initial pelvic examination, uterine descent may not be obvious. In patients with no apparent prolapse, poor pelvic support can often be demonstrated by observing descent of the uterus with a series of Valsalva or strong cough maneuvers. Although vaginal hysterectomy is easier to perform when the uterine support ligaments are lax, it is not an absolute requirement. Some surgeons advocate the practice of applying traction to the cervix with a tenaculum to demonstrate descent of an apparently well-supported uterus, however, this is not recommended as it is uncomfortable and not necessarily predictive of success of the vaginal approach to hysterectomy. Uterine size and shape should be carefully considered when contemplating whether the vaginal approach to hysterectomy is feasible. If the office examination is not adequate as a result of patient body habitus, imaging can be helpful. The most critical aspect of uterine size and shape is the width of the uterus, specifically in the lower uterine segment, because one must control the blood supply (uterine vessels) before morcellating, which is often required in an enlarged uterus. Typically, it is difficult to clamp the uterine arteries if the width of this area is >9 to 10 cm, because this width often will not allow enough descent to safely ligate these vessels. There is no firm upper limit on the vertical measurement of the uterus but most surgeons are not comfortable with the vaginal approach if the uterine size is greater than 16 to 18 weeks.

Assessment of the bony pelvis should be performed. Ideally, the angle of the pubic arch should be 90 degrees or greater and the bituberous diameter, should exceed 10 cm. The size and shape of the female pelvis contributes to increased exposure. The importance of a wide pubic arch was underscored by the result of a study of 25 failed vaginal hysterectomies that were compared with 50 successful vaginal hysterectomies. Risk factors, such as age, parity, body weight, surgical indication, uterine size, presence of leiomyomata in the anterior lower uterine segment, previous pelvic surgeries, adhesions, location and length of the cervix, and narrow pubic arch (less than 90 degrees), were examined. In the study, only the presence of a narrow pubic arch increased the risk of failed vaginal hysterectomy (57).

No additional work-up (laboratory, imaging) specific to the vaginal approach is required. In cases where the surgeon is uncertain if the vaginal approach to hysterectomy can be successfully performed, a patient may be consented for "hysterectomy, vaginal or laparoscopic/abdominal approach." A more thorough

evaluation can be performed under anesthesia and the final determination of approach can be made at the time of surgery.

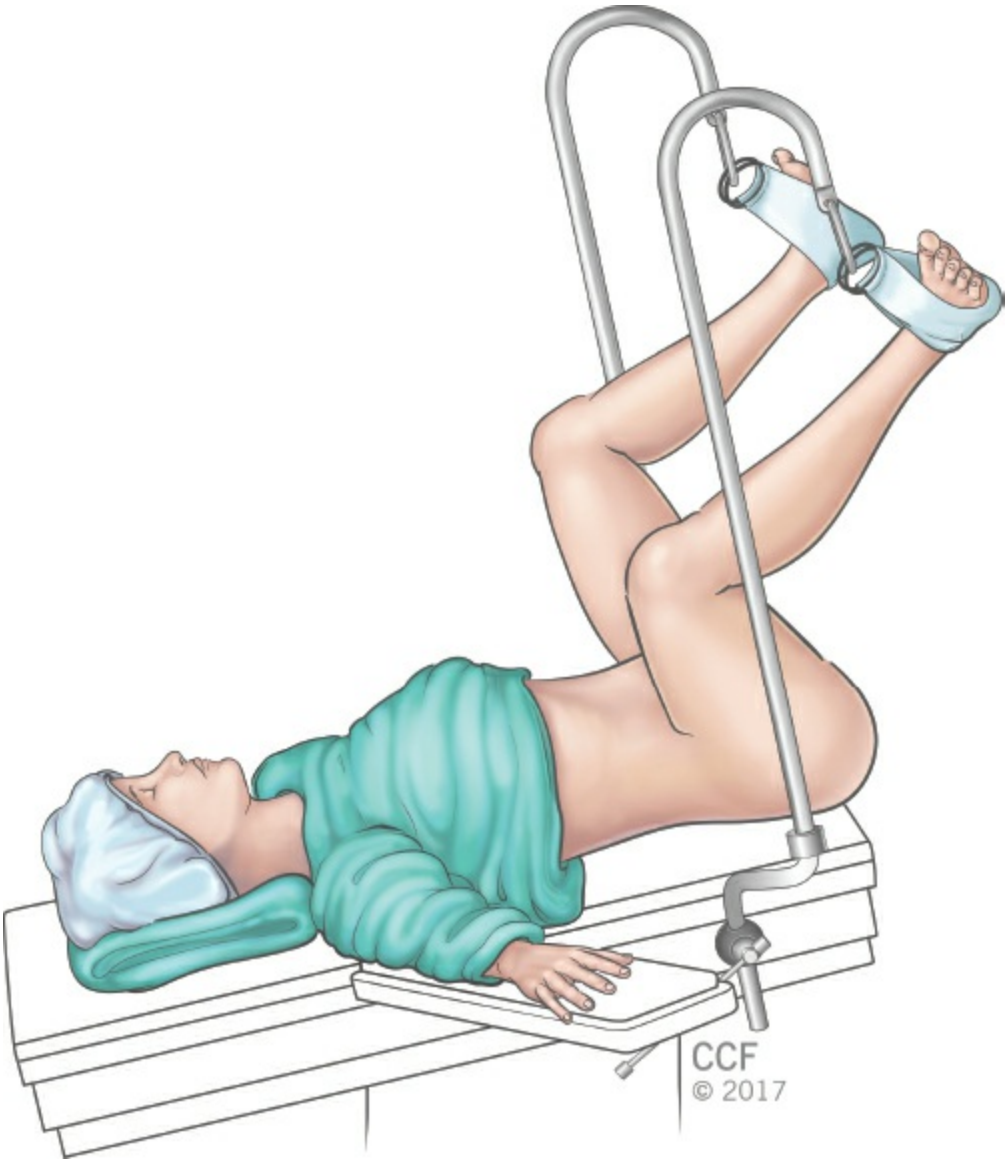


FIGURE 27-8 The patient in high lithotomy position. Care is taken to not overflex or overextend at the hips and knees.

Perioperative Considerations

Patient Positioning

When the patient is in the dorsal lithotomy position, the buttocks should be positioned just over the table's edge (Fig. 27-8). Several stirrup types are available, including those that support the entire leg and those that suspend the feet in straps. The advantage of the stirrups that suspend the feet in straps is that it allows two assistants to actively assist during the hysterectomy. **To avoid nerve injury, adequate padding should be used; flexion at the hip should be >60 degrees and flexion at the knee**

should range from 90 to 120 degrees and pressure points should be avoided. Trendelenburg (10- to 15-degree) positioning aids in the intravaginal visualization needed during surgery.

Examination Under Anesthesia and Patient Preparation

When the patient is positioned, a thorough examination under anesthesia is performed. In most cases, it is much easier to determine uterine mobility, uterine descent, and uterine size and shape at this time. A tenaculum can be placed on the cervix to thoroughly evaluate uterine descent without causing the patient discomfort.

The pubic hair is clipped from the labia majora from the clitoris to the perineal body to prevent the pubic hair from compromising the field.

A dilute 4% chlorhexidine-alcohol is applied to the vagina, vulva, mons, inner thigh, perineal, and anal areas (51). A Foley catheter is inserted into the bladder. Several methods for draping are proposed, including individual or single-piece drapes; the method chosen is at the surgeon's discretion, though an adhesive barrier surrounding the operative site should be used.

Instruments

Instruments specific to and useful in performing a vaginal hysterectomy include weighted specula, single- or double-toothed tenacula, right-angled retractors, Heaney needle holders, and Breisky–Navratil vaginal retractors. Heaney and Heaney–Ballantine hysterectomy clamps are preferable. Curved Mayo scissors, Russian pick-ups, rat-tooth pick-ups, and scissors to cut suture will also be used. Some surgeons advocate the use of a vessel-sealing device and data are accumulating. These instruments may be helpful in cases of big uteri and have been shown to decrease operative time, but increase the cost of the operation, and may not be necessary in an average case.

Lighting

Overhead high-intensity lamps should be used and positioned to direct light over the operator's shoulder. The surgeon may use a headlight, which can be worn to provide direct horizontal lighting. A fiberoptic-lighted irrigating suction system can provide additional light.

Suture Material

Various suture materials are advocated for gynecologic surgery. The type of suture material chosen is based on the surgeon's preference. A synthetic-delayed–absorbable polyglactin or polyglycolic acid suture and tapered needles are preferable.

Procedure

Grasping and Circumscribing the Cervix

A short-weighted speculum in placed in the vagina. Sidewall retractors are placed

lateral to the cervix. The anterior and posterior lips of the cervix are grasped with a single- or double-toothed tenaculum. With downward traction applied on the cervix, the locations of the bladder and posterior cul-de-sac are evaluated **(Fig. 27-9)**. **The incision should be made at least 1-cm distal to the bladder and with the goal of preserving vaginal length.** If the initial incision is made too close to the external cervical os, a greater amount of dissection is required and anterior and posterior peritoneal entry can be challenging. In cases where the bladder location cannot be determined, the Foley catheter can be manipulated, the bladder can be back-filled, or a uterine sound can be bent and inserted into the bladder. **The epithelium of the planned incision is injected with dilute local anesthetic and epinephrine.** A circumferential incision is made in the vaginal epithelium at the junction of the cervix **(Fig. 27-9)**. The incision is carried slightly toward the cul-de-sac at the posterior cervix in order to facilitate posterior entry **(Fig. 27-9 inset)**.

Dissection of Vaginal Epithelium

After the initial incision is made with a scalpel, additional dissection perpendicular to the cervix may be required to reach the right plane. The goal is to divide all tissue to the level of the cervical stroma. When the cervical stroma is reached, the vaginal epithelium may be dissected sharply from the underlying cervix using curved Mayo scissors. This will be performed circumferentially.

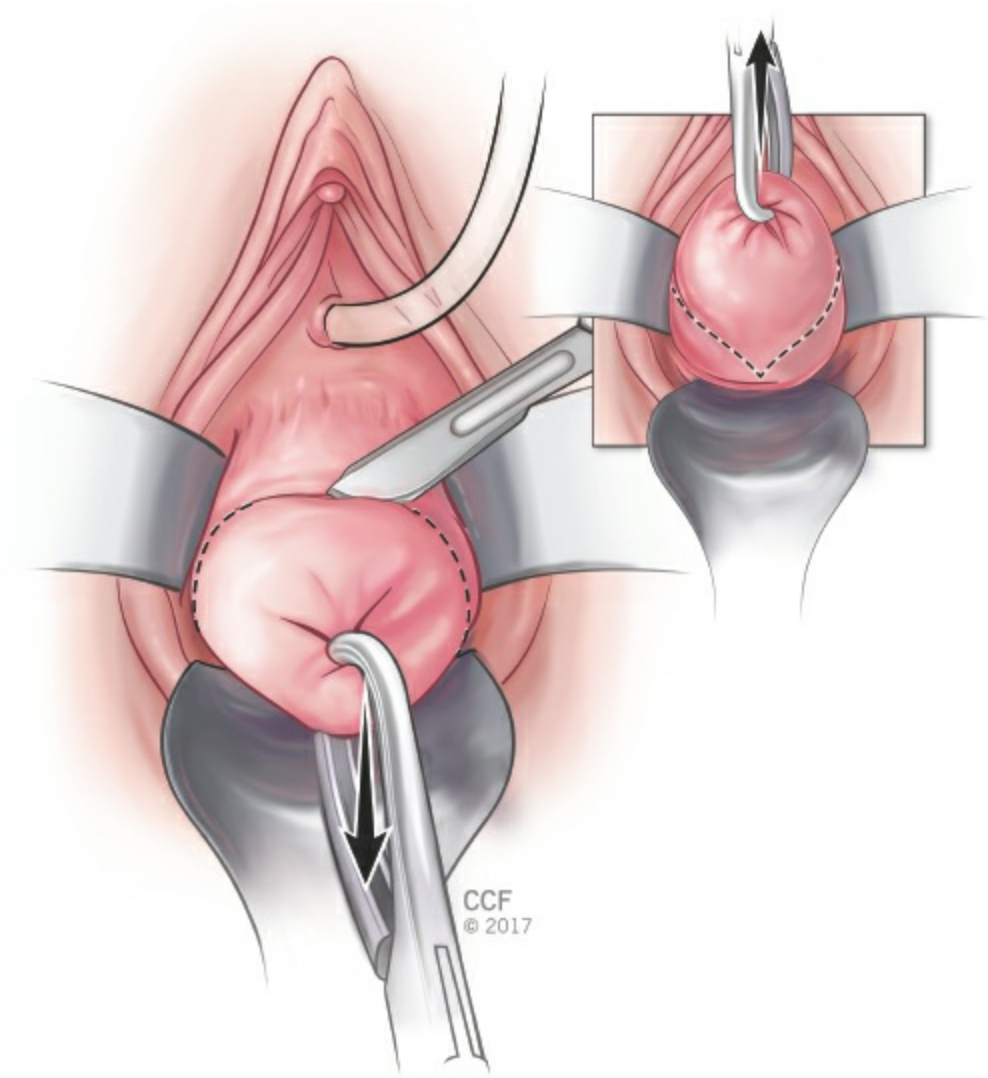


FIGURE 27-9 A tenaculum is placed on the cervix. A circumferential incision of the cervical epithelium is made.

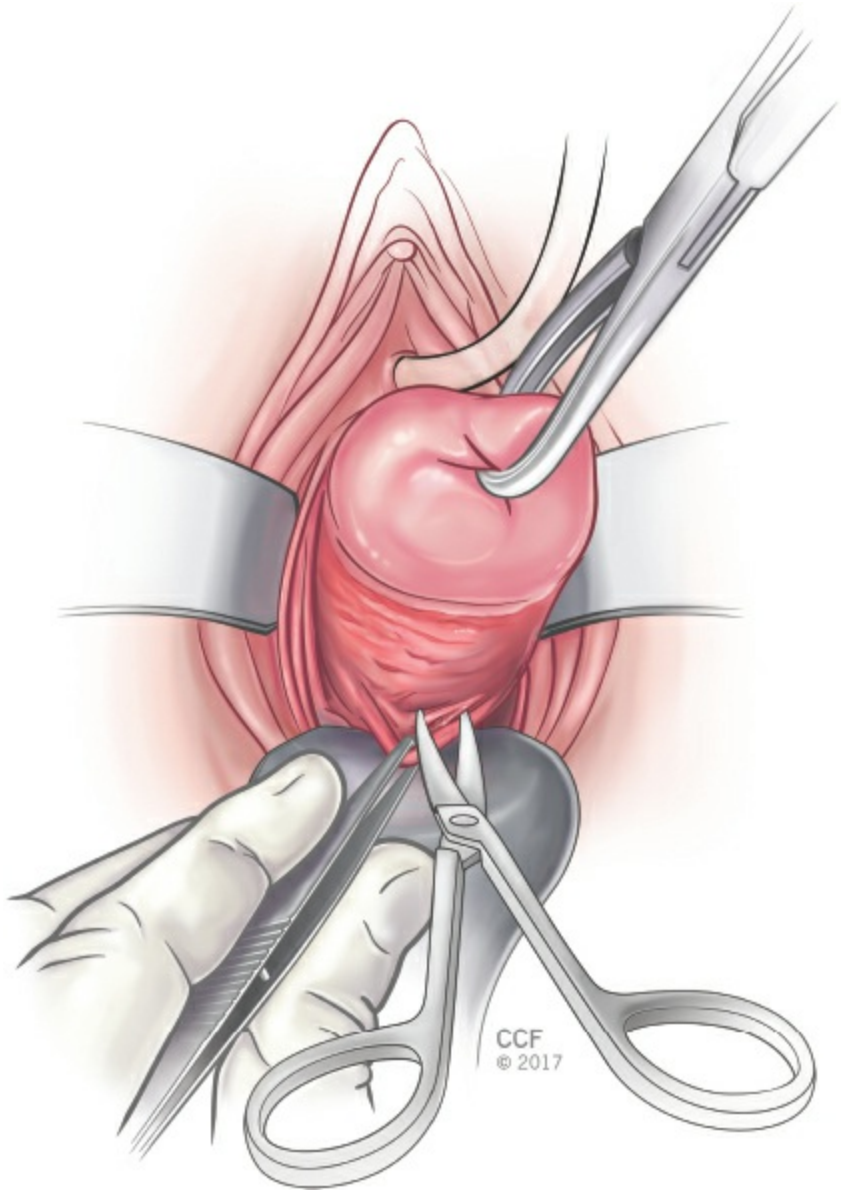


FIGURE 27-10 The posterior peritoneum is identified and entered sharply. Interrupted suture is placed on posterior vaginal cuff and peritoneum for hemostasis.

Posterior Cul-de-Sac Entry

The posterior cul-de-sac is examined and the peritoneal reflection of the posterior cul-de-sac (cul-de-sac of Douglas) is identified. The vaginal portion of the epithelium is placed on traction and the peritoneum is entered sharply **(Fig. 27-10)**. One finger is inserted to assure proper entry and the incision is extended sharply. The posterior peritoneum is secured to the posterior epithelium with a figure-of-eight suture for hemostasis and orientation. The posterior pelvic cavity is examined for pathologic alterations of the uterus or adhesive disease of the cul-de-sac.

If gaining posterior entry into the peritoneal cavity is difficult (e.g., if the cervix is elongated or the peritoneum is not evident), there are several options: (a) The hysterectomy may begin extraperitoneally by clamping and cutting the uterosacral and

cardinal ligaments close to the cervix. This will often allow additional descent and the posterior cul-de-sac will be identifiable; (b) Entry into the anterior peritoneum can be performed first, and a finger can be hooked into the posterior cul-de-sac to place tension on the peritoneum; (c) The posterior cervix and vaginal epithelium may be incised vertically (from the cervix toward the cul-de-sac) to the point at which the cul-de-sac becomes more apparent.

Uterosacral Ligament Ligation

With retraction of the lateral vaginal wall and counter traction on the cervix, the uterosacral ligaments are clamped with the tip of the clamp incorporating the lower portion of the cardinal ligaments (Fig. 27-11). The clamp is placed perpendicular to the uterine axis, with the clamp tips touching the cervix, and the pedicle is cut and sutured close to the clamp. A small pedicle (<0.5 cm) distal to the clamp is optimal because a larger pedicle becomes necrotic.

When suturing any pedicle, the needle point is placed at the tip of the clamp, and the needle is passed through the tissue by a rolling motion of the operator's wrist. The suture is moved around the back of the clamp, the needle is placed through the middle of the pedicle, and the suture is tied behind the clamp **(Fig. 27-11 inset)**. This suture is held with a hemostat to identify the most inferior pedicle and facilitate localization of any bleeding at the completion of the procedure. A long weighted speculum is placed into the abdominal pelvic cavity (Fig. 27-12).

Entry into the Vesicouterine Space (Cul-de-Sac)

Downward traction is placed on the cervix. Using Mayo scissors, with the points directed toward the uterus, the anterior dissection is performed, separating the bladder from the uterus. When the correct plane is achieved, the dissection will become much easier and gentle dissection with one's finger can be performed. If any resistance is encountered digitally, this is not the right plane and additional sharp dissection is required. After the bladder is advanced, a Heaney retractor is placed in the midline, holding the bladder out of the operative field (Fig. 27-13).

If the vesicouterine peritoneal reflection is identified at this point, it can be elevated with forceps, and the vesicouterine space may be entered sharply with scissors with tips pointed toward the uterus (Fig. 27-14). A finger is placed into the peritoneal cavity, proper entry is confirmed, and a Heaney retractor is placed between the uterus and the operator's finger (Fig. 27-15). This retractor serves to keep the bladder out of the operative field.

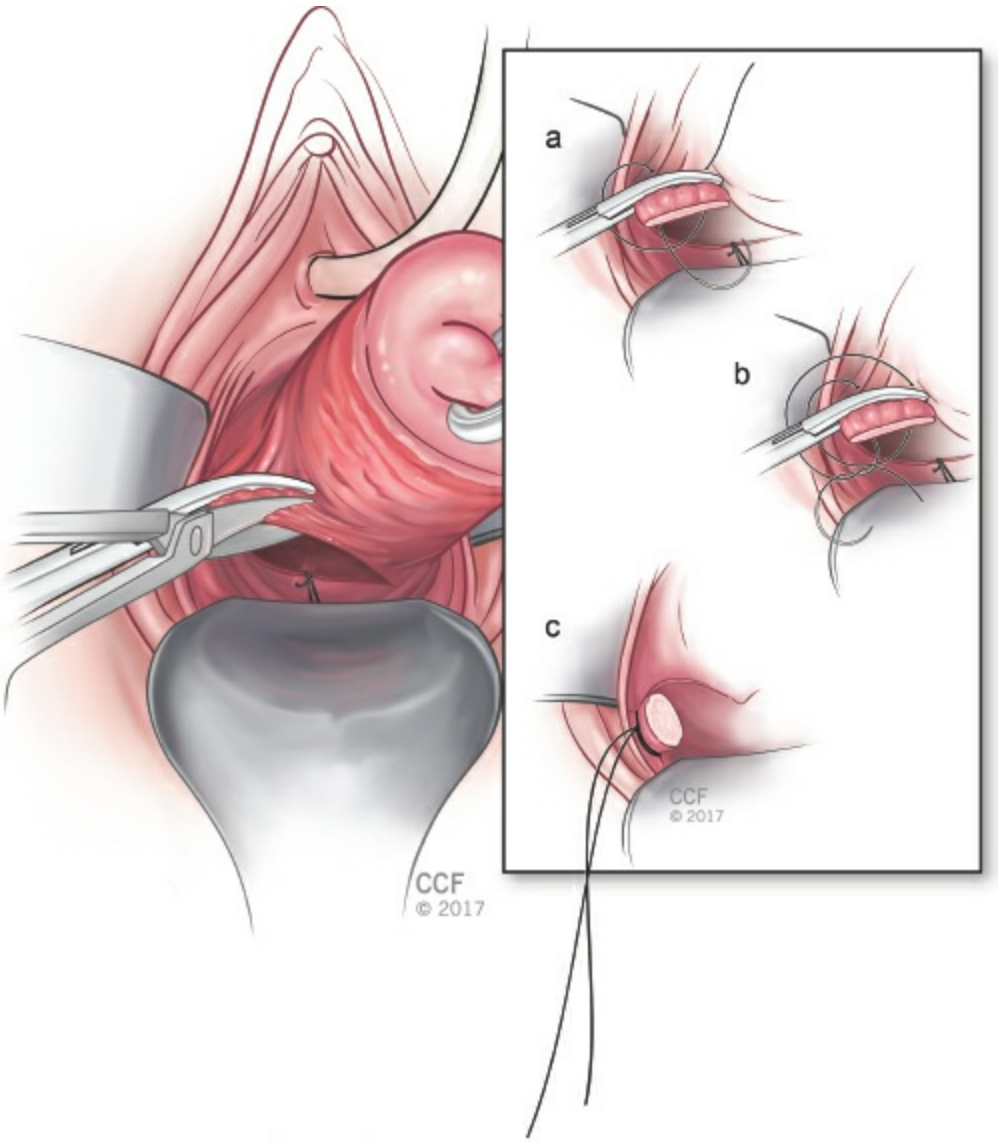


FIGURE 27-11 The uterosacral ligament is cross-clamped, transected, and suture ligated (*inset*).

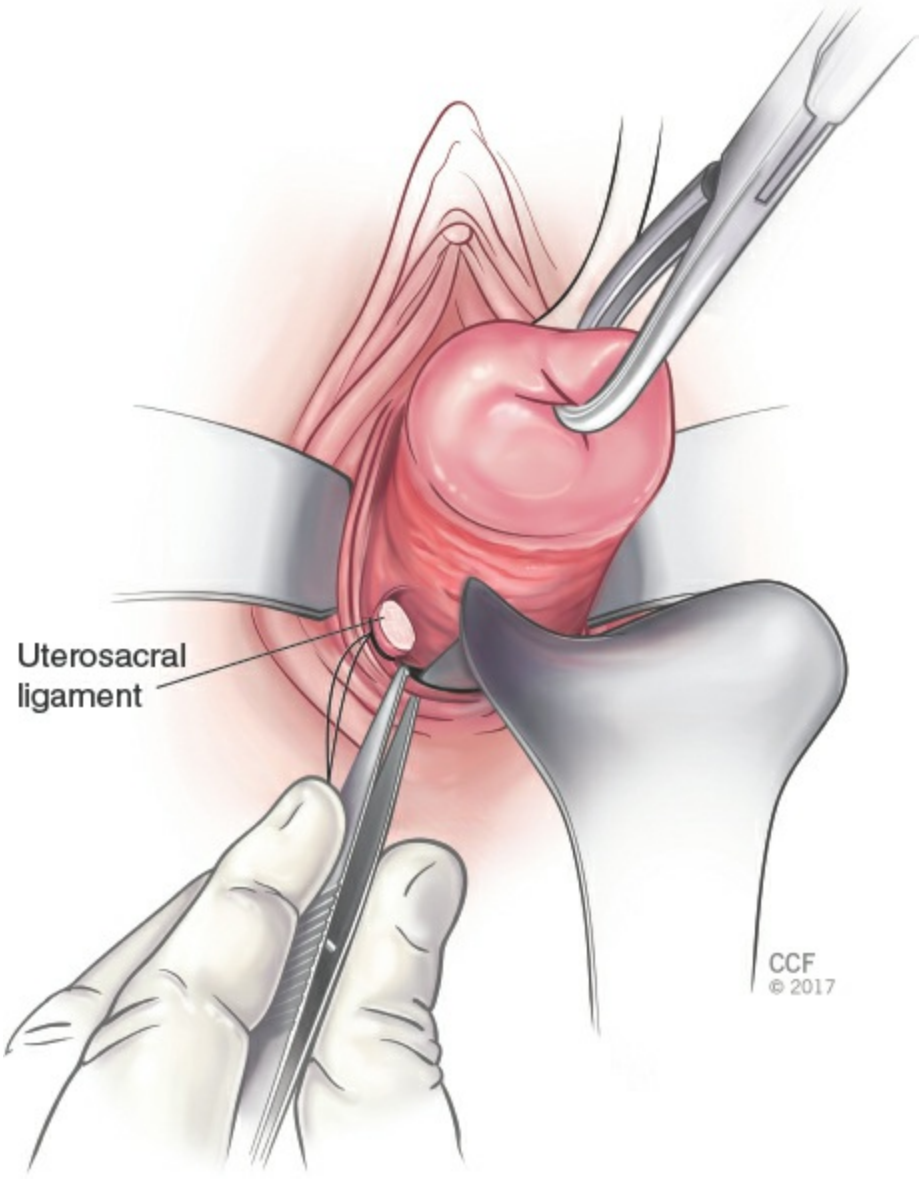


FIGURE 27-12 A long-weighted speculum is placed in the peritoneal cavity.

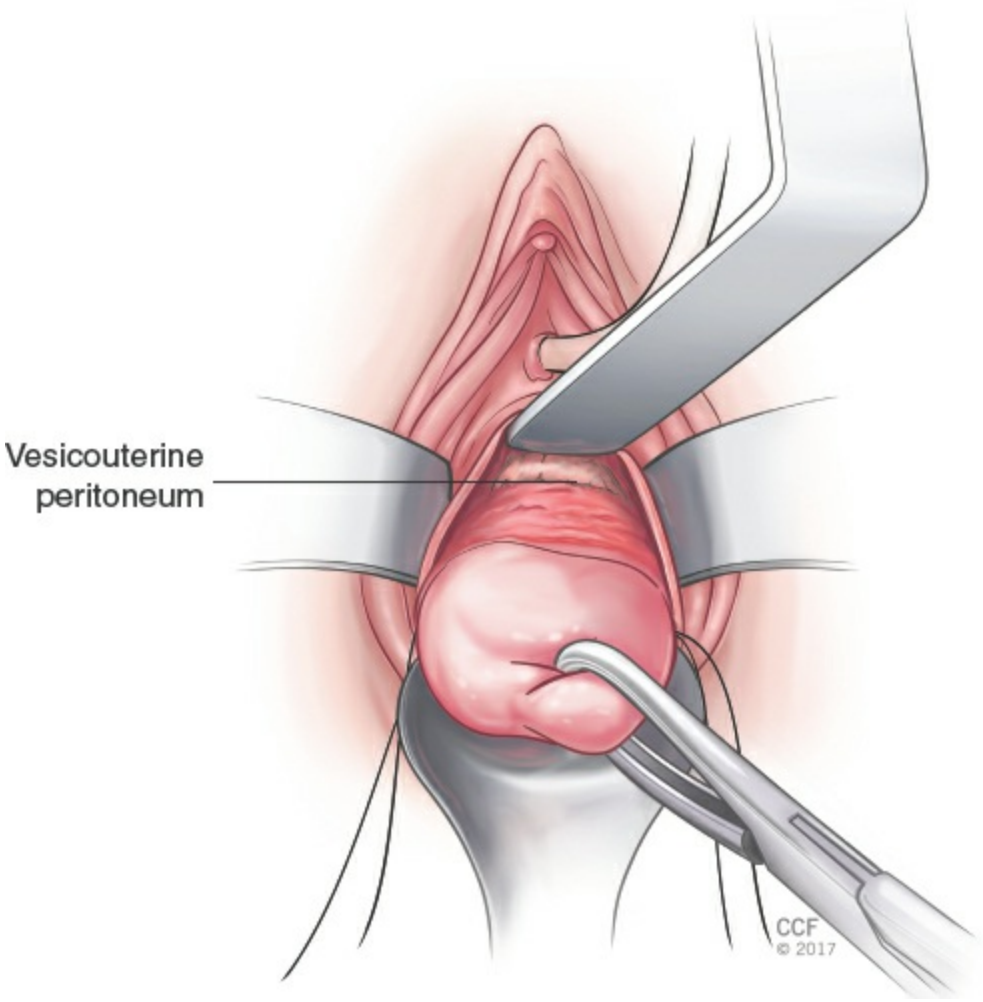


FIGURE 27-13 Dissection is carried along the cervix until the vesicouterine peritoneum is identified. A retractor protects the bladder.

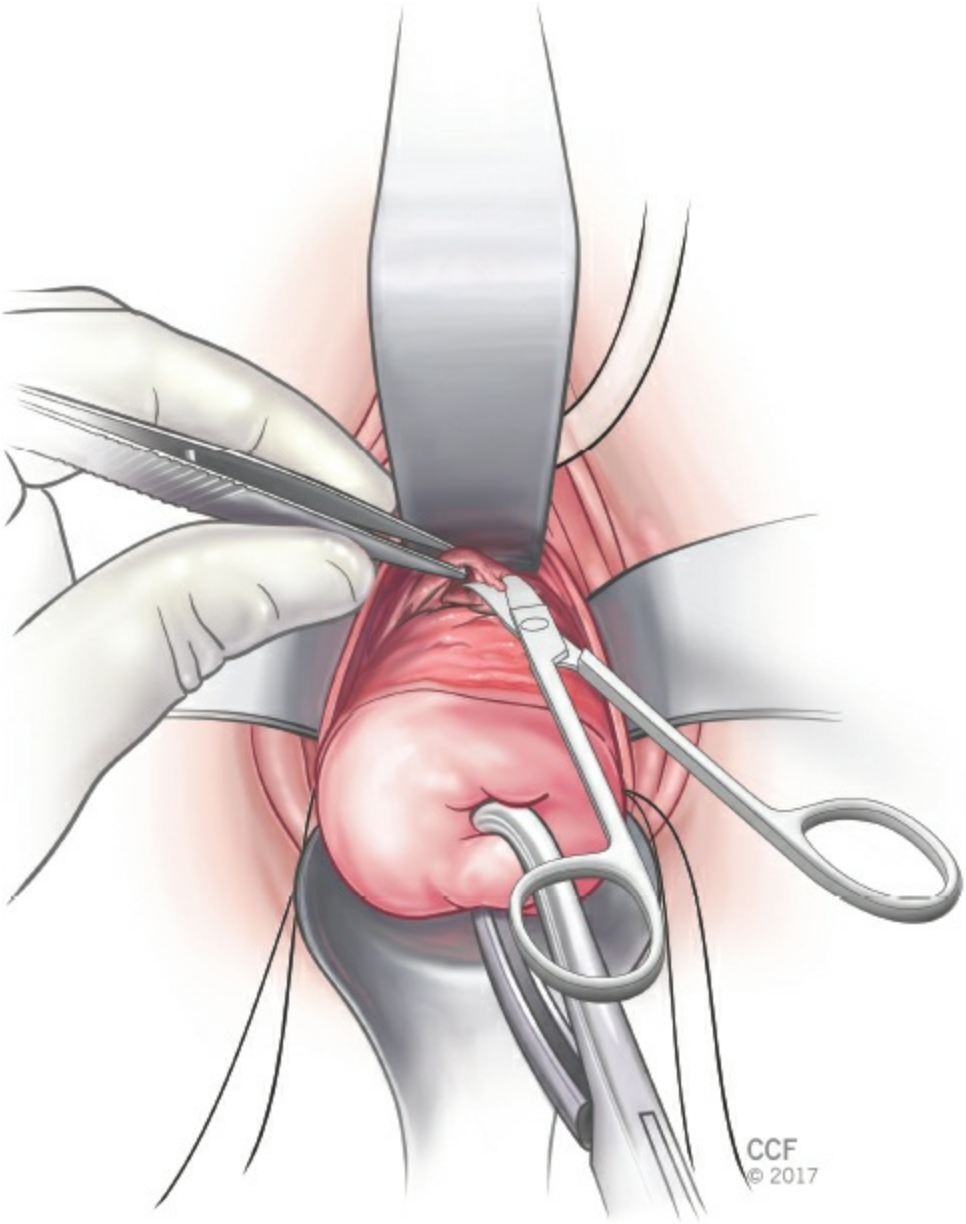


FIGURE 27-14 The vesicouterine peritoneum is entered sharply.

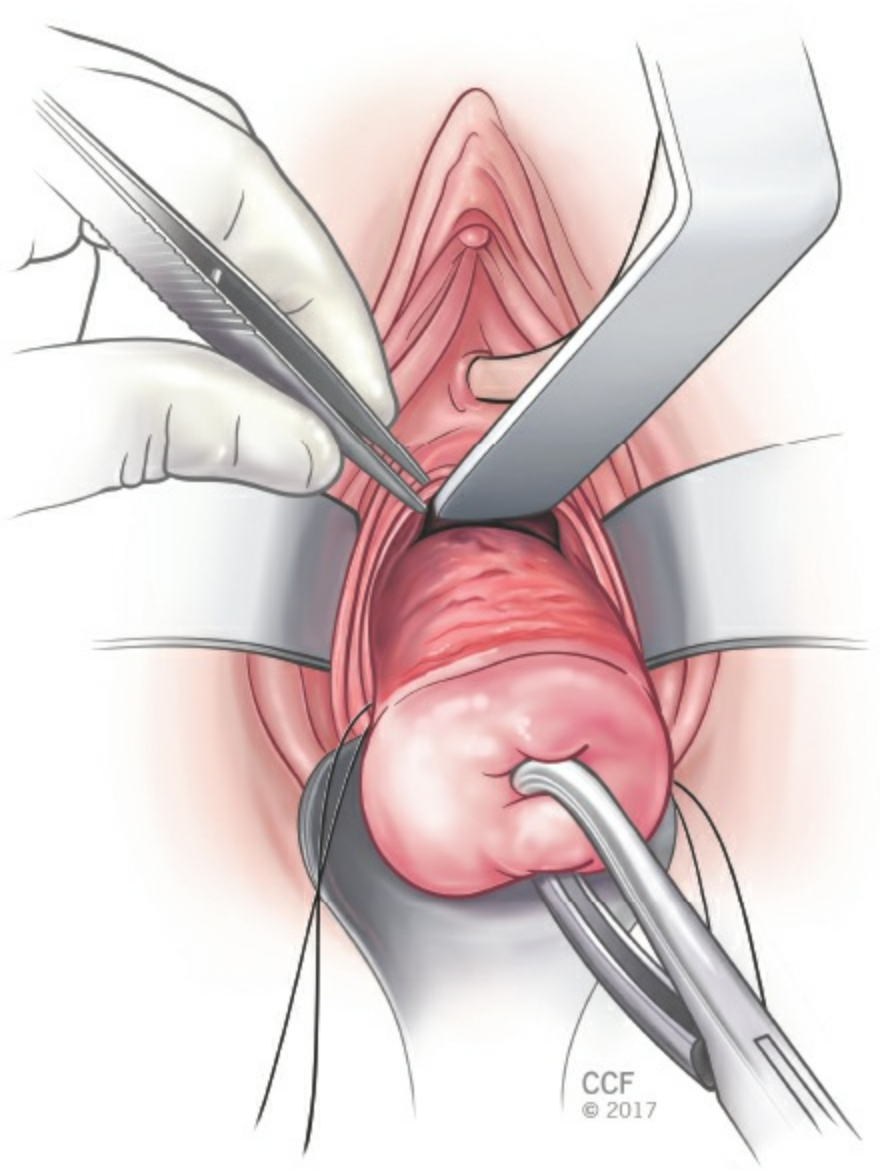


FIGURE 27-15 A long right-angle retractor is placed in the peritoneal cavity to protect the bladder.

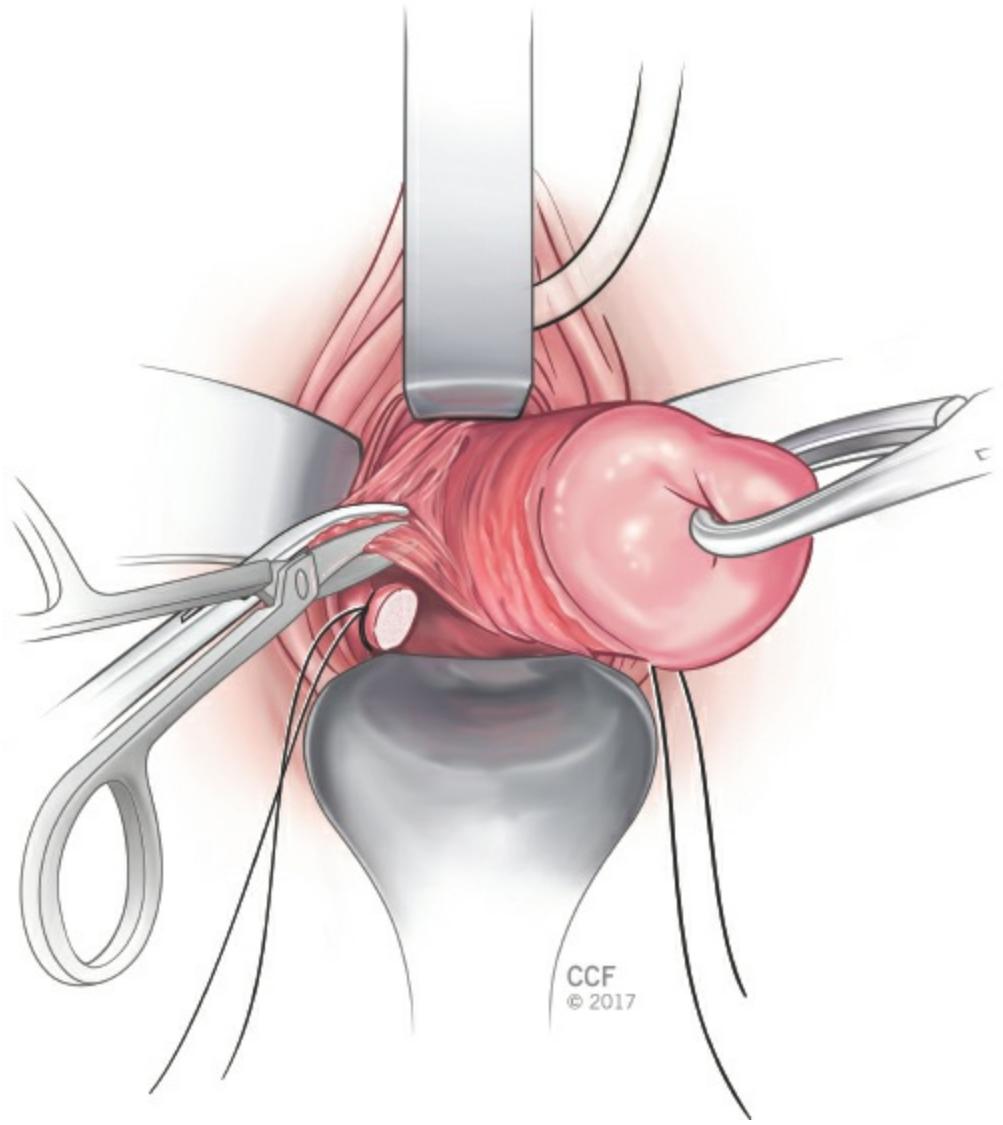


FIGURE 27-16 Clamps are advanced medial to the previous pedicle and the cardinal ligament and uterine vessels are ligated.

The anterior peritoneal cavity should not be opened blindly because of the increased risk of bladder injury. In cases where the peritoneum cannot be identified, there is no danger in delaying entry so long as the operator ascertains that the bladder is continually advanced prior to each additional pedicle.

Cardinal Ligament Ligation

With traction on the cervix continued, the cardinal ligaments are identified, clamped, cut, and suture ligated (Fig. 27-16). If possible, the anterior and posterior peritoneum is incorporated into the clamp during this step. This assists in anatomic definition and aids in hemostasis. If bowel is noted in the operative space, it can be packed cephalad using a moistened, tagged laparotomy sponge.

Uterine Artery Ligation

Contralateral and downward traction are placed on the cervix. With an effort to incorporate the anterior and posterior leaves of the visceral peritoneum, the uterine vessels are identified, clamped, cut, and the pedicle is suture ligated. A single suture and single clamp technique is adequate and decreases the potential risk for ureteral injury. When the uterus is large or when a fibroid distorts the anatomic relationships, a second suture may be required to ligate any remaining branches of the uterine artery. With the posterior and anterior peritoneum opened, the remainder of the broad ligament and utero-ovarian ligaments are clamped, cut, and ligated.

Delivery of the Uterus

A tenaculum is placed onto the uterine fundus to deliver the fundus posteriorly **(Fig. 27-17)**. The operator's index finger is used to identify the utero-ovarian ligament and aid in clamp placement.

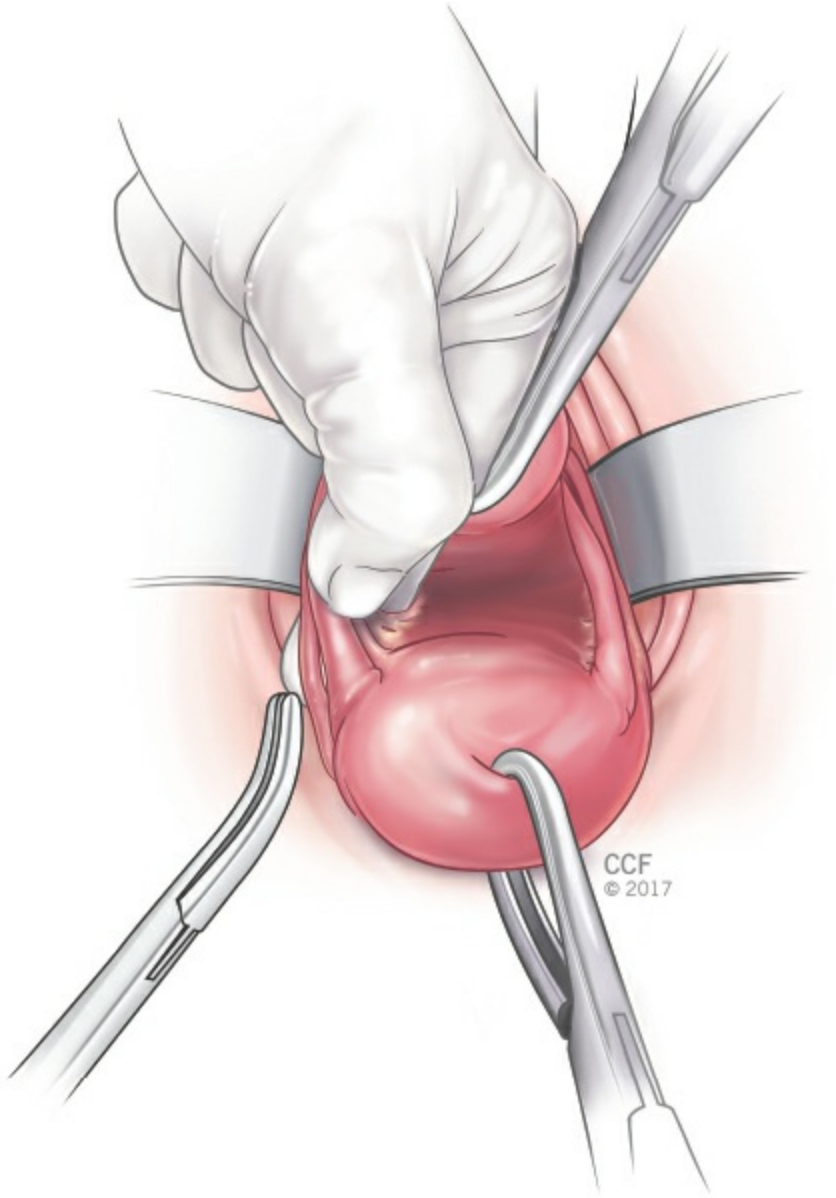


FIGURE 27-17 The uterine fundus is grasped, traction is placed inferiorly, delivering the fundus posteriorly. The surgeon's finger is placed behind the utero-ovarian ligament, allowing the surgeon to place the clamp tip against her index finger and safely deliver the clamp around the pedicle.

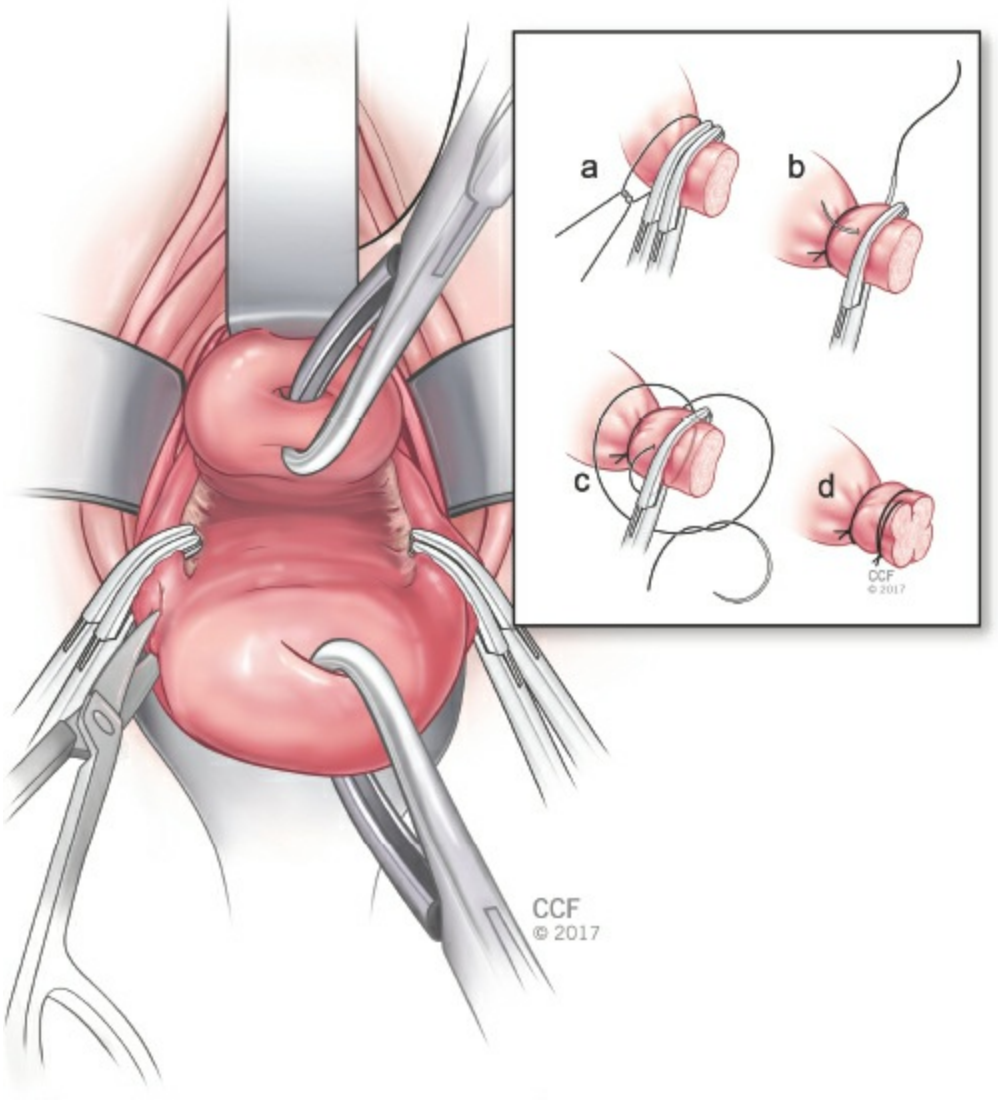


FIGURE 27-18 The utero-ovarian ligaments are cross-clamped, transected, and suture ligated.

Utero-ovarian and Round Ligament Ligation

In order to atraumatically place the clamp, the clamp tips can be placed on the operator's index finger, which can guide the clamp in the correct plane (Fig. 27-17). **The utero-ovarian and round ligament complexes are cut (Fig. 27-18) and double ligated with a suture tie followed by a ligature medial to the first suture (Fig. 27-18, inset).** If the pedicle is large, the surgeon may consider having the assistant briefly flash the second clamp while the first tie is placed, in order to assure the pedicle is secure. A hemostat is placed on the sutures to define this as the upper pedicle and aid in the identification of any bleeding (Fig. 27-19).

Removal of the Ovaries and/or Fallopian Tubes

During the removal of the adnexa, the round ligaments should be separated from the adnexal pedicles. Traction is placed on the utero-ovarian pedicle. If the uterus has been removed, the round ligament portion of the utero-ovarian pedicle can be clamped lateral to the suture ligation. This smaller pedicle can be cut and independently ligated. The ovary is drawn medially into the operative field by grasping it with a Babcock clamp. A Heaney clamp is placed across the ovarian vessels (infundibulopelvic ligament), and the ovary and tube are excised **(Fig. 27-20)**. A transfixion tie and suture ligature are placed on the ovarian vessels. In cases where the adnexa is high or the pedicle is too large to be taken safely, the surgeon may take several bites along the mesosalpinx until the infundibulopelvic ligament can be isolated and safely ligated (31). Care must be taken during these steps as the mesosalpinx is delicate and prone to shearing. If the surgeon wishes to perform opportunistic salpingectomy, a similar technique can be used. The round ligament is isolated and the ovary is retracted medially. The fimbria is identified, grasped, and moved caudad. With the entire fallopian tube in view, the surgeon places a clamp across the mesosalpinx lateral to the fallopian tube, not including the infundibulopelvic ligament. This pedicle is cut and the suture ligated.

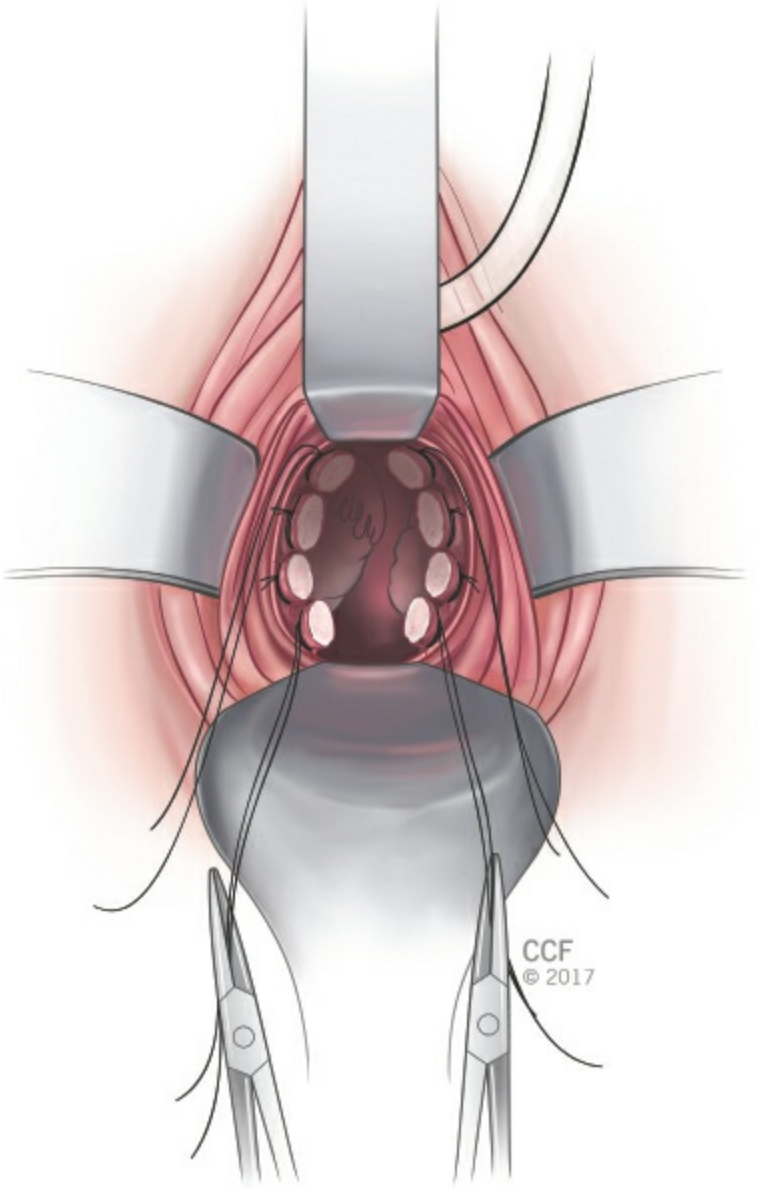


FIGURE 27-19 All pedicles are inspected for hemostasis. The most superior pedicle is the utero-ovarian ligament and the most inferior pedicle is the uterosacral ligament.

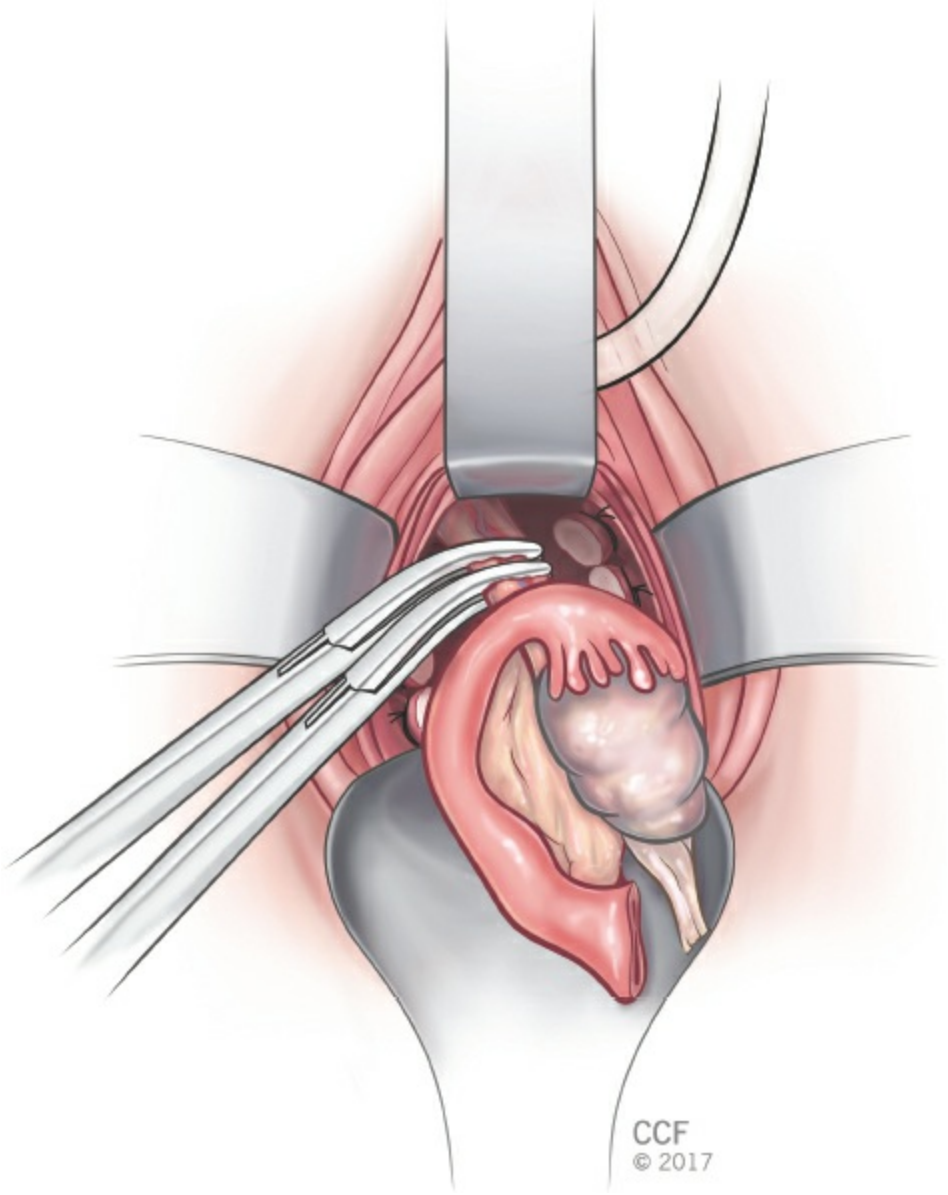


FIGURE 27-20 The infundibulopelvic ligament is ligated.

Hemostasis

A retractor or tagged sponge is placed into the peritoneal cavity, and each of the pedicles is visualized and inspected for hemostasis. **Having previously tagged the most superior and inferior pedicles aids in assuring that all pedicles are evaluated (Fig. 27-19).** Additional sutures may be placed to obtain hemostasis. These can be placed freely or an Allis clamp or Tonsil clamp can be placed on the bleeding area.

Peritoneal Closure

Because the pelvic peritoneum does not provide support and reforms within 24 hours after surgery, the peritoneum need not be reapproximated routinely.

McCall Culdoplasty

McCall culdoplasty prevents and treats vaginal apex prolapse and should be performed following vaginal hysterectomy when feasible (58,59). An absorbable suture is placed through the full thickness of the posterior vaginal wall at the point of the highest portion of the vaginal vault. The patient's left uterosacral ligament pedicle is identified and a suture is placed lateral to medial through the ligament. The suture is run toward the patient's right side incorporating the posterior peritoneum, between the uterosacral ligaments. The right uterosacral ligament is identified and the suture is placed lateral to medial through the right uterosacral ligament. The suture is passed from the inside to the outside at the same point at which it was begun and tagged **(Fig. 27-21)**.

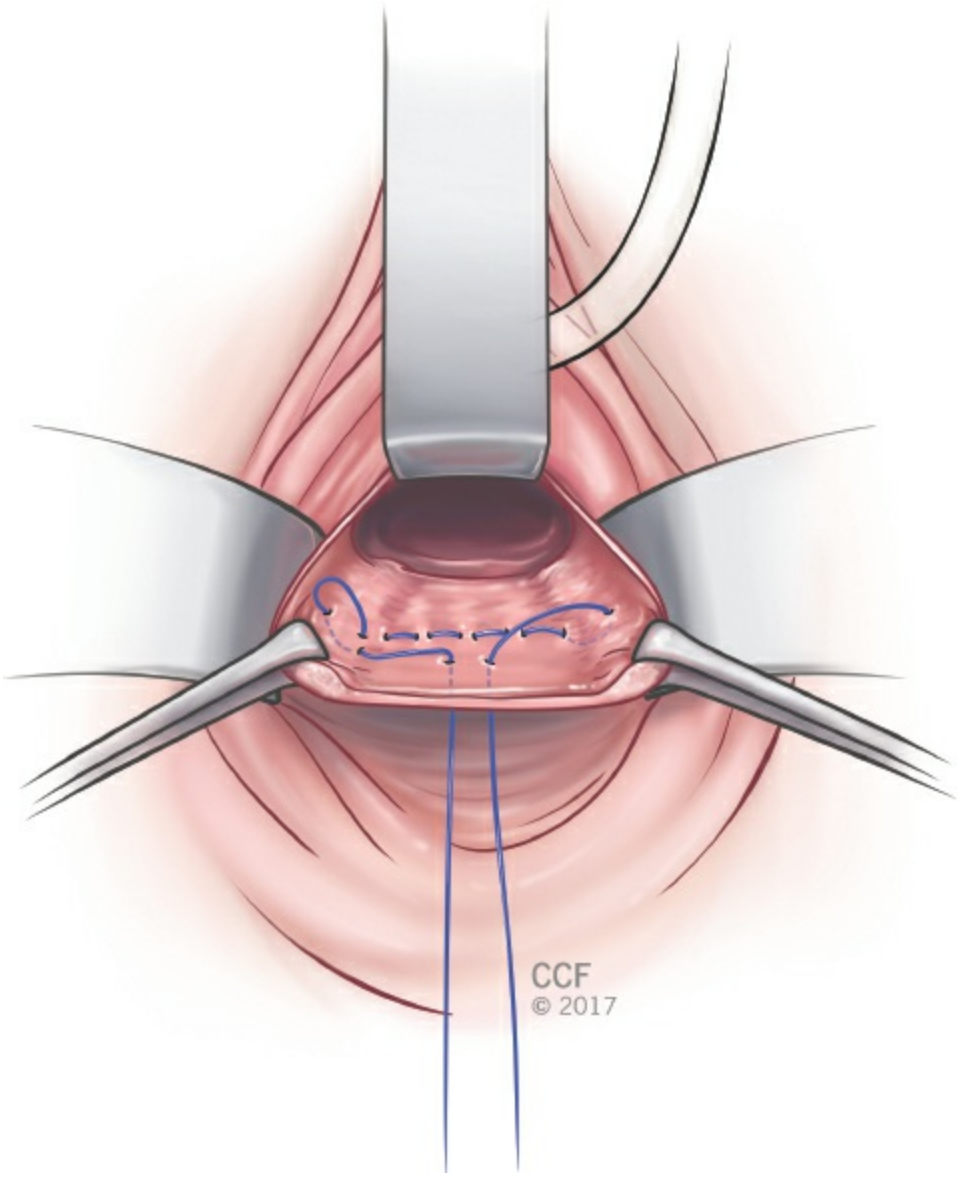


FIGURE 27-21 A McCall culdoplasty is placed.

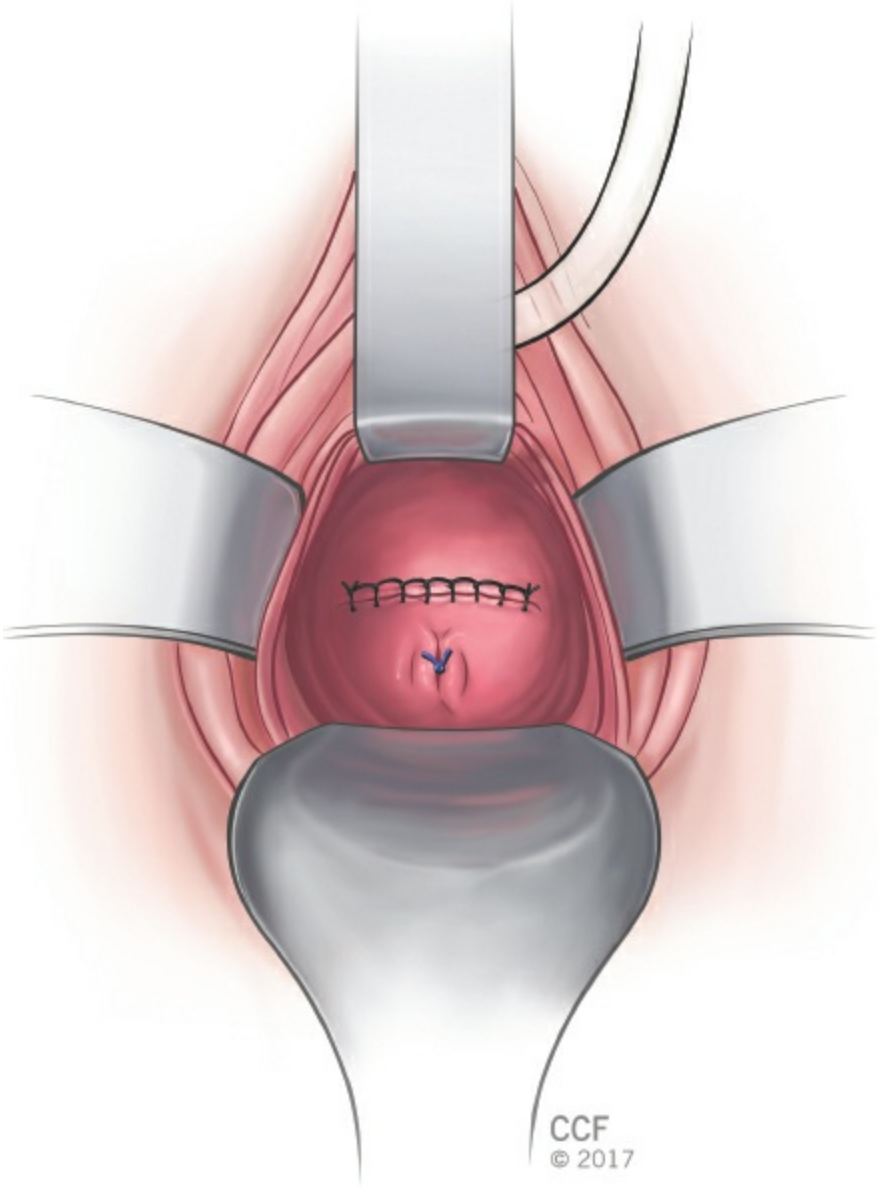


FIGURE 27-22 Closure of the vaginal cuff.

Vaginal Epithelial Closure

The vaginal epithelium can be reapproximated in a vertical or horizontal manner, using either interrupted or continuous sutures (Fig. 27-22). The vaginal epithelium is, in this case, reapproximated horizontally using a running locked suture. Care must be taken not to place sutures through the previously placed McCall culdoplasty suture as it will make it difficult to tie down the McCall suture following cuff closure. The epithelial closure sutures are placed through the entire thickness of the vaginal epithelium, with care taken to avoid entering the bladder anteriorly. These sutures will obliterate the underlying dead space and produce an anatomic approximation of the vaginal epithelium, thereby decreasing the postoperative formation of granulation tissue. The McCall suture is now tied, thereby approximating the uterosacral ligaments and the posterior peritoneum.

Bladder Drainage

After completion of the procedure, the Foley catheter may be continued overnight or discontinued prior to leaving the operating room. Unless there is a complication or the patient is unable to void, the catheter should be discontinued within 24 hours. For a routine vaginal hysterectomy, vaginal packing is not recommended.

Surgical Techniques for Selected Patients

Morcellation of the Large Uterus

Vaginal uterine morcellation is a well-known but underutilized surgical procedure whereby the uterus is removed piecemeal. Several methods of uterine morcellation have been described, including hemisection or bivalving, wedge or "V" incisions, and intramyometrial coring (32). **Before beginning any morcellation procedure, the uterine vessels must be ligated, and the peritoneal cavity must be entered anteriorly and posteriorly.**

When uterine hemisection or bivalving is performed, the cervix is split at the midline, and the uterus is cut into halves, which are removed separately (32). This method seems best suited for fundal, midline leiomyomas.

Wedge morcellation is best suited for anterior or posterior fibroids or for fibroids in the broad ligament. A single tooth tenaculum is placed at an angle from lateral to medial above the cervix bilaterally so that the tips meet in the middle. A wedge, including the cervix, is sharply removed distal to the clamps. This reduces the midline bulk, allowing the remaining lateral portions of the uterus to move medially. Keeping the apex of the wedge in the midline, the tenacula are advanced and additional wedges are resected. This process is repeated until the uterus can be removed or until a pseudocapsule of a fibroid can be grasped with a Leahy clamp or towel clamp. Traction is applied, and a "myomectomy" is performed.

When the intramyometrial coring technique is used, the myometrium above the site of the ligated vessels is incised parallel to the axis of the uterine cavity and serosa of the uterus. This incision is continued around the full circumference of the myometrium in a symmetrical fashion beneath the uterine serosa. Traction is maintained on the cervix, and the avascular myometrium is cut to allow the undisturbed endometrial cavity, with a thick layer of myometrium, to be delivered with the cervix. As a result, the inside of the uterus with its unopened endometrial cavity is brought closer to the operator. Incision of the lateral portions of the myometrium medial to the remaining attachment of the broad ligament results in considerable additional descent of the uterus and greatly increases the mobility of the uterine fundus. The uterus is converted from a globular to an elongated tissue mass. The cored uterus is removed by clamping the utero-ovarian pedicle and fallopian tubes.

Limited data are available on outcomes following uncontained vaginal morcellation using cold-knife techniques. However, that which is available does not

demonstrate an increased risk of worsening disease prognosis following the diagnosis of occult uterine malignancy (40).

Schuchardt Incision

When vaginal exposure is difficult, the Schuchardt incision may be used. To decrease blood loss, the area can be infiltrated with *lidocaine*-containing *epinephrine*. The incision follows a curved line from the 4-o'clock position at the hymenal margin to a point halfway between the anus and the ischial tuberosity. The incision may be continued into the vaginal vault as high as necessary to gain exposure. The depth of the incision is the medial portion of the pubococcygeus muscle, which may be divided in extreme cases. The incision must be closed in layers at the completion of the procedure.

Intraoperative Complications

Bladder Injury

Injury to the urinary bladder is one of the most common intraoperative complications associated with vaginal hysterectomy. If the bladder is inadvertently entered, the cystotomy should be carefully inspected. Its relationship to the trigone and ureteral orifices should be examined. Concomitant injury to the ureter should be ruled out. Ideally, the repair should be performed when the injury is discovered and not delayed until completion of surgery. However, if it occurred during a difficult part of the case, access to the bladder can be utilized to define tissue planes and prevent additional injury. If a delayed repair is planned, the cystotomy should be marked with a single suture to aid in future identification. When repairing a bladder injury, the edges of the wound should be mobilized to assess the full extent of the injury and allow repair without tension. The bladder may be repaired with a single- or double-layered closure with a small-caliber absorbable suture. **If the repair is close to the trigone or ureteral orifices, it is critical to verify ureteral patency.** This can be performed by filling the bladder with just enough fluid to see the trigone and administering 0.25 to 1 mL of sodium fluorescein IV. Following bladder injury and repair, the bladder should be continuously drained for 3 to 10 days depending on the size and location of the injury.

Bowel Injury

Because patients with suspected pelvic adhesions or obvious pelvic disease are excluded as candidates for vaginal hysterectomy, bowel injuries do not occur often. Rarely, small bowel injury can occur during pedicle ligation. If the small bowel is injured, the area should be marked and a consultant should be called. In the event a consultant is not available, the bowel may be repaired. It is controversial whether this can be done from a vaginal approach or if laparotomy is required. Ideally, the bowel is run to verify no other injuries are present. Small defects of the serosa or muscularis may be repaired using a single or double layer of continuous or interrupted 3-0 braided

absorbable suture. The defect should be closed in a direction perpendicular to the intestinal lumen. If a large area is injured, resection with reanastomosis may be necessary. Rectal injury can occur when the posterior colpotomy is performed in cases of an obliterated cul-de-sac. If the rectum is entered, the injury is repaired with a single- or double-layer closure using a small-caliber absorbable suture, followed by copious irrigation. Postoperatively, the patient should be given a stool softener or osmotic laxative to prevent constipation.

Hemorrhage

Intraoperative hemorrhage invariably is the result of failure to ligate securely a significant blood vessel, bleeding from the vaginal cuff, slippage of a previously placed ligature, or avulsion of tissue before clamping. Most intraoperative bleeding can be avoided with adequate exposure and good surgical technique. Using square knots with attention to proper knot-tying mechanisms will prevent bleeding in most cases. The use of Heaney-type sutures may minimize ligature slippage and subsequent bleeding from bulky pedicles. **When bleeding does occur, blind clamping, which may endanger the ureter, should be avoided.** The surgeon should first optimize exposure by packing away bowel, using additional retractors, and adjusting the OR lights. The bleeding vessel should be identified and precisely ligated, with visualization of the ureter if necessary. If the vessel cannot be identified or ligated or the pertinent anatomy cannot be visualized, conversion to a laparotomy may be necessary.

Perioperative Care

Bladder Drainage

Postoperative bladder drainage should be employed after any procedure in which spontaneous, complete voiding is not anticipated. Reasons to consider closed bladder drainage include significant local pain, additional vaginal reconstructive procedures, surgery for stress incontinence, and the use of a vaginal pack. After vaginal hysterectomy without additional repair, most patients can void spontaneously, and catheter drainage is not required. The relative amount of pain after a vaginal hysterectomy is less than with abdominal hysterectomy and, in the absence of additional repairs or a pack, no obstructive effect should be present.

If a catheter is required, the catheter is removed without clamping within 24 hours. There is no need to obtain a urine specimen for culture and sensitivity.

Diet

The patient is often the best judge of what she can tolerate following surgery. There is no medical reason to limit any type of food that the patient wishes to eat. Given the possibility of nausea, small frequent meals can be encouraged.

Laparoscopic Hysterectomy

Preoperative Preparation

The main limitations to a laparoscopic approach are medical or anesthetic disorders that do not allow adequate pneuomperitoneum or proper ventilation (32). Extensive and dense pelvic abdominal adhesions from previous surgery and very large uterine size are relative contraindications, although this decision can be made after assessing the peritoneal cavity (see Chapter 26). **If the uterine size limits access to the uterine vessels, laparoscopic hysterectomy may not be possible.** Obesity is not a contraindication to laparoscopic hysterectomy. The increased morbidity from laparotomy in patients with high body mass (BMI) can be minimized with laparoscopy.

Different classifications were proposed for the types of laparoscopic hysterectomy. **Laparoscopic hysterectomy is defined as a laparoscopic-assisted vaginal hysterectomy (LAVH) if the uterine vessels are occluded vaginally.** The Cochrane review authors recommended that if the vessels are occluded laparoscopically, or if part of the operation is performed vaginally, the procedure be called *laparoscopic hysterectomy,* and, if no component is performed vaginally, the procedure should be called a *total laparoscopic hysterectomy* (32).

Patient Positioning

The patient is placed in dorsal lithotomy position with legs placed in Allen or Yellowfin stirrups (Allen Medical Systems, Acton, MA). Attention to proper leg placement will avoid nerve injury. Hyperflexion of the hips should be avoided because this may cause femoral nerve palsy. The patient should be placed on an egg crate mattress or beanbag cushion to limit patient movement in the Trendelenburg position. The arms are tucked on the patients' side and protected with egg crate–type material. No shaving or clipping is necessary. Shoulder braces should not be used as they are associated with brachial plexus injury.

The steps to follow before introducing the first trocar are:

- Perform an examination under anesthesia.
- Place a Foley catheter to drain the bladder.
- Introduce a uterine manipulator (e.g., Koh colpotomizer [Cooper Surgical Inc., Trumbull, CT] or VCare [Conmed Corp., Utica, NY]).
- Place an oral gastric tube.

Instrumentation

The most important instrument is the one used to occlude blood vessels. A multitude of energy forms exist, including electrosurgery, lasers, and ultrasonic scalpel (see Chapter 26). Some surgeons use stapling devices, although the cost of these stapling

devices is high, and an energy-occluding device is needed to access areas that a stapler cannot. The versatility of the devices with energy makes them the method of choice to occlude vessels. There are no valid clinical data showing that one instrument is safer than another. The preferred one involves bipolar energy because gynecologists are experienced with this form of energy.

Surgical Technique of Laparoscopic Hysterectomy

Peritoneal Access

The most important technical consideration for all laparoscopic surgery is port placement (see Chapter 26). The umbilical site typically is used in patients without a previous history of surgery or intra-abdominal infection. In cases of previous surgery where there was a midline incision or a history of a pelvic-abdominal incision, an open laparoscopy is recommended or an alternate site can be chosen to introduce the primary cannula. The open laparoscopy is essentially a mini-laparotomy at the umbilicus. The alternative site is the left upper quadrant. The standard closed technique involves the use of pneumoperitoneum needle (Veress needle), insufflation, and primary trocar insertion. An alternative technique is the direct trocar insertion (no insufflation prior to trocar insertion). **There is no advantage of one technique over the other** (32). **Gynecologists should use the approach with which they have most experience.**

If the left upper quadrant is used, the surgeon should be aware of the closest anatomic structures to the left costal margin (see Chapter 26, Fig. 26-7). Typically the cannula is introduced below the left costal margin in the midclavicular line. The closest structures to this area are the stomach and the left lobe of the liver. Therefore, **an oral gastric tube should be introduced to empty the stomach before starting the procedure.**

The patient is kept in a horizontal (not Trendelenburg) position until proper peritoneal access is confirmed. The angle of insertion of the primary trocar will depend on the size of the patient. Typically for nonobese or overweight patients a 45-degree angle from the horizontal is used and with obese patients a 60- to 80-degree angle or open technique is used.

Proper placement of accessory ports is critical to allow the steps of a laparoscopic hysterectomy. The authors typically use three lateral accessory ports and do not use a suprapubic port **(Fig. 27-23)**. Lateral ports offer the surgeon an ergonomic approach in which both hands can be used comfortably. The most important step when placing lateral ports is to avoid the inferior epigastric vessels, which are branches of the external iliac artery and vein (see Chapter 26, Fig. 26-7). **Direct visualization is best.** These vessels (typically two veins and an artery) are seen through the peritoneum medial to the insertion of the round ligament in the deep inguinal ring. They cannot be transilluminated. Ports are placed approximately 8 cm from the midline and 8 cm above

the pubic symphysis.

Laparoscopic hysterectomy requires traction and countertraction to identify the vascular pedicles and the ureter, which is accomplished with the uterine manipulator. In the case of a large uterus, a laparoscopic tenaculum is required. **If the fallopian tubes are removed, the procedure starts with coagulating and transecting the mesosalpinx, followed by the same actions with the round ligament (Figs. 27-24 and 27-25). The incision is carried anteriorly to create a bladder peritoneal flap by sharp dissection of the loose areolar cervicovesical tissue.** The utero-ovarian ligaments are coagulated and transected, depending on whether the ovaries will be removed (Figs. 27-25 and 27-26). **The retroperitoneal space is opened and the ureter identified on the medial leaf of the broad ligament (Figs. 27-24 and 27-25).** The surgeon can proceed vaginally (LAVH), but there will not be any improved uterine descent because the transected tissue has no major role in uterine support.

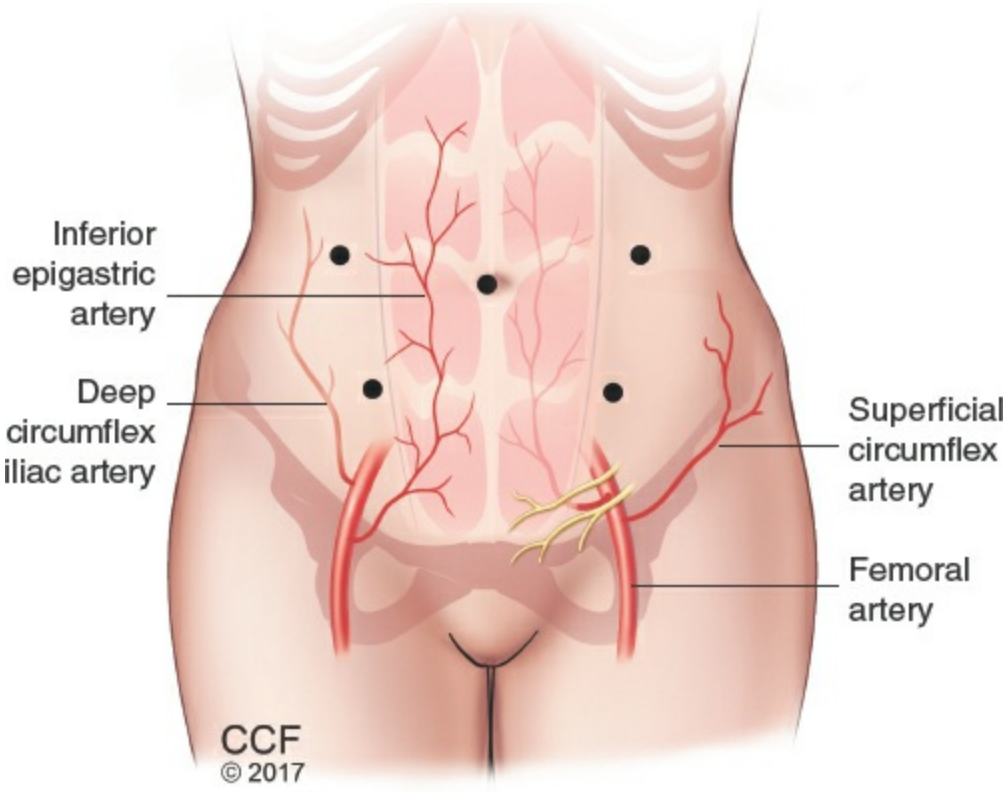


FIGURE 27-23 Port placement for laparoscopic hysterectomy.

The uterus is torqued away from the uterine artery to be occluded. **The uterine artery is skeletonized by cutting the posterior peritoneum up to the uterosacral ligament, coagulated, and transected (Fig. 27-27).** The procedure is carried out on the other side. This area of occlusion is approximately the level of the internal os. If a supracervical hysterectomy was performed, the uterus can now be amputated. When this is done, the remaining endocervical canal should be ablated.

The anterior dissection should be completed so that the bladder is completely off the anterior fornix area of the vagina. Using a vaginal device such as the Koh, the surgeon can identify this area. **Ensuring that no CO_2 escapes from the vagina, and an incision is made on the vagina circumferentially around the cervix (Fig. 27-28).** The uterus can be pulled out though the vagina or can be morcellated, and removed either vaginally or laparoscopically, whichever is easier.

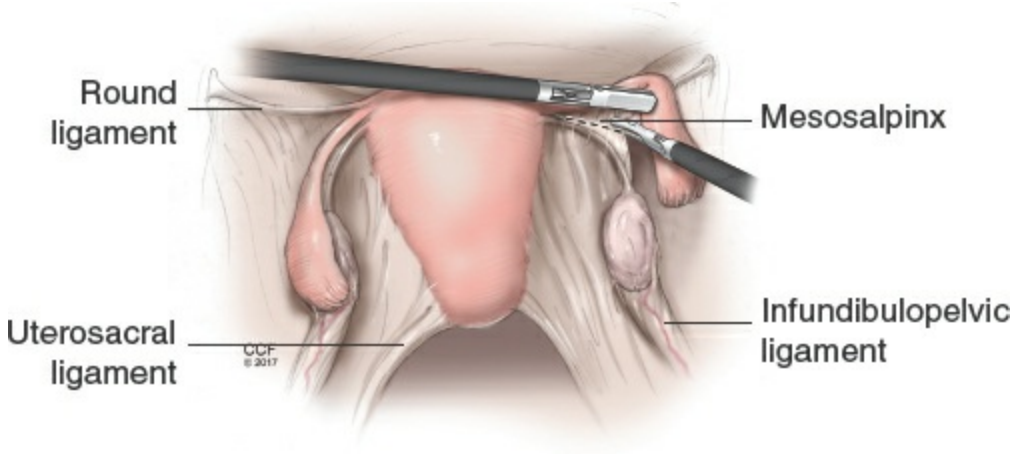


FIGURE 27-24 Ligation and transection of the mesosalpinx.

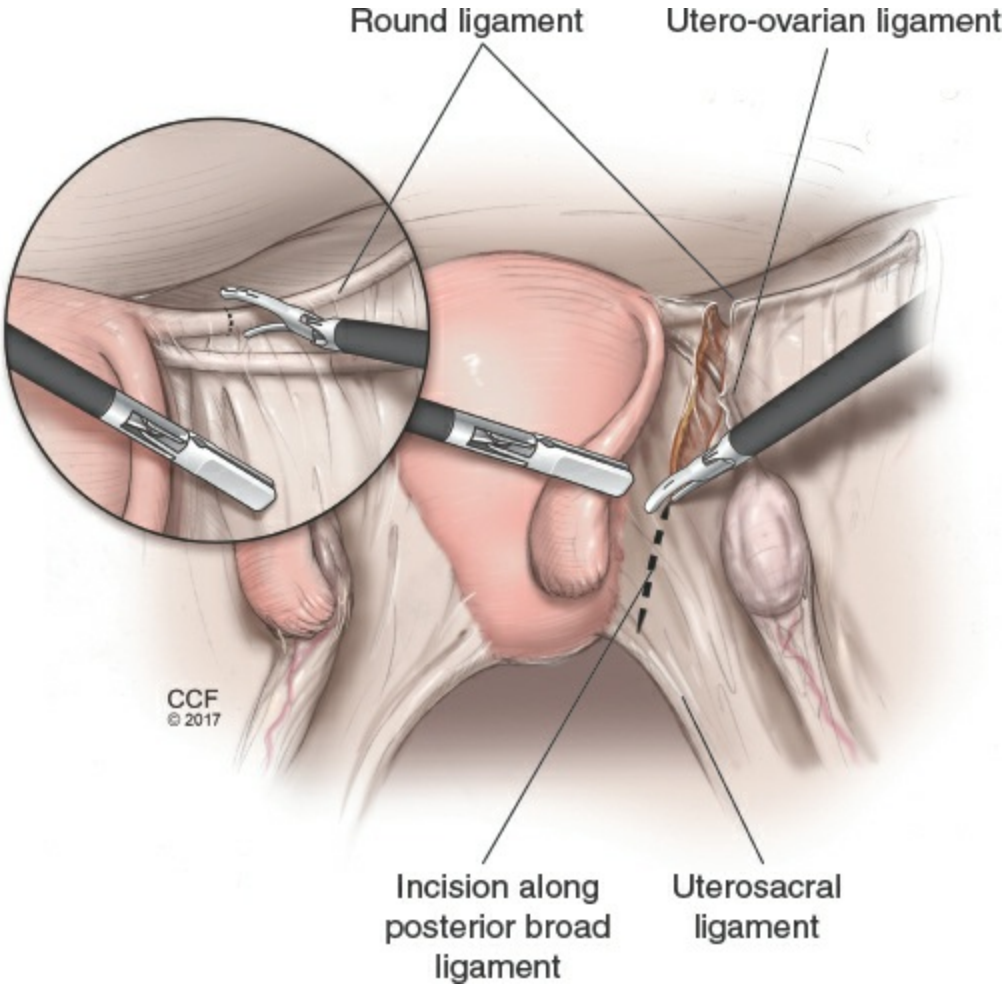


FIGURE 27-25 The round ligament is transected and the posterior broad ligament is opened toward the uterosacral ligament.

The vaginal cuff is closed laparoscopically or vaginally with interrupted or continuous-delayed absorbable suture (Fig. 27-29). To give added pelvic support, the uterosacral ligaments are reattached to the vagina (McCall culdoplasty) with delayed absorbable suture (Fig. 27-29). Intravenous *sodium fluorescein* is given and the integrity of the bladder and ureters confirmed with cystoscopy, if desired, by the surgeon.

At the end of the procedure, the secondary ports should be removed under direct visualization to ensure that there is no bleeding. In order to minimize the risk of herniation, the fascia should be closed at port sites that are greater than 8 mm and at those sites where smaller ports have been used but there has been prolonged manipulation.

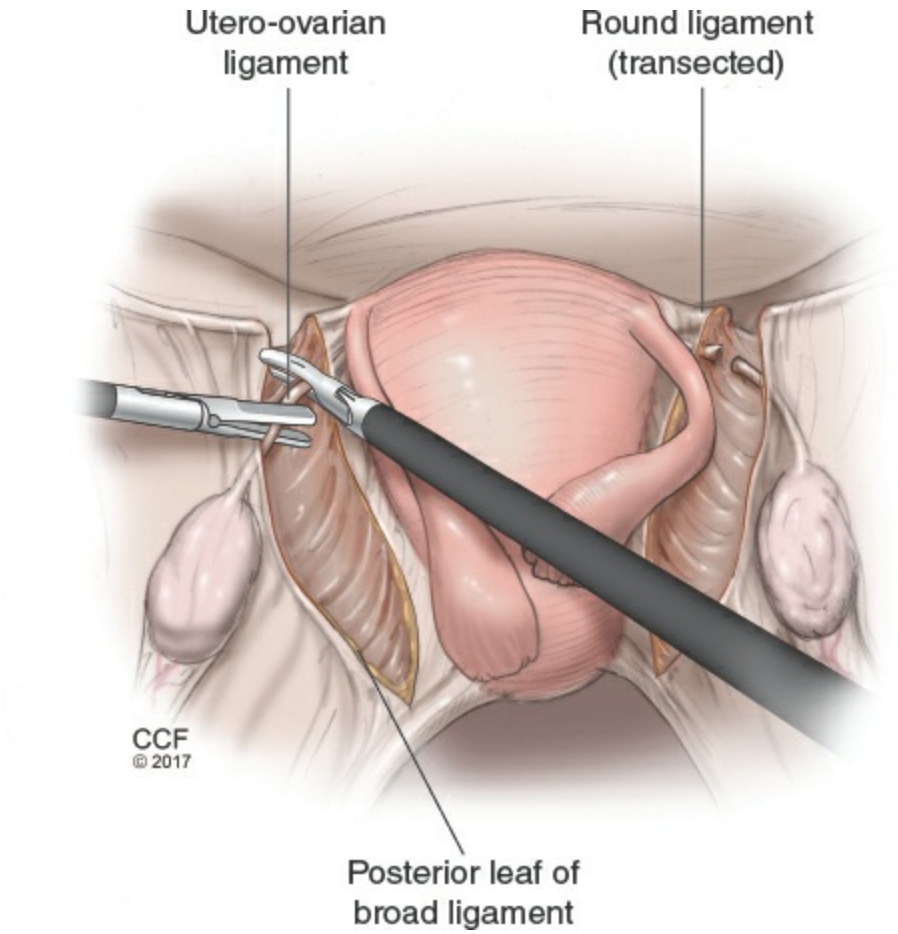


FIGURE 27-26 The utero-ovarian ligament is transected.

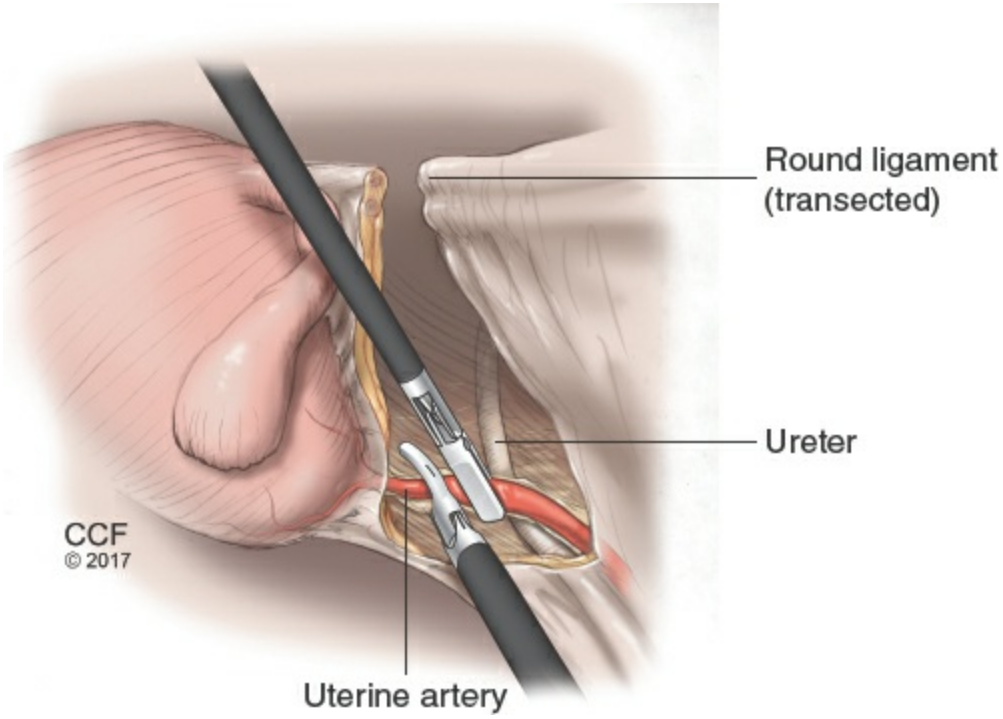


FIGURE 27-27 With the ureter in view, the uterine artery is identified and coagulated.

Robotic-Assisted Laparoscopic Hysterectomy

A surgical robot consists of a surgeon's console with the instrument manipulators and view screen, a robot tower with telerobotic arms that are attached to the patient, and the computer interface equipment, which is housed in a separate tower (see Chapter 28 for a more complete discussion). Robotic assistance at laparoscopy has some advantages, including a three-dimensional view, instruments with articulating tips that offer 7 degrees of movement, scaling of movement, and more precise movements. The disadvantages are the bulky device around the patient that limits the assistant's movements, the lack of haptic feedback, and the high cost of the robot. The robot device uses a 12-mm laparoscope and instruments that require 8-mm ports.

The robotic tower can be docked between the legs or on the patient's side (side docked). Side docking allows access to the perineum and vagina so that the assistant can comfortably manipulate the uterus. A robot-assisted hysterectomy goes through the same steps as a laparoscopic hysterectomy. A right-handed surgeon should have the monopolar scissors or harmonic scalpel through a right robotic port and a vessel-sealing device such as a bipolar instrument through a left-sided robotic port.

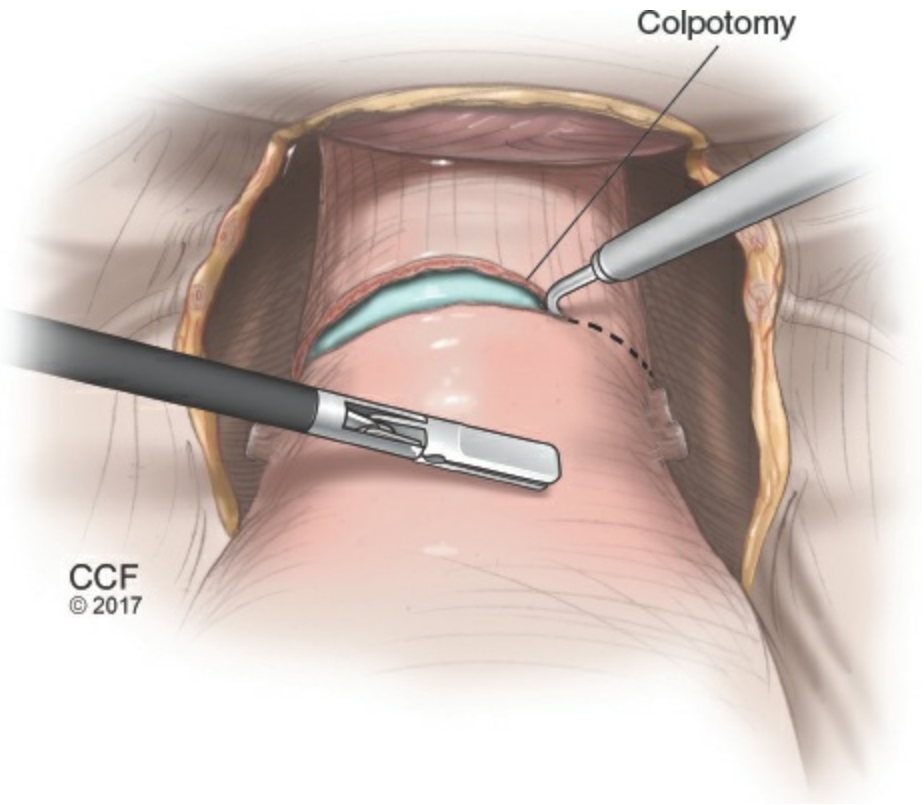


FIGURE 27-28 Monopolar cautery is used to make the colpotomy against the uterine manipulator.

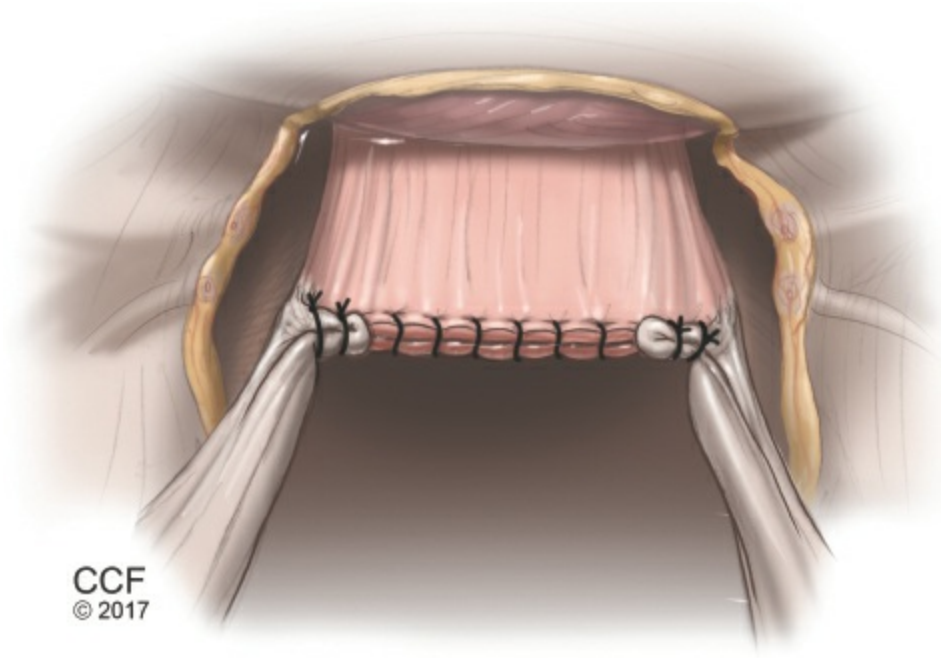


FIGURE 27-29 The vaginal cuff is closed. The uterosacral ligaments are incorporated to provide vaginal apex support.

Laparoendoscopic Single-Site Surgery

Another modification of laparoscopic hysterectomy is the introduction of laparoendoscopic single-site surgery or single-port surgery. Because some surgeons use multiple ports at one site, laparoendoscopic single-site surgery is probably the best term. Specifically designed umbilical port systems that admit multiple instrument access have enabled the development of this technique. The availability of flexible instruments and flexible tip laparoscopes allows the surgeon to perform a hysterectomy by reducing instrument crowding and clashing at the umbilicus. The basic hysterectomy steps are the same. **Although quite feasible the data do not show any advantage over conventional laparoscopy** (60).

Intraoperative Complications: Laparoscopic Hysterectomy

The intraoperative complications of a laparoscopic hysterectomy are similar to an open hysterectomy. These are injury to the ureter, bladder, bowel, and hemorrhage. Recognition and management are similar. Intraoperative bleeding during a laparoscopic procedure is handled by use of a bipolar electrosurgery instrument. The same principles apply as with an open case. Electrosurgery should not be used without proper localization of the ureters. If it is not apparent where the bleeding is occurring, the procedure should be converted to an open one. As with abdominal hysterectomy the value of intraoperative cystoscopy in the setting of laparoscopic hysterectomy without pelvic support procedures is unclear and depends on the incidence of urinary tract injury (51).

Many surgeons remove the bladder catheter at the end of the laparoscopic hysterectomy. A regular diet as tolerated is given on the same day as the surgery. Preemptive analgesia with intravenous *acetaminophen*, anticonvulsants such as *gabapentin* and *ketorolac* demonstrate opioid-sparing benefits (61). Postoperative pain control is similar to that described for abdominal hysterectomy. Transition to oral analgesics can be made the same day. Ambulation is encouraged as soon as possible. Median time to return to work is 3 to 4 weeks (45).

POSTOPERATIVE COMPLICATIONS OF HYSTERECTOMY

A comprehensive discussion of postoperative complications after gynecologic surgery is presented in Chapter 25.

Incisional Pain and Infections

Wound infections occur in 2% of abdominal hysterectomies but incidence is thought to be far less with laparoscopic surgery (51). Incisional pain can occur at trocar sites, especially if located in the region of the ilioinguinal or iliohypogastric nerves (62). Pfannenstiel incisions can be a source of chronic pain at the incision site as a result of nerve entrapment (63).

Hemorrhage

Immediately after hysterectomy, hemorrhage may become apparent in one of two ways. Bleeding from the vagina may first be noted by the nursing staff or physician within the first few hours after surgery. Second, the patient may be noted to have little bleeding from the vagina but deteriorating vital signs manifested by low blood pressure and tachycardia, falling hematocrit level, and flank or abdominal pain. The first presentation is in the form of bleeding from the vaginal cuff or one of the pedicles. The second presentation may be a retroperitoneal hemorrhage. Each situation is approached differently in its evaluation and treatment, but both involve the same general principles of rapid diagnosis, stabilization of vital signs, appropriate fluid and blood replacement, and constant surveillance of the patient's overall condition.

After vital signs are assessed, attention should be directed to the amount of bleeding. A small amount of bleeding is expected after any hysterectomy. **Steady bleeding 2 to 3 hours after surgery suggests lack of hemostasis. The patient should be taken promptly to the examining room, where the operative site is viewed using a large speculum and good lighting.** If bleeding is not excessive, the vaginal cuff can be inspected, and in many instances, bleeding from the cuff edge will be found. Hemostasis can easily be achieved with one or two sutures placed through the epithelium.

If bleeding is excessive or appears to be coming from above the cuff, or if the patient is too uncomfortable to tolerate adequate examination, she should be taken to the operating room. General anesthesia should be administered and the vaginal operative site should be thoroughly explored. Any bleeding point may be sutured or ligated. Bleeding that is coming from above the cuff or is extremely heavy usually cannot be controlled through the vaginal route. An exploratory laparotomy is necessary to examine the pelvic floor, identify and isolate the bleeding vessel, and achieve hemostasis. The ovarian vessels and uterine arteries should be thoroughly inspected because they often are the source of excessive vaginal bleeding. If it is difficult to localize bleeding to a specific pelvic vessel, or if these maneuvers do not work, ligation of the hypogastric artery may be performed.

In the patient with little vaginal bleeding in whom vital signs have deteriorated, retroperitoneal hemorrhage should be suspected. Input and output should be monitored. Hematocrit assessment, along with cross-matching of packed red blood cells, should be performed immediately. Examination may reveal tenderness and dullness in the flank. In cases of intraperitoneal bleeding, abdominal distention may occur. Diagnostic radiologic studies can be used to confirm the presence of retroperitoneal or intra-abdominal bleeding. Ultrasonography is one option for viewing low pelvic hematomas; CT provides better visualization of retroperitoneal spaces and can delineate a hematoma.

If the patient's condition stabilizes rapidly with intravenous fluids, one of the two approaches may be used for continued care. The first is to give the patient a transfusion and follow serial hematocrit assessments and vital signs. In many instances, retroperitoneal bleeding will tamponade and stop, forming a hematoma that may eventually be resorbed. The risk with this approach is that the hematoma will become infected, necessitating surgical drainage. In some instances when the patient's condition is stable, radiologic embolization may be considered.

Another option is to perform abdominal exploratory surgery while the patient's condition is stable. This approach adds the morbidity of a second procedure but avoids the possibility of the patient's condition deteriorating with continued delay or the formation of a pelvic abscess. When adequate exposure is obtained, the peritoneum over the hematoma should be opened and the blood evacuated. All bleeding vessels should be identified and ligated. If bleeding is difficult to control, consideration should be given to unilateral or bilateral ligation of the anterior division of the internal iliac artery. After hemostasis is achieved, the pelvis should be drained using a closed system.

Urinary Tract Complications

Urinary Retention

Urinary retention after hysterectomy is an uncommon occurrence. If the urethra is

unobstructed and retention occurs, it is usually the result of either pain or bladder atony resulting from anesthesia. Both are temporary effects.

If a catheter was not placed after surgery, retention can be relieved initially with the insertion of a Foley catheter for 12 to 24 hours. Most patients are able to void after the catheter is removed 1 day later.

Ureteral Injury

In patients who develop flank pain soon after hysterectomy, ureteral obstruction should be suspected.

In a patient with flank pain in whom ureteral obstruction is suspected, a CT urogram and a urinalysis should be performed. If obstruction is noted on CT scan, it is usually present near the ureterovesical junction. The immediate step is attempted passage of a stent through the ureter under cystoscopic guidance. If a catheter can be passed through the ureter, it should be left in place for at least 4 to 6 weeks, allowing sutures to absorb and the obstruction or kinking to release. If the catheter cannot be passed through the ureter, the best course is to perform abdominal exploratory surgery and repair the ureter at the site of obstruction. If an exploratory surgery cannot be performed immediately, a temporary percutaneous nephrostomy tube may be considered.

Vesicovaginal Fistula

In developed countries, vesicovaginal fistulas occur most often after total abdominal hysterectomy for benign gynecologic disease. Intraoperative steps to avoid the formation of a vesicovaginal fistula include correct identification of the proper plane between the bladder and cervix, sharp rather than blunt dissection of the bladder, and care in clamping and suturing the vaginal cuff. **The development of a postoperative vesicovaginal fistula after hysterectomy is rare; the incidence is as low as 0.2%.**

Patients who have a postoperative vesicovaginal fistula develop a watery vaginal discharge 10 to 14 days after surgery. Some fistulas resulting from surgery are noted as early as the first 48 to 72 hours after surgery. After vaginal examination with a speculum, the diagnosis can usually be confirmed with the insertion of a cotton tampon into the vagina followed by the instillation of *methylene blue* dye through a transurethral catheter. If the tampon stains blue, a vesicovaginal fistula is present. If no staining occurs, the presence of an ureterovaginal fistula can be ruled out by the administration of oral pyridium. Within 20 minutes, the tampon should stain orange if an ureterovaginal fistula is present. A CT urogram should be performed in cases of suspected vesicovaginal fistula and ureterovaginal fistula to fully evaluate ureteral integrity and rule out obstruction.

If a vesicovaginal fistula is diagnosed, a Foley catheter should be inserted for prolonged drainage. Up to 15% of fistulas close spontaneously with 4 to 6 weeks of

continuous bladder drainage. If closure has not occurred by 6 weeks, operative correction is necessary. Waiting 3 to 4 months from the time of diagnosis before operative repair is recommended to allow reduction of inflammation and to improve vascular supply. After hysterectomy, the fistula site is above the bladder trigone and away from the ureters. Vaginal repair can be anticipated in most patients. The surgical correction is undertaken in a four-layered closure: the bladder mucosa, the seromuscular layer, the endopelvic fascia, and the vaginal epithelium.

Incidental cystotomy at the time of hysterectomy is more common than vesicovaginal fistula. **When identified and repaired correctly, cystotomy rarely results in the development of a fistula.**

Prolapse of the Fallopian Tube

Posthysterectomy prolapse of the fallopian tube is a rare event and can be confused with granulation tissue at the vaginal apex. Predisposing factors for the development of fallopian tube prolapse include development of a hematoma and an abscess at the vaginal apex. In patients in whom granulation tissue persists after attempts to cauterize it or pain is experienced with attempts to remove it, fallopian tube prolapse should be suspected. A biopsy of the area is warranted and usually reveals tubal epithelium if a fallopian tube is present.

If fallopian tube prolapse is diagnosed, it should be repaired with surgery. The surrounding vaginal mucosa should be opened and undermined widely. The tube is ligated high and removed, followed by closure of the vaginal epithelium.

Vaginal Cuff Dehiscence

Patients with cuff dehiscence present with pain, vaginal bleeding, vaginal discharge, or gush of fluid 2 to 5 months after surgery. The most common initiating event is coitus. Immediate examination for cuff integrity is necessary. Treatment typically requires surgical repair in the operating room. Some studies show a higher frequency with robotic surgery (64).

DISCHARGE INSTRUCTIONS

Before discharging the patient, instructions should be reviewed. Printed postoperative instructions are helpful to the patient and a suggested set of instructions are as follows:

1. Avoid strenuous activity for the first 2 weeks, and increase activity level gradually.
2. Avoid heavy lifting, douching, or sexual intercourse until instructed by the physician.
3. Keep the wound (if applicable) clean and dry.
4. Bathe as needed using shower or tub baths.
5. Follow a regular diet.
6. Avoid straining for a bowel movement or urination. To prevent constipation, use a

stool softener (docusate sodium), fiber, or osmotic laxative (polyethylene glycol). To treat constipation, increase the use of an osmotic laxative or consider a stimulant laxative (magnesium hydroxide, senna, or bisacodyl).
7. Call the physician if excessive vaginal bleeding or fever occurs.
8. Schedule a return appointment at the time specified by the physician.

The physician should provide telephone numbers for emergencies during and after office hours. **Typically, the first postoperative visit is scheduled about 4 to 6 weeks after discharge from the hospital.** At the time of that visit, the patient should be ambulating well, and vaginal discharge or bleeding should be minimal. Speculum examination of the cuff should be gentle and cursory, but the patient should be assured that the healing process is proceeding normally. Finally, the patient's questions should be answered and advice given on increasing her activity level, including sexual activity, work, and normal household activity.

Readmission and Emergency Department Visits after Discharge

In one study, after hysterectomy for benign disease approximately 9% of women return to the emergency with a condition that does not require admission (65). **Pain control was the presenting complaint in almost 30% of patients.** Better education and communication should improve this outcome. Other presenting complaints were gastrointestinal such as nausea, vomiting, constipation, and diarrhea and genitourinary such as urinary tract infection or retention (65). Risk factors for readmissions after hysterectomy for benign pathology include preoperative comorbidities such as diabetes and hypertension, long operative time and major intraoperative or postoperative surgical or medical complications such as sepsis and return to the operating room (66).

GENERAL PELVIC SYMPTOMS AND QUALITY OF LIFE

Patient satisfaction after hysterectomy is related to the initial indication for surgery and patient expectation. The Maine Women's Health Study evaluated the effect of hysterectomy for nonmalignant disorders on quality of life (13). They documented a marked improvement in pelvic pain, urinary symptoms, and psychological and sexual symptoms at 1 year in the majority of patients. In the Maryland Women's Health Study patients were followed for up to 2 years after hysterectomy for nonmalignant conditions (67). **Symptoms related to the underlying indication for surgery, and associated symptoms of depression and anxiety and quality of life, improved after hysterectomy.** Each study reported that about 8% of patients had new symptoms, such as depression and lack of interest in sex or lack of improvement in quality of life. Although women with pelvic pain and depression did not show the same

level of improvement as other groups, there was significant improvement over baseline. **Patient satisfaction is very high after hysterectomy** (67).

Sexual Function

There is considerable debate in the lay literature about the effect of hysterectomy on sexual function, although evidence consistently suggests that the majority of women have unchanged or improved sexual function 1 to 2 years after hysterectomy (13,67). Few women who had a hysterectomy had a measurable worsening in sexual function during this time period. The long-term effects of hysterectomy on sexual function remain largely unknown. Studies have addressed the short-term effects of hysterectomy on dyspareunia, frequency of intercourse, orgasm, libido or sexual interest, vaginal dryness, and overall sexual function. The Maine Women's Health Study demonstrated a significant decrease in the number of women who reported dyspareunia 12 and 24 months after hysterectomy compared to the preoperative period (13). Eighty-one percent of the women who experienced dyspareunia preoperatively had an improvement in this symptom at 24 months after hysterectomy, while only 1.9% of women without preoperative dyspareunia developed it by 24 months after surgery. In this study, 39% of women reported dyspareunia preoperatively, and only 8% had this complaint 12 months after hysterectomy. Women who were managed nonsurgically showed no decline in the mean frequency of dyspareunia (13).

Most studies report that hysterectomy has little impact on the frequency of intercourse, libido, and sexual interest. Orgasmic function before and after hysterectomy is somewhat more controversial, but the largest study by Carlson et al. reported a slight increase in the proportion of women who experienced orgasms after a hysterectomy (13). It is plausible that removal of the uterus and/or cervix (especially if the ovaries are also removed) may adversely affect sexual function in some women, but this may be offset by the improvement in sexual function that could result from cessation of abnormal or heavy vaginal bleeding, dysmenorrhea, or symptoms of prolapse. It is likely that vaginal dryness is not affected by hysterectomy and depends more on age and postoperative hormonal status. **Body image and sexual function are improved after vaginal, abdominal, and laparoscopic hysterectomy, but no differences were found between the three routes** (13).

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CHAPTER 28

Robotics



Megan N. Wasson, Javier F. Magrina

Robotic Technology and Differences With Laparoscopy
- Robotic Column
- Robotic Console
- Instrumentation

Types of Instruments
- Trocars
- Docking

Certification and Credentialing in Robotics
- Assistant

Teaching Robotics

Robotic Applications in Benign Gynecology
- Hysterectomy
- Myomectomy
- Adnexectomy
- Endometriosis
- Tubal Reversal
- Appendectomy
- Sacrocolpopexy

Gynecologic Oncology
- Endometrial Cancer
- Cervical Cancer
  - *Early Cervical Cancer*
  - *Radical Hysterectomy*
  - *Radical Nerve-Sparing Hysterectomy*
  - *Other Applications of Robotics for Cervical Cancer*
- Advanced Cervical Cancer: Retroperitoneal Lymphadenectomy Prior to Chemoradiation
  - *Transperitoneal*

Extraperitoneal
Recurrent Cervical Cancer: Robotic Pelvic Exenteration
Ovarian Cancer
Primary Disease
Recurrent Disease
Summary
Complications Unique to Robotics
Disadvantages of Robotics

KEY POINTS

1 Robotic surgery is a form of facilitated laparoscopy that utilizes robotic technology to enhance the performance of the operation by placing a computerized interface between the patient and surgeon.
2 Two of the most important differences between conventional laparoscopic instruments and robotic instruments are articulation and intuitive movements.
3 The robotic system offers advantages for the surgeon, but it is particularly useful in the following circumstances: obese patients, long surgeries, operations requiring extensive suturing and dissection, or high precision.
4 High precision and absence of tremor are useful for retroperitoneal lymphadenectomy, adhesiolysis, parametrial ureteral dissection, and accurate suturing, in such procedures as ureteral anastomosis or reimplantation, and genitourinary fistula repair.
5 Applications of robotic technology include simple and radical hysterectomy, myomectomy, appendectomy (in conjunction with other procedures), adnexectomy, excision of severe pelvic and upper abdominal endometriosis, tubal anastomosis, and rectovaginal or vesicovaginal fistulas.
6 Studies show the feasibility of robotics for the treatment of patients with cervical, endometrial, tubal, and ovarian cancer, with apparent similar or better perioperative outcomes compared to laparoscopy and with improved outcomes compared to laparotomy.

[1] Robotic surgery as applied to laparoscopy utilizes robotic technology to facilitate the performance of the operation by placing a computerized interface between the patient and surgeon. Although originally designed for cardiovascular surgery and approved for that use by the U.S. Food and Drug Administration (FDA) in 2003, it has found applications in urology and gynecology, and in otolaryngology, general surgery, plastic surgery, and colorectal surgery.

There are studies showing that the use of robotic technology for the performance of preset laboratory exercises results in faster performance times, increased accuracy, enhanced dexterity, easier and faster suturing, and fewer errors when compared to conventional laparoscopic instrumentation (1–4). The physical stress for medical students learning robotics is significantly less than what they encounter when learning the same tasks by laparoscopy (5). The technologic advantages of robotics can facilitate learning surgical techniques when compared to acquiring similar skills in laparoscopy, as demonstrated by a shorter learning curve for robotic surgery. There is a flattening of the operating time after 20 to 50 robotic hysterectomies, while for laparoscopically assisted vaginal hysterectomy (LAVH) a similar facility with

the requisite skills does not occur until after 80 procedures (6–9). In gynecologic oncology, a flattening of the operating time was noted after approximately 20 procedures for endometrial cancer when using the robotic technology, compared to nearly 50 cases when using conventional laparoscopy (10,11).

ROBOTIC TECHNOLOGY AND DIFFERENCES WITH LAPAROSCOPY

There is only one robotic system available, brand-named da Vinci (Intuitive Inc., Sunnyvale, CA), which received FDA approval for the performance of hysterectomy in 2005. A second generation of the device, the da Vinci S, was released in 2006, and the third generation of the da Vinci robotic system, the Si model, was released in 2009 and it incorporates a resident teaching console. The fourth-generation robotic system (Xi model) was released in 2014 and allows for multiquadrant abdominal access. Both the Si and Xi models allow for single-site robotic surgery.

A robotic system is composed primarily of a robotic column, which holds the robotic arms **(Fig. 28-1)** and a surgeon's console **(Fig. 28-2)**. The robotic arms that hold the robotic instruments **(Fig. 28-3)** are fastened to the robotic trocars **(Fig. 28-4A–C)**. Commonly used robotic instruments for gynecologic surgeries are shown in **Figure 28-5A–I**.

For single-site robotic surgery, a single-site port is placed through a 1.5-cm fascial incision. The robotic trocars are placed through the port and cross midline. The robotic technology allows the surgeon's hands to be associated with the opposite trocar to allow for natural movement of the instruments. Commonly used robotic instruments for single-site surgery are shown in **Figure 28-5H–I** and include Maryland bipolar forceps, fenestrated bipolar forceps, monopolar hook, and wristed needle driver. With the exception of the needle driver, single-site robotic instruments do not have wristed movement (28).

Robotic Column

The robotic column has four robotic arms **(Fig. 28-1)**. The fourth arm is extremely useful for assisting with tissue retraction. The robotic arms function toward the direction of the robotic column and not away from it. For this reason, the robotic column must be positioned strategically in response to the location of the surgery that will be performed.

For pelvic surgery the robotic column is commonly side-docked over the patient's hip, while for upper abdominal surgery it is positioned over the patient's shoulder **(Fig. 28-6)** (28). Side-docking allows easy access to the entrance of the vagina and rectum.

An advantage of the Xi model is that it allows for multi-quadrant abdominal access. The Xi robotic column can be side-docked over the patient's hip to allow for pelvic surgery. If upper abdominal access is needed for procedures such as resection of diaphragmatic endometriosis or aortic lymphadenectomy, the robotic boom can be rotated without repositioning of the robotic column.

Robotic Console

The surgeon sits at the console **(Fig. 28-2)** away from the patient **(Fig. 28-7)** and the assistant remains at the bedside next to the patient. The surgeon has a stereoscopic image, which is different from the laparoscopic image, and controls the movements of the robotic arms using two hand controls and several foot pedals. The movements of the robotic arms are managed by the hand controls and allow for wristed movement of the robotic instruments. The finger controls allow the camera to be focused and have a clutch feature that permits ergonomic repositioning of the hand controls throughout the surgery **(Fig. 28-8)**. Robotic movements are intuitive; the tip of the instrument mimics the movement of the surgeon's hands, in contrast to the experience in laparoscopy when the movements of the tip of the instrument are counterintuitive, opposite to the movements of the surgeon's hands. The three foot pedals controlled by the left foot include clutch, camera, and arm swap. The four foot pedals controlled by the right foot allow for energy activation (i.e., monopolar, bipolar, vessel sealing) **(Fig. 28-9)**. The left aspect of the surgeon console allows for ergonomic adjustments and the right aspect houses the power and emergency stop buttons **(Fig. 28-10A–C)**.

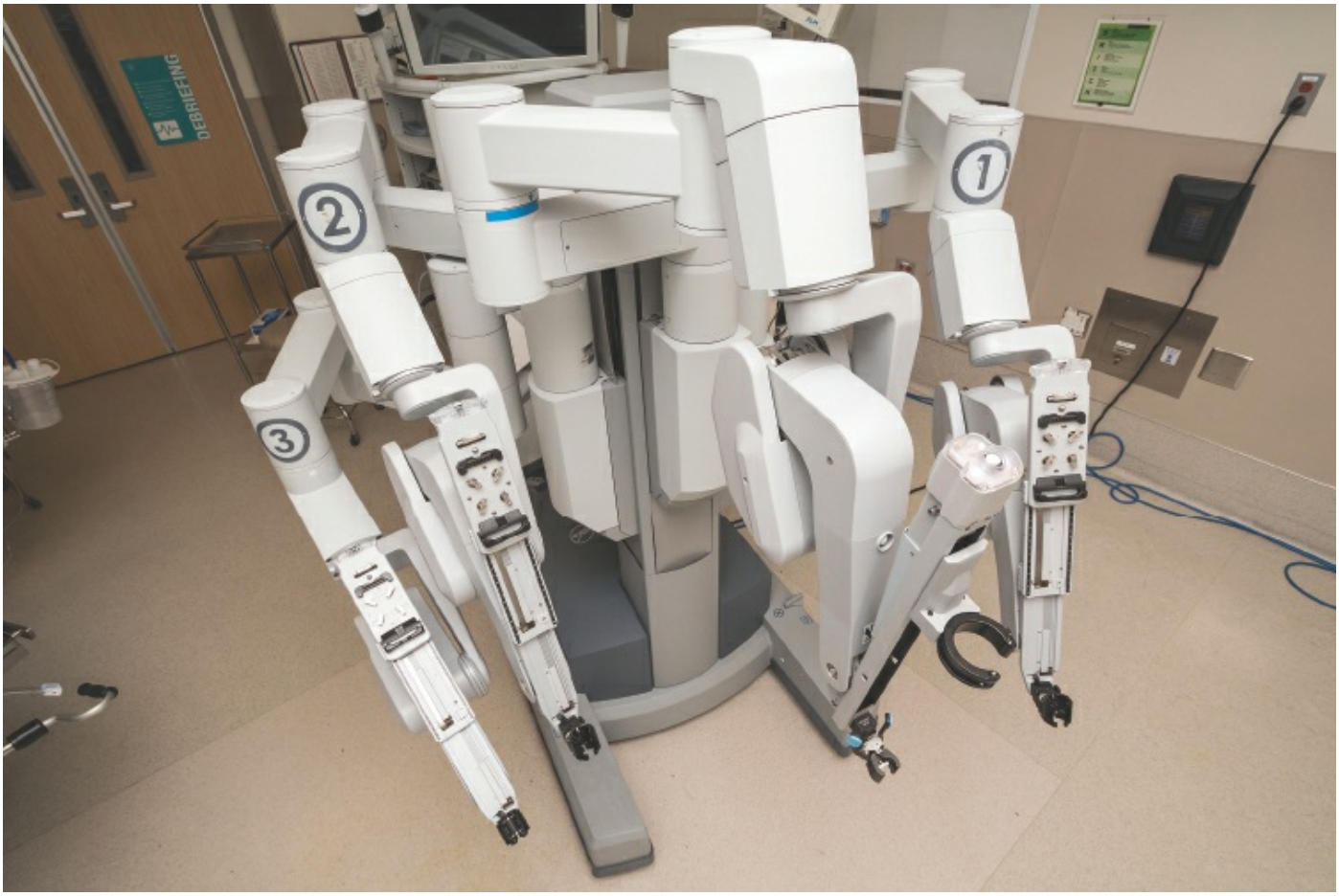


FIGURE 28-1 Robotic column with robotic arms.



FIGURE 28-2 Robotic console with hand controls and foot switches.

Because the surgeon is separated from the patient, there is a time delay that permits

the performance of telesurgery, as long as the latency time does not exceed 150 ms. The surgeon can control the movements of the robotic arms and instruments in a patient located at a different geographic location (12). Telementoring allows the mentor surgeon to guide another surgeon through a surgical procedure at a remote location by using superimposed electronic signals (telestration), direct voice commands, and control of the laparoscope via joystick and the electrosurgical instruments (13).

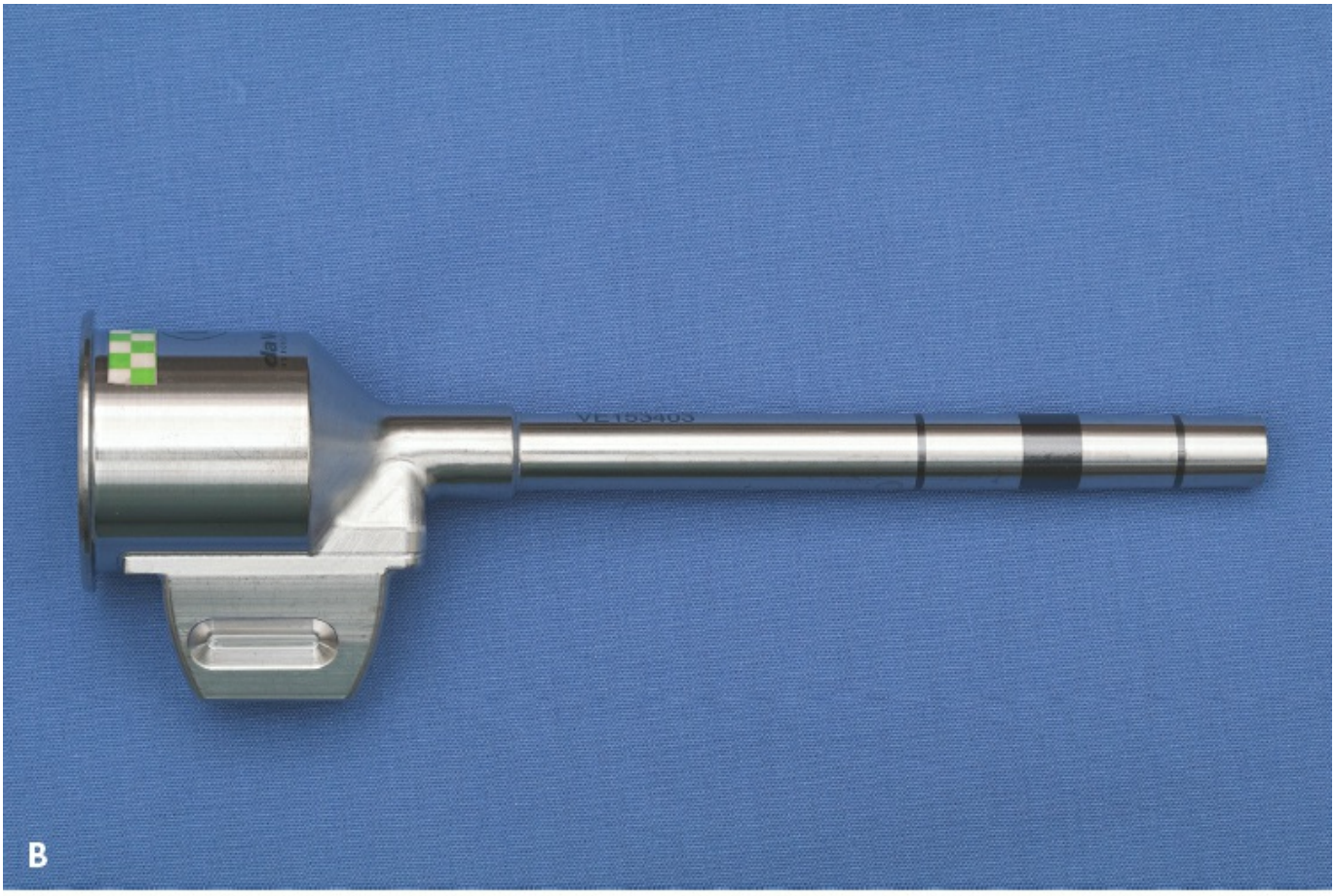
Other technologic advantages include downscaling of movements, absence of tremor, and stillness. In laparoscopy the amplitude of movement of the tip of the instrument is the same as the amplitude of the movement of the surgeon's hands, whereas in robotics it can be downsized, resulting in increased precision. The computerized interface between surgeon hands and robotic instruments eliminates unwanted tremor, increasing precision. When placed in a specific position, such as for retracting bowel or uterus, the robotic instruments remain in place until repositioned, which can be different from human assistance.

The lack of tactile feedback (haptics) is a drawback for the neophyte, but the stereoscopic view rapidly compensates for it. There is a degree of resistance felt at the hand controls of the console, which, coupled with the stereoscopic view, allows the surgeon to obtain visual haptics and determine the consistency of tissues, whether soft or hard, such as "to palpate" the rim of the cervical cup of a uterine manipulator, or "feel" a hard probe introduced in the rectum. The lack of tactile feedback is an advantage when operating in obese patients, because the surgeon cannot feel the resistance of the instruments being inserted through a thick abdominal wall, a difference from laparoscopy.

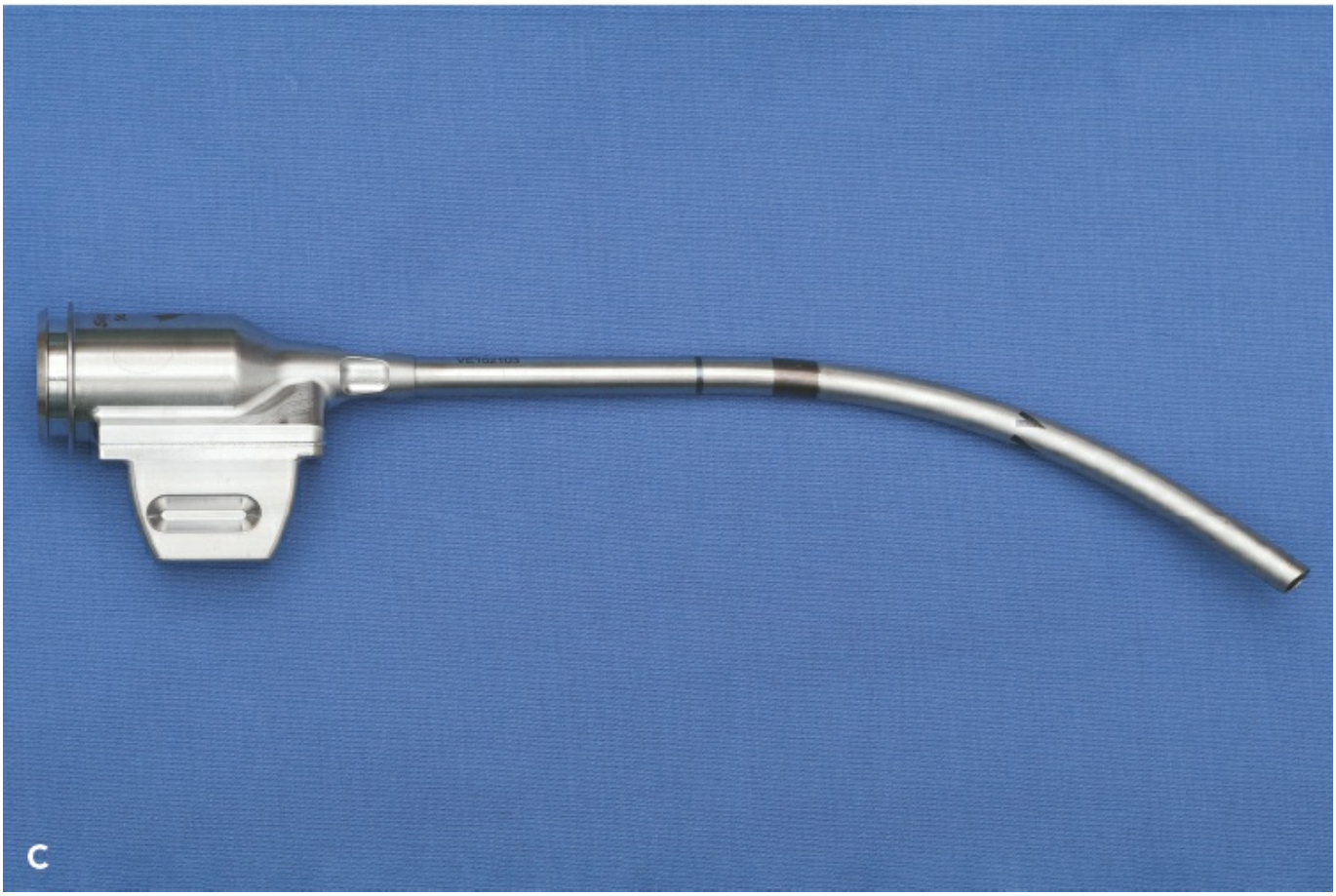


FIGURE 28-3 Robotic laparoscope and two robotic arms with robotic instruments inserted. The tip of the instruments can be appreciated in the insert.


da Vinci S
8mm
A



B



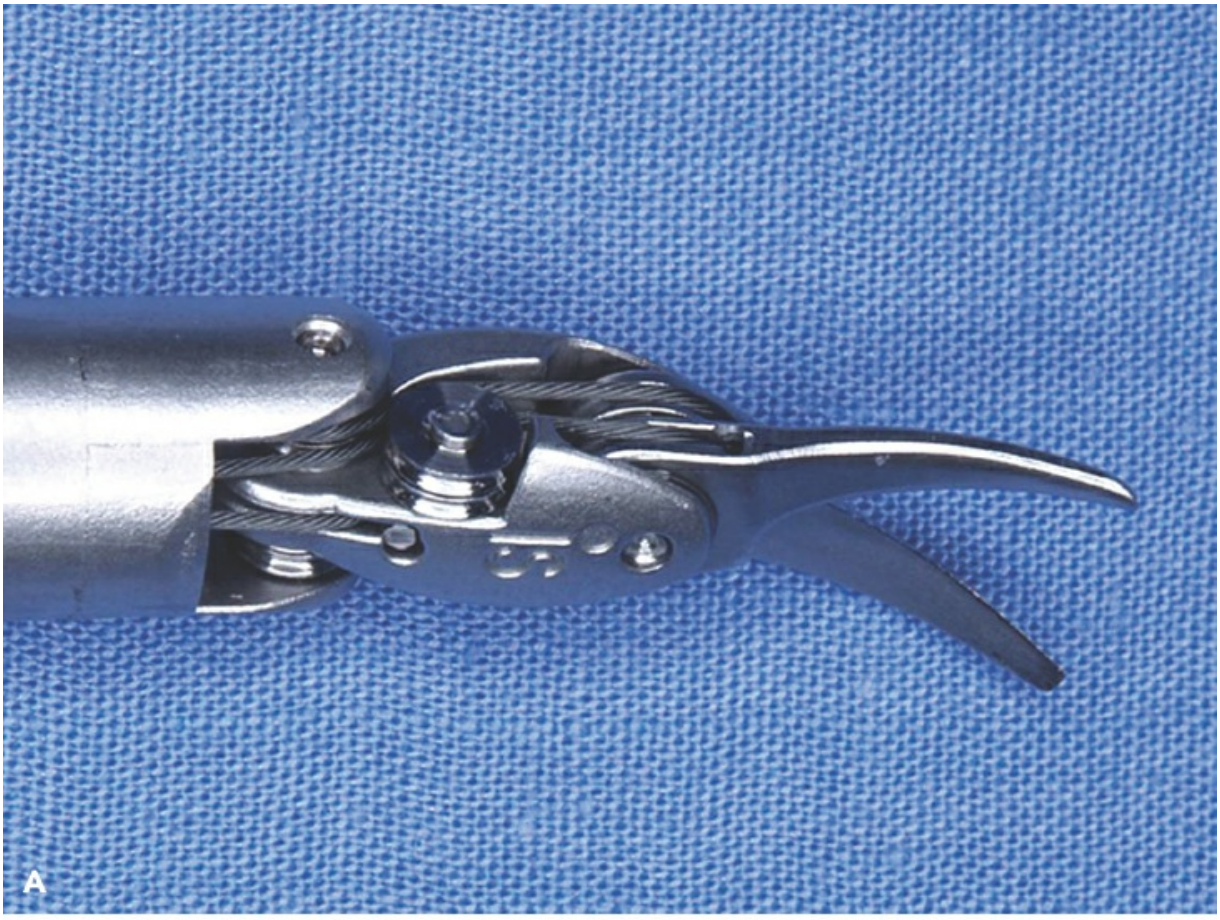
C

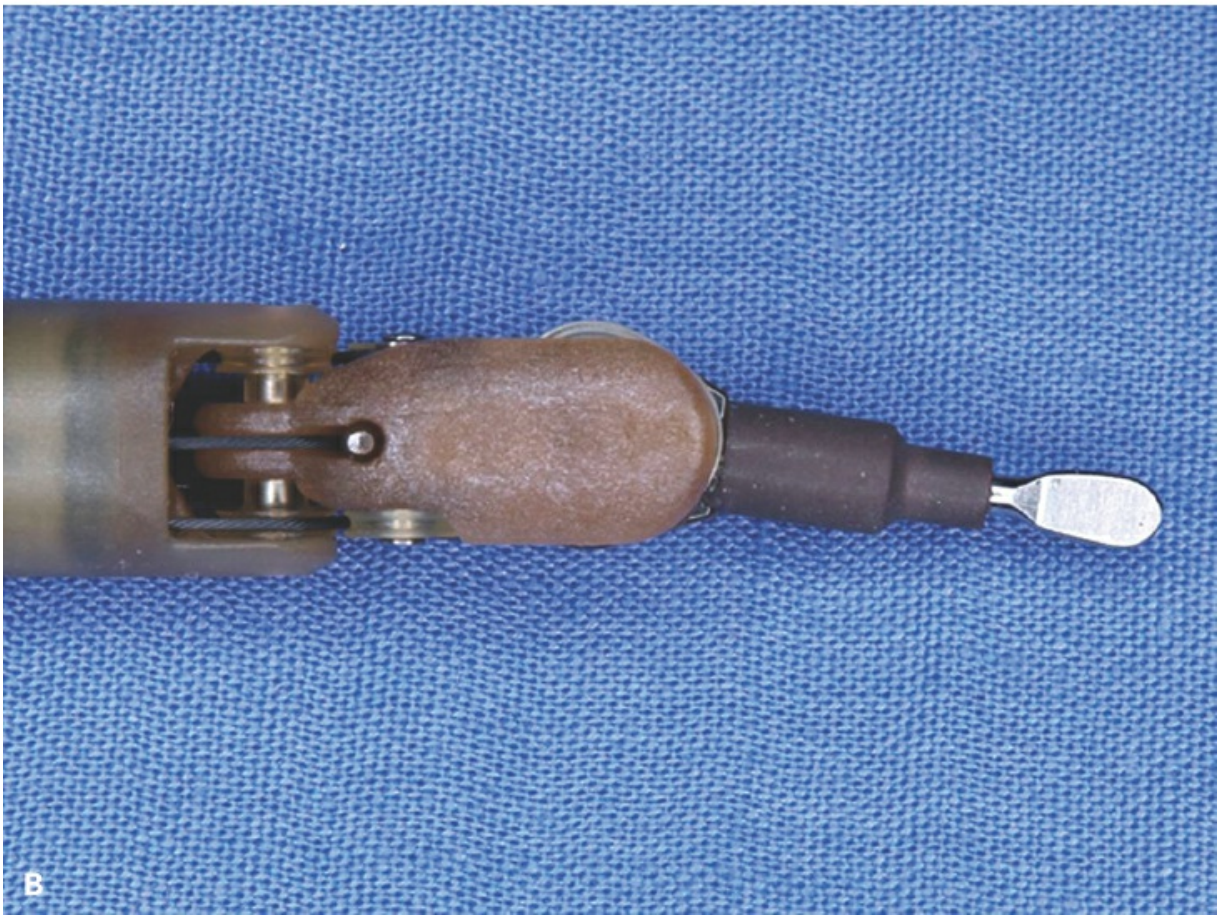
FIGURE 28-4 The robotic trocars are metallic. **A:** daVinciS and Si trocars. The three types of available trocar obturators are on the left of the picture: blunt (***left***), tissue-spreading (***middle***) and cutting (***right***). **B:** daVinci Xi trocar. **C:** daVinci Single-Site curved trocar.

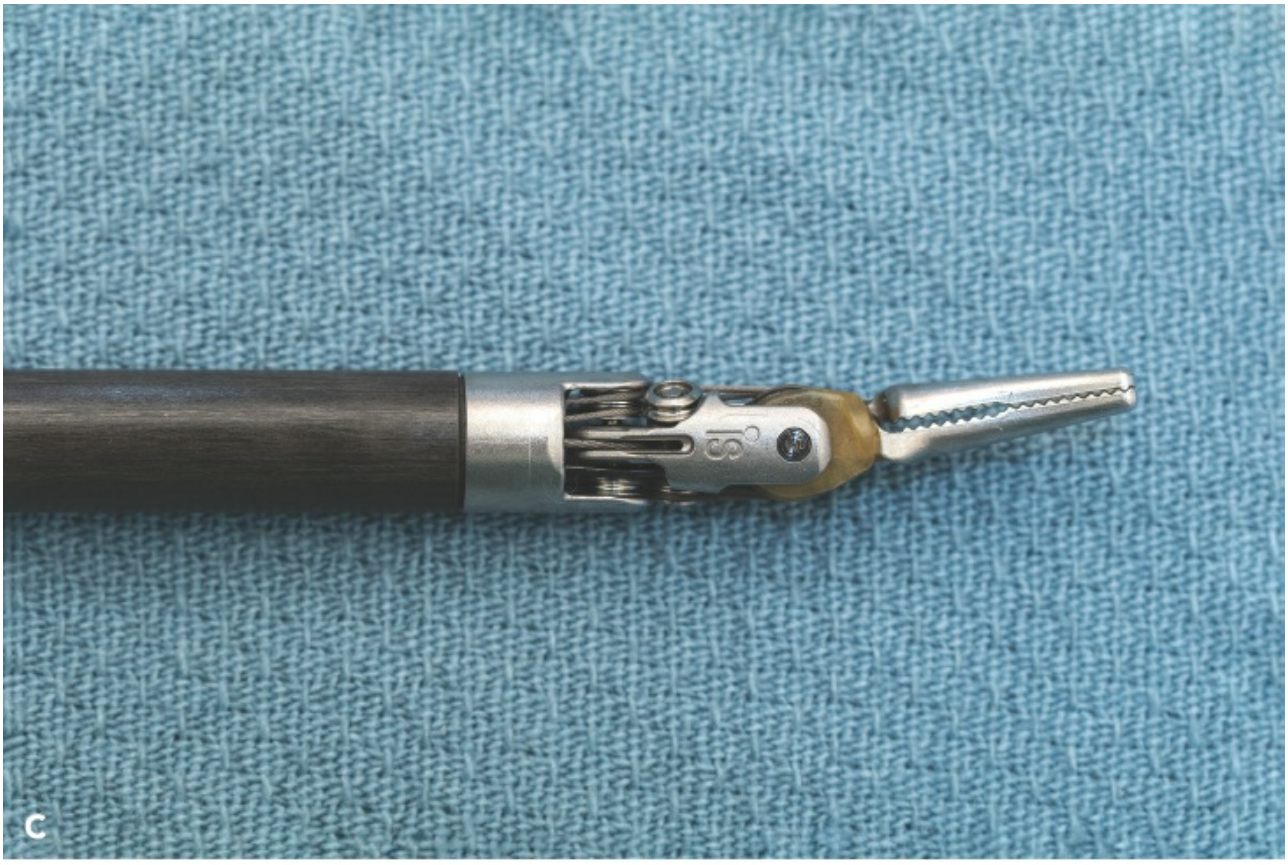
Another potential advantage of the robotic laparoscopy technique compared to laparoscopy without the assistance of robotics is that it may decrease the number of injuries in surgeons. There are multiple reports of laparoscopic-related surgeon morbidity syndromes, resulting from the unnatural forced position of wrists, fingers, elbows, and shoulders and the awkward standing position of the surgeon (14). A lower number of surgeon injuries and lower perception of surgeon's pain, numbness, and fatigue has been shown to occur when using robotics compared to conventional laparoscopy (15). Both physical and cognitive ergonomics are significantly improved with robotic surgery as compared to laparoscopic surgery (16).

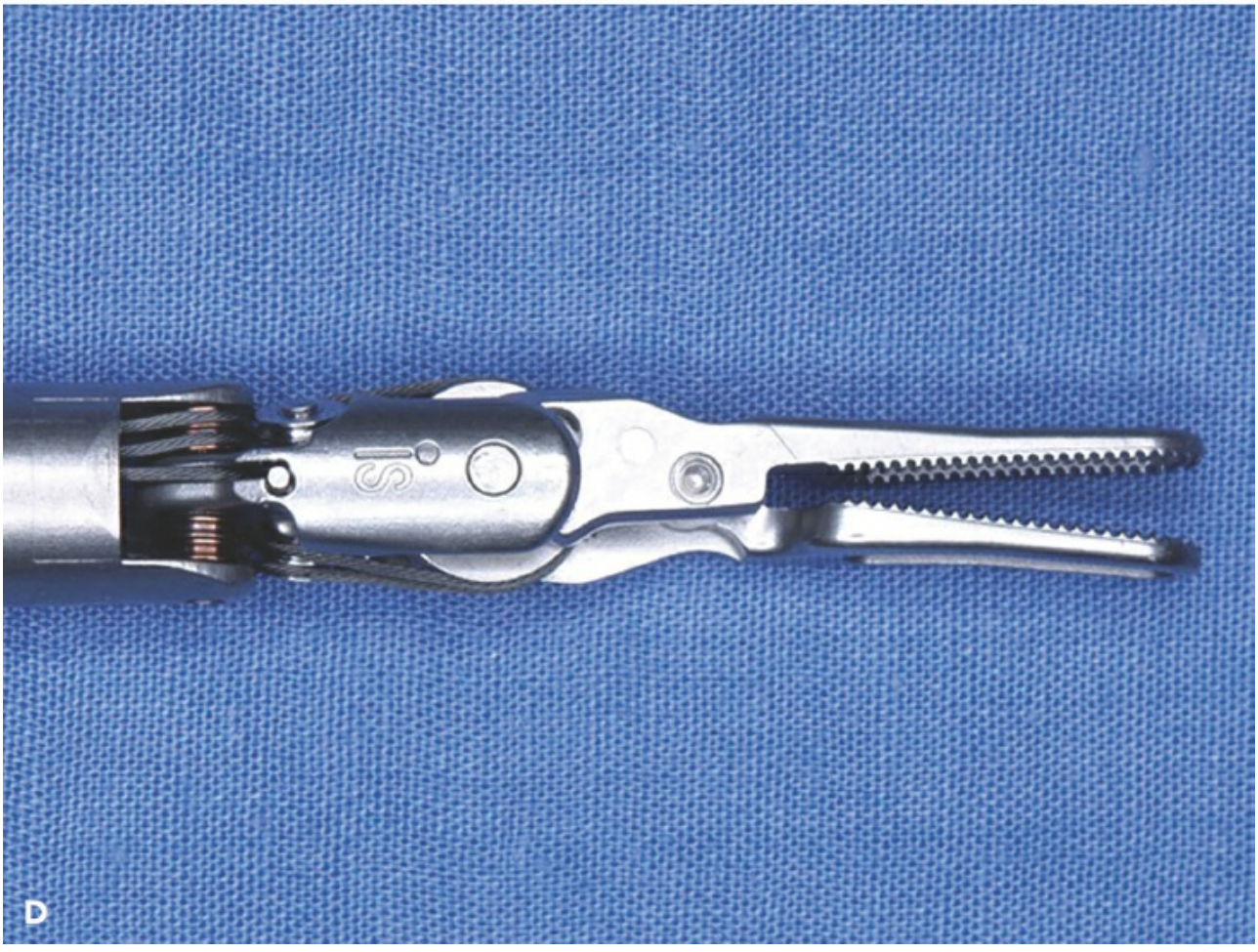
Instrumentation

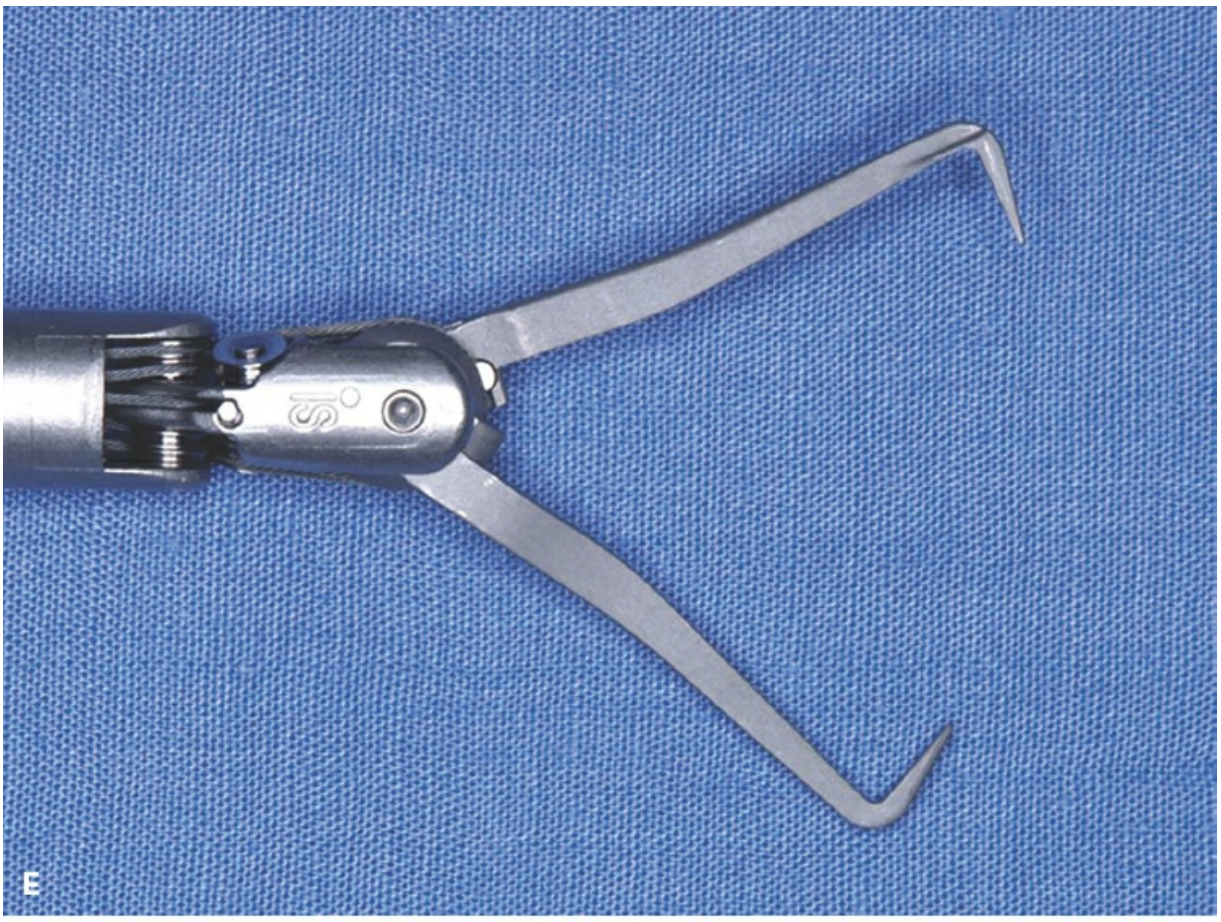
[2] Two of the most important differences between conventional laparoscopic instruments and robotic instruments are articulation and intuitive movements. The tip of a laparoscopic instrument is rigid and the instrument has only 4 degrees of freedom. With the exception of single-site instruments, the tips of robotic instruments are articulated with 7 degrees of freedom, reproducing the movements of the human wrist and fingers **(Fig. 28-5A–I)** (EndoWrist Instruments, Intuitive Surgery Inc., Sunnyvale, CA). The articulation allows the performance of complex maneuvers in small spaces; it accommodates the instrument to the correct plane of dissection (instead of forcing the tissue to the direction of the instrument as in laparoscopy), eliminates changing instruments from one port to another as in conventional laparoscopy, and facilitates suturing and intracorporeal knot tying. As indicated above, the movement of the robotic instruments is intuitive, following the movement of the surgeon hands.

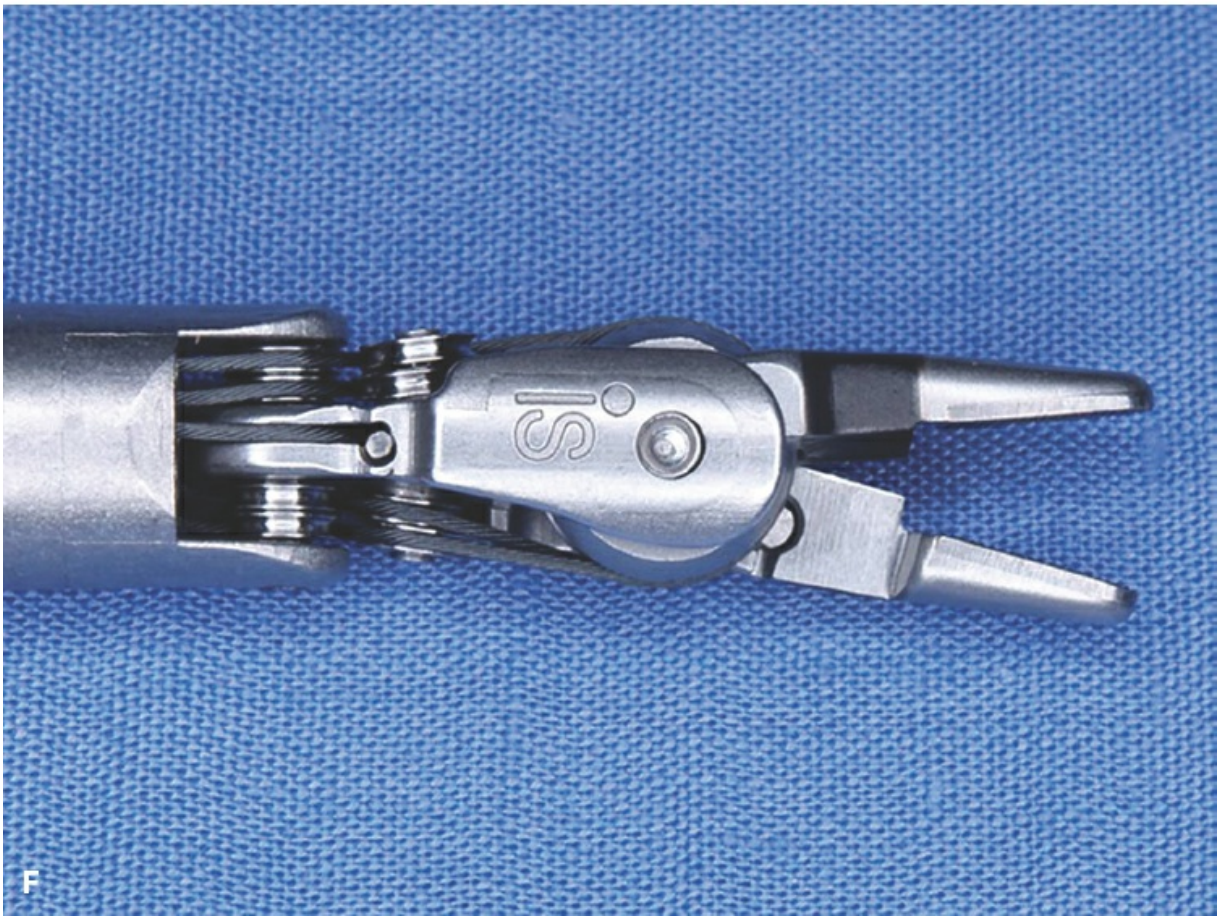

A


B


C

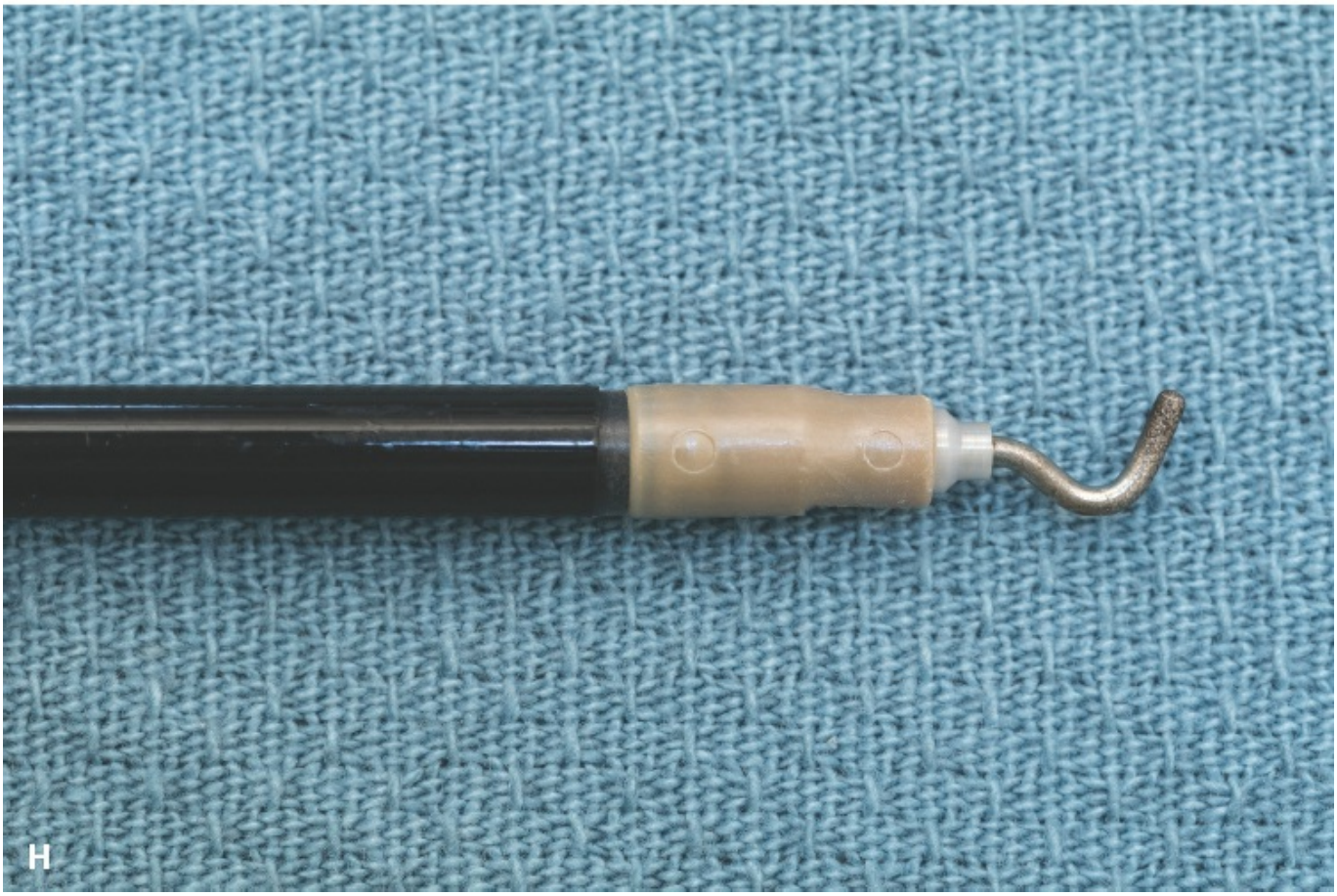

D


E


F



G



H



FIGURE 28-5 Robotic instruments commonly used in gynecologic surgeries. **A:** Monopolar curved scissors. **B:** Monopolar spatula. **C:** PK (plasma kinetic) dissecting forceps, bipolar. **D:** ProGrasp forceps, bipolar. **E:** Tenaculum forceps used for myomectomy. **F:** Needle grasper used for suturing. **G:** Vessel sealer. **H:** Single-site monopolar hook. **I:** Single-site needle grasper.

TYPES OF INSTRUMENTS

Robotic instruments useful for gynecologic surgery include ProGrasp forceps, PK dissecting forceps, tenaculum forceps, SutureCut needle driver, monopolar curved scissors, monopolar cautery spatula, and vessel sealer (Fig. 28-5A–I).

Trocars

The robotic trocars are 8 mm, metallic and have three different types of obturators: blunt, tissue-spreading, and cutting (Fig. 28-4A–C). **The robotic trocars are placed in a different configuration than conventional laparoscopy trocars because of technical limitations imposed by the robotic arms.** They are usually placed at the level of the umbilicus or higher for pelvic surgery and must be 10 cm away from each other and from the laparoscope to prevent collision of the robotic arms (Fig. 28-11). If

an assistant trocar is necessary, it must be placed 3 to 5 cm away from any of the other trocars. The trocar configuration, when using the S or Si models, is in the shape of an "M" directed toward the target anatomy. When using the Xi model, the trocar configuration is a line parallel to the target anatomy.

Docking

***Docking* is a robotic term defined as the attachment of the robotic arms to the robotic trocars inserted in the patient.** A mean docking time of about 3 minutes was reported in an initial study of 93 patients undergoing robotic hysterectomy (6). Docking times per surgeon improved progressively after groups of 10 patients each.

CERTIFICATION AND CREDENTIALING IN ROBOTICS

There is a mandatory training course of 2 days to obtain certification in robotics provided by the manufacturing company Intuitive, Inc. (Sunnyvale, CA) in centers located in the United States, Europe, and Asia. The gynecologist learns the robotic system and logs about 8 hours of dry and animal laboratory tasks. Residents or fellows completing training programs with robotics must demonstrate proficiency with documented basic robotic training and successfully perform a minimum of 10 robotic surgeries, preferably of the same type, and obtain a letter from the program director attesting to their level of robotic proficiency. Credentialing is dependent on each hospital credentialing body and is different for each institution: while some require robotic practice in five animals and having a proctor for the first five robotic surgeries, others mandate having a proctor for only two to five robotic procedures prior to obtaining robotic privileges.

Assistant

An assistant is needed for docking, exchanging robotic instruments, solving robotic arm collision, retrieving small specimens, and retracting tissue. The assistant must be trained in robotics and be very knowledgeable about the procedure, because the surgeon is seated in a separate place and not scrubbed.

TEACHING ROBOTICS

The robotic teaching console allows the surgeon and the resident or fellow to each have his or her own console while having dual control. The surgeon is able to demonstrate the performance of a specific task to the trainee, or to assist the resident with one robotic arm, or prevent an imminent injury by disengaging the robotic arms from the resident's hands, while both surgeon and resident are seated and viewing the

stereoscopic image. Use of a teaching console versus single console in training programs has been shown to improve perioperative outcomes (17).

Previous laparoscopic experience was considered an advantage to learning robotics. Multiple reports show that transitioning from laparotomy to robotics is easier than transitioning from laparoscopy to robotics (18). A large number of gynecologic oncologists and gynecologists incorporated robotics into their daily practice without having incorporated laparoscopy into their practice or performing advanced laparoscopic procedures. In one study the initiation of robotics in a gynecologic oncology program reduced laparotomy from 78% to 35% in the first year of implementation and it increased the number of minimally invasive procedures from 22% performed by laparoscopy to 65% being robotic assisted (18). Robotic technology is relatively easy to use, associated with a short learning curve, and comfortable for the surgeon (18–20). It is less stressful to learn robotics than laparoscopy. Reduced stress and ease of learning with robotics compared to laparoscopy was demonstrated when 16 medical students were exposed to both techniques (5).

ROBOTIC APPLICATIONS IN BENIGN GYNECOLOGY

[3] **The robotic system offers advantages for the surgeon, but it is particularly useful in the following circumstances: obese patients, long surgeries, and operations requiring extensive suturing or high precision.** There is no resistance felt by the surgeon's hands during the movement of the robotic instruments, regardless of the thickness of the patient's abdominal wall. Suturing and intracorporeal knot tying are greatly facilitated by the articulation of the robotic instruments. The surgeon's fatigue is decreased when seated for long operations. [4] **High precision and absence of tremor is useful for retroperitoneal lymphadenectomy, adhesiolysis, parametrial ureteral dissection, and accurate suturing, such as for ureteral anastomosis or reimplantation and genitourinary fistula repair.** [5] **Applications of robotic technology include simple hysterectomy, myomectomy, appendectomy (in conjunction with other procedures), adnexectomy, excision of severe endometriosis, tubal anastomosis, and rectovaginal or vesicovaginal fistulas, especially those in the upper vagina** (1,4). Robotic surgery is associated with a similar or shorter surgical time than conventional laparoscopy for the performance of simple hysterectomy and myomectomy, with reduced blood loss, complication rates, and hospital stays (2,4).



FIGURE 28-6 The robotic column is positioned over the patient's hip for pelvic surgery and over the patients shoulder for upper abdominal surgery as shown here.



FIGURE 28-7 The surgeon is seated at the console and is able to maintain a relaxed position for the arms and legs.

Hysterectomy

Laparoscopic-assisted vaginal hysterectomy was introduced in 1989. Laparoscopic approach to hysterectomy peaked at 15.5% of all hysterectomies in 2006 (21). By contrast, 5 years after FDA approval of robotic hysterectomy in 2005, 8.2% of hysterectomies were performed robotically in 2010 (21).



FIGURE 28-8 The finger controls allow the camera to be focused and have a clutch feature for ergonomic repositioning of the hand controls.



FIGURE 28-9 The foot pedals controlled by the left foot include clutch, camera, and arm swap. The foot pedals controlled by the right foot allow for energy activation (i.e., monopolar, bipolar, vessel sealing).

A report on 569 women who underwent robotic hysterectomy and 230 women who underwent laparoscopic hysterectomy showed reduction in estimated blood loss and hospital length of stay with the robotic approach. No difference was noted in surgical time (117.2 vs. 118.3 minutes respectively) (22). Rates of conversion were four times greater in laparoscopic approach compared to robotic hysterectomy (22).

Myomectomy

Laparoscopic myomectomy provides less morbidity and a shorter recovery time compared to open myomectomy in two prospective randomized studies (23,24). Similarly, robotic myomectomy morbidity and recovery times appear preferable to open myomectomy. In a comparison of both techniques, robotic patients experienced less blood loss, no blood transfusions, lower postoperative complications, and shorter hospital stays. The operating time and cost were increased in the robotic group (25). A series of 575 myomectomies (393 abdominal, 93 laparoscopic, 89 robotic) was evaluated (26). Surgical time was greatest in robotic approach when compared to abdominal or laparoscopic (181, 155, 126 minutes respectively) (23). Estimated blood

loss (100, 150, 200 mL) and hemoglobin decrease (1.3, 1.55, 2 g/dL) were least in robotic myomectomy (26). Hospital length of stay and need for blood transfusion were superior in both the robotic and laparoscopic myomectomy groups (26).

Robotic myomectomy provided comparable perioperative results to laparoscopy in three retrospective studies of patients with symptomatic myomas (26–28). No significant differences were noted between both groups for blood loss, complications, and hospital stay. The robotic operating time was longer than laparoscopy in two of the studies and no different in the other (26–28). In our comparison study, we noted differences favorable to the robotic group relative to operating time (141 vs. 166 minutes), blood loss (100 vs. 250 mL), and hospital stay more than 2 days (12% vs. 23%). There were no significant differences between groups when patients were adjusted for uterine size and myoma weight. There were no differences in intra- or postoperative complications. Postmyomectomy pregnancy rates, uterine rupture, and late operative complications using robotics remain undetermined.

Adnexectomy

Numerous studies show the benefits of laparoscopy over laparotomy for patients with an adnexal mass. Robotics provides similar perioperative outcomes when compared to laparoscopy for patients with an adnexal mass. Outcomes were improved with robotics for obese patients (body mass index [BMI] ≥30) with an adnexal mass. In a comparison series of 176 patients with an adnexal mass, 85 operations were by robotics and 91 by laparoscopy (29). The operating time was 12 minutes longer for the entire robotic group (83 vs. 71 minutes), but it was similar to laparoscopy when comparing only patients with a BMI 30 or more (80 vs. 71 minutes). Blood loss was similar for both groups (39.1 vs. 41.2 mL), but lower for the robotic group when comparing only obese patients (BMI ≥30) (39 vs. 60 mL). The length of hospital stay, as measured by the number of patients staying longer than 2 days (0 vs. 3) was similar for both groups.

Endometriosis

Robotics has been shown to be feasible for the resection of pelvic endometriosis. A prospective randomized trial showed no differences in perioperative outcomes and quality of life issues between robotics and laparoscopy for patients with pelvic endometriosis or pelvic pain without endometriosis (30). In a retrospective study comparing robotics and laparoscopy for stage III and IV pelvic endometriosis, there was a 16% reduction of operating time with robotics when the number and type of procedures were accounted for (31).

Tubal Reversal

Robotic tubal reversal may be preferable to laparotomy. In a prospective study comparing both techniques on patients with a previous tubal ligation, the operating time was longer using robotics (201 vs. 155 minutes), but the hospital stay (4 hours vs. 1.3 days), and recovery time to normal activities (11.1 vs. 28.1 days) were improved for robotic patients (32). Both groups had similar pregnancy rates (62.5% vs. 50%). In another retrospective case-control study of outpatient tubal anastomosis performed by robotics or minilaparotomy, perioperative outcomes were similar except for a longer operating time, increased cost, and a shorter time to patient's recovery with robotics (33).

Appendectomy

Reported results on 107 robotic appendectomies performed in conjunction with other pelvic procedures had a mean time for appendectomy of 3.4 minutes. No perioperative complications related to appendectomy were encountered. Increased abnormal pathologic findings were observed in patients with pelvic pain compared to those without pain (37% vs. 15%, respectively). Appendiceal metastases were found in 43% of patients with ovarian malignancy (34).


PUSH
A


B



FIGURE 28-10 The wrist level of the surgeon console houses the control panel **(A)**. **B:** The left controls ergonomic adjustments. **C:** The right controls the power and emergency stop buttons.

Sacrocolpopexy

The robotic approach to sacrocolpopexy facilitates ease of suturing and intracorporeal knot tying. A report of feasibility experience with 80 patients demonstrated total operating time of 197.9 minutes, and most patients underwent additional procedures at the same surgical setting (35). There was a 25.4% decrease of the operating time after the first 10 surgeries. Complications were minimal. Other reported operating times are 317 and 328 minutes (36,37).

A randomized controlled study evaluating robotic versus laparoscopic sacrocolpopexy showed laparoscopic approach to be superior for operating room time (199 vs. 265 minutes), sacrocolpopexy time (162 vs. 227 minutes) and sacrocolpopexy suturing time (68 vs. 98 minutes) (38). Hospital stay was similar for both groups (38).

Robotic sacrocolpopexy is preferable to laparotomy because of improved perioperative outcomes and similar anatomical results. A comparison of 73 robotic with 105 laparotomy sacrocolpopexies for vaginal and uterine prolapse revealed a longer operating time (328 vs. 225 minutes) but reduced blood loss (103 vs. 255 mL) and

shorter hospital stay (1.3 vs. 2.7 days) for the robotic group. Anatomical improvement was similar for both groups as determined by pelvic organ prolapse quantification (POP-Q) C point (−9 vs. −8) (see Chapter 30) (37). Late complications, such as erosion rate and long-term anatomical results of robotic sacrocolpopexy are unknown.

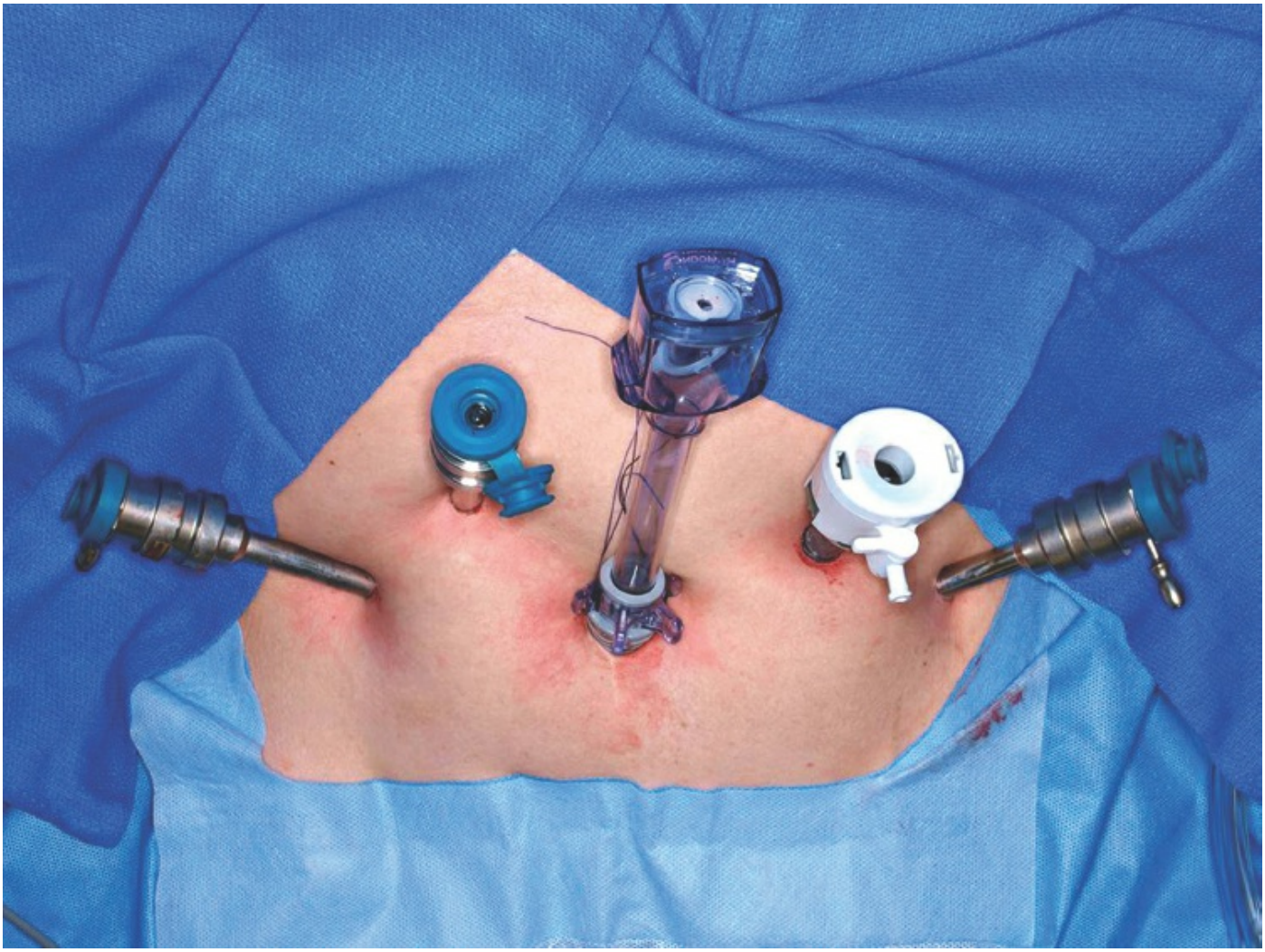


FIGURE 28-11 Trocar position for robotic pelvic surgery. The optical trocar is at the umbilicus. Two robotic trocars are placed 10 cm lateral to the right and left of the umbilicus, respectively. The assistant white trocar is 3-cm cranial and equidistant between the umbilical and left robotic trocar. An additional robotic trocar is 3-cm cranial and equidistant between the umbilical and the right robotic trocar.

GYNECOLOGIC ONCOLOGY

[6] Studies show the feasibility of robotics for the treatment of patients with cervical, endometrial, tubal, and ovarian cancer, with apparent similar or better perioperative outcomes, compared to conventional laparoscopy and with improved outcomes compared to laparotomy (39–45). A survey of Society of Gynecologic Oncologists members indicated 24% are regular users of robotics and 66% believed their use would increase (39).

Endometrial Cancer

Laparoscopy provides similar or longer operative times, less blood loss, fewer postoperative complications, shorter hospital stay and recovery times, with similar recurrence and survival rates compared to laparotomy (40–45). The laparoscopic approach is now considered standard for endometrial cancer. Robotic technology may be preferable to conventional laparoscopy in selected patients for surgery for endometrial cancer, especially in morbidly obese patients. In expert hands, the use of minimally invasive techniques—laparoscopy and robotics—may facilitate the operations.

Studies comparing robotics to laparotomy suggest improved perioperative outcomes for robotics. Operative times are similar or longer, blood loss and hospital stay are reduced, the number of lymph nodes is comparable or higher, and postoperative complications are similar or decreased with robotics (18–20,46–51). Studies comparing robotics with conventional laparoscopy for endometrial cancer show similar or superior results for robotics. Some showed reduced blood loss, shorter hospital stay, increased lymph node yield, and lower morbidity with robotics compared to conventional laparoscopy (47,51). Others reported longer operating time but reduced blood loss, lower transfusion rate, lower conversion rate to laparotomy, and reduced hospital stay, even though the robotic patients had a higher BMI compared to laparoscopy (50,51). Robotics, as with laparoscopy, resulted in a shorter recovery time for endometrial cancer patients compared to laparotomy (46,51,52).

In an initial review of 38 patients with robotics operations, the perioperative outcomes were similar to patients treated by laparoscopy ($n = 22$). Results were similar to patients treated by laparotomy ($n = 16$) other than a larger blood loss and longer hospital stay for this group of patients. The operating times were similar for the three groups, blood loss was lower for the robotic and laparoscopy groups (283, 222, and 517 mL), and length of hospital stay was shorter for the robotic and laparoscopy groups (2, 2.5, and 6 days). There was no difference relative to the number of lymph nodes removed (18.4, 26.3, and 18.4, for robotics, laparoscopy, and laparotomy, respectively), number of lymph node metastases, positive cytologic findings, or tumor recurrence. Postoperative complications were comparable among the three groups.

Boggess et al. compared 103 robotic patients with 81 laparoscopy patients and 138 laparotomy patients (47). The operating times for robotic and laparoscopy procedures were similar, but longer than laparotomy (191.2 minutes, 213.4 minutes, and 146.5 minutes, respectively). The blood loss, hospital stay, and number of nodes were all improved for the robotic group. Bell et al. compared a group of 40 robotic patients with 30 patients operated by laparoscopy and 40 patients operated by laparotomy (46). Robotic and laparoscopy operating times were comparable (184 minutes and 171 minutes, respectively) and longer than laparotomy (108.6 minutes). Blood loss was similar to laparoscopy, and both were lower than the laparotomy group. The number of

lymph nodes removed was similar among the three groups. Postoperative complications were lower in the robotic group compared to the other two groups (7.5%, 27.5%, and 20%, respectively).

Another study evaluated the results of robotics and conventional laparoscopy for obese and morbidly obese patients (BMI 30 to 60) with endometrial cancer (48). Robotics was found to be preferable to the laparoscopic approach because of a shorter operative time, reduced blood loss, increased number of lymph nodes removed, and shorter hospital stay. The benefits of robotics for obese patients were noted with simple robotic hysterectomy, where the operating time remained unchanged in spite of the patient's increased BMI (6). This may result from the absent awareness of the resistance of the robotic instruments being inserted through a thick abdominal wall because of the lack of tactile feedback.

When comparing 67 robotic patients, 37 laparoscopic patients, 99 laparotomy patients, and 47 vaginal/laparoscopic patients with endometrial cancer, robotics was the preferred approach (51). Robotics, laparoscopy, vaginal/laparoscopy techniques have longer operative times when compared to laparotomy (181.9, 189.5, 202.7, and 162.7 minutes respectively) (51). The vaginal/laparoscopic approach is associated with the longest operating time. Mean blood loss (141.4, 300.8, 300.0, 472.6 mL respectively) and hospital length of stay (1.9, 3.4, 3.5, 5.6 days respectively) were superior (61). A major benefit of the robotic approach was a lower conversion rate to laparotomy (2.9%) as compared to laparoscopy (10.8%) (51). No significant differences were noted in perioperative complications or recurrence rates (51).

The increased cost of this technology is a criticism of robotics. Because cost is tied to frequency of use, when used on a regular basis the cost becomes similar to laparoscopy and less expensive than laparotomy as a result of shorter hospital stay. A comparison study of costs for robotics, conventional laparoscopy, and laparotomy for endometrial cancer showed a significantly reduced cost for robotics and laparoscopy compared to laparotomy and comparable costs for robotics and laparoscopy with regular use of robotics (46).

Cervical Cancer

Early Cervical Cancer

Robotic and laparoscopic radical hysterectomy may provide patient benefits over a laparotomy approach relative to blood loss, blood transfusions, and length of hospital stay. Retrospective studies have shown lower or similar operating times and postoperative complications (53–59). Recurrence and survival rates remain unchanged when comparing the results of both techniques (53–55,58,59). An international, multicenter, prospective randomized trial compared laparoscopy/robotics with laparotomy (60). The trial included patients with cervical cancer FIGO stage IA1 with

lymphatic invasion to stage IB1. Minimally invasive surgery had a worse recurrence and survival as compared to open surgery (disease-free survival 3-year rate, 91.2% vs. 97.1%; hazard ratio for disease recurrence or death from cervical cancer, 3.74; 95% CI, 1.63 to 8.58. Overall survival 3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30) (60). It is important to emphasize that there was no difference in recurrence or survival for patients with tumors <2 cm; all recurrences occurred in 14 of the 33 participating centers; the recurrence rate with open surgery was extremely low compared to most published rates; and out of the 319 patients assigned to the minimally invasive surgery only 45 (16%) were operated by robotics.

Radical Hysterectomy

The surgical technique for robotic radical hysterectomy is described elsewhere (61). A rapid learning curve is noted with robotic radical hysterectomy, with a 44-minute reduction in operating time after the first 34 procedures in association with a low complication rate and high nodal count (62).

In several retrospective studies comparing laparotomy with robotic radical hysterectomy, there was a shorter, similar, or longer operating time; reduced blood loss; shorter hospital stay; lower, similar, or higher number of lymph nodes removed; and similar rate of postoperative complications (56,63–66). In comparison with laparoscopy, robotics is associated with a shorter, similar, or longer operating time; reduced blood loss; shorter hospital stay; similar or lower postoperative complications; and comparable or higher number of nodes (56,57,63,65).

Tumor recurrence does not appear increased with robotics compared to laparoscopy. At a mean length of follow-up of 31.1 months (range, 10 to 50 months), none of the patients in the robotic group experienced recurrence, and there was no difference with the laparoscopy group (57).

Radical Nerve-Sparing Hysterectomy

The technique of robotic nerve-sparing radical hysterectomy has been described (67). In a comparison study with robotic radical hysterectomy there were no differences with operating time, blood loss, complications, and length of hospital stay (67). Studies with open nerve-sparing radical hysterectomy have shown no differences with recurrence and survival.

Other Applications of Robotics for Cervical Cancer

Occult Cervical Cancer on an Extrafascial Hysterectomy Specimen

Radical parametrectomy is a surgical option for patients with an occult invasive cervical carcinoma discovered on an extrafascial hysterectomy specimen with negative margins and with no gross visible disease. The feasibility of robotic radical parametrectomy was reported by Ramirez et al. in five patients with minimal

complications (68). There are no comparison studies of robotic radical parametrectomy with laparoscopy or laparotomy (69).

Cancer of the Cervical Stump

Radical trachelectomy for cancer of the cervical stump is preferable to pelvic irradiation in some patients because of the increased risk of bowel complications from intestinal adhesions to the remaining cervix. The laparoscopic approach is previously reported (70). The use of robotic radical trachelectomy in a patient with a "cut-through" endometrial cancer discovered in the subtotal hysterectomy specimen was reported (71).

Cervical Cancer With Desire for Fertility

Radical trachelectomy is an alternative to radical hysterectomy for cervical cancer in young patients desiring fertility and with a tumor size of 2 cm or less, no lymphatic invasion or nodal metastases, and potential for preservation of the upper portion of the cervix. The feasibility of robotic radical trachelectomy was demonstrated in two patients with early-stage cervical cancer (72). The operative times were longer (387 and 358 minutes), because of the novelty of the procedure and the required waiting time for the frozen section. No intra- or postoperative complications were observed. There are no comparison studies of robotic radical trachelectomy with laparoscopy or laparotomy. A review of eight reported patients until May 2009 showed a median operating time of 339 minutes, median blood loss of 62.5 mL, no intraoperative complications, no blood transfusions, no conversions to laparotomy, and a median length of hospital stay of 1.5 days (73). The median number of pelvic lymph nodes removed was 20.

Advanced Cervical Cancer: Retroperitoneal Lymphadenectomy Prior to Chemoradiation

The laparoscopic approach to pelvic and aortic lymphadenectomy prior to chemoradiation for patients with advanced cervical cancer is well-documented, both transperitoneal and extraperitoneal (74–79). There are many studies discussing robotic pelvic and aortic lymphadenectomy for different types of gynecologic malignancies, including cervical, endometrial, and ovarian malignancies (19,56,57,62–66,80,81).

Transperitoneal

A novel technique and the results of robotic transperitoneal infrarenal aortic lymphadenectomy in 33 patients with different gynecologic cancers have been reported (82). This technique requires rotation of the operating table 180 degrees and insertion of additional trocars in the lower pelvis after completion of the robotic pelvic operation (82). The mean console time was 42 minutes, the mean number of nodes 12.9, and the

mean number of positive nodes 2.6. There was one conversion to laparotomy caused by bleeding. These results are comparable to those reported with laparoscopic aortic lymphadenectomy. Placing the robotic column at the patient's head and inserting additional trocars in the lower pelvis were requirements to remove the infrarenal aortic nodes with robotics. Previous attempts to remove the left infrarenal aortic lymph nodes in a frozen cadaver were unsuccessful when the robotic column was stationed at the level of the patient's feet.

A comparison study of robotic versus laparoscopic transperitoneal infrarenal aortic lymphadenectomy revealed similar operating times, blood loss, and complications (83). However, the cost was higher for the robotics approach.

Extraperitoneal

The feasibility of the extraperitoneal robotic approach to aortic lymphadenectomy has been reported (84,85). The development of the robotic extraperitoneal technique in frozen cadavers, successfully applied to a patient with cervical cancer stage IB2 presenting with enlarged left aortic lymph nodes, is reported (84). It was noted that appropriate placement of the robotic trocars and the robotic column is necessary to prevent robotic arm collision and to reach the different aortic lymph nodal areas. The operating, docking, and console times were 103, 3.5, and 49 minutes, respectively. The blood loss was 30 mL. Selective removal of five enlarged aortic lymph nodes as noted on CT scan revealed no evidence of metastases.

Another study by Vergote et al. reported the development of their technique for inframesenteric aortic lymphadenectomy in five patients (85). All console times were less than 1 hour. The operating times and number of aortic lymph nodes in both studies are within the range of those reported with the laparoscopic approach. Both studies concluded that the robotic approach was technically easier than the conventional laparoscopy procedure (84,85).

A comparison study of robotics versus laparoscopic extraperitoneal aortic lymphadenectomy (86) revealed similar findings with both techniques. It was noted that surgeon experience with either of the two techniques will provide optimal results. Cost estimate was not evaluated in that study.

Recurrent Cervical Cancer: Robotic Pelvic Exenteration

Isolated reports with small numbers of patients have demonstrated the feasibility of robotic pelvic exenteration for advanced primary and recurrent cervical cancer (87). The latter are more difficult and longer surgeries because of the adhesions from previous surgery and/or irradiation. A review of the literature revealed most cancers are primary squamous cell carcinomas treated by anterior pelvic exenteration (7), with only one patient receiving a total pelvic exenteration. The operating time ranges from 375 to 600 minutes, blood loss from 200 to 550 mL and hospital stay from 3 to 53 days. The operating times are longer than by laparotomy, blood loss is markedly decreased,

and hospital stay is usually similar, although shorter in some cases. In some patients, a paramedian incision is used for the creation of a urinary pouch (87).

Whether the robotic approach to pelvic exenteration will become routinely preferable to laparotomy is debatable in the context of the longer operating time and similar hospital stay. However, for selected patients it is a good alternative with excellent results.

Ovarian Cancer

Surgery for ovarian cancer requires access to all four abdominal quadrants. The ability to operate in all four quadrants using the da Vinci S or Si can be achieved only by rotating the operating table, while maintaining the robotic column on the same location. The recent da Vinci Xi system allows access to the upper and lower abdomen by 180-degree rotation of the robotic arms instead of moving the operating table. This makes it possible to excise the aortic lymph nodes to the level of the renal vessels and resect upper abdominal metastases, including diaphragm, liver, and supracolic omental disease.

Robotics is useful for selected patients with ovarian cancer. The optimal use of the surgical robotic system for ovarian cancer is for early disseminated disease localized in different areas, whether at primary, interval, or secondary debulking, allowing complete resection.

Primary Disease

Initial experience with 21 patients with advanced ovarian cancer whose operations were by robotics was reported (88). Included were 12 primary, 4 interval, and 5 secondary cytoreductive surgeries for ovarian cancer. In addition to primary tumor excision, major procedures included modified posterior pelvic exenteration, rectosigmoid resection, small bowel resection, diaphragm resection, and resection of liver metastases. The operating times had a wide range (103 to 454 minutes) resulting from the extent of procedures. Blood loss was low (25 to 300 mL). Postoperative complications were low, and directly related to the number of prior procedures per patient.

Other reports of robotics for ovarian cancer consist of an occasional patient included within a series of patients with different types of gynecologic cancers (86,89–92).

A comparison of robotics, laparoscopy, and laparotomy for ovarian cancer revealed advantages of laparoscopy and robotics over laparotomy for blood loss, complications and hospital stay (86). The advantages were only for patients requiring primary tumor removal including hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, omentectomy, removal of tumor implants, appendectomy, and one additional major procedure, such as diaphragm, small bowel, sigmoid, liver or spleen resection. Patients requiring two or more major procedures or with multiple peritoneal implants are best

operated by laparotomy because of similar complications and hospital stay.

Recurrent Disease

The benefits of a minimally invasive approach, robotics and laparoscopy, for secondary cytoreduction compared to laparotomy, were demonstrated in an early study (93). Robotics and laparoscopy provided similar results. Optimal candidates for the minimally invasive approach are patients with localized recurrent disease amenable to complete resection.

Similar findings and conclusions were reached in a subsequent multicenter study including 48 patients. Optimal debulking was achieved in 82% of patients. Conversion to laparotomy was required in 8.3% of patients (94). In cases not requiring conversion, median operative time was 179.5 minutes, estimated blood loss was 50 mL and length of stay was 1 day.

Summary

Robotics and laparoscopy have advantages compared to laparotomy for selected patients with cervical, endometrial, and early ovarian cancer. Prospective data has established a minimally invasive approach as standard surgical treatment using laparoscopy or robotics. Although prospective randomized trials are desirable, the retrospective evidence supports the use of minimally invasive surgery for selected endometrial and cervical cancer patients and those with patients with primary or recurrent ovarian cancer.

COMPLICATIONS UNIQUE TO ROBOTICS

There is a linear relationship with perioperative complications of robotic gynecologic surgery as the complexity of the procedure increases, which is directly related to the operator's skill and patient's pathology (89). This is no different than previously noted for laparoscopic surgeries. There are complications related to the robotic technology.

Because there is no tactile feedback, the robotic arms can injure any organ not under visual control. The potential for injury is higher with the fourth retracting arm when it is out of the visual field and repositioned without visual control. Constant visual control of the robotic instrument position is mandatory for the prevention of injuries. Collision of the robotic arms is felt as an unwanted resistance, which is realized when the instruments are brought under view. When the robotic arm is not under direct visual control, removal and reinsertion of instruments can result in unintended injury.

Constant pressure of the robotic arms on the patient thighs or arms may result in injury. This can be prevented during positioning of the patient and the robotic arms. Movement of a robotic arm by anyone other than the surgeon may result in patient

internal injury. A rapid move by the surgeon on any robotic instrument may result in hitting the assistant near the operating table with the robotic arm.

Because the robotic trocars are fastened to the robotic arms, and the arms are fixed to the robotic column, any sudden loss of the pneumoperitoneum may result in the instruments being pulled off the anterior abdominal wall as it becomes flattened. Similarly, any sliding of the patient on the operating table as a result of the Trendelenburg position will result in pressure at the trocar site and potential injury or increased postoperative trocar-site pain.

Insulation failures occur when the electricity escapes through small, usually not visible, defects in the insulation material involving the shaft of monopolar and bipolar instruments. This has resulted in unrecognized thermal bowel injuries with subsequent bowel perforation. Insulation failures are more common with robotic as compared to laparoscopic instruments (95).

Disadvantages of Robotics

The present robotic system has limited surgical field reach. It allows for pelvic or abdominal surgery, but not both, unless the operating table, robotic column (da Vinci S or Si) or boom (da Vinci Xi) is rotated 180 degrees. This repositioning increases surgical time and, depending on the procedure, may require the insertion of additional trocars.

An assistant versed in robotics is necessary at the patient's side to be able to provide the required assistance without the surgeon's help other than verbal directions, because the surgeon is not in surgical sterile condition. Tissue traction is not as efficient as with conventional laparoscopic instruments, for instance for myomectomies, when necessary. Because there is no tactile feedback when grasping a tissue, there is only visual control of the traction exerted upon any structure. While **the lack of tactile feedback is an advantage in obese patients it is a disadvantage when the instruments are not in the visual field.**

Cost is a common reason why many institutions have delayed the initiation of robotic programs. The initial purchase of the robotic system is high, and there is an additional annual maintenance fee, and all reusable robotic instruments become functionless after 10 uses. Some robotic instruments, such as the vessel sealer, are only single use.

The robotic column and its arms are bulky, with a total weight of 1,200 lb. An operating room must have adequate space, preferably about 600 square feet. There must be a dedicated team for robotic surgery and preferably a specific team for each surgical specialty.

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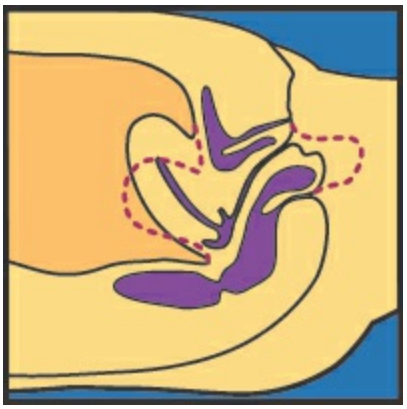
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SECTION V

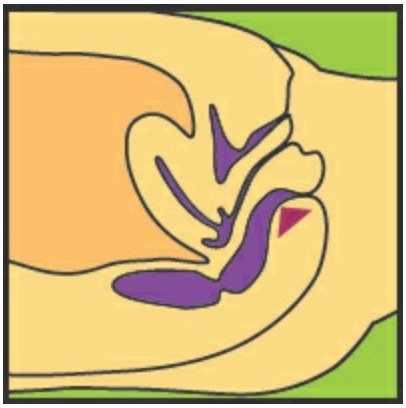
Urogynecology



CHAPTER 29
Urinary Tract
Vatché A. Minassian, Iwona Gabriel



CHAPTER 30
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Alicia V. Ballard, Isuzu Meyer, Robert Edward Varner, Jonathan L. Gleason, Holly E. Richter



CHAPTER 31
Anorectal Dysfunction

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CHAPTER 29

Urinary Tract



Vatché A. Minassian, Iwona Gabriel

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KEY POINTS

1 The lower urinary tract comprises of the bladder and urethra; it is under autonomic and somatic nervous system control, and is anatomically supported by the pelvic floor musculature.

2 Urinary incontinence, although underdiagnosed, is very common, has a significant impact on quality of life, and is generally treated successfully with conservative or surgical treatments.

3 Stress urinary incontinence is the most common subtype and occurs with increases in abdominal pressure; it can be treated with pelvic floor exercises, pessaries, behavioral modification, and surgery.

4 Urgency urinary incontinence occurs with a sudden desire to urinate that cannot be postponed; it can be treated with bladder training, medications, behavioral modification, bladder onabutulinumtoxinA injections, and neuromodulation.

5 Mixed urinary incontinence is the co-occurrence of stress and urgency incontinence; it is the most bothersome and impactful subtype, and most common in late adulthood.

6 Voiding dysfunction and bladder pain syndrome are less common than urinary incontinence, but more challenging to treat successfully.

INTRODUCTION

[1] The urinary tract in women is comprised of the bladder that receives and stores urine from the kidneys as it is propelled downstream via the right and left ureters. The bladder expels the urine out of the body through the urethra when it reaches capacity or when it is socially appropriate to do so. To help accomplish this dual role of storage and voiding, the bladder and urethra are enveloped with muscles whose fibers are innervated by an intricate network of autonomous and somatic nerves, and they are anatomically supported by a complex system of pelvic floor muscles, fascia, connective tissues, and nerves within the pelvis.

Anatomy of the Lower Urinary Tract

In the supine position, the bladder is positioned between the pubic bone and transversalis fascia anteriorly and the endopelvic fascia, vagina, and uterus posteriorly. The lateral margins of the bladder abut the obturator fascia and the condensation of muscle and connective tissue known as the arcus tendinous muscle fascia (white line). The bladder is comprised of three layers including the mucosa, detrusor (mostly smooth muscle), and serosa. The bladder mucosa consists of the urothelium, basement membrane, and lamina propria. The latter is composed of an extracellular matrix with different cell types, nerve endings, lymphatic and blood vessels, all of which may play a role in maintaining bladder compliance and act as a communication portal between the nervous system and bladder muscle (1). The trigone, which is the base of the bladder, gets its name from the triad of the two ureteral orifices and the proximal urethra that make up the three corners of the triangle. The urethra is a 4-cm tubular structure surrounded by skeletal muscles. It travels over the anterior wall of the vagina and exits the urogenital diaphragm under the pubic symphysis as it opens into the top of the

introitus (Fig. 29-1).

Innervation of the Bladder and Urethra

The bladder is primarily innervated by the autonomic, the sympathetic and parasympathetic, nervous systems. The sympathetic nervous system originates from the thoracolumbar region of the spinal cord. Signal transmission occurs via the paraspinal ganglia with norepinephrine being the primary postganglionic neurotransmitter stimulating two different adrenergic receptor types: (a) the alpha receptors are mostly located in the urethra and trigone; and (b) the beta receptors are primarily located in the body of the detrusor muscle. The parasympathetic nervous system originates from the sacral region of the spinal cord. Unlike the sympathetic system, the parasympathetic system has long neurons that exit from S2 to S4, synapse with their ganglia closer to the end organ (bladder), and transmit their signals via short postganglionic neurons to the body of the detrusor muscle. Here, transmission of messages occurs through acetylcholine neurotransmitters stimulating muscarinic (or cholinergic) receptors. The somatic nervous system plays a secondary role in the lower urinary tract system. It originates from the sacral (S2–S4) region of the spinal cord via the pudendal nerve; it provides motor innervation to the urethral sphincter and pelvic floor muscles, and sensory innervation to the perineum (2).

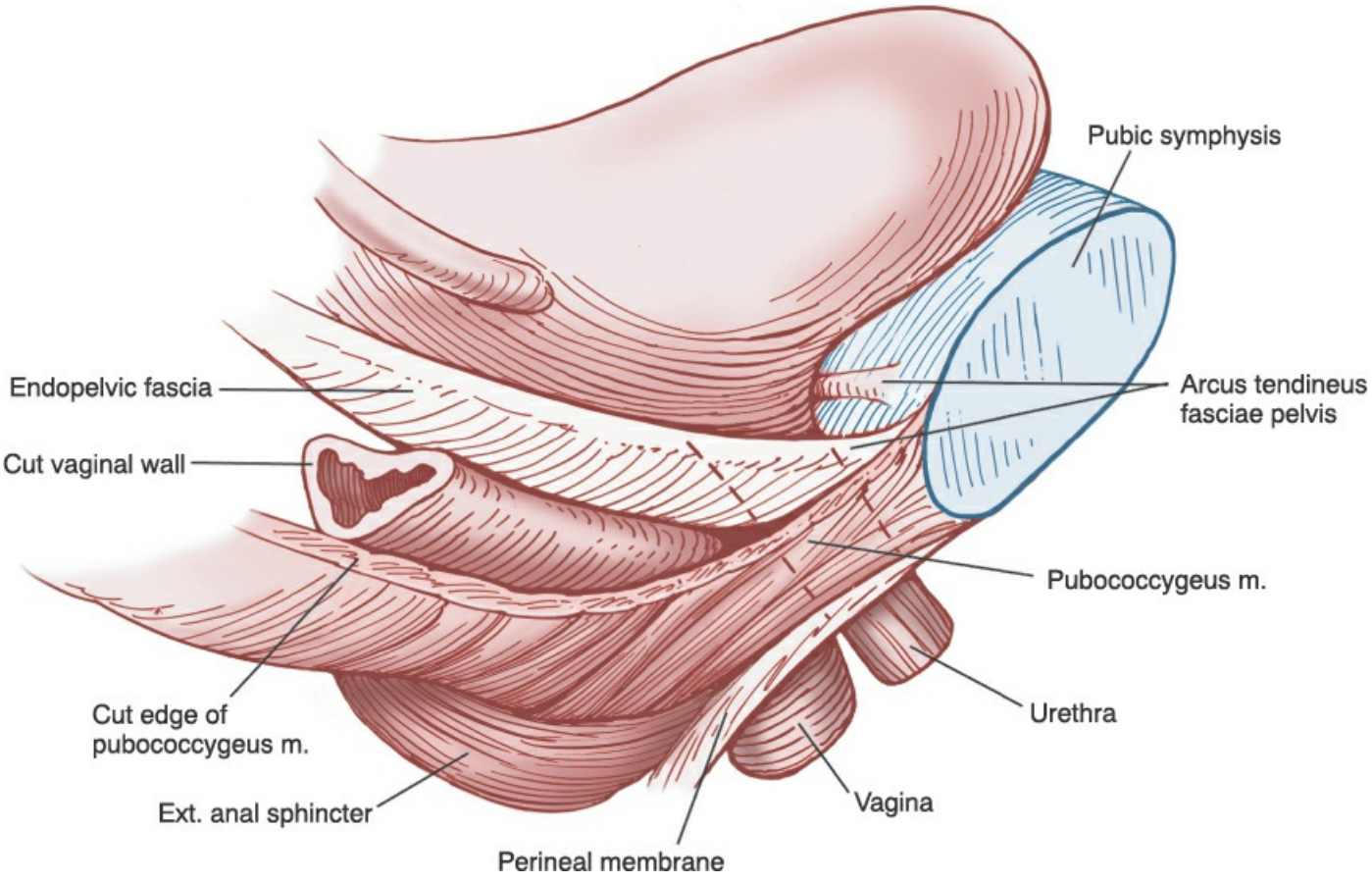


FIGURE 29-1 Lateral view of the pelvic floor showing the anatomic location of the bladder, urethra, vagina, and pelvic floor support structures transected at the level of the vesical neck.

The central command of the sacral micturition center comes from impulses generated at the level of the pontine micturition center located in the brain stem which is regulated by signals that arise from higher levels of the cerebellum and cortex of the brain. This complex interplay between the upper cortex, cerebellum, and brainstem plays a key and dual role of: (a) *inhibition* that supports the storage function during the filling phase; and (b) *stimulation* that facilitates the micturition function of the bladder during the voiding phase (3).

The Physiology of Storage and Voiding

The primary role of the bladder is to store urine produced by the kidneys and excreted through the ureters, and to subsequently eliminate the urine outside the body through the urethra. The function of storage is made possible by several factors including: (a) intrinsic factors to the bladder such as the ability of its elastic smooth muscle fibers to stretch as the volume of urine distends its capacity; (b) extrinsic factors to the bladder including excitatory neurologic stimuli that constrict the proximal urethra and urethral sphincter, and inhibitory neurologic stimuli that inhibit (or relax) the detrusor muscle of the bladder. This reservoir function of the bladder, which in effect translates into its continence mechanism, is dependent on the proper functioning of the autonomic (sympathetic and parasympathetic) nervous system, and the somatic nervous system (4).

Continence during storage is dependent on the integrity of the bladder muscle, urethra, and the pelvic floor support structures surrounding the lower urinary tract, including the levator ani muscles, endopelvic fascia, and their attachments to the pelvic sidewall and the white line. The urethra has several components within or around it that play an important role. These include the striated muscles of the urethral sphincter, the smooth muscles of the urethra, and the neurovasculature of the urethral wall, all of which help maintain elasticity and the epithelial coaptation function of the urethra during times of bladder filling (5,6). **The extrinsic structures supporting the urethra and the intrinsic urethral function are equally important, to the extent that a defect in the former can lead to urinary incontinence resulting from hypermobility of the urethrovesical junction, and a defect in the latter can lead to urinary incontinence caused by intrinsic sphincter deficiency.**

During the filling phase, the sympathetic nervous system through the lumbar region of the spinal cord sends inhibitory signals to the beta receptors in the bladder to relax, and excitatory signals to the smooth muscles of the trigone and urethra to contract. As the bladder gets distended, afferent fibers from the bladder send impulses to the central

nervous system through the pelvic nerve to the sacral spinal cord. This initiates two types of impulses: one that is transmitted horizontally via the micturition reflex back to the bladder, and another that is transmitted vertically up to the brain. The latter will make one of two conscious decisions. If it is socially inappropriate to initiate micturition, it will send excitatory impulses via the pudendal nerve to contract the pelvic floor muscles and external urethral sphincter, and inhibitory impulses to supplement the function of the sympathetic system **(Fig. 29-2)**. Alternatively, the brain may decide it is an opportune time to eliminate the urine. In this instance, it will send voluntary impulses to the striated muscles to relax the pelvic floor and urethral sphincter. It will also send facilitative impulses to the pontine micturition center to release its bladder inhibition. This transmits impulses down the spinal cord to activate the sacral micturition reflex via the parasympathetic system, resulting in stimulation of the cholinergic receptors and bladder contraction while the urethra is relaxed (7).

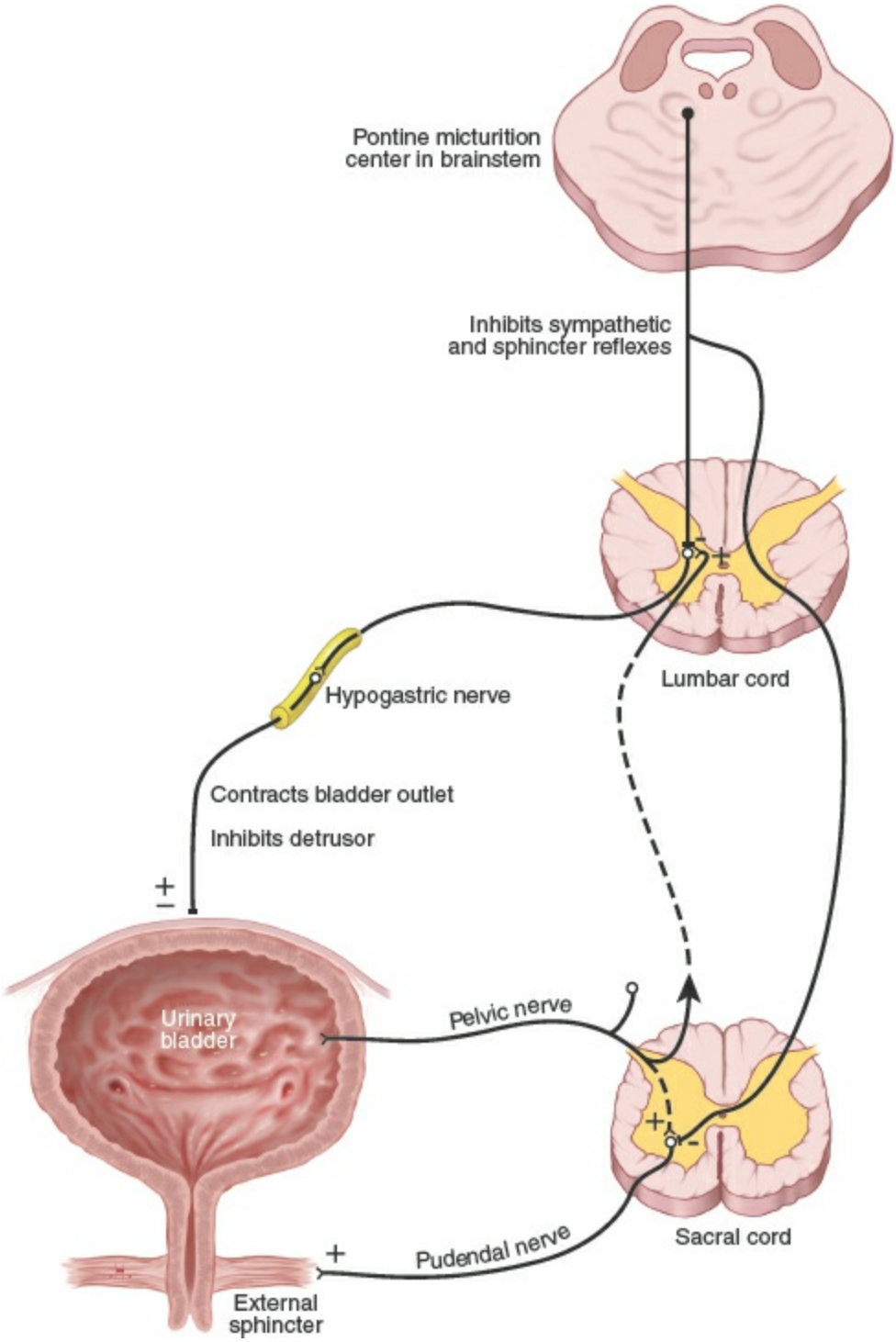


FIGURE 29-2 Detrusor–sphincter reflex during urine storage: The sympathetic system promotes the bladder to relax (inhibition) and the outlet to contract (stimulation). Concurrently, the pudendal nerve stimulates the urethral sphincter to contract. (**DeGroat WC.** A neurologic basis for the overactive bladder. *Urology* 1997;50(Suppl 6A):36–52; Figure 4, need permission.)

URINARY INCONTINENCE

[2] Disorders of urine storage are typically expressed by patients with a limited

number of bladder control symptoms that include urinary urgency, frequency, nocturia, and urinary incontinence. Urgency is defined as a sudden, compelling desire to pass urine which is difficult to defer (8). **Frequency (i.e., increased daytime voids) and nocturia (increased nighttime voids) are surrogates of urgency, and they are more commonly used than urgency in epidemiologic and clinical trials because they are easier to measure** (9). **The present International Continence Society (ICS) guidelines define nocturia as waking up one or more times to urinate; whereas frequency occurs when the patient considers that she is going to the bathroom more often than her normal** (8).

[2] Urinary incontinence, defined as any involuntary leakage of urine, is easier to measure or quantify than urgency. Of all the urinary storage symptoms, it tends to be the most distressing, impactful, and costly. Although the signs and symptoms of urinary incontinence appear to be a straightforward expression of bladder disorder, its diagnosis and treatment is anything but simple. The *complexity* of the bladder is in its *simplicity*. There are many underlying causes that can potentially lead to urinary incontinence. In the following sections, we will define urinary incontinence and its subtypes, describe its epidemiology and impact, discuss the pathophysiology and associated risk factors, discuss evaluation and examination of women with incontinence, explore the various diagnostic tools, and propose available treatment modalities.

Definitions

Defining urinary incontinence has been challenging. Should urinary incontinence be defined as any amount of urine loss, then the overwhelming majority of women may fit the definition. Conversely, should urinary incontinence be defined with stricter criteria, such as losing a certain volume of urine with a specific number of episodes in a month, then only a minority of women would fit that definition. A key consideration is to be able to distinguish normal from abnormal lower urinary tract function. While much of the focus of clinical research is on individuals with frank urinary incontinence, the ultimate challenge is to understand when preclinical urinary incontinence starts, and more importantly the trajectory it takes to progress into a clinically relevant and persistent condition.

Historically, urinary incontinence was defined as the involuntary loss of urine represented as an objectively demonstrable event, and described to be a social or hygienic problem (10). Although highly specific, this definition was clinically impractical. Women who presented with subjective incontinence received little to no attention if it was not observed by their clinicians during an examination, or if it was not reported by patients to be a “hygienic” problem. Presently, **urinary incontinence is defined as the complaint of any involuntary leakage of urine** (8). Paradoxically, this

new definition includes a substantial spectrum of women who have experienced rare incidental urine loss events. Consequently, some studies report **urinary incontinence prevalence estimates of up to 60%** (11).

Urinary incontinence has two main subtypes, stress and urgency urinary incontinence, that either occur in isolation of each other, or they co-occur and present as mixed urinary incontinence. [3] Stress urinary incontinence is defined as loss of urine associated with activities such as coughing, sneezing, lifting, or laughing. [4] Urgency urinary incontinence is defined as loss of urine associated with a strong desire to urinate. Of note is that the term "urgency" has replaced "urge" as a symptom of storage disorder; the latter is considered to be a normal (nonpathologic) desire to void urine when the bladder is full. **[5] Mixed urinary incontinence is defined as urine loss associated with activity *and* with a strong desire to urinate** (8). **Women with urinary incontinence may express their symptoms continuously (continuous urinary incontinence), with intercourse (coital incontinence), with change in position (postural incontinence), with retention or incomplete bladder emptying (overflow incontinence), during sleep (nocturnal enuresis), or without being aware of it (insensible incontinence).** Finally, the term ***functional incontinence*** **is used to define women who have an intact bladder function, but still report incontinence caused by factors extrinsic to the bladder.** Examples include elderly women who have mental, psychological, or mobility ailments that prevent them from making it to the bathroom on time. A summary of current definitions of symptoms of lower urinary tract storage disorders is shown below **(Table 29-1)**.

Table 29-1 Classification and Definition of Lower Urinary Tract Symptoms in Women

I. Abnormal Storage	Symptoms and Signs
Incontinence (symptom)	Any involuntary leakage of urine
Stress urinary incontinence (symptom)	Involuntary leakage on effort or exertion, or on sneezing or coughing
Stress urinary incontinence (sign)	Observation of involuntary leakage from the urethra, synchronous with exertion/effort, or sneezing or coughing
Urgency urinary incontinence (symptom)	Involuntary loss of urine associated with urgency
Mixed	Involuntary loss of urine associated with urgency and also with effort or physical

incontinence	exertion or on sneezing or coughing
Continuous urinary incontinence	Continuous involuntary loss of urine
Frequency	Number of voids per day, from waking in the morning until falling asleep at night
Increased daytime urinary frequency	Micturition occurs more frequently during waking hours than previously deemed normal by women (traditionally defined as more than seven episodes)
Nocturia	Interruption of sleep one or more times because of the need to micturate (each void is preceded and followed by sleep)
Nocturnal enuresis	Involuntary loss of urine that occurs during sleep
Urgency	Sudden, compelling desire to pass urine, which is difficult to defer
Postural urinary incontinence	Involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position
Insensible urinary incontinence	Urinary incontinence where the women has been unaware of how it occurred
Coital incontinence	Involuntary loss of urine with coitus. This symptom might be further divided into that occurring with penetration or intromission and that occurring at organism.
Overactive bladder syndrome (OAB)	Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology

Although stress and urgency urinary incontinence are regarded as different disease entities, **it is important to note that women move among and between stress and urgency urinary incontinence.** In one large study of over 10,500 women, significant changes in incontinence status were reported over a 2-year period: of those with baseline urgency urinary incontinence, 34% to 38% remitted, 4% to 9% transitioned to stress urinary incontinence, and 16% to 20% transitioned to mixed urinary incontinence; of those with baseline stress urinary incontinence, 32% to 41% remitted, 4% transitioned to urgency urinary incontinence, and 16% to 23% transitioned to mixed urinary incontinence; of those with baseline mixed urinary incontinence, 22% to 27% remitted, 10% to 11% transitioned to urgency urinary incontinence, and 11% to 15% transitioned to stress urinary incontinence (12).

Epidemiology of Urinary Incontinence

Prevalence

Prevalence estimates of urinary incontinence among community-dwelling women range from 2% to 58% (11). This wide range in estimates results from variation in

definitions used, populations surveyed, age of study participants, and other reasons. Over their lifetime, urinary incontinence affects more than one in three women (13). Recent U.S. population data show that more than 20 million women have urinary incontinence, and this is projected to increase by more than 50% in the coming decade (14). Although urinary incontinence prevalence overall increases with age, prevalence patterns differ by incontinence subtype. [3] **Stress urinary incontinence peaks in the fifth decade of life and is the most common subtype overall.** Prevalence of urgency and mixed urinary incontinence is relatively low up to the fourth decade of life, but gradually increases thereafter. The average prevalence of stress, urgency, and mixed urinary incontinence is 13%, 5%, and 11%, respectively. [5] **Mixed urinary incontinence becomes the most dominant subtype in late adulthood** (15) (Fig. 29-3).

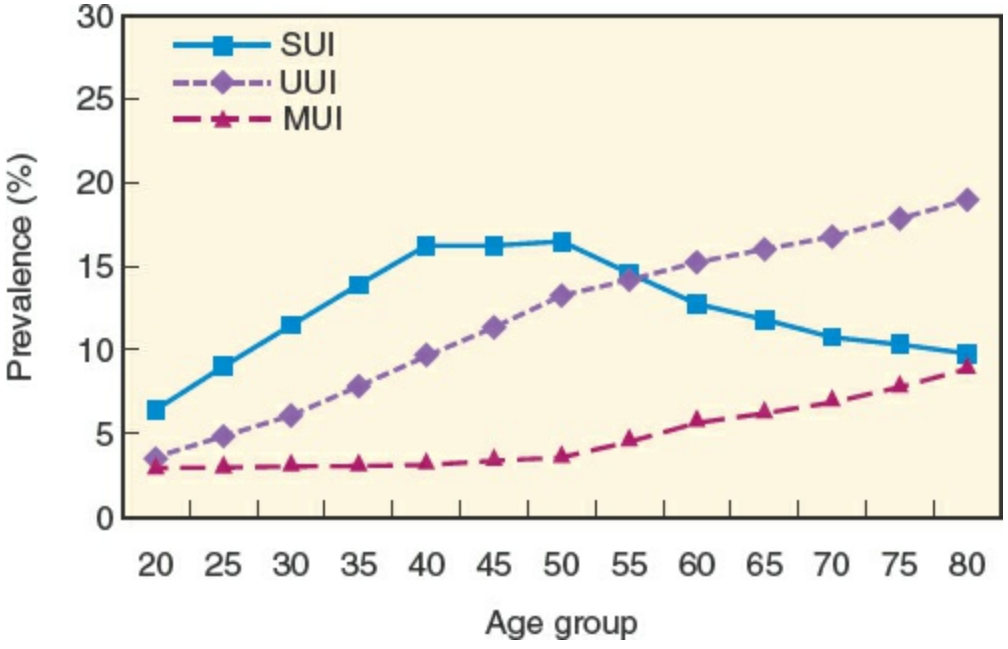


FIGURE 29-3 Prevalence of stress, urgency, and mixed urinary incontinence by age. Note the peak prevalence of stress urinary incontinence at 50 years of age followed by a decline; also note the continuous increase in mixed urinary incontinence into late adulthood where it becomes the most prevalent subtype. SUI, stress urinary incontinence; UUI, urgency urinary incontinence; MUI, mixed urinary incontinence. (**Minassian VA, Stewart WF, Hirsch A.** Why do stress and urge incontinence co-occur much more often than expected? Int Urogynecol J Pelvic Floor Dysfunct 2008;19:1429–1440; Figure 1, need permission.)

Incidence and Remission

Longitudinal studies report high variations in urinary incontinence incidence rates that range between 5% and 20%. In one meta-analysis, age-specific incidence varied between 2/1,000 person-years before age 40 and increased to 5/1,000 person-years at age 50 (16). **Remission rates of urinary incontinence are equally high and range between 3% and 12%. Data from longitudinal studies suggest that urinary incontinence is highly dynamic where women cycle in and out of active disease** (17–20). It is noteworthy that most longitudinal studies that describe incidence and

remission of urinary incontinence offer little insight on the natural history of the urinary incontinence subtypes and transition rates between stress, urgency, and mixed urinary incontinence (12).

Impact of Urinary Incontinence

Urinary incontinence is an emotionally, socially, physically, and economically burdensome condition (21,22). **It has a significant impact on quality of life (QOL), where urinary incontinence has been shown to be associated with embarrassment, anxiety, and depression (**22–24). These emotional burdens may lead women to adopt coping strategies that further alienate them from their social environment resulting in further deterioration of QOL. There is a downward cycle of impairment resulting in worsening psychological function. Studies examining the burden of disease have shown that mixed urinary incontinence is more severe, bothersome, and impactful on QOL than stress or urgency urinary incontinence (25,26).

Despite the wide-ranging impact of urinary incontinence, only a minority of women seek or receive care for their condition, resulting in underdiagnosis and undertreatment. Since most women with early stages of urinary incontinence (i.e., mild to moderate urinary incontinence) do not seek care, when they finally present with advanced symptoms (severe urinary incontinence), there is lost opportunity to prevent or reverse disease progression (11). Managing urinary incontinence is a substantial burden and cost for caregivers and the community. Presence of urinary incontinence increases risk of nursing home admissions, and in community-dwelling women, total urinary incontinence costs (direct and indirect) are about $11.2 billion/year (27,28).

Pathophysiology

Stress Urinary Incontinence

Historically, the key urethral support responsible for continence was considered to be at the bladder neck and proximal urethra. The pubourethral ligaments, extending from the undersurface of the pubic bone down to the urethra, were thought to be structurally important to maintain continence (29). **DeLancey used cadaveric studies to formulate the *Hammock Theory* where he proposed that the primary support of the bladder neck and urethra to be an intact vaginal wall at the base of the bladder** (30). **Through its fibrous and muscular attachments to the pelvic sidewall, namely to the condensation of the levator ani muscles, the vagina was shown to act as a hammock to support the bladder neck, compress the urethra, and therefore maintain continence. Loss of integrity of the hammock resulted in stress urinary incontinence (**30).

Concurrently, Petros and Ulmsten proposed the *Integral Theory* of continence (31). **They built on the work by DeLancey and others, and hypothesized that stress urinary incontinence occurs as a result of connective tissue laxity in the vagina and**

its supporting ligaments, namely the pubourethral, cardinal/uterosacral, and arcus tendineus fascia pelvis. The integral theory highlighted the role of the suspensory ligaments supporting the proximal vagina that supports the mid-urethra. It hypothesized that the multidirectional movement of the pelvic floor muscles coordinated the urethral continence mechanism: (a) the forward direction of the pubococcygeus muscle stretches the mid-vagina forward against the pubourethral ligament to close the urethra from behind; (b) the backward direction of the levator plate stretches the upper vagina and bladder base backward and downwards in a plane around the pubourethral ligament to close off the proximal urethra (32). In subsequent years, using urodynamic, radiologic, and clinical observations, DeLancey proposed that the integrity of the urethra is as, if not more, important in maintaining continence than the underlying support structures. These structures include the epithelial coaptation of the urethral mucosa with its neurovasculature, smooth muscles, and the striated sphincteric muscles (6). **Therefore, the current most accepted theory of stress urinary incontinence pathogenesis is loss of integrity of structures intrinsic to the urethra, and, to a lesser extent, the pelvic support structures in close proximity, but extrinsic, to the urethra.**

Urgency Urinary Incontinence

The pathophysiology of urgency urinary incontinence is not well-developed, as the etiology of this condition in most women remains idiopathic. The term "urgency urinary incontinence" is often used interchangeably with the term "overactive bladder (OAB)." OAB is a syndrome associated with urgency, usually accompanied by frequency, nocturia with (OAB-wet) or without (OAB-dry) urgency urinary incontinence, and in the absence of a urinary tract infection or other obvious pathology (8). Certain neurologic conditions are known to be associated with urgency urinary incontinence (33). Women with multiple sclerosis, Parkinson, or spinal cord injuries have a disruption of the neuronal circuits at different levels of the central nervous system resulting in loss of inhibitory control on the bladder voiding mechanism (34). The micturition center in the brain maintains continence while the bladder fills up by suppressing the urgency to urinate (35). **Any abnormality in the pathways between the micturition center and the bladder can lead to urgency urinary incontinence (**36).

Several theories have been developed for nonneurogenic OAB or idiopathic urgency urinary incontinence. The *epithelial hypersensitivity theory* proposes presence of chemosensitizing agents leading to bladder instability. These are believed to be inflammatory substances such as nerve growth factor, prostaglandins, and acetylcholine that increase detrusor muscle sensitivity and neuronal excitability. The influence of these agents may be compounded by the presence of a defective uroepithelium that leads

to increased sensitivity of the detrusor muscle (33,37). The *myogenic theory* suggests that the pelvic floor sustains a physical strain during the developmental years. Myogenic dysfunction ensues secondary to altered structure or disordered function of a group of myocytes within the detrusor smooth muscle independent of its nerve supply (38). Prolonged bladder outlet obstruction or bladder ischemia (from atherosclerosis or diabetic neuropathy) can lead to denervation of detrusor muscle, muscle damage, and increased hyperexcitability to acetylcholine (38). These and other proposed theories are likely influenced by psychosocial disturbances, genetic predisposition, inflammatory, and drug-induced conditions (37).

Mixed Urinary Incontinence

Mixed urinary incontinence is the most common incontinence subtype in later adulthood. Women with mixed urinary incontinence tend to have more severe symptoms that are bothersome and with a higher impact on QOL. Mixed urinary incontinence may represent a combination of bladder storage conditions of different etiologies. These may include women with independently co-occurring stress or urgency urinary incontinence where symptoms of both conditions are expressed on the same day or at different time periods; or stress urinary incontinence that has predated urgency urinary incontinence or resulted in stress-induced urgency urinary incontinence; or stress urinary incontinence associated with urgency (OAB-dry) without incontinence. It is likely that mixed urinary incontinence comprises different pathophysiologic subtypes that are still not well understood (39).

Other Causes of Urinary Incontinence

Other conditions that may be associated with urinary incontinence where urine loss occurs through the urethra include *urethral diverticuli,* and *ectopic urethra*. A urethral diverticulum is a localized herniation of urethral mucosa into the surrounding tissues. Diverticuli occur mostly in the distal urethra of women between the ages of 30 and 60 years. The etiology of acquired diverticula is unknown, but one accepted hypothesis is injury and blockage of periurethral glands from repeated urinary tract infections with subsequent rupture into the urethral lumen resulting in formation of a diverticulum. Diverticuli could be congenital in nature likely representing a remnant of Gartner duct (40). Although urine loss (dribbling) is reported with urethral diverticuli, women commonly present with symptoms similar to urinary tract infections such as dysuria, urethral pain, dyspareunia, and hematuria. On examination, a tender urethral mass is often palpable **(Fig. 29-4)**. An ectopic ureter is a congenital anomaly where the ureter opens distally into the urethra or more commonly into the vagina. Here, the mother of a baby girl usually presents to her pediatrician complaining of constant wetness in the perineum of her child resulting from absence of any sphincteric control.



FIGURE 29-4 Urethral diverticulum. (**Iyer S, Minassian VA.** Resection of urethral diverticulum in pregnancy. Obstet Gynecol 2013;122:467–469; Figure 2, need permission.)

Extraurethral incontinence occurs when a part of the urinary system drains through an abnormal opening bypassing the urethra. These are conditions that could be either congenital such as *bladder extrophy,* or traumatic such as a *fistula*. A bladder extrophy is a rare condition that involves a congenital absence of the anterior vaginal wall and base of the bladder/urethra. This is usually identified at birth and may require several and complicated surgical procedures to reconstruct. A fistula is an acquired condition where there are one or more direct communications between the vagina and ureter (*ureterovaginal fistula*), bladder (*vesicovaginal fistula*), or the urethra (*urethrovaginal fistula*). The vesicovaginal fistula is the most common, and usually arises from a prolonged obstructed labor, in younger and poorly developed women in rural, underdeveloped regions of the world. With prolonged labor, caused by malpresentation

or inadequately sized pelvis, the lower urinary tract and vagina are compressed between the head of the unborn child and the maternal pelvic bones, sometimes for days. This leads to ischemic injuries resulting in tissue breakdown, necrosis, and development of a fistula (Fig. 29-5). Another obstetrics-related condition, known as Youssef syndrome, may arise from a fistulous tract developing between the uterus and vagina, commonly after repeated cesarean sections. Here, patients present with cyclic hematuria, urinary incontinence, and amenorrhea.

Unlike obstetric causes of fistula formation, in the developed countries, a genitourinary fistula usually arises from gynecologic causes. These include pelvic malignancies, gynecologic surgeries such as hysterectomy, and pelvic irradiation. Undiagnosed bladder or ureteral trauma, or an inadequately treated injury during a hysterectomy (vaginal, laparoscopic, or abdominal) can result in fistula formation, usually within the first 2 weeks after surgery. An alternate process of fistula formation occurs from an occult injury to the bladder or ureter, typically during a laparoscopic hysterectomy where an energy source is used to transect the uterine pedicles. Here, the fistula may develop as a result of a latent injury from spread of energy to the genitourinary system.

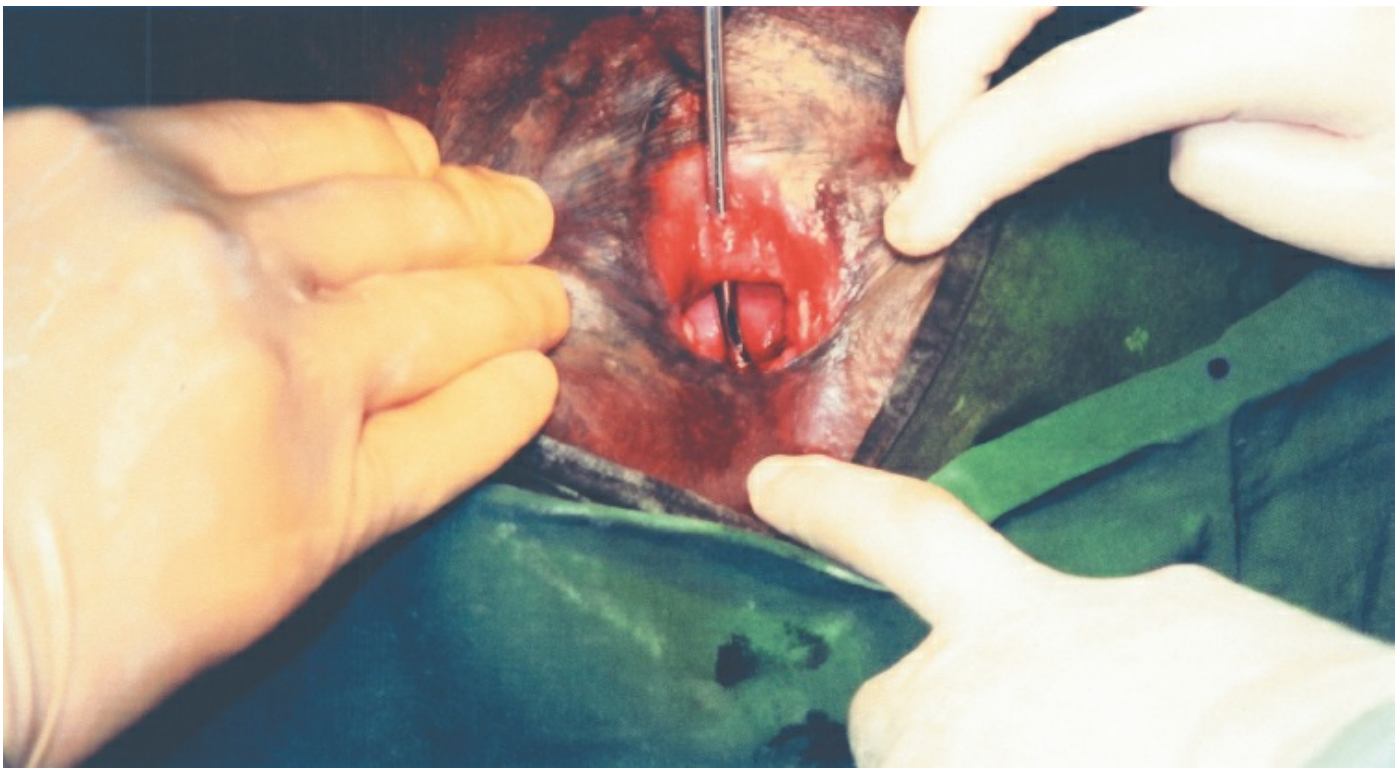


FIGURE 29-5 Vesico-vaginal fistula.

Risk Factors of Urinary Incontinence

To better understand the pathophysiology of urinary incontinence and its subtypes, it is important to identify risk factors associated with, or that mediate onset and progression

of disease. **Known risk factors for urinary incontinence include: race, age, parity, obesity, diabetes, chronic cough, COPD and smoking, previous pelvic surgery, medications, and functional and motor impairment** (Table 29-2). Evidence for an association between risk factors and urinary incontinence is strong for some, and inconclusive for others. ***Race*** **has been shown to have a variable effect on urinary incontinence by subtype. In general, white women have a higher prevalence and incidence of urinary incontinence than Hispanic, Asian and black women.** More specifically, across urinary incontinence subtypes, **white women are at a higher risk of developing stress urinary incontinence, whereas black women are at a higher risk of developing urgency urinary incontinence** (41,42).

Age **has a variable effect on urinary incontinence subtypes. Prevalence of stress urinary incontinence peaks in the fifth decade and then declines thereafter. Advancing age past the 50s is not a risk factor for stress urinary incontinence alone** (15). **This is because vaginal birth is strongly associated with stress urinary incontinence in the first two decades after childbirth, but has little to no effect beyond that.** Hence, as the time interval increases between a woman's age and the birth of her children, there is decreasing effect of childbirth and onset of stress urinary incontinence (43,44). In contrast, **advancing age is a strong predictor of both urgency and mixed urinary incontinence.**

Pregnancy **increases the risk of stress urinary incontinence with about 50% of pregnant women reporting symptoms. Although most women report resolution of their stress incontinence symptoms after birth, recurrence within 5 years is high.** ***Parity*****, is another strong risk factor of urinary incontinence, and primarily for stress urinary incontinence.** A recent 2016 meta-analysis showed that vaginal birth had a twofold increased risk of stress urinary incontinence when compared with cesarean delivery (43). **Parity is a risk factor for mixed urinary incontinence;** however, controlling for its association with stress urinary incontinence in women with mixed urinary incontinence, parity is not a risk factor for urgency urinary incontinence (45). Most epidemiologic data suggest that having a cesarean section reduces the risk of subsequent urinary incontinence (43,46).

Table 29-2 Common Risk Factors by Urinary Incontinence Subtype

Risk Factor	Urinary Incontinence Subtype		
	Stress UI	Urgency UI	Mixed UI
Age			
<50	++	+	+
>= 50	No effect	++	++
Race (white = referent)			
Black	–	–	–
Hispanic	–	–	–
Parity	++	No effect	+
Obesity	++	++	++
Diabetes	++	++	+
COPD/smoking	++	+	++
Surgery for stress UI	–	+	–

Minassian VA, Bazi T, Stewart WF. Clinical epidemiologic insights on urinary incontinence. *Int Urogynecol J* 2017;28:687–696; Table 1, need permission.

***Obesity* is another major risk factor for urinary incontinence and its subtypes** (47,48). Similar to vaginal birth, the effect of increasing weight on the pelvic floor may lead to pudendal nerve injury with subsequent levator ani muscle atrophy leading to weakening of the pelvic floor urethral support structures (49). **The effect of increased weight is a risk for new-onset stress urinary incontinence, and for urgency urinary incontinence secondary to detrusor overactivity** (50). *Diabetes* and obesity are strongly correlated, but controlling for obesity, **diabetes still stands out as an independent risk factor for urgency urinary incontinence**, and to a lesser extent, for stress and mixed urinary incontinence (51). The mechanism of action of diabetes is believed to be multifactorial including: (a) its diuretic effect leading to frequency and urgency urinary incontinence; (b) microvascular injury to the nerves supplying the detrusor muscle leading to detrusor overactivity; and (c) microvascular injury to the pudendal somatic nerve supplying the urethral sphincter (37).

Risk factors such as *previous pelvic surgery, chronic cough or pulmonary disease*, and *smoking* have potentially similar detrimental effects on the pelvic floor resulting in urinary incontinence. For instance, **previous hysterectomy has been shown to be associated with stress and urgency urinary incontinence** (15), **surgery for prolapse increases risk of new-onset stress urinary incontinence** (52), **and surgery for stress urinary incontinence may lead to *de novo* or worsening**

urgency urinary incontinence. History of smoking is associated with all urinary incontinence subtypes (48). Other risk factors, also referred to urinary incontinence caused by functional or transient causes, are described within the DIAPPERS mnemonic (Table 29-3). These include certain *medications* (e.g., psychotropic medications), *urinary tract infections*, *stool impaction*, and *psychologic* and *motor impairment*. Unlike age, race, and parity, these risk factors are modifiable by directly treating or altering their effect on the individual, and more specifically on the bladder.

Table 29-3 Reversible Causes of Urinary Incontinence

D	Delirium
I	Infection
A	Atrophic urethritis and vaginitis
P	Pharmacologic causes
P	Psychological causes
E	Excessive urine production
R	Restricted mobility
S	Stool impaction

From **Resnick NM, Yalla SV.** Management of urinary incontinence in the elderly. *N Engl J Med* 1985;313: 800–805, with permission.

Diagnosis

Historically, diagnosis of urinary incontinence required a big workup. First, a detailed history and extensive physical and pelvic examination including Q-tip testing were performed. Exhaustive 7-day long bladder diaries were required of patients, and multiple urogynecologic surveys were administered. Laboratory and bladder testing including urine analysis and urine culture, 24-hour pad test, cystoscopy, urodynamics, and other tests were frequently performed. Mounting evidence indicates that most of these diagnostic modalities are not cost-effective, and unnecessary during the initial workup of a woman with urinary incontinence. **Based on the new AUA and ACOG guidelines, the workup of urinary incontinence has become more streamlined** (53,54). **The urethral Q-tip test has mostly been eliminated, and the 7-day bladder diary has been replaced with a 2- to 3-day diary** (55–57). **Similarly, simpler and shorter forms of QOL, bother, and sexual dysfunction questionnaires, specific to urinary incontinence, have been developed.** Cystoscopy is rarely an indication for uncomplicated urinary incontinence, and **urodynamics is no longer necessary prior to treatment for simple urgency urinary incontinence, or prior to surgery for**

uncomplicated stress urinary incontinence (58,59).

History Taking

Medical history taking from a woman with urinary incontinence should explore the duration of time with urine loss, associated symptoms, and their severity. Questions are asked to identify incontinence subtype based on the circumstances surrounding the urinary incontinence episodes. Urine loss associated mostly with activities such as coughing, sneezing, or laughing is suggestive of stress urinary incontinence; women with stress urinary incontinence report urine loss that occurs while they are on the trampoline with their children, during activities such as running and jumping, and at times, with intercourse. Symptoms associated with or immediately preceded by an urgency episode are indicative of urgency urinary incontinence. The latter may present with reports of increased urinary frequency, or nocturia. Women describe symptoms of urgency with or without incontinence provoked by the sound of running water (e.g., washing dishes), change in temperature, getting out from the car, or as they open the door to get into their homes. Many women, especially the older age group, report mixed symptoms of stress and urgency urinary incontinence, and information on bother and impact on QOL by subtype should be solicited.

Other relevant clinical information is history of previous medical or surgical treatment for incontinence, coexisting urinary tract infection with symptoms such as dysuria, hematuria, or suprapubic pain, fluid intake, and other health conditions (e.g., neurologic), or medications that may be associated with incontinence. For example, a woman with past history of stress urinary incontinence who underwent a mid-urethral sling may now be presenting with urgency symptoms; another woman presenting with occasional urgency urinary incontinence, a frequency of 15 episodes during the day and only once at night may admit to drinking a gallon (about 4 L) of liquids, including coffee and soda; alternatively, a poorly controlled diabetic woman who is a smoker may present with urgency (diuretic effect of sugar) and stress (chronic cough effect from smoking) urinary incontinence symptoms. Many medications taken for other medical conditions can impact the lower urinary tract and should be discussed with patients as potential contributors to their symptoms **(Table 29-4)**.

Table 29-4 Medications that May Affect the Function of the Urinary Tract

1. Sedatives such as the benzodiazepines may cause confusion and secondary incontinence, particularly for elderly patients
2. Alcohol may have similar effects to benzodiazepines and also impairs mobility and causes diuresis
3. Anticholinergic drugs may impair detrusor contractility and may lead to voiding difficulty and overflow incontinence. Drugs with anticholinergic properties are widespread and include antihistamines,

antidepressants, antipsychotics, opiates, antispasmodics, and drugs used to treat Parkinson disease
4. Alpha agonists, which are often found in over-the-counter cold remedies, increase outlet resistance and may lead to voiding difficulty
5. Alpha blockers, sometimes used to treat hypertension (e.g., prazosin, terazosin), may decrease urethral closure pressure and lead to stress incontinence
6. Calcium channel blockers may reduce bladder smooth muscle contractility and lead to voiding problems or incontinence; they may also cause peripheral edema, which may lead to nocturia or nighttime urine loss
7. Angiotensin-converting enzyme inhibitors may result in a chronic and bothersome cough that can result in increasing stress urinary incontinence in an otherwise asymptomatic patient

Physical Examination

All women presenting for evaluation of urinary incontinence should undergo a routine general physical examination with particular attention given to conditions that may impact their incontinence. These include: mental and cognitive function (e.g., dementia and its association with urgency, frequency, and enuresis), neurologic function (e.g., Parkinson disease and multiple sclerosis and their effect on urgency urinary incontinence), cardiovascular status (e.g., vascular insufficiency and lower extremity edema and their association with nocturia secondary to night time fluid mobilization in the recumbent position), pulmonary function (e.g., chronic obstructive pulmonary disease and its effect on stress urinary incontinence), nutritional status (effect of obesity on stress and urgency urinary incontinence), mobility, gait, and dexterity (urgency urinary incontinence).

The pelvic examination includes palpation of the pelvis and lower abdomen for presence of masses. Lower extremity (deep tendon reflexes) and perineal sensation and sacral nerve reflexes, including the anal wink and bulbocavernosus reflexes, are evaluated. The latter reflexes are elicited by gently stroking or tapping the clitoral and perianal skin to elicit a contraction of the external anal sphincter. **The goal of the pelvic examination is to investigate the underlying cause of urinary incontinence and to identify associated pelvic support defects. Examination is performed in the lithotomy position, but may require a semi-upright or standing position.** Evaluation of the vulva and vagina may reveal atrophy, vaginitis, dermatoses, or pain associated with symptoms of incontinence, urgency, and frequency. Inspection or palpation of the urethra may reveal tenderness or mass, suggestive of an infection or diverticulum. **Prolapse staging of the different pelvic floor compartments is performed (see Chapter 30). Integrity of the pelvic floor and levator ani muscles can be assessed. With two fingers in the vagina, the patient is asked to contract the muscles used to "hold urine" or to "avoid passing gas." The ability to contract and strength and duration of the contraction are all measured. Finally, bimanual and rectovaginal examinations are performed to assess for pelvic or adnexal masses, integrity of the**

anal sphincter, and pelvic tenderness.

Q-tip Test

The Q-tip test, which is no longer recommended, involves introducing a cotton-tipped swab into the urethra and asking the patient to Valsalva to measure the angle deviation of the urethra from baseline. More than a 30-degree deviation is consistent with hypermobility of the urethra, and/or urethrovesical angle. Minimal to no angle deviation in a woman with stress urinary incontinence may indicate intrinsic sphincter deficiency, also known as stove-pipe urethra. The Q-tip test is no longer recommended because of the discomfort associated with inserting the cotton swab into the urethra. Equivalent information can be obtained from a vaginally placed swab to measure urethral mobility while the patient is asked to Valsalva (55).

Cough Stress Test

During the pelvic examination, a cough stress test is performed. This can be done either with a full or an empty bladder. The advantage of doing it with a full bladder is that it is easier to demonstrate urine loss from the urethra in a woman with stress urinary incontinence. If history is suggestive, but urine loss is not observed in the lithotomy position, the patient may be asked to stand up and possibly jump and/or cough vigorously while the examiner observes for urine loss. Note that a positive cough test with a full bladder cannot rule out overflow incontinence; here, a patient may demonstrate objective evidence of urine loss with a stress activity, but may concurrently have incomplete bladder emptying. Clearly, offering a surgical intervention, like a mid-urethral sling, to such a patient is not ideal because it can result in urinary retention. Alternatively, a cough test can be done after asking the patient to empty her bladder. A positive empty bladder cough test is strongly indicative of stress urinary incontinence and at times may be suggestive of intrinsic sphincter deficiency.

Postvoid Residual

The postvoid residual (PVR) volume of urine is the amount of urine remaining in the bladder within 10 minutes from voiding. This can be measured either using a small-caliber catheter during the pelvic examination or via ultrasound. The latter is less invasive and has a standard error of less than 20%, with more accuracy for smaller PVRs (i.e., less than 200 mL) (60). Alternatively, using the catheter to measure a PVR may result in a more exact volume of urine, especially for large bladder volumes, and has the added benefit of testing a more sterile urine specimen for a urine analysis or urine culture, if indicated. **Normal values for PVRs are not well established; however, most would consider a PVR <50 mL to be within normal and a PVR >150 mL to be abnormally elevated (**61,62).

Simple Bladder Testing

Other simple tests are available that can be administered before (*bladder diary*), during (*urinalysis*), or after (*pad test*) a clinical encounter to assist the clinician in making a firm diagnosis.

Bladder Diary

The bladder diary, also referred to as the voiding diary, is meant to represent the total amount of fluid intake, by type, in a 24-hour period. Historically, voiding diaries were administered over a 7-day period. But these were too inconvenient for patients to complete, and evidence shows that a 2- to 3-day diary is equally reliable (56). **The information gained from fluid intake is important because it helps put into context symptoms of urgency, frequency, and nocturia.** In addition to fluid intake, the bladder diary offers information on various measures of urine output, urinary incontinence, and circumstances surrounding the urinary incontinence episode(s). The patient is asked to measure the amount of voided urine by time of day and night; here, one can assess the 24-hour total urine output, number of voids per day, average voided volume, and bladder capacity (largest voided volume). The patient also documents the time a urine loss occurs, and whether the event is associated with a stress activity (e.g., with a cough, sneeze, or laugh) or with urgency **(Fig. 29-6)**.

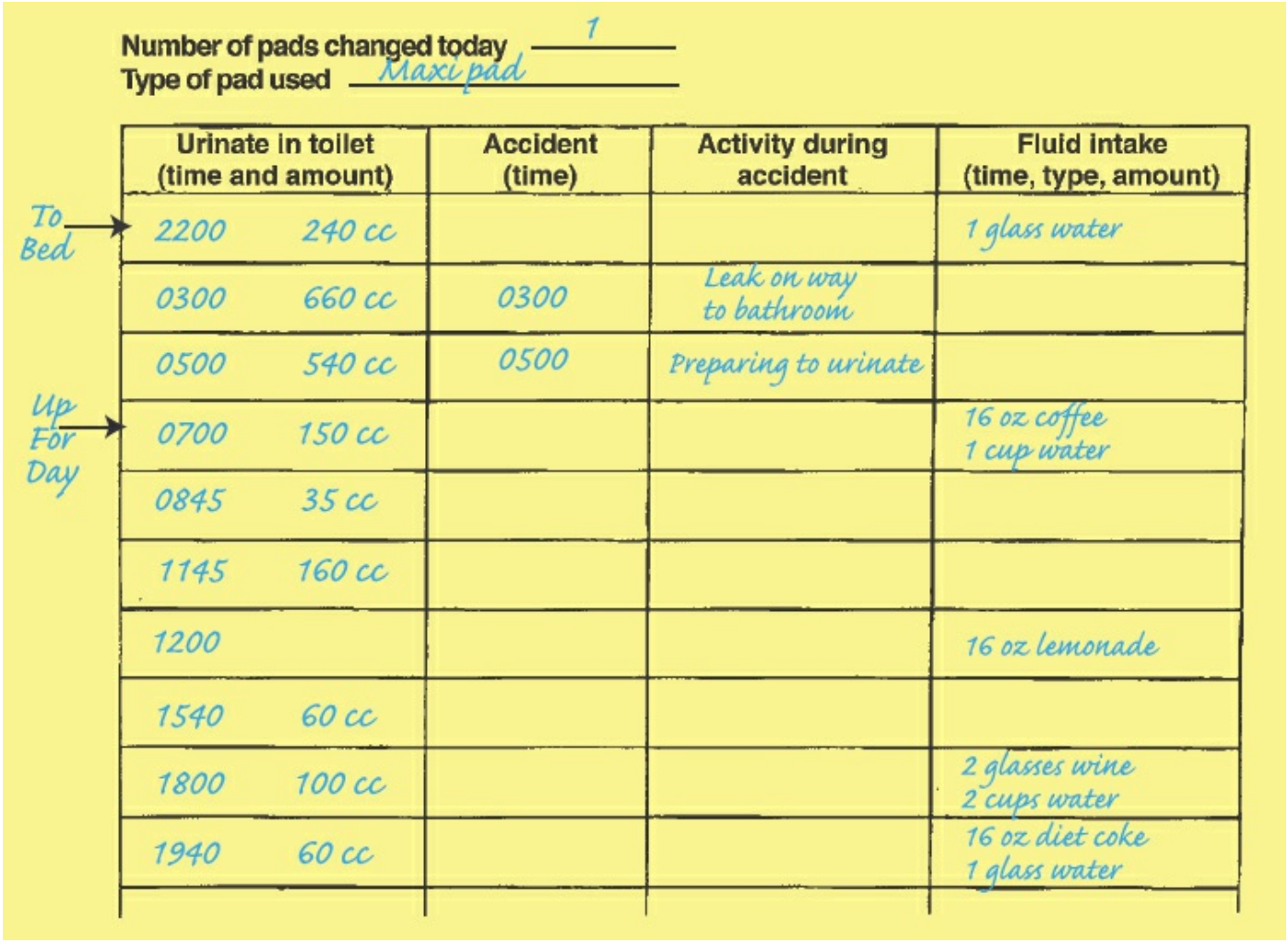


FIGURE 29-6 An example of a voiding diary including time and amount of urination during the day and at night, urinary incontinence episodes and associated activity, volume, type, and time of fluid intake.

The bladder diary helps clarify the diagnosis when information gathered during the history and pelvic examination is inconclusive. For example, intake of large fluid volumes or consumption of large amounts of caffeine and alcohol can easily explain why a woman may report a physiologic increase in urinary frequency and urgency. Alternatively, a voiding diary that shows a 24-hour fluid intake of 50 ounces (1.5 L), and nothing to drink 3 hours before bedtime in a patient who reports a daytime frequency of every 2 hours, nocturia of 3 to 4 times, and with small voided volumes may represent a pathologic condition like OAB or urgency urinary incontinence.

Urinalysis

The urinalysis by simple dipstick is helpful to rule out a urinary tract infection, especially in the presence of irritative lower urinary tract symptoms such as urgency, frequency, nocturia, and dysuria. Presence of nitrites, leukocytes and/or hematuria on dipstick may indicate the presence of a urinary tract infection. It is important to note that hematuria on a dipstick is not conclusive for presence of blood in

the urine and should be confirmed by a formal microscopic evaluation. A urine culture can be sent to confirm the presence of a urinary tract infection. Treatment of a urinary tract infection may help improve these symptoms. It is generally not recommended to treat bacteriuria in a woman who is otherwise asymptomatic.

Pad Tests

These are not routinely performed in the clinical setting. They are helpful objective tools used in research since they quantify the volume and frequency of urine loss by counting and weighing the pads used in a 24- to 48-hour period. One research application of pad tests may include a new drug trial to treat urgency urinary incontinence. In this instance, patients may be asked to wear incontinence pads before and after taking the medication, to determine if the drug (compared to placebo) results in a decrease in the volume and frequency of urinary incontinence episodes. Pad tests can be employed to help objectify the presence of urinary incontinence that is not demonstrable in the clinical setting, even with a full bladder (i.e., negative cough stress test). An example may be a competitive female athlete who reports loss of urine that occurs only during strenuous exercise and which significantly impedes her performance. The patient is given 100 mg of phenazopyridine (changes the color of urine into orange) to take before her exercise routine while wearing a pad. The presence of orange staining on the pad may help in the diagnosis of stress urinary incontinence.

Table 29-5 Symptom Questionnaires for Women with Pelvic Floor Disorders

Urinary Incontinence: • Incontinence Severity Index • International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) • Urogenital Distress Inventory (UDI) • Urogenital Distress Inventory Short Form (UDI-6) • Kings Health Questionnaire • Bristol Female Lower Urinary Tract Symptom Questionnaire (BFLUTS)
All pelvic floor disorders (urinary incontinence, fecal incontinence, prolapse): • Pelvic Floor Distress Inventory (PFDI) • Pelvic Floor Distress Inventory Short Form (PFDI-20)

Adapted from **Barber MD.** Questionnaires for women with pelvic floor disorders. *Int Urogynecol J Pelvic Floor Dysfunct* 2007;18:461–465; permission needed?

Quality of Life Measures

Although urinary incontinence is a health condition with limited immediate physical sequelae to the individual woman, it can have tremendous psychological, social, and general health effects. Some women stop exercising as a result of constant urine loss with activity; others limit the amount of fluids to reduce their urgency and urinary

incontinence episodes; women may stop going out because of fear of not finding a bathroom when one is needed; yet others may not wish to have intercourse with their partner due to embarrassment from having an accident. Clinical evaluation is not complete without an assessment of these behavioral changes in response to bother from urinary incontinence that can lead to profound consequences on an individual's psychological, sexual, social, and ultimately her physical well-being. **There are several validated questionnaires specifically developed to better assess severity of urinary incontinence, its bother, impact on QOL, and sexual health** (63). **Many of those have short versions that can be easily administered to patients during the initial visit, and repeated in the future after an intervention, to measure change (improvement) over time. The following two tables list a summary of common symptom questionnaires (Table 29-5) and QOL and sexual function scales for women with urinary incontinence pelvic floor disorders (Table 29-6).**

Table 29-6 Quality of Life and Sexual Function Scales for Women with Pelvic Floor Disorders

Generic Quality of Life Questionnaires	Urinary Incontinence-Specific QOL Questionnaires	All Pelvic Floor Disorders	Sexual Function Questionnaires
SF-36	Incontinence Impact Questionnaire (IIQ)	Pelvic Floor Impact Questionnaire (PFIQ)	Female Sexual Function Index (FSFI)
EuroQol EQ-5D	IIQ short form (IIQ-7)	PFIQ Short Form (PFIQ-7)	McCoy Female Sexual Function Questionnaire (MFSFQ)
	Incontinence Quality of Life Questionnaire (I-QOL)		Prolapse and Incontinence Sexual Function Questionnaire (PISQ)
	Kings Health Questionnaire		PISQ Short Form (PISQ-12)
	Urge Incontinence Impact Questionnaire (Urge IIQ)		

Adapted from **Barber MD.** Questionnaires for women with pelvic floor disorders. *Int Urogynecol J Pelvic Floor Dysfunct* 2007;18:461–465; permission needed?

Advanced Bladder Testing

Urodynamics

The hallmark of advanced bladder testing is the urodynamics test. This test is an adjunct to history taking, clinical examination, and simple bladder testing. The scope of its indications and use in clinical practice has narrowed over time as clinicians have improved their diagnostic acumen in identifying different bladder control conditions. Examples where urodynamics are not necessary include: the diagnosis of incontinence is straightforward and consistent with history, physical examination, and simple bladder testing; a woman with predominantly subjective stress urinary incontinence symptoms with positive cough test and minimal PVR, irrespective of whether an anti-incontinence surgery is planned or not; a woman with urgency urinary incontinence symptoms, even prior to initiation of medical treatment.

When performed, urodynamics provides objective data on lower urinary tract function and serves two purposes: the first is to help characterize bladder storage

conditions by distinguishing stress, urgency, and mixed urinary incontinence from each other; the second is to assist in establishing a diagnosis for bladder voiding dysfunction. Urodynamics has many useful applications in situations where: the diagnosis is not clear because of inconsistencies between the history, physical examination, symptom scales, and voiding diary; women have mixed or complex symptoms where conservative treatment options have failed; surgery for prolapse is being planned in a woman without any symptoms of urinary incontinence, or with a negative cough stress test, to elicit the presence or absence of occult stress urinary incontinence; previous surgery for incontinence has failed or symptoms of urinary incontinence have recurred; incomplete bladder emptying is reported (high PVR); symptoms of incontinence are compounded by the presence of neurologic conditions like multiple sclerosis (64).

Urodynamics can be simple or complex. A summary of all the definitions and terms used in urodynamics is shown (Table 29-7) (65). **A simple urodynamics consists of *uroflowmetry, PVR*, and simple *filling cystometry.*** This may be the procedure of choice when someone has predominant stress urinary incontinence with a negative cough stress test.

Table 29-7 Urodynamic Definitions

I. Bladder sensation	
A. *First sensation*	First becomes aware of bladder filling
B. *First desire to void*	Feeling that would lead the person to void at next convenient moment, but voiding can be delayed if necessary
C. *Strong desire to void*	Persistent desire to void without the fear of leakage
D. *Sensation*	Classified as:
	1. Increased
	2. Reduced
	3. Absent
	4. Nonspecific bladder sensations (other symptoms make person aware of bladder filling, like abdominal fullness)
	5. Bladder pain (is abnormal)
	6. Urgency (sudden compelling desire to void)
II. Detrusor function	

A. *Normal*	Allows bladder filling with little or no change in pressure; no involuntary phasic contractions
B. *Detrusor overactivity*	Involuntary detrusor contractions during filling
1. *Phasic*	Characteristic wave form; may or may not lead to incontinence
2. *Terminal*	Single involuntary detrusor contractions occurring at cystometric capacity, which cannot be suppressed, and results in incontinence usually resulting in bladder emptying
3. *Detrusor overactivity incontinence*	Incontinence that is due to an involuntary leakage episode
4. *Neurogenic detrusor overactivity*	There is a relevant neurologic condition (replaces term *detrusor hyperreflexia*)
5. *Idiopathic detrusor overactivity*	No definite cause (replaces term *detrusor instability*)
C. *Bladder compliance*	Fill volume/change in detrusor pressure (Pdet)
	1. Calculate at start of bladder filling (usually 0)
	2. At cystometric capacity (excluding any detrusor contraction)
D. *Bladder capacity*	
1. *Cystometric capacity*	Volume at end of cystometrogram; capacity is volume voided together with any residual urine
2. *Maximum cystometric capacity*	Volume at which person feels she can no longer delay voiding
III. Urethral function	
A. *Normal urethral closure mechanism*	Maintains a positive urethral closure pressure during bladder filling
B. *Incompetent urethral closure mechanism*	Allows leakage of urine in the absence of a detrusor contraction
C. *Urethral relaxation incontinence*	Leakage that is due to urethral relaxation in the absence of raised abdominal pressure or detrusor overactivity
	Involuntary leakage of urine during increased abdominal pressure, in the

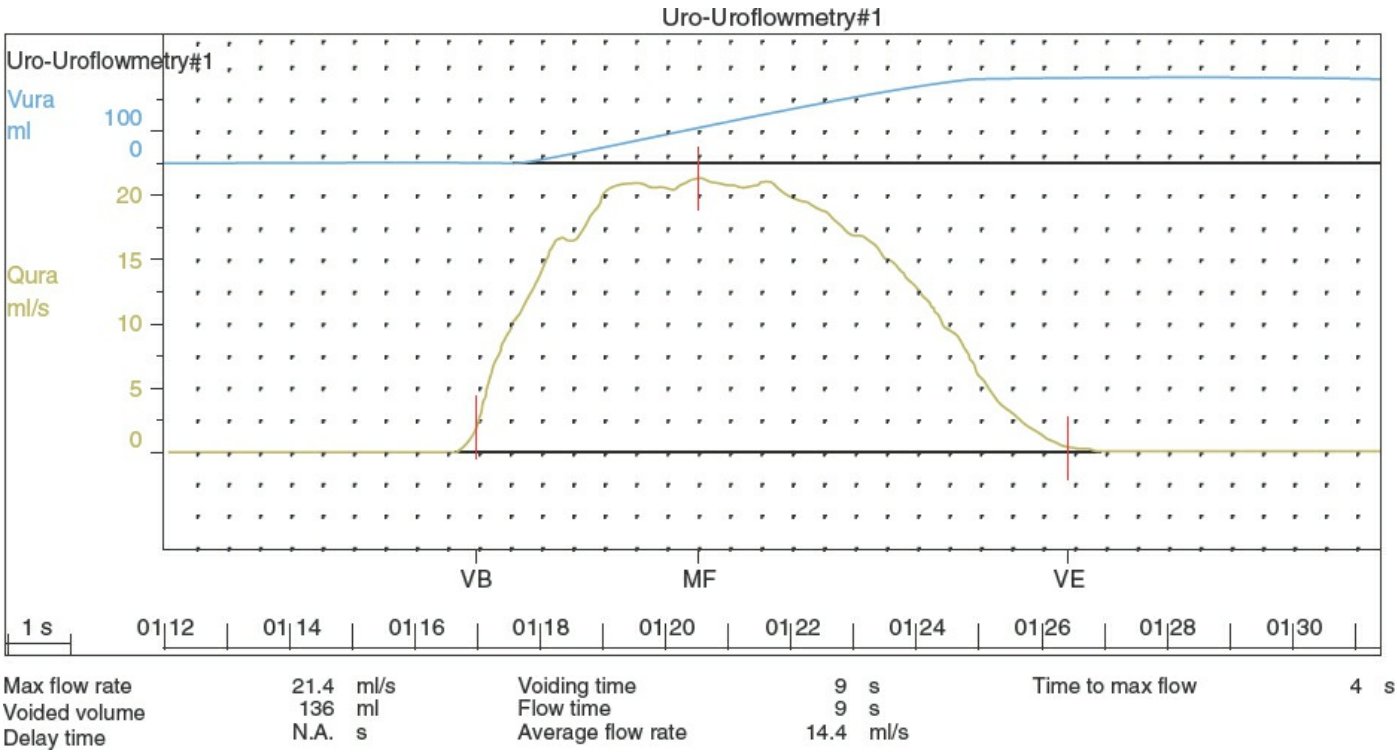
D. *Urodynamic stress incontinence*	absence of detrusor contraction (replaces term *genuine stress incontinence*)
E. *Urethral pressure (P_{ura})*	Fluid pressure needed to open closed urethra
1. *Pressure profile*	Pressure along length of urethra
2. *Urethral closure pressure*	$P_{ura} - P_{ves}$
3. *Maximum urethral closure pressure (MUCP)*	Maximum difference between P_{ura} and P_{ves}
4. *Pressure transmission ratio*	Increment in urethral pressure on stress as percentage of simultaneously recorded increment in intravesical pressure
F. *Abdominal leak point pressure*	Intravesical pressure at which urine leakage occurs because of increased abdominal pressure
IV. Pressure flow studies	
A. *Urine flow*	Defined as:
	1. Continuous
	2. Intermittent
a. *Flow rate*	Volume voided/unit time
b. *Voided volume*	Total volume voided
c. *Maximum flow rate*	
d. *Voiding time*	Includes interruptions
e. *Flow time*	Time over which measurable flow actually occurs
f. *Average flow rate*	Voided volume/flow time
g. *Closing pressure*	Pressure measured at end of measured flow
h. *Detrusor function during voiding*	Classified as:

1. Normal	
2. *Detrusor underactivity*	Contraction of reduced strength resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying
3. *Acontractile*	Cannot be demonstrated to contract
i. *Urethral function during voiding*	Classified as:
1. *Normal*	Continuously relaxed
2. *Dysfunctional voiding*	Intermittent and/or fluctuating flow rate that is due to involuntary intermittent contractions of the periurethral striated muscle during voiding in neurologically normal people
3. *Detrusor sphincter dyssynergia*	Detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle
4. *Nonrelaxing urethral sphincter obstruction*	Usually occurs in people with a neurologic lesion

From **Abrams P, Cardozo L, Fall M, et al.** The standardization of terminology of lower urinary tract function: Report from the Standardization Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21:167–178, with permission.

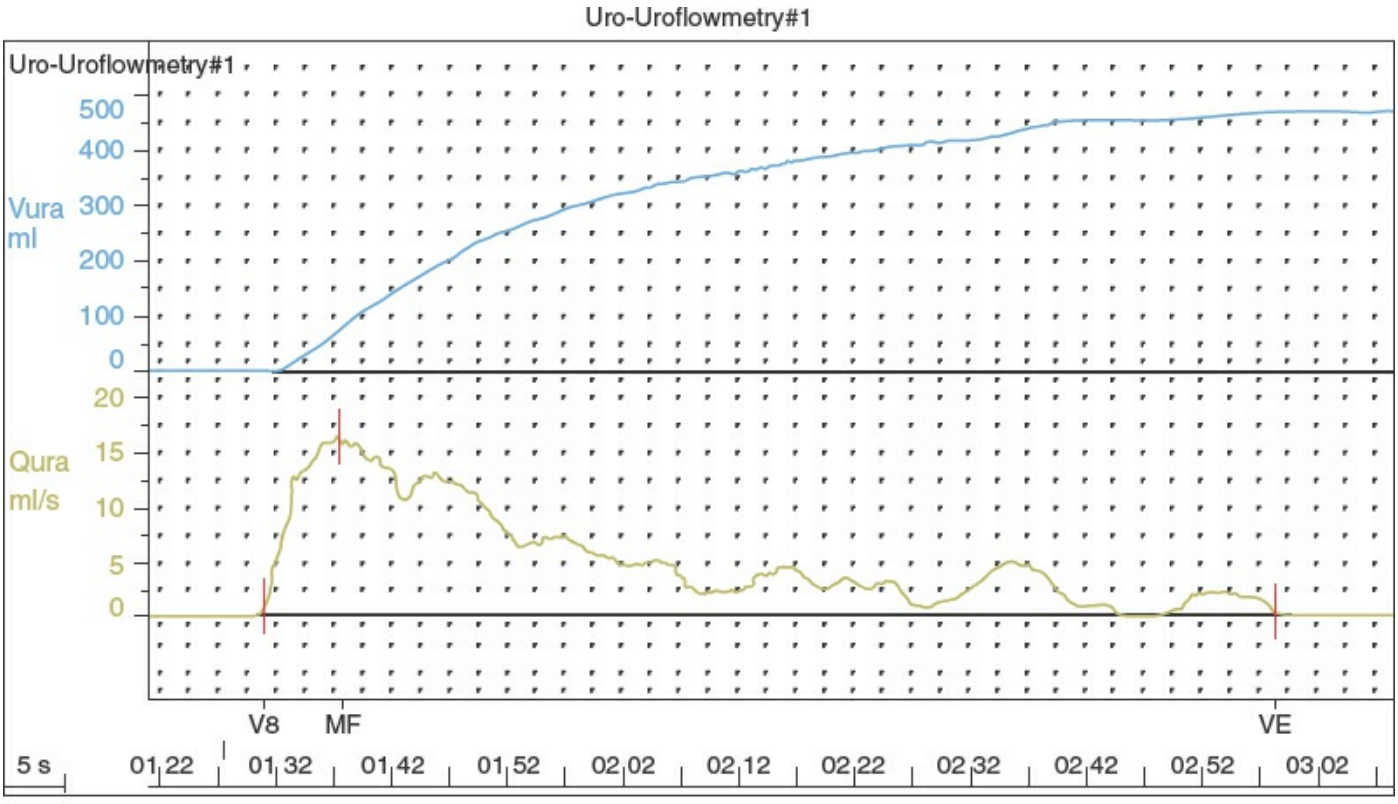
Uroflowmetry

This a study that assess voiding function. Here, the patient is asked to come to the office with a comfortably full bladder and void while sitting on a special commode attached to a funnel that directs the voided volume into a spinning receptacle that measures the amount of voided volume of urine over time. Several data points are obtained through this study that include the total amount of voided urine, the average and peak flow of urine, the time to peak flow, flow time, and total time to void. A normal uroflow has a continuous bell-shaped configuration, a short time to peak flow, and a high peak flow (Fig. 29-7); whereas an obstructed flow may have two or more lower peaks with an interrupted flow pattern or a prolonged tail (Fig. 29-8).



Max flow rate	21.4	ml/s	Voiding time	9	s	Time to max flow	4 s
Voided volume	136	ml	Flow time	9	s		
Delay time	N.A.	s	Average flow rate	14.4	ml/s		

FIGURE 29-7 Normal uroflow with a bell-shaped pattern, a short time to peak flow, and a continuous flow with complete bladder emptying.



Max flow rate	16.6	ml/s	Voiding time	87	s	Time to max flow	6 s
Voided volume	468	ml	Flow time	82	s		
Delay time	N.A.	s	Average flow rate	5.7	ml/s		

FIGURE 29-8 Abnormal uroflow showing a prolonged and interrupted voiding pattern with an initial high peak followed by several smaller peaks.

Filling Cystometry

After completion of the uroflowmetry, the patient is placed in a lithotomy position and a catheter is placed to measure the PVR volume, which, if normal, is generally less than 50 mL. In a simple urodynamics, filling cystometry involves backfilling the bladder manually through the catheter at 60 mL increments or via a water pump at a rate of 50 to 100 mL per minute. There are several sensory parameters that are measured during the filling phase including (with their typical normal values): first filling sensation (50 mL); first desire to void (150 mL); strong desire to void (250 mL), and maximum cystometric capacity (400 mL). Reduced volumes in several of these parameters may be consistent with OAB or urgency urinary incontinence. Once the bladder capacity is attained, the catheter is removed, and the patient is asked to cough or Valsalva. Loss of urine associated with an increased abdominal pressure is indicative of stress urinary incontinence.

Complex Urodynamics

Women with predominant urgency urinary incontinence, mixed or complex symptoms, with previous failed incontinence surgery, or neurologic conditions may be more suited for a complex urodynamics. In addition to the uroflowmetry, this test includes *complex filling cystometry, urethral pressure profilometry, and pressure flow studies.* In addition, *electromyography* (EMG) of the urethral sphincter is commonly performed. Although complex urodynamics is a more advanced form of bladder testing, it is not a perfect test. A false negative test can occur in a woman with subjective stress urinary incontinence where no urine loss is observed even with a full bladder in the lying or standing position; it can also occur with urgency urinary incontinence where a patient may report sensory urgency, but no detrusor activity is visible. A false positive is uncommon with stress but may happen with urgency urinary incontinence where the presence of the catheter or patient's anxiety may provoke an iatrogenic bladder contraction.

Filling Cystometry (Complex)

Similar to the simple urodynamics, filling cystometry is performed to assess bladder and urethral function during the filling phase. The catheter placed in the bladder has two transducers, one is situated at the tip of the catheter measuring the intravesical pressure, and another is positioned a few centimeters behind the tip measuring the transurethral pressure. A pressure transducer is placed either inside the vagina, or the rectum, to approximate the intra-abdominal pressure. Since the intravesical pressure (Pves) is a measure of the detrusor pressure (Pdet) plus the pressure of the abdomen and surrounding organs (Pabd), then the true detrusor pressure is obtained by subtracting the value of the abdominal pressure from the intravesical pressure:

$$Pdet = Pves - Pabd$$

The advantage of complex cystometry is a more accurate assessment of the detrusor pressure (activity) during the filling phase. For instance, should the patient inadvertently sneeze, Valsalva, or increase her intra-abdominal pressure during the test, a stable Pdet in the presence of an increased Pves is expected in a normal bladder because the rise in Pves and Pabd cancel each other. Alternatively, if a woman develops an unprovoked bladder contraction, Pabd will remain neutral while Pves and Pdet show a spike. In this situation detrusor overactivity is observed **(Fig. 29-9)**.

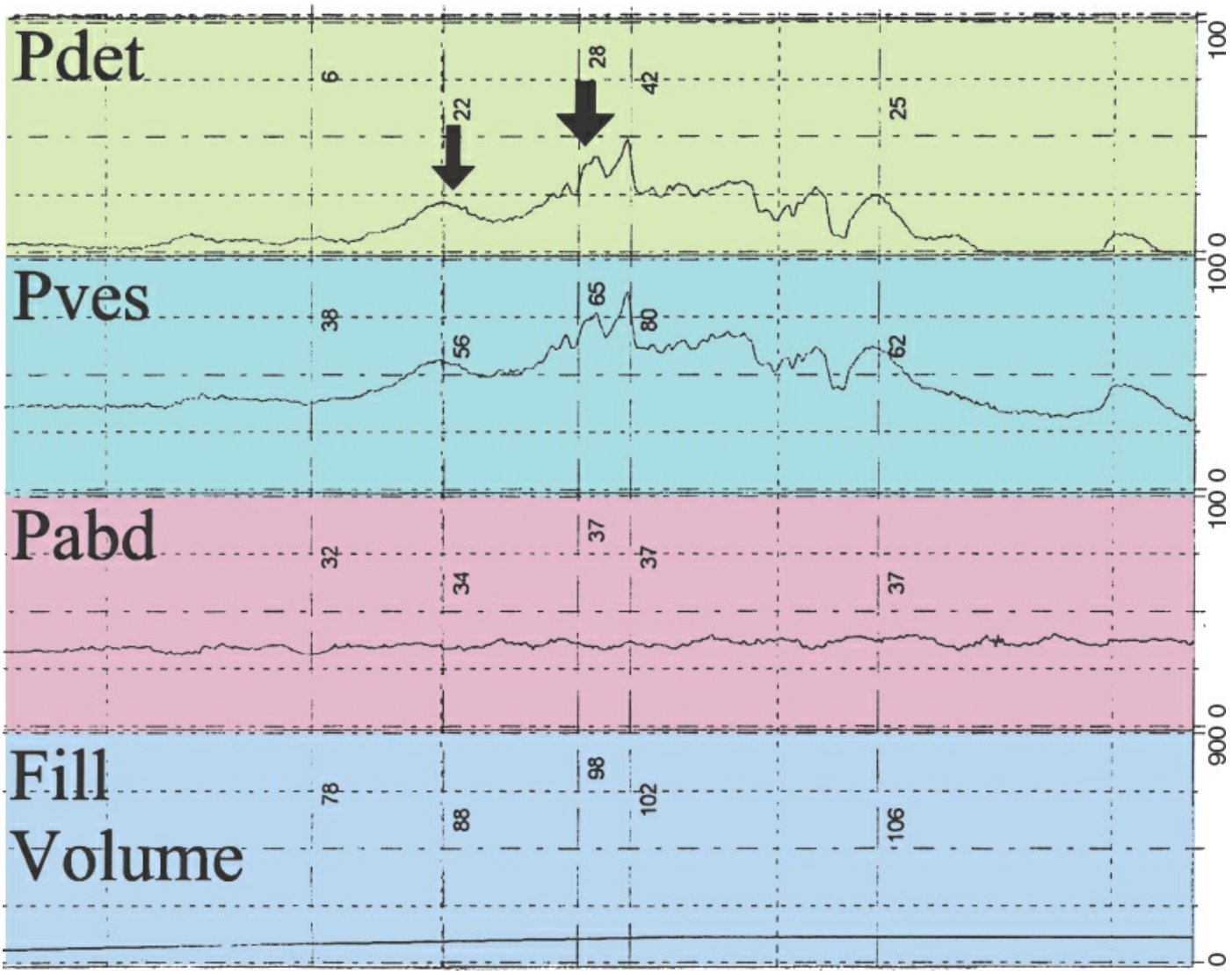


FIGURE 29-9 Detrusor overactivity on filling cystometrography. The patient begins to sense urgency, accompanied by an unstable bladder contraction, when 88 mL of water are instilled into the bladder. The detrusor pressure rises, and when 96 mL of water are instilled, she leaks. Pabd, abdominal pressure; Pves, vesical pressure; Pdet, detrusor pressure.

Urethral Pressure Profilometry

The urethral pressure profilometry is a measure of the function of the urethra. When the

bladder capacity is attained during cystometry, filling is stopped. The pressure inside the bladder (Pves), and that of the urethra (Pure) are noted. In a healthy normal bladder and urethra, the Pure is higher than Pves during filling, the opposite is true during voiding. The difference between the urethral and bladder pressures is denoted as Pclose where:

$$Pclose = Pure - Pves$$

Because the urethra is approximately 4-cm long and the urethral sphincter is located in the proximal urethra, it is important to identify the maximum urethral closure pressure (MUCP). The catheter inside the bladder is typically attached to a pulley which, when engaged, will pull the catheter in and out of the bladder as the urethral transducer measures the Pure. The MUCP is the highest value of Pclose along the urethral pressure continuum. MUCP values of less than 20 cm of H_2O may represent intrinsic sphincter deficiency; whereas a normal urethra has MUCP value >40 cm of H_2O.

Another test of urethral integrity is known as the *Valsalva leak point pressure* (VLPP) which represents the value of the intra-abdominal or intravesical pressure at which point urine loss occurs. This is usually performed when the bladder is comfortably filled to 200 cc and the patient is asked to Valsalva or cough with gradually increasing force. The point at which leakage of urine is observed during this exercise is marked and denoted as VLPP. Typically, a VLPP >60 cm of H_2O is used as a cut-off representing normal urethral function, and below which may be consistent with diminished urethral sphincter tone **(Fig. 29-10)**.

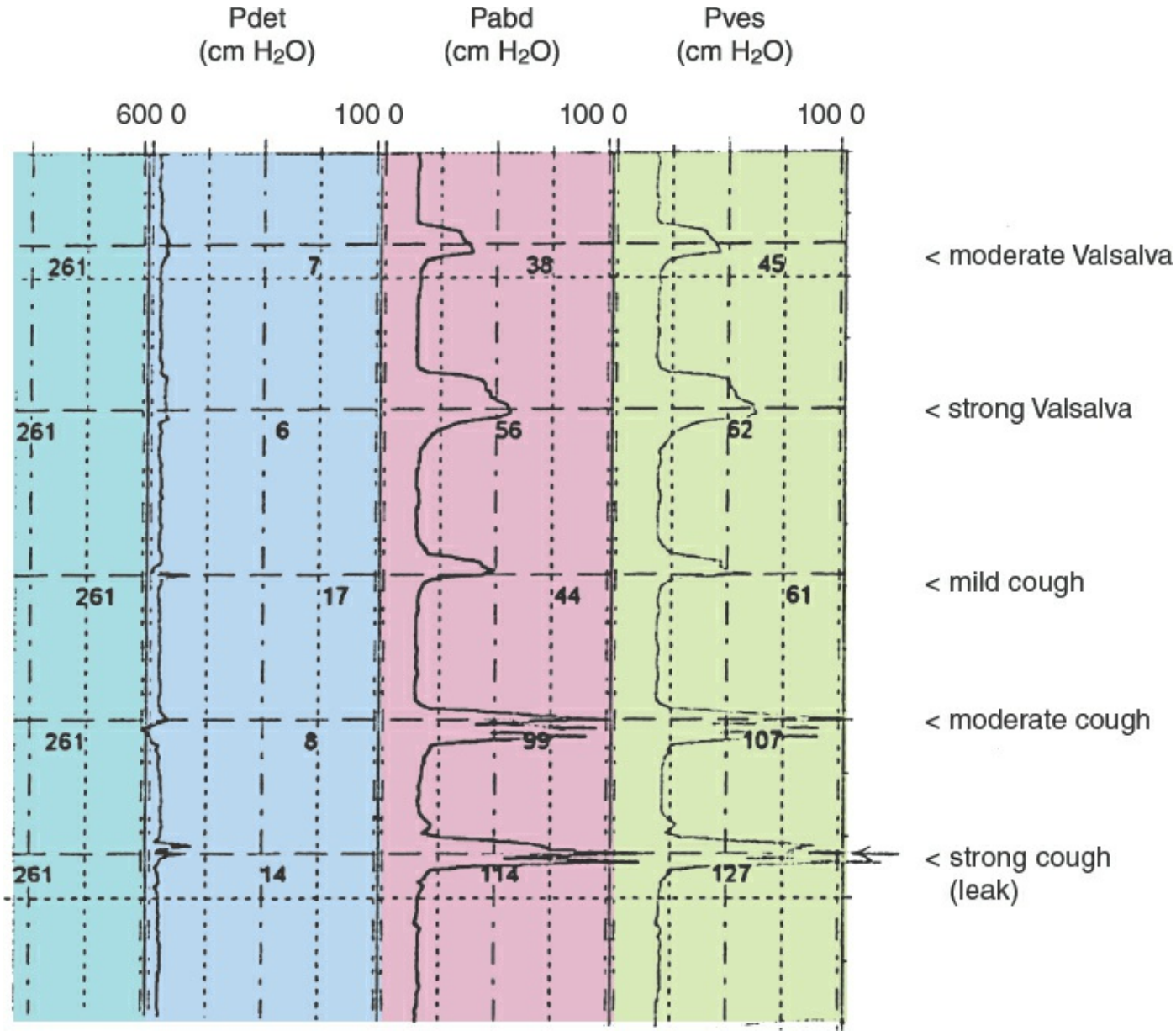


FIGURE 29-10 Valsalva leak point pressure. The abdominal Valsalva leak point pressure (VLPP) is 114 cm H_2O (the abdominal pressure at which the patient leaked urine).

Electromyography

EMG leads are usually placed around the external anus to indirectly assess the activity in the urethral sphincter. Since the anal sphincter and urethra are primarily innervated by the pudendal nerve, the EMG activity generally represents a good estimation of the urethral striated muscle activity. In a normal individual, and during the filling phase, there is increased EMG activity; during the voiding phase, there is decreased EMG activity. In women with neurologic conditions or spinal cord injuries with retention or dysfunctional voiding, there is often dyssynergia between the detrusor function and the urethral muscle activity.

Pressure Flow Studies

The final component of a complex urodynamics study is the pressure flow study or voiding cystometrogram. Here the Pves, Pabd, and Pure are measured concurrently as the patient is asked to void. This study offers information on the voiding mechanism of the bladder, presence of dysfunctional voiding, and the potential risk for retention or incomplete bladder emptying after surgery for incontinence. Normative values for all the components of a urodynamics study are shown (Table 29-8).

Other Bladder Studies

Fluoroscopy

Fluoroscopy is sometimes used, but generally not recommended, in conjunction with urodynamics (also referred to as video urodynamics) to assess for a cystocele and hypermobility of the urethrovesical junction. This information could be equally gathered during a pelvic examination; imaging studies do not have any significant added value, and they expose patients to unnecessary radiation. Moreover, the presence of funneling, or bladder neck opening with Valsalva does not necessarily equate to stress urinary incontinence as many women with normal functional urethras, and who are continent, show evidence of bladder neck opening during fluoroscopy (66).

Cystoscopy

A typical office-rigid cystoscope consists of a 17-French caliber sheath, through which the endoscope is introduced. This is attached to a fiber-optic light source, camera, and distending medium (sterile water or normal saline). The lenses on the endoscope are 0, 12, 30, 70, or 120 degrees. The lesser angle lenses are well-suited to inspect the urethra (Fig. 29-11), and perform office procedures like urethral bulking or bladder botox; whereas the 30- and 70-degree lenses are best to identify the ureteral orifices, trigone and bladder walls, and stent the ureters. The 120-degree scope, which is helpful to have a retroview of the bladder neck, is not routinely used in women. Instead, a flexible cystoscope, that has a smaller caliber and is more comfortable to patients, can be used in those instances. In fact, many specialists preferentially use the flexible cystoscope. However, the advantage of a rigid versus a flexible cystoscope is that the former has an operative channel through which it is easier to take a biopsy, should an abnormality be identified.

Table 29-8 Approximate Normal Values of Female Bladder Function

• Residual urine <50 mL
• First desire to void occurs between 150 and 250 mL infused
• Strong desire to void does not occur until after 250 mL
• Cystometric capacity between 400 and 600 mL

• Bladder compliance between 20 and 100 mL/cm H_2O measured 60 sec after reaching cystometric capacity
• No uninhibited detrusor contractions during filling, despite provocation
• No stress or urge incontinence demonstrated, despite provocation
• Voiding occurs as a result of a voluntarily initiated and sustained detrusor contraction
• Flow rate during voiding is >15 mL/sec with a detrusor pressure of <50 cm H_2O

From **Wall LL, Norton P, DeLancey JO.** *Practical Urogynecology*. Baltimore, MD: Williams & Wilkins, 1993, with permission.

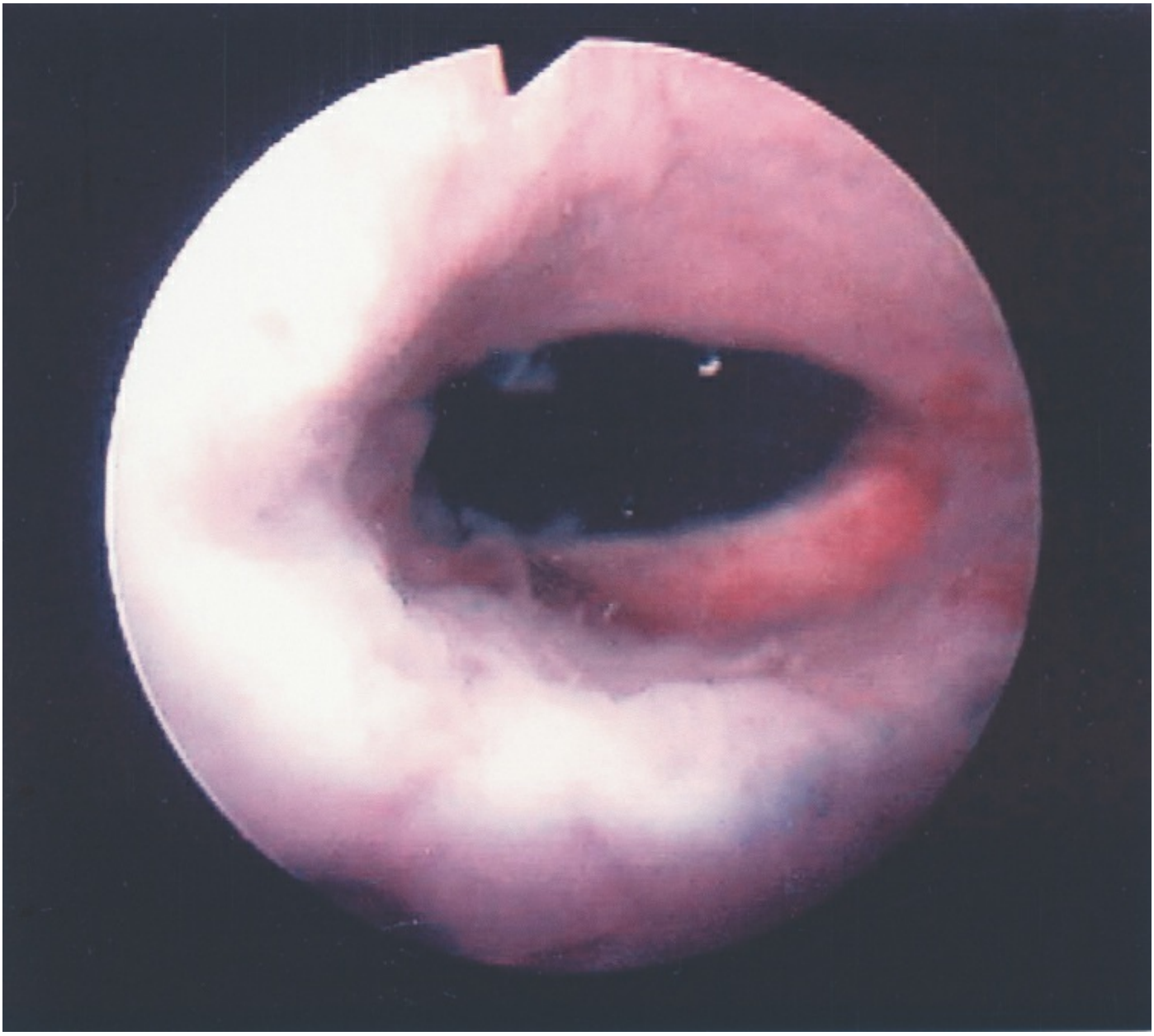


FIGURE 29-11 Cystoscopic view of a scarred urethra using a smaller angle lens.

Cystoscopy is a simple office procedure that is frequently performed in the evaluation of various bladder conditions. But, it has a limited role in the initial workup of basic urinary incontinence. Instances where cystoscopy is important include stones, bladder tumors, foreign bodies, or chronic cystitis. Other indications in women include: (a) microscopic hematuria (presence of red blood cells in the urine) that is unrelated to a urinary tract infection; (b) OAB that is refractory to conservative or medical treatment, especially in older women; (c) urinary incontinence with suspected vesicovaginal fistula; (d) symptoms such as frequency, urgency, dysuria, in the absence of a urinary tract infection; (e) women presenting with recurrent urinary tract infections; (f) recurrent urinary incontinence or OAB symptoms following previous anti-incontinence surgery; (g) complications from previous vaginal mesh or sling procedures (54,67).

Experts agree that cystoscopy is essential intraoperatively during any prolapse, incontinence, or bladder surgery. Injuries to the bladder and ureters are well-documented during such procedures (68–71). For instance, incidence of ureteral injury is as high as 11% after a high uterosacral colposuspension (69); whereas, the incidence of cystotomy could be up to 5% after mid-urethral slings (68). Identification of these injuries is relatively simple via the cystoscope, and intraoperative or early treatment of the injury results in better long-term outcomes. However, there is no consensus about performing cystoscopy universally at the time of a hysterectomy (72–74). Rates of ureteral and bladder injuries after hysterectomies for benign indications are reported to range between 0.02% and 1.8% and 0.85% to 2.9%, respectively (74,75).

Ultrasound and MRI of the Pelvis

Although pelvic ultrasound has been a gold standard diagnostic tool in many areas of gynecology, its clinical utility in bladder control conditions has been limited to research and experimental purposes. Imaging technologies such as the pelvic ultrasound and MRI have enabled researchers to develop a better understanding of the urinary continence mechanism, and the pathophysiology of stress urinary incontinence (6). With the advancements of 3D and 4D imaging, diagnostic ultrasound modalities have shown some promise in clinical practice (76). They help in defining the morphology of the urethra and its sphincter where women with stress urinary incontinence are noted to have shorter urethra and smaller urethral sphincter volumes. Ultrasound can help assess changes in morphology of the urethra, bladder neck mobility, pelvic support structures at rest or with Valsalva, and to quantify these changes. These variations are accentuated in women who have concomitant stress urinary incontinence and pelvic organ prolapse. Moreover, it is possible to assess the integrity and strength of the levator muscles during a pelvic floor contraction, and measure PVR bladder volume (77). Other useful properties of the ultrasound include observation of urethral coaptation after an injection of bulking agent for intrinsic sphincter deficiency, identification of previous

pubovaginal or mid-urethral sling location and tightness, and detection of urethral diverticulum, foreign bodies or implants in the urinary system.

MRI is another radiologic modality that has been used mostly in research to better understand the anatomy of the pelvis and the organs within. It has played a significant role in improving our understanding of the pathophysiology of pelvic organ prolapse and stress urinary incontinence. Static MRI gives detailed information of the urethral anatomy, the striated sphincter, and its surrounding structures (78,79). Dynamic MRI can delineate compartments of the female pelvis, including the urethra, with and without intra-abdominal straining to characterize presence of prolapse (80). However, MRI is not routinely used in clinical practice because of its expense and the availability of the simple pelvic examination in the office that gives equally valuable information. Nonetheless, one condition for which MRI is the diagnostic modality of choice is a urethral diverticulum (81).

Neurophysiologic Testing

The function of the bladder, urethral sphincter, and pelvic floor are dependent on the integrity of the nervous system, from the brain down to the terminal sensory and motor nerve endings supplying the genitourinary system. Several imaging and nerve conduction techniques are available to study the normal function and pathophysiology of the neuromuscular system. These include modalities such as functional CT and MRI scanning and somatosensory-evoked potentials (mostly for urgency urinary incontinence), and pudendal or sacral nerve motor latency, and EMG (mostly for stress urinary incontinence). These tests are usually performed in specialized centers and are not routinely used in the clinical setting during the workup of most women with urinary incontinence.

Prevention

Successful prevention and treatment strategies for all urinary incontinence subtypes exist. Early detection is specially challenging because most patients do not seek care, and specialists see only a small fraction of women with urinary incontinence. **Programs to mitigate onset and progression of disease should start at the primary care level. Known risk factors that promote new-onset urinary incontinence, such as age, BMI, and parity, have a long latent period. There exists some evidence that early interventions may delay or reduce risk of subsequent onset of urinary incontinence symptoms** (46). **One such example is the effect of introduction of pelvic muscle training exercises during pregnancy on prevention of urinary incontinence in the short term.** Large longitudinal population-based studies show that cesarean delivery, as opposed to vaginal birth, may have a beneficial effect in reducing subsequent risk of stress urinary incontinence. In the absence of other indications,

promoting elective cesarean section as the preferred method of delivery to prevent future pelvic floor dysfunction, including stress urinary incontinence, is a topic of debate. Other risk reduction interventions include: (a) weight loss in obese women; (b) management of blood sugar control in diabetics; (c) reduced consumption of high levels of alcohol and caffeine (46).

Conservative Nonpharmacologic Treatment

Conservative options should be offered to all patients as a first-line treatment. To optimize treatment benefits, diagnosis should be made early during the course of disease, and sometimes before onset of overt symptoms. Conservative treatments are generally simple, noninvasive, readily available and inexpensive, relatively effective and with little to no side effects. **[3] Examples of conservative nonpharmacologic interventions [4] include lifestyle modification, counseling and patient education, bladder training (or retraining), relaxation and urgency suppression, exercise training (e.g., pelvic floor muscle exercises), biofeedback, electric stimulation (E-stim), pessaries, and urethral plugs** (82).

Lifestyle Modification

This includes avoidance of risky behavior associated with urinary incontinence, urgency, frequency, and nocturia such as smoking and alcohol consumption. It includes staying healthy, developing an active lifestyle, being physically fit and losing weight (if obese). In obese or overweight women, there is ample evidence that weight loss improves both stress and urgency urinary incontinence symptoms (83). A 10% weight loss leads to more than 50% improvement in stress urinary incontinence symptoms (84). It requires that women modify or alter their dietary habits, mostly the amount and type of fluid intake. The recommended amount of fluid intake in a 24-hour period varies from an individual to another depending on their activity level, their weight, and other comorbidities. An assessment of a 24-hour bladder diary can help individualize optimal amount, type, and timing of fluid intake for a particular patient. **Caffeine reduction is helpful in women with urgency and urgency urinary incontinence (**58).

Counseling and Education

This usually starts at the physician's office, be it the patient's primary care, gynecologist, or female pelvic floor specialist. Patients can further be referred to a dietician, physical therapist, counselor, or others to assist in establishing and maintaining the health lifestyle modifications discussed above. Counseling and education can take the form of different strategies such as supplying them with educational material, motivational interviewing, empowering patients with tools and coping strategies as it relates to their incontinence, and enabling patients to take control of their condition and care for themselves (*self-care or self-help*).

Bladder Training

This intervention includes prompted voiding, and timed toileting and it aims at assisting women with idiopathic OAB or urgency urinary incontinence to minimize frequency of uncontrolled bladder urges and improve voluntary control of urine. It is generally coupled with restricting fluids in women who drink large quantities of liquid. Using her voiding diary as a guide, the patient is asked to void at a fixed time interval that is comfortably long enough (e.g., every 2 hours). Should she develop a strong desire to void before the end of the time interval, she is asked to suppress the urge. Women are instructed to *double void.* Here, the patient is asked to void normally in the bathroom with a pelvic floor relaxation to allow the urine to flow; when the flow of urine stops, the patient is instructed to voluntarily strain followed by another relaxation period to allow additional unemptied urine to flow. This regimented schedule of timed toileting and double voiding is continued for a whole week and increased by an interval of 15 minutes every subsequent week. The goal of bladder training is to prolong voiding and improve bladder capacity while reducing urgency and incontinence episodes. The whole intervention program usually takes up to 6 weeks and has been shown to be effective when compared to medications (85).

Relaxation and Urgency Suppression

There are several maneuvers whereby a patient with a strong desire to void can help mitigate the urgency sensation. One technique is to ask the patient to do something that distracts her mind off the bladder urge, such as deep breathing, singing silently, solving a simple mathematical problem, or switching from the activity she was engaged in to a moment of inactivity. Concurrently, the patient is asked to tighten her pelvic floor muscles, knee and ankle flexion, sitting on a chair (if on her feet). Many of these can be applied to women with history of stress urinary incontinence who anticipate a urine loss episode with an imminent stress activity such as coughing or sneezing.

Pelvic Floor Muscle Training

Historically, pelvic floor exercises were described by Arnold Kegel in 1948 as a nonsurgical method to restore anatomy and function of *genital relaxation* (86). Over time these exercises were structured into a physical therapy routine and collectively termed pelvic floor muscle training (PFMT). There have been several randomized trials demonstrating the benefits of PFMT (vs. placebo or no treatment) in treating urinary incontinence, in general, and stress urinary incontinence, in particular. **A Cochrane review in 2015 showed that women receiving PFMT reported improvement with fewer urine loss episodes or cure, and a better QOL than**

controls. However, since most studies follow patients up to a year or less, there is limited to no robust information on the long-term benefits of PFMT (87).

Commonly, during a PFMT program, women are encouraged to contract their pelvic floor muscles for 3 seconds, 10 to 15 times per session, and 3 times a day. Helpful hints to contracting the right pelvic floor muscles include: keeping the abdomen and hips relaxed; imagining that one is trying to prevent passing of gas, tightening the rectum, or bringing the buttock cheeks together. They should be done in a comfortable laying or sitting position. It can be done while watching TV, in front of a computer on a desk, or while driving a car. A common misconception is that women try to do their Kegels in the bathroom every time they are voiding. However, this can lead to voiding dysfunction and worsening OAB symptoms in the long run, and Kegels are best done with an empty bladder.

Physical therapists often use adjunctive aids such as biofeedback and E-stim to supplement the PFMT, especially when patients are not able to generate a good squeeze during the physical therapy session. Biofeedback can be auditory or visual and gives the patient a sensory feedback of the strength of her pelvic floor squeeze. Electrical stimulation therapy delivers low levels of current via a probe placed in the vagina or rectum. There is no evidence that biofeedback or E-stim are superior to PFMT alone, especially when the latter are done regularly and properly in women with stress urinary incontinence (87).

Mechanical Devices for Urinary Incontinence

Several devices are available to treat mostly women with stress urinary incontinence (Fig. 29-12). These can be divided into two main groups: urethral and vaginal. The urethral devices create a temporary occlusion of the urethral meatus to prevent urine loss. One example of a urethral device is the urethral insert *FemSoft* where a woman is instructed to place the insert into the urethra and then remove it before urinating. These could be beneficial in female competitive athletes who may have stress urinary incontinence episode only during a sporting event (e.g., tennis). Although incontinence episodes are reported to decrease, about one-third of women developed urinary tract infections in one long-term follow-up study (88).

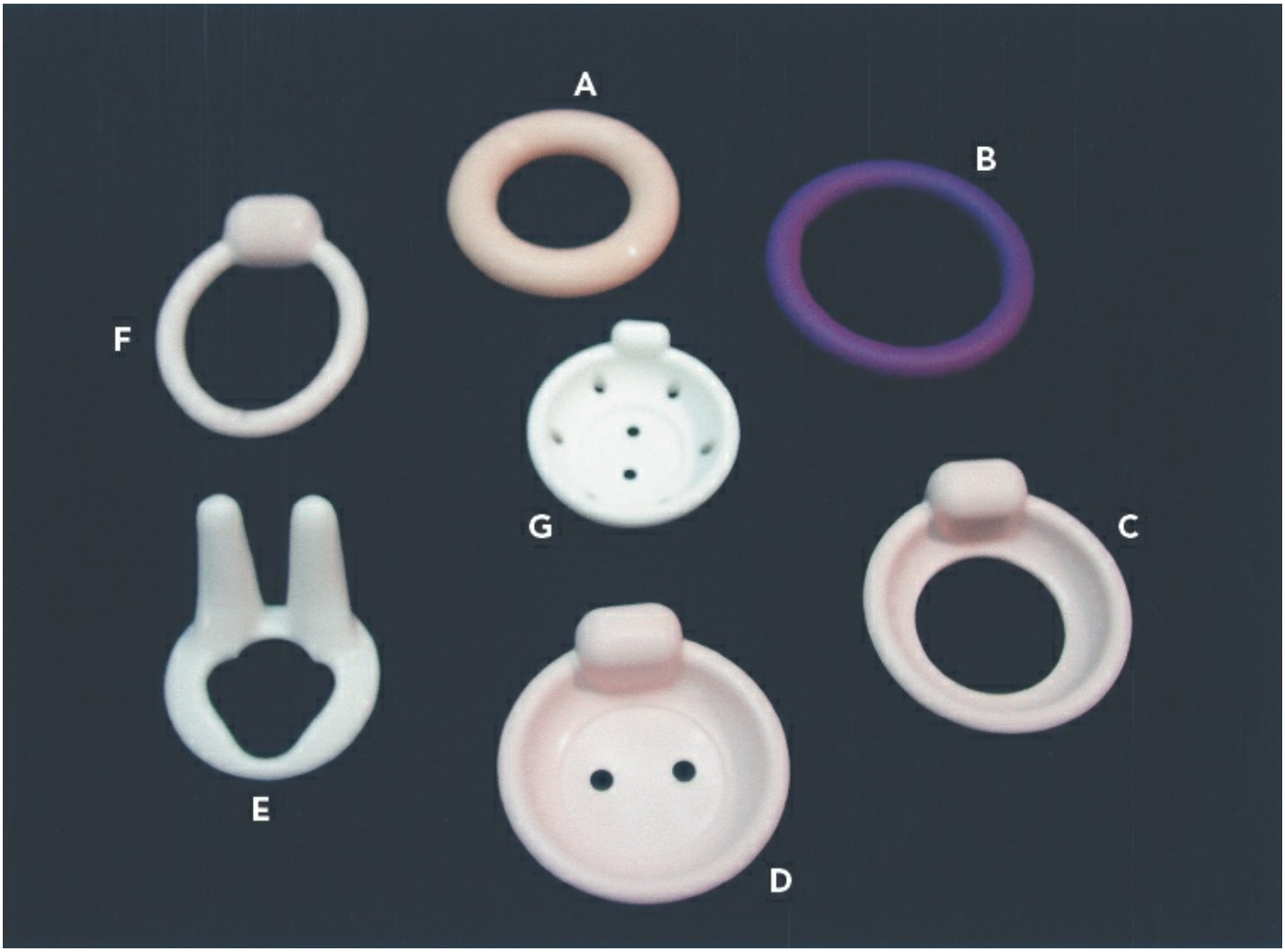


FIGURE 29-12 Vaginal incontinence pessaries: (clockwise from top): **A:** Suarez ring (Cook Urological, Spencer, IN), **B:** PelvX ring (DesChutes Medical Products, Bend, OR), **C:** Incontinence dish (Milex Inc., Chicago, IL), **D:** Incontinence dish with support (Mentor Corp., Santa Barbara, CA), **E:** Introl prosthesis (was Johnson and Johnson; currently not available), **F:** Incontinence ring with support (Milex Inc., Chicago, IL), (middle): **G:** Incontinence dish with support (Milex Inc., Chicago, IL).

Vaginal devices consist of two categories. The first type of device is used as an adjunct to PFMT such as vaginal weights or cones. These devices are placed in the vagina by the patient for short periods of time in an effort to improve the strength of the pelvic floor muscles. Alternatively, the second type of a vaginal device is meant to be used long-term and throughout the day to help support the bladder neck and assist in the urethral closure mechanism of the urethral sphincter. These devices include pessaries, vaginal sponges, or tampons. One randomized controlled trial comparing pessary use to behavioral therapy to a combination treatment for stress urinary incontinence showed that behavioral therapy produced greater patient satisfaction with fewer incontinence symptoms that were bothersome at 3 months. By 12 months there were no differences, and patient satisfaction persisted similarly in all three groups. Single modality was similar to combination therapy (89). However, a recent

Cochrane review concluded that there is little evidence from controlled trials on the role of mechanical devices on long-term sustained beneficial effects in the management of urinary incontinence (90).

Other Treatment Options

Electric stimulation (E-stim) and magnetic stimulation (M-stim) are two alternative conservative options that are available in specialized centers. Evidence regarding those modalities in the management of urinary incontinence is not well-established and more research is needed to show whether they are more beneficial than the traditional and less costly conservative options available.

Medications for Stress Urinary Incontinence

Historically, *estrogen* replacement therapy was used to treat women with stress and urgency urinary incontinence. Based on large randomized trials including the Women's Health Initiative (WHI), estrogen (with or without progesterone) has been shown to be associated with increased prevalence (worsening incontinence) and incidence (new-onset incontinence), and with the negative effect being more pronounced for stress than urgency urinary incontinence (91). **Similar results were found with the Heart Estrogen and Progestin Replacement Study (HERS) comparing oral conjugated equine estrogen and medroxyprogesterone acetate to placebo where 1,525 women were followed for 4 years. More specifically, the HERS study showed that the odds ratio for worsening incontinence was 1.5 among women with baseline urinary incontinence; the odds ratio for developing new stress urinary incontinence was 1.7, and new urgency urinary incontinence was 1.5** (92,93). **A Cochrane review on this topic confirmed these findings and concluded that estrogen replacement therapy should *not* be offered to women as a treatment for urinary incontinence, with the caveat that local (vaginal) use of estrogen may improve symptoms of urgency and frequency in the short term** (94).

Other medications have been used to treat stress urinary incontinence. These are typically drugs that have a stimulating effect on the alpha-adrenergic receptors present in the urethral sphincter. Examples include *epinephrine* and *norepinephrine, ephedrine* and *pseudoephedrine,* and *phenylpropanolamine.* These alpha-stimulating drugs are nonspecific and can be associated with other systemic effects including on the heart, brain, and blood pressure. They are not FDA approved and rarely, if ever, used purely for stress urinary incontinence. *Imipramine,* a tricyclic antidepressant, has been used with variable success, especially in women who have a coexisting stress and urgency urinary incontinence. This may relax the bladder through its anticholinergic effect, and constrict the urethra through its alpha-agonistic effect. One other drug worthy of mention is *duloxetine*. It is an FDA-approved serotonin and norepinephrine reuptake inhibitor drug to treat depression, chronic pain, and

anxiety, but not for stress urinary incontinence. Its mechanism of action on the bladder is to increase bladder storage and improve urethral sphincter function via its effect on the central nervous system. In one study, duloxetine was shown to be equally effective as PFMT (95). But, but the presence of side effects (nausea, fatigue, insomnia, somnolence, dizziness, and blurred vision) may preclude it from being used as a first-line therapy for stress urinary incontinence.

Medications for Urgency Urinary Incontinence and Overactive Bladder

Medical treatment for urgency urinary incontinence and OAB is less controversial than for stress urinary incontinence. Medications are usually offered either when conservative treatment options have failed or in conjunction. Their efficacy, however, is modest. **One major medication class represents the anticholinergic drugs.** These include drugs that produce their effect by inhibiting the stimulatory effect of the parasympathetic nervous system on the detrusor muscle by blocking the cholinergic (acetylcholine or muscarinic) receptors. **Several of these drugs exist with similar efficacy profiles. These drugs differ in duration of action (immediate release vs. long acting) and route of administration (oral, patch, or gel) (Table 29-9) (**58). **In 2009, the Agency for Healthcare Research and Quality published an evidence-based review of over 230 publications on the medical treatment modalities for urgency urinary incontinence and OAB** (96). **They showed that anticholinergic medications reduced number of voids (and urinary incontinence episodes) by 1.5 to 2.2 per day, with the short-acting drugs being on the lower range, and the long-acting drugs on the higher range. Interestingly, a relatively high placebo effect exists in most randomized trials which is as high as 1.5 voids per day reduction.**

The immediate-release *oxybutinin* was the first FDA-approved anticholinergic drug, but it has a short half-life and is taken three times a day to be optimally effective. Extended-release medications tend to be better tolerated because of their once daily administration, and a lower side-effect profile (97). **In general, anticholinergics are administered at a low dose, with subsequent increase in dosage after a period of 4 to 6 weeks should there be no significant improvement. In the presence of side effects, it is reasonable to try another anticholinergic. Because anticholinergics are not purely specific to the bladder muscarinic receptors, they all produce side effects with a varying degree on other tissues or organs These include the salivary glands resulting in dry mouth, the iris and ciliary muscles of the eyes resulting in blurry vision, the gastrointestinal system resulting in constipation, the heart resulting in altered heart rate, and the brain resulting in memory problems. One exception may be *trospium chloride*, a quaternary amine anticholinergic, which is hydrophilic with a large molecular size limiting its distribution into the central nervous system and reducing its effect on cognition.**

Table 29-9 Pharmacologic Therapies Indicated for Overactive Bladder with or without Urgency Incontinence

Compound	Usual Dose
Oxybutynin chloride (Ditropan, Ortho-McNeil–Janssen Pharmaceuticals and available as generic formulation)	5 mg by mouth 3–4 times daily
Oxybutynin chloride extended release (Ditropan XL, Ortho-McNeil–Janssen Pharmaceuticals and available as generic formulation)	5, 10, or 15 mg by mouth once daily
Oxybutynin transdermal patch (Oxytrol, Watson Pharmaceuticals)	One patch applied twice weekly
Oxybutynin gel 10% (Gelnique, Watson Pharmaceuticals)	One sachet applied daily
Tolterodine tartrate (Detrol, Pfizer)	2 mg by mouth twice daily
Tolterodine tartrate long acting (Detrol LA, Pfizer)	4 mg by mouth once daily
Fesoterodine fumarate (Toviaz, Pfizer)[a]	4 or 8 mg by mouth once daily
Solifenacin succinate (Vesicare, Astellas Pharmaceuticals)	5 or 10 mg by mouth once daily
Trospium chloride (Sanctura, Allergan)	20 mg by mouth twice daily
Trospium chloride extended release (Sanctura XR, Allergan)	60 mg by mouth once daily
Darifenacin (Enablex, Novartis Pharmaceuticals)	7.5 or 15 mg by mouth once daily

[a]Tolterodine is the active metabolite of fesoterodine.
Nygaard I. Clinical practice. Idiopathic urgency urinary incontinence. *N Engl J Med* 2010;363:1156–1162; Table 1, need permission.

There has been increased concern regarding the cumulative effect of anticholinergics on cognition, dementia, and onset of Alzheimer's disease. In one review study of patients prescribed anticholinergic medications over a follow-up period of 7 years, 797 participants (23%) developed dementia (of whom, 637 developed Alzheimer's). There was a significant 10-year cumulative dose–response relationship for dementia and Alzheimer disease (98). Based on this and other evidences, AUGS published a consensus statement in 2017 recommending behavioral therapies as a first-line treatment for urgency urinary incontinence,

followed by medical interventions. More specifically, AUGS recommends " . . . caution in prescribing anticholinergic medications in frail or cognitively impaired patients" and that " . . . providers should counsel on the associated risks, prescribe the lowest effective dose, and consider alternative medications in patients at risk" (99).

A second class of medications to treat urgency urinary incontinence includes the beta agonists. This class currently includes only one FDA-approved (2012) medication known as *mirabegron*, which is a specific beta-3 receptor agonist. It produces its effect via the sympathetic system by stimulating the beta receptors on the bladder, leading to relaxation of the detrusor muscle (100). **Unlike anticholinergics, it does not have dry mouth, constipation or blurred vision as side effects, but it ought to be used with caution in women with uncontrolled hypertension (it increases blood pressure), renal or hepatic impairment and urinary retention.** It can be used in women with cognitive impairment. In one recent randomized trial comparing mirabegron to *tolterodine*, patient tolerability for mirabegron was higher than tolterodine which was associated with more side effects, but patient preference and OAB symptom improvements were similar between the two drugs (101).

Medications for Nocturia and Enuresis

Nocturia, especially in the elderly, may be multifactorial. Waking up to go to the bathroom one or more times during the night may be the consequence of increased fluid intake, caused by bladder storage conditions like OAB, or other comorbidities unrelated to the bladder, such as vascular insufficiency, heart disease, or others. *Desmopressin,* a medication used to treat nocturia or enuresis, is effective mostly through its central inhibitory action on reducing urine production. It is available as a nasal spray and as an oral preparation. Caution is recommended in the elderly or in women with hypertension; it requires periodic measurement of sodium levels. *Imipramine,* may work centrally to improve sleep, and peripherally on the bladder and urethra to improve bladder storage. *Anticholinergics* can be used to help with nocturia, especially in women with OAB. Diuretics like *furosemide*, can be helpful, especially in the presence of vascular insufficiency and peripheral edema.

Medications to Treat Overflow Urinary Incontinence or Urinary Retention

Overflow urinary incontinence or urinary retention is a condition more prevalent in men, and commonly occurs as a result of benign prostatic hyperplasia. In women, in the absence of an anatomic obstruction, such as a urethral stricture, previous anti-incontinence surgery or advanced prolapse, overflow incontinence can occur because of bladder detrusor muscle underactivity, diabetic neuropathy, or central nervous system conditions. Different drugs have been used, albeit with limited

success, to either stimulate the detrusor muscle or to reduce urethral sphincter resistance, and therefore improve voiding (102). Examples of detrusor muscle stimulants include muscarinic receptor agonists, such as *bethanechol*, or cholinesterase inhibitors, such as *distigmine*. There is no evidence from controlled clinical studies that these medications offer substantial benefit, and these drugs may be associated with significant side effects (103). A hypoactive or atonic bladder is generally not responsive to medical treatment. Alpha-receptor blockers such as *alfuzosin* have been shown to be beneficial in men by reducing the resistance in the bladder neck and urethra to facilitate bladder emptying. Although these medications have been used in women with urinary retention, they have produced variable results (104,105).

Surgical Treatment of Urinary Incontinence

Pubovaginal Slings

At the turn of the 20th century, one of the earliest described surgeries reported in Europe for stress urinary incontinence involved placing an organic sling at the bladder neck (106). These operations, presently referred to as traditional slings, are performed through two incisions, one in the vagina to pass the sling around the urethra, and one through the abdomen to gain access around the space of Retzius. The two free ends of the sling material are passed up from the vagina and then attached commonly to the fascia of the rectus muscle (or other pelvic structures) to create a fixed loop around the bladder neck and proximal urethra **(Fig. 29-13)**. This provides support to the urethral closure mechanism at times of increased abdominal pressure (107). Over the years, use of different sling materials has been described including autologous (e.g., fascia lata, rectus muscle, or fascia harvested from the patient), allografts obtained from donors (e.g., cadaveric fascia lata), heterologous obtained from other species (e.g., bovine or porcine), or synthetic (e.g., prolene or Gore-Tex) (108).

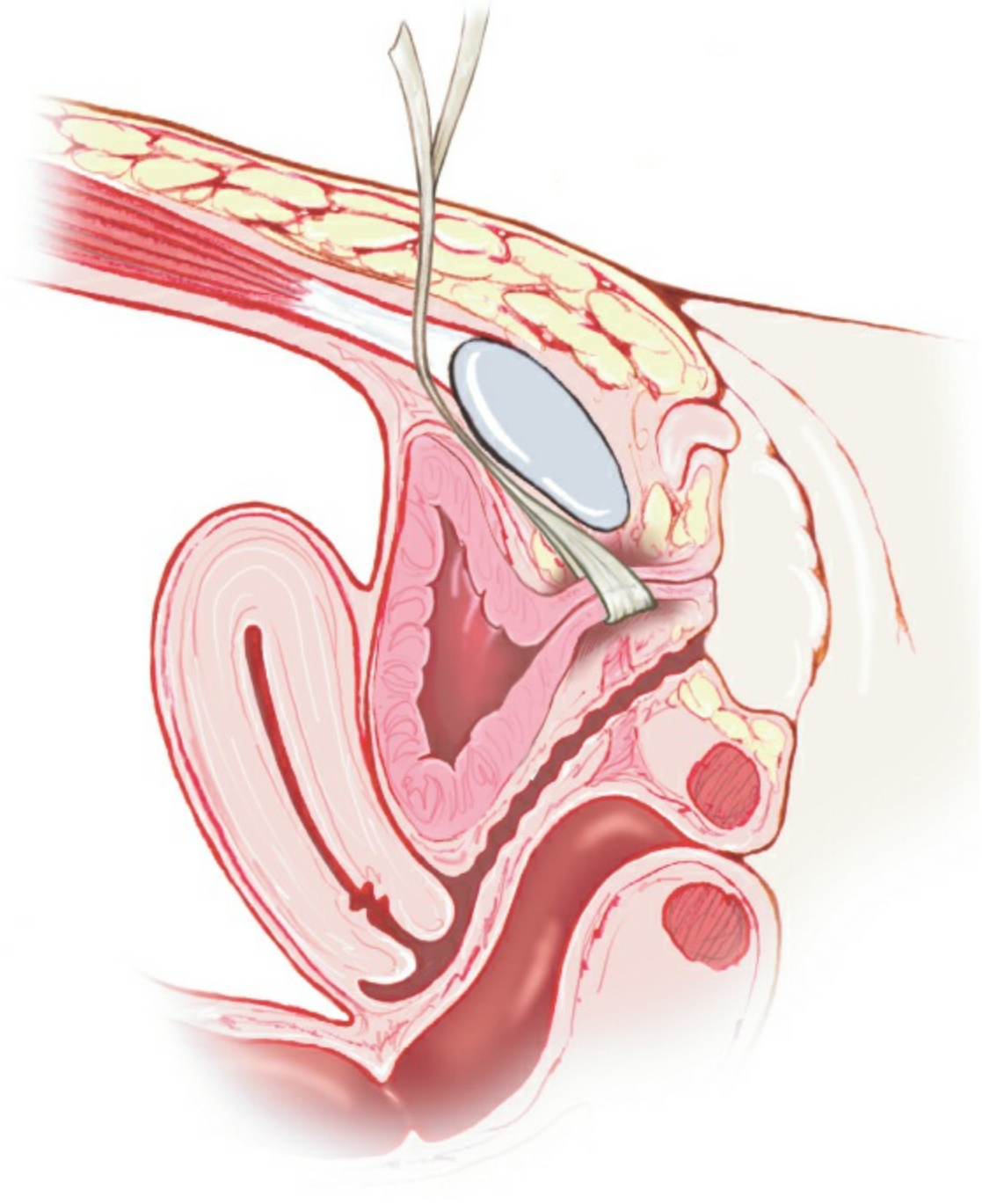


FIGURE 29-13 A completed traditional suburethral sling procedure with the fascia located at the bladder neck with the ends of the sling tied to or above the rectus fascia. The classic procedure uses autologous fascia; however, some surgeons use allograft or xenograft tissue performed in a similar fashion. (Redrawn from original by Jasmine Tan.)

Although successful, the pubovaginal slings can result in urinary retention requiring further surgery to resolve ensuing voiding dysfunction. Synthetic slings can be associated with risk of erosion (109). In a large randomized surgical study, women with stress urinary incontinence who underwent fascial pubovaginal sling had a higher success rate than a Burch colposuspension at 2-year follow-up (47%

vs. 38%; *P* = 0.01). However, there was a higher rate of complications in the pubovaginal sling group, including voiding dysfunction, urinary tract infections, and new-onset urgency urinary incontinence (110). **Of the original 655 women in the initial randomized clinical trial, 482 (75%) were enrolled in a follow-up study up to 7 years. The vigorously defined composite success rate decreased from 42% to 13% in the Burch group and 52% to 27% in the sling group** (111). **When success was defined using only one criterion (e.g., 1-hour pad test), reported rates were much higher and similar between the two groups (84% for the Burch group and 85% for the sling group)** (110). **Based on this and other evidences, the pubovaginal sling using autologous fascia remains a viable option to treat women with predominant stress urinary incontinence (**64).

Anterior Vaginal Wall Repair

A few years after the publication of the initial pubovaginal sling procedures to treat stress urinary incontinence, Kelly reported on the anterior vaginal repair (or anterior colporrhaphy) in 1914 (112). This operation was a simple procedure and based on case series, it was initially thought to be a very successful surgery, and therefore became quite popular for over half a century. The key concept of the anterior vaginal repair is to plicate the pubovesical fascia around the bladder neck and proximal urethra to give it the necessary support and to assist in the sphincteric closing mechanism by preventing urine loss. Randomized controlled trials comparing the anterior vaginal wall repair to alternative procedures revealed that the former's long-term success was suboptimal (113,114). The Kelly plication (anterior vaginal wall repair) is not recommended to treat women with stress urinary incontinence (64,109).

Needle Suspension Surgeries

One of the earliest needle suspension procedures was introduced by Pereyra in 1959 (115). The technique of this surgery and several of its subsequent modifications involved passage of a special needle carrier introduced bilaterally through an abdominal incision down into the vagina. Sutures were placed on both sides of the urethra within the vaginal and underlying connective tissue, brought up and then attached to the rectus fascia. It was presumed that this suspension would provide lasting bladder neck support and help mitigate stress urinary incontinence episodes. However, similar to the Kelly plication, long-term success of needle suspension procedures failed to withstand the test of time in randomized controlled trials (109,114), and they are no longer recommended for the treatment of stress urinary incontinence (64).

Retropubic Colposuspension Surgeries

Because most women with stress urinary incontinence have hypermobility of the bladder neck, DeLancey's *Hammock Theory* made clinical sense (30). As a result, retropubic colposuspensions (urethropexies), where the endopelvic fascia around the

bladder neck and proximal urethra is suspended to structures on the anterior pelvis, were shown to be good surgeries to treat stress urinary incontinence **(Fig. 29-14)**. **The two most commonly performed retropubic urethropexies are the Marshall–Marchetti–Krantz (MMK) and Burch procedures** (116,117). **The procedures are similar in that the approach is abdominal, requiring entry into the retropubic space. The MMK was initially described in a man with urinary incontinence following prostatectomy where the endopelvic fascia was attached to the pubic bone** (116). **With the Burch retropubic urethropexy, the periurethral tissue was fixed to Cooper ligament** (117). **Burch followed 143 of his patients up to 9 years and reported a success rate of 82%** (118).

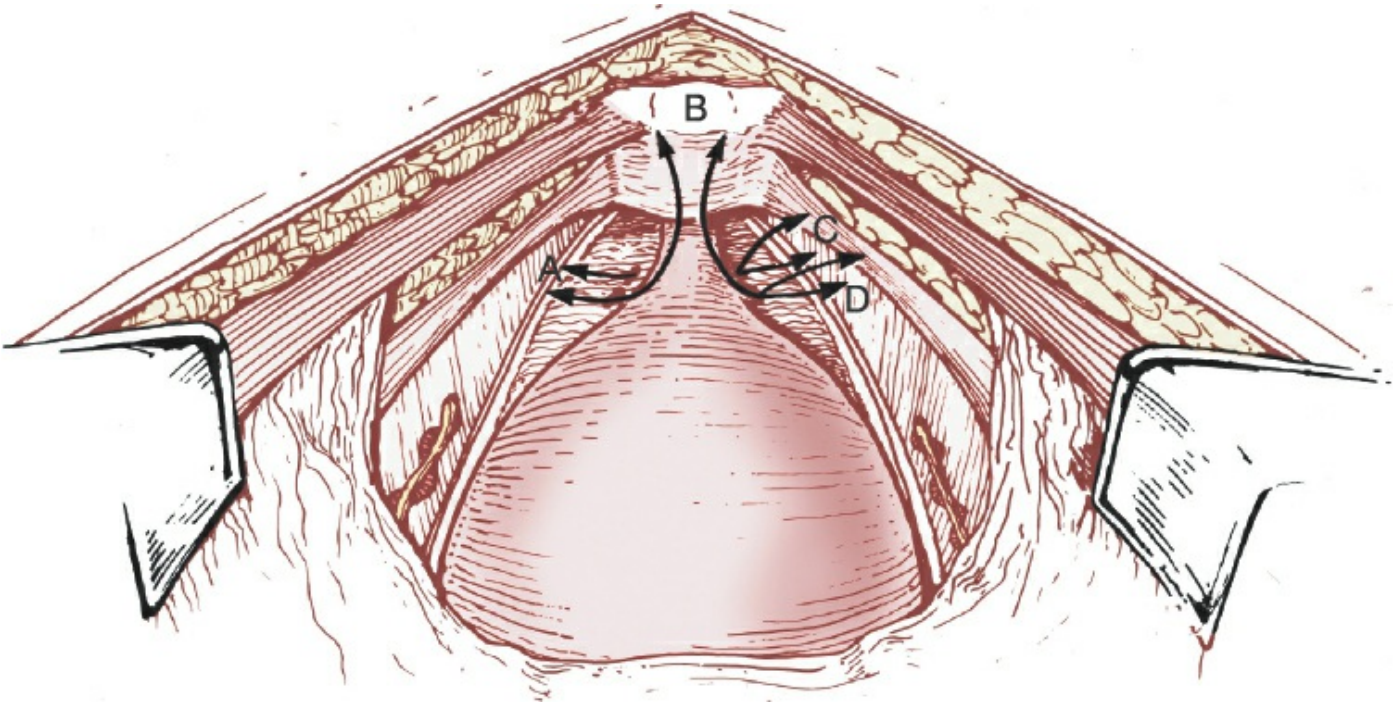


FIGURE 29-14 Points of reattachment of the endopelvic fascia during retropubic bladder neck suspensions. ***A*:** Arcus tendineus fascia pelvis (for paravaginal repair). ***B:*** Periosteum of pubic symphysis (for Marshall–Marchetti–Krantz procedure). ***C:*** Ileopectineal, or Cooper, ligament (for Burch colposuspension). ***D:*** Obturator internus fascia (also used for paravaginal, or obturator shelf, repair).

In a randomized trial comparing the open Burch urethropexy to the mid-urethral sling procedure, success rate (reported as a negative 1-hour pad test) was 44/49 (90%) versus 58/72 (81%), respectively ($P = 0.21$) at 5 years (119). Retropubic urethropexies can be performed laparoscopically, but there are limited data on their long-term efficacy (120). In one randomized trial, patients were followed for a median of 65 months (range 12 to 88 months). Here, 58% of women reported *any* urinary incontinence after a laparoscopic Burch compared with 48% after a mid-urethral sling, with no statistically significant difference between the two groups; stress urinary incontinence bother symptoms were reported in only 11% and 8% of women, respectively (121). Using

strict criteria to define urinary incontinence yields a higher failure rate, but most women report significant improvement in bother symptoms and impact on QOL after colposuspension procedures. A recent 2017 Cochrane review showed that the open Burch and other retropubic colposuspension procedures remain very successful operations to treat stress urinary incontinence, with long-term (5 years or more) success rates of around 70% (120). **Compared to pubovaginal slings, open colposuspension is associated with a lower risk of voiding dysfunction, but with a higher risk of subsequent pelvic organ prolapse (**110,119).

Mid-Urethral Slings

The mid-urethral slings were developed as a direct consequence of the *integral theory* that was promoted by Petros et al. (31). **The polypropylene tension-free vaginal tape (TVT) was the original mid-urethral sling described by Ulmsten in 1996 as a simple minimally invasive outpatient procedure under local or regional anesthesia** (122). **With this procedure, a synthetic sling is placed under the mid-urethra (in contrast to pubovaginal slings that are placed at the bladder neck) in a tension-free manner. The two ends of the sling are not attached or sutured to a pelvic structure, but rather the urethra is free of any tension upon placement of the sling. The TVT is commonly placed in a bottom-up direction through a small 1 to 2 cm mid-urethral vaginal incision, and the two free ends are passed up and behind the pubic bone through the space of Retzius and out through two suprapubic incisions (Fig. 29-15)**. As each side of the sling is advanced around the urethra using a trocar, the bladder is deviated to the contralateral side via a guide wire placed through a Foley catheter to minimize the risk of a cystotomy. Cystoscopy is performed to confirm the integrity of the bladder. Although mid-urethral slings were initially received with skepticism, over time they have proven to be very effective surgeries with low rates of complications replacing all other procedures as the gold standard to treat stress urinary incontinence (123,124). Of the original 90 women who underwent the TVT procedure, 78% were followed-up to 17 years. Of those evaluated either by a clinic visit or by phone, about 90% had objective and 87% had subjective cure or significant improvement (125).

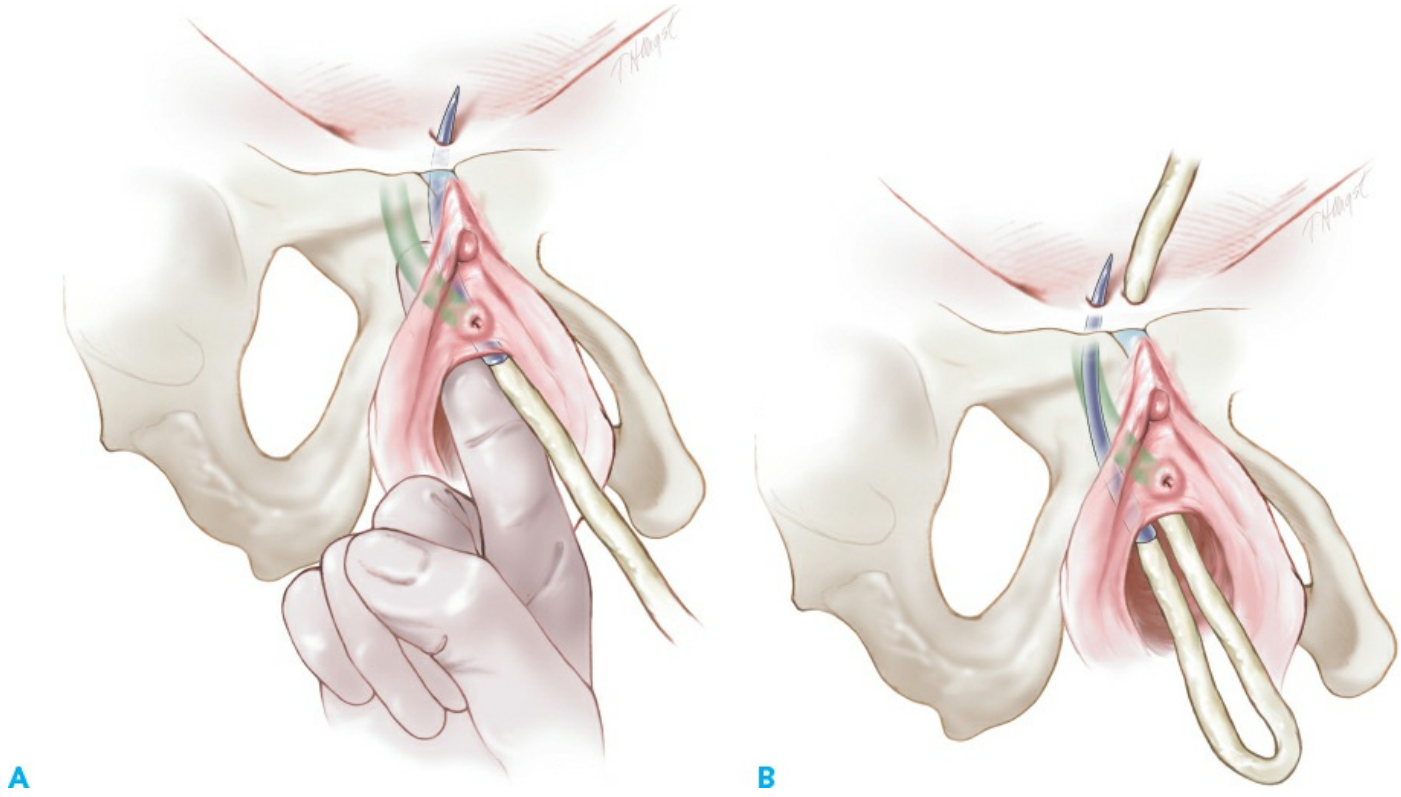


FIGURE 29-15 Midurethral synthetic slings involve the use of large pore, monofilament polypropylene mesh placed after minimal dissection at the midurethra followed by placement of a trocar through the retropubic route. **A:** The trocar is guided into the previously performed midurethral incision with care to place the trocar against the pubic bone to avoid entry into the peritoneal cavity. The trocar handle has been removed in this view after perforation through the abdominal incision. **B:** The synthetic sling should rest in the midurethra location and is brought through two stab incisions above the pubic symphysis. (Redrawn from original by Jasmine Tan.)

In 2001, Delorme reported on the transobturator tape (TOT) where the sling position is still mid-urethral, however its general direction is through the ischiorectal fossa and the free ends exit via the obturator canal and out through the genitofemoral creases bilaterally (126). **The TOT sling can be placed in an outside-in or inside-out direction. The TOT mid-urethral slings were developed in an attempt to reduce complications associated with the TVT procedure, including bowel, bladder, and vascular injury. Subsequent studies have shown that women undergoing TOT procedures are still at risk of vascular and bladder injuries, although rare.** Over the past two decades, there has been an accumulation of a large body of evidence on mid-urethral slings from randomized controlled trials, including several meta-analyses and Cochrane reviews (120,123,124,127,128). **The overarching summary is that mid-urethral slings have become the procedure of choice in treating women with stress urinary incontinence.** They have a good safety profile with a significant improvement of QOL measures, and irrespective of route of placement, they are highly effective in the short, medium, and long term. There is evidence to suggest that the mid-urethral slings are more effective than the Burch

colposuspension procedure, and as effective as the autologous pubovaginal sling (123).

Concerning the choice of mid-urethral sling (retropubic vs. transobturator), data show that the retropubic approach may be favored in terms of long-term efficacy, but with the risk of higher overall complication rates (123,127,129). In a large national cohort of more than 8,600 women undergoing mid-urethral slings in Denmark over a 10-year span, the reoperation rate at 5 years was 6% for the TVT and 9% for the TOT. In the adjusted model, the TOT sling was associated with a twofold higher risk of reoperation (HR, 2.1; 95% CI, 1.5–2.9) than the TVT sling. In terms of complications, urinary tract infections occur in up to 10% after mid-urethral slings (130). Bladder perforation is another complication that can occur with both approaches but more commonly with the TVT. Of note is that bladder perforations are mostly inconsequential. With universal cystoscopy at the time of sling placement, the cystotomy, typically at the dome of the bladder, is easily identified. Repositioning of the sling, and ensuring subsequent proper placement is generally sufficient. In certain cases, keeping the Foley catheter in for up to a week may be necessary. Other complications that are more common with the TVT include bleeding (intra and postoperative), and postoperative voiding dysfunction necessitating sling revision; in contrast, the TOT has a higher rate of mesh erosion, and postoperative groin and leg pain (123,130). Rare complications include bowel injuries, and patient deaths after retropubic slings, and severe infections after transobturator slings (131).

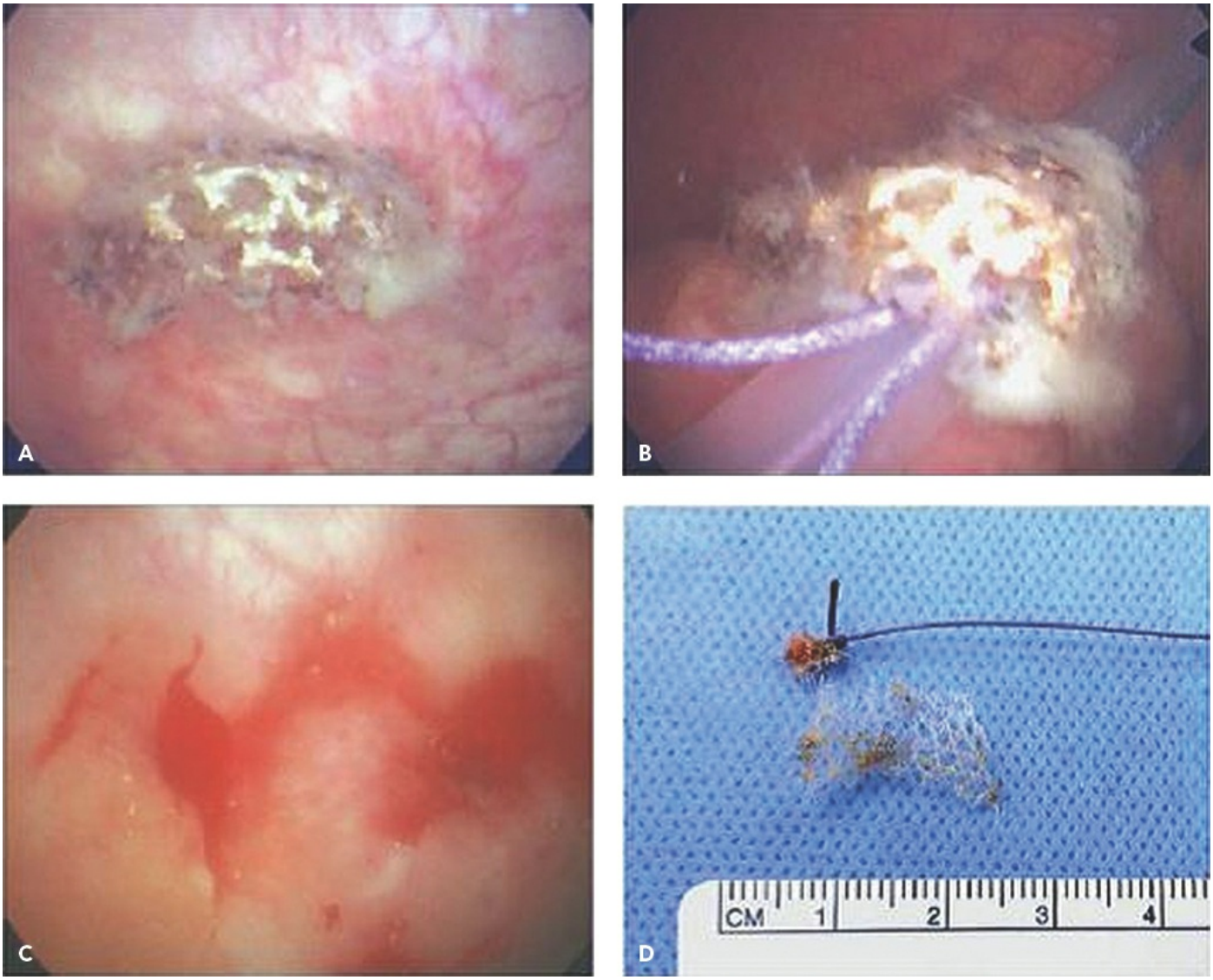


FIGURE 29-16 Sling erosion into the bladder. (**Bieniek JM, Holste TL, Platte RO, et al.** Cystoscopic removal of intravesical synthetic mesh extrusion with the aid of Endoloop sutures and endoscopic scissors. Int Urogynecol J 2012;23:1137–1139; Figure 1, need permission.)

A unique complication associated with mid-urethral slings is erosion of the sling material (130). Although uncommon, sling erosion into the vagina generally requires surgical repair which involves resection of the segment eroding into the vagina and repairing the vaginal mucosa over the involved site. When the sling erodes into the bladder (and uncommonly into the urethra), this requires more complicated surgery to resect the eroded segment (Fig. 29-16). Rarely, the whole sling material (TVT or TOT) may need to be removed typically because of chronic pain resulting from placement of the sling.

Certain mid-urethral sling characteristics and indications worthy of mention include the following: (a) with retropubic slings, the bottom-up route may be more effective than top-down route; (b) with the exception of leg and groin pain, fewer

adverse events occur with the transobturator than the retropubic approach; (c) the transobturator may be more cost-effective compared with the retropubic sling, although studies looking at cost do not take into account the potential impact of repeat surgery to address recurrence of incontinence on overall cost; (d) the retropubic sling is favored over the transobturator sling in cases of fixed immobile urethra (intrinsic sphincter deficiency) and mixed urinary incontinence; and (e) the transobturator approach may be favored in cases where there is previous significant bowel or pelvic adhesive disease.

Single incision (mini) slings have been introduced with the goal of further minimizing surgical complications while maintaining efficacy. A mid-urethral incision is made to introduce the sling while fixing (or anchoring) the two shorter arms to the fascia in the obturator or retropubic space. However, their short- to mid-term results are not very promising. **In a recent Cochrane review, mini-slings were reported to be either inferior, or they lacked enough evidence to support their endorsement over the retropubic or transobturator slings (**132). More studies with longer-term follow-up are needed to establish their safety profile in treating women with stress urinary incontinence without compromising surgical success. When a mid-urethral sling is chosen as a treatment option, the AUA guidelines recommend either a retropubic or transobturator sling as a first choice, and if a mini-sling is to be used, patients are to be informed that not enough short-, medium- and long-term data exist in its support (64).

Over the past century, surgical standards of care for stress urinary incontinence have made a full circle from slings (mostly pubovaginal) to bladder neck and retropubic suspensions and back to slings (mostly mid-urethral). These transitions in surgical care have occurred mostly on the heels of an in-depth understanding of the anatomy of the pelvic floor and rigorous evidence-based epidemiologic and clinical research.

Bulking Agents

Urethral bulking agents are an accepted treatment option for women with stress urinary incontinence. They are typically injected around the proximal urethra submucosally to give it bulk, either transurethrally or periurethrally, using an operative cystoscope. When compared to the mid-urethral slings, the colposuspension, and pubovaginal slings, there exist little data evaluating their long-term success. Repeat operations are common after bulking agent therapy. However, they are appropriate procedures for patients who are poor surgical candidates, on anticoagulation therapy, with high PVRs, or in older women with high surgical anesthesia risk (133). The advantage of injectable agents is that they are less invasive and they can potentially be done in a clinic setting without the need for general or regional anesthesia.

Available and FDA-approved bulking agents for stress urinary incontinence treatment include pyrolytic carbon–coated zirconium oxide spheres (beads) (Durasphere), cross-

linked polydimethylsiloxane (Macroplastique), and spherical particles of calcium hydroxylapatite (Coaptite). The glutaraldehyde cross-linked bovine collagen (Contigen) is not being produced by its manufacturer and is no longer available in the United States market. Injection of the bulking agent into the urethral submucosa produces its coaptation to help maintain continence in the presence of an increased abdominal pressure (134–136). In one review article, it was noted that subjective success rates ranged from 66% to 90% at 12-months follow-up, whereas objective improvement ranged from 25% to 73% (137). **A 2017 Cochrane review showed that limited data exist beyond 2 years posttreatment with urethral bulking agents. Short-term data are suggestive of an improvement, but they lack the robust success or cure rates associated with mid-urethral slings** (138). **Reported complications of the urethral bulking agents include urinary tract infections, urinary retention, erosion and migration of the implanted material** (139).

Other Potential Future Therapies

Autologous *stem cells* have been used experimentally to help regain bladder control. Most studies have used stem cells derived from muscle or adipose tissue. The stem cells can be injected periurethrally or into the pelvic floor to regenerate damaged urethral sphincter or repair/reconstruct pelvic support structures using tissue engineering techniques. Although preclinical and early clinical trials have demonstrated safety, efficacy of those techniques to treat stress urinary incontinence is still in question (140,141). *Radiofrequency* applied transurethrally to promote collagen denaturation is another modality that has been proposed as a nonsurgical procedure to treat stress urinary incontinence. However, a Cochrane review demonstrated no benefit (or insufficient evidence) of radiofrequency when compared with sham treatment (142). *Vaginal laser therapy* is another technique that is being marketed as a safe and office-based treatment modality for female stress urinary incontinence. There is no evidence to support this use in clinical practice over conventional treatment options (143).

Procedures for Urgency Urinary Incontinence

When conservative and pharmacologic options fail, second-line treatments for urgency urinary incontinence include injection of onabotulinumtoxinA (Botox) in the bladder, percutaneous tibial nerve stimulation (PTNS), and sacral neuromodulation (Interstim) (144).

Botox Injections

OnabotulinumtoxinA (Botox) is a neurotoxin that produces its paralytic effect on the detrusor muscle of the bladder by blocking the calcium channels and inhibiting release of acetylcholine at the presynaptic neuromuscular junction. Its use was initially FDA-approved in women with neurogenic detrusor overactivity with a typical injected dose being 200 units (U) (145). **In 2013, its use was approved for idiopathic**

OAB and urgency urinary incontinence. The typical dose for nonneurogenic OAB is 100 U where injection of onabotulinumtoxinA is performed cystoscopically with about 20 injection points within the detrusor muscle sites and mostly supratrigonal (Fig. 29-17). When successful, the effect of the injection typically lasts for 6 months to 2 years with repeat injections needed in 50% of women within 12 months (146).

The FDA approval decision was mostly based on a multicenter double-blind, randomized controlled trial comparing one intradetrusor injection of 100 U of onabotulinumtoxinA to daily oral anticholinergic medication (solifenacin or trospium) in 249 women with urgency urinary incontinence over a period of 6 months. This study demonstrated similar reductions in daily urgency, frequency, and urgency urinary incontinence episodes between the two groups. Complete resolution of urgency urinary incontinence occurred in more than twice of the onabotulinumtoxinA (27%) than the anticholinergic (13%) group, P = 0.003. Side effects with the injection group included catheter use up to 2 months (5%) and urinary tract infections (33%) (147).

A meta-analysis of 56 randomized controlled trials showed that patients receiving onabotulinumtoxinA (100 U) had improvements in urgency, frequency, and incontinence episodes similar or better than medications, and significantly better than placebo (146). The AUA currently recommends intradetrusor onabotulinumtoxinA (100 U) when conservative and medical treatments have failed in women with OAB. It is noteworthy that the patient must be taught and be willing to perform self-catheterization, if needed, after the injection. In addition to urinary tract infections and retention, side effects include gross hematuria, dry mouth, dysphagia, impaired vision, and muscle weakness (144).

Percutaneous Tibial Nerve Stimulation

PTNS was approved by the FDA in 2000 for OAB. PTNS involves introducing an acupuncture-type needle electrode (34-gauge) at a 60-degree angle around the ankle, about 3 fingerbreadths above the medial malleolus and posterior to the tibia. The electrode is connected to a battery-charged stimulator, and treatment involves 30-minute weekly sessions for 12 weeks. If successful, maintenance involves once monthly sessions thereafter. A multicenter trial of 220 women with OAB symptoms randomized to 12 weeks of treatment with PTNS versus sham therapy resulted in marked improvement of symptoms in 55% compared to 21% in the respective groups (148).

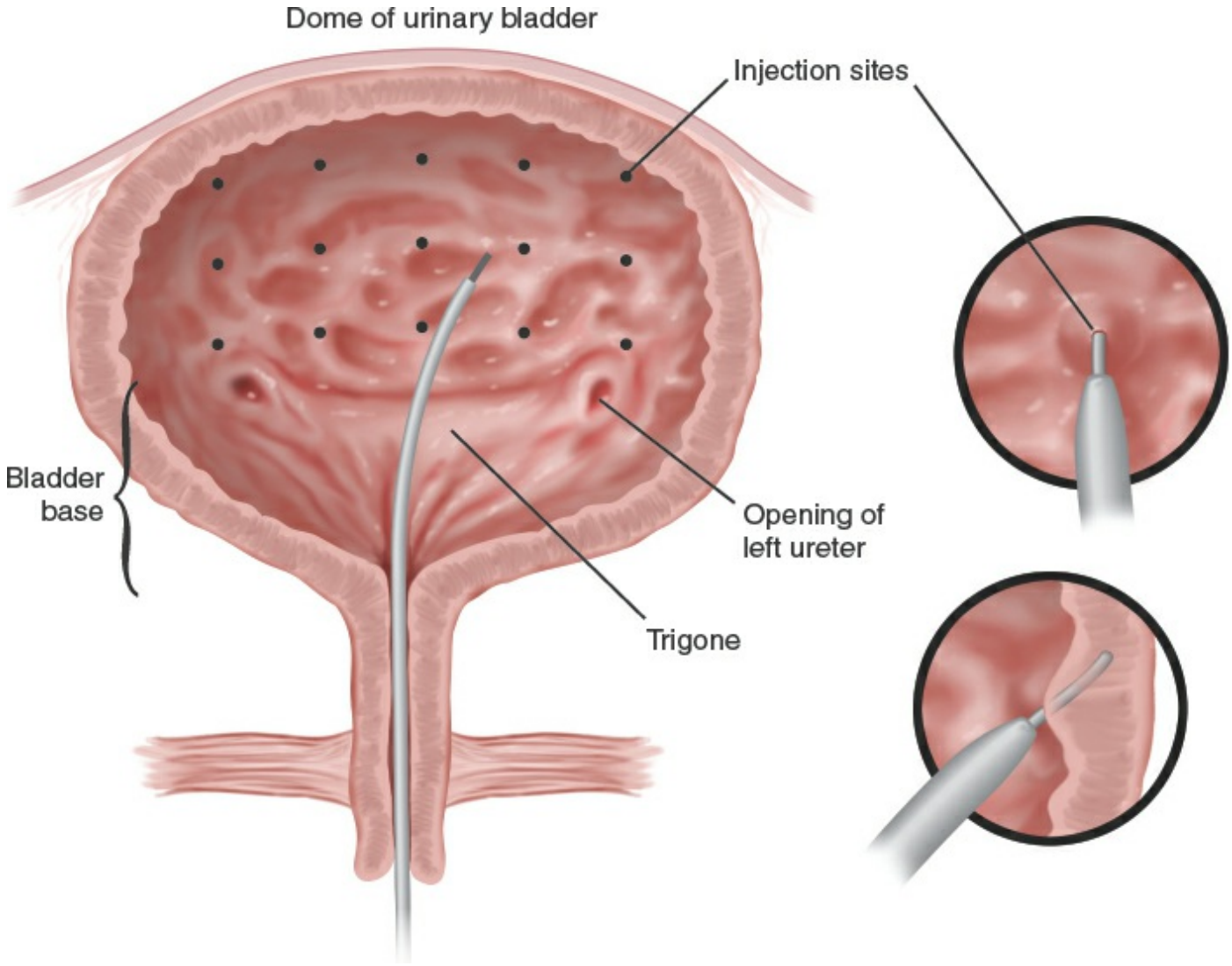


FIGURE 29-17 Injection of onabotulinumtoxinA into the detrusor muscle. (**Ginsberg D, Gousse A, Keppenne V, et al.** Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol 2012;187:2131–2139; Figure 1, need permission.)

PTNS has been compared to anticholinergic medications including long-acting toleterodine and oxybutynin in different studies (149). **Similar improvements have been shown in urinary frequency, incontinence, nocturia, bother, and QOL scores in the short term (12 weeks) between the two treatment modalities** (150). **At 2- to 3-years follow-up, the medication group reported worsening symptoms especially that many women on anticholinergics are not compliant with taking medications long term because of side effects** (149,151). **PTNS is considered an acceptable alternative to medical treatment, in the short term in patients who cannot tolerate anticholinergic side effects, or in the long term in patients who show signs of impaired cognition and memory loss.** It is important to emphasize to patients that for optimal results, treatment sessions are administered weekly for the initial 12 weeks, and women should have the appropriate resources to make frequent clinic visits. Side

effects of PTNS are limited and they include minor bleeding, pain, or tingling sensation at the needle site.

Neuromodulation

Sacral nerve stimulation (also known as neuromodulation) is another FDA-approved treatment modality for refractory OAB, urgency urinary incontinence, and voiding dysfunction in women who have failed conventional treatment options. Sacral nerve stimulation involves an initial phase with a 1- to 2-week trial lead placed percutaneously to evaluate response to treatment. Those reporting at least 50% improvement in their OAB symptoms move on to phase two where a permanent electrode lead is introduced through the back and placed around the third sacral nerve root. This electrode is connected to a pulse generator that is implanted in the patient's buttock. Unlike PTNS and onabotulinumtoxinA, sacral nerve stimulation is a more complex procedure that generally requires fluoroscopy in an operating room setting and is associated with a different adverse event profile (152). **It is contraindicated to perform an MRI in women with an implanted neurostimulator.**

A randomized controlled trial of 147 women compared medical treatment to sacral nerve stimulation over a period of 6 months. At baseline, women reported bothersome symptoms of OAB with more than two urgency incontinence episodes within 3 days and more than eight voids per day. Results showed that women who received the neurostimulator (61%) had significantly higher treatment success than women receiving medical treatment (42%) (P = 0.02). Adverse events were similar between the two group at 31% and 27%, respectively (153). In another prospective multicenter study, 272 patients implanted with the sacral nerve stimulation were followed for a year. Using diary data at 12 months showed a therapeutic improvement rate of 85% including a mean reduction of urgency incontinence episodes of 2.2 leaks/day (down from 3.1) and urinary frequency of 5.1 voids/day (down from 12.6), both P <0.0001. Women reported significant improvement in their QOL measures and decreased interference of urinary symptoms with their daily activities (154). Device-related adverse events occurred in 30% (82/272) of women with an implanted neurostimulator at 12 months. These included undesirable change in stimulation (12%), implant site pain (7%), and implant site infection (3%). Of the 26 women with implant site pain, 13 underwent surgical intervention, and two had removal of the stimulator. Of the 13 cases with implant site infection, five received antibiotics and eight required removal (155).

A randomized controlled trial compared 364 women with OAB who underwent treatment either with onabotulinumtoxinA or sacral nerve stimulation. Women who received onabotulinumtoxinA reported greater reduction in 6-month mean number of urgency incontinence episodes per day than those who received sacral neuromodulation (–3.9 vs. –3.3; P = 0.01). Participants treated with onabotulinumtoxinA showed greater

improvement in symptom bother (–46.7 vs. –38.6; $P = 0.002$) and treatment satisfaction (68 vs. 60; $P = 0.01$) than those receiving sacral neuromodulation. There were no differences in treatment preference (92% vs. 89%; $P = 0.49$) or adverse events, except for urinary tract infections which were more frequent in the onabotulinumtoxinA group (35% vs. 11%; $P < 0.001$). Urinary retention requiring self-catheterization was 2% at 6 months in the onabotulinumtoxinA group, and stimulator device revisions or removals occurred in 3% (156).

Augmentation Cystoplasty and Urinary Diversion

Augmentation cystoplasty and urinary diversion, typically using segments of the patient's intestine, are procedures that are rarely performed to treat urinary incontinence, and typically fall in the advance urology domain. They have been reported in women with chronic and debilitating detrusor overactivity unresponsive to second or third-line treatment options (157). A 2012 updated Cochrane review found a handful of small studies with limited information to guide clinical practice (158). As neuromodulation and cystoscopic injection with onabotulinumtoxinA become more prevalent and better studied, there will be limited, if any, role for augmentation cystoplasty and urinary diversion to treat women with urgency urinary incontinence.

Surgery for Fistula Repair

Genitourinary fistula repair is commonly performed vaginally, but can be repaired through an abdominal access, either open, laparoscopic, or robotically. For very small pinpoint fistulae, there may be a role for conservative options with an attempt of 10 to 14 days of transurethral catheterization and to allow the fistula to close spontaneously. If that fails, or for larger fistulae, surgery is the mainstay (Fig. 29-18). Proper surgical technique involves: (a) identification of fistula (ae); (b) getting adequate access and exposure (e.g., if a vaginal approach is preferred, a pediatric Foley catheter can be placed vaginally and the balloon inflated to put downward traction on the fistula for better visualization); (c) debridement of nonviable tissue; (d) mobilization of fresh and viable tissue (1 to 2 cm) around and all along the fistulous tract; (e) repair of the fistula in several layers starting at the bladder end and going out to the vagina; (f) minimal tension on the repaired layers; (g) 7 to 14 days of postoperative catheterization; (h) use of tissue grafts (e.g., Martius labial fat-pad) as needed for larger or recurrent fistulae.

Voiding Dysfunction

Definition

The mechanism of normal bladder emptying is a coordinated effort that is initiated by the individual. It involves a detrusor muscle contraction associated with urethral

sphincter relaxation. The pressure generated by the detrusor muscle contraction should be of an appropriate duration and a magnitude that is higher than the pressure in the urethra to produce the desired effect of completely emptying the bladder. The neurophysiology of micturition has previously been described. In addition to an intact neuromuscular control and support, voiding is dependent on the volume of urine within the bladder and intravascular volume that gets filtered through the kidneys. One study of 165 women with no history of urologic diseases and/or pelvic surgery showed a significant difference in the frequency and volume of urine produced in 24 hours (range between 437 and 3,861 mL) (159). In addition to the bladder volume at the time of voiding, the maximum urine flow rate (range between 16 and 37mL/s) is variable and dependent on patient position, age, and menopausal status among other factors (160).

[6] Voiding dysfunction occurs when a woman loses the ability to empty her bladder effortlessly and completely within a limited time frame (usually within 60 seconds or less). Objectively, voiding dysfunction can be identified on a uroflow when the voiding time is prolonged, the flow pattern is interrupted (see Fig. 29-8 above), or the maximum flow rate is diminished. During complex urodynamics, additional objective measures of voiding dysfunction include increased urethral pressure (resistance) with an increased detrusor pressure (detrusor–sphincter dyssynergia), or a low detrusor pressure with a normal or low urethral pressure (detrusor underactivity) at the time of urination (65). **[6] Patients with voiding dysfunction may express a host of sensory and abnormal bladder emptying symptoms including hesitancy, slow or intermittent urinary stream, straining on urination, feeling of incomplete bladder emptying, reduced bladder sensation and others (Table 29-10).**

Etiology

Acute urinary retention is a sudden and often painful inability to void despite the sensation of a full bladder and desire to urinate. It is mostly iatrogenic resulting from neurologic injury after radical pelvic surgery (radical hysterectomy, radical perineal resection, colorectal extensive resections), neurologic injury during spinal surgery or commonly after female pelvic reconstructive surgery, and incontinence surgery (e.g., mid-urethral sling). Rarely, and uniquely in pregnant patients, especially in the peripartum period, the bladder is vulnerable to urinary retention; if undetected, this can lead to bladder underactivity, recurrent urinary tract infection, and incontinence (161).

Chronic urinary retention may be caused by neurogenic (e.g., multiple sclerosis, diabetic neuropathy) or nonneurogenic conditions (e.g., advanced prolapse) (162). This can lead to serious conditions like hydronephrosis and chronic renal insufficiency, but is more commonly associated with conditions that impair an

individual's daily activities like recurrent urinary tract infections, feelings of incomplete bladder emptying, and overflow incontinence. Chronic urinary retention is defined as PVR of more than 300 mL persisting for more than 6 months which has been documented in two separate occasions (162**). Common conditions associated with incomplete bladder emptying and retention in women are outlined below (Table 29-11).**

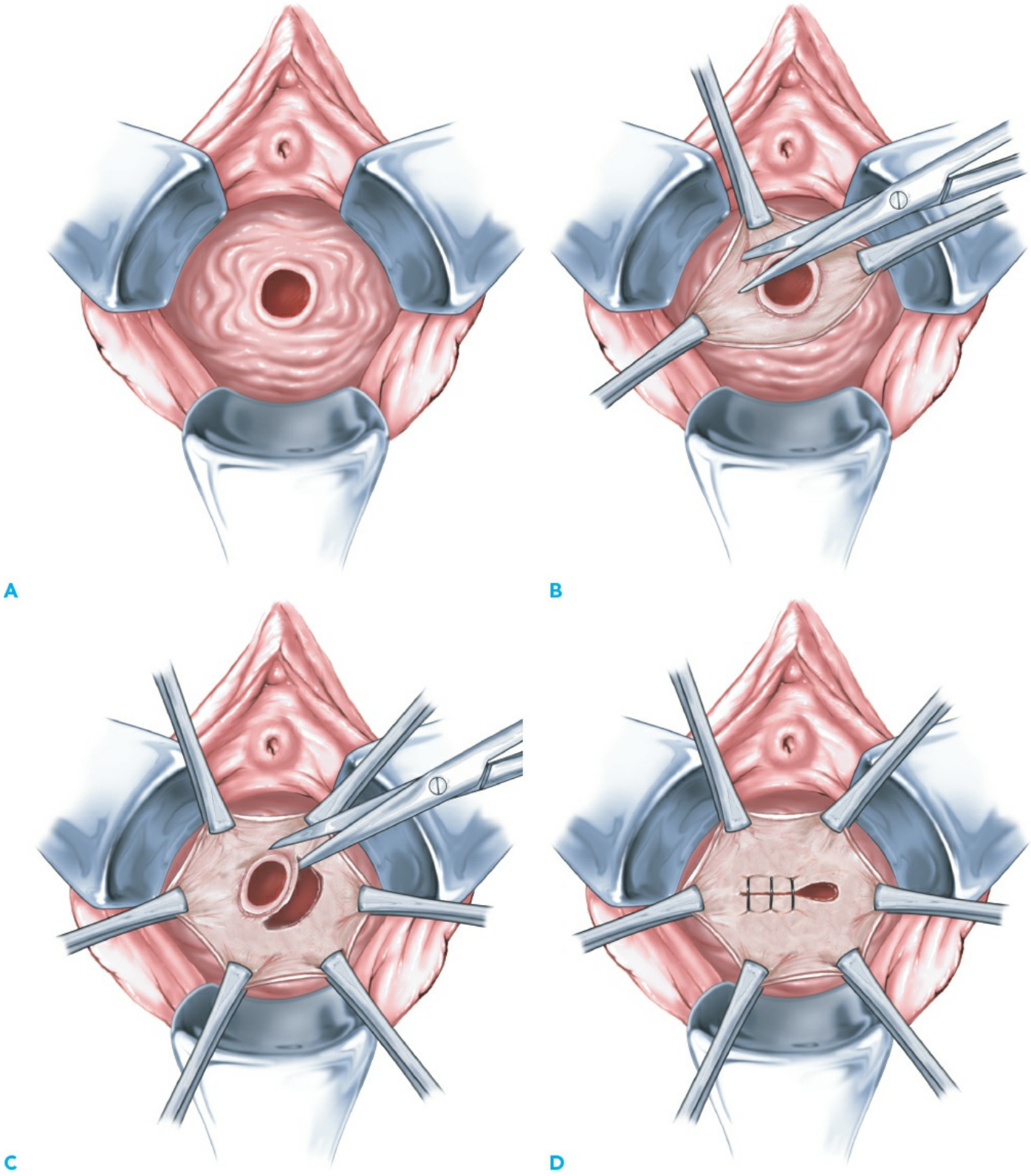


FIGURE 29-18 Repair of apical vesicovaginal fistula. **A:** The fistula at the vaginal apex is exposed with adequate retraction. A pediatric Foley can be placed into the fistula tract to aid in traction and dissection. **B:** The vaginal epithelium is dissected from the fistula to mobilize the tissue to allow for tension-free closure. In the classic Latzko procedure, the vaginal epithelium 2 cm around the opening of the fistula is removed. **C:** The fistula tract may either be completely excised, or in the Latzko procedure, the fistula edge may freshened up slightly but is not excised. **D:** Interrupted absorbable sutures are placed in an extramucosal

location in an interrupted fashion. An additional layer of interrupted sutures is often placed to invert the initial suture line. The vaginal epithelium is then closed over the repair. In the classic Latzko procedure, the initial layer involves closure of the vagina over the fistula tract, then two additional layers with the vaginal epithelium result in an apical colpocleisis. (Redrawn from original by Jasmine Tan.)

Evaluation

Evaluation starts with a careful medical history to eliminate possible conditions associated with voiding dysfunction (e.g., multiple sclerosis, diabetes, psychiatric disorders) and concomitant medications. Should medical history reveal previous surgical treatment for urinary incontinence, it is important to obtain medical records or operative reports to determine the exact nature of the surgery. A careful pelvic examination is conducted with special attention to urethral orifice and anterior wall of vagina to rule out possible pelvic or vaginal masses causing urethral obstruction. Abdominal palpation or suprapubic percussion may indicate a full bladder. Cystoscopy can help diagnose the presence of urethral polyps or bladder tumors, stones, or foreign bodies causing obstruction. Evaluation of the strength of the detrusor muscle contraction during voiding and urethral outlet relaxation, or lack thereof (i.e., urethral resistance) can be undertaken at the time of urodynamics, including measurement of PVR.

Table 29-10 Classification and Definition of Lower Urinary Tract Symptoms in Women

II. Abnormal Sensory Symptoms	
Increased bladder sensation	Desire to void during bladder filling occurs earlier or is more persistent from that previous experienced (differs from urgency by the fact that micturition can be postponed despite the desire to void)
Reduced bladder sensation	Definite desire to void occurs later than that previously experienced, despite an awareness that the bladder is filling
Absent bladder sensation	Absence of the sensation of bladder filling and a definite desire to void
III. Abnormal Emptying	
Hesitancy	Delay in initiating micturition
Straining to void	Need to make an intensive effort (by abdominal straining, Valsalva or suprapubic pressure) to initiate, maintain, or improve urinary stream
Slow stream	Urinary stream perceived as slower compared to previous performance or in comparison with others
Intermittency	Urine flow that stops and starts on one or more occasions during voiding
Feeling of incomplete bladder emptying	Bladder does not feel empty after micturition

Postmicturition leakage	Involuntary passage of urine following the completion of micturition
Spraying of urinary stream	Urine passage is a spray or split rather than a single discrete stream
Position-dependent micturition	Requiring specific positions to be able to micturate spontaneously or to improve bladder emptying, for example, leaning forward or backward on the toilet seat or voiding in a semi-standing position
Urinary retention	Inability to pass urine despite persistent effort

From **Haylen BT, de Ridder D, Freeman RM, et al.** An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn* 2010;29:4–20, with permission.

Treatment

Prior to treatment initiation for chronic urinary retention, the AUA guidelines recommend evaluation of the upper tracts to assess the functional integrity of the kidneys (creatinine clearance) and rule out hydronephrosis (renal ultrasound or CT urogram) (162). Low-risk, asymptomatic individuals can be surveilled with yearly urinalysis and urine culture with no unnecessary treatment. **[6]** In symptomatic patients (e.g., recurrent urinary tract infections), treatment is symptom driven. Patients are encouraged to double void and have frequent trips to the bathroom (162). Patients can be referred to pelvic floor physical therapy for bladder retraining.

Table 29-11 Conditions Associated with Voiding Dysfunction and Urinary Retention

Effect on Bladder Muscle CONTRACTION	Effect on Urethra OUTFLOW
• Medications (anticholinergics, opioids, beta adrenergic agonists, Ca channel blockers, NSAIDs, tricyclic antidepressants, benzodiazepines, antipsychotics)	• Urethral or bladder neck stricture (post-incontinence surgery, prior vaginal or reconstructive surgery)
• Diabetes mellitus	• Urethral narrowing, swelling or obstruction due to sling, urethral bulking agent or other
• Long-standing outlet obstruction	• Pelvic organ prolapse (high grade)
• Constipation	• Urethral diverticulum, stones, or tumor
• Neurologic diseases (MS)	• Primary bladder neck obstruction
• Aging	• Extrinsic compression (tumors)
• Fowler syndrome	• Neurologic disorders
• Acontractile bladder (Detrusor sphincter dyssenergia)	

[6] In high-risk patients, intermittent catheterization is recommended. Although there is lack of evidence comparing intermittent self-catheterization to indwelling catheters, expert opinion, favors intermittent catheterization for better long-term outcomes (163). **Either the patient or her caregiver can be instructed to perform bladder self-catheterization.** In the presence of advanced prolapse, a trial of pessary can be performed with the goal of reducing the prolapse to relieve the obstruction on the urethra resulting in improved voiding and decreased retention (162).

[6] Acute urinary retention is addressed according to the specific situation causing the retention. This may take the form of expectant management with an indwelling catheter for postradical hysterectomy, pelvic reconstructive, or incontinence surgery. The catheter can be plugged after a week of retention and continued voiding dysfunction to allow the bladder to recover filling sensation. When a full bladder in sensed by the patient, she is instructed to remove the plug and drain the bladder. Alternatively, patients can be instructed to self-catheterize until resolution of the retention (usually a PVR of volume of 100 mL or less is acceptable). Should the patient continue to have voiding dysfunction for several weeks after surgery, a sling revision and/or urethrolysis may be necessary (164). **[6]** In the absence of an obstruction, medications can be used for urinary retention caused by either detrusor underactivity or increased resistance in urethral sphincter. These include alpha blockers or beta agonists, however these drugs have proven to be generally ineffective and there is lack of clear evidence to support their routine use (104,105,165).

Neuromodulation and intravesical electrical stimulation may be effective in select patients (166). In addition to urgency, frequency, and urgency urinary incontinence, sacral neuromodulation has been used to treat nonobstructive voiding dysfunction in women (167). Long-term follow-up shows promising results in idiopathic retention (Fowler syndrome, patients with multiple sclerosis and painful bladder syndrome) with a success rate of as high as 73% (168).

Bladder Pain Syndrome

The recent IUGA/ICS report on management of pelvic floor dysfunction defines *acute pain* as that related to recent trauma, infection or other disease and *chronic pain* as either persistent or recurring pain for at least 6 months (82). It is important to differentiate *pain* which is a sensation expressed subjectively by the individual from *tenderness* which is a sensation of discomfort, with or without pain, and that may be elucidated by palpation on a physical examination.

Definition

[6] Bladder pain syndrome is challenging to diagnose, prevent, and treat because its basic science and pathophysiology is poorly understood. Bladder pain is defined

as the complaint of suprapubic or retropubic pain, pressure, or discomfort related to the bladder. It usually increases in intensity with bladder filling and may persist or disappear after voiding (8**). Women with bladder pain syndrome usually have other associated urinary symptoms, such as urinary urgency or frequency; the pain is of a duration of at least 6 weeks or more in the absence of urinary tract infections or other identifiable causes** (169). **The prevalence of bladder pain syndrome varies widely, based on definitions used, from less than 1% to as high as 20% (**170,171). Some authors have developed an interstitial cystitis/bladder pain syndrome questionnaire for use in epidemiologic studies (172). Based on this questionnaire, the prevalence in adult U.S. females ranges between 3% and 7% with the peak prevalence being in the 50's (173).

The terms "bladder pain syndrome" and "interstitial cystitis" have been used interchangeably in the literature, where the latter was first described as an inflammatory bladder condition, sometimes associated with ulceration of the bladder wall, named Hunner lesion (174). Interstitial cystitis is believed to be associated with a defective glycosaminoglycan sulfate layer that covers the bladder mucosa. To standardize definitions and enable comparative research, the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) developed strict criteria for interstitial cystitis; however, these definitions have been shown to be too restrictive to use in clinical practice. NIDDK criteria include the presence of pain and urgency associated with objective findings of glomerulations or Hunner ulcers during cystoscopy and hydrodistention of the bladder, including a small bladder capacity and terminal hematuria (175). Most clinicians prefer to use Looser criteria when treating women with bladder pain syndrome. The understanding of bladder pain syndrome is that it is not limited to an inflammatory mechanism but may encompass a spectrum of conditions including OAB, other chronic pain conditions, somatization disorders, and neurologic diseases (176).

Diagnosis

Basic assessment in a woman with bladder pain syndrome consists of obtaining a detailed medical history, physical examination, bladder diary (frequency/volume chart) and urinalysis with culture (177). The workup should be supplemented with urine cytology in older women, especially those who report history of smoking or prior exposure to chemical. Bladder pain syndrome is a diagnosis of exclusion. A differential diagnosis includes chronic or recurrent urinary tract infections, urethral diverticulum, vulvovaginal atrophic, inflammatory, allergic, or infectious conditions, chronic pelvic pain related to endometriosis, inflammatory bowel conditions, myofascial pain, and others. Exclusion of these diseases may require further imaging, cystoscopy, urodynamics, and even laparoscopy.

Treatment

The initial management of bladder pain syndrome relies on patient education, dietary modification, stress reduction, and pelvic floor relaxation techniques (177). Women are encouraged to avoid bladder irritants such as caffeinated beverages, alcohol, carbonated drinks, acidic drinks, and spicy foods. **When the conservative approach fails, medication, physical therapy or intravesical treatment are implemented. Referral to a pain specialist can be beneficial.** Effectiveness of medical therapy is not well-proven, and long-term follow-up is not well-studied. One study reviewed treatments received by 581 women enrolled in the interstitial cystitis database study group between 1993 and 1997. A total of 183 different types of treatments were reported, with the most commonly prescribed being cystoscopy and hydrodistention, *amitriptyline*, *phenazopyridine*, special diet, and intravesical *heparin* (178).

Urinary analgesics like *phenazopyridine* and *Prosed DS* have been offered to patients with painful bladder syndrome for pain or bladder spasm relief. The latter is a mixture of *methenamine, methylene blue, phenyl salicylate, benzoic acid,* and *hyoscyamine. Amitryptyline*, a tricyclic antidepressant, has been studied for symptom relief in women with painful bladder syndrome, and it has been shown to be beneficial only when a dose of 50 mg or more is achieved (179). Antihistamines have been proposed as potentially being helpful for bladder pain syndrome since pain may be the consequence of histamine release. Hydroxyzine is a commonly used antihistamine; however, a multicenter, randomized clinical trial showed only a 30% versus 20% response for those who were treated with hydroxyzine versus placebo, respectively (180). Another antihistamine includes cimetidine; but studies on its use have included a very small number of patients with inconclusive results (181,182).

***Pentosan polysulfate (elmiron)* is an FDA-approved heparinoid medication to treat women with bladder pain syndrome/interstitial cystitis. The recommended dose is 100 mg three times per day and symptom relief may not be achieved for at least 3 months. The efficacy of pentosan polysulfate has been brought to question by a placebo-controlled randomized trial showing similar symptom relief between the two groups (**183). As an alternative to oral medications, intravesical treatment may be offered to patients with bladder pain syndrome. *Dimethylsulfoxide* (DMSO) is the only FDA-approved intravesical treatment. This involves instilling the bladder with 50 mL of 50% solution of DMSO for 20 to 30 minutes, and to be repeated weekly or every other week for six sessions. It is believed to reduce inflammation, relax muscles, and alleviate pain. As side effects, patients report garlic odor and transient bladder irritation (177). Alternative intravesical instillations that have been investigated include hyaluronic acid, chondroitin sulfate, cyclosporine A, bacillus Calmette–Guerin, oxybutynin, bupivacaine/heparin/steroid (mix), and others (184–188). Other treatment

options include cystoscopy under anesthesia with hydrodistention, neuromodulation, transcutaneous electrical stimulation (TENS), and intradetrusor botulinum toxin A injection (189–191).

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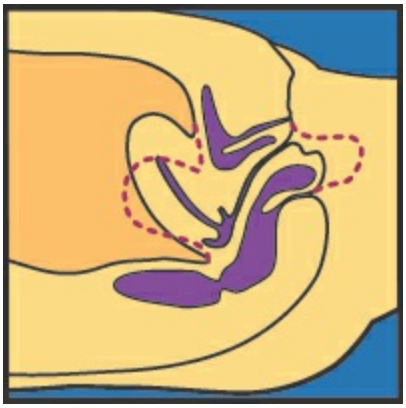
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CHAPTER 30

Pelvic Organ Prolapse



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KEY POINTS

1 Pelvic organ prolapse is an increasingly common condition seen in women commensurate with an aging population.

2 Causes of pelvic organ prolapse are multifactorial and contribute to the weakening of the pelvic support connective tissue and muscles as well as nerve damage.

3 It is important to understand the three levels of pelvic support in order to optimally identify defects in a consistent and individualized manner.

4 Physical examination includes thoughtful attention to all parts of the vagina, including the anterior, apical, and posterior compartments, levator muscle, and anal sphincter complex. Objective evaluation using the validated pelvic organ prolapse quantification system (POP-Q) allows the ability to follow prolapse over time and evaluate results of treatment.

5 Nonsurgical treatment options include pelvic floor muscle training and the use of intravaginal devices.

6 Surgical treatment involves an individualized, multicompartmental approach consistent with the patient's previous treatment attempts, activity level, and health status. This involves consideration of approach (vaginal or abdominal), reconstructive versus obliterative, and use of native tissue versus graft augmentation. Increasing level I evidence exists to guide us in individualized treatment approaches.

INTRODUCTION

Pelvic organ prolapse (POP) is defined as the "descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina (vaginal vault or cuff scar after hysterectomy)," correlated with symptoms, assisted by any relevant imaging (1). **[1]** It is the progressive herniation of the pelvic organs through the urogenital diaphragm that most commonly leads to vaginal bulge symptoms (2,3). Women with prolapse beyond the hymen may also report lower urinary tract (incontinence, urgency-frequency, or voiding difficulty) and bowel (obstructed defecation, fecal incontinence) symptoms.

Pelvic floor disorders, including POP, increase with age. Based on a cross-sectional

study of a nationally representative population of women in the United States, the prevalence of at least one pelvic floor disorder (PFD) was 23.7%; the prevalence more than doubled in women 80 years or older (4). Variations in the definitions of symptomatic POP (objective and subjective criteria), both in clinical practice and in the literature, create variability in estimates of prevalence and incidence. For instance, mild POP, defined as any degree of prolapse on examination, is practically universal in older women; but women may not have symptoms unless the prolapse is more severe. The reported prevalence of POP is thus impacted by the threshold used to define the condition (5). Age, as a risk factor for prolapse, plays an impactful role in the public health burden of pelvic floor disorders. The older population in the United States is expected to more than double to 88.5 million by 2050; the 85-and-older segment of the population is expected to triple to 19 million (5). With the aging population, health care utilization for pelvic floor disorders (including vaginal prolapse) is predicted to grow, resulting in a significant and growing burden on health services.

POP is often managed surgically. The probability lifetime risk that a woman will undergo surgical correction of any primary surgery for stress urinary incontinence (SUI) or POP (repeat procedures excluded) by 80 years of age is estimated to be 1 in 5, the cumulative risk for POP surgery being 12.6% (95% confidence interval [CI], 12.4–12.7). The age-specific annual risk of POP increased progressively until 73 when the annual risk was 4.3 per 1,000 women. A woman's combined risk for either surgery is 11.4% by the age of 60, rising to 15.9% at age 70, and to 20.2% by age 80 (6). This is almost twice the risk previously quoted (11% lifetime risk figure from a 1995 study) (7). Using the U.S. Census Bureau population projections, it is estimated that the total number of women anticipated to undergo surgery for POP from 2010 to 2050 will increase by 46%, with predictions of up to one-third of the female population suffering from at least one PFD in 2050. Estimated annual procedure rates will increase from 166,000 to 245,970 for POP (8).

The economic burden of pelvic floor disorders on the health care system is substantial. In 2006, the estimated direct annual cost of ambulatory care for PFDs in the United States was $412 million (8). The 5-year risk of undergoing repeat SUI or POP surgery is thought to be less than 10% (7.8% for women aged <65 years and 9.9% for women aged ≥65 years) with higher risks for women aged ≥65 years and for those who underwent an initial POP surgery (9). Prolapse significantly impacts quality of life causing discomfort, urinary symptoms, and psychosexual issues. A better understanding of the multifactorial etiology for POP may help to reduce the numbers of POP surgery by means of primary prevention.

In light of the increasing prevalence and social burden of this disorder, researchers and surgeons continue to hope for a universally successful and risk-minimizing solution for POP. A variety of surgical approaches have been developed and optimized over the last half century to enhance durability, minimize risks, and shorten recovery. **[1]** The

treatment of prolapse remains a matter of individualizing patient outcome goals while navigating the risks of recurrence, surgical, and functional complications.

In the United States, 11% of women up to the age of 80 years have surgery for POP or urinary incontinence, and nearly one-third of procedures are repeat surgery (3). Data from the Women's Health Initiative revealed anterior POP in 34.3%, posterior wall prolapse in 18.6%, and uterine prolapse in 14.3% of women (10). In this study, a significant risk factor associated with prolapse was vaginal delivery. After adjusting for age, ethnicity, and body mass index, women with at least one vaginal delivery were twice as likely as nulliparous women to have POP. Causes of pelvic support disorders are most likely multifactorial, however; factors other than vaginal delivery are associated with the development of these disorders. **[2]** In addition to parity and vaginal delivery, nonobstetric risk factors for POP surgery include age, constipation, increasing weight, and chronic obstructive pulmonary disease (11). Other reported risk factors for the development of POP include history of hysterectomy, obesity, history of previous prolapse operations, and race (10,12,13).

PATHOPHYSIOLOGY

The interaction between the pelvic floor muscles, fibromuscular connective tissue and intact innervation are key to maintaining support of the pelvic organs in their normal locations. The levator ani/coccygeus muscles hold the pelvic floor closed and provide lifting and closing forces to prevent pelvic floor descent. These muscles provide a supportive diaphragm through which the urethra, vagina, and rectum egress **(Fig. 30-1)**. POP results from attenuation of the supportive structures, whether by actual tears or "breaks" or by neuromuscular dysfunction or both. Muscle damage (or weakening) allows the levator hiatus to enlarge, facilitating pelvic organ descent with one or both of the vaginal walls, allowing them to protrude through the levator hiatus. Birth-induced injury to the pubococcygeal portion of the levator ani muscles is seen in 55% of women with prolapse and 16% of women with normal support. Support of the vaginal canal is provided by the enveloping endopelvic connective tissue and its condensations at the vaginal apex, which form the cardinal uterosacral ligament complex. Failure of the connective tissue attachments between the uterus and vagina to the pelvic wall (cardinal, uterosacral, paravaginal) are strongly related with prolapse and are also highly correlated with one another (14).

[3] The support system for the uterus and vagina has been described as consisting of three levels (15).

Level I refers to the uterosacral/cardinal ligament complex, which serve to maintain the vaginal length and axis.

Level II support consists of the paravaginal attachments of the lateral vagina and endopelvic fibromuscular connective tissue to the arcus tendineus and levator fascia that

maintain the midline position of the vagina.

Level III support pertains to the distal vagina and is made up of the muscles and connective tissue surrounding the distal vagina and perineum.

Definitions

Prolapse can involve three different compartments: anterior vaginal wall, posterior vaginal wall, and the apical compartment (uterus or vaginal apex). This condition is unique to women and is distinct from rectal prolapse, where the rectum protrudes through the anus and is seen in men and women. **The common pelvic support disorders include rectocele, cystocele (Fig. 30-2), enterocele (Fig. 30-3), and uterine prolapse (Fig. 30-4)**; reflecting displacement of the rectum, bladder, small bowel, and uterus, respectively; resulting from failure of the endopelvic fibromuscular connective tissue, levator ani muscular support, or both (15).

A rectocele is a protrusion of the rectum into the vaginal lumen resulting from weakness in the muscular wall of the rectum and the paravaginal fibromuscular connective tissue, which holds the rectum in place posteriorly.

An enterocele is a herniation of the peritoneum and small bowel and is the only true hernia among the pelvic support disorders. Most enteroceles occur downward between the uterosacral ligaments and the rectovaginal space, but they may also occur primarily apically, especially in the setting of a previous hysterectomy.

A cystocele is descent of the urinary bladder with the anterior vaginal wall. Cystoceles usually occur when the pubocervical fibromuscular connective tissue weakens midline or detaches from its lateral or superior connecting points.

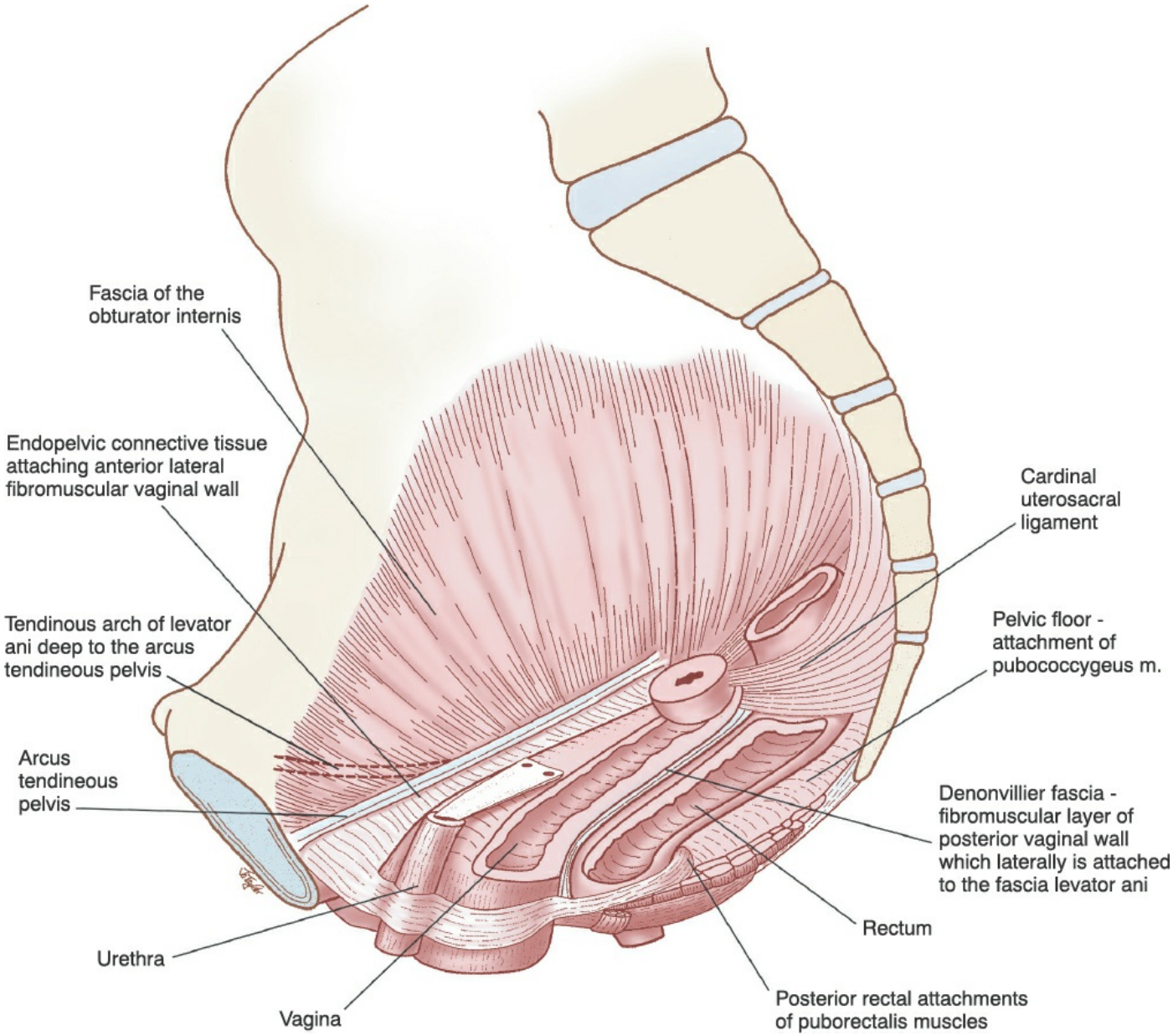


FIGURE 30-1 A sagittal view of the female pelvis with bladder and uterus removed (ureters, trigone, and cervix intact) illustrating anterior and posterior vaginal fibromuscular planes, their endopelvic fascial attachments, and a functional pelvic floor.

Uterine prolapse is generally the result of poor cardinal or uterosacral ligament apical support, which allows downward protrusion of the cervix and uterus toward the introitus. In women after hysterectomy, the vaginal apex can shift downward toward the introitus, which is referred to vaginal vault (or apical) prolapse in the absence of uterus.

***Procidentia* is prolapse of the uterus and vagina, whereas *complete vaginal vault prolapse,* which can occur after hysterectomy, represents eversion of the entire vagina (Fig. 30-5).**

These descriptive terms are somewhat inaccurate and misleading, focusing on the

pelvic organs (bladder, rectum, small bowel, or uterus) rather than the specific defects responsible for the alterations in vaginal support. Specific defect support issues will be discussed in the Surgical Management section.

SURGICAL ANATOMY

Pelvic support structures include:

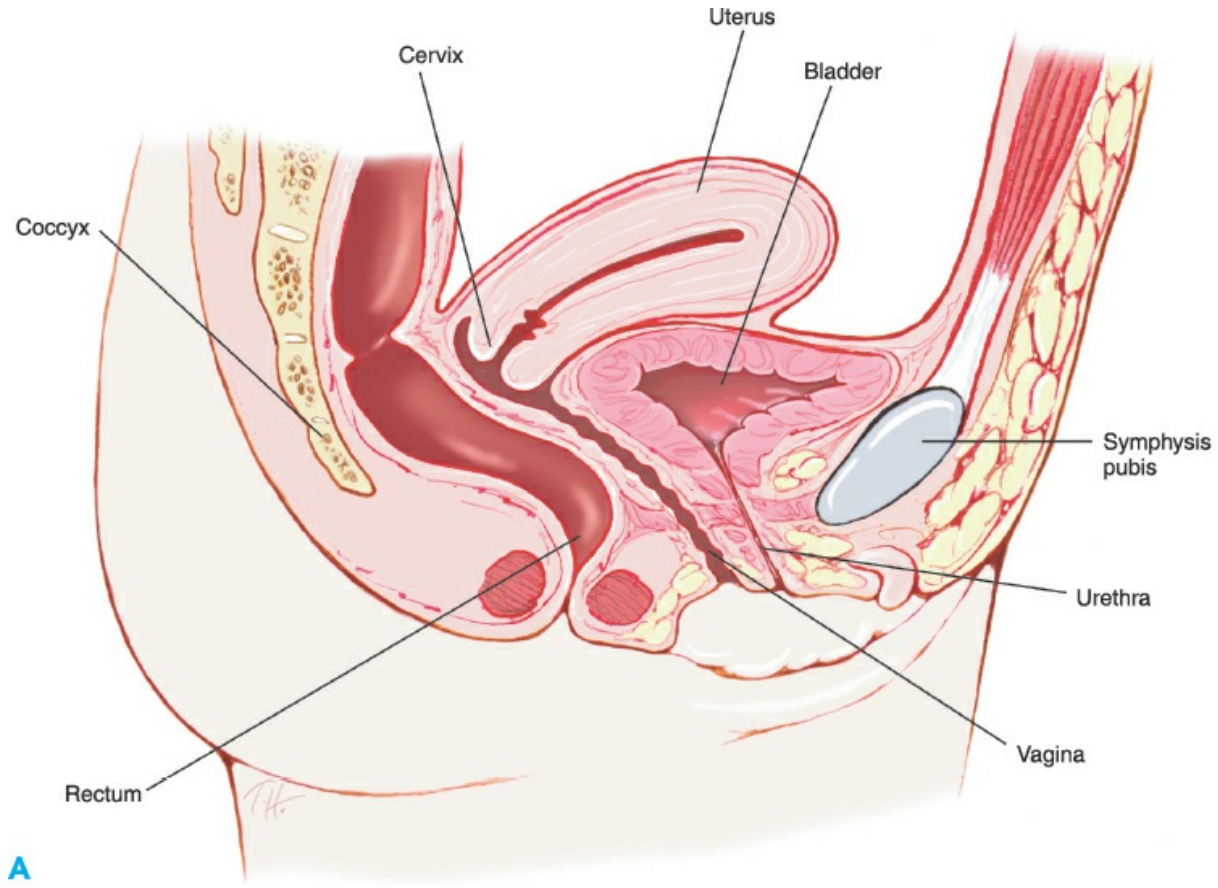
1. The muscles and connective tissue of the pelvic floor
2. The fibromuscular tissue of the vaginal wall
3. The endopelvic connective tissue

Endopelvic connective tissue includes:

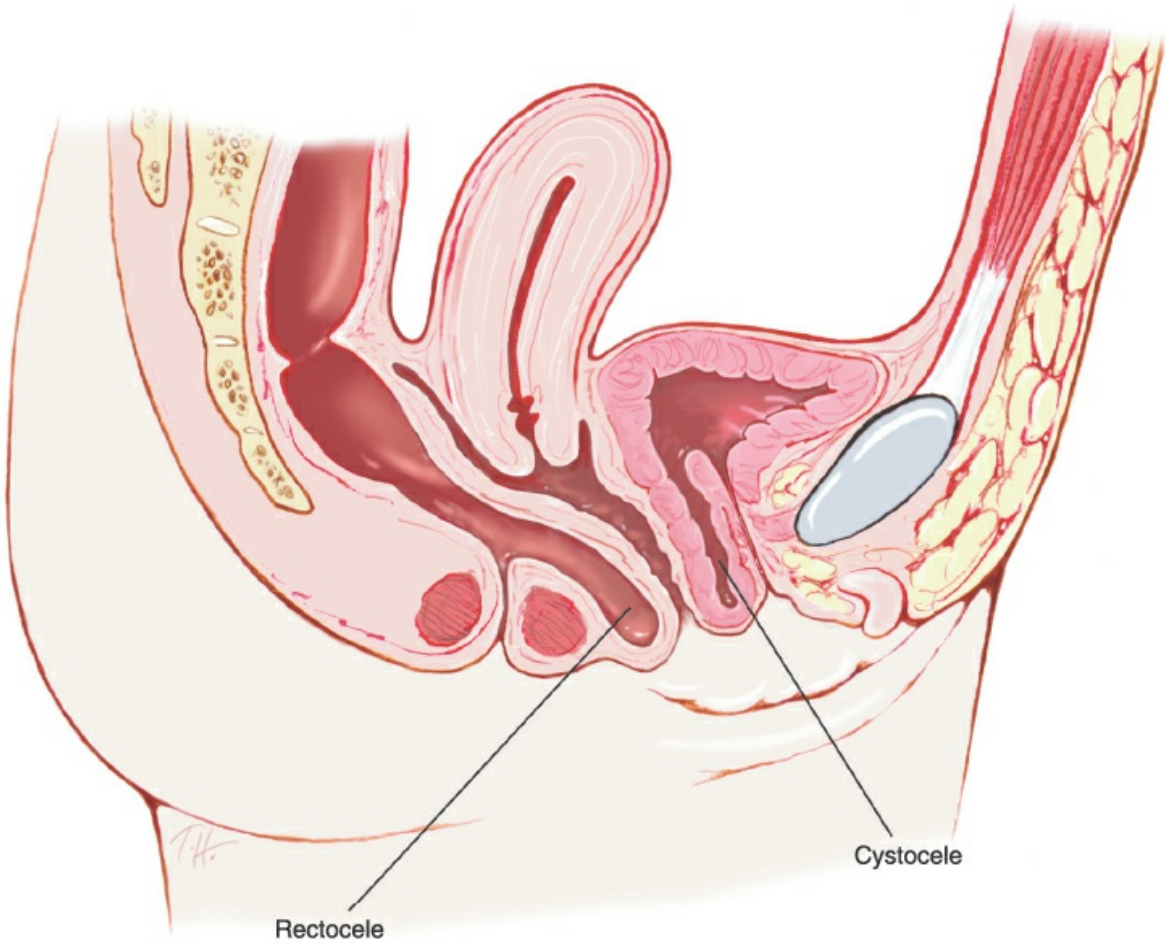
1. The cardinal/uterosacral complex, which attaches the upper vagina and cervix posteriorly
2. Lateral connective tissue attachments of the anterior vaginal wall to the arcus tendineus pelvis and of the posterior vaginal wall to the fascia of the levator ani and to the posterior arcus tendineus near the ischial spine
3. Less dense areolar connective tissue surrounding retroperineal portion of the pelvic organs

The orientation of these structures is noted in **Figure 30-1**.

In general, an intact pelvic floor, including a functional puborectalis muscle and an intact cardinal/uterosacral complex, should prevent POP by allowing posterior deflection of the rectum and vagina and compression of these structures against the pelvic floor in the upright position **(Fig. 30-6)**. The fibromuscular layer of the vaginal wall and the other endopelvic connective tissue attachments augment the support structure and are particularly important when pelvic floor function is compromised.


Uterus
Cervix
Bladder
Coccyx
Symphysis pubis
Urethra
Vagina
Rectum

A

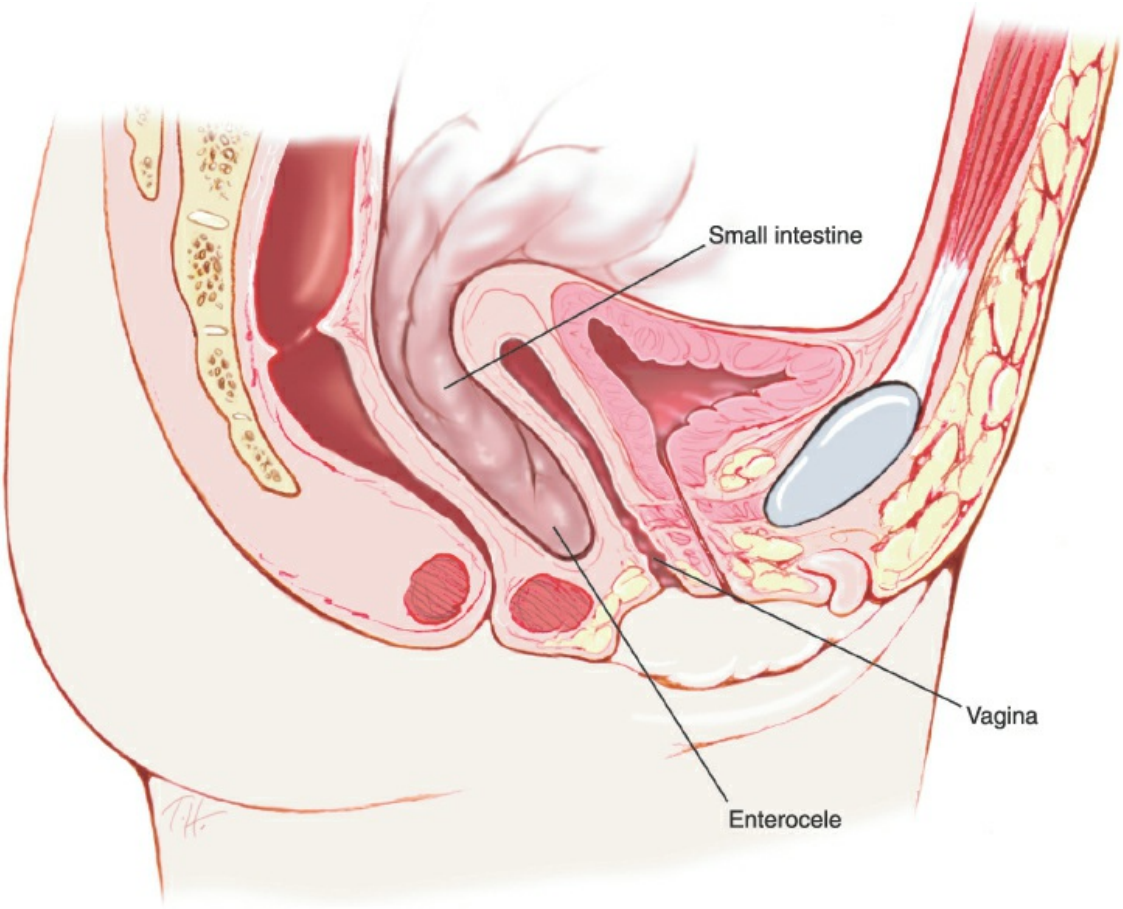

Cystocele
Rectocele

B

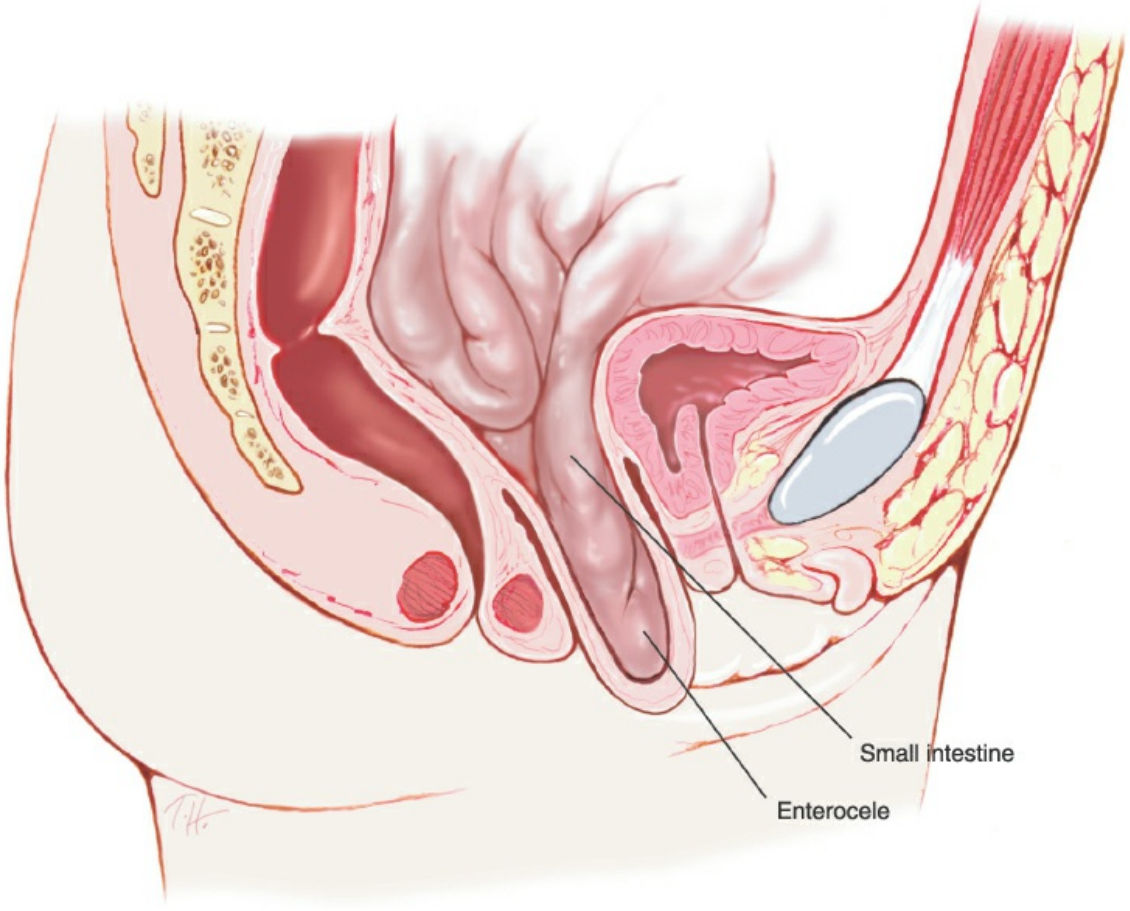
FIGURE 30-2 **A:** Sagittal section of the pelvis showing normal anatomy. **B:** Cystocele and rectocele.

Apical Compartment

Normal apical support includes the integrity of the cardinal/ uterosacral ligaments, the upper paravaginal fibromuscular connective tissue, and, when the uterus is present, the paracervical fascia. The fibromuscular tissue of the upper vagina blends in with the paracervical fascia. Both of these are attached laterally and posterior laterally to the cardinal ligaments and uterosacral ligaments (Fig. 30-1). The vaginal fibromuscular tissue is also attached to the upper anterior rectum at its sigmoid junction and forms the inferior border of the cul-de-sac of Douglas. The cardinal and uterosacral ligaments are condensations of areolar connective tissue and they contribute level I support for the vagina. Their origin is at the lateral borders of sacral vertebra 2 to 4, and they travel retroperitoneally to their insertion at the upper vagina and cervix (Fig. 30-1). They serve as the anterior and lateral borders of the cul-de-sac and cross at or just anterior to the ischial spines. The ureter is closest to the uterosacral ligament at or just posterior to its insertion on the posterior lateral cervix. If anterior cephalad traction is placed on the ureter or cervix, frequently the cardinal uterosacral ligaments will stand out as ridges lateral to the cul-de-sac; however, peritoneal folds may have similar appearance. Therefore, placement of sutures in such structures based on visual appearance may not be reliable.


Small intestine
Vagina
Enterocele

A


Small intestine
Enterocele

B

FIGURE 30-3 **A:** Posterior enterocele without eversion. **B:** Enterocele with eversion.



FIGURE 30-4 Uterine prolapse with apical detachment from the uterosacral ligament complex and lateral wall detachment from the endopelvic connective tissue.



FIGURE 30-5 Procidentia of the uterus and vagina.

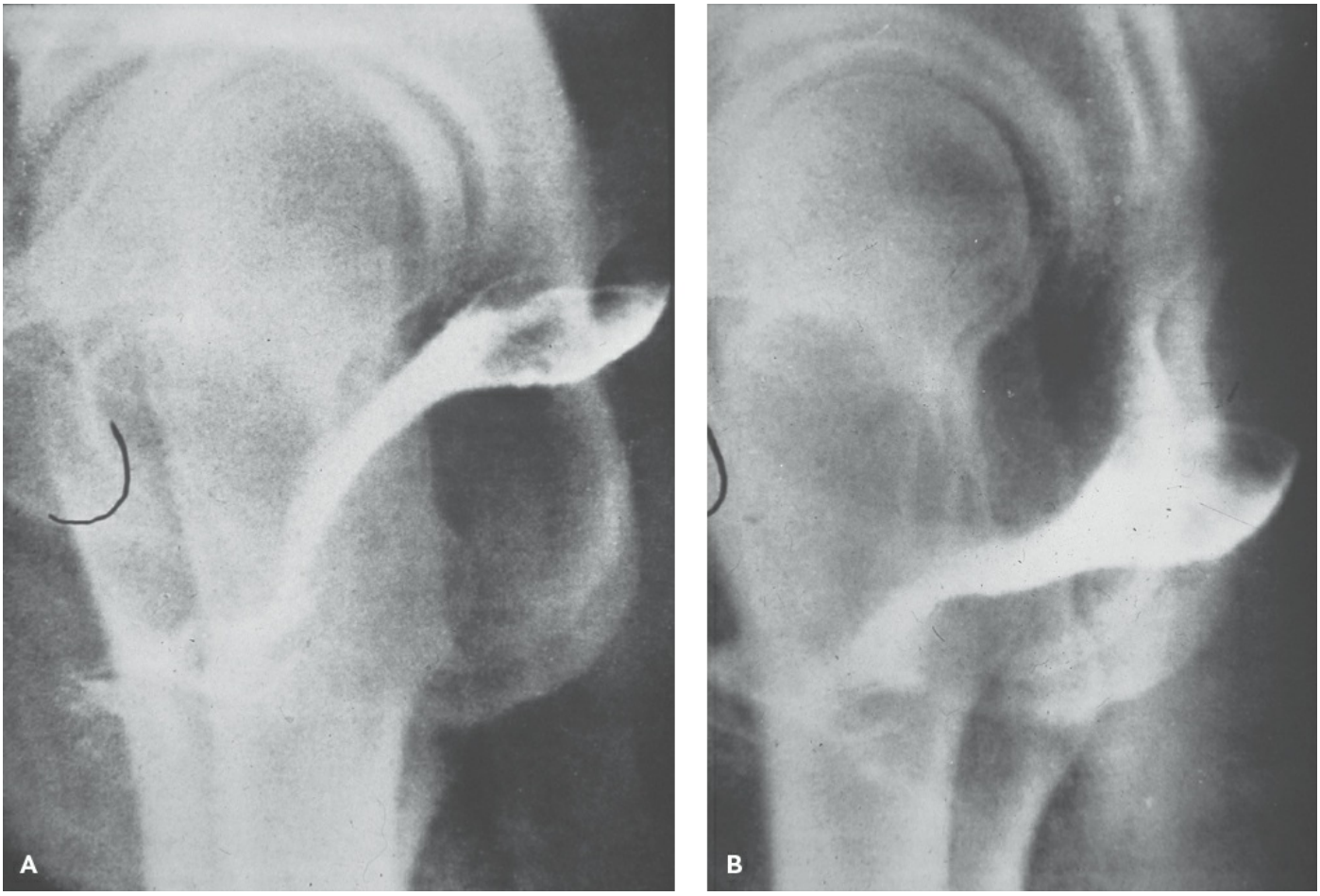


FIGURE 30-6 Vaginograms from the same patient at rest (**A**) and during Valsalva maneuver (**B**). Illustrates posterior vaginal deflection maintained by apical cardinal/uterosacral posterior suspension and the anterior sling effect of the puborectalis muscle and more distal perineal structures. (From **Nichols DH, Randall CL**. *Vaginal Surgery*. 4th ed. Baltimore, MD: Williams & Wilkins; 1996:4–5, with permission.)

Defects in apical support include:

1. The loss of cardinal/uterosacral support with resultant cervical/uterine or vaginal cuff descent
2. The detachment of the fibromuscular vagina from the anterior rectum with resultant enterocele or, at times, sigmoidocele into the rectovaginal space
3. Tears or attenuation of the upper fibromuscular tissue, usually after hysterectomy, leading to a central apical descent that frequently presents as a ballooning defect

Often, these defects occur concurrently. Defects in cardinal/uterosacral attachment are at sites close to their insertion into the cervix and upper vagina where breaks or tears occur; in those with apical descent, condensations of cardinal/uterosacral tissue can be found adjacent to the peritoneum just cephalad to the ischial spines (16).

Anterior Compartment

The anterior vaginal compartment includes the anterior vaginal wall, its attachments, the urethra, and the bladder. When the anterior vaginal wall prolapses to the level of the hymen (point Ba = 0)—the point at which most women will become symptomatic—the apex is ≥4.5 cm inside the hymen (i.e., when a woman has clinically significant prolapse to the hymen, she will have nearly 5 cm of apical support loss) (17). **The support structure for the bladder is the rhomboid-shaped anterior vaginal wall (specifically its fibromuscular layer), which is attached laterally to the arcus tendineus fascia (Fig. 30-7). Inferiorly, the fibromuscular layer blends in with the connective tissue, which spans the two bands of puborectalis and pubococcygeus muscles and the pubic rami. The urethra appears to be preferentially supported by these connective tissues and by the pubourethral ligaments. In the apical area, the vaginal fibromuscular layer blends in with the precervical fascia and the connective tissue of the cardinal ligament complex.** In the upright position, the rhomboid-shaped anterior vaginal wall is oriented approximately 30 degrees from the horizon (from pubis to ischial spines). There is some downward bulge of the central area of the rhomboid plate, which should be minimized by the back-stop effect of the posterior vagina and rectum if the pelvic floor anatomy and function are normal.

Defects of this support structure may include tears or attenuation of the vaginal fibromuscular wall, or detachment from the pelvic sidewalls, the cervix or cardinal ligament complex, or from the pubis. Specific sites of fibromuscular tears are frequently difficult to recognize.

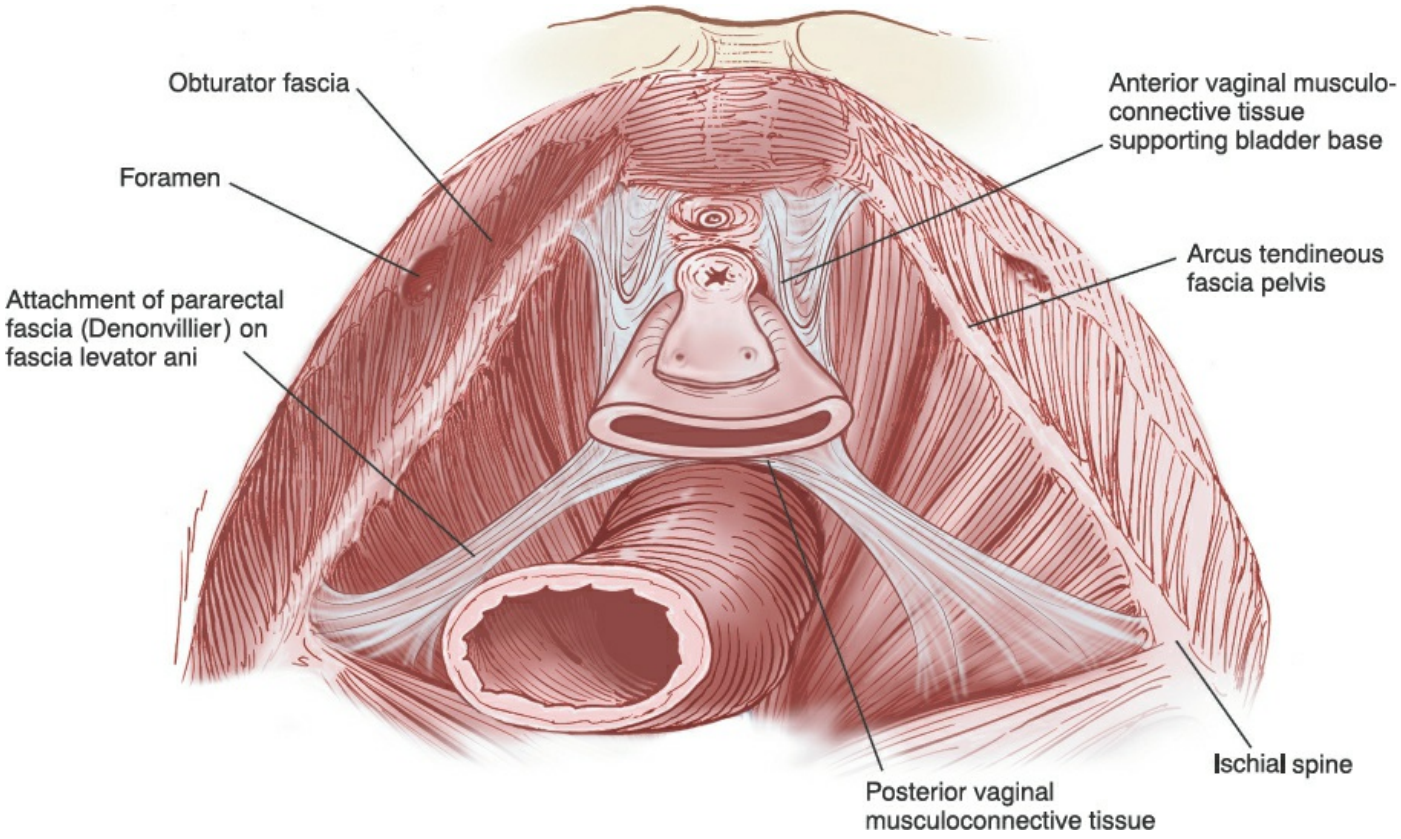


FIGURE 30-7 View of the pelvic cavity with bladder, upper vagina, and sigmoid colon removed. The fibromuscular wall of the anterior vagina is attached to the arcus tendineus fascia pelvis by endopelvic connective tissue and supports the bladder. The pararectal fascia (Denonvillier fascia) includes the fibromuscular tissue of the posterior vagina and its lateral attachment to the fascia levator ani.

Physical examination may reveal the following findings:

1. The presence of a central ballooning-type defect
2. Descent of the area of the vaginal wall below the bladder neck
3. Descent of the cervix or apical vaginal area
4. The presence or absence of sulci extending lateroanteriorly, which would indicate that lateral detachment to the arcus is maintained or lost.

Posterior Compartment

The support of the rectum and posterior vagina includes the pelvic floor musculature and connective tissue posteriorly and Denonvillier (pararectal) fascia, which is the fibromuscular layer of the posterior vaginal wall and its lateral attachments to the lateral pelvic floor (levator) musculature and its fascia (Fig. 30-8). This lateral attachment site, the fascia levator ani, fuses with the arcus tendineus fascia pelvis at the middle to upper level of the vagina and continues to the level of the ischial spine. Less dense, areolar, connective tissue surrounds the rectum and vagina and may supply some support to these structures as well.

The fibromuscular layer at the upper vagina fuses with the paracervical fascia and the fan-shaped cardinal ligament structure. The integrity of the attachment of this posterior vaginal layer to the anterior rectal wall just below the rectal sigmoid junction prevents enterocele formation. In the distal vagina, the fibromuscular layer fuses laterally with the fascia of the puborectalis, pubovaginalis, and then the bulbocavernous muscles and centrally with the perineal connective tissue. Thus, normal posterior support includes a plate of connective tissue which includes the fibromuscular layer of the posterior vaginal wall that is attached laterally as noted, posteriorly toward sacral segments 2 to 4, and inferiorly to the perineum. This fibromuscular plane holds the rectum in place posteriorly, and aids in preventing perineal descent by suspending the perineum to the sacrum. The constant resting tone of the pelvic floor muscles, particularly the puborectalis, serve to close the genital hiatus, pulling the distal vagina and anorectal junction toward the pubic symphysis and creating an anorectal angle and a posterior deflection of the rectum, vagina, and bladder base.

It has been hypothesized, based on careful cadaveric dissections, that most rectoceles were caused by discrete tears in the Denonvillier fascia at its lateral, apical, and perineal attachments and centrally within the vaginal muscular connective tissue (18). Perineal detachment, along with a defect in the perineal membrane, has been described as a perineal rectocele, which is most commonly associated with reports of difficulty with defecation. Apical attachment defects are generally associated with enteroceles and occasionally sigmoidoceles.

EVALUATION

Approximately 10% to 20% of symptomatic women seek medical help, both conservative and surgical interventions have been shown to improve quality of life (19). **The paucity of reported prolapse symptoms may result from a number of causes, including lack of symptoms, embarrassment, or misperceptions about available treatment options. Although POP is not life-threatening, it can impose a significant burden of social and physical restrictions of activities, impact on psychological well-being, and overall quality of life.**

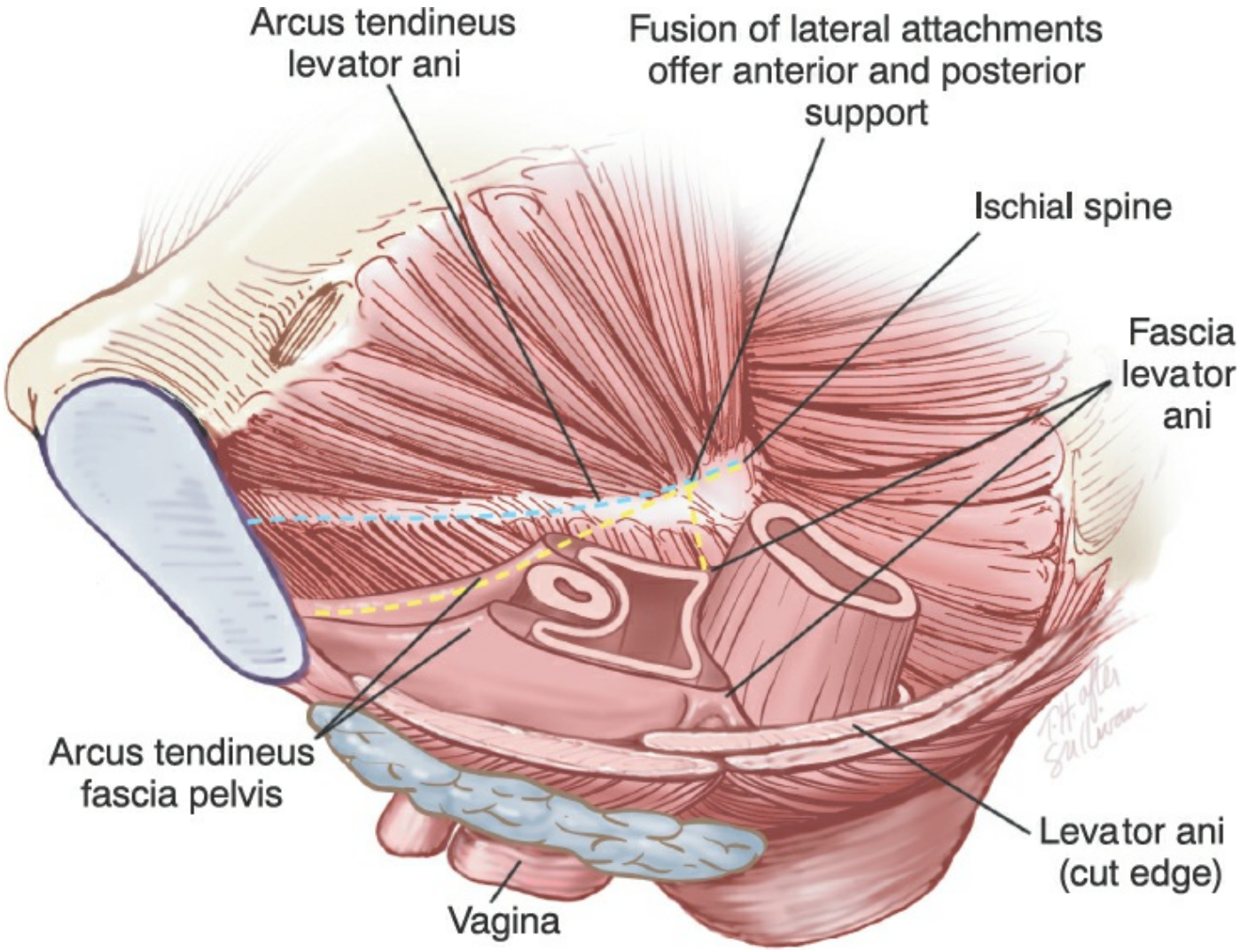


FIGURE 30-8 Sagittal oblique view of the distal midvagina illustrating lateral connection of the posterior musculoconnective tissue wall to the fascia levator ani and anterior wall to the arcus tendineus pelvis. The attachment sites fuse together at a point closer to the ischial spine where the vagina assumes a more oval shape. (Modified by J. Taylor from illustration by Lianne Krueger Sullivan. From **Cundiff GW, Fenner D.** Evaluation and treatment of women with rectocele: Focus on associated defecatory and sexual dysfunction. Obstet Gynecol 2004;104:1403–1421, erratum in *Obstet Gynecol* 2005;105:222, with permission.)

Symptoms

POP often is accompanied by symptoms of voiding dysfunction, including urinary incontinence, obstructive voiding symptoms, urinary urgency and frequency, and, at the extreme, urinary retention and upper renal compromise with resultant pain or anuria. Other symptoms often associated with POP include pelvic pain, defecatory problems (e.g., constipation, diarrhea, tenesmus, fecal incontinence), back and flank pain, overall pelvic discomfort, and dyspareunia. Patients seeking care for prolapse may have one or several of these symptoms involving the lower pelvic floor. **Choice of treatment usually depends on severity of the symptoms, the degree of prolapse, and on the patient's general health and level of activity** (20).

Data relating to pelvic floor symptoms to the extent and location of prolapse are weak (21–23). Vaginal descensus 0.5-cm distal to the hymen was shown to most accurately predict bulge symptoms with the sensitivity and specificity 69% and 97%, respectively. However, the "threshold" of prolapse severity varies depending on the patient (24). In a study including 192 women, the symptom of a vaginal bulge was shown to have an 81% positive predictive value and 76% negative predictive value (25). Any symptoms associated with physical findings of lower-stage prolapse require careful evaluation, especially if surgery is being considered. **[4]** A retrospective study of 330 patients reported that women with more advanced prolapse were less likely to have symptoms of stress incontinence and more likely to use manual reduction of the prolapse to void. Therefore, careful consideration of lower urinary tract symptoms is important. Prolapse severity was not associated with bowel or sexual problems in this study (26).

Physical Examination

In evaluating patients with POP, it is particularly useful to divide the pelvis into compartments, each of which may exhibit specific defects. The use of a Graves speculum or Baden retractor can help to evaluate the apical compartment of the vagina. The anterior and posterior compartments are best examined with the use of a univalve or Sims speculum. The speculum is placed posteriorly to retract the posterior wall downward when examining the anterior compartment and placed anteriorly to retract the anterior wall upward when examining the posterior compartment. A rectovaginal examination may be useful in evaluating the posterior compartment to distinguish a posterior vaginal wall defect from a dissecting apical enterocele or a combination of both.

If an anterior lateral detachment defect is suspected, an open ring forceps (or a Baden retractor) may be placed in the vagina at a 45-degree angle posteriorly cephalad to hold the lateral fornices adjacent to the pelvic sidewall.

During the evaluation of each compartment, the patient is encouraged to perform Valsalva so the full extent of the prolapse can be ascertained. If the findings determined with Valsalva are inconsistent with the patient's description of her symptoms, it may be helpful to perform a standing straining examination with the bladder empty (26,27).

Pelvic Organ Prolapse Quantification System

Many systems for staging prolapse have been described. Typically, it is graded on a scale of 0 to 3 or 0 to 4, with the grade increasing with the severity of prolapse (28). **The system approved by the International Continence Society is the Pelvic Organ Prolapse Quantification system, or POP-Q** (29). This standardized quantification

system facilitates communication between physicians in practice and research and enables progression of these conditions to be followed accurately. In this system, anatomic descriptions of specific sites in the vagina are used in place of traditional terms. The system identifies nine locations in the vagina and vulva in centimeters relative to the hymen, which are used to assign a stage (from 0 to IV) of prolapse at its most advanced site **(Fig. 30-9)**. Although probably more detailed than necessary for general practice, clinicians should be familiar with the POP-Q system because most published studies use it to describe research results. Its two most important advantages over previous grading systems are (1) it allows the use of a standardized technique with quantitative measurements at straining relative to a constant reference point (i.e., the hymen); and (2) its ability to assess prolapse at multiple vaginal sites.

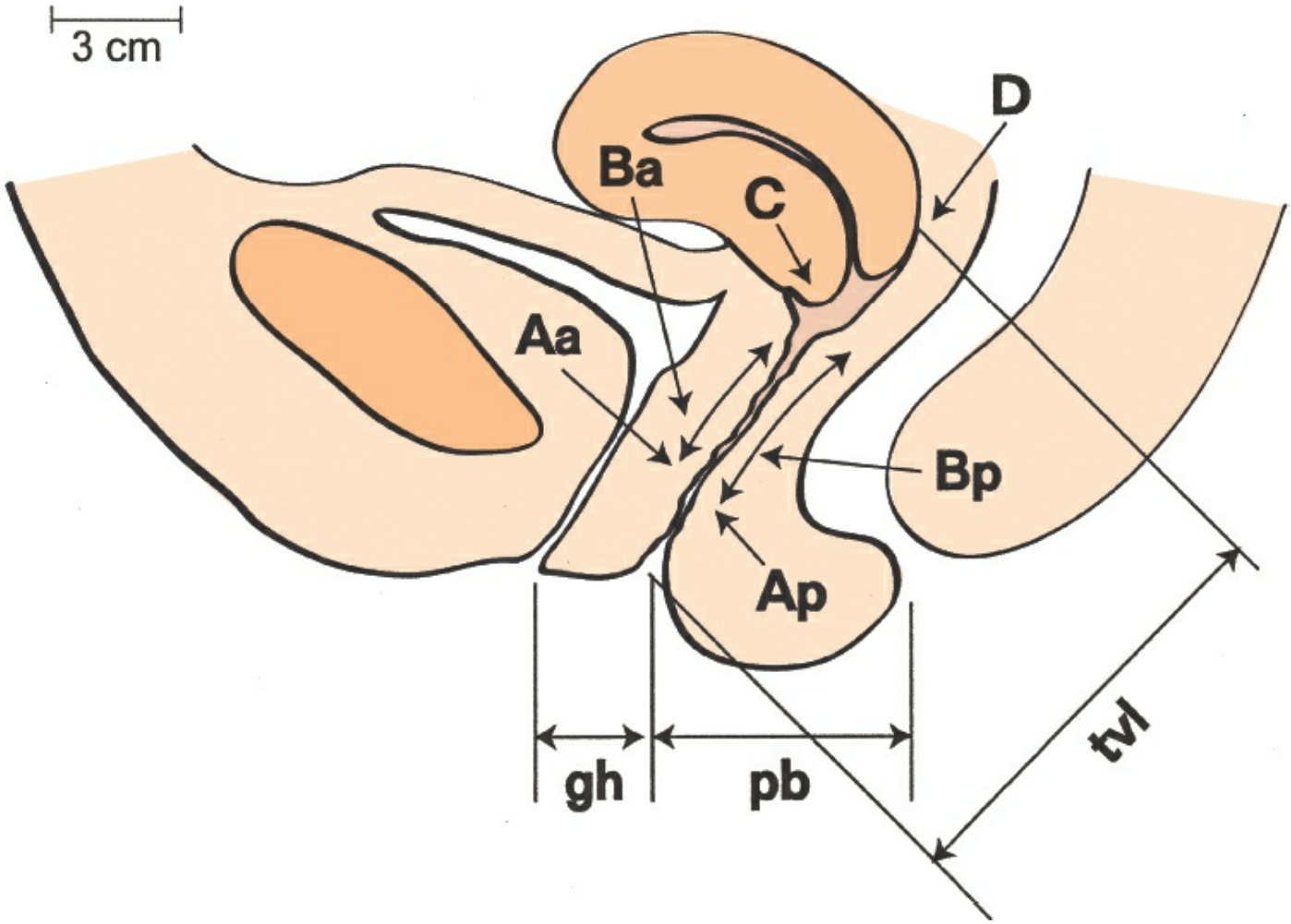


FIGURE 30-9 Standardization of terminology for female pelvic organ prolapse (POP-Q) classification. This diagram demonstrates the anatomic position of the POP-Q sites, including six sites involving the anterior (*Aa*, *Ba*), middle (*C*, *D*), and posterior (*Ap*, *Bp*) compartments with the genital hiatus (*gh*), perineal body (*pb*), and total vaginal length (*tvl*). (From **Bump RC, Mattiason A, Bo K, et al.** The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10–17, with permission.)

The classification uses six points along the vagina (two points on the anterior, middle, and posterior compartments) measured in relation to the hymen. The anatomic position of the six defined points should be measured in centimeters proximal to the hymen (negative number) or distal to the hymen (positive number), with the plane of the hymen representing zero. Three other measurements in the POP-Q examination include the genital hiatus, perineal body, and the total vaginal length (29).

The genital hiatus is measured from the middle of the external urethral meatus to the posterior midline hymen. The perineal body is measured from the posterior margin of the genital hiatus to the mid-anal opening. The total vaginal length is the greatest depth of the vagina in centimeters when the vaginal apex is reduced to its full normal position. All measurements except the total vaginal length are measured during maximal straining.

The anterior vaginal wall measurements are termed Aa and Ba, with the Ba point moving depending on the amount of anterior compartment prolapse. Point Aa represents a point on the anterior vagina 3-cm proximal to the external urethral meatus, which corresponds to the bladder neck. By definition, the range of position of this point is –3 to +3. Point Ba represents the most distal or dependent point of any portion of the anterior vaginal wall from point Aa to just anterior to the vaginal cuff or anterior lip of the cervix. This point can vary depending on the nature of the patient's support defect. For example, point Ba is –3 in the absence of any prolapse (it is never less than –3) to a positive value equal to the total vaginal length in a patient with total eversion of the vagina.

The middle compartment consists of points C and D. Point C represents the most dependent edge of the cervix or vaginal cuff after hysterectomy. Point D is the location of the posterior fornix; it is omitted if the cervix is absent. This point represents the level of the attachment of the uterosacral ligament to the posterior cervix. It is intended to differentiate suspensory failure from cervical elongation.

The posterior compartment is measured similarly to the anterior compartment: the corresponding terms are Ap and Bp. The nine measurements can be recorded as a simple line of numbers (i.e., –3, –3, –8, –10, –3, –3, 11, 4, 3 for points Aa, Ba, C, D, Ap, Bp, total vagina length, genital hiatus, and perineal body, respectively). The six vaginal sites have possible ranges that depend on the total vaginal length **(Table 30-1)**. After collection of the site-specific measurements, stages are assigned according to the most dependent portion of the prolapse **(Table 30-2)**.

The POP-Q examination often appears confusing on initial review; however, a measuring device (i.e., a marked ring forceps or marked cotton-tip applicator) can assist in instructing those unfamiliar with this staging system. **The POP-Q examination provides a standardized measurement system to allow for more accurate**

assessments of postoperative outcome and to ensure uniform, reliable, and site-specific descriptions of POP. There is interest in using the POP-Q examination to measure prolapse as a continuous variable rather than in stages because it would provide greater statistical power in clinical research (30). The American Urogynecology Society provides a video (31) that describes the POP-Q examination and demonstrates its use.

Table 30-1 Possible Ranges of the Six Site-Specific Pelvic Organ Prolapse Quantitative Examination Measurements

Points	Description	Range
Aa	Anterior wall 3 cm from hymen	−3 cm to +3 cm
Ba	Most dependent portion of rest of anterior wall	−3 cm to +TVL
C	Cervix or vaginal cuff	±TVL
D	Posterior fornix (if no prior hysterectomy)	±TVL or omitted
Ap	Posterior wall 3 cm from hymen	−3 cm to +3 cm
Bp	Most dependent portion of rest of posterior wall	−3 cm to +TVL

TVL, total vaginal length.
Adapted from **Bump RC, Mattiasson A, Bo K, et al.** The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996; 175:10–17, with permission.

In a clinical setting, at least three measurements should be obtained: the most advanced extent of the prolapse in centimeters relative to the hymen that affects the anterior vagina, the posterior vagina, and the cervix or vaginal apex.

Whether the older staging systems or the POP-Q system is used, it is important to document the most pertinent findings on examination. This will help in documenting the baseline extent of prolapse and the results of treatment.

Pelvic Muscle Function Assessment

Pelvic muscle function should be assessed during the pelvic examination. Following bimanual examination with the patient in the lithotomy position, the examiner can palpate the puborectalis and pubococcygeus muscles inside the hymen along the pelvic sidewalls at approximately the 4 and 8 o'clock positions. One can appreciate basal muscle tone and whether there is increased tone with contraction as well as strength, duration, and symmetry of contraction (32). **A rectovaginal examination should also be performed to assess basal and contraction muscle tone of the anal sphincter complex.**

Table 30-2 Stages of Pelvic Organ Prolapse

Stage 0	No prolapse is demonstrated. Points Aa, Ap, Ba, Bp are all at –3 cm, and point C is between total vaginal length (TVL) and –(TVL –2 cm)
Stage I	The most distal portion of the prolapse is greater than 1 cm above the level of the hymen
Stage II	The most distal portion of the prolapse is less than 1 cm proximal or distal to the plane of the hymen
Stage III	The most distal portion of the prolapse is less than 1 cm below the plane of the hymen but no further than 2 cm less than the total vaginal length
Stage IV	Complete to nearly complete eversion of the vagina. The most distal portion of the prolapse protrudes to greater than (TVL –2) cm

From **Bump RC, Mattiassion A, Bo K, et al.** The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996; 175:10–17, with permission.

As a part of the POP examination, urethral mobility often is measured. **Many women with prolapse will have urethral hypermobility (defined as a resting urethral angle greater than 30 degrees or a maximal strain angle greater than 30 degrees).** The presence of urethral mobility in combination with symptoms of stress incontinence may help determine whether an incontinence procedure should be performed. However, studies have shown that nearly all women with stage II to IV prolapse have urethral hypermobility, and asymptomatic parous women have an average maximum straining angle of 54 degrees (33,34). During pelvic examination, the urethra is typically swabbed with *Betadine*, and *lidocaine* jelly is placed in the urethra or on a cotton-tip swab. The swab is placed in the urethra at the urethrovesical junction and, with the use of a goniometer **(Fig. 30-10)**, the baseline urethral angle from the horizontal and maximal strain angles is measured.

Bladder Function Evaluation

Patients with prolapse exhibit the full range of lower urinary tract symptoms. Despite the fact that some patients may not have significant symptoms, it is important to obtain objective information about bladder and urethral function. With severe POP, the urethral kinking effect of the prolapse may mask a potential urine leakage problem; therefore, basic office bladder testing with prolapse reduction should be performed to mimic bladder and urethral function if the prolapse were treated. At a minimum, the following assessments should be performed: a clean catch or catheterized urine sample to test for infection, a postvoid residual volume (PVR), and assessment of bladder sensation, which can be performed as a part of office cystometrics. Although there is no consensus as to what constitutes an abnormal PVR volume, provided the patient has voided 150 mL or more, a PVR less than or equal to 100 mL is acceptable (33). Reduction stress testing at the time of simple office cystometrics can be performed

with the use of a pessary, large cotton swab, ring forceps, or the posterior blade of a speculum. Care should be taken that the urethra not be overly straightened (with a resultant false-positive test result) or obstructed (with a resultant false-negative test result), or that tension is not placed on the puborectalis muscles by excessive posterior retraction. These risks can be minimized by orienting the vaginal apex toward the sacrum.

Bowel Function Evaluation

When a decision is made to perform surgical repair of the posterior compartment based on symptoms, type, and location of defects, an appropriate approach should be determined and the patient should be made aware of the expected outcomes and potential adverse effects such as pain and sexual dysfunction. **If the patient has defecatory dysfunction with a rectocele and symptoms of constipation, pain with defecation, fecal or flatal incontinence, or any signs of levator spasm or anal sphincter spasm, appropriate evaluation and conservative management of concurrent conditions could be initiated before repair of the rectocele and continued postoperatively** (34).

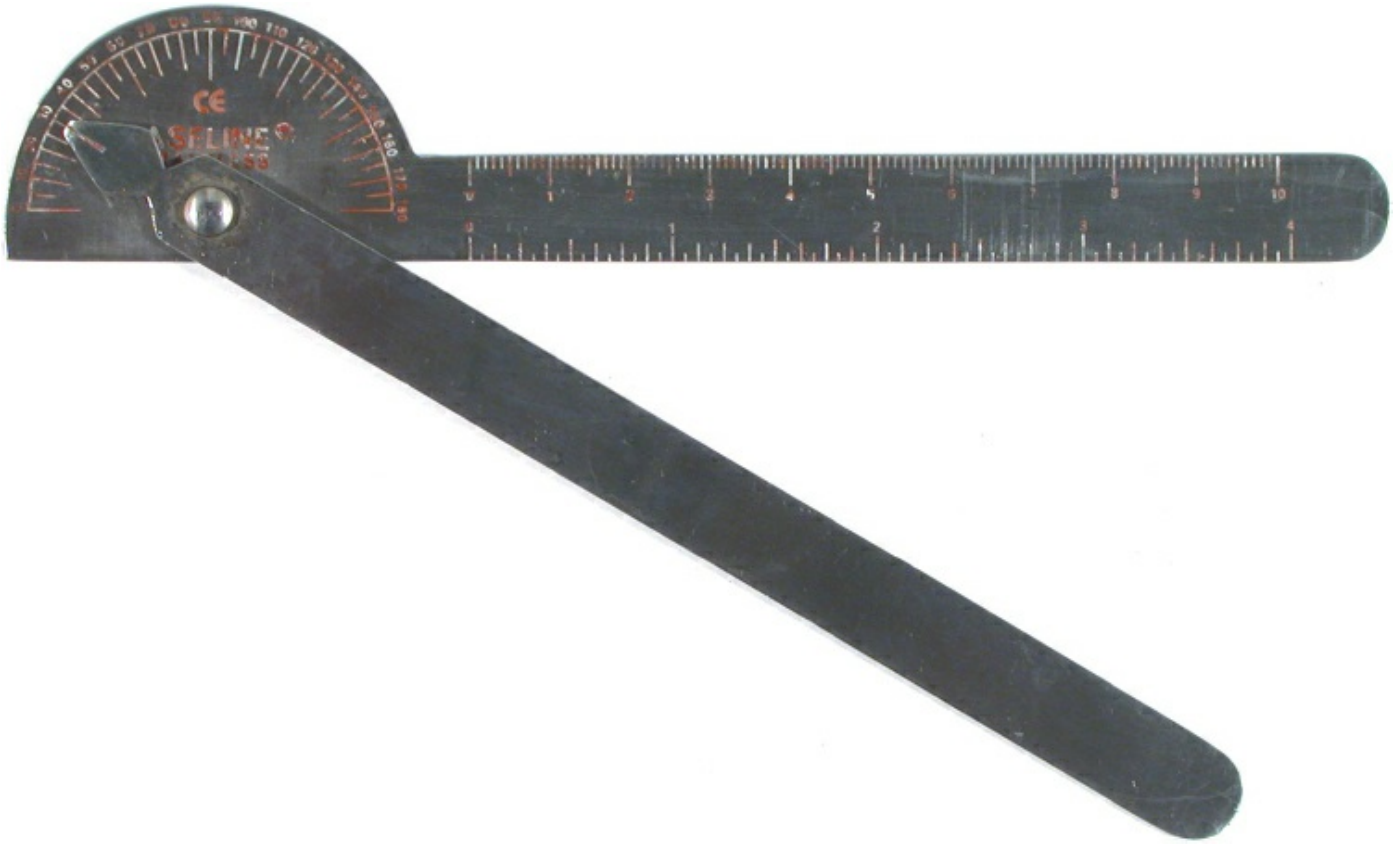


FIGURE 30-10 Goniometer, which is used to measure baseline urethral angle and maximal strain angle of the urethra with a cotton-tip swab in place.

Imaging

Diagnostic imaging of the pelvis in women with POP is not routinely performed. However, if clinically indicated, tests that may be performed include fluoroscopic evaluation of bladder function, ultrasound of the pelvis, and defecography for patients in whom intussusception or rectal mucosal prolapse are suspected. Magnetic resonance imaging is increasingly being used for the evaluation of pelvic pathology such as mullerian anomalies and pelvic pain; however, generalized use in women with prolapse is not clinically indicated and is used primarily for research purposes.

[5] TREATMENT

Nonsurgical Therapy

Nonsurgical therapy of POP includes conservative behavioral management and the use of mechanical devices. **A nonsurgical treatment approach is usually considered in women with mild to moderate prolapse, those who desire preservation of future childbearing, those in whom surgery may not be an option, or those who do not desire surgical intervention.** As not all prolapse progresses over time, expectant management is an option for some women, especially if they are mostly asymptomatic. A 4-year prospective observational study of 259 postmenopausal women reported the maximum vaginal descent increased by at least 2 cm was seen in 11%. Three percent had at least 2-cm regression of prolapse (35).

Conservative Management

Conservative management approaches include alteration of lifestyle or physical intervention such as pelvic floor muscle training (PFMT). These approaches are used mainly in cases of mild to moderate prolapse; however, their true role in managing prolapse and associated symptoms is unclear (36). **The goals of a conservative therapy approach to the treatment of prolapse are as follows** (37):

- Prevent worsening prolapse
- Decrease the severity of symptoms
- Increase the strength, endurance, and support of the pelvic floor musculature
- Avoid or delay surgical intervention

Prevention of prolapse progression and life-altering interventions are lacking robust data.

Pelvic floor muscle exercises may limit the progression of mild prolapse and related symptoms; however, a lower response rate has been noted when prolapse extends beyond the vaginal introitus (38). A recent randomized trial evaluated the effectiveness of one-to-one individualized PFMT for the reduction of symptomatic

stages I to III prolapse (39). Women in the intervention group reported fewer prolapse symptoms at 12 months compared to those provided a lifestyle advice leaflet without muscle training.

The efficacy of biofeedback therapy in the treatment of impaired defecation associated with a rectocele has been determined (40). Thirty-two female patients, median age 52 years (range, 34 to 77 years), experiencing impaired rectal evacuation with a rectocele greater than 2 cm at proctography underwent a structured behavioral retraining. Immediate and medium-term follow-up results were reported (median 10 months; range 2 to 30 months). Fifty-six percent of patients ($n = 14$) felt a little and 16% ($n = 4$) felt major improvement in symptoms, including 3 (12%) with complete symptom relief. Immediately after biofeedback there was a modest reduction in need to strain (67; 50%), feeling of incomplete evacuation (73; 59%), and need to assist defecation digitally (79; 63%) that was maintained at follow-up. Bowel movement frequency was significantly normalized at follow-up ($p = .02$). These investigators concluded that **behavioral retraining, including biofeedback therapy, may be an effective primary therapy for some patients with a rectocele associated with impaired defecation** (40).

Mechanical Devices

The use of mechanical devices such as pessaries is usually considered for women who cannot undergo surgery for medical reasons, desire to avoid surgery, or have a significant degree of prolapse that makes other nonsurgical approaches unfeasible. Some practitioners extend indications to include pregnancy-related prolapse as well as prolapse and incontinence in elderly women. Reports have shown that age older than 65 years, the presence of severe medical comorbidity, and sexual activity were associated with unsuccessful pessary usage (41,42). Unsuccessful use or a preference for surgery has been associated with a shortened vaginal length (≤6 cm), a wide vaginal introitus, sexual activity, stress incontinence, stage III or IV posterior compartment prolapse, and desire for surgery at a first office visit (43).

Pessaries provide pelvic organ support within the vaginal vault. **Two categories of pessaries—support and space filling—exist for prolapse. The ring pessary (with diaphragm) is a commonly used support pessary, and the Gelhorn pessary is a commonly used space-filling pessary. Traditionally, the ring and other support pessaries are used for stage I and II prolapse, whereas the space-filling pessaries are used for stage III and IV prolapse** (44). In a randomized trial comparing ring with support versus Gellhorn for prolapse treatment in women with stage II to IV prolapse, no difference was noted between the two pessaries for the treatment efficacy in relieving symptoms of protrusion and voiding dysfunction. This trial reported older and more parous women preferred ring pessaries whereas those without prior pelvic surgery preferred Gellhorn. The continuation rate was 45% at 3 months (45).

It is unclear whether pessaries can prevent the progression of POP with regular use. A prospective cohort study addressed this issue in a series of 56 women who were fitted with a pessary, of which 33.9% (n = 19) continued use for at least 1 year (46). Baseline and follow-up pelvic examinations were performed using the POP-Q system. The women removed the pessary 48 hours before one visit, but there was no information to ascertain adherence to pessary use. No woman had worsening of the prolapse, and four women (21.1%; 95% CI, –0.2, 43.7%) had an improvement. Improvement overall was noted in women with anterior compartment prolapse (46).

No consensus guidelines on the care of pessaries (i.e., intervals between changes), the role of local estrogens, or the type of pessary indicated for specific types of POP (47). Different pessary types can be seen in **Figure 30-11**. After 2 to 6 months, 77% to 92% of women with a successful pessary fitting were satisfied and, using intention-to-treat analysis, 44% to 67% of all women who were treated initially with a pessary for prolapse were satisfied. There is a paucity of long-term follow-up data on pessary use, however, the continuation rate of 14% at 14 years has been reported (41,43,48).

Possible complications associated with pessary use include vaginal discharge and odor. Failure to retain the pessary may occur or, conversely, the pessary may be too large, which could lead to excoriation or irritation. With reduction of vaginal prolapse, *de novo* or increased stress incontinence may occur, and in rare instances, more severe complications, including vesicovaginal or rectovaginal fistula, small bowel entrapment, hydronephrosis, and urosepsis, have been described (49–51).

Placement and Management

Pessary placement involves consideration of a number of issues, primarily the patient's desire and motivation to use this type of device. Typically, if she has had previous surgery or strongly desires to avoid surgery, she may be motivated enough for a primary attempt at pessary placement. Other issues include current sexual function status, type and duration of exercise in which the patient engages, and the status of the vaginal walls and cervix. In hypoestrogenic women, treatment of the vagina with estrogen and maintenance of intravaginal estrogen treatment is recommended.

Fitting a Pessary

The patient should be examined in the lithotomy position after emptying her bladder. The clinician should use a dry glove to better grasp the pessary and water-soluble lubricants as needed. The size of the pessary is estimated after a digital examination and use of ring forceps to reduce the prolapse or bladder neck. After the approximate size is determined, the appropriate type is selected based on the patient's needs and activity level. **When fitted, the patient is asked to stand, perform Valsalva, and cough to ensure the pessary is retained.** The pessary should be assessed to ensure it is providing the desired support and leakage control. The patient

should be able to void with the pessary in place before leaving the office. Proper size is ensured by the ability to sweep the index finger between the pessary and the vaginal wall. The patient should feel comfortable with the pessary in place.

Insertion of the pessary is eased by using a water-soluble lubricant for insertion, folding or collapsing the pessary to reduce its size, and when it is inside the vagina, pushing it high to an area behind the symphysis pubis and inserting the device more posteriorly to avoid the urethra. Instructing the patient how to insert and remove the pessary may be done with the patient in a standing or supine position, depending on her dexterity (52).

Ring pessaries, with or without support, are the most commonly used type. They are the easiest to fold, insert, and remove. **Gellhorn** and **cube** pessaries are typically more difficult to insert and remove by the patient. They are held in place by significant space occupation and suction and offer strong support. The suction of the cube pessary needs to be broken, facilitating removal. Cube pessaries should be removed daily; Gelhorns can stay in longer (up to 6 to 8 weeks). **Donut pessaries,** which are very popular, are considered a space-fitting pessary for large vaginal vault prolapse, complete procidentia with decreased perineal support, and good introital integrity. **The patient should be questioned about a latex allergy and instructed to remove and clean the device every 2 to 3 days.** Continence pessaries, rings, and dishes with support typically also are easy to fold, insert, and remove.

Follow-Up Recommendations

After the initial fitting, the patient should return in 1 to 2 weeks and then at 4 to 6 weeks, depending on her independence with the pessary, her proficiency in placement and removal, and her cognitive and motor abilities. After this initial follow-up, follow-up should continue at 6- to 12-month intervals at the discretion of the provider and depending on the patient's ability to insert and remove the pessary effectively. If the patient needs to return to the provider for removal and cleaning of the pessary, 4- to 12-week intervals are more appropriate.

On follow-up visits, proper placement of the pessary, support of the prolapse and continence efficacy should be ensured. Because pessaries are fitted through a process of trial and error, it is not uncommon to change the size or type at least once after the initial fitting. **[6]** The pessary's integrity should be checked, and the tissues should be evaluated for irritation, pressure sores, ulceration, and lubrication.

UTERINE PROLAPSE

I. 1st & 2nd DEGREE

- **O** Ring with Support
- **U** Ring without Support
- **R** Shaatz
- **I** Regula

II. 3rd DEGREE

- **X** Donut
- **L,M,N** Gellhorns
- **W** Inflatoball
- **G** Cube
- **F** Tandem-Cube

CYSTOCELE and/or RECTOCELE

- **J** Gehrung
- **I** Regula

CYSTOCELE + SUI

- **K** Gehrung with Knob

SUI

I. SIMPLE

- **T** Ring Incontinence
- **A,D,E,H** Hodge

II. + MILD PROLAPSE

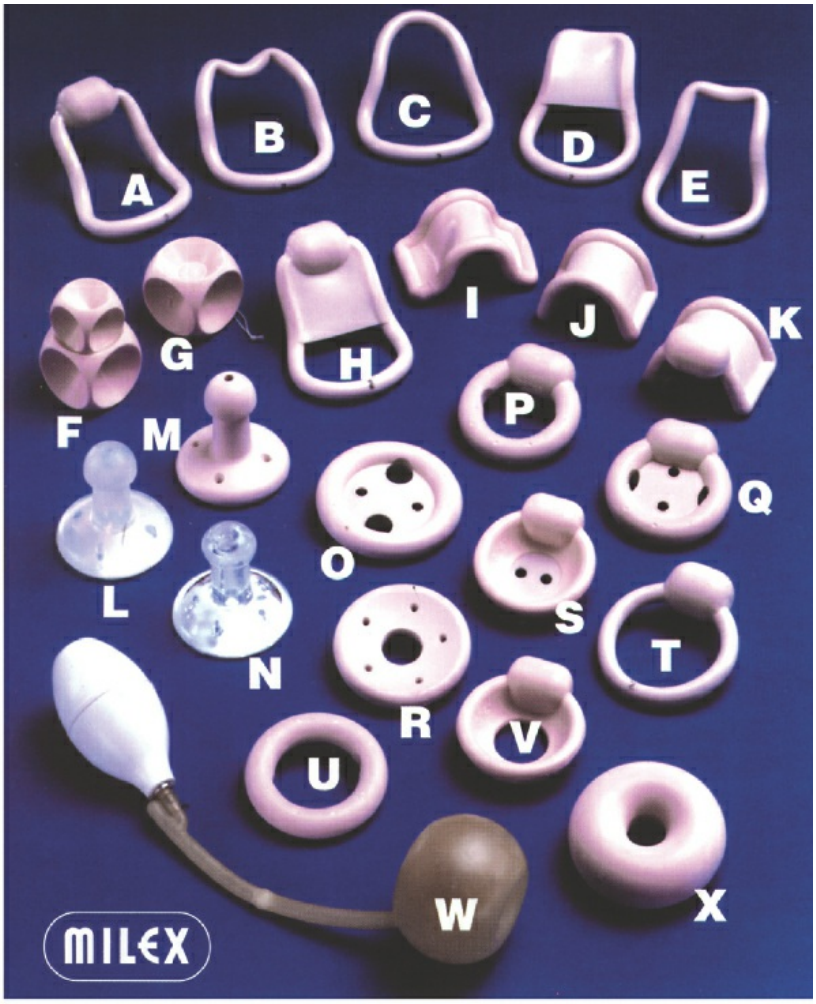
- **P,Q** Ring with or without Support + Knob
- **V** Incontinence Dish

III. + PROLAPSE & CYSTOCELE

- **S** Dish with Support
- **Q** Ring with Support + Knob

INCOMPETENT CERVIX

- **E** Hodge } Used with or without cerclage
- **C** Smith }



A Hodge with Knob (Silicone) **B** Risser (Silicone) **C** Smith (Silicone) **D** Hodge with Support (Silicone) **E** Hodge (Silicone)
F Tandem-Cube (Silicone) **G** Cube (Silicone) **H** Hodge with Support+Knob (Silicone) **I** Regula (Silicone) **J** Gehrung (Silicone)
K Gehrung with Knob (Silicone) **L** Gellhorn 95% Rigid (Silicone) **M** Gellhorn Flexible (Silicone)
N Gellhorn Rigid (Acrylic) **O** Ring with Support (Silicone) **P** Ring with Knob (Silicone) **Q** Ring with Support+Knob (Silicone)
R Shaatz (Silicone) **S** Incontinence Dish with Support (Silicone) **T** Ring Incontinence (Silicone) **U** Ring (Silicone)
V Incontinence Dish (Silicone) **W** Inflatoball (Latex) **X** Donut (Silicone)

FIGURE 30-11 Pessaries used to treat the various degrees of prolapse. (Milex Company, a Division of Cooper Surgical.)

Surgical Management

The primary aims of surgery are to relieve symptoms, which may be caused by prolapse, and, in most cases, to restore vaginal anatomy so that sexual function may be maintained or improved without significant adverse effects or complications. Occasionally, when sexual function is not desired, obliterative or constrictive surgery is more appropriate and may relieve symptoms. There is no steadfast rule as to when surgery is indicated. Many patients with more advanced prolapse have few or no symptoms, whereas some with lesser degrees of prolapse have what they describe as severe symptoms. This is confounded by the observation that

many of the "symptoms" may not be specifically related to the anatomic defect or may be worsened by anxiety. **In general, surgery should be offered to patients who have tried conservative therapy and were not satisfied with the results or who do not desire conservative therapy.** The prolapse should be symptomatic or should be greater than or equal to stage II with apparent progression. All patients should be given the alternative of trying conservative treatments when applicable. A prospective study of 680 women with prolapse reported that women choosing surgical over conservative management tend to be younger, more bothered by lower abdominal pain, pressure, need for vaginal digitation, incomplete bowel emptying, and sexually active (53).

Approaches to surgery include vaginal, abdominal, and laparoscopic routes, or a combination of approaches. Depending on the extent and location of prolapse, surgery may involve a combination of repairs directed to the anterior vagina, vaginal apex, posterior vagina, and perineum. Concomitant surgery may be planned for urinary or fecal incontinence. The surgical route is chosen based on the type and severity of prolapse, the surgeon's training and experience, the patient's preference, and the expected or desired surgical outcome.

Procedures for prolapse can be broadly categorized into three groups: (1) reconstructive, which use the patient's endogenous support structures (native tissue repair); (2) compensatory (augmentation), which attempt to replace deficient support with permanent graft material; and (3) obliterative, which close or partially close the vagina.

These groupings are somewhat arbitrary and not entirely exclusive. For example, grafts may be used to reinforce repairs, such as colporrhaphy, or to replace support that is deficient or lacking. Graft use in sacrocolpopexy substitutes for the connective tissues attachments (cardinal and uterosacral ligaments) that would normally support the vaginal apex. In addition to the primary goal of relieving symptoms related to prolapse, urinary, defecatory, and sexual function must be considered in choosing the appropriate procedures.

Whether to repair all defects is controversial. Restorative repairs may be less successful than compensatory repairs in patients with generally "poor tissue," and at times one defect repair may exert more tension on the repair of another defect. Management should be based on the patient's presentation, expectations, the specific anatomical defects noted (preoperatively and, at times, intraoperatively), and on the presence or absence of lower urinary and bowel dysfunction.

Vaginal Procedures

The Apical Compartment

Apical support is the key to a successful prolapse repair. Multiple studies

demonstrate that the apex descends with the anterior compartment and that correction of the anterior wall without addressing the apex increases the risk of recurrent prolapse. Despite compelling evidence as to the importance of suspending the apex, not all surgeons perform this critical portion of the surgery, suggesting an ongoing discrepancy between evidence-based medicine and adoption into clinical practice (54). **Examination for apical defects is at times difficult. Such defects may be missed when large anterior or posterior defects are present.** In cases when apical defects are suspected but not confirmed, surgeons should evaluate the apical support intraoperatively and plan for management of these defects when they are found. Traction on the cervix with a tenaculum or on the vaginal cuff both centrally and laterally with Allis clamps may reveal otherwise unrecognized defects.

Transvaginal repairs include extraperitoneal procedures such as sacrospinous suspensions, iliococcygeal suspensions, and high paravaginal suspensions of the apical vaginal fornices to the arcus tendineus at the level of the ischial spine or to the endopelvic fascia, and intraperitoneal suspensions such as uterosacral suspensions and McCall culdoplasties. Accepted practice is that the vaginal apex should be resuspended in a posterior cephalad direction to a site or sites posterior and caudad to the sacral promontory. Anterior apical suspensions change the direction of the vaginal axis and may be fraught with a greater incidence of posterior compartment defects, including rectoceles, enteroceles, and sigmoidoceles.

1. If present, the attenuated part of the upper vaginal wall (fibromuscular defect) should be repaired or covered by graft material. If the attenuation is severe and cannot be thickened by preoperative vaginal estrogen treatment, removal of that portion of the upper vaginal wall should be considered.
2. The vaginal cuff or, in some instances, the cervix should be suspended without excessive tension.
3. Any defect in the attachment of the upper vagina to the rectum at or below its sigmoid junction should be corrected.

Enterocele repairs may include:

1. Removal of the peritoneal sac with closure of the peritoneal defect, followed by closure of the fascial or fibromuscular defect or both below it
2. Dissection and reduction of the peritoneal sac and closure of the defect
3. Obliteration of the peritoneal sac from within with transabdominal Halban or Moschcowitz type procedures or transvaginal McCall or Halban procedures
4. If the posterior vaginal wall is significantly elongated and enlarged, excision of that area to establish an acceptable vaginal length and to eliminate redundancy

With increasing evidence that suspension of the apex plays an integral role in prolapse surgery, the focus is shifting to identifying the optimal procedure to suspend the apex. One aspect of apical support in women with uterovaginal prolapse is discussion of the role of hysterectomy versus uterine preservation at the time of prolapse repair. Perception by patients and physicians differ. Historically, the treatment for symptomatic uterine prolapse has been concomitant hysterectomy, which is performed vaginally or abdominally in combination with an apical suspension procedure, and repair of coexisting defects. As the focus on patient reported outcomes has become increasingly recognized, it became apparent that patient and surgeon expectations and goals of surgery were somewhat different, and that traditional methods of evaluating treatment success (i.e., physical examination findings) may not be sufficient to give a full representation of surgical outcomes and patient satisfaction. PFD treatment goals (referred to as patient-centered, patient-identified, or patient-selected goal) have been called the "fourth dimension" of assessment of PFD treatment outcomes. PFD treatment goal attainment is associated with improved condition-specific QOL and patient satisfaction (55).

Uterine Preservation

The number of women favoring uterine preservation is increasing. When presented with the choice to undergo a hysterectomy at the time of POP surgery, 36% to 60% of women presenting for POP care would decline a hysterectomy (56,57).

Although hysterectomy has been performed routinely at the time of uterovaginal prolapse repair (as a means to access the uterosacral ligaments), high-level evidence-based data regarding the potential benefits comparing uterine preservation versus hysterectomy are lacking in the literature. The proponents of uterine conservation might argue that disruption of the uterosacral/cardinal ligament complex may weaken the pelvic floor supports even further. Existing data suggest that uterine preservation POP surgeries reduced risk of mesh erosion, operative time, blood loss, and hospital stay compared to similar surgical routes with concomitant hysterectomy and do not significantly change short-term prolapse recurrence (58). A recent randomized trial, "Study of Uterine Prolapse Procedures—Randomized Trial" or "SUPeR," was designed to address the question regarding the benefits of concomitant hysterectomy versus uterine preservation at the time of uterovaginal prolapse repair. This is a multicenter, single-blinded trial which randomizes women to a vaginal hysterectomy with uterosacral ligament suspension versus a vaginal mesh hysteropexy. Results of this trial are expected to be available in 2018 (59).

Additional factors to be considered when planning uterine-sparing prolapse surgery would include: women with a history of cervical pathology or abnormal uterine bleeding who may not be good candidates for uterine preservation, or those women who are at high risk of uterine malignancy (and may be best served with a hysterectomy as

part of their prolapse repair). Uterine preservation necessitates routine surveillance for malignancies (uterine, cervical), which may be more technically challenging as a result of anatomical position changes from surgery. **Additional apical support procedures that have been described for use when the uterus or cervix is to be kept in place include Manchester and Gilliam procedures and fixation of the cervix to the sacrospinous ligament.**

The other procedures described in this section may be used in women who desire uterine preservation. When the cervix is absent, in addition to repair of fibromuscular defects, both fibromuscular planes anterior and posterior to the vaginal cuff should be attached to whatever suspension is employed.

Sacrospinous Ligament Fixation

The fixation of the vaginal apex to the sacrospinous ligament, the tendineus component of the coccygeus muscle, was first described in 1958 and was subsequently modified in Europe and the United States (60–63). **Access is traditionally extraperitoneal via the rectovaginal space with penetration of the pararectal (Denonvillier fascia) at the level of the ischial spine to expose the muscle and ligament. Variations in this approach to the ligament include entrances through an anterior lateral access, an apical passage posterior to the uterosacral ligament, and a laparoscopic approach** (64–66). Bilateral sacrospinous ligament suspensions have been advocated; however, these techniques may impose a greater degree of tension on the sutures and, at times, create a band of apical vagina across the rectum at the level of the suspension. Whether this can cause defecatory dysfunction remains unknown. The advantages of the sacrospinous fixation procedure include: (1) its transvaginal extraperitoneal approach; (2) resultant posterior vaginal deflection; and (3) the fact that it is a durable repair if performed correctly. Reported success for apical support has been good (89% to 97%) with follow-up times ranging from 1 month to 11 years (67). However, there have been subsequent reports of high rates of anterior vaginal prolapse. It is not clear whether this observation is related to the procedure and its exaggerated posterior vaginal deflection or to the fact that many patients with apical descent also have defects in the upper vaginal fibromuscular tissue. Failure to address an anterior defect concurrently with suspension of the posterior apical vagina may predispose the patient to such a defect postoperatively. Other disadvantages of the procedure include: (1) relative difficulty in adequately exposing the ligament; (2) an unnatural lateral vaginal deflection toward the fixation site; (3) an inability to perform without excessive tension when the vaginal length is compromised, as may be the case in repeat procedures; (4) potential risk for injury to the sciatic nerve or pudendal nerve or vessel; and (5) occasional need to shorten or narrow the upper vagina when a fibromuscular defect involves much of the apical area.

Iliococcygeal Vaginal Suspension

Iliococcygeal vaginal suspension involves the attachment, usually bilaterally, of the vaginal apex to the iliococcygeus muscle and fascia (68,69). Extraperitoneal access is achieved via the posterior vagina. Compared with other vaginal suspension procedures, the iliococcygeal suspension has the fewest case series in the literature (68–72); however, cure rates appear comparable to the sacrospinous suspension technique. The dissection of the area to the ischial spine is approached from a midline posterior vaginal wall incision using the ischial spine as a landmark for identifying the sacrospinous ligament and the iliococcygeal fascia anteriorly and caudad to it. A polydioxanone suture is placed through the fascia and attached to the vaginal apex as a pulley stitch. This procedure is more easily performed bilaterally than the sacrospinous suspension and should be considered preferentially in the presence of a shortened vagina. Risk of major vessel, nerve, or ureteral injury should be relatively low compared with other transvaginal suspensions.

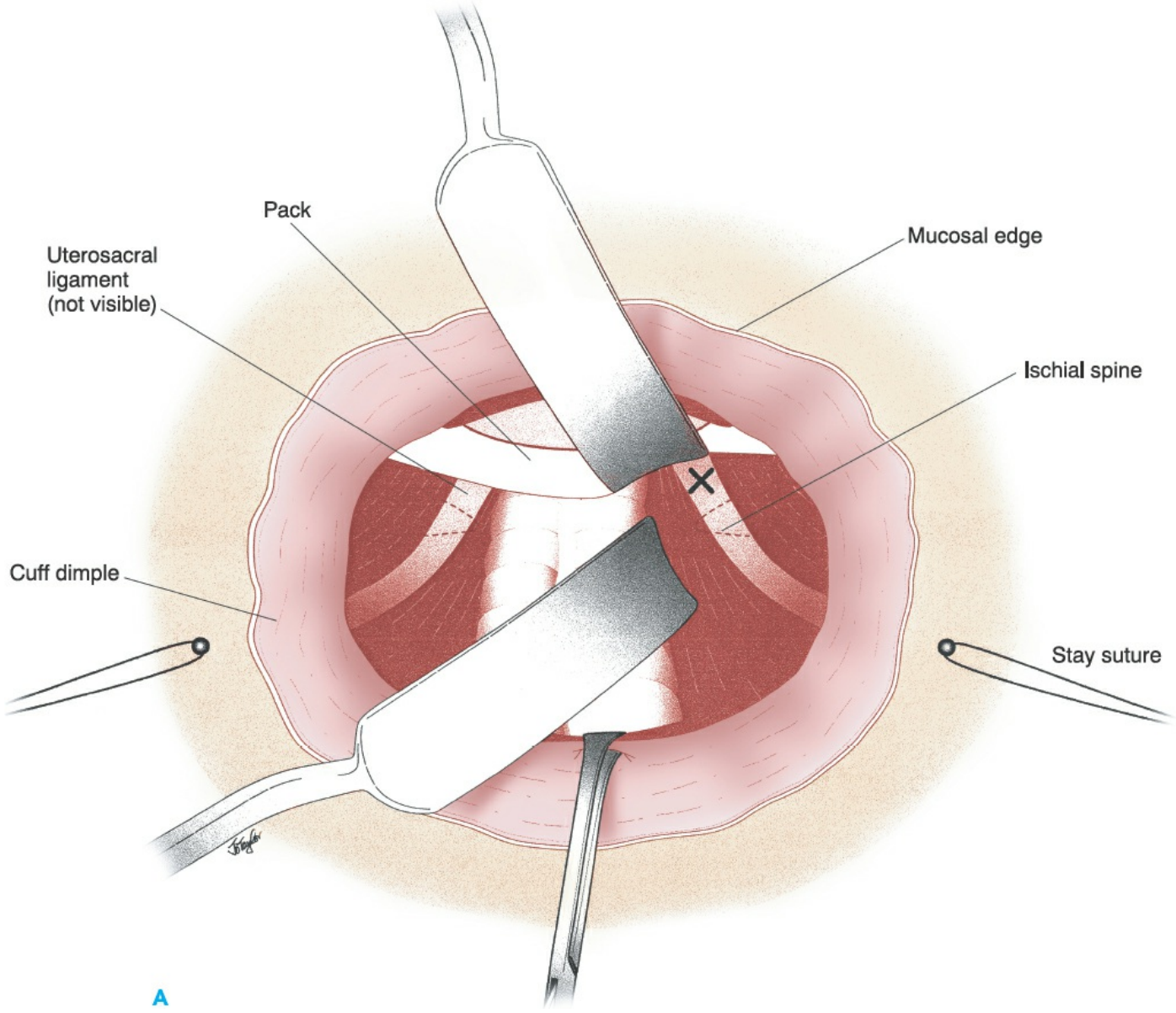
Uterosacral Ligament Suspension

Surgical variations of the uterosacral ligament suspension originally described in 1938 have been used prophylactically during hysterectomy or therapeutically for vaginal apical suspension (68,71). **A therapeutic procedure in which the vaginal apex is suspended to the uterosacral ligaments above the level of the ischial spines had excellent success rates in an observational study of 302 participants** (72). When access to the posterior cul-de-sac is attained, the uterosacral ligament remnant can usually be found adjacent to the pelvic sidewall peritoneum just cephalad to the palpable ischial spine. Up to three sutures are placed in each ligament and incorporated into the anterior and posterior fibromuscular layer of the vagina. Some surgeons approximate the ligaments in the midline to close the cul-de-sac with the intention to treat or prevent enterocele formation (73). Other surgeons suspend the right and left vaginal apex to the ipsilateral uterosacral ligament, leaving the cul-de-sac open to avoid impinging on the rectum and adversely affecting bowel function.

The most common serious complication was ureteral obstruction secondary to ureteral kinking or incorporation of a ureter in a suspension stitch. This occurs in approximately 2% to 3% of the cases, however as high as 11% of intraoperative ureteral kinking has been reported (74,75). Intraoperative cystoscopy—with documentation of ureteral patency whereby such a problem can be corrected—is recommended.

Multiple sutures may increase the incidence of tissue devascularization and necrosis, resulting in failure of the suspension. One case series of bilateral single suture uterosacral suspensions demonstrated a 15% stage I and no stage II recurrence among 71 women with a mean follow-up of 21.3 months (76). Exposure can be accomplished through the vaginal cuff after hysterectomy, a transverse incision at the vaginal cuff in cases of vaginal vault prolapse or descent, and, rarely, through a

posterior colpotomy when uterine or cervical conservation is desired. When the apical vaginal wall is attenuated, it is excised. The pelvic sidewall, lateral to the sigmoid colon, is exposed using Breisky–Navratil retractors and a pack to hold the small bowel cephalad and to place the sigmoid colon and sidewall peritoneum on stretch **(Fig. 30-12A)**. After palpation of the ischial spine, single permanent sutures of 0 or 1 polypropylene are placed through the peritoneum and adjacent ligament approximately 1-cm cephalad to and at the same posterior level as the ischial spines. Traction on the sutures and palpation of the site should reveal that the sutures are firmly attached to the ligamentous structures. The sutures are tagged for use after repair of defects of the anterior compartment. The peritoneum is dissected off the vaginal fibromuscular wall posterior to the vaginal cuff. The suspension sutures are secured with large bites into the posterior vaginal fibromuscular tissue and anterior fibromuscular tissue, then locked in place to approximate anterior to posterior connective tissue and to fix the suture to the vaginal apex so that it may be moved up to the ligament **(Fig. 30-12B)**. For large vaginal cuffs a second suspension suture (delayed absorbable can be used on each side and tied after the prolene sutures are secured. If a rectovaginal enterocele is present, it is dissected, reduced, and closed, approximating the prerectal fascia or anterior rectal wall to the posterior fibromuscular vaginal tissue just caudad to the suspension sutures. Absorbable cuff closure sutures can be placed at each cuff angle and one to two bites are taken to approximate anterior to posterior vaginal cuff over the suspension suture sites. When indicated, plication of the central cuff anterior to the posterior fibromuscular tissue with a box stitch is performed. These sutures are secured after the suspension sutures are tied, then cuff closure is completed from each side with the absorbable sutures in a running fashion. The closure of the cuff hides the knots of the suspension sutures. Cystoscopy is performed to document ureteral patency. Ureteral compromise has been noted in only 2 of 150 cases performed. The procedure provides adequate support of POP-Q point C and D in all 58 subjects evaluated more than 1-year postoperatively (76).


Pack
Uterosacral ligament (not visible)
Mucosal edge
Ischial spine
Cuff dimple
Stay suture
A

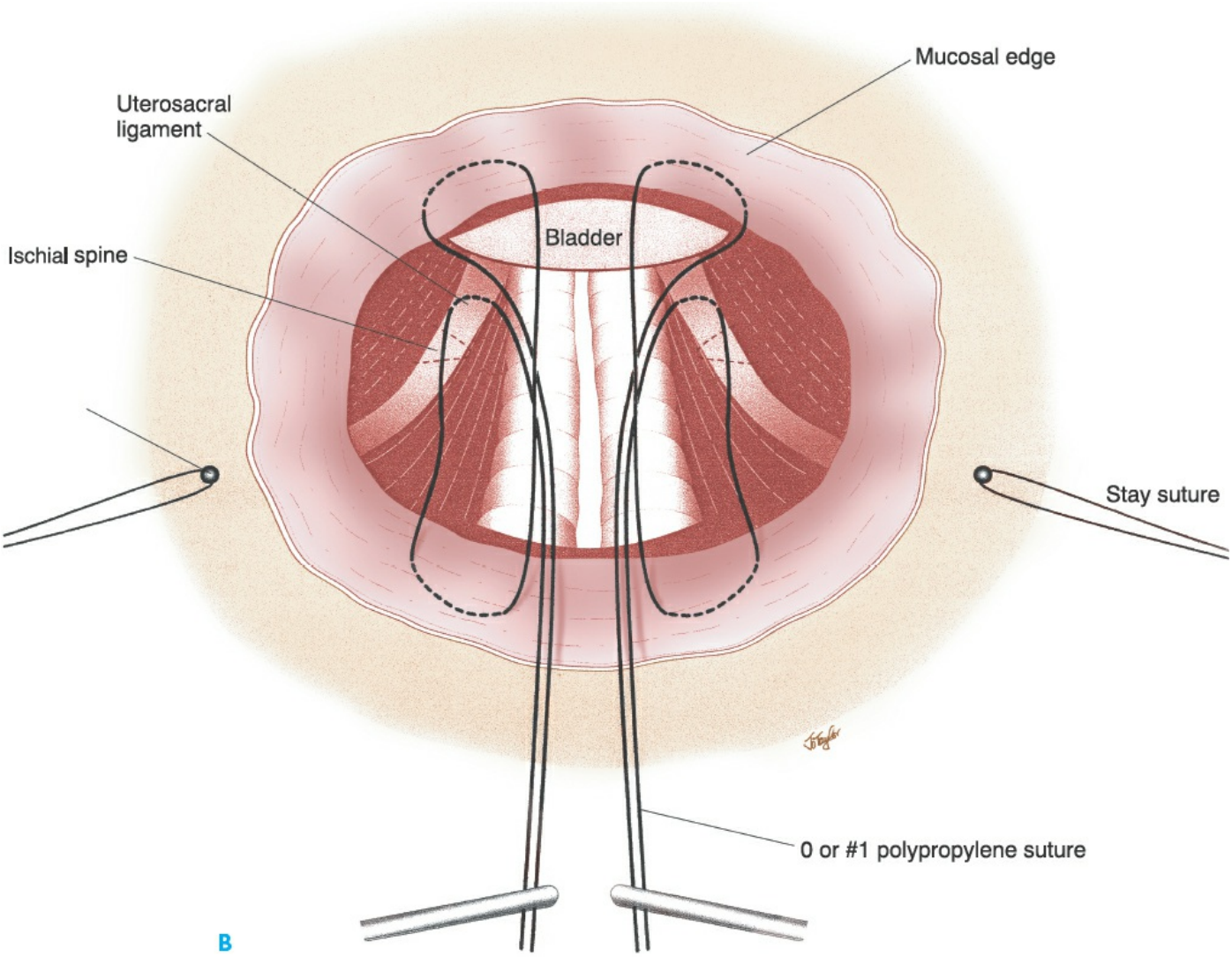


FIGURE 30-12 Diagrams illustrating open vaginal apical area with (**A**) exposure of site for suture placement or lateral pelvic side wall and (**B**) suture placement through ligament then through the posterior and anterior paravaginal tissue where they are locked to enable pulley action to the ligaments when tied. (Redrawn from an image by J. Taylor.)

The two most commonly performed transvaginal native tissue apical prolapse repairs are the sacrospinous ligament suspension and uterosacral ligament suspension. A randomized controlled trial in 374 women with POPQ stage II to IV comparing the two vaginal approaches, or the Operations and Pelvic Muscle Training in the Management of Apical Support Loss (OPTIMAL) trial, showed that there was no difference in a composite surgical success defined as the absence of: (1) vaginal apical descent to more than one-third of the total vaginal length; (2) anterior or posterior vaginal wall descent beyond the hymen; (3) bothersome vaginal bulge symptoms; and (4) retreatment of prolapse. The 2-year success rate was 59% versus 61% for uterosacral and sacrospinous ligament suspension, respectively. The success rates decreased overtime to 44% and 33% at 5 years after surgery (77,78).

The Anterior Compartment

Anterior Vaginal Colporrhaphy

Anatomic correction of an anterior defect or cystocele will generally relieve symptoms of protrusion and pressure and usually will improve micturition function when abnormal micturition is associated temporally with the defect and if there is no associated neuropathy. If a single, well-defined midline defect is recognized, excision of the weak vaginal wall and an imbricating closure of the defect may be performed. Most central anterior defects require a more extensive dissection of the vesicovaginal space. Following this dissection, many surgeons separate the vaginal mucosa and submucosal layers from the fibromuscular layer out to a point lateral to the defect, followed by midline plication of this tissue, then excision of excess epithelium, and closure (79–84). It appears important to maintain the continuum of repaired fibromuscular tissue to a well-supported vaginal apex. If the repair is being performed simultaneously with a vaginal apical suspension, the anterior colporrhaphy is typically performed after the apical support sutures have been placed and prior to tying them down. The dissection is carried out starting from the everted vaginal cuff edge and dissecting toward the bladder neck. A high central defect may be corrected via a transabdominal approach by dissecting between the base of the bladder and the upper one-third of the anterior vaginal wall. The defective tissue may be wedged out and the defect closed with running or interrupted sutures. This approach may be of use when performing transabdominal procedures for apical suspension.

If the patient has significant stress incontinence (based on report or the presence of occult or potential incontinence), an appropriate incontinence procedure may be performed simultaneously with the anterior repair. When performing midurethral sling procedures, it is not preferable to extend the repair procedure distal to the bladder neck, but instead to make a separate incision for the sling. If the patient has voiding dysfunction (reports of incomplete emptying and a high-residual urine) and stress incontinence, appropriate urodynamic evaluation should be performed before a procedure is selected, and the patient should be made aware of the potential for continued problems after surgery (84).

Recurrence rates of traditional "fibromuscular plication" anterior repairs vary from 3% to 92%; however, studies define recurrence in numerous ways, from minimal prolapse to stage III descent (79–85). The clinical significance of recurrent mild cystoceles (stage I) that are asymptomatic is debatable because many of these defects do not progress to larger ones. When traditional anterior repairs are performed in patients with POP-Q stage II or greater cystoceles (frequently concurrently with other procedures), a 20% recurrence rate of stage II or greater prolapse is not uncommon, although overall recurrence rates as low as 3% have been reported (82). Many studies do not define how the participants were evaluated postoperatively and vary with

respect to patient populations, type and severity of defects, presence of concurrent defects, surgical technique, and follow-up time and length. Some studies have suggested higher recurrence rates when these repairs are performed concurrently with sacrospinous suspensions and hypothesize that this type of apical suspension may predispose the repaired anterior wall to greater pressure transmission (86). These studies may show higher failure rates because patients having such concurrent repairs may be more likely to have more complicated forms of prolapse or more extensive pelvic floor defects than other patients.

Paravaginal Repair

The paravaginal or "lateral defect" repair involves reattachment of the anterior lateral vaginal sulcus to the obturator internus fascia and, in some cases, muscle at the level of the arcus tendineus pelvis ("white line"). It is usually performed as a bilateral procedure via transvaginal or retropubic (abdominal or laparoscopic) access. The procedure essentially restores normal anatomy; however, because it is not practical to rebuild the defective endopelvic–fascial bridge to the pelvic sidewall, it attaches the vaginal wall. Observational studies have reported good success with this procedure (80% to 95%); however, long-term data on durability and function are lacking (15,87,88). Most women with anteriolateral detachments usually have separation of the upper vaginal fornices from the arcus tendineus immediately adjacent to the ischial spine **(Fig. 30-13)** (89). Thus, it is important to resuspend those specific areas.

It is difficult to achieve optimal results when the paravaginal repair is used in combination with traditional central repairs because of the creation of tension on opposing suture lines. A repair that removes a weakened central vaginal wall may decrease the side-to-side dimensions of the anterior vaginal wall, making it difficult to suspend its lateral points more laterally. When large central defects coexist with lateral defects, one option is an extensive central repair accompanied by an apical support procedure. This changes the shape of the vagina to a more cylindrical structure. Another choice is placement of a graft to span the entire anterior rhomboid-shaped plate, thus augmenting anterior paravaginal tissue strength. The graft with tension adjusted may be anchored to the arcus tendineus along with the adjacent vaginal wall from the level of the pubic rami to the ischial spine (88).

Although most reports indicate that repair of anterior defects with all of these procedures relieves symptoms directly related to prolapse, there are very few data on patient satisfaction and quality-of-life improvement over time (88).

The Posterior Compartment

As with the anterior compartment, restoring apical compartment support frequently corrects posterior compartment prolapse.

Traditional Posterior Colporrhaphy

The first description of the **posterior colporrhaphy** involved plication of the pubococcygeus muscles across the anterior rectum and perineal body reconstruction (90). The technique has subsequently been modified in attempts to preserve sexual function. Typically, a midline incision is extended from the perineal body to the vaginal apex or to the cephalad border of a small or distal rectocele. **The Denonvillier fascia is mobilized from the vaginal epithelium, leaving as much of this tissue as possible attached laterally to the levator fascia. After obvious defects in the rectal muscularis are repaired, the fascia is plicated in the midline with interrupted or continuous sutures.** The authors prefer delayed absorbable sutures for this plication. Permanent nonbraided suture material can be used. Braided permanent suture material is associated with a greater incidence of stitch infection and formation of granulation tissue (91). The vaginal epithelium is trimmed and closed with absorbable sutures.

When a defective perineal body or perineal membrane is present, reconstruction is performed after accompanying posterior colporrhaphy. The superficial muscles of the perineum and bulbocavernous fascia are plicated in the midline and the skin closed as in an episiotomy repair. Detachments of the inferior portion of the Denonvillier fascia from the perineal body are corrected. The puborectalis muscles are plicated concurrently with these procedures by some surgeons, but this approach is associated with a high incidence of sexual dysfunction and thus is not recommended routinely (91). It may be worth consideration in patients who have severe prolapse accompanied by a large genital hiatus with palpable levator weakness or who are unable to contract their pelvic floor muscles. Sutures should be placed carefully through the puborectalis muscles at least 3 cm or greater posterior to their insertion on the pubic rami, thereby decreasing the tension of the plication. For those women with an enlarged hiatus and weakened puborectalis muscles who desire sexual function, an attempt can be made to plicate the muscles far enough posteriorly to allow two fingers to easily pass through the vaginal introitus and to reconstruct the distal posterior vagina and perineum, whereby there will not be a ledge at the site of the puborectalis plication (91). Outcome data on such procedures are inadequate to make conclusions regarding its efficacy; however, it is reasonable to postulate that pelvic floor defects producing an enlarged genital hiatus are common reasons for failure of support procedures, and puborectalis plication may decrease the incidence of such failures.

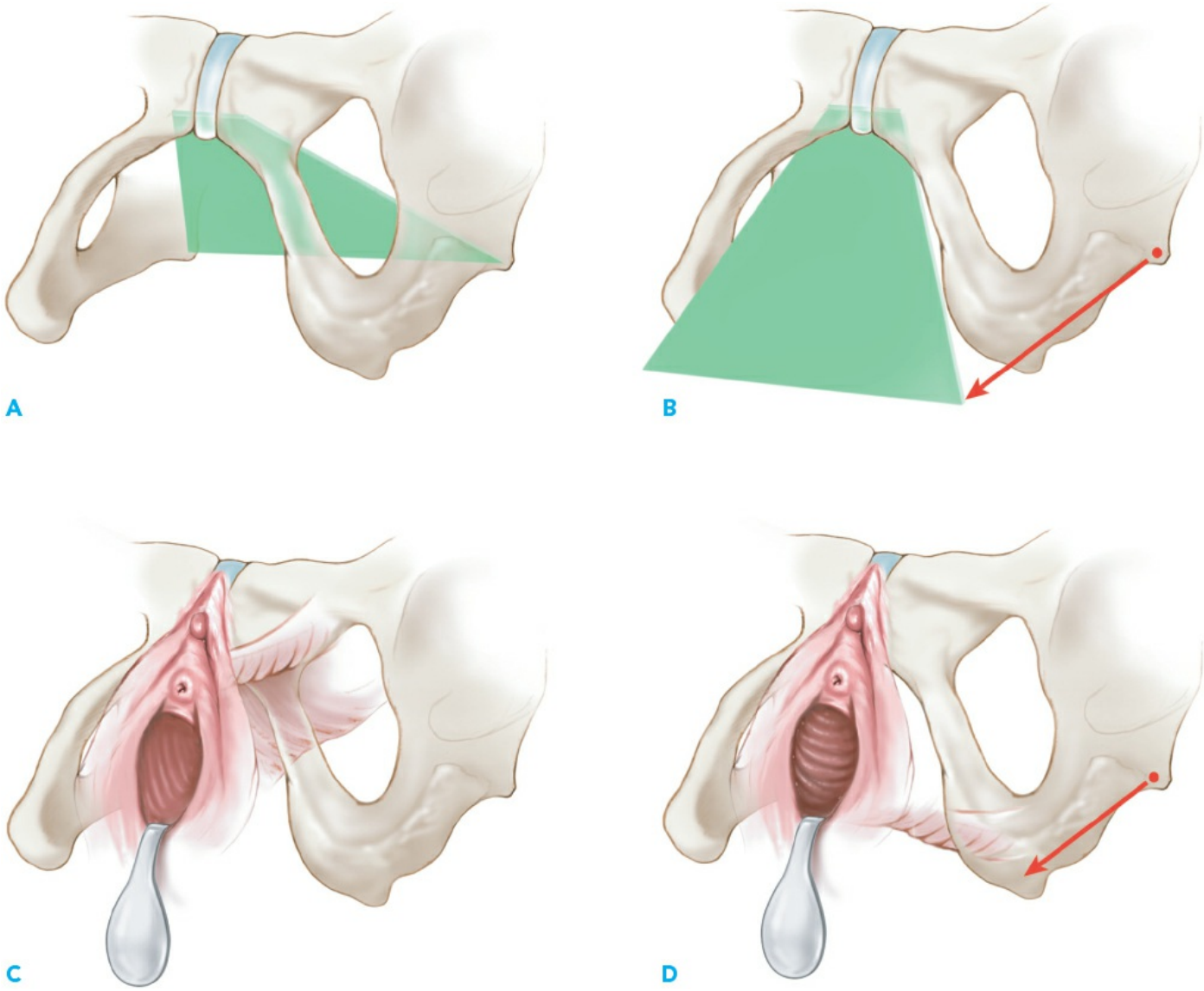


FIGURE 30-13 Schematics illustrating normal attachments of the anterior fibromuscular vaginal plane (**A** and **C**) and bilateral detachments of that plane from the arcus tendineus up to the level of the ischial spines (**B** and **D**). Note: For **B** and **D** to occur, there will either be concurrent apical descent or a detachment of the upper fibromuscular plane from the apical structures. (From **Delancey JO.** Fascial and muscular abnormalities in women with urethral hypermobility and anterior vaginal wall prolapse. Am J Obstet Gynecol 2002;187:93–98, with permission.)

A complete review of rectocele, anorectal functional disorders, and various repairs can be found elsewhere (92). Reported anatomic cure rates for traditional posterior colporrhaphy have ranged from 76% to 90% with variable follow-up intervals (93–96). Most studies show a benefit in ease of defecation if patients are using splinting preoperatively; however, overall defecatory dysfunction (defined as constipation) was not relieved in most patients and increased (approximately 30%) after the procedure in one study (94). These repairs appear to have little to no benefit in the treatment of fecal incontinence. It is not surprising that the repairs are not particularly effective for defecatory dysfunction related to disorders of constipation or for fecal incontinence

because these problems have multifactorial causes. ***De novo*** **dyspareunia is reported to occur in 8% to 26% of sexually active patients who have traditional posterior colporrhaphy** and is not always associated with levator plication procedures (94,95,97). Potential causes for dyspareunia, other than vaginal strictures or introital tightness, include scarring with immobility of the vaginal wall, levator spasm, and neuralgia associated with sutures or dissection. Dyspareunia may occur when a Burch procedure or other procedures that anteriorly displace the vaginal canal are combined with a posterior repair (95). Careful surgical technique and appropriate choice of procedure should decrease the incidence of postoperative dyspareunia.

Defect-Specific Posterior Repair

Defect- or site-specific posterior repairs are restorative procedures by which posterior defects are corrected. These repairs begin with midline posterior vaginal incision through the epithelium and continue with separation of the epithelium from the fibromuscular wall. After irrigation to provide better exposure, a finger is inserted into the rectum to help define defects of the rectal wall and the fibromuscular layer that has been dissected from the vaginal wall submucosa. The specific defects are closed with either interrupted or running sutures (preferably the delayed absorbable type). Defect closure is accomplished in such a way as to minimize tension on the surrounding tissue and may involve vertical, horizontal, or oblique approximation. When fibromuscular tissue has separated from the perineum, the upper anterior rectum, or a well-supported cervix or vaginal cuff, it is important to reapproximate these connections. Repairs of coexistent perineal and apical support defects are important. **The object of the surgery is to reestablish an intact plane of connective tissue that positions the rectum against the pelvic floor and obliterates any potential space between a well-supported cervix or vaginal cuff and the cephalad edge of the tissue plane and upper rectum.** The technique should minimize tension and potential strictures, which may be more likely to occur with traditional posterior colporrhaphy (96).

Initial case series reveal anatomical cure rates with mean follow-up times less than 18 months from 82% to 100% and *de novo* dyspareunia rates of 2% to 7%, which are much lower than those seen with traditional repairs (97–100). Symptom relief appears to be as good as that seen with traditional repairs. The greatest concern with these and other procedures has been durability. A recent report indicates that the recurrence rate of rectocele beyond the midvaginal plane was higher with defect-specific posterior repairs than with side-to-side plication procedures using laterally attached fascia pulled to the midline (33% vs. 14%) and beyond the hymenal ring (11% vs. 4%) (96). The study was not randomized; however, the procedures were performed during the same period with consistent follow-up evaluations 1 year after surgery. Symptoms (dyspareunia, constipation, and fecal incontinence) after surgery did not differ between the two groups. Long-term follow-up of previously reported case series that had good

short-term success or prospective randomized trials looking at modifications of traditional repairs versus defect-specific repairs should clearly delineate durability of these procedures.

Transanal Posterior Repair

The aim of transanal rectocele repair, usually performed by colorectal surgeons rather than gynecologists, is to remove or plicate redundant rectal mucosa, to decrease the size of the rectal vault, and to plicate the rectal muscularis. The rectovaginal adventitia and septum are plicated as well, probably along with the posterior vaginal muscularis. The vaginal epithelium is not incised or excised with this procedure, which probably accounts for the reported lack of adverse effects on sexual function in contrast to the vaginal approach to posterior repair. Complications included infections and rectovaginal fistulas, which are rare. Transanal posterior repair should be considered mainly for defecatory dysfunction and not for prolapse of the posterior vaginal wall. The literature, including three randomized controlled trials, suggests that a vaginal approach is more effective than a transanal approach. The failure rate was 10% versus 42% (relative risk 0.24, 95% CI, 0.09–0.64). In addition, the vaginal approach resulted in superior anatomic results. The risk of *de novo* dyspareunia was similar in both approaches (101).

Transvaginal Mesh Procedures

Transvaginal mesh procedures use "bridging material to reinforce native structures" (102). The patient's own connective tissue may grow into the graft, and, if the graft is degradable, replace the graft as a supportive structure. An ideal graft material should be: (i) nonantigenic; (2) exhibit a low infection rate; (3) decrease or negate recurrence of anatomic defects; (4) cause no harm with respect to bowel or renal function; and (5) be relatively inexpensive. Graft materials include autologous tissues, cadaveric allografts and fascia, dermis and other connective tissues, xenografts from animal sources, and various synthetic materials. Allografts and xenografts are treated with processes to remove living cells, thus negating their antigenic potential and allowing them to serve as a temporary connective tissue scaffold. It is assumed that fresh, autologous grafts work similarly; however, there may be some fibroblast survival in fresh harvested tissue. Autologous grafts have limitations in size and shape compared with tissue taken from cadaveric or animal sources. Synthetic grafts are permanent and, as long as the tissues to which they are secured retain their position and strength, they should be durable. **Autografts, allografts, and xenografts depend on adequate tissue growth from the subject and may have higher failure rates than synthetic ones. Synthetic grafts are more subject to exposure and erosion. Graft exposure/erosion may produce bothersome discharge, pain, and sexual dysfunction with vaginal scarring. Monofilament and large pore size grafts (type 1) are the only synthetic-**

type mesh available in the United States (103–110). **In addition to exposure and erosion, other mesh-related complications can result from a potential injury to pelvic structures during mesh augmentation surgeries. Pelvic pain, a potential complication of mesh placement, can be related to mesh exposure or erosion. Given the unique complication related to synthetic mesh, POP surgery using synthetic graft should be limited to** high-risk patients when the benefit of vaginal mesh augmentation is greater than the risks involved. The high-risk population includes women with recurrent prolapse (anterior or apical) or poor candidates for prolonged, more invasive, surgery, such as abdominal and laparoscopic approaches (111).

Midurethral sling procedures that use such mesh have reported exposure rates of 1% to 2%; however, a wider range of exposure rates (2% to 19%) have been reported with synthetic mesh augmentation for POP repair (106–110,112). Level I data regarding the consensus on treatment approaches for mesh exposure are lacking. Thus, management guidelines are based on expert opinion, clinical experience, and data from observational studies. The treatment should be tailored based on the individual's symptoms and examination findings. Asymptomatic exposures of type 1 meshes can be managed expectantly with close observation. If the exposure is small, typically less than 5 mm, a trial of vaginal estrogen is reasonable, typically 6 to 12 weeks. In case of a large mesh exposure, having persistent symptoms, such as vaginal bleeding, discharge, infections, or protracted pain, mesh revision/removal should be considered. A multicenter trial reported that 60% of women with mesh complications after POP surgery required at least two interventions; nearly half of these women underwent surgery as the first intervention (113). As pain after mesh augmentation is typically multifactorial, it often requires multidisciplinary approach including conservative management with pelvic floor physical therapy, trigger-point injections, and/or medications. Surgical management for pain after mesh augmentation can alleviate symptoms. Prior to surgery, the goals and expectations of surgery should be discussed with the patients as pain may persist after mesh removal.

An exposed polypropylene graft may be removed with the surrounding tissue to the point where there is good tissue growth into the graft, and the defect can be closed. Graft erosion into the bladder, urethra, or rectum is less common than into the vagina. When erosion occurs, management is more difficult and long-term adverse effects more common. Numerous surgeons have been reticent to use synthetic graft materials to augment paravaginal fibromuscular connective tissue support because of complications from erosion. There remains a need for long-term follow-up on patients who have repairs with graft material, to assess anatomical results and complications, including subsequent sexual function, presence and absence of pain, and patient satisfaction. A Cochrane Review noted that low-to-moderate–quality evidence reflects advantages of using transvaginal permanent mesh compared to native tissue repair, including lower awareness of prolapse, repeat surgery for prolapse, and objective prolapse recurrence.

However, there are risks of repeat surgery for mesh exposure (114). The U.S. Food and Drug Administration (FDA) has issued two final orders on surgical mesh for transvaginal POP repair (January 2016), including the reclassification of the synthetic mesh from class II to class III ("high-risk" devices) and requiring manufacturers to submit a premarket approval (PMA) application to support the safety and efficacy of surgical mesh for transvaginal POP repair. It is important to make the distinction between synthetic meshes for transvaginal prolapse surgery and midurethral slings for SUI as the latter (full-length midurethral sling) remain class II devices and do not require a PMA (115). The American Urogynecologic Society released guidelines for transvaginal and abdominal placement of surgical mesh for POP. These guidelines emphasize the importance of informed consent including potential benefits and complications of the approach (unique complications related to mesh placement), alternative options, including nonsurgical, and specialized training to acquire surgical skills ensuring patient safety and the ability to recognize and manage intraoperative and postoperative complications (116,117).

In summary, transvaginal mesh procedures utilize predominantly synthetic polypropylene mesh. This material may reduce recurrence of POP and is associated with some risk of vaginal mesh extrusion and chronic pain or dyspareunia. Patients should be counseled extensively about the risks and benefits of the use of mesh augmentation. Surgeons who use synthetic mesh should carefully follow their patients to identify complications.

Abdominal Procedures

Abdominal Uterosacral Suspension

Abdominal uterosacral colposuspension has been used prophylactically after hysterectomy and therapeutically for apical prolapse with cardinal/uterosacral defects (118). It can be performed through laparotomy incisions or by laparoscopic techniques. For the therapeutic procedure, a no. 1 polypropylene or delayed absorbable suture is placed cephalad and at the same level posterior as the ischial spines, which may be palpated transabdominally or with a vaginal finger to push a vaginal fornix to the spine under observation with a laparoscope. One technique is to place one or two permanent sutures through one ligament, then, after reefing across the cul-de-sac peritoneum at the sigmoid border, through the contralateral ligament, and through the fibromuscular tissue just anterior to the vaginal cuff. Tying the suture suspends the vaginal cuff and obliterates any enterocele defect. Another technique employs separate sutures placed at the same level into each uterosacral ligament and anchored anteriorly and posteriorly to the ipsilateral side of the vaginal cuff, similar to procedures performed transvaginally. Cystoscopy is performed after the procedure to document

ureteral patency. One study found subjective and objective recurrence rates to be low (12% and 5%, respectively) (118).

Abdominal Approach to Posterior Repair

When abdominal sacrocolpopexy is planned for apical vaginal prolapse and concomitant rectocele is present, some have advocated extending the posterior graft down the posterior vaginal wall to correct the defect. The technique of sacral colpoperineopexy is used to replace the normal vaginal suspensory ligaments and to augment or replace the posterior fibromuscular plane with graft material that runs from the sacrum to the perineal body (119). Its purpose is to correct the posterior compartment defects and to suspend the perineal body, thus preventing descent and opening of the genital hiatus.

Laparoscopic Approach to Posterior Repair

Laparoscopic rectocele repair involves the dissection of the rectovaginal space to the perineal body with either plication of levator fascia or suturing absorbable or permanent mesh in place (120). A few small case series have been reported with variable results.

Abdominal Sacrocolpopexy

These procedures use graft material attached to the prolapsed region of the anterior and posterior vaginal walls at or encompassing the vaginal apex and suspended to the anterior longitudinal ligament of the sacrum. Cervical sacral suspensions may be performed when uterine or cervical conservation is desired. Surgical variations abound and include configuration of the graft on the vagina, the extent to which the anterior and posterior vagina are attached to the graft, variable graft and suture materials, presence or absence of peritoneal closure over the graft, and obliteration of the cul-de-sac for treatment or prevention of the enterocele or sigmoidocele. **A thorough preoperative evaluation is important to exclude more distal defects or stress incontinence, which should be repaired concurrently, and other lower urinary tract or anorectal problems.** In published reports, cure rates for apical prolapse range from 78% to 100% (most greater than 90%); when cure is defined as no postoperative prolapse, the range widens from 56% to 100%, although subsequent anterior or posterior vaginal prolapse has not been as consistently reported as has apical prolapse (121–123). Potential advantages of this procedure over transvaginal procedures are less paravaginal scarring and denervation than may be present with transvaginal approaches, and fixation of the entire vaginal apical area by a permanent piece of material to a stable structure (the anterior sacral ligament), which may be more durable than transvaginal techniques that use the patient's own connective tissue. Long-term outcomes of abdominal sacrocolpopexy with or without concomitant urethropexy have been described and are notable. Estimated probabilities of treatment failures for anatomic POP were 0.27 and

0.22 for the urethropexy and no urethropexy groups (treatment differences, 0.05, 95% CI, –0.161 to 0.271). Mesh erosion probability at 7 years was 10.5% (95% CI, 6.8, 16.1) (124).

Complications of these procedures include: (1) erosions of graft material or suture material, which may be caused by graft or suture infection usually secondary to vaginal wall penetration, or performing the procedure adjacent to a vaginal incision, or securing the graft to an attenuated avascular wall with inadequate fibromuscular tissue (3.4%); (2) significant intraoperative hemorrhage (especially in the presacral space) (4.8%); (3) postoperative ileus, which may be secondary to the need for excessive packing of the bowel or to extensive Halban or Moschcowitz culdoplasty procedures (3.6%); (4) small bowel obstruction, requiring reoperation (1.1%); (5) development of intra-abdominal adhesions with resultant pain and bowel dysfunction (unknown incidence); and (6) wound complications, such as seromas and infections (4.6%) (120).

Several management techniques have been advocated to minimize these problems. Empiric ways to prevent graft erosions include: (1) preoperative tissue optimization with vaginal administration of estrogen and treatment of vaginitis and infection of eroded areas; (2) the use of small-gauge monofilament sutures placed in the fibromuscular tissue, thus avoiding full-thickness passage; and (3) excision of a portion of the vaginal apex when the vaginal wall is thin and depleted of its fibromuscular layer and vascularity. Graft attachment to "healthy" fibromuscular tissue rather than to thin avascular tissue should help prevent erosion. **If such excision is necessary, or if the suspension is to be performed concurrently with a hysterectomy, good approximation of the fibromuscular layers above the mucosa, thorough irrigation, prophylactic use of antibiotics, and avoidance of graft placement across the suture line may decrease the likelihood of graft erosion. Choice of graft material may be important.** One would expect synthetic grafts to have greater durability than tissue grafts; however, erosion rates are more serious with the synthetic grafts. Less porous graft material, such as GORE-TEX, has a greater likelihood of becoming infected and eroding than do macroporous, filamentous polypropylene meshes. Numerous case series report serious episodes of hemorrhage from the presacral venous plexus (mean incidence 4.8%; range 0.18% to 16.9% of sacrocolpopexies requiring, at a minimum, transfusion) (121). This problem is less likely if dissection and graft fixation is limited to the level of S1 and S2 just caudad to the promontory and with the use of good light and meticulous dissection techniques to expose the anterior sacral ligament.

Careful tissue handling and packing technique may minimize postoperative ileus and adhesions. Incorporation of the sigmoid into a closure of the cul-de-sac posterior to the graft may slow bowel function postoperatively. Small bowel obstruction has resulted from direct adhesive processes involving grafts to small bowel (120). Complete extraperitonealization of the graft using flaps of peritoneum

dissected from the prolapsed area and the peritoneum anterior to the sacral promontory and lateral to the right side of the sigmoid colon should prevent this complication. However, loops of bowel have been seen to prolapse through small defects in peritoneal closure with the same effect. Careful technique with adherence to basic surgical principles may help prevent this and other complications related to laparotomy.

Laparoscopic and Robotic Techniques

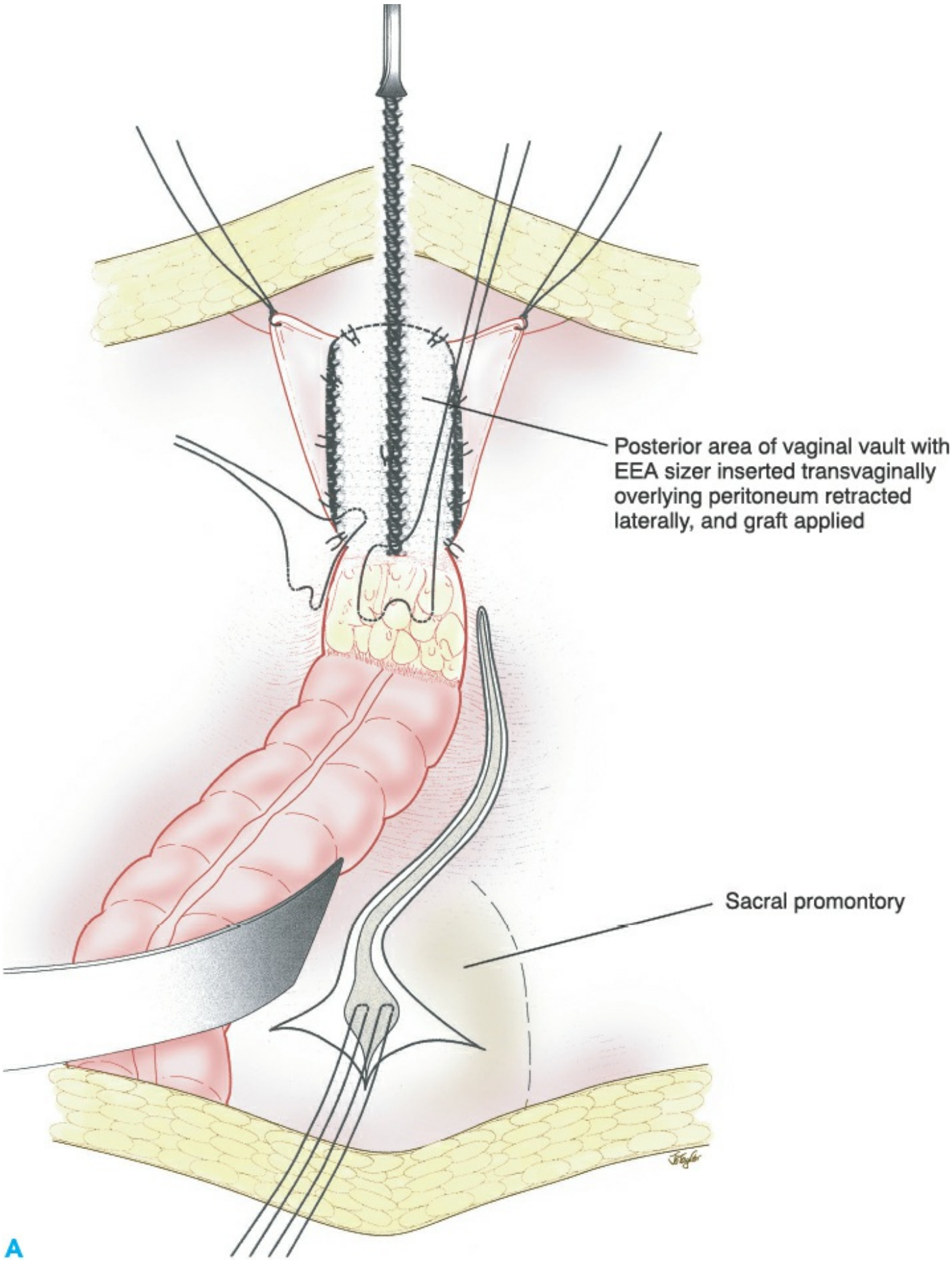
As with most pelvic operations, sacrocolpopexy has been successfully accomplished by the laparoscopic and robotic route and has the potential to offer patients the benefits of less postoperative discomfort, faster recovery and potentially lower risks for adhesions and ileus. Outcomes depend on the expertise and experience of the surgeon; "cutting corners" to shorten the procedure could affect anatomical success. The applicability of the laparoscopic technique is limited by the need for a relatively high level of technical skill. The authors have found that straight self-righting–needle drivers and nonself-righting–curved needle drivers are useful in attaching the mesh to the vagina. The Carter–Thompson suturing device is sometimes helpful to aid in elevating the sigmoid colon away from the pelvic cul-de-sac by tagging the peritoneal edge. The robot has provided an easier platform for a minimally invasive approach to the sacrocolpopexy. It has been noted that clinical outcomes of prolapse repair are similar with robotic-assisted laparoscopic sacrocolpopexy versus laparoscopic alone however the robotic approach may be less efficient with respect to cost (125,126). **For sacrocolpopexy, whether through laparotomy or laparoscopy, the pelvis should be completely exposed with the lower sigmoid colon stretched cephalad (Fig. 30-14)**.

1. With a vaginal obturator (an EEA sizer) placed vaginally to visualize the area that is not covered by the bladder or rectum, the peritoneum is dissected from the underlying vaginal fibromuscular layer anteriorly to bladder reflection and posteriorly at least to the level of the sigmoid rectal junction, creating bilateral peritoneal flaps. Laterally, vascular bundles are visible.
2. Two separate loosely woven polypropylene mesh grafts are shaped similar to boat paddles. Alternatively, a prefabricated "Y-shaped" mesh graft may be used. The "paddle" portions are shaped to cover the areas anterior to the apex and posterior to the apex, respectively, and the long sacral tail (or "handles" if using 2 separate grafts) is anchored to the anterior sacral ligament. The paddle portions are affixed circumferentially to the anterior and posterior vaginal fibromuscular layers with six to eight monofilament sutures and one or two sutures placed centrally **(Fig. 30-14A)**.
3. When the fibromuscular tissue in the area is attenuated, a portion of the vaginal wall is excised and closed. The graft should not be attached to the closure line.
4. The peritoneum overlying the sacral promontory is incised while retracting the sigmoid colon to the left. Careful dissection is employed to expose the anterior

longitudinal ligament. Care is taken to stay medial to the right ureter and hypogastric vessels. Hemoclips are placed caudad and cephalad on the middle sacral vessels if it is felt that this will allow more optimal suture placement. The peritoneal incision is extended into the cul-de-sac area to the right to the sigmoid aimed at the posterior vagina.

5. Closure of the cul-de-sac lateral to the sigmoid on the left and approximation of the distal presigmoid fat to the distal edge of the posterior graft is accomplished with box stitches of 0-delayed absorbable sutures. It is thought that these procedures and the retroperitonealization of the graft through the right side of the cul-de-sac will prevent posterior enterocele and sigmoidocele as well as a Halban or Moschcowitz procedure.
6. The two "handle" ends of the graft are then brought to the point of sacral attachment, where their length is adjusted to remove any tension on the vaginal sutures and secured to the anterior longitudinal ligament with 2 to 3 monofilament sutures **(Fig. 30-14B)**.
7. Reperitonealization of the graft is performed using the right cul-de-sac peritoneum and peritoneal flaps dissected from the vaginal apical area.

Following this procedure, adjunctive procedures, such as paravaginal repair, Burch procedure, midurethral sling, and any transvaginal procedure that is indicated, are performed. When rectocele and pelvic floor defects are present, one option is the sacral colpoperineopexy, as discussed in the posterior compartment section. A vaginal pack is inserted to ensure that the graft is well applied to the fibromuscular layer at points other than where sutures are placed.


Posterior area of vaginal vault with EEA sizer inserted transvaginally overlying peritoneum retracted laterally, and graft applied
Sacral promontory
A

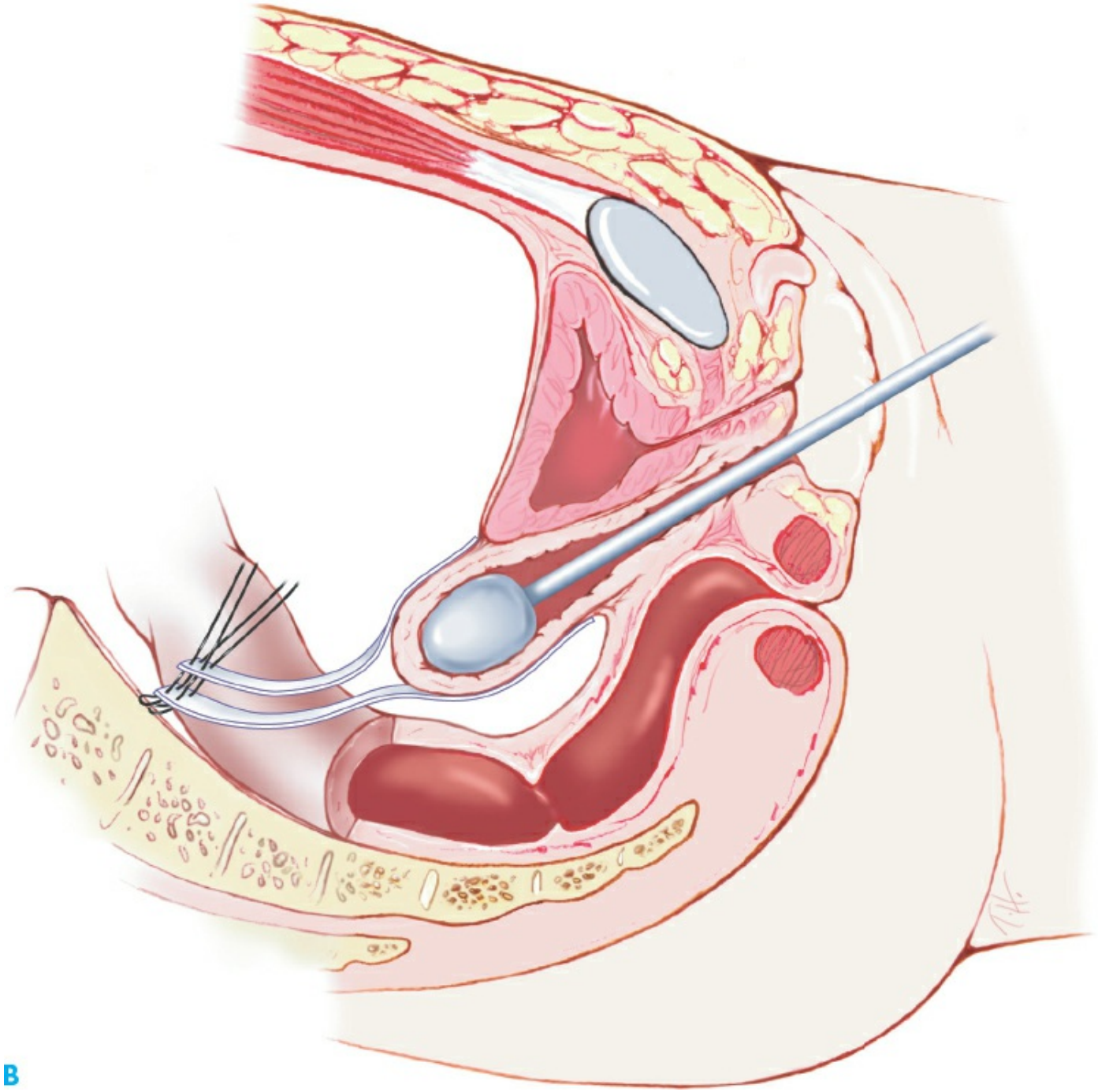


FIGURE 30-14 Sacrocolpopexy. **A:** Illustrates (1) graft attachment to the posterior area of prolapsed vagina to or below the rectal–sigmoid junction after the overlying peritoneum has been dissected and flapped laterally; and (2) exposure of the presacral space with suture placement through the anterior sacral ligament. An appropriately shaped second graft is placed anteriorly. **B:** Illustrates attachment of both grafts without tension to the sacrum. Prevention of subsequent enterocele and/or sigmoidocele is accomplished by box closure of the cul-de-sac peritoneum lateral to the left side of the sigmoid, attachment of the presigmoid fat to the graft centrally, and reperitonealization of the graft through the right side of the cul-de-sac. EEA, end-to-end anastomosis sizer. (Redrawn by J. Taylor.)

Vaginal Obliterative Procedures

Colpocleisis or vaginal narrowing procedures may be appropriate choices for debilitated patients who do not desire vaginal function, because complete vaginal reconstructive procedures take longer and are associated with potentially higher blood loss and increased morbidity. Obliterative surgery does not appear to alter body image, and regret after the procedure is rare (127,128). Many variations exist, from partial colpocleisis (where some portion of the vaginal epithelium is left to provide drainage tracts for cervical or upper genital discharge) to total colpectomy (where all of the vaginal epithelium is removed from the hymen posteriorly to within 0.5 to 2 cm of the external urethral meatus anteriorly). If hysterectomy is performed, blood loss is greater and operative time is longer than procedures without hysterectomy (129). These techniques should include a high perineorrhaphy and often a plication of the puborectalis muscles to reinforce posterior support and to reduce the genital hiatus, with the goal of decreasing the chance of recurrent prolapse. Case series have reported success rates as high as 100%, although the population of patients, by nature of their relatively short-life expectancy and limited activity, are probably at lower risk for recurrence. In some instances, in which most of the defects are anterior and posterior, a modified anterior and posterior colporrhaphy may be performed, whereby relatively large portions of the anterior and posterior vaginal wall are removed and closed, creating a narrow (1 to 2 cm diameter) cylindrical vagina. As with the colpocleisis, the success of the procedure is augmented by an extensive perineorrhaphy and puborectalis plication. Such a procedure may be performed quickly and with relatively low morbidity. The prevention or treatment of stress incontinence, voiding dysfunction, and colorectal dysfunction in the context of these procedures can be problematic. Careful preoperative history and evaluation, if indicated, is important so that additional conservative therapies or operative techniques such as midurethral slings may be employed.

Management of Urinary Symptoms With Pelvic Organ Prolapse Repair

All women who are undergoing surgery for repair of POP should be evaluated for urinary incontinence. Women who report SUI and who demonstrate it on preoperative examination and have no contraindications to a continence procedure should have concomitant procedures for the treatment of these symptoms. The management for women with symptomatic prolapse but without symptoms of SUI is challenging, especially those with advanced prolapse. Surgeons often perform a reduction stress test to finalize the surgical plan. The literature supports a continence procedure at the time of surgery regardless of preoperative prolapse reduction stress test (the “universal” approach) for women with stage II to IV prolapse undergoing abdominal sacrocolpopexy as reported in the Colpopexy and Urinary Reduction Efforts (CARE) trial (130). The best approach for the management is more controversial in women undergoing vaginal prolapse surgery without SUI symptoms. A randomized

controlled trial, the Outcomes Following Vaginal Prolapse Repair and Midurethral Sling (OPUS) trial, showed similar outcomes to the CARE trial, where the rates of *de novo* SUI were lower in women having a concomitant midurethral sling procedure. However, the sling group had higher rates of complications including bladder perforation, UTI, bleeding, and transient postoperative voiding dysfunction. The rate of *de novo* SUI was higher in women with occult SUI demonstrated on preoperative reduction stress test (131). Based on these data, surgeons often prefer a selective approach, where a concomitant continence procedure is suggested if occult SUI is detected on reduction stress test.

Comparison of Abdominal Versus Vaginal Approaches

There has been controversy as to whether transvaginal or transabdominal procedures are better for prolapse. One should not discern which is optimal from reports of retrospective and prospective case series because of the considerable differences in numerous factors, including follow-up, characteristics of the subjects, definitions of success and failure, and the expertise or experience of the surgeons performing the procedures.

A recent meta-analysis comparing abdominal sacrocolpopexy to transvaginal apical repairs, mostly sacrospinous ligament fixation, concluded that sacrocolpopexy is likely to result in lower rates of "bulge" symptoms and recurrent prolapse. However, the quality of evidence included in the analysis ranged from low to moderate (132). The abdominal approach resulted in longer procedure times and greater delay in resumption of activities, higher-associated costs. Although rare, the intraperitoneal access can result in potential serious adverse events including bowel injury and sacral osteomyelitis. Transvaginal surgery is the most commonly performed approach for POP repairs in the United States, given the minimally invasive nature of the surgery, and the ability to address all three vaginal components more efficiently than with an abdominal approach. Native tissue vaginal surgery eliminates the risk of mesh-related complications associated with abdominal support procedures, which is important in women at higher risk of mesh exposure or erosion.

Older, less healthy individuals who are more likely to have surgical and medical complications and cannot or will not tolerate a pessary would derive greater benefit from transvaginal approaches and as indicated, obliterative approaches, and relatively healthy, sexually active women with relatively short vaginas and apical prolapse would derive greater benefit from sacrocolpopexy. For the remainder of the patients with apical prolapse, with or without more distal defects, most surgeons choose the approach based on the individual's skills, training, and past experience. High-quality long-term data are urgently needed to better understand and compare the efficacy of each approach. A three-arm randomized controlled trial of three

apical suspension approaches in women with posthysterectomy vaginal vault prolapse is being performed comparing sacrocolpopexy, transvaginal mesh augmentation repair, and native tissue apical repair (ASPIRe trial; NCT02676973).

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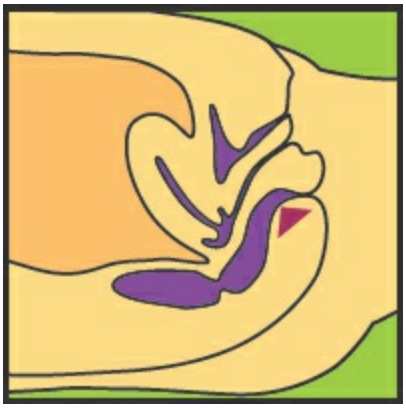
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CHAPTER 31

Anorectal Dysfunction



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Posterior Colporrhaphy
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KEY POINTS

1 Defecatory dysfunction and fecal incontinence are common conditions that have tremendous psychosocial and economic implications.

2 The differential diagnosis for anorectal dysfunction is broad and can be classified into systemic factors, anatomic/structural abnormalities, and functional disorders.

3 A thorough history, physical examination and appropriate ancillary testing are critical for the evaluation of fecal incontinence and defecatory dysfunction.

4 Treatment of anorectal dysfunction should focus on nonsurgical management before surgery, which should be reserved for those with poor response to noninvasive treatment.

5 Sacral nerve stimulation should be considered the procedure of choice for moderate to severe fecal incontinence that does not respond to conservative measures and biofeedback.

6 Overlapping sphincteroplasty is an alternative for patients with a disrupted anal sphincter in whom conservative therapies have failed.

Anorectal dysfunction encompasses a variety of conditions that disrupt normal anorectal function. Such conditions can be subdivided into those that cause constipation (defecatory dysfunction) and those that result in fecal incontinence. The evaluation and treatment of anorectal dysfunction involves the expertise of several medical and surgical specialties, mainly urogynecology-female pelvic medicine, gastroenterology, and colorectal surgery. The pathophysiology, evaluation, and management of conditions relevant to gynecologists are presented in this chapter.

NORMAL COLORECTAL FUNCTION

Anal continence and defecation are complex physiologic processes that require intact and coordinated neurologic and anatomic function. Necessary elements include colonic absorption and motility, rectal compliance, anorectal sensation, and the multifaceted continence mechanism. An understanding of normal physiology and pathophysiology is essential to the treatment of women with anorectal dysfunction.

Stool Formation and Colonic Transit

The colon plays an important role in absorption and regulation of water and electrolytes. **As much as 5 L of water and associated electrolytes can be absorbed in a single day.** The parasympathetic-mediated peristaltic contraction of colonic smooth muscle normally transfers fecal material to the rectum. There is a delay in stool transit at the rectosigmoid region that allows for maximal absorption of water and sodium.

Storage

As stool accumulates in the rectosigmoid, the rectal distention triggers the *rectoanal inhibitory reflex*, a transient decrease in the internal anal sphincter (IAS) tone and an increase in the external anal sphincter (EAS) tone. Exposure of the anal canal to fecal matter facilitates *sampling*, whereby the anal canal and its abundant sensory nerves determine stool consistency (i.e., solid, liquid, or gas). *Accommodation* occurs as the normally compliant rectal vault relaxes in response to increased volume. This cycle, combined with increased rectal distention, stimulates an urge to defecate. This urge can be voluntarily suppressed through cortical control, resulting in further accommodation and activation of the continence mechanism.

Continence Mechanism

Muscles

The key muscles of the continence mechanism are the puborectalis, IAS, and EAS. The paired puborectalis muscles originate from the pubic rami at the level of the arcus tendineus levator ani and pass laterally to the vagina and rectum in a U-shaped configuration, creating a sling around the genital hiatus. Contraction of the puborectalis muscles narrows the genital hiatus, and pulls the rectum anteriorly, producing the near 90-degree anorectal angle. **The resting tone of the puborectalis muscle serves as the primary continence mechanism for solid stool. The IAS and EAS are essential for continence of flatus and liquid stool.** The IAS maintains most of the resting tone for the sphincter complex through autonomic reflex arcs and is essential for passive continence. Although the EAS maintains constant resting tone, it is ultimately responsible for preventing fecal urgency and stress incontinence of stool associated with sudden increases in intra-abdominal pressure. This function is under voluntary and involuntary control. The final anatomic barrier of the continence mechanism is the seal provided by coaptation of the anal cushions occluded by pressure within the hemerrhoidal veins.

Nerves

Denervation is a common pathway for pathologic states to disrupt normal function. **The IAS receives its sympathetic innervation from L5, which passes through the pelvic plexus via the hypogastric plexus.** The parasympathetic supply from S2–S4 synapses at the pelvic plexus, where it joins the sympathetic nerves. In addition to the parasympathetic and sympathetic components, the autonomic nervous system of the gut has an enteric nervous system (ENS). The ENS provides local circuitry that can contract or relax the gut muscles, and impact absorption and secretion. The autonomic ganglia of the ENS, located in the gut, are interconnected to provide local integration and processing of information. The IAS acts through reflex arcs at the spinal cord without voluntary control. The puborectalis (levator ani) is innervated bilaterally by branches of the S2–S4 sacral roots and does not receive direct innervation from the pudendal nerve (1,2). The EAS is innervated bilaterally by the pudendal nerve (S2–S4) via Alcock canal. The pudendal nerve fibers cross over at the level of the spinal cord, allowing preservation of EAS function in the event of unilateral damage. The rich sensory supply from the anal canal travels along the inferior rectal branch of the pudendal nerve.

Evacuation

Initiation of defecation is normally under cortical control. Delivery of stool to the rectum stimulates the rectoanal inhibitory reflex, permitting sampling followed by accommodation. Further rectal distention results in an urge to defecate. Evacuation occurs with voluntary relaxation of the pelvic floor muscles (puborectalis muscle and EAS) in conjunction with increased intra-abdominal and intrarectal pressure from Valsalva. This results in widening of the anorectal angle and shortening of the anal

canal, which facilitates emptying. Coordinated peristaltic activity of the rectosigmoid assists evacuation. After this process is complete, the closing reflex is initiated, resulting in contraction of the pelvic floor muscles and reactivation of the continence mechanism.

EPIDEMIOLOGY

The epidemiology of anorectal dysfunction has been best defined in terms of the incidence and prevalence of fecal incontinence. Few studies have been done to assess the incidence and prevalence of defecatory dysfunction.

Defecatory Dysfunction

The term *defecatory dysfunction* often is used synonymously with the symptom of constipation. ***Constipation*** **is an imprecise term used by patients to report a variety of symptoms, including infrequent stools, dyschezia, straining, variation in stool consistency and caliber, incomplete emptying, bloating, and abdominal pain. The most common symptoms associated with constipation are straining and hard stools** (3). **Defecatory dysfunction is defined by many physicians as infrequent stools, typically fewer than three bowel movements per week.** This definition is based on stool frequency studies in which 95% of women have more than three bowel movements per week. Using this definition, the prevalence of constipation should be 5% (4). However, the prevalence of constipation has been estimated to range from 2% to 28%, depending on the definition applied (5,6).

The prevalence of constipation is higher among women, elderly individuals, nonwhite individuals, and those with low income, and low education levels (3,7). Based on an estimated 2.5 million visits to U.S. physicians per year for constipation (8), the annual cost for evaluation of constipation would be over $7 billion. Direct individual annual costs of chronic constipation range from $1,912 to $7,522 per year (9). An estimated 85% of physician visits result in a prescription; thus, inclusion of drug costs would increase this amount substantially (8). Aside from economic burden, constipation has a detrimental effect on health-related quality of life (QoL), which contributes to the indirect costs of this disease (3,9,10).

Fecal Incontinence

The reported prevalence of fecal incontinence varies between 2% and 3% for community-dwelling individuals, 3% to 17% for those of increased age, and 46% to 54% for nursing home residents (11,12). A prevalence of 28% has been reported among patients seeking benign gynecologic care and 36% of primary care patients

surveyed (13). The prevalence of fecal incontinence in the United States is expected to increase 59% from 10.6 million in 2010 to 16.8 million in 2050 as the population ages (14). Epidemiologic studies of fecal incontinence are compromised by social stigmata and the lack of a uniform definition. **Definitions of fecal incontinence vary with respect to the type of material passed (solid, liquid, or gas), the frequency and duration of events (once in a lifetime to twice a week), and the impact on QoL.** Most authors agree that the true prevalence of this condition is underestimated in the scientific literature (15). A large health survey in the United States found age, female sex, physical limitations, and poor general health to be independent risk factors associated with fecal incontinence (16).

[1] Fecal incontinence has tremendous psychosocial and economic implications for individuals and society as a whole. The loss of such a basic function can be emotionally devastating, leading to poor self-esteem, depression, social isolation, and decreased QoL (12,13,17). Fecal incontinence is the second leading reason for nursing home placement in the United States, even though less than one-third of individuals with this condition seek medical attention (12,17). The overall annual cost to treat fecal incontinence is difficult to pinpoint (17).

SYMPTOM-BASED APPROACH TO COLORECTAL DISORDERS

Several medical conditions cause defecatory dysfunction, fecal incontinence, or combined symptoms. **[2]** The differential diagnosis is organized into a classification system based on systemic factors, anatomic/structural abnormalities, and functional disorders.

Differential Diagnosis

Disordered Defecation

Causes of defecatory dysfunction have traditionally been divided into systemic disorders and idiopathic constipation (all nonsystemic causes). Idiopathic constipation can be subdivided into anatomic/structural abnormalities and functional disorders (Table 31-1).

Diabetes, hypothyroidism, and pregnancy are the most common endocrinologic systemic factors that cause constipation, and all have a component of decreased gastrointestinal motility and intestinal transit. In one study, gastrointestinal symptoms were present in 76% of patients with diabetes, including constipation, which occurred in 60% (18). In patients with diabetes, constipation is believed to be secondary to intestinal autonomic neuropathy, resulting in delayed or absent gastrocolic reflex and decreased bowel motility. This enteric neuropathy may also cause gastroparesis and diarrhea. Although diabetes has been classified with the endocrinologic causes, it

should be grouped with the enteric neuropathies. Pregnancy is not considered a disease state; however, there is an 11% to 38% prevalence of constipation that is believed to result primarily from the effect of progesterone on smooth muscle (19–21). Other contributors to constipation during pregnancy include medication use (e.g., iron, *ondansetron*) and poor oral fluid intake (e.g., dehydration, nausea/vomiting of pregnancy) (21). Postpartum constipation is even more common, likely worsened by pain and discomfort from hemorrhoids and perineal repair (22).

The systemic neurologic factors can be divided into central and peripheral processes. Spinal cord lesions, multiple sclerosis, and Parkinson disease affect the autonomic nervous system. Trauma to the sacral nerves often leads to severe constipation from decreased left-sided colonic motility, decreased rectal tone and sensation, and increased distention. These findings are seen in patients with myelomeningocele, damage to the lumbosacral spine, and pelvic floor trauma (23,24). Higher spinal cord lesions result in delayed sigmoid transit and decreased rectal compliance. In these upper motor neuron lesions, colonic reflexes are intact, and defecation can be initiated by digital stimulation of the anal canal (25). Individuals with multiple sclerosis can have no gastrocolic reflex, decreased colonic motility, decreased rectal compliance, and even rectosphincteric dyssynergia (26). Constipation worsens with the duration of illness and may be compounded by the side effects of medical therapy. Similar findings of rectosphincteric dyssynergia and medication side effects are present with Parkinson disease.

Among the peripheral neurogenic disorders, dysfunction occurs at the level of the ENS. The ultimate example of this is congenital aganglionosis (Hirschsprung disease). The absence of intramural ganglion cells in the submucosal and myenteric plexuses of the rectum causes loss of the rectoanal inhibitory reflex. Patients with this illness usually present with functional obstruction and proximal colonic dilation. In most patients, the condition is diagnosed within 6 months of age, although milder cases can be seen later in life.

Other systemic factors to consider are collagen vascular and muscle disorders. Some of the most commonly used prescription and over-the-counter medications, including aluminum antacids, beta blockers, calcium channel blockers, anticholinergics, antidepressants, and opiates, cause defecatory dysfunction **(Table 31-2)**. Lifestyle issues, such as inadequate fiber intake and insufficient fluid intake, can exert similar effects independently or in conjunction with other disorders.

Structural abnormalities refer to the obstructive disorders, such as pelvic organ prolapse, perineal descent, intussusception, rectal prolapse, and tumors. Functional disorders are those that do not have an identifiable anatomic or systemic etiology. Most functional disorders are motility disorders, such as slow-transit constipation/colonic inertia, irritable bowel syndrome (IBS) (constipation predominant), and functional constipation (FC). The Rome IV Criteria created strict

definitions for these idiopathic conditions (Table 31-3) that are believed to result from the complex interaction of psychosocial factors and altered gut physiology via the gut–brain axis (27). This classification started as a somewhat arbitrary system, as several of these conditions are interrelated, however evidence-based adjustments have been made (28).

Table 31-1 Causes of Defecatory Dysfunction and Fecal Incontinence

Fecal Incontinence		Defecatory Dysfunction
	Systemic Factors	
	Metabolic/Endocrine	
•	Diabetes mellitus	•
•	Thyroid disease	•
	Hypercalcemia	•
	Hypokalemia	•
	Neurologic	
•	Central Nervous System	•
	Multiple sclerosis, Parkinson disease, stroke, tumor, dementia	
•	*Peripheral Nervous System*	•
	Hirschsprung disease, spina bifida, autonomic neuropathy, pudendal neuropathy	
	Infectious	
•	Bacterial, viral, parasitic diarrhea	
	Collagen Vascular/Muscle Disorder	
	Systemic sclerosis, amyloidosis, myotonic dystrophy, dermatomyositis	•
	Idiopathic/Autoimmune	
•	Inflammatory bowel disease	
•	Food allergy	
	Medications	
•	Prescription, over the counter	•

	Anatomical/Structural Abnormalities	
	Pelvic Outlet Obstruction	
•	Pelvic organ prolapse	•
•	Descending perineum syndrome	•
	Anismus/rectosphincteric dyssynergia	•
•	Intussusception, rectal prolapse	•
	Volvulus	•
•	Neoplasia	•
•	Benign strictures	•
•	Hemorrhoids	•
	Anal Sphincter Disruption/Fistula	
•	Obstetrical trauma	
•	Surgical trauma	
•	Anal intercourse	
•	Injury (trauma, radiation proctitis)	
	Functional	
	Motility Disorders	
	Global motility disorder	•
	Colonic inertia/slow-transit constipation	•
•	Irritable bowel syndrome	•
	Functional constipation	•
•	Functional diarrhea	
	Functional Limitations	
•	Decreased mobility	•
•	Decreased cognition	•

Table 31-2 Drugs Associated with Constipation

Over-the-Counter Medications	
Antidiarrheals (loperamide, Kaopectate)	

Antacids (with aluminum or calcium)	
Iron supplements	
Prescription Medications	
Anticholinergics	*Others*
Antidepressants	Iron
Antipsychotics	Barium sulfate
Antispasmodics	Metallic intoxication (arsenic, lead, mercury)
Antiparkinsonian drugs	Opiates
Antihypertensives	Nonsteroidal anti-inflammatory agents
Calcium channel blockers	Anticonvulsants
Beta blockers	Vinca alkaloids
Diuretics	5-HT_3 antagonists (ondansetron, granisetron)
Ganglionic blockers	

Fecal Incontinence

Fecal incontinence is defined as the involuntary loss of solid or liquid stool. Anal incontinence is defined as the involuntary loss of solid or liquid stool or flatus. Anal continence depends on a complex interaction of cognitive, anatomic, neurologic, and physiologic mechanisms. The continence mechanism can often compensate for a deficiency in one of these processes, but it can be overwhelmed over time with increased severity or decreased function. Systemic etiologies of fecal incontinence often are the result of disease states that cause diarrhea. The rapid transport of large volumes of liquid stool to the rectum can produce urgency and incontinence even in individuals with healthy continence mechanisms (29). Fecal incontinence frequently results from infectious diarrhea caused by bacteria (e.g., *Clostridium, Escherichia coli, Salmonella, Shigella, Yersinia, Campylobacter*), viruses (e.g., Rotavirus, Norwalk, human immunodeficiency virus [HIV]), and parasites (e.g., *Entamoeba, Giardia, Cryptosporidium, Ascaris*). Numerous medications and dietary items cause diarrhea and fecal incontinence (Table 31-4). Endocrine factors that can lead to fecal incontinence include diabetes mellitus and hyperthyroidism. With diabetes, diarrhea can develop from autonomic dysfunction, bacterial overgrowth, osmotic diarrhea with sugar substitutes, and pancreatic insufficiency.

Inflammatory bowel disease is considered an idiopathic/autoimmune systemic factor. Ulcerative colitis and Crohn disease cause fecal incontinence during exacerbations with bouts of bloody diarrhea. Inflammatory bowel disease can result in structural

abnormalities, such as anal fissures, fistulas, abscesses, and operative complications that lead to fecal or anal incontinence.

Table 31-3 Rome IV Criteria (27)

C. Bowel Disorders	
C1. Irritable bowel syndrome (IBS) IBS with predominant constipation (IBS-C) IBS with predominant diarrhea (IBS-D) IBS with mixed bowel habits (IBS-M) IBS unclassified (IBS-U)	C2. Functional constipation C3. Functional diarrhea C4. Functional abdominal bloating/distension C5. Unspecified functional bowel disorder C6. Opioid-induced constipation
F. Anorectal Disorders	
F1. Fecal incontinence F2. Functional anorectal pain F2a. Levator ani syndrome F2b. Unspecified functional anorectal pain F2c. Proctalgia fugax	F3. Functional defecation disorders F3a. Inadequate defecatory propulsion F3b. Dyssynergic defecation

Table 31-4 Drugs and Dietary Items Associated with Diarrhea

Over-the-Counter Medications	
Laxatives	
Antacids (with magnesium)	
Prescription Medications	
Laxatives	Chemotherapy
Diuretics	Colchicine
Thyroid preparations	Cholestyramine
Cholinergics	Neomycin
Prostaglandins	Para-aminosalicylic acid
Dietary Items	
Dietetic foods, candy or chewing gum, and elixirs with sorbitol, mannitol, or xylitol	
Olestra	
Caffeine	
Ethanol	
Monosodium glutamate	

As with defecatory dysfunction, neurologic causes of fecal incontinence can be

divided into central and peripheral disorders. Among the central nervous system disorders, upper motor neuron lesions above the level of the defecation center (located in the sacral cord) cause spastic bowel dysfunction. Cortical communication is disrupted, resulting in impaired cognitive control and sensory deficit. The anal sphincter is under spastic contraction, but digital stimulation can be performed to initiate reflex evacuation. **Head trauma, neoplasms, and cerebral vascular accidents that damage portions of the frontal lobe result in loss of control of both micturition and defecation.** Greater loss of inhibition is present when the lesion is located more anteriorly in the frontal lobe. Spinal cord trauma and lower motor neuron lesions above the defecation center tend to cause permanent loss of cortical control. For 2 to 4 weeks following spinal cord injury, "spinal shock" occurs, resulting in a temporary loss of reflexes below the level of the lesion, flaccid bowel function, constipation, and fecal impaction. After the initial shock, spastic paralysis ensues with hyperactive bowel function. The gastrocolic reflex, along with digital stimulation, initiates reflex evacuation in the absence of cortical inhibition. Fortunately, IAS tone is maintained despite the loss of EAS control for stress and urge situations. Both constipation and fecal incontinence can occur in these patients.

The demyelination that is seen in multiple sclerosis is randomly distributed and can occur at any level in the central nervous system. In addition to the somatic disruption that is similar to spinal cord injury, autonomic dysfunction frequently is present. **People with dementia and other degenerative disorders that cause cognitive impairment frequently have fecal incontinence caused by overflow incontinence as a result of constipation.** Although sensory nerves are functioning properly, these individuals lack the cognitive awareness necessary to inhibit defecation until a socially acceptable time, and they develop overflow incontinence.

Lower motor neuron lesions occurring at or below the level of the defecation center in the sacral cord cause flaccid bowel dysfunction. Cortical communication is disrupted, resulting in impaired cognitive control and sensory deficit. The bowel reflexes, including the bulbocavernosus and anal reflexes, are interrupted. The anal sphincter is flaccid, and fecal retention with overflow incontinence usually occurs. Digital disimpaction and Valsalva often are required for evacuation. Digital stimulation has no effect, and medications tend to work poorly. Examples of motor neuron lesions include tumor or trauma to the cauda equina, tabes dorsalis, spina bifida, and peripheral neuropathy.

The classic example of peripheral neuropathy is congenital aganglionosis (Hirschsprung disease). The most common peripheral neuropathy occurs with diabetes. **Diabetic enteropathy occurs in up to 75% of patients and may manifest as a variety of gastrointestinal symptoms. Approximately 20% of individuals with diabetes have fecal incontinence** (30,31). The cause tends to be multifactorial with the exact

mechanism uncertain. The long-standing belief that vagal autonomic neuropathy is the primary cause of diabetic enteropathy has been challenged by newer theories of hyperglycemia causing oxidative stress on neural networks affecting the small bowel (31). Fecal incontinence can occur with diabetic diarrhea or years later from progressive disease. Individuals with diabetes frequently experience intestinal autonomic neuropathy, an abnormal gastrocolic reflex, and chronic constipation. The subsequent pelvic floor denervation causes fecal incontinence by sensory neuropathy, failure of the rectoanal inhibitory reflex, and sphincter dysfunction (32). Consequently, fecal incontinence from peripheral neuropathy can be the result of defective sampling, a disrupted rectoanal inhibitory reflex, small intestine neuronal oxidative stress, or pudendal neuropathy with sphincter dysfunction.

Anatomic and structural causes of fecal incontinence are usually caused by obstetric or surgical trauma. Damage or dysfunction of the IAS, EAS, and puborectalis can result in varying degrees of anal incontinence. Those with impaired resting tone from a defective IAS will have passive incontinence (incontinence at rest), which is worse during sleep when there is decreased EAS activity (33). An inability to respond to sudden distention and to suppress defecation is often seen with EAS dysfunction. EAS and IAS dysfunction often results in incontinence of liquid stool. Incontinence of solid stool is usually seen with widening of the anorectal angle from damage to the puborectalis muscles. Damage to the anal cushions usually causes minor soiling. Other anatomic and structural abnormalities associated with fecal incontinence include obstructive disorders such as pelvic organ prolapse, descending perineum syndrome, anismus, and intussusception; fistulas from diverticulitis, inflammatory bowel disease, cancer, or surgical trauma; and decreased rectal compliance from inflammatory bowel disease, cancer, and radiation. Decreased compliance results in higher intraluminal pressures with smaller volumes of stool, poor storage capacity, urgency, and incontinence (34).

Functional disorders associated with fecal incontinence include IBS diarrhea variant (IBS-D), functional diarrhea, decreased mobility, and decreased cognition.

Combined Disorders of Defecation and Fecal Incontinence

Several conditions have the potential to cause both defecatory dysfunction (constipation) and fecal incontinence (see Table 31-1). Most of these disorders cause combined symptoms through the development of fecal impaction followed by overflow incontinence. This situation can be seen with many of the neurologic conditions, pelvic outlet obstructive disorders, functional disorders of IBS, decreased mobility, and decreased cognition. The cause of these symptoms often is multifactorial.

Structural Versus Functional Disorders

Disordered Defecation

Disordered defecation (constipation) can result from outlet obstruction or functional motility disorders.

Outlet Obstruction

Anismus/Rectosphincteric Dyssynergia

Anismus is also known as rectosphincteric dyssynergia, pelvic floor dyssynergia, dyssynergic defecation, spastic floor syndrome, and paradoxical puborectalis syndrome. The anorectal angle narrows as a result of paradoxical contraction of the puborectalis and EAS during defecation, instead of relaxation. Frequent symptoms include dyschezia, straining, hard stools, incomplete emptying, and tenesmus. A prospective study of 120 consecutive patients with dyssynergic defecation found a higher prevalence in women (77%) (35,36). The need for digital assistance (digital disimpaction or splinting) to evacuate the rectum occurs in up to 58% of patients. **Psychosocial factors, such as a history of sexual abuse, depression, eating disorder, obsessive-compulsive disorder, and stress, may play an important role in this disease.** In this study, 22% reported a history of sexual abuse, and 31% reported a history of physical abuse. One-third believed the problem began during childhood, and 24% reported a precipitating illness or surgery was related to a particular event. Five percent of women claimed that pregnancy or childbirth was a precipitating factor. This condition is seen in young children with constipation and dyschezia. The response to biofeedback and pelvic floor physical therapy, and the aforementioned patient characteristics, indicate a learned response mechanism is involved (35,36). While this is categorized as an outlet obstruction, the Rome IV Criteria for functional gastrointestinal disorders places this in the category of functional defecation disorders **(Table 31-3)**. The specific Rome IV Diagnostic Criteria for dyssynergic defecation includes "inappropriate contraction of the pelvic floor as measured with anal surface EMG or manometry with adequate propulsive forces during attempted defecation" (37).

Pelvic Organ Prolapse

Pelvic organ prolapse bears special mention because it is often seen by gynecologists but inconsistently associated with defecatory dysfunction. Prolapse is very common, although many women with this condition are asymptomatic. Those with symptoms may report incomplete evacuation and the need to apply digital pressure to the posterior vaginal wall or perineum to aid in evacuation of stool (digitation or splinting). It is important to rule out other causes of obstructed defecation, because these symptoms are nonspecific. Moreover, rectocele, enterocele, and perineal descent can result from chronic straining and increased intra-abdominal pressure caused by other etiologies of defecatory dysfunction. **Defecatory dysfunction related to pelvic organ prolapse can result from rectocele, enterocele, or perineal descent, either**

individually or in combination.

***Rectocele, also known as posterior vaginal wall prolapse,* is a herniation of the rectal mucosa through a defect in the fibromuscular layer of the posterior vaginal wall.** These site-specific defects can be transverse or longitudinal through the inferior, middle, or superior regions of the rectovaginal fibromuscular layer (38).

***Enterocele* is a herniation of a peritoneal sac and bowel through the pelvic floor, typically between the uterus or vaginal cuff and rectum. It is more common following hysterectomy and retropubic urethropexy.** There are two theories surrounding the formation of an enterocele. The first theory implicates a defect in the fibromuscular endopelvic fascia of the vagina, allowing peritoneum and bowel to herniate. The second theory attributes its formation to a support defect with full-thickness protrusion, including endopelvic fascia (39). Ultimately, the mechanism might be attributed to a combination of the two theories because some support defects are secondary to superior breaks in the anterior and posterior pubocervical and rectovaginal fibromuscular layers.

Patients with rectocele and enterocele may have symptoms of pelvic pressure, vaginal protrusion, obstipation, fecal incontinence, and sexual dysfunction. Although associations have been made between defecatory dysfunction and advanced stages of pelvic organ prolapse, a causal relationship remains to be established (40,41). Controversy remains as to whether anatomic herniation is the cause of these symptoms or the effect of underlying colonic dysfunction, chronic constipation, and straining.

***Descending perineum syndrome* is defined as descent of the perineum (at the level of the anal verge) beyond the ischial tuberosities during Valsalva.** Excessive perineal descent was first described in the colorectal literature by Parks et al. in 1966 (42,43). It occurs as a result of inferior detachment of the rectovaginal septum from the perineal body. As the condition progresses, the patient can develop pudendal neuropathy from stretch injury. Perineal descent has been associated with a variety of defecatory disorders, including constipation, obstructed defecation, fecal incontinence, rectal pain, solitary rectal ulcer syndrome, rectocele, and enterocele (44).

Rectal Intussusception

Rectal intussusception or intrarectal prolapse is the circumferential prolapse of the upper rectal wall into the rectal ampulla but not through the anal verge. It occurs most often in women in the fourth and fifth decade. The most common symptoms are obstructive, including incomplete emptying, manual disimpaction, splinting, pain with defecation, and bleeding. Other symptoms include fecal incontinence, decreased urge to defecate, inability to distinguish between gas and feces, and mucus discharge with pruritus ani. Forty-five percent to 80% of patients with rectal intussusception have a solitary rectal ulcer which may cause bleeding (45). **Intussusception is seen in as many as one-third of women with defecatory disorders.** It has been seen in 20% to

50% of asymptomatic volunteers on defecography and does not commonly develop into total rectal prolapse (45).

Functional Motility Disorders

Functional Bowel Disorders

Functional bowel disorders, as defined by the Rome IV Criteria (46), consist of IBS, FC, functional diarrhea, functional abdominal bloating/distension, unspecified functional bowel disorder, and opioid-induced constipation. This section will focus primarily on IBS.

IBS has been estimated to have a prevalence of 10% to 20% and is more common in women and younger individuals. It accounts for 25% to 50% of all referrals to gastrointestinal clinics. IBS has distinct diagnostic criteria, including the exclusion of structural or metabolic abnormalities. **These patients often have other gastrointestinal, genitourinary, and mental health concerns, including gastroesophageal reflux disease, fibromyalgia, headache, backache, chronic pelvic pain, sexual dysfunction, lower urinary tract dysfunction, depression, and anxiety.** Stressful life events may correlate with the onset and exacerbation of symptoms. A detailed history frequently reveals a history of abuse. Diagnostic Criteria for IBS include recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria: (1) related to defecation; (2) associated with a change in frequency of stool; and (3) associated with the change in form (appearance) of stool. The criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis (Table 31-5). **Specific criteria allow for classification of IBS into constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), mixed bowel habits (IBS-M) and unclassified (IBS-U) as outlined in** Table 31-3. The constipation variant is most commonly associated with defecatory dysfunction, whereas the diarrhea variant causes fecal incontinence. The Rome IV Criteria has a sensitivity and specificity of 62.7% and 97.1% for IBS, respectively (47).

Table 31-5 Irritable Bowel Syndrome (C1) (46)

Diagnostic Criterion[a]
Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria: 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool

[a]Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Table 31-6 Functional Constipation (C2) (46)

Diagnostic Criteria[a]
1. Must include two or more of the following[b]: a. Straining during more than one-fourth (25%) of defecations b. Lumpy or hard stools (Bristol Stool 1–2) more than one-fourth (25%) of defecations c. Sensation of incomplete evacuation for more than one-fourth (25%) of defecations d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (e.g., digital evacuation, support of the pelvic floor) f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

[b]For research studies, patients meeting criteria for OIC should not be given a diagnosis of FC because it is difficult to distinguish between the opioid side effects and other cause of constipation. However, clinicians recognize that these two conditions might overlap.

FC is a term created to unify the definition of constipation (Table 31-6). Patients with FC should not meet IBS criteria; abdominal pain and/or bloating may be present but not predominant symptoms (46).

Table 31-7 Functional Defecation Disorders (F3) (37)

Diagnostic Criteria[a]
1. The patient must satisfy diagnostic criteria for functional constipation and/or irritable bowel syndrome with constipation (Tables 31-5 and 31-6)
2. During repeated attempts to defecate, there must be features of impaired evacuation, as demonstrated by two of the following three tests: a. Abnormal balloon expulsion test b. Abnormal anorectal evacuation pattern with manometry or anal surface EMG c. Impaired rectal evacuation by imaging
Subcategories F3a and F3b apply to patients who satisfy criteria for FDD F3a. Diagnostic Criteria for Inadequate Defecatory Propulsion Inadequate propulsive forces as measured with manometry with or without inappropriate contraction of the anal sphincter and/or pelvic floor musclesb F3b. Diagnostic Criteria for Dyssynergic Defecation Inappropriate contraction of the pelvic floor as measured with anal surface EMG or manometry with adequate propulsive forces during attempted defecation[b]

[a] *Criteria* fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
[b] These criteria are defined by age- and sex-appropriate normal values for the technique.

Functional Defecation Disorders

Functional defecation disorders are divided into dyssynergic defecation and inadequate defecatory propulsion (colonic inertia). For the purposes of this chapter, we have included dyssynergic defecation under the structural category of outlet obstruction; however, Rome IV considers it as a functional disorder (Table 31-7). **Both of the functional defecation disorders require the presence of FC or IBS-C. Tables 31-5 and 31-6 list the criteria for diagnosing these conditions.**

Colonic Inertia/Slow-Transit Constipation

Severe constipation, defined as fewer than three stools per week and refractory to therapy, is relatively rare; however, these patients frequently suffer from motility disorders such as *global motility disorder* and *colonic inertia*. Women are more likely to be affected than men. Colonic inertia or slow-transit constipation is defined as the delayed passage of radiopaque markers through the proximal colon without retropulsion of markers from the left colon and in the absence of systemic or obstructive disorders. The cause remains unclear. Patients with this disorder have impaired phasic colonic motor activity and diminished gastrocolic reflexes (48,49). Studies on the role of laxatives, absorption, hormones, psychological abnormalities, and endogenous opioids have been inconclusive. The literature suggests a possible neurologic or smooth muscle disorder (49,50). The smooth muscle-specific contractile protein "smoothelin" is being studied (51). QoL is impaired in patients with obstructive defecation and colonic inertia, however, those with obstructive defecation are affected to a greater extent (52).

Fecal Incontinence

The terms anal and fecal incontinence are used interchangeably, but have subtle differences. **Fecal incontinence is defined as the involuntary loss of solid or liquid stool. Anal incontinence is defined as the involuntary loss of solid or liquid stool or flatus.** Anal incontinence implies transanal pathology, whereas fecal incontinence may also occur from a fistula. **Accidental bowel leakage** is a newer term preferred by patients, that describes the symptom of fecal incontinence.

Sphincter Disruption

In women, obstetric anal sphincter injury is the most common cause of accidental bowel leakage. The mechanism of injury can be from anatomic disruption of the anal sphincter complex, pelvic floor denervation, or a combination of the two conditions. The risk factors for anal sphincter laceration are primiparity, high birth weight, operative delivery, and episiotomy, especially midline episiotomy (53–56). There are

several other factors that have been proposed and studied which demonstrate a variable relationship with perineal laceration or anal sphincter injury (56–58). Studies suggest that women who have slower labor without the normal deceleration phase, and with late descent of the fetal head, are more likely to have anal sphincter injuries (57,59). The duration of the second stage is an independent risk factor for all women, and duration of pushing greater than 60 minutes is a significant risk factor for anal sphincter injury in primiparous patients (59). There are limited long-term prospective studies demonstrating the natural history of anal sphincter injury, pelvic floor neuropathy, and the progression of these conditions to fecal incontinence. The literature supports the relationship of early-onset symptoms to sphincter damage and delayed-onset symptoms to neuropathy (60–62).

Obstetric Trauma

Third- and fourth-degree lacerations at delivery are associated with an increased risk of fecal incontinence (OR = 2.66 to 3.09) (60,61). The incidence of clinically documented third- and fourth-degree anal sphincter tears are 0.5% and 5.9% respectively and have been increasing over the last 10 years (55,63). This increase is most likely a result of improved diagnosis, as the occult third- and fourth-degree defects described in 28% to 35% of primiparous women and 44% of multiparous women are not missed by better trained maternity providers. **Patients with occult anal sphincter tears are 8.8 times more likely to have fecal incontinence** (55,64). Both forceps and vacuum-assisted vaginal delivery significantly increase this risk, with vacuum being less traumatic than forceps (58). Scheduled cesarean delivery without labor, in contrast with emergency cesarean delivery, was believed to prevent anal incontinence, but studies argue against any protective effect with cesarean delivery, irrespective of timing (65,66). **A Cochrane review from 2010 concludes that there is insufficient evidence to support primary elective cesarean delivery for the purpose of preserving fecal continence** (67). **Midline episiotomy is strongly linked to sphincter damage and fecal incontinence** (54,64) and the consequences are additive when combined with the use of forceps and vacuum. Mediolateral episiotomy with instrumentation, however, is found to be protective compared to instrumentation alone (68). A Cochrane review supports the restrictive use of midline and mediolateral episiotomy because of less posterior perineal trauma, less suturing, and fewer healing complications. There were no differences in severe trauma, pain, dyspareunia, or urinary incontinence, but there was an increase in anterior perineal trauma with restrictive use (69). Another study suggests that if an experienced care provider is not available immediately or locally, repair of the third- or fourth-degree tear can be delayed for 8 to 12 hours with no impact on anal incontinence and pelvic floor symptoms (70).

Surgical Trauma

Iatrogenic injury follows obstetric trauma as the second most common cause of direct sphincter damage. Surgical procedures that have been associated with fecal incontinence include anal fistula repair, anal sphincterotomy, hemorrhoidectomy, and anal dilation. **Fistulotomy is the most common procedure that results in fecal incontinence.** Rectovaginal or anovaginal fistulas can develop after obstetric injury, operative complications during pelvic surgery, and inflammatory bowel disease exacerbations. Fistulas cause fecal incontinence, and the degree of postoperative dysfunction depends on the location of the fistula and the amount of sphincter that is disrupted during the surgical repair. It also depends on the preoperative level of sphincter function and pudendal nerve function. Anal sphincterotomy to treat painful anal fissures can lead to incontinence by disruption of rectal sensory innervation and anal cushions and transection of the anal sphincter (71,72). Hemorrhoidectomy often results in minor soiling as a result of resection of the anal cushions, which act as the final mucosal barrier. Similar to sphincterotomy, rectal sensory innervation can be disrupted, and injury to the IAS can occur during sharp dissection (72,73).

Sphincter Denervation

Idiopathic (primary neurogenic) fecal incontinence results from denervation of both the anal sphincter and pelvic floor muscles. Denervation injury related to obstetric trauma accounts for approximately three out of every four cases of idiopathic fecal incontinence and is the most common overall cause of fecal incontinence (70,71).

Obstetric Trauma

The two proposed mechanisms of pudendal neuropathy are stretch injury during the second stage of labor and compression of the nerve as it exits Alcock canal (74). **Established risk factors for pelvic floor neuropathy include multiparity, high birth weight, forceps delivery, prolonged active second stage, and third-degree laceration** (75,76). Several studies have shown increased pudendal nerve terminal motor latencies following vaginal delivery, especially after sphincter laceration (55,77,78). Most women will recover function within a few months postpartum. Others will have evidence of injury several years later, which may represent the cumulative effects of subsequent deliveries (77,79). However, fecal incontinence will develop in only a fraction of patients with neuropathy (76).

Descending Perineum Syndrome

Prolonged straining for any reason can cause descending perineum syndrome. This syndrome is defined as descent of the perineum beyond the ischial tuberosities during Valsalva (42,43). Pudendal neuropathy results from stretching and entrapment of the pudendal nerve. This diagnosis is supported by findings of elongation of the pudendal nerve, prolonged pudendal nerve motor terminal latency, and decreased anal sensation in women with perineal descent (80–82). As pudendal neuropathy progresses,

it ultimately leads to fecal incontinence (83,84).

Functional Bowel Disorders

Fecal Incontinence

The Rome III Criteria established well-defined guidelines for functional causes of fecal incontinence, however these were cumbersome and seldom used. The Rome IV Criteria (Table 31-8) now uses a more simplified definition for any recurrent uncontrolled passage of fecal material. Fecal incontinence is often multifactorial and occurs in conditions that cause diarrhea, impair colorectal storage capacity and/or weaken the pelvic floor (Table 31-9).

Irritable Bowel Syndrome

The diarrhea variant of IBS is often associated with fecal incontinence and disordered defecation. The criteria for diagnosis are in Table 31-5.

Functional Diarrhea

The Rome IV Criteria create a unifying definition of diarrhea called functional diarrhea (Table 31-10). The rationale for the criteria listed in Table 31-10 stems from the variability in patients' descriptions of diarrhea (37).

Pitfalls for the Pelvic Floor Surgeon

It is sometimes easy to overlook or misinterpret signs and symptoms of constipation and defecatory dysfunction. **Red flags such as unintentional weight loss, blood in the stool, fever, and iron-deficiency anemia should prompt further investigation. Any acute change in bowel habits must be evaluated thoroughly, and malignancy must be considered in the differential diagnosis. Even in the presence of chronic disease, malignancy must still be excluded.** Persistent symptoms after an empiric trial of medical therapy should prompt further evaluation, including colonoscopy or flexible sigmoidoscopy. It is possible to mistakenly attribute symptoms of defecatory dysfunction and constipation to pelvic organ prolapse when prolapse is actually the result of an underlying bowel disorder. In this case, surgical treatment of prolapse will have little lasting benefit if the underlying bowel disorder remains untreated.

Table 31-8 Fecal Incontinence (37)

Diagnostic Criteria[a]
Recurrent uncontrolled passage of fecal material in an individual with a developmental age of at least 4 years

[a]Criteria fulfilled for the last 3 months. For research studies, consider onset of symptoms for at least 6 months previously with 2–4 episodes of FI over 4 weeks.

Table 31-9 Common Causes of Fecal Incontinence (37)

Anal sphincter weakness Traumatic: obstetric, surgical (e.g., hemorrhoidectomy, internal sphincterotomy, fistulectomy) Nontraumatic: scleroderma, idiopathic internal sphincter degeneration Neuropathy Peripheral (e.g., pudendal) or generalized (e.g., diabetes mellitus)
Pelvic floor disorders Rectal prolapse, descending perineum syndrome
Disorders affecting rectal capacity and/or sensation[a] Inflammatory conditions: radiation proctitis, Crohn disease, ulcerative colitis Anorectal surgery (pouch, anterior resection) Rectal hyposensitivity Rectal hypersensitivity
Central nervous system disorders Dementia, stroke, brain tumors, multiple sclerosis, spinal cord lesions
Psychiatric diseases, behavioral disorders
Bowel disturbances Irritable bowel syndrome, postcholecystectomy diarrhea Constipation and fecal retention with overflow

[a]These conditions may also be associated with diarrhea.

HISTORY AND PHYSICAL EXAMINATION

History

[3] A thorough history and physical examination are critical to the evaluation of fecal incontinence and defecatory dysfunction. **The history of present illness should focus on the bowel habits, including frequency and consistency of bowel movements (hard vs. soft, formed vs. unformed, diarrhea vs. constipation). The duration and severity of symptoms and exacerbating factors are important to understanding the impact on QoL.** Patients should be questioned about straining with bowel movements, symptoms of incomplete emptying, and splinting of the perianal region, perineal body, or posterior vaginal wall to assist with evacuation. They should be asked about the need to perform digital disimpaction because they are unlikely to volunteer this information. With respect to fecal incontinence, information should be obtained about leakage with solids, liquid, and flatus and the ability to discriminate between these different types of stool (sampling). Similar to urinary incontinence, fecal incontinence can be stress related, urge related, or may occur without awareness. Questions about alternating diarrhea and constipation, mucus or blood in the stools, constitutional symptoms, and changes in stool caliber can help the investigator uncover systemic and functional

etiologies. Finally, it is important to ask about adaptive behaviors, pad or diaper use, and past and present treatments including surgery, physical therapy, and medications.

Table 31-10 Functional Diarrhea (C3) (46)

Diagnostic Criterion[a]
Loose or watery stools, without predominant abdominal pain or bothersome bloating, occurring >25% of stools[b]

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
[b]Patients meeting criteria for diarrhea-predominant IBS should be excluded.

A large amount of information can be obtained efficiently through questionnaires. Validated questionnaires quantify symptoms, which are subjective in nature, to objectively measure response to treatment. **A valuable survey to assess defecatory dysfunction is the ColoRectal-Anal Distress Inventory (CRADI), which has been incorporated into the Pelvic Floor Distress Inventory (PFDI)** (85). The latter is a useful tool for evaluating symptoms of prolapse, urinary incontinence, fecal incontinence, voiding dysfunction, and defecatory dysfunction. Other useful symptom scales and bother scores for fecal incontinence include the Wexner Score (86), Fecal Incontinence Severity Index (87), and Fecal Incontinence QoL (FIQoL) Scale (88). The Rome IV Diagnostic Questionnaire for Adults focuses on clinical diagnoses of IBS, functional dyspepsia (FD) and FC. Sensitivity was 62.7% for IBS, 54.7% for FD, and 32.2% for FC. Specificity was 97.1% for IBS, 93.3% for FD, and 93.6% for FC (47).

The medical history, surgical history, family history, and review of systems should focus on uncovering potential systemic and obstructive disorders shown in Table 31-1. **A complete obstetric history should include the number of vaginal deliveries, operative vaginal deliveries, or presence of a third- or fourth-degree laceration, which is critical for patients with fecal incontinence.** Length of the second stage of labor, birth weight, and the use of episiotomy should be ascertained because they may pose risk factors for sphincter damage and denervation. A sexual history should be obtained by first asking if the patient has had any negative sexual experiences. This will allow details regarding sexual assault, anal penetration, and dyspareunia to be ascertained. Use of over-the-counter, prescription, recreational and illegal drugs, and allergies should be recorded.

Physical Examination

The evaluation of anorectal dysfunction requires a basic general examination and a focused abdominal and pelvic examination. The general physical survey should include a global assessment of mobility and cognitive function. Routine examination of

the abdomen involves inspection, palpation, and auscultation to rule out the presence of masses, organomegaly, and areas of peritoneal irritation. This examination should be followed by a detailed evaluation of the vagina, perineum, and anorectum. The goals of the pelvic examination are to define objectively the degree of prolapse and determine the integrity of the connective tissue, neurologic function, and muscular support of the pelvic organs.

Neurologic Examination

Important elements of the neurologic examination are assessment of cranial nerve function, sensation and strength of the lower extremities, and reflexes for the lower extremities, bulbocavernosus, and anal wink. These examinations evaluate the function of the lower lumbar and sacral nerve roots, recognizing the importance of the second through fourth sacral nerve roots in pelvic floor dysfunction. The perineal reflexes can be elicited by stroking the labia majora and perianal skin with a cotton-tipped swab. The anal wink, bulbocavernosus, and cough reflexes all test the integrity of motor innervation to the EAS (S2–S4). Sensation over the inner thigh, vulva, and perirectal areas should be tested for symmetry to light touch and pinprick.

Muscle Strength

The integrity of the pelvic floor muscles should be assessed at rest and with voluntary contraction to determine strength, duration, and anterior lift. The insertions of the puborectalis and pubococcyguous muscles should be checked for avulsion, which presents as asymmetry. Palpation allows assessment of tenderness, strength and ability to relax these muscles. Several standardized systems have been described to objectively measure muscle strength including manual palpation and scoring of Kegel strength on a scale of 1 through 5, but none has been accepted as a standard (89). The puborectalis muscle should be readily palpable posteriorly as it creates a 90-degree angle between the anal and rectal canals. Voluntary contraction of this muscle "lifts" the examining finger anteriorly toward the pubic rami. An intact EAS muscle that has decreased tone and contractility often indicates pudendal neuropathy. Neuropathy affecting the puborectalis can be recognized by an obtuse anorectal angle and weak voluntary contraction. Similar to the urethral axis, the anorectal angle can be tested using a cotton-tipped swab, although this test is rarely performed. Deflection is measured in the supine position at rest, with strain, and with squeeze.

Vaginal Support

The salient points of pelvic organ prolapse (see Chapter 30) **for patients with defecatory dysfunction are the support of the vaginal apex, posterior wall, and perineal body, although some experts believe anterior wall defects can affect defecatory dysfunction.** The posterior wall is assessed while supporting the vaginal

apex and anterior wall with a split speculum. This permits the examiner to focus on identifying specific locations of rectovaginal fascial defects. A rectovaginal examination aids in identification of defects in the rectovaginal fascia or perineal body. Loss of vaginal rugation has been reported overlying the site of a rectovaginal fascial tear (90). This technique is especially useful for enteroceles, which have a smooth, thin epithelium over the enterocele sac or peritoneum.

Normally, the perineum should be located at the level of the ischial tuberosities, or within 2 cm of this landmark. A perineum below this level, either at rest or with straining, represents perineal descent. Subjective findings of perineal descent include widening of the genital hiatus and perineal body, and flattening or a convex intergluteal sulcus. Women with perineal descent tend to have less severe stages of pelvic organ prolapse based on the **Pelvic Organ Prolapse Quantification (POP-Q) staging system** (91) because it measures descent from the hymenal ring. Consequently, an increase in the length of the perineal body and genital hiatus with straining suggests perineal descent. The degree of perineal descent can be measured objectively with a St. Mark's perineometer, although a thin ruler placed in the posterior introitus at the level of the ischial tuberosities can be used. Descent is measured as the distance the perineal body moves when the patient strains. Although pelvic floor fluoroscopy is the standard technique for measuring perineal descent, this technique is most useful in patients with symptoms of severe defecatory dysfunction and evidence of perineal descent on pelvic examination.

Anorectal Examination

Visual and digital inspection of the vagina and anus will help to identify structural abnormalities such as prolapse, fistulas, fissures, hemorrhoids, or prior trauma. A rectovaginal examination provides useful information regarding the integrity of the rectovaginal septum and can demonstrate laxity in the support of the perineal body. The rectovaginal examination is helpful in the diagnosis of enteroceles, which can be felt as protrusion of bowel between the vaginal and rectal fingers with straining. Digital rectal examination should be performed at rest, with squeeze, and while straining. The presence of fecal material in the anal canal may suggest fecal impaction or neuromuscular weakness of the anal continence mechanism. Circumferential protrusion of the upper rectum around the examining finger during straining suggests intussusception, which often occurs in combination with laxity of the posterior rectal support along the sacrum.

The integrity of the EAS and puborectalis muscle can be evaluated by observation and palpation of these structures during voluntary contraction. Evidence of dovetailing of the perianal skin folds and the presence of a perineal scar with an asymmetric contraction often indicates a sphincter defect. When a patient is asked to contract her pelvic floor muscles, two motions should be present: The EAS

should contract concentrically, and the anal verge should be pulled inward. These actions should be apparent on digital rectal examination. The 90-degree angle created by the puborectalis should be readily palpable posteriorly and, with voluntary contraction, the examining finger should be lifted anteriorly toward the pubic rami. Both the puborectalis and EAS should relax during Valsalva effort. Patients with anismus may experience a paradoxical contraction of these muscles during straining. Finally, defects in the anterior aspects of the EAS may be detected by digital examination. The Digital Rectal Examination Scoring System (DRESS) is a 5-point scale that is quantified during resting and squeeze. A score of 3 is assigned to a normal tone (Table 31-11).

TESTING

Sophisticated diagnostic testing is being used in clinical and research anorectal physiology laboratories to quantify the function of the colon and anorectum. Following is a description of these techniques as they relate to the management of fecal incontinence and disordered defecation.

Table 31-11 The Digital Rectal Exam Scoring System (DRESS) (92)

Resting Score
0 No discernable tone at rest, an open or patulous anal canal 1 Very low tone 2 Mildly decreased tone 3 Normal 4 Elevated tone, snug 5 Very high tone, a tight anal canal, difficult to insert a finger
Squeeze
0 No discernable increase in tone with squeezing effort 1 Slight increase 2 Fair increase but below normal 3 Normal 4 Strong squeeze 5 Very strong squeeze, to the point of being painful to the examiner

Fecal Incontinence

Endoanal Ultrasonography

Endoanal ultrasonography permits accurate imaging of both the IAS and EAS. It can assess the continuity and thickness of the muscle and is considered the single best method for detecting anal sphincter defects. Endoanal ultrasonography is performed using a Bruel–Kjaer (Copenhagen, Denmark) ultrasound scanner with a 360-degree rectal endoprobe (type 1850) with a 7 MHz transducer (focal length, 2 to 5 cm)

housed within a plastic cone (Fig. 31-1). On images from this device the normal IAS is a continuous hypoechoic band of smooth muscle surrounded by the thick echogenic layer of the striated EAS. A sphincter defect appears as a disruption in these muscle bands. Location and severity of the defect can be described by circumferential distance in degrees, percent thickness, and distance from the anal verge (Fig. 31-2). Measurements are usually taken in the proximal, middle, and distal anal canal. It is important to recognize the physiologic split in the proximal EAS as it merges with the puborectalis muscle of the levator ani. Misinterpretation of this finding as a sphincter defect can lead to inaccurate diagnosis. The puborectalis muscle appears as a U-shaped or V-shaped thick echogenic layer outside the IAS and contiguous with the EAS in the proximal anal canal.

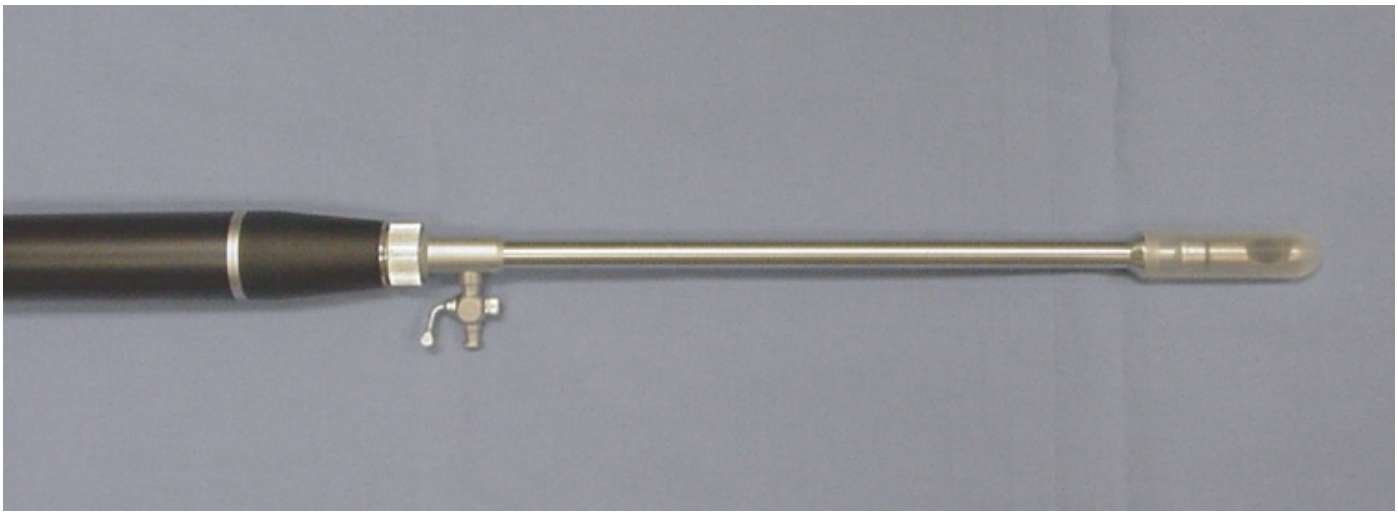


FIGURE 31-1 Bruel–Kjaer (Copenhagen, Denmark) ultrasound probe (type 1850) with a 7 MHz transducer (focal length, 2 to 5 cm) housed with a plastic cone.

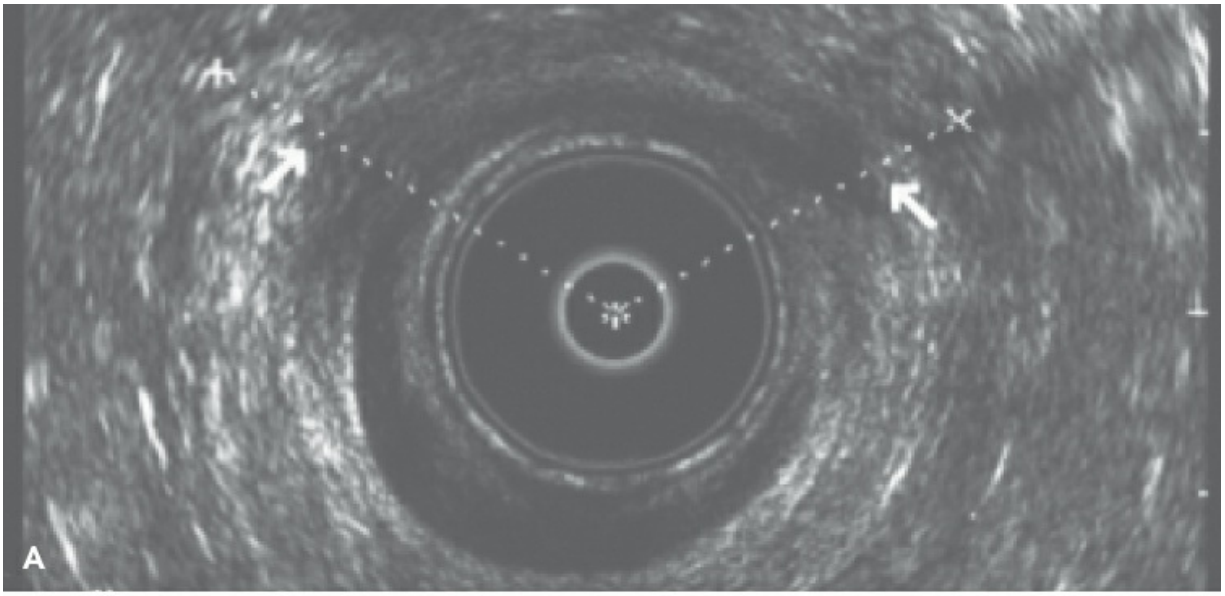
Magnetic resonance imaging (MRI) is an alternative to endoanal ultrasound that is equally effective at diagnosing sphincter defects, and with the use of a vaginal or rectal coil, better at imaging fistulae. Because MRI is more expensive, endoanal ultrasound is the preferred imaging modality for evaluation of the sphincter complex, and MRI use is largely investigational or for diagnosis of fistulae. It may be beneficial in cases in which endoanal ultrasonography results are inconclusive or the quality of the study is poor.

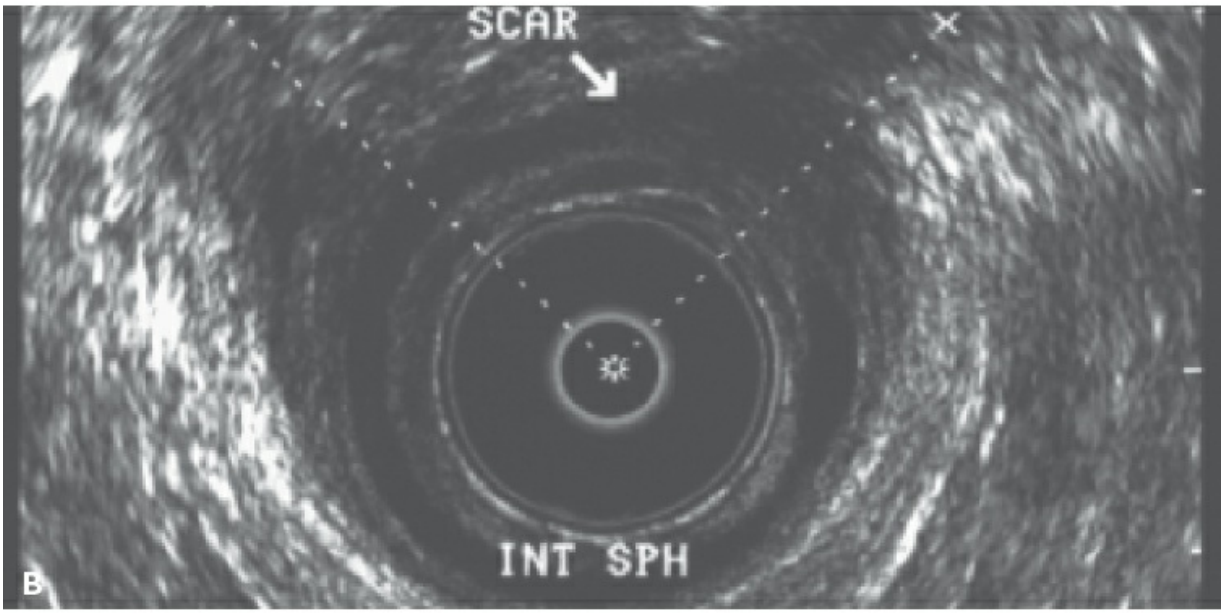
Electromyography

Electromyography (EMG) is useful to evaluate neuromuscular integrity of the EAS and pelvic floor muscles following a traumatic injury such as childbirth (93). This technique measures the electrical activity arising in muscle fibers during contraction and at rest. Different types of electrodes may be employed, including surface electrodes, concentric needle electrodes, and single-fiber electrodes. Surface electrodes are less

invasive because they are applied near or within the anal canal, but are limited to recording basic anal sphincter activity. This technique often is used in conjunction with biofeedback therapy. Concentric needle electrodes are most commonly used in anorectal physiology laboratories to selectively survey an individual muscle's activity. Insertion of the thin needle-like cannulas containing steel wire electrodes can be painful. The smaller single-fiber EMG electrodes are used to record the activity of single muscle fibers, which can be quantified to calculate fiber density. Following denervation injury, increased muscle fiber density occurs during reinnervation. Thus, single-fiber EMG can provide indirect evidence of neurologic injury by mapping the EAS and identifying injured areas. This technique is rarely used in clinical practice as endoanal ultrasonography offers better patient comfort and more reliable results than EMG.

Motor nerve conduction studies provide another means of measuring pelvic floor neuropathy. The axon of a nerve is stimulated, and the time it takes the action potential to reach the muscle supplied by the nerve is recorded. The delay between stimulation and the muscle response is called the nerve latency. Pudendal nerve terminal motor latency (PNTML) can be determined by transrectal stimulation of the pudendal nerve using a St. Mark's electrode (94). A nerve stimulator is mounted on an examination glove at the fingertip **(Fig. 31-3)** and positioned transrectally over each ischial spine. A stimulus of up to 50 mV over a duration of 0.1 milliseconds is applied, and the latency of the EAS muscle contraction is measured. A value of 2.2 milliseconds or less is considered normal. Early studies of PNTML suggested that bilateral pudendal neuropathy tended to occur more frequently in older women (95). A study evaluating normative values for pudendal and perineal nerve latencies observed increased latencies with increased age (96). Prolongation of the PNTML is indicative of damage to that nerve or the presence of a demyelinating condition. Pudendal nerve function has prognostic value in the surgical repair of traumatic sphincter injuries (96) and may be useful in preoperative counseling.


A


SCAR
INT SPH
B

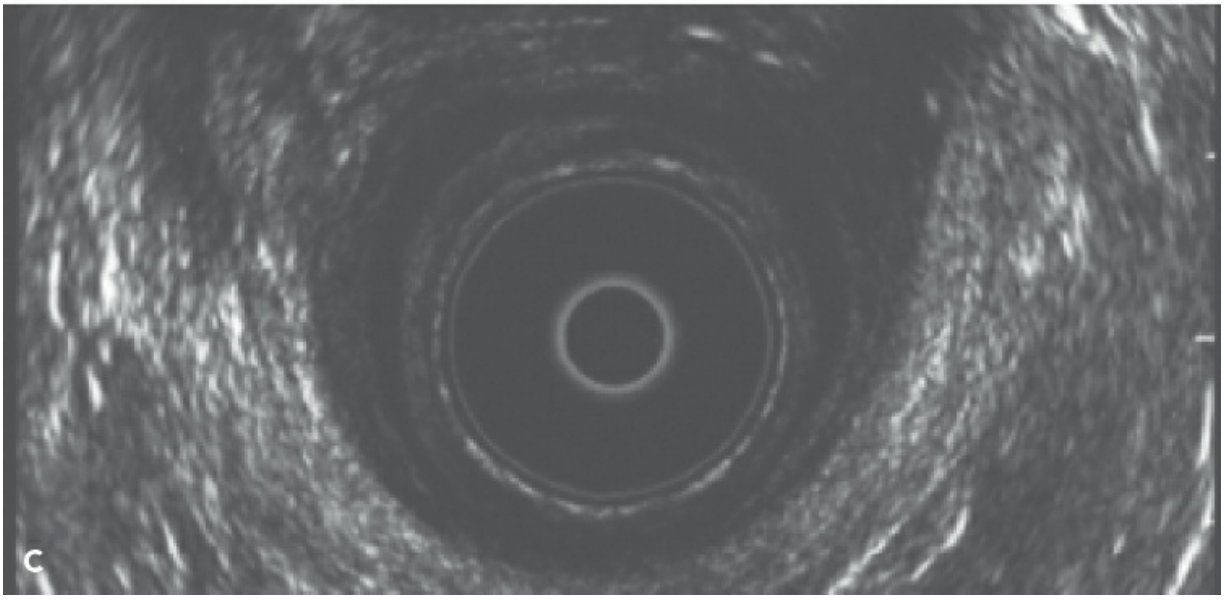

C

FIGURE 31-2 A: Endoanal ultrasound image from the distal anal canal demonstrating defects in the internal sphincter from 10 to 3 o'clock and the external sphincter from 10 to 2 o'clock. **B: Endoanal ultrasound image from the middle anal canal** demonstrating defects in the internal sphincter from 12 to 2 o'clock and the external sphincter from 10 to 1 o'clock. **C: Endoanal ultrasound image from the proximal anal canal** demonstrating an intact IAS and a normal physiologic split in the external sphincter.

Anal Manometry

Anal manometry is used to quantify function of the anal sphincter mechanism. Water-perfused manometry catheters or water-filled balloons are most often used to measure anal canal pressures. Resting anal canal pressures reflect IAS function, and pressures in the lower anal canal during maximal voluntary contraction reflect EAS function. Vector analysis can be used to detect asymmetry within the anal sphincter. Anal manometry can provide indirect evidence of sphincter injury; low resting tone indicates IAS injury, and decreased maximum squeeze pressures indicates EAS injury. However, anal pressures are influenced by a variety of factors, including tissue compliance and muscular tone. Consequently, anal manometry results are difficult to interpret and correlate poorly with the specific anatomic defect. Interpretation is further complicated by the wide variation of normal pressure values that change with age and parity. Significant overlaps occur between manometric values for incontinent patients and those without incontinence. Thus, anal manometry may be of limited value in the evaluation and treatment of anal sphincter defects and fecal incontinence.

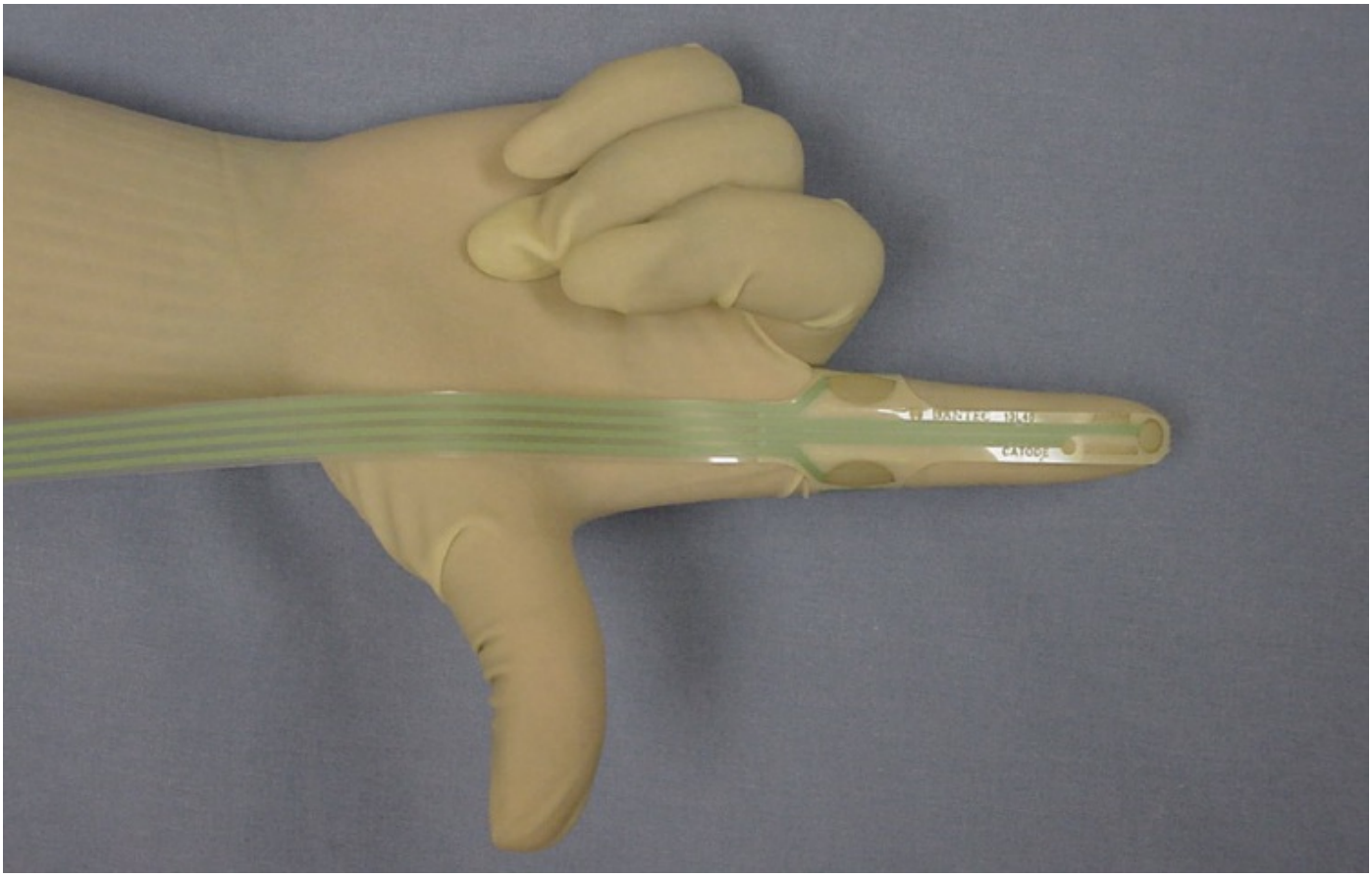


FIGURE 31-3 St. Mark's electrode used for measuring pudendal nerve motor terminal latency. The stimulating electrode is on the fingertip, and the receiving electrode is on the proximal finger near the knuckle.

Proctoscopy and Flat Tire Test

Proctoscopy has an important role in the evaluation of fecal incontinence. It can be performed independently or during colonoscopy, flexible sigmoidoscopy, and flat tire test. **Proctoscopy can detect anorectal pathology, such as prolapsing hemorrhoids, intussusception, ulcerative or radiation proctitis, or a solitary rectal ulcer.** The flat tire test is useful when a rectovaginal or colovaginal fistula is suspected but cannot be visualized on routine office evaluation or MRI. This test usually is performed under anesthesia but can be done in the office setting. Saline or water is placed in the vagina with the patient in Trendelenburg position. Air is instilled into the rectum using a proctoscope or rigid sigmoidoscope. Vaginal retractors provide visualization of the posterior vaginal epithelium and vaginal apex. Observation of bubbling into the vaginal fluid confirms the diagnosis and location of a rectovaginal or colovaginal fistula. The rectal site of the fistula is usually visible, depending on the size and location of the fistula and the quality of the bowel preparation.

Disordered Defecation

Sitzmark Study

Colonic transit studies are useful to evaluate colonic motility, and are performed using serial abdominal radiography after the patient ingests radiopaque markers. The purpose is to differentiate between normal-transit, slow-transit and outlet dysfunction categories of primary constipation (97). Patients are asked to follow a high-fiber diet over the test period and avoid the use of laxatives, suppositories, or enemas. A capsule containing 20 to 24 markers is ingested initially, and abdominal radiography is performed either daily or on the 4th day, the 7th day, and every 3 days thereafter until all the markers are gone. Segmental transit times are then calculated using a mathematical formula. Colonic transit study results are used to classify patients with constipation into delayed transit, normal transit, and outlet obstruction. After day 6, there should be fewer than five markers remaining in the colon. With slow transit, more than five markers are scattered throughout the colon. With outlet obstruction, more than five markers are in the rectosigmoid region, and transit is normal throughout the rest of the colon.

Pelvic Floor Fluoroscopy and Magnetic Resonance Imaging

Pelvic fluoroscopy permits dynamic radiologic evaluation of pelvic floor and anorectal anatomy and physiology. It is particularly useful in obstructive defecation disorders, such as intussusception, rectocele, enterocele, anismus, and perineal descent. The patient is placed on a radiolucent commode, and contrast material is instilled into the rectum. The addition of vaginal, bladder, and oral contrast material is helpful diagnostically when multicompartmental prolapse is suspected. A series of lateral still images or continuous imaging using videography are made with fluoroscopy while the patient is at rest, during defecation, and with contraction of the anal sphincter. Similar films can be obtained for evacuation of the bladder. Pelvic fluoroscopy has many names, including defecography, defecating proctography, defecating cystoproctography, and colpocystoproctography, depending on the technique used. The measurements obtained include size of the rectal ampulla, length of the anal canal, anorectal angle, puborectalis motion, and pelvic floor descent. Severity and location of prolapse and pelvic floor descent is quantified in relation to the pubococcygeal line. Pelvic fluoroscopy is superior to physical examination for diagnosing enterocele (98,99), and this technique has the advantage of being able to distinguish enteroceles from sigmoidoceles. Rectosphincteric dyssynergia may be present when the patient experiences incomplete relaxation of the puborectalis muscle during rectal evacuation, the anorectal angle is preserved, and there is incomplete emptying. Pelvic fluoroscopy is considered the definitive test for diagnosing intussusception (91,99), and it is the preferred technique for quantifying perineal descent. **Dynamic MRI with luminal contrast is an imaging modality similar to pelvic fluoroscopy.** Its ability to detect prolapse is similar to that of fluoroscopy, but MRI can visualize pelvic floor

musculature and soft tissue, giving it the advantage of detecting ballooning of the levator muscles and levator ani hernias. The supine position of the testing is a drawback; however, there are isolated reports of upright dynamic MRI using open scanners that show results comparable to fluoroscopy for detection of anorectal pathology (100). Fluoroscopy and dynamic MRI can be used in situations involving severe multicompartmental prolapse or in which the severity of the symptoms is disproportionate to examination findings.

Anal Manometry

Anal manometry is useful to evaluate obstructed defecation, through determination of maximum resting pressure, maximum squeeze pressure, rectal sensation and compliance, and the presence of an intact rectoanal inhibitory reflex. With disordered defecation, it can be used to diagnose Hirschprung disease and anismus. The addition of surface EMG to document relaxation helps exclude anismus as a cause of obstructed defecation. Failure of the anal sphincter to relax with defecation and increased electrical activity of the EAS and puborectalis are seen in patients with anismus. In contrast, there should be no increase in the electrical activity measured by surface electrodes for patients with Hirschprung disease. A rectal balloon expulsion test can be of assistance in the evaluation of rectal emptying and may be valuable during physiotherapy for diagnosing dyssynergic defecation.

Colonoscopy

Standard gastrointestinal evaluation for patients with symptoms of disordered defecation, and anyone above the age of 50, should include routine colorectal cancer screening. The lifetime incidence for patients at average risk is 4.3% in the United States (101). Accepted modalities for screening include stool-based testing (guaiac-based fecal occult blood test [gFOBT], fecal immunochemical test [FIT], FIT-DNA) and visualization-based testing (colonoscopy, computed tomography colonography, flexible sigmoidoscopy + FIT/gFOBT). Office-based gFOBT, digital rectal examination and barium enema/double-contrast barium enema are no longer recommended as screening tests because of low sensitivity and specificity compared with other techniques (102).

THERAPEUTIC APPROACH TO FECAL INCONTINENCE

Treatment of fecal incontinence should focus on nonsurgical options, including dietary modification, medical therapy, and biofeedback. Any underlying systemic conditions or gastrointestinal disorders should be treated before initiating an extensive evaluation for other causes of fecal incontinence. If symptoms persist, further investigation should be undertaken. If the evaluation discloses an underlying EAS defect

and conservative therapy has been unsuccessful, it is reasonable to proceed with surgical treatment provided the patient's decision is well informed concerning potential benefits and risks.

Following is an overview of treatment options and the efficacy of each approach. The lack of consistent outcome measures makes it difficult to compare efficacy among treatments. Some studies base success on strict conformity with criteria for continence, but the results vary for continence of flatus, liquid, or solid stool. Other studies base success on more subjective criteria, such as improvement following treatment. Daily diaries can be maintained, but the results may be unreliable. Even if a validated symptom survey and QoL scale is employed, few studies use the same outcome measures.

Nonsurgical Treatment

Nonsurgical management focuses on maximizing the continence mechanism through alteration of stool characteristics or behavioral modification. Stool consistency and volume can be manipulated by dietary and pharmacologic means to achieve passage of one to two well-formed stools per day. The rationale for this approach is that **formed stool is easier to control than liquid stool.** Behavior modification can be employed using bowel regimens that focus on the predictable elimination of feces. Physical therapy and biofeedback can be useful for strengthening the continence mechanism.

Pharmacologic Approaches

Dietary Modification and Fiber

Dietary modification for treatment of fecal incontinence frequently involves avoidance of foods that precipitate loose stools and diarrhea. Common dietary irritants include spicy foods, coffee, and other caffeinated beverages, alcohol, and citrus fruits. Avoidance of dairy products or the addition of lactase dietary supplements is essential for those with lactose intolerance.

The addition of fiber may improve fecal incontinence by functioning as a stool-bulking agent to increase volume and density. The average individual in the United States consumes less than one-half of the recommended daily fiber intake (25 to 35 g). Various fiber sources are listed in Table 31-12, with the highest content found in fiber cereals. It is difficult to consume the recommended daily amount from diet alone, and fiber supplements often are useful. Although the increased stool volume and density helps many individuals maintain continence, excessive fiber with inadequate fluid intake may predispose elderly patients to fecal impaction.

Constipating Agents

Constipating agents have the most value in patients with chronic loose stools or

diarrhea. They can help improve symptoms in patients with fecal frequency, urgency and incontinence.

Loperamide (Imodium) and *diphenoxylate hydrochloride with atropine (Lomotil)* are the most commonly used agents. *Loperamide* is a synthetic peripheral μ-opioid receptor agonist that has been shown to prolong transit time and stimulate anal sphincter function. With either of these agents, careful titration is recommended to prevent the primary side effect of constipation. It is generally preferable to begin using 2 to 4 mg of *loperamide* every other day to daily and then titrate up to 4 mg three to four times per day. A 4-mg dose before meals has been shown to increase anal tone and improve continence (103). Use should be avoided in patients with risk factors for QT prolongation.

Lomotil is started at a dose of 1 to 2 tablets every day or every other day and titrated up to 1 to 2 tablets three to four times a day as needed. Caution should be exercised for patients taking other anticholinergic medications. Anticholinergic side effects include dry mouth, drowsiness, lightheadedness, and tachycardia.

Table 31-12 Fiber Sources

Cereals		**Fiber Supplements**	
All-Bran Extra Fiber (1/2 c)	15 g	Konsyl (1 tsp)	6.0 g
Fiber One (1/2 c)	14 g	Perdiem (1 tsp)	4.0 g
Raisin Bran (1/2 c)	7 g	Metamucil (1 tsp)	3.4 g
All Bran (1/2 c)	6 g	Maalox w/fiber (1 tbs)	3.4 g
Fruit & Fiber (2/3 c)	5 g	Mylanta w/fiber (1 tsp)	3.4 g
Frosted Mini Wheats (1/2 c)	3 g	Citrucel (1 tbs)	2.0 g
Breads		**Vegetables**	
Whole wheat (1 slice)	2.0 g	Lettuce (1 c)	1.4 g
White (1 slice)	0.5 g	Celery (1)	0.5 g
Bagel (1)	1.0 g	Tomato, raw (1)	1.0 g

Modified from **Ellerkmann MR, Kaufman H.** Defecatory dysfunction. In: Bent AE, Ostergard DR, Cundiff GW, et al, eds. *Ostergard's Urogynecology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:362, with permission.

Codeine is a constipating agent, but should be used with caution, especially in those with chronic disorders and in elderly patients because of side effects associated with narcotics, including addiction with prolonged usage and central nervous system and respiratory depression. With these limitations in mind, there is evidence of efficacy for

codeine in a study of geriatric patients with fecal incontinence (104). Eighty-two patients were treated based on the underlying cause: lactulose and enemas for fecal impaction, and codeine phosphate and enemas for neurogenic fecal incontinence. The rate of cure for fecal incontinence was 60% in the treatment group versus 32% for controls (P <0.001).

Drugs that act on the anal sphincter may have a role to play in those with fecal incontinence, including phenylephrine gel, zinc-aluminium ointment and oral sodium valproate (105). A Cochrane review published in 2013 confirms improvement in fecal incontinence with medication, but with a higher rate of adverse effects such as constipation, compared with placebo (105).

Medications for Irritable Bowel Syndrome

Dietary treatment of IBS consists of avoiding foods that are associated with symptoms, including alcohol, caffeine, sorbitol, and foods that increase gas production. Although increased dietary fiber or fiber supplementation has been shown to improve the constipation-predominant form of this illness (IBD-C), fiber supplementation has little effect on the diarrhea variant associated with fecal incontinence. The Rome IV collaboration describes dietary fiber supplementation as a cornerstone of IBS management, although its optimal use can be nuanced (46). Benefits appear to be confined to soluble (psyllium/ispaghula husk) and not insoluble (bran) fiber, as the latter can instead exacerbate problems of distention and flatulence. Low gluten diet and dietary FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) restriction may offer some benefit. Pharmacologic therapy is directed toward the predominant symptom. Agents and rationale for their use are reviewed in the Rome IV papers (46) **(Table 31-13)**, and some are reviewed here.

Loperamide and *Lomotil* tend to be useful first-line agents for treating diarrhea. Tricyclic antidepressants improve abdominal discomfort and are valuable in diarrhea-predominant patients because of their constipating effect. The serotonin type 3 (5HT3) antagonist *alosetron (Lotronex)* has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe diarrhea-predominant IBS refractory to treatment. It has shown improvement in global assessment measures, but its use is limited because of multiple isolated case reports of ischemic colitis. The recommended dose is to begin at 0.5 mg once or twice daily. It does not appear to be effective for the spastic-pain variant of IBS.

Ondansetron and *ramosetron* appear effective in the treatment of IBS-D. Anticholinergics (*dicyclomine, hyoscyamine*) and antispasmodics (*mebeverine, pinaverine*) are targeted at the pain and bloating symptoms but may be useful for the diarrhea variant because of their constipating side effects. Studies comparing medications with anticholinergic properties show inconclusive results with only modest benefits. Anticholinergic agents typically used for overactive bladder have not been

well-studied in the fecal incontinence/diarrhea population, but anecdotally may have dual benefit in patients with both problems.

A study of *tolteridine* in 36 healthy subjects for 6 days compared to placebo examined bowel effects using habits recorded by diaries and concluded that *tolterodine* did not significantly affect stool consistency or ease of defecation at the therapeutic dose used to treat overactive bladder (106). *Tolteridine* is a nonselective muscarinic antagonist and is known to have a lower incidence of constipation compared to other anticholinergic agents used for overactive bladder, which may be M3 selective.

Table 31-13 Laxatives and Other Treatments of Disordered Defecation/Functional Constipation/IBS-C (46)

Agent	Adult Dose	Onset of Action	Side Effects
Bulk-forming soluble fiber			
Natural (*psyllium*)	up to 30 g/d in divided doses	12–72 hrs	Impaction above strictures
Synthetic (*methylcellulose*)	4–6 g PO	12–72 hrs	Fluid overload
Emollient laxatives			
Docusate salts	50–500 mg PO	24–72 hrs	Skin rashes
Mineral oil	15–45 mL PO	6–8 hrs	Decreased vitamin absorption
Hyperosmolar/osmotic laxatives			
Polyethylene glycol	17–34 g/day	1 hr	Abdominal bloating
Lactulose	15–60 mL PO	24–48 hrs	Abdominal bloating
Sorbitol	120 mL 25% solution PO	24–48 hrs	Abdominal bloating
Glycerine	3 g suppository	15–60 min	Rectal irritation
	5–15 mL enema	15–30 min	Rectal irritation
Sodium phosphate	120 mL enema	15-60 min	Electrolyte derangement in elderly
Saline laxatives			
Magnesium sulfate	15 g PO	0.5–3 hrs	Magnesium toxicity, (caution in low eGFR)
Magnesium phosphate	10 g PO	0.5–3 hrs	

Magnesium citrate	200 mL PO	0.5–3 hrs	
Chloride channel activators			
Lubiprostone	8 µg PO BID–24 µg BID		Nausea, diarrhea
Guanylate cyclase C agonists			
Linaclotide	145 µg–290 µg PO daily		Diarrhea
Plecanatide	3 mg PO daily		Diarrhea
Serotonin 5-HT$_4$ Receptor Agonist			
Prucalopride[a]	1–4 mg/day PO		Transient headaches, nausea, diarrhea
Stimulant laxatives			
Castor oil	15–60 mL PO	2–6 hrs	Nutrient malabsorption
Diphenylmethanes			
Phenolphthalein	60–100 mg PO	6–8 hrs	Skin rashes
Bisacodyl	30 mg PO	6–10 hrs	Gastric irritation
	10 mg PR	0.25–1 hr	Rectal stimulation
Anthraquinones			
Cascara sagrada	1 mL PO	6–12 hrs	Melanosis coli
Senna	2 mL PO	6–12 hrs	Degeneration of Meissner and Auerbach plexuses
Aloe (Casanthrol)	250 mg PO	6–12 hrs	
Danthron	75–150 mg PO	6–12 hrs	Hepatotoxicity (w/docusate)

[a]Not currently available in the United States.
PO, by mouth; PR, per rectum.
From **Wald A.** Approach to the patient with constipation. In: Yamada T, ed. *Textbook of Gastroenterology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1999:921, with permission.

Table 31-14 Agents for the Management of Functional Diarrhea/IBS-D/Fecal incontinence (46,114)

Type of Laxative	Adult Dose	Side Effects
Bulk-forming laxatives		
Natural (*psyllium*)	up to 30 g/day in divided doses	Impaction above strictures

Synthetic (*methylcellulose*)	4–6 g PO	Fluid overload
μ-*Opioid agonist*		
Loperamide	2–4 mg po; titrate up to 16 mg/day prn	
Diphenoxylate/atropine	5 mg QID until control achieved (maximum 20 mg/day); maintenance may be lower	
Bile salt sequestrants		
Cholestyramine	9 g BID–TID	Bleeding (high chronic doses)
Colestipol tablets	2 g daily–BID	
Colesevelam	625 mg daily–BID	
Probiotics	Multiple products available	
Antibiotics		
Rifaximin	550 mg po TID × 14 days	
Serotonin 5-HT_4 receptor agonist		
Alosetron	0.5–1 mg po daily–BID	Ischemic colitis risk
Ondansetron	4–8 mg TID	
Ramosetron	5 μg daily	
Mixed opioid agonists/antagonists		
Eluxadoline	100 mg BID	
Enhancement of anal sphincter tone		
Phenylepinephrine gel, sodium valproate, zinc-aluminum ointment, L-erythro methoxamine gel		
Barrier creams		
Zinc oxide, calmoseptine ointment, alkagin powder, aquaphor ointment		

Antispasmodic agents may be of value and are available in many countries but are not approved for use in the United States. Additional 5HT3 antagonists and 5HT4 antagonists are under development and are approved for use in Europe but not in the United States. Most studies are poorly designed and difficult to interpret because of a high placebo response rate that often exceeds 30% (107,108). Finally, patients with functional diarrhea and a previous cholecystectomy may find benefit from bile salt sequestrants such as cholestyramine, colestipol, and colesevalam (**Table 31-14**).

Behavioral Approaches

Biofeedback

Biofeedback can be an effective therapeutic modality provided patients are motivated and comprehend instructions. Three main modalities have been described: rectal sensitivity training (afferent), strength training (efferent), and coordination training. Afferent training focuses on improving sensation in the anorectal canal through recruitment of adjacent neurons to decrease the sensory threshold of volume stimulation. The goal of this training is to enhance and restore anal sensation and the rectoanal inhibitory reflex. Efferent training enhances and restores voluntary contraction of the EAS, which permits additional recruitment of motor units and stimulates muscle hypertrophy. These three methods of training are often combined for maximal therapeutic benefit. The most common training method uses an intrarectal balloon. The balloon acts to stimulate rectal distention and provide pressure feedback from coordinated or synchronized contraction of the pelvic floor muscles. Other techniques focus on strength training of the EAS alone using anal pressure feedback or EMG or afferent training alone using an intrarectal balloon without pelvic floor muscle contraction in response to the stimulus. There are many variations in protocol such as the number, frequency, intensity, and duration of sessions.

Several studies have been done to evaluate the efficacy of biofeedback for treatment of fecal incontinence, and several review articles and meta-analyses have determined the effects of individual treatments and predictors of patient response to treatment (109–114). The results of all of these studies uniformly agree that biofeedback and pelvic floor exercises improve fecal incontinence and have a role in clinical practice. They also agree that the literature is fraught with methodologic problems and lacks validated outcomes and controls, making it difficult to directly compare study results.

Biofeedback is an ideal first-line therapy because it offers an effective, minimally invasive treatment without any reported adverse events. Biofeedback appears to provide a higher probability of successful outcome than standard medical care for treating functional fecal incontinence (67% vs. 36%, respectively, $P < 0.001$) (109).

Combined biofeedback and electrical stimulation may be the best second-line treatment for fecal incontinence. A Cochrane review of biofeedback and exercises for treatment of fecal incontinence found 21 eligible studies with a total of 1,525 participants (115). The authors concluded that biofeedback and electrical stimulation may enhance treatment outcomes compared to either individual treatment alone. Transanal electrical stimulation may be more beneficial than vaginal exercises for women with fecal incontinence after childbirth. A systematic review and meta-analysis published in 2013 identified 128 studies examining electrical stimulation and biofeedback for the treatment of fecal incontinence. Twenty-three observational studies

and 13 RCTs were included. Outcomes varied from remission, response, or disease-related QoL on validated scales. Electrical stimulation alone was inferior to control (i.e., pelvic floor exercises) (RR 0.47, CI 0.13–1.72), whereas biofeedback alone was superior to control (RR 2.35, CI 1.33–4.16) for symptom improvement. Combination of biofeedback and electrical stimulation together compared to each monotherapy alone was superior. The authors concluded that higher-quality randomized controlled trials showed more significant differences between treatment groups, and support electrical stimulation plus biofeedback as the optimal second-line treatment for fecal incontinence after dietary and medical management (116).

There are no clear indicators to predict which patients will benefit from biofeedback. Potential factors include age, duration and severity of incontinence, prior treatments or surgery, and severity of neurologic or physical damage. Controversy exists as to whether response to biofeedback is dependent on the presence of a structurally intact anal sphincter or normal pudendal nerve function (115,116). There continues to be a need for well-designed controlled trials using validated symptom surveys and QoL instruments. More objective measures are desirable, and studies should carefully document duration of treatment and length of follow-up.

Bowel Regimens

The goal of bowel regimens is to achieve predictable elimination of feces. This can be accomplished by using the gastrocolic reflex and by dietary and pharmacologic means. Defecation immediately following meals involves the physiologic response of the gastrocolic reflex to facilitate predictable emptying. The strength of the gastrocolic reflex varies among individuals and may be hypoactive or hyperactive with certain systemic disorders, such as diabetes and multiple sclerosis. This technique can be especially useful in the morning to give the individual freedom from fecal incontinence throughout the day. The use of suppositories or enemas in the morning or at night in conjunction with the gastrocolic reflex may provide further relief of daytime symptoms. The goal is to leave the rectum empty between evacuations. Enema use, typically once or twice daily, should be titrated to the patient's baseline colonic activity. **Regular toileting is effective in institutionalized elderly patients with fecal incontinence caused by overflow incontinence from fecal impaction.** The use of cone-tip colostomy-irrigation catheters is reserved for patients in whom other therapeutic modalities have failed. These catheters avoid the risk of rectal perforation and provide a dam to prevent efflux of the irrigating solutions (117,118).

Barrier Devices

First described in the 1980s, barrier devices for fecal incontinence may be an appropriate option for some patients (119). There is a variety of available plugs, all

with the goal to block the escape of stool. They were initially designed for fecal incontinence in patients with neurogenic fecal incontinence, but can be used in any patient. Anal plugs are disposable inserts that sit in the anal canal and may be left in for a maximum 12 hours. A Cochrane review of four studies suggests that if tolerated, anal plugs are can be successful in maintaining fecal continence. High discontinuance rates (35%) occur as a result of rectal discomfort with these devices. Higher satisfaction was reported in the polyurethane plug than in the polyvinyl-alcohol plug groups (120). The American Gastroenterology Association clinical practice update reviews other devices such as anal insert devices (available in the United States) and vaginal inserts with pumps (118). The LIFE Study published in 2015 evaluated the effectiveness and safety of a vaginal bowel-control device and pump system, Eclipse (*Pelvalon, Sunnyvale, California*) in 61 women. At one month, intention-to-treat success was 79% and over 85% considered bowel symptoms "much better" or "very much better." There were no serious adverse events and the most common occurrence was pelvic pain (22.7%), mostly occurring during the fitting period (121). Controlled studies of longer duration are needed to fully assess barrier devices as safe and effective treatment options, and to define the subset of patients for whom they are effective.

Perianal Bulking Agents

The purpose of injecting a biomaterial into the anal canal is to augment anal canal coaptation and treat incontinence. *Dextranomer microspheres* in nonanimal-stabilized hyaluronic acid (NASHA Dx) is the only FDA-approved perianal bulking injection agent available. In a randomized-controlled study of 206 patients, 52% in the NASHA Dx group and 31% in the sham injection control group had improvement based on validated scales from baseline at 6 months (OR 2.36) (122). Eleven percent experienced complete continence and the majority needed two injections to achieve success. There were several criticisms raised about this study, including that patient selection should have been limited to those with passive incontinence and low anal canal pressures, and should have included anorectal sensory or motor function testing (123). Potential complications included abscess, proctalgia, and rectal hemorrhage.

Surgical Treatment

[4] In general, surgical treatment should be considered after conservative measures have failed. Although there may be exceptions to this principle, most surgeons follow this recommendation because of the poor long-term outcomes and high complication rates associated with surgery for fecal incontinence. The American Gastroenterology Association proposes a step-wise approach to the management of fecal incontinence starting with the least to most invasive **(Fig. 31-4)**.

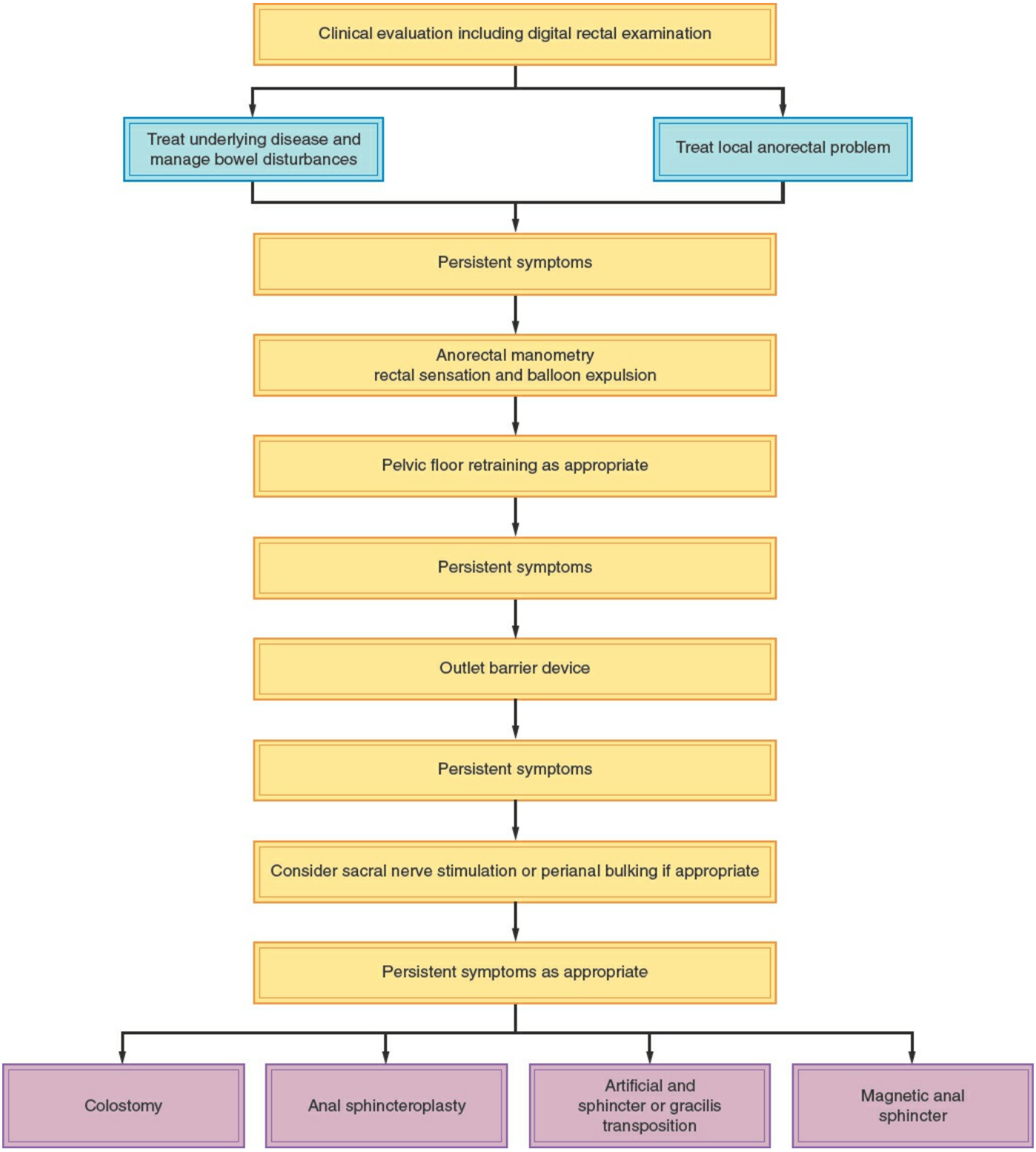


FIGURE 31-4 Step-wise approach to the management of fecal incontinence (American Gastroenterology Association) (118).

Neuromodulation

Sacral Nerve Root Stimulation

Sacral neuromodulation (InterStim®, Medtronic, Minneapolis, Minnesota, USA) was

approved by the U.S. FDA for treatment of urinary urge incontinence in 1997 and for nonobstructive urinary retention and urgency in 1999. It has been employed experimentally for the treatment of fecal incontinence since 1995 and was approved for this indication in 2011. The exact mechanism of action has not been fully elucidated. **[5]** The goal of sacral nerve stimulation is to recruit residual function of the continence mechanism through electrical stimulation of its peripheral nerve supply. Initially, indications were confined to patients with deficient EAS and levator ani function without gross morphologic defects and intact neuromuscular connections. The acceptable indications have expanded to include deficiency of the IAS, limited structural defects, and functional deficits of the IAS and EAS.

Technique

The device is placed exactly the same way as for treatment of urinary incontinence. Application is performed as a two-stage outpatient surgical procedure. The first stage involves placement of the electrodes. The electrode is placed through the S2–S4 foramen using minimally invasive surgical technique. Proper location is confirmed intraoperatively using fluoroscopy and visualization of an appropriate pelvic floor muscle response (bellows) with minimal plantar flexion of the first and second toes, which usually corresponds to S3 stimulation. An interval testing phase utilizes an external pulse generator that typically lasts 2 weeks. Those with a good response (decrease in fecal incontinence episodes of at least 50% documented by bowel habit diary) will proceed to the second stage with a permanent implantable pulse generator (IPG). Typically, only one electrode is left in place at the end of the second stage. After the permanent pulse generator is implanted, all adjustments are made using telemetry. The patient has a basic remote control that enables her to turn the device on or off and adjust the amplitude of the stimulation. The battery must be replaced every several years.

Efficacy

Data from over two decades on the efficacy of sacral neuromodulation have reported success rates of up to 54% in the long term (median follow-up 56 months) (124). By the end of 2003, sacral nerve stimulation had been used to treat more than 1,300 patients with fecal incontinence (125). Despite this large number, the analysis of the results was limited to several small case series. In all studies, significant improvements in continence scores lasting up to 99 months occurred. Most patients experienced at least a 75% improvement in continence scores. Improvement occurred in the frequency of incontinence episodes, the ability to postpone defecation, and bowel emptying. Intent-to-treat analysis revealed 80% to 100% therapeutic success. There were significant improvements in QoL measures using validated measurement scales. Complications occurred in 0% to 50% of patients, with the most common complications consisting of pain at the electrode or IPG site, electrode migration, infection, or worsening of bowel

symptoms. No permanent sequelae occurred. Effects of anorectal physiology varied among the published studies, highlighting the fact that the precise mechanism of action remains unclear.

A Cochrane review of six crossover trials and two parallel trials concluded that the limited data suggest that sacral nerve stimulation provides improvement in fecal incontinence but not in constipation (126). In the seminal multicenter trial conducted to evaluate the efficacy of sacral nerve stimulation for fecal incontinence, 90% of 133 patients proceeded from temporary to permanent stimulation. Wexner et al. prospectively followed 120 patients (110 female, 10 male) for a mean of 28 (2 to 70) months. Subjects completed validated QoL measures and bowel diaries. Success defined as a 50% or greater improvement and reduction in fecal incontinence episodes per week was achieved in 83% at 1 year and 85% at 2 years. Forty-one percent achieved total continence at 1 year and mean incontinent episodes decreased from 9.4 to 1.9 per week. The same group reported an overall 10.8% infection rate (13/120), with 9 occurring within the first month and 4 occurring after 1 year (127,128). This study served as the driving force for FDA approval of sacral nerve stimulation for the indication of fecal incontinence in 2011. Among the early infections, five responded to antibiotics, one resolved spontaneously, and three were treated surgically. For the late infections, all four had to be removed. The same group has published long-term follow-up data. Seventy-six of the total of 120 women with sacral nerve stimulation for chronic fecal incontinence were followed for 5 to 8 years. Eighty-nine percent reported having greater than 50% improvement and 36% reported complete continence (129). The most common adverse event in this trial was infection, at a rate of 10%.

Another large multicenter study of 200 patients revealed decreased severity scores and improved QoL with sacral nerve stimulation. Loose stool consistency and low-stimulation intensity were predictive of successful outcomes on multivariate analysis. Ultrasound findings, manometry, age, and gender did not impact outcomes (130). Tjandra et al. (131) performed a RCT of 120 subjects with 1-year follow-up comparing sacral nerve stimulation to best supportive therapy consisting of pelvic floor exercises, bulking agent, and dietary manipulation. Fecal incontinence outcomes improved dramatically in the stimulation group with 47% achieving complete continence. In contrast, there were no significant improvements observed in the supportive therapy group. This study suggests that sacral nerve stimulation is the optimal therapy for severe incontinence (131). Bharucha et al. summarize randomized controlled trials comparing neuromodulation with medical treatment and percutaneous tibial nerve stimulation (PTNS) (118). In these studies, sacral nerve stimulation was significantly better than medical treatment but not significantly better than PTNS.

The UK National Institute for Health and Care Excellence (NICE) guidelines recommend chronic, electrical stimulation of the sacral root as the first-line surgical intervention for fecal incontinence (132). In the American Society of Colon and Rectal

Surgeons Clinical Practice Guideline for the Treatment of fecal incontinence, SNS is given a "1B" recommendation: strong recommendation, moderate-quality evidence (133).

Thus, sacral nerve stimulation appears to be a promising treatment for fecal incontinence with relatively limited complications. The minimally invasive nature of this procedure makes it a desirable first-line surgical option.

Overlapping Sphincteroplasty

[6] Overlapping sphincteroplasty is the procedure of choice for fecal incontinence caused by a disrupted anal sphincter. Most authorities believe that an overlapping technique is superior to an end-to-end repair, although there are few direct comparisons in the literature. The rationale for the overlapping technique is that a more secure repair can be accomplished by placing sutures through the scarred connective tissue rather than the sphincter muscle itself. The idea is that sutures should be less likely to tear through or pull out of connective tissue than muscle. Therefore, the key component of the overlapping technique is preservation of the scarred ends of the ruptured EAS for suture placement. Proponents of the end-to-end repair suggest that the overlapping technique requires a wider dissection of the EAS that is more likely to result in a muscle denervation that could impact future function.

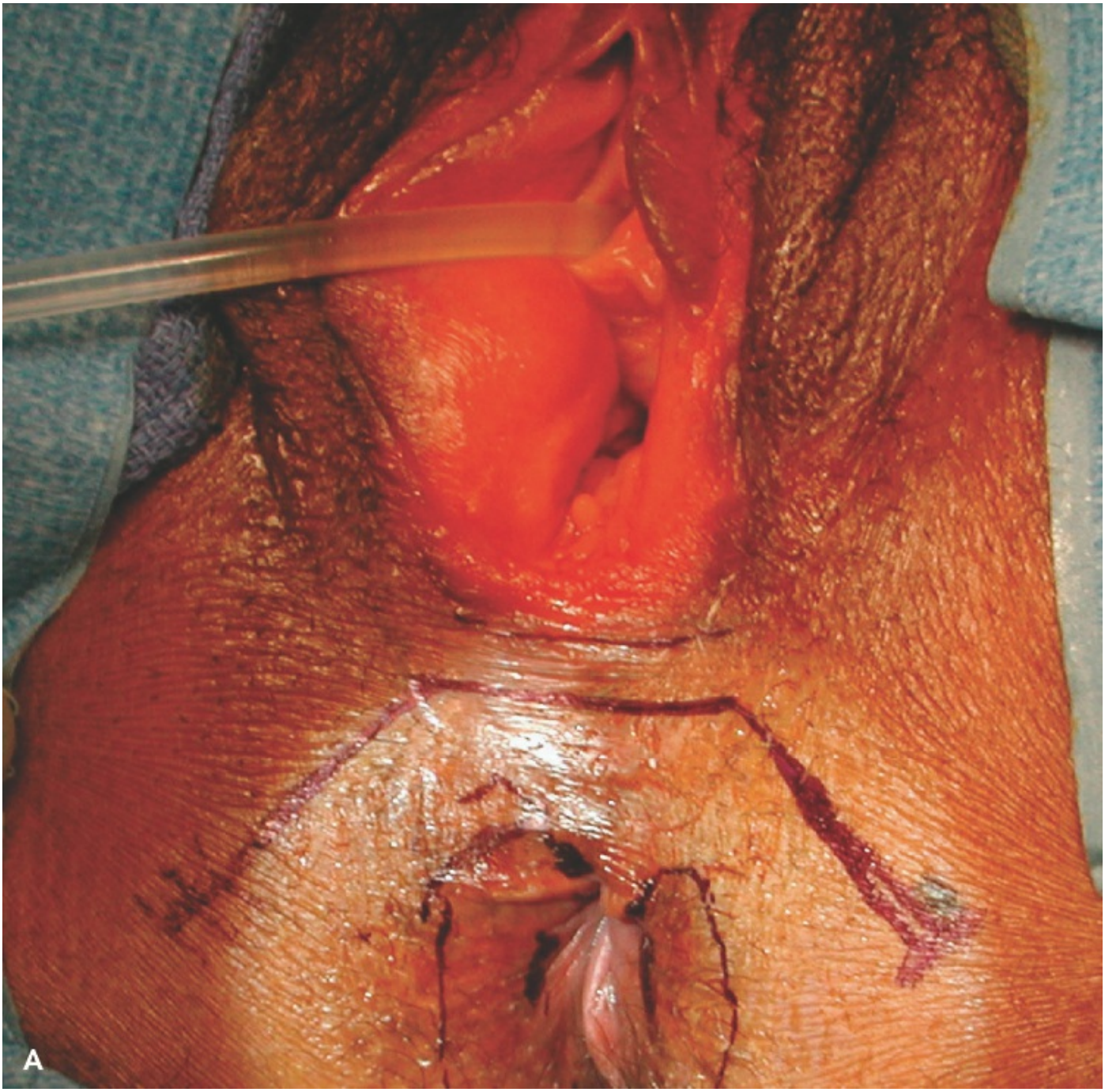
Technique

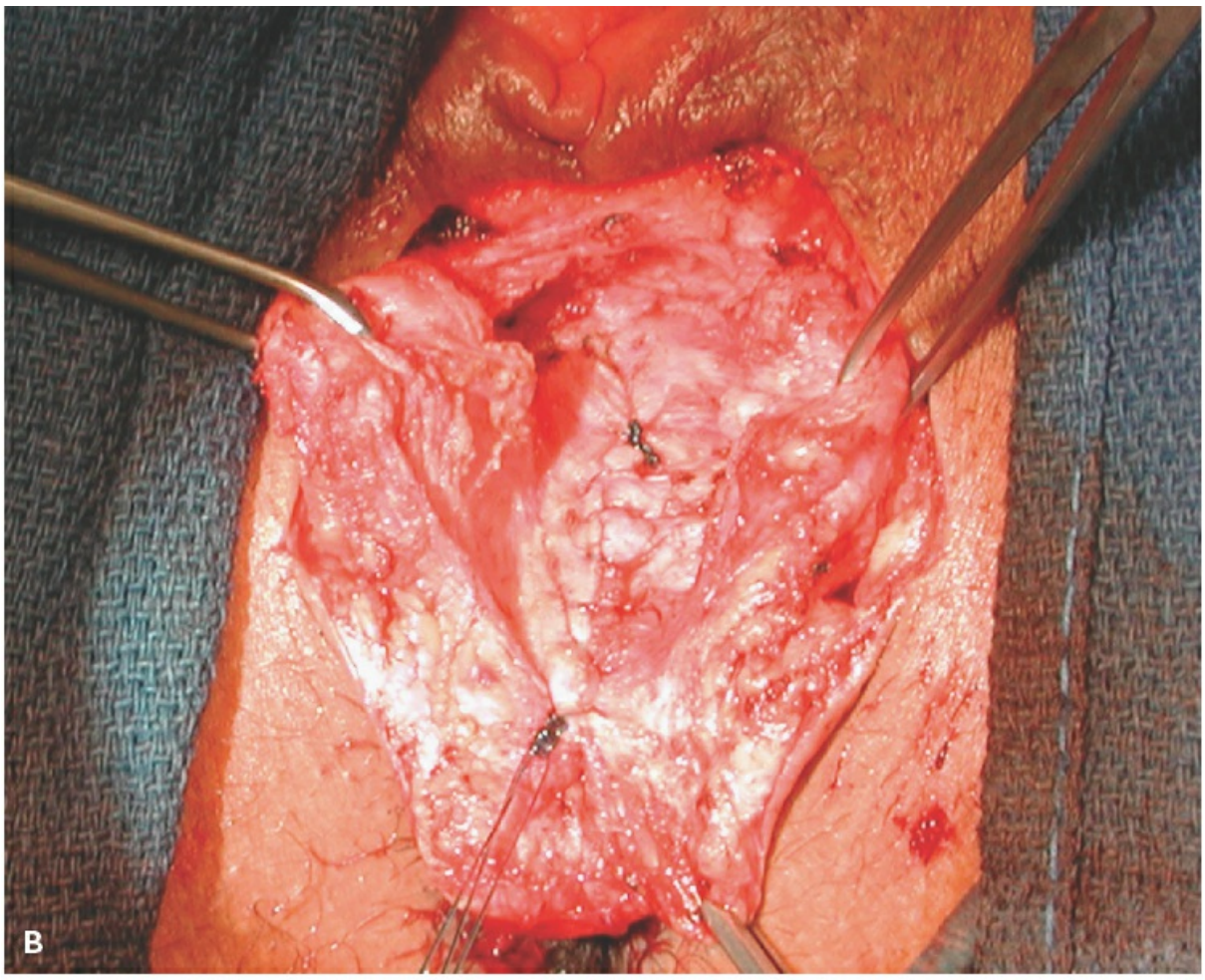
The initial step involves wide mobilization of the ruptured EAS without excision of the scarred ends of the sphincter. This is accomplished through an inverted semilunar perineal incision or a transverse incision near the posterior vaginal fourchette with inferiolateral extension. The latter incision facilitates repair in patients with concurrent damage to the rectovaginal septal attachment to the perineal body. Patients with EAS defects have either a band of intervening fibrous scar tissue between the viable muscular ends of sphincter or a complete separation with scar tissue present only on the ruptured ends of the sphincter. In the presence of complete separation of scar tissue, perineal body reconstruction usually is indicated at the time of repair to restore normal anatomy. A Peña muscle stimulator aids in identification of the course of the EAS and differentiates viable muscle tissue from scar tissue. The stimulator can be used to outline the sphincter before incision and during the dissection. It is important to apprise the anesthesiologist of the stimulator usage so that paralytic agents are avoided.

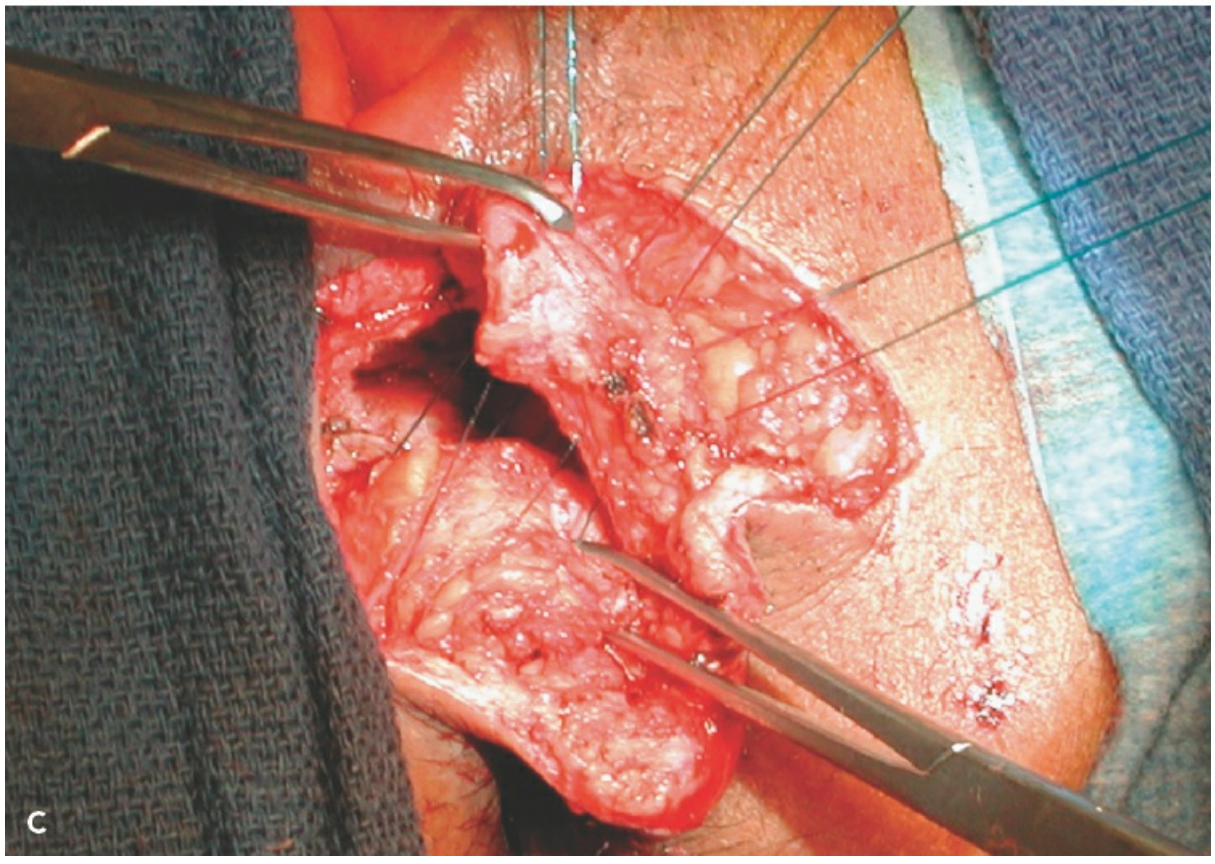
Excessive lateral dissection of the EAS past the 3 and 9 o'clock positions potentially jeopardizes the inferior rectal branches of the pudendal nerve that innervate the EAS. Moderate bleeding is often encountered during this dissection, making a needlepoint electrocautery useful to maximize hemostasis. The colorectal literature suggested that identification and reconstruction of the IAS was not necessary, although more recent experience demonstrates continued fecal incontinence associated

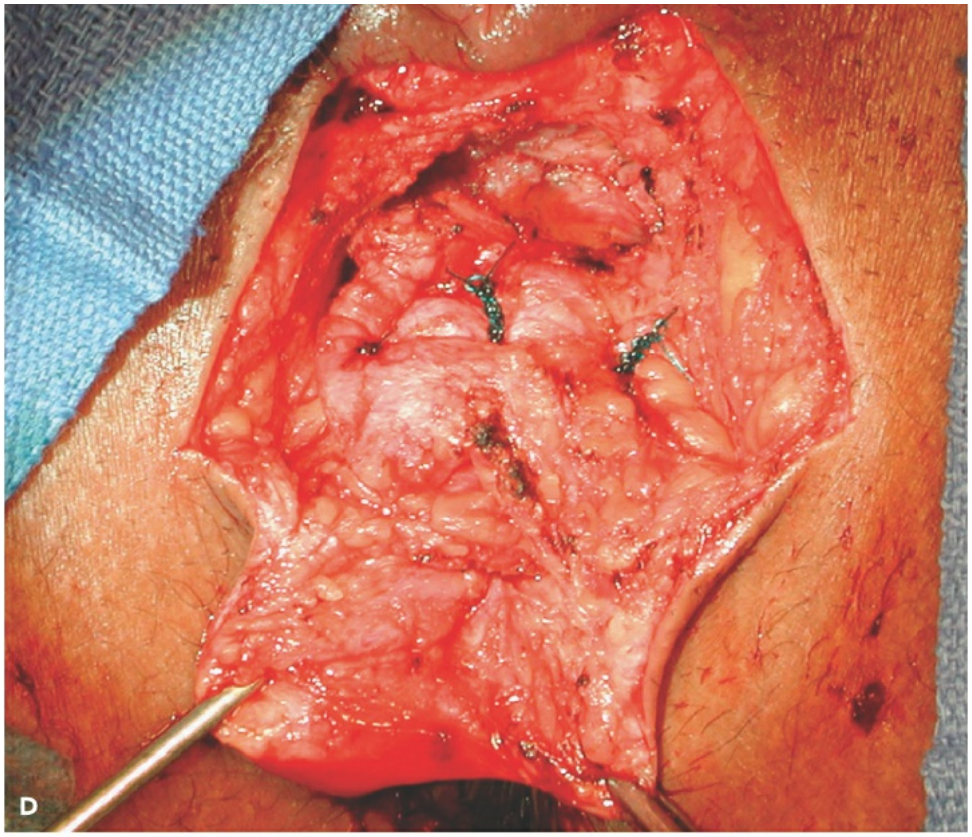
with discontiguous IAS. Consequently, dissection and repair of the IAS is recommended. Identification of the intersphincteric groove facilitates dissection of the EAS and IAS. Dissection in this plane is relatively simple and avoids damage to either sphincter. Defects in the IAS can be more difficult to visualize because this muscle is intimately associated with the rectal mucosa. Examination with a finger in the anal canal is often helpful.

The reconstruction begins with repair of an existing IAS defect using a 3-0 delayed absorbable monofilament suture. Next, the EAS defect is repaired with the primary goal of overlapping at least 2 to 3 cm to ensure adequate bulk of sphincter muscle encircling the anal canal. The EAS is overlapped using three to four mattress sutures of 2-0 delayed absorbable monofilament suture through the distal scar tissue. After the sutures are tied, there should be resistance palpable with placement of a finger in the anal canal. Copious irrigation is performed throughout the procedure. Following sphincter repair, a perineal body reconstruction and rectocele repair should be undertaken, if indicated, to maximize the normal continence mechanism. Finally, the perineal skin is closed with interrupted absorbable monofilament sutures. Closure frequently requires modification of the initial incision because of changes in the perineal architecture that result from the repair. The most common approach is an inverted Y-shaped closure of the incision **(Fig. 31-5)**.


A


B


C


D


E

FIGURE 31-5 Overlapping sphincteroplasty procedure. A: Inverted semilunar perineal incision with the distal ends of the external sphincter outlined using the Peña muscle stimulator. **B:** The external sphincter has been dissected, the scar divided in the midline, and the internal sphincter repaired. **C:** The external sphincter is overlapped using three mattress sutures of 2-0 delayed absorbable monofilament suture through the distal scar tissue. **D:** The sutures are tied. **E:** The skin is closed.

Some surgeons recommend the overlapping repair regardless of whether it is performed immediately postpartum, delayed postpartum, or several years after obstetric injury. Long-term analyses of RCTs comparing end-to-end and overlapping sphincter repairs in primary repairs suggest better long-term outcomes for the overlapping technique (134). Performance of the overlapping technique immediately postpartum, requires adequate anesthesia, exposure, and equipment best accomplished in the operating room. This repair lacks the theoretical advantage of using scar tissue to improve suture holding; however, it maximizes surface area for scarification of the sphincter ends. For a delayed postpartum repair, some surgeons recommend waiting 3 to 6 months until inflammation is resolved and reinnervation is completed. Cessation of breastfeeding may be beneficial for postoperative wound healing by restoring normal vaginal estrogen status.

The Cochrane review comparing end-to-end approximation versus overlapping sphincteroplasty after an acute obstetric injury included six randomized control trials involving 588 women. Outcomes included reducing subsequent anal incontinence, perineal pain, dyspareunia and improving QoL (134). Given data heterogeneity, the literature does not support recommending one obstetric anal sphincter repair technique over the other, however there were some differences shown between the two groups. For example, women in the overlapping repair group from one trial (52 women followed up for 12 months) had less fecal urgency and lower fecal incontinences scores (135). Another trial showed that these differences were no longer present at 36 months (136).

Efficacy

Despite the many large series reporting the outcomes of overlapping sphincteroplasty, almost all are retrospective in nature and lack validated measures of symptom severity and QoL considerations. Several overlapping sphincteroplasty series with a total of 891 patients were evaluated from 1984 to 2001. Although the length of follow-up was variable, the results showed good outcomes in approximately two-thirds of patients (median 67%, range 52% to 83%) (115). None of these studies had long-term outcomes.

Some studies suggest poor long-term outcomes for the overlapping sphincteroplasty.

Short-term outcomes in the first 12 months after sphincter repair are favorable in up to 85% of patients (137) but failure rates of over 50% are noted by 5 years (138–141). Rezvan et al. summarized 10 studies on long-term outcomes of sphincter repair (142).

Three of these studies are described here.

In a series of 55 women who underwent overlapping sphincteroplasty for fecal incontinence secondary to obstetric trauma (138), researchers contacted 47 (86%) patients by postal questionnaire and telephone interview with a median time since surgery of 77 months (range 60 to 96 months). The investigators observed less symptomatic improvement when compared with the results at 15 months postoperative evaluation. After excluding one patient because of Crohn disease, eight (17%) failed because they required additional surgery, such as colostomy, postanal repair, and artificial bowel sphincter. Among the remaining 38 patients, 27 (71%) reported improved bowel control, 5 (13%) were unimproved, and 6 (16%) were worse. No patient was fully continent to solid and liquid stool and flatus. Only 23 (50%) patients had "good" outcomes defined as not requiring further continence surgery and fecal incontinence less than once per month.

In another study, investigators contacted 49 (69%) of 71 patients by telephone interview (141). All underwent overlapping sphincteroplasty with a median follow-up of 62.5 months (range 47 to 141 months). Only 6 (12%) patients were totally continent, and another 18 (37%) were continent to liquid and solid stool. In other words, more than half of the patients had incontinence to liquid or solid stool. The largest series with long-term follow-up involved contact of 130 (71%) of 191 patients using a postal or telephone questionnaire (118). The median time from surgery for respondents was 10 years (range 7 to 16 years). Of those who responded, 6% had no incontinence, 16% were incontinent of flatus only, 19% had soiling only, and 57% were incontinent of solid stool. These outcomes were significantly worse than the previously reported 3-year assessment (143). Despite the fact that 61% had a poor outcome defined as having fecal incontinence or requiring additional surgery for incontinence, 62% still considered their bowel control to be better than before surgery, and 74% were satisfied with the results of their surgery. Thus, although control may be improved when compared with preoperative status, continence outcomes do not seem to be maintained at long-term follow-up.

The cause of this deterioration in long-term outcomes is unknown. Possible explanations include weakening of the muscles with normal aging, repair breakdown, and underlying nerve damage from either obstetric injury or the repair itself. A problem with most studies is the lack of a follow-up ultrasonography to determine if the repair is intact. The effect of pudendal nerve function on overlapping sphincteroplasty is somewhat controversial. Significantly lower success rates have been shown in a comparison of those with normal pudendal nerve terminal motor latencies to those with abnormal latencies (63% vs. 17%, $P < 0.01$) (144). Some studies have confirmed this finding, while others refute it (138,145). Other factors that may affect outcome include age, duration of fecal incontinence, size of the defect, and anal manometry results. Recognizing that an overlapping sphincteroplasty only addresses one aspect of the

continence mechanism helps to put these results into perspective.

Although there are many controversial aspects to overlapping sphincteroplasty, the literature is in agreement that diverting colostomy is not necessary; bowel confinement does not improve outcomes (146–149); clinical improvement correlates with postoperative endoanal ultrasonography results (138,150,151); and prior sphincteroplasty does not affect outcomes (144,150,152).

Subsequent Deliveries

Multiple studies confirm the impact of anal sphincter laceration during the first delivery on the risk of a sphincter laceration in a second delivery (153–160). These studies have calculated odds ratios ranging between 3.8 and 5.9 for a second sphincter disruption compared to women without prior obstetrical anal sphincter injury (58). Although higher than in women without a prior injury, the risk of having a recurrent obstetric anal sphincter injury is the same for a woman with previous injury as the baseline risk for a primiparous delivery; both around 5% (58,161). The vast majority of women with a third- or fourth-degree tear (~91%) will not have a recurrent sphincter injury. Therefore, **although a history of prior sphincter laceration increases the risk of recurrent sphincter laceration, the risk remains relatively small.** Nevertheless, the rate of anal incontinence worsens, especially if she had transient anal incontinence after the index anal sphincter injury (58). A decision analysis modeling study concluded that in women with prior obstetrical anal sphincter injury 2.3 elective cesarean sections would need to be done to prevent one case of anal incontinence, at a cost of increased maternal morbidity related to cesarean section (162), which many women will find to be an acceptable risk. It is therefore important to accurately counsel expectant mothers about their risk of sphincter laceration. Using this information, they can decide whether the risk of recurrent laceration outweighs the risk of elective cesarean birth. The risk of subsequent vaginal delivery on symptoms of fecal incontinence is unknown for women with a repaired anal sphincter. The presence or absence of pre-existing fecal incontinence, and the estimated fetal weight, should be considered in counseling for a subsequent pregnancy. Cesarean section is more advantageous for those women with prior anal sphincter injury who are symptomatic.

Graciloplasty

Surgical reconstruction with a muscle flap is an option in cases that have insufficient muscle to repair the EAS when all conservative measures have failed. Insufficient muscle can be caused by trauma, infection, or severe atrophy that results from denervation injury and congenital disease. Most patients considering this procedure have already undergone an overlapping sphincteroplasty that failed. Graciloplasty, first described by Pickrell et al. in 1952 (170), is a skeletal muscle transposition procedure that uses the gracilis to create a new anal sphincter. There are

three suitable muscles for this type of procedure: the gracilis, sartorius, and gluteus maximus. Ideally, the muscle should be easily mobilized and transposed but not essential for locomotion or posture. The sartorius and gluteus maximus are suboptimal because the sartorius receives segmental vascularization, which restricts rotation, and the gluteus maximus is important in daily activities such as running, climbing stairs, and rising from a sitting position. **The gracilis is a better choice because it can easily be mobilized without damage.** As the most superficial adductor, it receives neurovascular supply proximally and has no important independent function.

Technique

Either one long incision or three small incisions are made in the medial thigh. The gracilis muscle is identified and mobilized toward its insertion onto the medial aspect of the tibia where the tendon is divided. Anterior and posterior perianal incisions are made approximately 1.5 cm from the anal verge. Tunnels are developed in the extrasphincteric space and from the proximal thigh to the anterior perianal incision. The gracilis muscle is gently delivered to the anterior perianal incision, guided around the anus to the posterior perianal incision, and returned to the anterior incision encircling the anal canal. The distal tendon of the gracilis is passed behind the muscle and anchored to the contralateral periosteum of the ischium. In cases when there is inadequate length, it can be sutured to the ipsilateral ischium. This procedure can be performed bilaterally. In patients with a large rectovaginal fistula or cloaca, a myocutaneous flap can be mobilized and used to help close the defect. Improvement of fecal incontinence is caused by passive increase of the resistance of the anal canal by the bulk of the encircling muscle **(Fig. 31-6)**.

Experimental efforts to improve the efficacy of this procedure have focused on dynamic graciloplasty, which develops resting tone in the transposed muscle through the use of an implanted neurostimulator. The intent of the stimulated graciloplasty is to convert the fast-twitch muscle fibers into slow-twitch muscle fibers, which are more fatigue resistant. Initially, implantation of the pacemaker was performed at 6 weeks after the graciloplasty, but now most are performed concomitantly. Stimulation can be applied directly to the obturator nerve or intramuscularly to the nerve branches inside the muscle. The muscle is stimulated at a cyclic frequency, with gradual increases every 2 weeks. After 2 months, continuous stimulation is performed. Stimulation is adjusted to maintain tonic contraction around the anus, and it is interrupted or turned off to defecate.

Efficacy

The dynamic graciloplasty restores fecal continence in 42% to 85% of patients (171). However, given the high rates of morbidity, this procedure is rarely pursued. Complications include surgical-site infection, rectal pain, rectal injury, stimulator malfunction and device erosion, and the rate of postsurgical obstructive constipation is as high as 50% (172).

An exhaustive review of the literature identified 37 articles of patients undergoing dynamic graciloplasty (171). Most of these articles were case series, and there were no randomized trials or cohort studies evaluating safety and efficacy. Mortality rate was 1% (range 0%–13%, 95% CI, 1%–3%) after excluding cancer deaths. There was a high rate of morbidity (1.12 events per patient). Thus, most patients will have at least one adverse event, and several will have multiple complications. There is a very high reoperation rate. The most common complications were infections (28%), stimulator and lead faults (15%), and leg pain (13%). Satisfactory continence was achieved 42% to 85% of the time, although satisfaction was not defined consistently across studies. The authors concluded that dynamic graciloplasty appeared to have equal or better efficacy than colostomy but carried a higher morbidity rate. Two review articles state this procedure is no longer being performed routinely in the United States (113,118).

Artificial Sphincter

The artificial anal sphincter is an alternative to a graciloplasty. This is a modification of the device originally designed to treat urinary incontinence. The current device is the Acticon® Neosphincter (American Medical Systems, Minnetonka, Minnesota, USA). The indications for its use are similar to those for the graciloplasty. A silastic inflatable cuff is placed around the native sphincter to occlude the anal canal. A pressure-regulating balloon containing radio-opaque solution is situated in the retropubic space, and a control pump is positioned in the labia majora. Activation of the control pump deflates the cuff, permitting defecation (see **Fig. 31-7**).

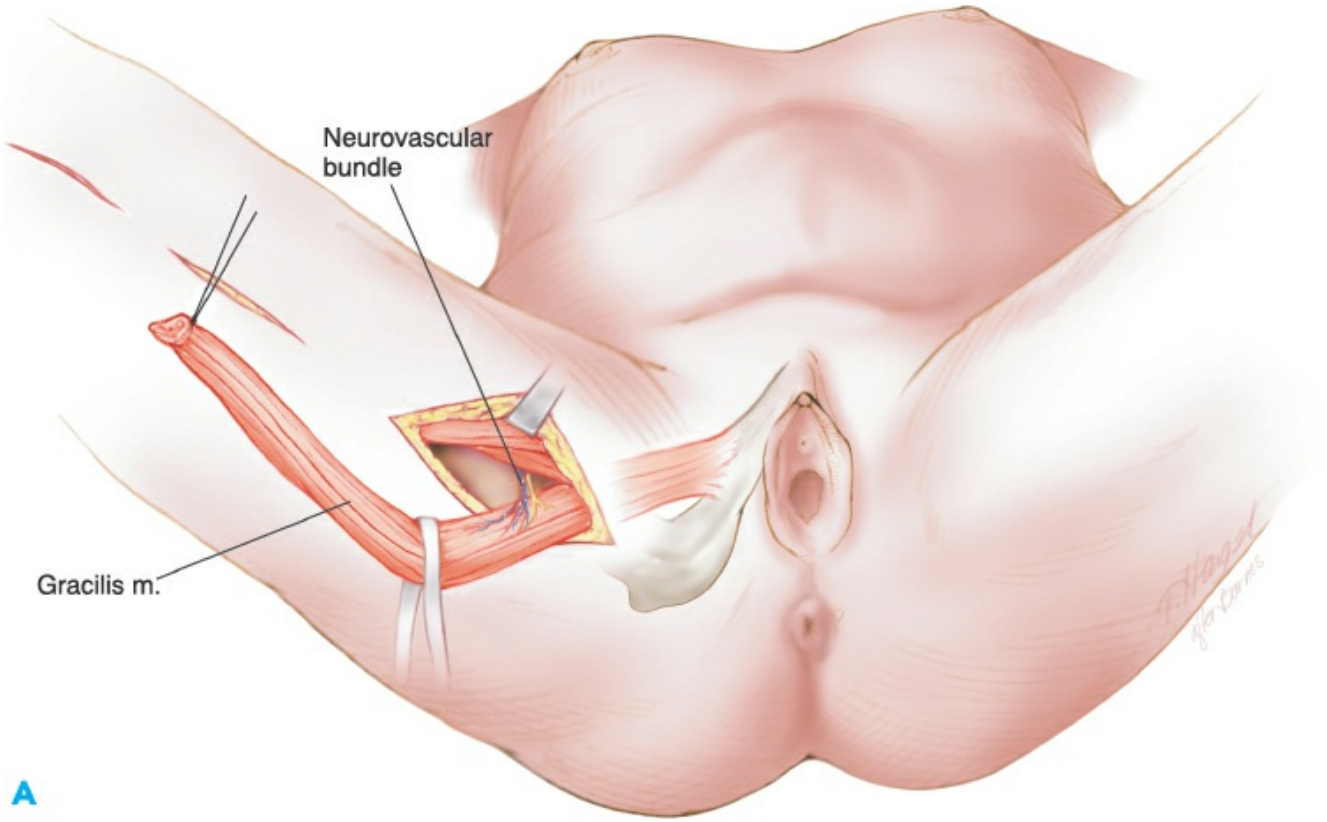
Technique

Implantation of the artificial anal sphincter is performed, similar to the graciloplasty, through perianal tunnels.

Efficacy

An extensive review of the literature summarized 13 case series and one case report from 1996 to 2003. There were no randomized trials or cohort studies (163). The largest series consisted of 112 patients (164). Explantation was required in 17% to 41% of patients. Reasons for explantation included infection, erosion, device malfunction, pain, incontinence, and dissatisfaction, with infection being the most common. Surgical revision was necessary in 13% to 50% of the reports. Almost everyone had at least one adverse event, and more than one-third of these events required surgical intervention. Reasons for surgical revision were similar to those for explantation. Rates of fecal impaction ranged from 6% to 83%. All studies recorded statistically and clinically significant improvement in continence scores for patients with a functional artificial sphincter; however, most did not report the continence status for those in whom the device was explanted. The proportion of patients with a functional device ranged from 49% to 85%. The authors concluded that there is insufficient evidence on the safety and

effectiveness of the artificial sphincter for fecal incontinence. In 2011 this same group published their experience over one decade (mean follow-up >5 years) in 52 patients. All patients had failed conservative management and undergone preoperative assessment with anal endosonography, manorectal manometry, and physiologic testing. Mean follow-up was 64.3 months. Fifty percent of patients required revision surgery after a mean of 57 months, with the most common indication being leaking from the cuff as a result of a microperforation. Twenty-seven percent of patients required explantation, with the most common indication being infection. In the 35 patients with an activated device *in situ*, there was a significant improvement in median FIQoL Scores compared to those with devices explanted or deactivated. The authors conclude that favorable long-term results can be achieved with careful patient selection, meticulous surgical technique and dedicated surveillance (165).



A



B

FIGURE 31-6 Graciloplasty. A: The gracilis muscle is identified and mobilized toward its insertion onto the medial aspect of the tibia where the tendon is divided. **B:** Anterior and posterior perianal incisions are made approximately 1.5 cm from the anal verge. The muscle is then tunneled around the extrasphincteric space circumferentially. The distal tendon is passed behind the muscle and anchored to the contralateral periosteum of the ischium.

One randomized control trial of 14 patients compared artificial sphincter with a program of supportive care (166). Supportive care included all aspects of conservative management, such as physiotherapy, dietary advice, pharmacotherapy, and advice regarding skin care, odor management, anxiety reduction, and use of incontinence aids or appliances. Significant improvements in continence scores and QoL measures were seen in the artificial sphincter group but not in the control group at 6 months follow-up. Explantation rate was 14% (1 of 7 patients). Two other patients had complications, including severe fecal impaction and perineal wound erosion requiring reoperation. The authors conclude that **the artificial sphincter is safe and effective compared with supportive care alone.** They anticipate perioperative and late complications, which may require explantation in up to one-third of patients. It is remarkable that only one patient (14%) whose condition was managed conservatively had significant improvement based on continence scores, whereas the status of all others was relatively unchanged.

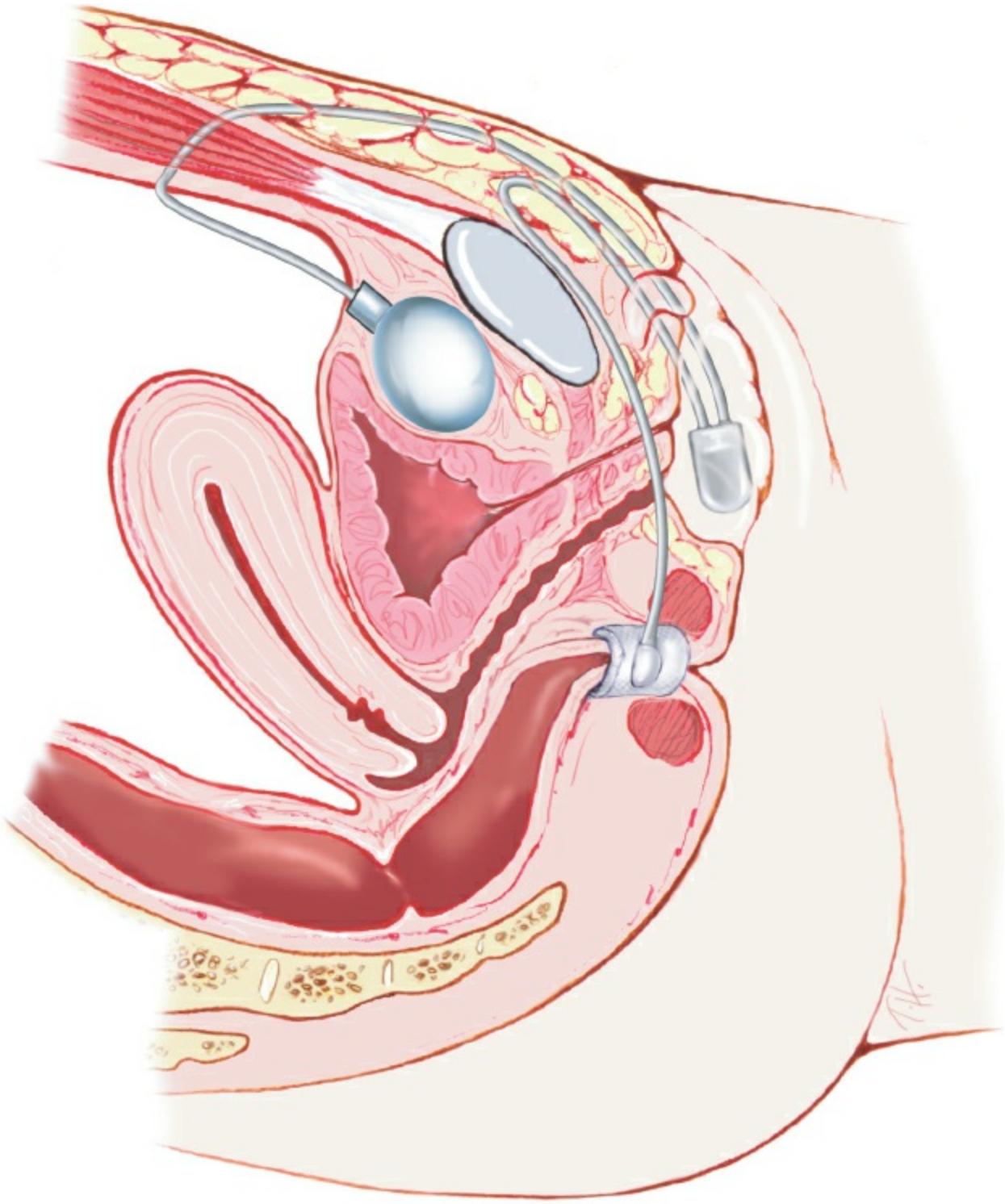


FIGURE 31-7 Acticon Neosphincter. This device includes an inflatable cuff placed around the anal canal, a balloon reservoir stored behind the pubic bone, and a pump located in the labia.

Another study compared the effectiveness of artificial sphincter with dynamic graciloplasty (167). Two surgeons each performed four consecutive operations with each technique to minimize the learning curve of a new operation. Each started with a different procedure to avoid discrepancies in the time of follow-up. This prospective cohort study involved eight patients in each group who had similar demographic

variables. Length of follow-up was 44 months in the artificial sphincter group and 39 months in the dynamic graciloplasty group. Early postoperative complications were similar in each group at 50%, as were late complications, with both groups reporting a high reoperation rate of 63%. There were six (75%) late complications in the artificial sphincter group, of which three (38%) were nonreversible and required explantation. Postoperative continence scores were significantly lower with the artificial sphincter than with graciloplasty. The authors conclude that **artificial sphincter has better efficacy and similar morbidity compared with dynamic graciloplasty.** The rate of late complications for the artificial sphincter exceeded that reported in the literature, which may indicate poor long-term durability. Postoperative continence scores reflect those reported for artificial sphincter but are far worse than those for dynamic graciloplasty. The authors feel that the learning curve with the artificial sphincter is less important than that with graciloplasty.

Artificial Magnetic Sphincter

The artificial magnetic sphincter (Magnetic Anal Sphincter; Fenix, Torax Medical Inc., Shoreline, MN) is a small, flexible band of connected titanium beads with magnetic cores. This encircles the EAS and creates a barrier. Pressure with defecation causes the beads to separate and the stool to be evacuated.

Technique

Access to the EAS is achieved in the same fashion as a sphincteroplasty. A tunnel is created circumferentially around the EAS taking care to avoid injuring the pudendal nerve bundles. This is done with probing with a single digit around the outside of the EAS. An introducer tool is placed around the anal canal in the tunnel created and the sizing tool is connected. When the proper size has been ascertained, the same introducer tool is used to introduce the implant by threading the suture through the cross-hole feature. The implant is introduced in a linear shape, then closed around the EAS to form an annular shape. The suture and introducer tool are removed after the implant is in place.

Efficacy

The magnetic anal sphincter has been available since 2011 and is available in Europe. The FDA approval in the United States is based on a multicenter, prospective nonrandomized clinical study of 35 subjects, of which a majority had sustained obstetrical injury, and were not candidates for or had previously failed conservative treatment with less invasive therapy options. This study examined the safety and probable benefit data at 6, 12, 24 and 36 months. Combining all adverse events, 37% of patients experienced moderate to severe complication. At 36 months, 57% of patients reported a 50% or greater reduction in fecal incontinence episodes and improvement in the FIQoL Score was seen in all categories (168). In 2011 a prospective,

nonrandomized study of 20 patients demonstrated significant improvement in fecal incontinence severity and the FIQoL Score, surgical time, and hospital stay were shorter for the magnetic sphincter group compared to the artificial sphincter group (165).

Percutaneous Tibial Nerve Stimulation

Based on the same principle of neuromodulation as sacral nerve stimulation, PTNS offers a more minimally invasive option.

Technique

The technique is identical to PTNS for urge urinary incontinence (Chapter 29, page 725). The tibial nerve is stimulated percutaneously with a small needle 5-cm cephalad to and 2-cm behind the medial malleolus. The needle is inserted and advanced 2-cm deep, then connected to the lead wire, which is connected to the stimulator. With this technique, the nerve is stimulated electrically for 30 minutes once or twice per week for several consecutive weeks. An alternative is to use a skin-surface electrode, referred to as "transcutaneous" stimulation.

Efficacy

The American Gastroenterology Association guidelines recommend sacral nerve stimulation, however, they state that PTNS should not be used for managing fecal incontinence until further evidence is available (118). The largest trial, published in the Lancet (CONFIDeNT; 227 patients randomized to PTNS vs. control) did not show a significant benefit of PTNS once per week for 12 weeks in their primary outcome, as 38% in the PTNS group had a 50% or greater reduction in the number of episodes of fecal incontinence per week compared to 31% in the control group (OR 1.28, CI 0.72–2.28). However, PTNS did result in a significant reduction in the mean number of total episodes of fecal incontinence per week and mean number of episodes of urge fecal incontinence per week, compared with control (a needle inserted to 2 mm but no electrical stimulation). Although statistically significant, the clinical interpretation of a reduction from 6 episodes of fecal incontinence per week to 3.5 episodes may or may not be interpreted as helpful to patients (169).

THERAPEUTIC APPROACH TO CHRONIC CONSTIPATION

As with fecal incontinence, it is imperative to attempt conservative management of constipation and defecatory dysfunction before pursuing surgery. Initial evaluation should focus on identifying any underlying systemic conditions (see Table 31-1) associated with disordered defecation and optimizing treatment for these conditions. In the absence of systemic etiologies, it is reasonable to proceed with empiric, nonsurgical management, such as diet, fiber supplementation, and toileting behavior. Biofeedback and laxatives can be used in more severe cases. Initially, disimpaction with regular

enemas or laxatives is essential if the patient has fecal impaction. **Symptoms that persist despite a trial of conservative management indicate the need for further evaluation of colonic and anorectal function.** A diagnostic and management algorithm for idiopathic (nonsystemic) constipation is shown in **Figure 31-8**. Treatment should be tailored to the underlying cause. Some conditions associated with disordered defecation are best treated using nonsurgical techniques, whereas others may benefit from surgery after conservative management has failed. As with fecal incontinence, the lack of consistent outcome measures in the literature makes it difficult to compare efficacy among treatments.

Nonsurgical Treatment

Nonsurgical management focuses on maximizing anorectal function through alteration of stool characteristics or behavioral modification. Stool consistency and volume can be manipulated by lifestyle, behavioral and dietary means to achieve passage of one stool every day or every other day. This is the mainstay of first-line treatment options for patients with normal and slow-transit constipation. These modifications include an increase in physical activity, toilet retraining, and dietary changes. Physical activity, most beneficial in early morning, can lead to intestinal gas clearance, less bloating and constipation. Toilet retraining includes instructions not to ignore urges to defecate, use a "brace-pump" technique with the knees higher than the hips and feet supported on a step to straighten the anorectal angle. The patient is instructed to do deep-relaxation while defecating, avoid straining when passing stool and not stay on the toilet for more than 5 to 10 minutes. Finally, drinking hot caffeinated beverages and eating breakfast within an hour of waking up can take advantage of the gastrocolic reflex and increase intestinal motility (98).

Abdominal massage produces a response in the rectum and anus by stimulating the somatovisceral reflexes resulting in bowel peristalsis which decreases colonic transit time and increases bowel movement frequency (173) **and has been shown to be acceptable and effective, especially with neurogenic bowel** (174,175).

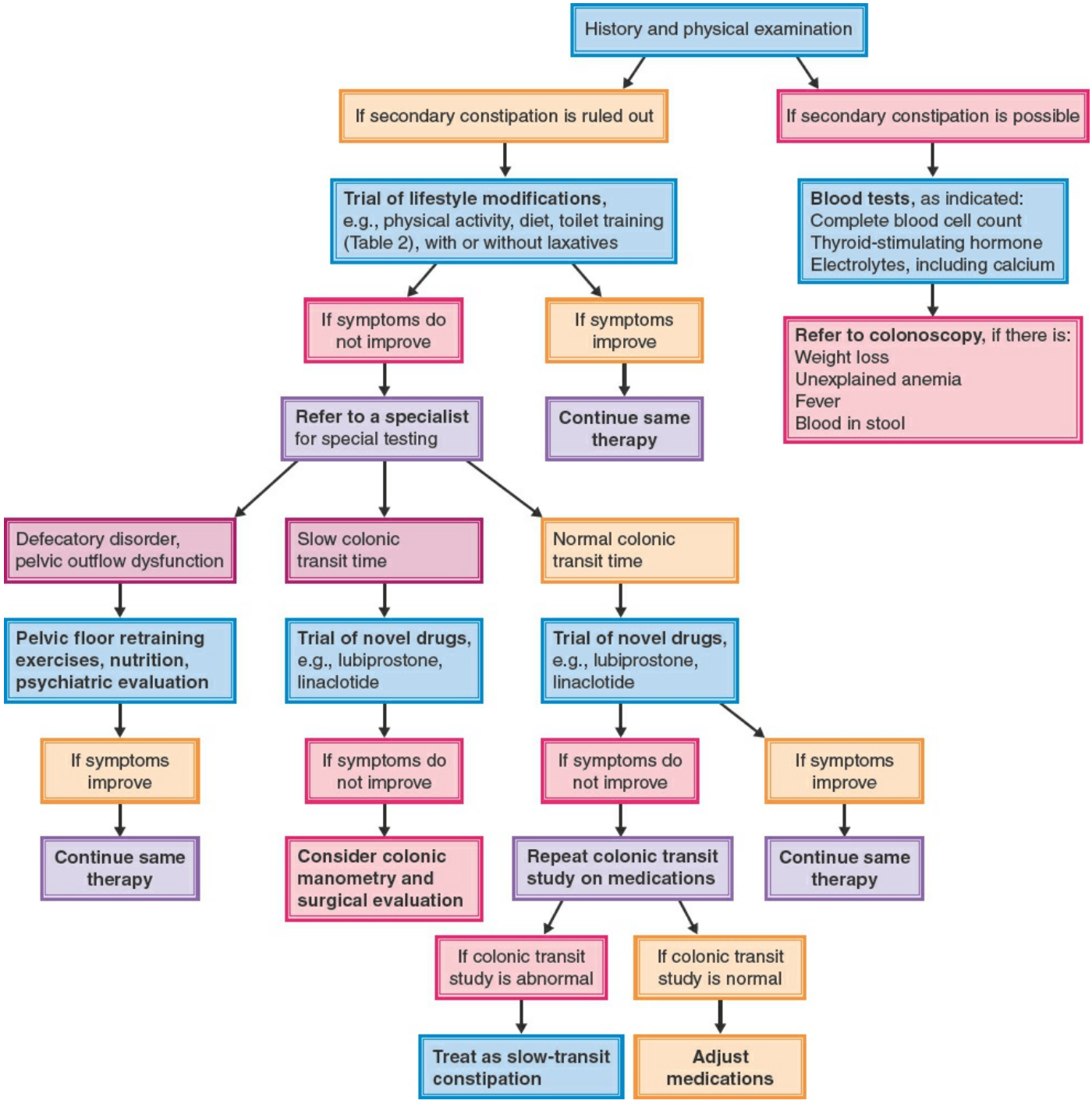


FIGURE 31-8 Diagnosis and management of chronic constipation. (From **Hayat U, Dugum M, Garg S.** Chronic constipation: update on management. Cleveland Clinic Journal of Medicine 2017;84(5):397–408.)

Physical therapy and biofeedback can be useful for coordinating pelvic floor and anal sphincter relaxation with defecation.

Pharmacologic Approaches

Dietary Modification and Fiber

The role of increased fluid and fiber intake for the treatment of constipation is

controversial. For years, it has been a commonly accepted belief that constipation is caused by low fluid intake and can be improved by increasing consumption. Several studies showed no association between fluid intake and constipation (3,176,177). However, one large study of 21,012 nursing home residents found a weak association between decreased fluid intake and constipation with an odds ratio of 1.49 (95% CI 1.21–1.82) (178). A review of articles examining water intake and constipation in children and adolescents found an association between decreased fluid intake and constipation, however, an association between increased fluid intake for the successful treatment of constipation could not be determined (179). Overall, the existing data do not support increased fluid intake to treat constipation unless there is evidence of dehydration (176,180).

The addition of fiber (25 to 30 grams daily) may improve constipation through several mechanisms. Bulk-forming laxatives include insoluble fiber (wheat bran) and soluble fiber (psyllium, methylcellulose, inulin, calcium polycarbophil). Fiber acts as a stool-bulking agent and improves stool consistency through water absorption. It can act as a substrate for bacterial proliferation and gas production. These mechanisms of action are believed to result in increased colonic motility, decreased transit time, and increased stool frequency.

Fiber therapy appears to have a beneficial effect in the treatment of diverticular disease (181), **constipation of pregnancy** (19), **and possibly IBS** (46). It is most effective for normal-transit constipation. Although psyllium fiber of up to 30 mg/day in divided doses is recommended as a therapeutic option for FC, dose-dependent bloating, distention and flatulence may affect tolerance to this regimen. Increasing dietary fiber is less likely to benefit patients with slow-transit constipation or refractory outlet dysfunction (19,27,97). Up to 60% of patients reported adverse effects with 1 month of insoluble fiber use (177). A review of 7 RCTs (n = 254) in which older adults were assigned to either dietary fiber or placebo showed no improvement in stool frequency in two trials looking at psyllium fiber. Results from three trials of galactooligosaccharide were mixed (the product is not readily available to consumers). The use of a mixture of fiber (guar gum and wheat bran) and lactitol (osmotic agent) in yogurt resulted in increased stool frequency in 51 medical and surgical inpatients. It is unclear whether the fiber or the osmotic agent was responsible for this result (3). Dietary fiber intake for patients with constipation was similar to that of controls in several studies (182,183). A meta-analysis of 36 randomized trials using laxatives or fiber therapy for the treatment of constipation showed that the use of fiber or laxatives resulted in increased stool frequency and improved symptoms without the presence of severe side effects (184). Conversely, another meta-analysis showed an inability to restore transit time and stool weight in constipated patients using dietary fiber (185). Approximately one-half of the patients in another study responded to fiber treatment, but a much better response occurred in patients without an identifiable structural or motility disorder (186).

Consequently, a low-fiber diet may be a contributing factor in chronic constipation, and an empiric trial of fiber therapy can be expected to help some patients. Side effects of increased gas production may limit compliance with treatment, so doses should be slowly titrated. Fiber therapy should be avoided in patients with impaction, megacolon or megarectum, or obstructive gastrointestinal lesions. Fiber therapy should be used with caution in patients with cognitive dysfunction (dementia), difficulty with ambulation, and underlying neurogenic disease for fear of worsening the condition. There is no evidence to substantiate the recommendation for extra water intake with fiber supplements (187) unless the patient is dehydrated (173).

Laxatives

Laxatives are commonly used to treat constipation and disordered defecation (Table 31-13). Many classes of laxatives are available over the counter.

Bulk-forming Laxatives

These come in a natural, soluble form (*psyllium*), and a synthetic form (*Metamucil, Konsyl, Citrucel*), and are felt to be the safest laxatives. They have mechanisms of action and side effects similar to that of fiber and may take several days to have an effect (173).

Hyperosmolar Laxatives

These consist of poorly absorbed substances that bulk and soften the stool, while stimulating and lubricating the gastrointestinal tract. This is done by increasing intraluminal osmolarity and water absorption. Because it is not absorbed systemically, this laxative has no drug interaction or contraindication, making it safe for children and the elderly. Examples include nonabsorbable sugars (*lactulose and sorbitol*), *glycerin*, and *polyethylene glycol* (*GoLytely, MiraLAX*). *Polyethylene glycol* is a common preoperative bowel preparation. Side effects are diarrhea, increased flatus, and abdominal cramping (188). A randomized-controlled trial of polyethylene glycol versus placebo in patients with irritable-bowel syndrome, constipation type (IBD-C) did show improvements in stool frequency consistency and straining. There was no difference in abdominal pain or bloating over 4 weeks (189).

Emollient Laxatives

These agents are divided into two subsets: *docusate salts* and mineral oil. The *docusate salts* have hydrophilic and hydrophobic properties similar to detergents. They soften stool and decrease surface tension by increasing stool water and lipid content. Examples include *docusate calcium* (*Surfak*), *docusate potassium* (*Dialose, Kasof*), and *docusate sodium* (*Colace, Comfolax*). They improve the absorption of other laxatives and are combined in preparations with stimulant laxatives such as *Correctol, Peri-Colace, and Feen-a-Mint*. The limited absorption of mineral oil allows it to penetrate and soften the stool. It can be used orally or rectally. Prolonged daily use can

lead to decreased absorption of the fat-soluble vitamins A, D, E, and K. Use of mineral oil should be avoided in elderly and debilitated patients, and in those with esophageal motility disorders because of the potential for aspiration pneumonia. Side effects include diarrhea, anal leakage, and pruritis ani (188).

Saline Laxatives

These usually contain magnesium cations and phosphate anions that are relatively nonabsorbable and produce an osmotic gradient with increased water absorption. They stimulate intestinal motility by increasing cholecystokinin release. Fast-acting effects can be seen with oral (2 to 6 hours) and rectal (15 minutes) preparations. Examples include *magnesium citrate, magnesium hydroxide* (*Milk of Magnesia*), *magnesium sulfate, sodium phosphate,* and *biphosphate* (*Phospho-soda, Fleet enema*). Although generally well tolerated, electrolyte abnormalities can occur. These side effects should be avoided in patients with renal insufficiency because of the potential for magnesium toxicity (188).

Stimulant Laxatives

These are found in three basic types: *castor oil*, anthraquinones, and diphenylmethanes. A metabolite of *castor oil, ricinoleic acid*, increases intestinal motility and secretion. Anthraquinones (*cascara sagrada, senna* [*Senekot*], *casanthranol* [*aloe*], and *danthron*) are absorbed by the small intestine and stimulate motility by increasing intraluminal fluid and electrolyte content. Diphenylmethanes (*phenolphthaleins* [*Feen-a-Mint, Correctol*] and *bisacodyl* [*Dulcolax*]) have a mechanism of action similar to anthraquinones. These agents are potent and are intended for short-term use in cases refractory to bulk or osmotic laxatives. They are rapid acting (under 12 hours). It has been a long-standing belief that prolonged use can lead to a dilated atonic colon known as cathartic colon syndrome, melanosis coli, or neuronal degeneration. Over the past decade the theory that stimulant laxatives damage the autonomic nervous system when used at recommended doses has been refuted (176). Other side effects include cramping, nausea, and abdominal pain (188).

Prokinetic Agents

Medications that stimulate gastrointestinal motility primarily through neuromodulation of acetocholine levels include *metoclopramide,* cholinergic agonists (*bethanechol*), cholinesterase inhibitors (*neostigmine*), and serotonin agonists. Their efficacy in the treatment of chronic idiopathic constipation is uncertain. *Metoclopramide* is better for upper gastrointestinal motility disorders (188). Selective serotonin $5HT_4$-receptor agonists (*prucalopride, naronapride, velusetrag*) stimulate serotonin receptors in the intestinal walls to increase muscular contraction of the colon (173). Adverse effects reported include headache, nausea, abdominal pain and cramps. Two 5-HT_4 receptor agonists were withdrawn from the market (*cisapride, tegaserod*) because of serious

cardiovascular adverse events resulting from their affinity for hERG-K+ cardiac channels, a property not found in the newer 5-HT_4 agonists (97).

Intestinal Secretagogues

Chloride channel activators (*lubiprostone*) increase intestinal fluid secretion and gut motility. A prostaglandin E1 derivative, this drug is licensed for the treatment of chronic idiopathic constipation and should only be prescribed by experienced clinicians. Adverse effects include nausea and headache (190). Guanylate cyclase-C receptor agonist (*linaclotide, plecanatide*) increases intestinal fluid secretion and transit and is licensed for the treatment of moderate-to-severe IBS associated with constipation as it decreases visceral pain (173).

Opioid-induced constipation (OIC) is a distinct diagnosis within the Rome IV framework with specific diagnostic criteria (46). Initial treatment is the same as for those patients with FC. Laxatives are recommended for the prophylaxis and management of OIC. Additional medications include opioid receptor antagonists. If the antagonist acts centrally, this may precipitate opioid withdrawal symptoms (*naloxone, nalbuphine*). Medications that act peripherally only block the opioid receptors in the gastrointestinal system and will not lead to withdrawal symptoms (*subcutaneous methylnaltrexone, alvimopan, naloxegol, naldemedine*), which may be an important method of providing constipation relief to palliative, oncology, and substance use disorder populations.

Behavioral Approaches

Behavioral techniques such as biofeedback and bowel regimens may have a role in certain conditions associated with constipation and defecatory dysfunction. Overall, these approaches have far less application to disordered defecation than to fecal incontinence. **Biofeedback is important in the treatment of dyssynergic defecation. Relaxation techniques and behavioral modification may be helpful for IBS. Bowel regimens in conjunction with laxatives, suppositories, and enemas can** facilitate emptying by optimizing the gastrocolic reflex and increased peristaltic activity.

Efficacy of Nonsurgical Treatment

Irritable Bowel Syndrome

The most commonly used first-line treatment for the constipation variant of IBS is fiber supplementation and osmotic laxatives. The efficacy of bulking agents for this condition is controversial, and many studies, including meta-analyses, exhibit an effect similar to placebo. There may be benefit to the use of fiber because of the high placebo effect with IBS treatment and lack of serious adverse events associated with its use. However, patients may experience exacerbation of bloating and abdominal discomfort with fiber therapy. Randomized trials and meta-analysis revealed a beneficial effect of

polyethylene glycol (MiraLAX) over placebo for the treatment of chronic constipation (191,192). They can be useful as adjunctive treatment options, but can exacerbate abdominal pain and discomfort.

Colonic Inertia and Slow-Transit Constipation

Patients with slow-transit constipation tend to respond poorly to fiber supplementation, although most have already tried an empiric trial of fiber before testing to confirm the diagnosis (186). Some patients may benefit from regular toileting, either in the morning or after meals when there is increased colonic motor activity. Biofeedback may have modest short-term benefits, but the long-term effect is questionable (193). A randomized-controlled trial of eight biofeedback sessions over a 4-week period conducted in 30 cognitively intact older people reported an increase in stool frequency from 2 to 4 bowel movements per week compared to controls who received counseling (194). Enemas and suppositories can be used in conjunction with bowel regimens. It is reasonable to attempt a trial of any of the laxatives listed in **Table 31-13**. Stimulant laxatives commonly are used, but questions remain about the development of neuronal degeneration with prolonged usage and the need for increasing doses to yield the same desired effect. It is imperative that patients adhere to and not exceed the recommended dosages. Osmotic agents are likely the safest and most effective. Increasing amounts of data regarding newer prokinetic agents may demonstrate that this class of medication is the ideal choice when the goal is to stimulate colonic motility.

Dyssynergic Defecation

As with slow-transit constipation, initial management using bowel regimens, laxatives, enemas, suppositories, and fiber supplementation is appropriate for patients with dyssynergic defecation, yet many will have already tried conservative management before undergoing testing to confirm the diagnosis. These treatments are relatively well tolerated with few serious side effects. They have not been shown to have greater efficacy when compared with placebo, and their role in the treatment of dyssynergic defecation remains uncertain. Specific treatment for this condition tends to focus on biofeedback because of studies indicating that this is an acquired behavioral disorder of defecation. Modalities such as diaphragmatic muscle training, simulated defecation, and manometric or EMG-guided anal sphincter and pelvic muscle relaxation have been employed independently or combined with other techniques. These techniques have yielded symptomatic improvement in approximately 60% to 80% of patients. Many patients with dyssynergic defecation have abnormal rectal sensation, so rectal sensory conditioning may provide additional benefits (37,195). Others have tried *botulinum toxin* injections to paralyze the puborectalis and anal sphincter muscle. Small case series, with and without ultrasound guidance have shown modest early

improvement but the results do not appear to be long lasting (196–198). A more recent randomized trial of 48 subjects comparing *botulinum toxin* to biofeedback retraining found better initial improvement with the *botulinum toxin* (70% vs. 50%) but no difference at 1 year (33% vs. 25%) (199). Thus, reapplication is necessary. Biofeedback and pelvic floor therapy should be first-line treatment, and in cases that are refractory, *botulinum toxin* injection into the puborectalis muscle can be considered (200).

Pessary for Treatment of Pelvic Organ Prolapse

Pessaries of various shapes and sizes have been used for centuries to treat pelvic organ prolapse (201). **They are a safe alternative to surgery, with the most common complications being increased vaginal discharge and erosion or ulceration of the vaginal wall.** Although pessaries represent a common therapeutic modality, there are limited data regarding fitting and management (202). Even less is known about which type of pessary is better for enteroceles and rectoceles, although the site of prolapse does not appear to affect the ability to retain a pessary (203). Pessaries can be divided into subtypes of supportive and space occupying (204). Some of the space-occupying pessaries, such as the Gellhorn and cube, use a suction mechanism to maintain vaginal retention, whereas others, like the donut, do not. In theory, space-occupying pessaries and those that exert forces against the posterior wall and vaginal apex (donut, inverted Gehrung) should aid in treatment of rectoceles and enteroceles. However, there is a lack of data regarding the efficacy of pessaries for relieving symptoms of disordered defecation. One prospective study found that stage III to IV posterior vaginal wall prolapse was an independent predictor for discontinuation of pessary use in favor of surgical repair (205). The only randomized crossover trial comparing different types of pessaries (ring and Gellhorn) found improvement in QoL measures that did not differ according to pessary type. Protrusion and voiding dysfunction symptoms were most improved (206). In a secondary analysis of women enrolled in a study that sought to evaluate if pessary use is associated with improvement of bulge symptoms from prolapse and perception of body image, 43 out of the original 104 woman completed validated questionnaires on bowel symptom severity and effect on QoL at baseline and again after 12 months of continuous pessary use (207). There is marked improvement in symptom severity and QoL by using a pessary. This suggests a potential role for nonsurgical management of pelvic organ prolapse to help provide relief of bowel symptoms. More research is needed to determine the role of pessaries for treatment of rectoceles, enteroceles and symptoms that are likely to be improved using a pessary.

THERAPEUTIC APPROACH TO ACUTE CONSTIPATION

Patients may present with severe abdominal pain postoperatively. Anesthetic effects, pain, and medications such as opioids, oral iron, NSAIDs, ondansetron, and gabapentin, for example, are known to have constipating effects (Table 31-2). The laxative therapies mentioned above have been tested in the chronic constipation population but not for this relatively common postoperative scenario. There is sparse literature examining prevention or treatment options for constipation postoperatively and evidence-based recommendations cannot be put forward (208–210). A randomized, double-blind, placebo-controlled trial of postoperative pelvic reconstructive surgery patients showed that women receiving senna (8.6 mg) with docusate (50 mg) had a shorter time to first bowel movement (3 vs. 4 days) and the placebo group needed a stronger agent (magnesium citrate) to initiate a bowel movement more often as compared to the treatment group (44% vs. 7%, P <0.01) (211). From the colorectal literature, a retrospective review of 183 patient charts concluded that early ambulation and routine polyethylene glycol each contribute to significantly shorter times to first bowel movement than those with routine care (212). From the urogynecology literature, a randomized controlled trial of 131 patients receiving polyethylene glycol with docusate sodium postoperatively compared to docusate sodium alone showed no difference in time to first bowel movement (213). It should be noted, however, that 42% of women in the placebo group took additional laxatives compared to only 23% in the PEG arm (P = 0.02). Opioid-induced constipation and ileus is better studied and a systematic review of the literature suggests that peripherally acting μ-opioid receptor antagonists may be effective in treating opioid-induced bowel dysfunction and postoperative ileus (214). After other causes of acute abdominal pain have been ruled out, constipation can be confirmed by flat-plate plain film x-ray. Once diagnosed, the following regimen of three medications can be used: (1) Magnesium citrate 300 mL po × 1; (2) Bisacodyl 30 mg po × 1; (3) Sodium Phosphate enema PR × 1.

This recommendation uses three agents with three different mechanisms of action. Other options include magnesium hydroxide 400 mg/5 mL 30 mL po TID or mineral oil 15 mL po TID. Each regimen can be titrated to the patient's needs; for example, the sodium phosphate enema may be too powerful and a tap water enema or glycerin suppository will suffice.

In the older adult susceptible to electrolyte derangements and renal dysfunction, sodium phosphate and magnesium-based products should be used with caution (215). **Other options include magnesium hydroxide 400 mg/5 mL 30 mL po TID or mineral oil 15 mL po TID. Ideally, if an iatrogenic cause is identified, this will be discontinued. If, however, constipating agents must be continued, using osmotic laxatives concomitantly should prevent constipation. For example, PEG 3350 17 g**

in 1 cup water/juice daily until soft BM, then as needed, may be recommended.

Adjunctive Therapies

Acupuncture, peppermint oil and probiotics are modalities that may help improve chronic constipation. A randomized trial of acupuncture for chronic severe FC in over 1,000 patients showed significant improvement over 8 weeks of treatment and 20 weeks of follow-up compared to the control group with about one-third of the treatment arm having three or more complete spontaneous bowel movements per week, compared to only 14% in the control arm (*P* <0.001) (216). **Peppermint oil has not been studied for constipation alone; however, in the IBS literature it has been reported to be safe and modestly effective in the short-term for global IBS symptoms** (217). **The most commonly reported adverse event is heartburn. A systematic review and meta-analysis of the efficacy of pro/pre/synbiotics in IBS and chronic constipation concludes that probiotics are effective for IBS symptoms, although the most beneficial species and strains are not yet known. Evidence for prebiotics and synbiotics are unclear, as are the efficacy of all three on chronic constipation** (218).

Surgical Treatment

Following is a review of the efficacy of various surgical treatments for specific conditions associated with constipation and disordered defecation.

Slow-Transit/Colonic Inertia

Subtotal colectomy with ileosigmoid or ileorectal anastomosis is considered by many to be the surgical treatment of choice for slow-transit constipation refractory to medical management. Most surgeons restrict the use of this surgical procedure to the most extreme cases and typically operate on fewer than 10% of patients. Strict criteria for surgery include the following: chronic, severe, disabling symptoms unresponsive to medical therapy; slow transit in the proximal colon; no evidence of pseudo-obstruction; and normal anorectal function (188). Success rates are variable and depend on several factors. An extensive review of colectomy for slow-transit constipation analyzed 32 studies from 1981 to 1988 and found satisfaction rates ranged from 39% to 100% (219). Higher success rates occurred in studies in the United States (n = 11, median 94%, range 75% to 100%) and prospective studies (n = 16, median 90%, range 50% to 100%). Superior outcomes occurred in those who had a complete physiologic evaluation and proven slow-transit constipation. Patients with anismus had higher rates of recurrent symptoms and lower satisfaction levels (220). Poorer outcomes occurred with ileosigmoid and cecorectal anastomosis than with ileorectal

anastomosis. Those with segmental resection (hemicolectomy) had the worst outcome. None of the studies had a comparison group, and outcomes were variable and lacking validated measures. Morbidity associated with the operation included small bowel obstruction (median 18%, range 2% to 71%), need for reoperation (median 14%, range 0% to 50%), diarrhea (median 14%, range 0% to 46%), fecal incontinence (median 14%, range 0% to 52%), recurrent constipation (median 9%, range 0% to 33%), persistent abdominal pain (median 41%, range 0% to 90%), and permanent ileostomy (median 5%, range 0% to 28%). Mortality ranged from 0% to 6% (184). A QoL study revealed that the score correlated poorly with frequency of bowel movements. However, a lower score was seen in those patients who had persistent abdominal pain, diarrhea, fecal incontinence, and permanent ileostomies. Overall satisfaction with the procedure was very high and correlated with the QoL score (221,222). **Surgical alternatives to subtotal colectomy include ileostomy, cecostomy with antegrade continence enemas, and sacral nerve stimulation.** Subtotal colectomy has never been directly compared with ileostomy, but those who had a permanent diversion after subtotal colectomy had lower QoL scores. Patients undergoing cecostomy with antegrade continence enemas can expect to have satisfactory function approximately one-half of the time, with most requiring additional revision procedures secondary to stomal complications (223). Although sacral nerve stimulation has primarily been used for fecal incontinence, the results of a few small studies evoked optimism for its use in chronic constipation and slow-transit constipation (224–226). The Cochrane review of sacral nerve stimulation for fecal incontinence and constipation cannot support its use for constipation as the two trials included did not improve symptoms in patients with constipation (126).

Pelvic Organ Prolapse

Women with defecatory dysfunction or fecal incontinence may have a concomitant posterior vaginal wall prolapse (rectocele). The variety of surgical treatment techniques for the repair of rectocele include posterior colporrhaphy, defect-directed repair, transanal repair, and abdominal repair with sacral colpopexy. When an enterocele is present, a culdoplasty usually is performed. In cases of perineal descent, abdominal sacral colpoperineopexy is the procedure of choice. Suture rectopexy can be performed in conjunction with sacral colpoperineopexy if rectal prolapse is present. **Despite the routine use of these procedures, data are limited regarding symptomatic improvement of disordered defecation. Rectocele repair is indicated for bothersome prolapse bulge symptoms and not to be done with the intent of correcting disordered defecation.** A systematic review and practice recommendation out of the United Kingdom confirms that the use of rectovaginal reinforcement procedures for the purpose of improving constipation symptoms is not supported by the literature (227). Greater detail regarding the specific techniques for

many of these procedures will be provided in Chapter 30. This section will focus on surgical outcomes, including anatomic cure of prolapse, improvement of defecatory dysfunction symptoms, and morbidity associated with the procedure.

Posterior Colporrhaphy

Posterior colporrhaphy has been the surgical procedure for rectocele repair preferred by gynecologic surgeons for more than 100 years. Traditional posterior colporrhaphy narrows the vaginal caliber through plication of the rectovaginal septum and usually includes a perineorrhaphy, which narrows the introitus. Despite its broad use, there is a paucity of data regarding long-term anatomic success, symptomatic improvement, and sexual function following the procedure. The outcomes of several studies are summarized in Table 31-15 (228–247). Anatomic cure and relief of vaginal bulge occurred in 76% to 96% of patients. In these studies, the procedure was ineffective at treating constipation, vaginal digitations (splinting), and fecal incontinence. Dyspareunia developed in 7% to 26% of patients with and without levator plication (228–232,248). As early as 1961, high rates of dyspareunia have been reported with this procedure in as many as 50% of patients (249).

The successful anatomic support obtained with this procedure is offset by the modest relief of functional symptoms and high rate of *de novo* dyspareunia. However, a prospective case series of 38 women undergoing posterior colporrhaphy along with concomitant procedures for rectocele and obstructed defecation revealed markedly different results (250). Fascial plication was performed without levator plication, and perineal body reconstruction rather than routine perineorrhaphy was employed when indicated. Anatomic cure rate was 87% at 12 months and 79% at 24 months. Subjective cure rate was 97% at 12 months and 89% at 24 months. There was significant improvement in preoperative and postoperative symptoms for constipation (76% vs. 24%), digitations (100% vs. 16%), awareness of prolapse (100% vs. 5%), obstructed defecation (100% vs. 13%), and dyspareunia (37% vs. 5%). There was no difference in fecal incontinence and only one case of *de novo* dyspareunia. The authors attribute their improved anatomic and functional outcomes and combined improvement in dyspareunia to exclusion of levator plication, perineorrhaphy, and excision of vaginal epithelium. An additional benefit may be derived during mobilization of the vaginal epithelium, when scar tissue from prior episiotomy or surgery is divided. They found that preoperative defecating proctography was of limited value and have stopped its routine use as part of the preoperative evaluation for women with symptomatic rectoceles and obstructive defecation. This group has developed a classification system of the perineum that can help surgeons decipher when to use a perineorrhaphy and when to exercise less aggressive perineal reconstructive techniques (251).

Table 31-15 Rectocele Repairs

Posterior Colporrhaphy												
	Arnold (227)		Mellgren (228)[a]		Kahn (229)		Weber (230)[a]		Sand (231)[a]		Sung (232)[a,d]	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
N	29		25	25	231	171	53	53	70	67	70	70
Follow-up (mean) months				12		42		12		12		12
Levator plication		Yes		Yes		Yes		No		No		No
Anatomical cure (%)		80		96		76				90		91
Constipation (%)	75	54	100	88	22	33						32
Protrusion (%)			21	4	64	31						7
Splinting/digitations (%)	20		50	0		33						16
Fecal incontinence %		36	8	8	4	11						
De novo dyspareunia[b] (%)		23		8		16		26				
Defect-Directed Repair												
	Cundiff (233)		Porter (234)		Kenton (235)		Glavind (236)		Singh (237)[a]		Sung (232)[a,d]	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
N	69	61	125	72	66	46	67	67	42	33	70	70
Follow-up (mean) months		12		6		12		3		18		12
Anatomic cure		82		82		90		100		92		No
Constipation (%)	46	13	60	50	41	57						91
Difficult defecation	32	15	61	44	53	46	40	4	57	27		32
Protrusion (%)	100	18	38	14	86	9			78	7		7
Splinting/digitations (%)	39	25	24	14	30	15						16
Fecal incontinence (%)	13	8	24	21	30				9	5		
Dyspareunia (%)	29	19	67	46	28	8	12	3	31	15		7
De novo dyspareunia[b] (%)		2		4		7		3		0		
Repairs with Grafts												
	Oster (238)		Sand (231)[a]		Goh (239)[a]		Kohli (240)		Mercer-Jones (241)[a]		Sung (232)[a]	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
Graft route	Autologous transvaginal		Polygalactin mesh transvaginal		Polypropylene transvaginal		Porcine dermis transvaginal		Polypropylene transperineal		Porcine dermis transvaginal	
N	15	15	73	65	43	43	43	30	22	22	67	67
Follow-up (mean) months		30		12		12		12		12		12
Anatomic cure		100		92		100		93		95		88
Constipation (%)		33							50	14		33
Difficult defecation	47	0							95	32		44
Protrusion (%)	80	0			100	0			86	23		3
Splinting/digitations (%)	100	12							64	23		10
Fecal incontinence (%)										5		
Dyspareunia (%)		20										13
Transanal Repair												
	Sullivan (242)		Sehapavak (243)		Jenssen (244)[a]		Van Dam (245)[a,c]		Ayabaca (246)[a]			
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop		
N	137	117	355	204	64	64	89	89	49	34		
Follow-up (mean) months		18				12		52		48		
Anatomic cure		96		98		70		72		90		
Constipation (%)			82	15			63	33	83	32		
Difficult defecation	58	2			72	16	92	27				
Protrusion (%)	27				38	3	40	28				
Splinting/digitations (%)			26		26	4	23	0	38			
Fecal incontinence (%)	39	3			40	9	10	16	71	27		
Dyspareunia (%)		0		20			28	44				

[a]Prospective.

[b]In sexually active patients.

[c]Combined transanal and transvaginal repair.

[d]Surgeon discretion for midline or defect-directed repair, equal in both groups.

Defect-Directed Repair

The goal of a defect-directed repair or site-specific repair is to restore normal anatomy (38). This procedure can be combined with a perineal body reconstruction, if necessary, but usually does not routinely involve perineorrhaphy. Table 31-15 lists the anatomic and functional outcomes for this type of repair. **Anatomic cure rates range from 82% to 100%, which are similar to those for posterior colporrhaphy. This procedure resulted in modest improvement for symptoms of difficult evacuation, vaginal bulge, and vaginal digitations** (234–238,248). Constipation symptoms significantly decreased in only one study (233,234). All studies reported low rates of *de novo* dyspareunia with good functional and anatomic outcomes, but the long-term durability of the procedure is unknown. All but one of these studies included concomitant prolapse and urinary incontinence procedures.

A randomized clinical trial of 106 women with stage II or greater posterior vaginal wall prolapse compared posterior colporrhaphy, defect-directed rectocele repair, and defect-directed repair augmented with a porcine small intestinal submucosal (252). Subjects completed validated pelvic floor instruments at baseline and 6 months, 1 year, and 2 years after surgery. Anatomic failure was defined as pelvic organ prolapse quantitation system (POPQ) point Bp > or = –2 at 1 year. There was a significant improvement in prolapse and colorectal scales in all groups with no differences between groups. The proportion of subjects with functional failures was 15% overall, and not significantly different between groups. **Posterior colporraphy and defect-directed repairs resulted in similar anatomic and functional outcomes, although the addition of a porcine-derived graft did not improve anatomic outcomes.** On average, all bowel symptoms evaluated were significantly improved 1 year after surgery, with no differences between treatment groups. The development of new "bothersome" bowel symptoms after surgery was uncommon (11%). After controlling for age, treatment group, comorbidities, and preoperative bowel symptoms, corrected postoperative vaginal support (stage 0/I) was associated with a reduced risk of postoperative straining (adj. OR 0.17 95% CI 0.03–0.9) and feeling of incomplete emptying (adj. OR 0.1 95% CI 0.01–0.52). **This led the authors to conclude that resolution or improvement in bowel symptoms can be expected in the majority of women after rectocele repair (**253). A similar study conducted in 2012 concluded that the underlying cause of the defecatory symptoms will likely dictate whether or not a woman finds improvement after rectocele repair and that women should be counseled that their defecatory symptoms and bowel habits may or may not improve after rectocele repair (233).

Transanal Repair

Transanal repair involves repair of the rectocele through a transanal incision with excision of redundant rectal mucosa and plication of the rectovaginal septum and

rectal wall. The procedure was developed and is primarily used by colorectal surgeons to treat constipation or obstructed defecation associated with "low" or distal rectoceles. The advantages of this approach include excision of redundant rectal mucosa and the ability to treat other anorectal pathologies, such as hemorrhoids or anterior rectal wall prolapse (254). Disadvantages include the inability to repair higher rectoceles, enteroceles, cystoceles, uterine prolapse, and defects in the perineal body or anal sphincter (255). Major complications of infection (6%) and rectovaginal fistula (3%) are relatively common compared to transvaginal repairs (202). Most studies did not require vaginal bulging or protrusion symptoms as a prerequisite for surgery. The results of several studies are summarized in **Table 31-15**. The anatomic cure rate was 70% to 98%, and symptoms of constipation, difficult evacuation, and vaginal digitations appeared to improve (243–248).

Reviews to compare transanal with transvaginal rectocele repair use the results of two small, randomized control trials (256–259). Women with compromised sphincter function and other symptomatic prolapse were excluded. **The results for transvaginal repair were superior to those for transanal repair with respect to subjective failure rate** (relative risk [RR] 0.36, 95% CI 0.13 –1) and objective failure rate (RR 0.24, 95% CI 0.09–0.64) (256). In one study, a significant decrease occurred in the depth of rectocele on postoperative defecography for the transvaginal group compared with the transanal group (2.73 cm vs. 4.13 cm, respectively) although the depth of rectocele on imaging does not correlate with symptoms (259). The transvaginal group had fewer problems with bowel evacuation, but this finding was not statistically significant. In one study, researchers discovered that 38% of patients developed fecal incontinence following transanal repair (228). In the two randomized trials, no significant differences were seen in the rate of fecal incontinence or dyspareunia, but the studies were underpowered to detect a difference (258,259). **Although a vaginal approach has been considered superior to a transanal approach for rectocele repair, studies are retrospective and impossible to compare because the indications for transanal repairs are generally different from those for transvaginal repairs.**

Posterior Fascial Reinforcement

Rectocele repair with graft augmentation became commonplace in the early to late 2000s despite a paucity of supporting evidence indicating its benefits over standard procedures. The reason for its emergence was the theory that vaginal hernia repairs behave similarly to abdominal hernia repairs, which have a documented decrease in recurrence when augmented with grafts. A variety of graft materials have been employed with posterior colporrhaphy and defect-directed repairs including autograft, allograft, xenograft, and synthetic mesh. Polypropylene type I monofilament, macroporous synthetic mesh is associated with lower complication rates compared with other nonabsorbable synthetic materials (260). The purpose of the graft is debatable. It

can either be intended to replace existing fascia as a permanent barrier or to provide an absorbable scaffold for collagen deposition, scar formation, and remodeling. The ideal material should have a low erosion rate, be relatively inexpensive, and decrease recurrence rates without causing bowel or sexual dysfunction. Experience has demonstrated that although reinforcement with graft augmentation may result in better anatomic outcomes, there is no difference in subjective success at the cost of higher complications such as mesh erosion and extrusion (261,262). Improvements in objective outcomes are limited to the anterior vaginal wall and do not extend to multicompartment or posterior vaginal wall mesh (261), thus confirming no role for synthetic mesh augmentation for posterior repair. **There is no evidence to suggest that the addition of a graft to the posterior compartment improves outcomes** (252,261–263).

Abdominal Rectocele Repair

The abdominal approach to rectocele repair may be of value when a superior defect in the rectovaginal fascia occurs in a patient with accompanying enterocele, uterine prolapse, or vault prolapse. If a patient is undergoing an abdominal or laparoscopic procedure such as a sacral colpopexy, the graft can be extended along the posterior vaginal wall to correct proximal defects in the rectovaginal septum (264). There are limited data regarding the efficacy of abdominal rectocele repair. The indication for this procedure, and the need for additional vaginal repair of distal defects, often is determined intraoperatively. An ancillary study from the Pelvic Floor Disorders Network evaluating bowel symptoms 1 year after sacrocolpopexy found that the majority of bothersome bowel symptoms resolve after this procedure. There was no difference in postoperative bowel symptoms among those who underwent a concomitant rectocele repair and those who did not. The study was not developed to evaluate the impact of concomitant rectocele repair on bowel symptom resolution and those who underwent a rectocele repair had more severe baseline bowel symptoms including worse obstructive symptoms (265).

Sacral Colpoperineopexy for Perineal Descent

Sacral colpoperineopexy is a modification of sacral colpopexy aimed at correction of apical prolapse combined with rectocele and perineal descent (39). A continuous graft is placed from the anterior longitudinal ligament of the sacrum down to the perineal body. This procedure can be accomplished either through a total abdominal approach or a combined abdominal and vaginal procedure. **If performing a total abdominal approach, the rectovaginal space is opened, and the rectum is dissected off the posterior vaginal wall and rectovaginal septum toward the perineal body. The graft is sutured to the perineal body or as close to it as possible.** A rectovaginal examination with the surgeon's nondominant hand facilitates this attachment by supporting the perineal body. The graft is secured to additional points along the

posterior vaginal wall and apex, and sacral colpopexy is completed in the usual fashion.

If performing a combined abdominal and vaginal approach, the graft is secured to the perineal body vaginally. The posterior vaginal wall is opened, and a defect-directed rectocele repair is performed. Sacral colpopexy is accomplished in the usual fashion except that the vaginal dissection is opened superiorly, creating a window to the abdominal dissection. The graft can be passed down from the abdominal field to the vaginal field and anchored inferiorly to the perineal body and laterally to the arcus tendineus fascia rectovaginalis **(Fig. 31-9)**.

Short-term outcomes for 19 patients who underwent sacral colpoperineopexy indicated good anatomic results for apical and posterior support and for perineal descent (39). Complete cessation of defecatory dysfunction symptoms was accomplished in 66% of patients. In a report of outcomes for a slightly different variation of the sacral colpoperineopexy, the authors' technique involved attachment of Marlex mesh to the perineal body using a needle carrier (266). The failure rate was 25% and mesh erosion rate was 5% for 205 patients with up to 10-year follow-up. A study of Mersilene mesh erosion rates related to sacral colpopexy and sacral colpoperineopexy noted similar erosion rates between sacral colpopexy and colpoperineopexy when the vagina was not opened, 3.2% versus 4.5%, respectively (267). However, the erosion rate was 16% with vaginal suture placement and 40% when the mesh was placed vaginally. The use of nonsynthetic grafts such as dermal allograft and xenograft may help prevent high erosion rates. In a case series of 11 patients, researchers performed sigmoid resection (if indicated) and suture rectopexy in conjunction with sacral colpoperineopexy using Alloderm for women with coexistent rectal prolapse, perineal descent, and defecatory dysfunction. Early follow-up (12.5 ± 7.7 months) revealed excellent improvement of defecatory dysfunction symptoms and QoL considerations, with an 82% cure of perineal descent (268). A retrospective cohort of 38 women revealed high satisfaction following abdominal sacral colpoperineopexy despite the persistence of obstructed defecation symptoms 5 years after surgery (269,270). **Sacral colpoperineopexy may have value for a select group of patients**, but larger prospective series with long-term anatomic and symptomatic outcomes are necessary to evaluate the durability of this procedure.

Rectal Prolapse

Rectal prolapse is an uncommon pelvic floor disorder with an incidence below 1% of the adult population; however, risk factors are similar between rectal prolapse and pelvic organ prolapse. Although considered a benign condition, symptoms can significantly negatively impact QoL. These include pain, bleeding, seepage, defecatory dysfunction, fecal incontinence, and mass symptoms. The prolapse may be occult (internal intussusception-producing symptoms but no visible protrusion), partial (mucosal prolapse only) or full thickness (all layers of the rectum come through the anus

as concentric rings). Prolapsed internal hemorrhoids are sometimes confused with rectal prolapse but are treated differently.

Although medical management may ease symptoms of rectal prolapse, a surgical consultation is usually warranted**. Surgical management is usually reserved for full-thickness complete rectal prolapse.** A number of surgical procedures are described for the treatment of rectal prolapse and are broadly categorized into perineal or abdominal approaches. The most commonly utilized perineal approaches are the Delorme procedure, which includes resection of redundant rectal mucosa and plication of redundant rectal mucosa, and the Altemeier (perineal rectosigmoidectomy) procedure that includes perineal resection of full-thickness rectum. These perineal approaches offer easier recuperation for patients, but have been considered to be less definitive in terms of preventing recurrent rectal prolapse. The abdominal approaches have been considered to be more durable, but with a higher incidence of surgical complications and more difficult recovery. This belief and practice that abdominal approaches have significantly lower recurrence rates has come from observational studies, but several randomized controlled trials, two Cochrane reviews, and a third systematic review have not been able to demonstrate this distinction (271). A true benefit/risk comparison of perineal and abdominal approaches is complicated by the significant variations in abdominal approaches, with major variations in; whether the retrorectal space is dissected, whether mesh is utilized, and whether a concurrent sigmoid resection is performed. Laparoscopic and robotic variations of these approaches have been described in an attempt to minimize the recovery time.

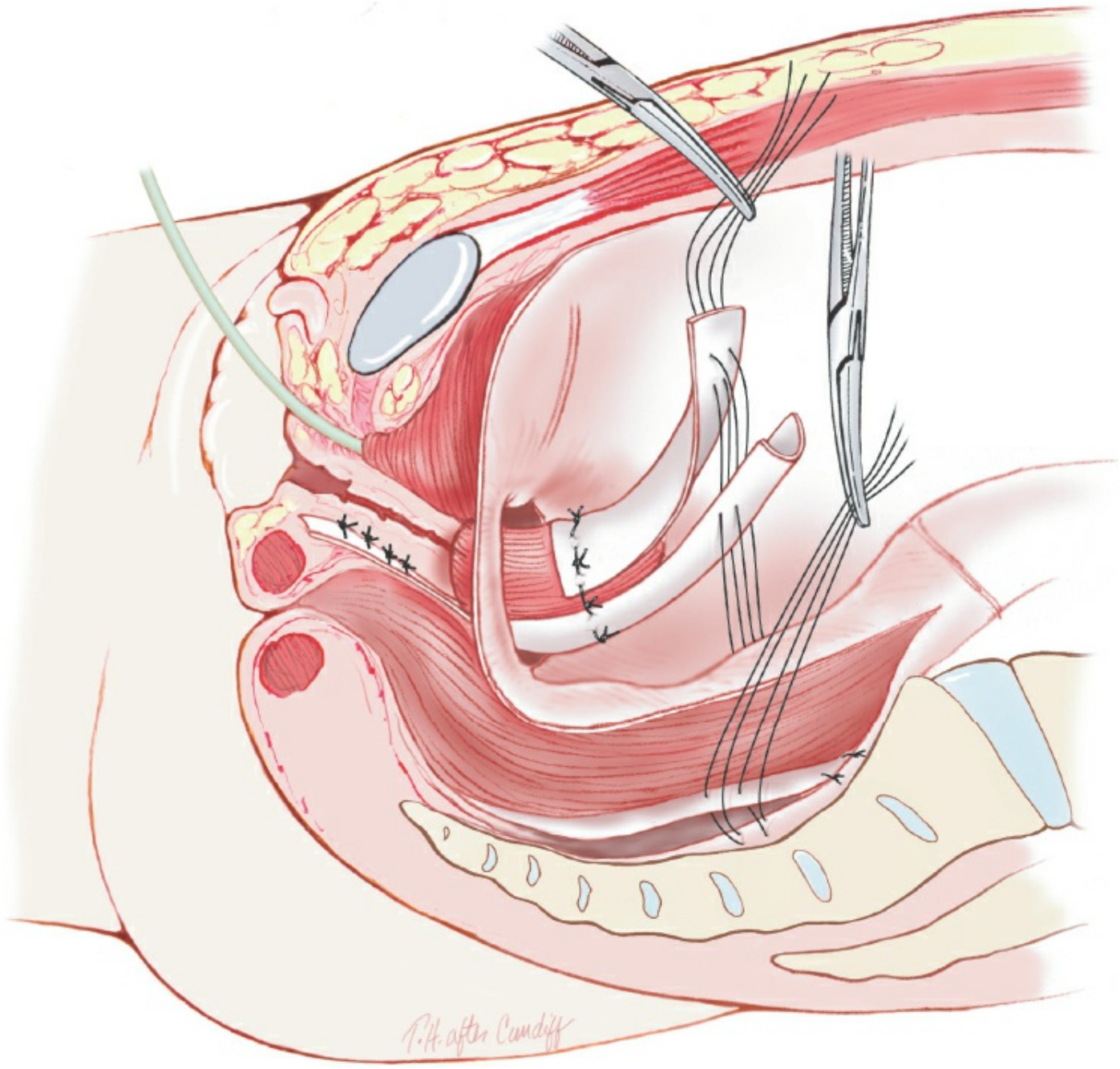


FIGURE 31-9 Abdominal sacral colpoperineopexy with sigmoid resection and suture rectopexy. This sagittal view shows the posterior graft sutured to the rectovaginal fascia and perineal body after defect-directed rectocele repair. The anterior graft is sutured to the pubocervical fascia. Both sheets will be secured to the sacral periosteum to the right of the rectum. Rectopexy sutures (*left*) have not yet been tied and secured. (Courtesy of Geoffrey W. Cundiff, MD.)

Perineal Procedures

Perineal procedures are more easily tolerated because they avoid laparotomy. They are ideal for patients at high-risk for perioperative and postoperative morbidity and mortality. There are basically two perineal procedures: the *Delorme procedure* and *perineal rectosigmoidectomy* (Altemeier operation). Perianal

encirclement procedures such as the Thiersch procedure are no longer used because of poor success rates, high recurrence rates, and fecal impaction.

The **Delorme procedure** was first described in 1900 and involves separation of the rectal mucosa from the sphincter and muscularis propria, followed by resection of the rectal mucosa, and plication of the distal rectal wall (muscularis propria) (272) **(Fig. 31-10)**. Recurrence rates range from 10% to 15% (273–276) and there is a low morbidity of 4% to 12%, which includes infection, urinary retention, bleeding, and fecal impaction. The recurrence rates were originally thought to be up to 38% (277), but new evidence indicates the range may be acceptable to patients who are eligible for abdominal surgery. There is a general improvement in fecal incontinence and constipation. Fecal incontinence, chronic diarrhea, and severe perineal descent are associated with failure of this procedure (278). The Delorme operation may be preferred in cases where the prolapsing segment is shorter than 3 to 4 cm or there is no circumferential full-thickness prolapse, making perineal rectosigmoidectomy difficult to perform (277,279).

Perineal rectosigmoidectomy (Altemeier operation) involves a transanal full-thickness resection of the prolapsed rectum and a coloanal anastomosis (280). Recurrence rates are described up to 30% but the only two randomized controlled trials comparing the Altemeier approach to an abdominal approach showed no statistically significant difference in recurrence rates, although the studies were not powered to show this (271). Patients generally have minimal pain and a relatively uneventful postoperative course. Recurrent prolapse probably reflects inadequate resection. Incontinence results are modest but seem to improve substantially with the addition of levatorplasty. The addition of levatorplasty appears to decrease the short-term recurrence rate (281), but there is no significant change in constipation with this procedure. Most agree that perineal rectosigmoidectomy with levatorplasty is the best procedure for very elderly patients and those with profound comorbidity. This is the preferred approach for patients with incarcerated, strangulated, or even gangrenous prolapsed rectal segments who are not candidates for abdominal rectopexy.

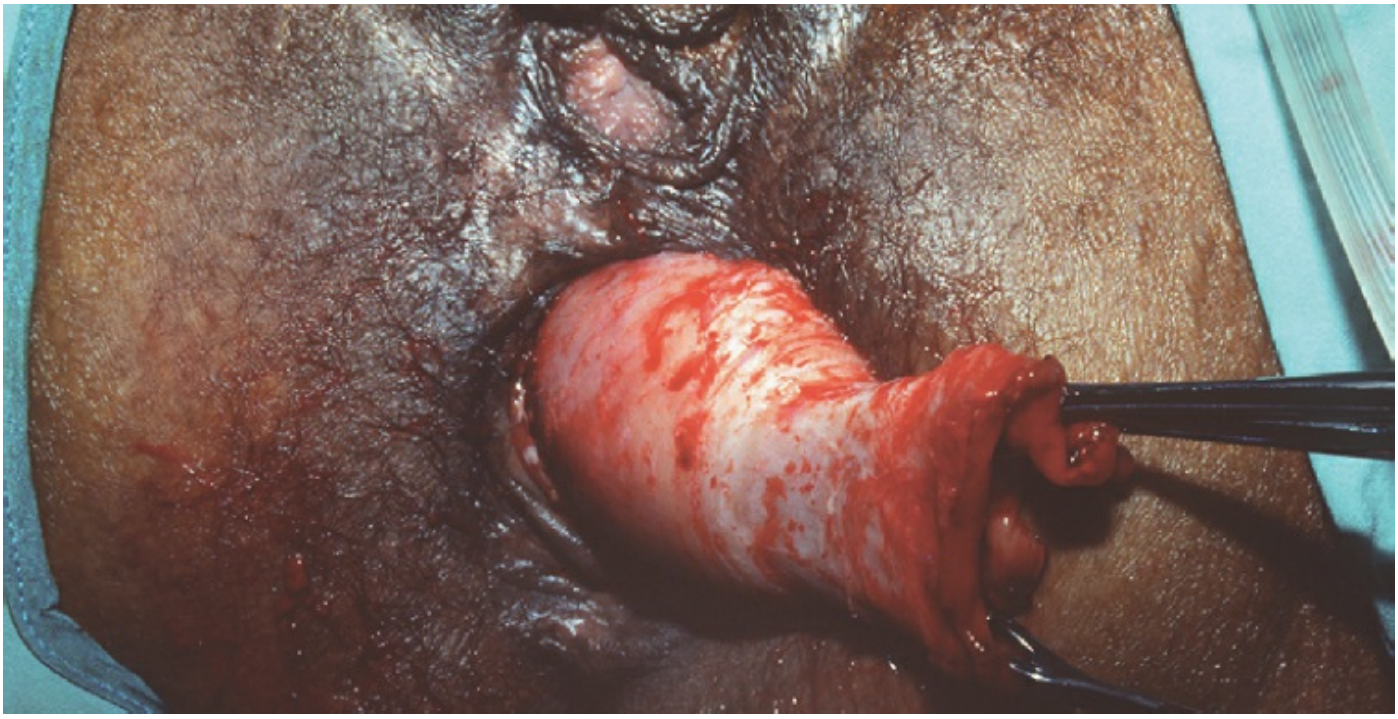


FIGURE 31-10 Delorme procedure. After mucosal stripping to the full extent of the prolapse, the circular smooth muscle or the rectum is plicated. A mucosa-to-mucosa anastomosis is then performed.

Abdominal Procedures

Abdominal procedures vary with respect to the extent of rectal mobilization, method of rectal fixation, and inclusion or exclusion of bowel resection.

The posterior approach is the most established and studied abdominal procedure. It begins with dissection of the retrorectal space to and beyond Waldeyer fascia. This dissection optimizes support by promoting fibrosis of the rectum to the sacrum, and includes the division of the lateral ligament stalks with a theoretical potential to cause an increased postoperative constipation as a result of rectal denervation. This association is supported by a Cochrane review of 15 randomized controlled trials (282). This may be balanced by a lower recurrence rate and may make this an attractive option for patients with fecal incontinence. The alternative to the posterior approach is the ventral rectopexy.

The posterior procedures include some method for anchoring the posterior rectum to the anterior sacrum. If performing a suture rectopexy, the fascia propria of the rectum is secured with sutures to the sacral periosteum from S1–S3 (283). The alternative is one of the mesh rectopexies**, posterior mesh rectopexy (Wells procedure), anterior mesh rectopexy (Ripstein, modified Ripstein), and ventral mesh rectopexy** (271,284,285). A variety of materials have been used for these procedures, including absorbable, autologous, and permanent mesh. The assumption is that the intervening material will provide increased support through increased fibrosis. The posterior mesh rectopexy has the mesh secured to the sacrum between the posterior rectum and the sacral promontory.

The ventral mesh rectopexy offers an alternative approach to the posterior approach. The ventral mesh rectopexy incorporates an anteriorly placed mesh support for fixation of the rectum to the sacral hollow. Rather than entering the retrorectal space, the rectovaginal septum is dissected to expose the proximal two-thirds of the rectovaginal septum (Denovillier fascia). A synthetic or biologic mesh buttress is sutured to the anterior wall of the rectum at the point of its intussusception and suspended to the sacral promontory. The available studies show acceptable short- and long-term complication rates (271). **There is insufficient evidence to argue that posterior rectal prolapse repairs are better or worse than anterior rectal prolapse repairs such as ventral mesh rectopexy** (271).

Aside from the dissection, and method of attachment, another surgical variation is performing a concurrent sigmoid resection with the rectopexy (Frykman–Goldberg resection rectopexy). The bowel resection is performed after mobilization and before suturing (286). The theoretical advantages of a rectosigmoid resection are: removal of abundant rectosigmoid, avoiding torsion or volvulus; additional fixation through straightening of the left colon and decreased mobility from the phrenocolic ligament; and creation of a dense area of fibrosis between the anastomotic suture line and the sacrum. It is typically reserved for patients with a long redundant sigmoid colon, although specific criteria have not been proposed. Mesh rectopexies are usually avoided at the time of a bowel resection because of concern for the increased complications and infections associated with placement of a foreign body near a new wound on the bowel.

Finally, minimally invasive approaches to abdominal rectopexies have been advocated as a means to decrease the recovery time. The laparoscopic approach has similar safety and efficacy to the open techniques, and the effect on continence and constipation tended to mirror the type of rectopexy performed. **In a small, randomized trial, there were significant short-term benefits with laparoscopic rectopexy compared with open rectopexy, including earlier ambulation, more rapid return to normal diet, shorter hospital stay, and lower morbidity** (287). Several studies have confirmed that recurrence rates are equivalent (4% to 8%) as are complication rates (10% to 33%) (271). Robotic surgery seems to be comparable to laparoscopic approaches.

Although there is a consensus that abdominal rectopexy is better than perineal approaches, the latest Cochrane review of 15 studies concludes that there is no difference in recurrence rates or postoperative complications. If constipation is a main symptom, bowel resection may help (282).

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SECTION VI

Early Pregnancy Issues



CHAPTER 32
Early Pregnancy Loss and Ectopic Pregnancy
Amy J. Voedisch, Erica P. Cahill



CHAPTER 33
Recurrent Pregnancy Loss
Lora K. Shahine, Ruth B. Lathi, Danny J. Schust

CHAPTER 32

Early Pregnancy Loss and Ectopic Pregnancy



Amy J. Voedisch, Erica P. Cahill

Abnormal Intrauterine Pregnancy
- Spontaneous Abortion
- Missed Abortion
- Threatened Abortion
- Inevitable Abortion
- Incomplete Abortion
  - *Management of Spontaneous Abortion*

Ectopic Gestation
- Incidence
- Etiology and Risk Factors
  - *Prior Ectopic Pregnancy*
  - *Tubal Surgery*
  - *Pelvic Infection*
  - *Infertility*
  - *Smoking*
  - *Contraceptive Use*
- Diagnosis
  - *History*
  - *Physical Examination*
  - *Laboratory Assessment*
  - *Serum Progesterone*
  - *Other Endocrine Markers*
  - *Ultrasonography*
  - *Dilation and Curettage*
  - *Culdocentesis*
  - *Laparoscopy*
  - *Diagnostic Algorithm*
- Treatment

Surgical Treatment
Medical Treatment
Types of Ectopic Pregnancy
Spontaneous Resolution of Pregnancies of Unknown Location
Persistent Trophoblastic Tissue
Nontubal Ectopic Pregnancy

KEY POINTS

1 Spontaneous pregnancy loss is common, occurring in up to 20% of recognized conceptions.
2 Following an ectopic pregnancy, approximately 15% of women will have a subsequent ectopic pregnancy.
3 Laparoscopy is the preferred approach for surgical management of ectopic pregnancies.
4 Single-dose *methotrexate* appears to be the treatment of choice if medical therapy is indicated and selected.
5 Surgical management and medical therapy have similar future reproductive outcomes.

An abnormal gestation can be either intrauterine or extrauterine. Abnormal intrauterine pregnancy often results in pregnancy loss early in gestation. Such losses can be related to a number of factors such as age, previous pregnancy loss, and maternal smoking **(Table 32-1)**. Extrauterine or ectopic pregnancy occurs when the fertilized ovum becomes implanted in tissue other than the endometrium. Although 70% of ectopic gestations are located in the ampullary segment of the fallopian tube, such pregnancies may occur in other sites **(Fig. 32-1)** (1). With abnormal intrauterine and extrauterine gestation, early recognition is key to diagnosis and management. Establishing a woman's goals for her pregnancy may alter management. Providers often incorrectly assume that all spontaneous abortions or abnormal pregnancies were intended pregnancies, when it is established that approximately 50% of pregnancies are unintended and may be undesired (2). As with all pregnancies, management must be highly dependent on each woman's pregnancy goals and her perceptions of the different risks.

ABNORMAL INTRAUTERINE PREGNANCY

Spontaneous Abortion

Spontaneous abortion is a pathologic process resulting in unintentional termination of the pregnancy prior to 20 weeks' gestation. **[1] About 8% to 20% of known pregnancies terminate in spontaneous abortion (3,4). About 80% of spontaneous pregnancy losses occur in the first trimester; the incidence decreases with each gestational week** (5,6). A large multicenter trial indicated the risk of loss in a pregnancy with documented fetal cardiac activity at 10 to 13 weeks gestation had a

spontaneous abortion rate of 0.96% before 24 weeks gestation (7). In women who had one prior spontaneous abortion, the rate of spontaneous abortion in a subsequent pregnancy ranges from 13% to 20%; in women who had three consecutive losses, the rate is 33% to 43% (8,9). Patients should be reassured that, in most cases, spontaneous abortion does not recur. Risk factors for spontaneous abortion include increasing maternal age, closely spaced pregnancies (less than 3 to 6 months apart), history of previous spontaneous abortion, maternal diabetes, and maternal smoking during pregnancy (10–14). Age is a dose-dependent risk factor for miscarriage; in women less than 36 years of age, when fetal cardiac activity is confirmed by ultrasound, the risk of spontaneous abortion is less than 4.5%. For women older than 36, the risk of spontaneous abortion rises to 10%, and above 40 years may approach 30% (15).

Spontaneous abortion can be differentiated into various categories, based on examination findings and ultrasound findings. The following sections review each of these categories in detail.

Table 32-1 Potential Causes of Spontaneous Pregnancy Loss

Increased maternal age
Previous spontaneous abortion
Maternal smoking
Maternal systemic disease (diabetes mellitus, infection, thrombophilia, etc.)
Maternal alcohol consumption (moderate to high)
Increasing gravidity
Amphetamine use
Chromosomal or other embryologic abnormalities
Anembryonic gestation
Uterine anomalies
Intrauterine device in place
Placental anomalies
Severe maternal trauma
Extremes of maternal weight

Missed Abortion

Missed abortion is defined as a nonviable intrauterine pregnancy in the presence of a closed cervix and minimal abdominal cramping or vaginal bleeding. Transvaginal

ultrasound evaluation is key to diagnosing a missed abortion and guidelines are available to aid in diagnosis (Table 32-2). These criteria are *guidelines*. They are more conservative than the studies and data used to develop these guidelines with the goal of eliminating the risk of intervening in what may have been a viable intrauterine pregnancy. These guidelines should be used in combination with clinical judgment and the patient's desires and wishes in deciding next steps in management.

Missed abortion can be subdivided into anembryonic gestation and embryonic demise. **Anembryonic gestation** is a pregnancy where the embryo failed to develop. This is confirmed when the mean gestational sac diameter measured by transvaginal ultrasound is greater than 25 mm and no embryonic pole is present. When an embryo is present with crown–rump length greater than 7 mm and no cardiac activity, this is classified as **embryonic demise** and the pregnancy is nonviable (16).

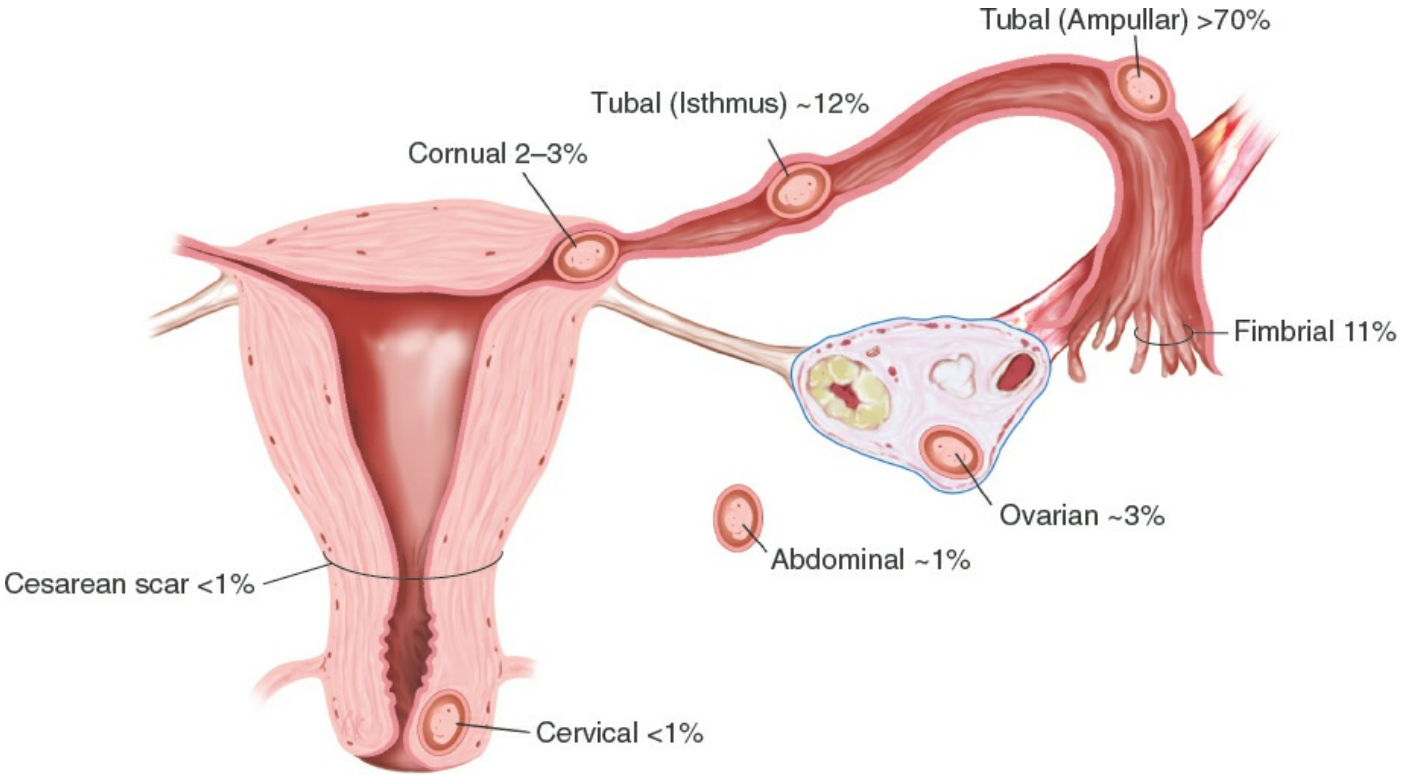


FIGURE 32-1 Common sites of ectopic pregnancy. (Adapted from **Seeber BE, Barnhart KT.** Suspected ectopic pregnancy. *Obstet Gynecol* 2006;107:399–413 and **Bouyer J, Coste J, Fernandez H, et al.** Sites of ectopic pregnancy: A 10 year population-based study of 1800 cases. *Hum Reprod* 2002;17:3224–3230.)

Threatened Abortion

Threatened abortion **is defined as any vaginal bleeding before 20 weeks of gestation. It occurs in at least 20% of all pregnancies** (17). **This is distinct from missed abortion by ultrasound documentation of an intrauterine embryo or fetus with cardiac activity.** The bleeding is usually light and may be associated with mild

lower abdominal or cramping pain (16). The differential diagnosis in these patients includes consideration of possible cervical polyps, vaginitis, cervical carcinoma, gestational trophoblastic disease, ectopic pregnancy, trauma, and foreign body. On physical examination, the abdomen usually is not tender, and the cervix is closed. Bleeding can be seen coming from the os and usually there is no cervical motion or adnexal tenderness.

In the vast majority of cases, threatened abortion does not result in a pregnancy loss, but may be associated with poor outcomes later in pregnancy. In a review of over 4,500 women presenting with first trimester vaginal bleeding, 12% with bleeding had a miscarriage which was similar to the rate in pregnancies with no bleeding (18). There is no effective therapy for a threatened abortion. Bed rest and progesterone treatment, although often advocated, have been demonstrated to be ineffective and carry their own risks (19). Women with first trimester vaginal bleeding with continuing pregnancies have nearly three times the risk of preterm birth between 28 and 31 weeks as women without bleeding and a 50% higher likelihood of preterm birth between 32 and 36 weeks (20). First trimester bleeding may be associated with higher risk of intrauterine growth restriction, preterm premature rupture of membranes, and placental abruption (21).

Inevitable Abortion

With an *inevitable abortion,* the cervical os is open and effaced prior to 20 weeks, but no tissue has passed. Most patients have crampy lower abdominal pain and some have cervical motion or adnexal tenderness. When the cervical os has dilated or excessive bleeding is present, the patient should be offered medical or surgical management. Blood type and Rh determination and a complete blood count should be obtained if there is any concern about the amount of bleeding. **Rho(D) immune globulin (RhoGAM) should be given if the patient's blood is Rh negative. It is acceptable to give a dose of 50 lg until 12 completed weeks; if this dose is not available, the standard 300 lg dose may be given** (22).

Incomplete Abortion

An incomplete abortion is a partial expulsion of the pregnancy tissue. Lower abdominal cramping is invariably present and the pain may be described as resembling labor. On physical examination, the cervix is dilated and effaced, bleeding is present and products of conception may be visible in the cervical canal. Often clots are admixed with products of conception. If the bleeding is profuse the patient should be examined promptly for tissue protruding from the cervical os; removal of this tissue with a ring forceps may reduce the bleeding. A vasovagal bradycardia may occur and

responds to removal of the tissue. A complete blood count, maternal blood type, and Rh determination should be obtained; **Rh-negative patients should receive *RhoGAM*. If the patient is febrile, broad-spectrum antibiotic therapy should be administered.**

Management of Spontaneous Abortion

All discussions of management of early pregnancy should start with asking the woman about her pregnancy intentions and reproductive planning. Providers often incorrectly assume that all spontaneous abortions were intended pregnancies, when it is established that approximately 50% of pregnancies are unintended and may be undesired (2). Establishing a woman's goals for her pregnancy may alter management. In women with stable vital signs and mild vaginal bleeding, three management options exist: expectant management, medical treatment, and suction curettage.

For expectant management, although there is a wide range (25% to 76%) of success cited in the literature, it may be a desirable option for a stable and carefully counseled patient (23,24). Success of expectant management varies based on the type of miscarriage and patients should be counseled accordingly. Incomplete, missed, and anembryonic abortions have a 91%, 76%, and 66% success rates respectively (25). Women should be counseled that it may take up to 4 to 8 weeks for the pregnancy to pass in any of these situations (26). Expectant management is associated with an increase in unscheduled surgical evacuations, bleeding and blood transfusions but no difference in infection rates (26,27).

Medical management with misoprostol is often successful in avoiding a surgical procedure. Misoprostol can be used vaginally, orally, sublingually, or bucally and the dose typically ranges from 400 to 800 µg. The American College of Obstetricians and Gynecologists recommends medical treatment of missed abortions with 800 µg of *misoprostol* placed vaginally with efficacy up to 84% in achieving complete abortion (28,29). It is acceptable to use 600 µg sublingually. For incomplete abortion, the *misoprostol* dose *can* be reduced to 600 µg orally or 400 µg sublingually, with efficacy greater than 90% (30,31).

Studies have investigated the benefit of adding mifepristone to the medical regimen in the hopes of improving success rates as the use of mifepristone with misoprostol has been well-documented in the effective treatment of medical abortion terminations. A study of 300 women with early pregnancy loss demonstrated improved success of misoprostol when women are pretreated with 200 mg of mifepristone 24 hours prior. Approximately 83% of the women in the group pre-treated with mifepristone experienced treatment success without intervention by the first follow-up visit compared with only 67% in the misoprostol only group. There were no significant differences in adverse events, bleeding intensity, pain, or satisfaction between the two groups (32).

Suction curettage should be performed in women who desire surgical management or

who have excessive bleeding, unstable vital signs, or in whom reliable follow-up is a concern.

ECTOPIC GESTATION

Incidence

The incidence of ectopic pregnancy has historically been underestimated. Previous reports mainly had used hospital records and many ectopic pregnancies are treated on an outpatient basis either in surgery centers or in outpatient clinics with methotrexate (33). Reports using insurance claims databases have estimated the overall rate of ectopic pregnancy to be between 1% and 2%. In one study using the insurance claims database of private insurance the rate of ectopic was 0.64%, with significant differences by age group. The rate of ectopic pregnancy increases with age, with 0.3% of pregnancies among 15- to 19-year-old women and 1% of pregnancies among 24- to 44-year-old women (34). This study found that up to 16% of women who present with first trimester bleeding, pain, or both, will ultimately be diagnosed with ectopic pregnancy (35). While uncommon, ectopic pregnancy accounts for approximately 2.7% of all maternal deaths and increases the risk of recurrence in future pregnancies (35). Studies have shown a decreasing mortality rate in ectopic pregnancy, attributed to improved early diagnosis and treatment. Similar to most causes of maternal mortality, the mortality from ectopic pregnancy varies by race, with African American women having 6.8 times the risk of mortality from ectopic pregnancy than Caucasian American women (36).

Etiology and Risk Factors

Ectopic pregnancy results from various factors that interrupt the successful migration of the conceptus to the endometrium. Up to half of women who present with an ectopic pregnancy have no identifiable risk factor, therefore a high index of suspicion is critical. Any condition that delays or interferes with the passage of an embryo through the fallopian tube increases the risk of ectopic pregnancy. **[2] The most important risk factor for an ectopic pregnancy is a prior ectopic pregnancy with a recurrent risk of 10% to 15% after first ectopic pregnancy and 30% after second ectopic pregnancy (37).** Other risk factors include a history of tubal surgery including tubal ligation, *assisted reproductive technology*, and history of pelvic inflammatory disease (PID). Anything that causes inflammation of the fallopian tube or disruption of tubal motility increases the risk of ectopic pregnancy. Inflammation of fallopian tube is present in up to 90% of ectopic pregnancies with causes including PID, tubal endometriosis, and salpingitis isthmica nodosa. Many other risk factors, including smoking and multiple lifetime sexual partners, are weakly associated with ectopic

pregnancy. Intrauterine devices (IUDs) are an effective contraceptive method, with an annual failure rate of <0.1%. While the overall risk of pregnancy is incredibly low in women using this type of contraception, those rare pregnancies that do occur are more likely to be ectopic (38).

Prior Ectopic Pregnancy

A previous history of ectopic pregnancy is the strongest risk factor for another occurrence. The increased recurrence exists because of the previous factors that led to the initial ectopic combined with the potential damage to the fallopian tube from the prior ectopic pregnancy and its treatment. **The rates for intrauterine pregnancy (40%) and ectopic pregnancy (15%, range 4% to 28%) are similar after tubal removal or conservation** (39). Tubal patency appears to be variably affected by medical treatment with methotrexate. In one study of 121 women who received methotrexate treatment, hysterosalpingograms (HSGs) done 3 months after treatment revealed 72% of women had bilateral tubal patency, 19% had unilateral tubal patency, and 3% had bilateral tubal obstruction. Of the women who had bilateral tubal patency on HSG, over 90% had a subsequent pregnancy, 78% without reproductive assistance. Given that 97% of women in the study had no change in their fertility, an HSG is not indicated or cost-effective after methotrexate treatment (40).

Tubal Surgery

It is clear that tubal surgery is associated with an increased risk for ectopic pregnancy, what is unclear is whether the increased risk results from the surgical procedure or from the underlying problem. Although tubal sterilization remains one of the most effective forms of contraception and pregnancy is unlikely, failures do occur; when they do, they are more likely to result in ectopic gestation. A large Cochrane review published in 2016 found that depending on the technique, the failure rate of tubal sterilization ranges from 36.5/1,000 procedures (Filshie clip) to 7.5/1,000 procedures (postpartum salpingectomy and unipolar coagulation) (41). **The 10-year cumulative incidence of tubal pregnancy after any sterilization procedure is 7.3 per 1,000 procedures** (42). The risk depends on the sterilization technique and the woman's age at the time of sterilization: postpartum partial salpingectomy and unipolar coagulation have the lowest rates of ectopic pregnancy (1.5 and 1.8 per 1,000 procedures), while bipolar coagulation techniques had the highest incidence (17.1 per 1,000 procedures). Spring clip and band application techniques have 10-year ectopic rates similar to the general incidence, 8.5 and 7.3 per 1,000 procedures, respectively (42). Women younger than 28 years at the time of sterilization are more likely to have a failure than women over 34 years.

Sterilization reversal increases risk for ectopic pregnancy. The exact risk depends on the method of sterilization, site of tubal occlusion, residual tube length, coexisting

disease, and surgical technique. In general, the risk of any pregnancy after a reanastomosis of a cauterized tube is up to 8% for laparoscopic procedures based on recent studies (43). There is insufficient evidence for a rate of ectopic pregnancy after hysteroscopic sterilization, but retrospective data and models show overall pregnancy rates are higher than with laparoscopic sterilization (44,45).

Pelvic Infection

The relationship of pelvic infection, tubal obstruction and ectopic pregnancy is well-documented. In a study of 2,500 women with suspected PID who underwent diagnostic laparoscopy, the incidence of ectopic pregnancy in the subsequent pregnancy for those with laparoscopically confirmed disease was 9.1% compared with 1.4% in the women with normal laparoscopy (46). In a study of 415 women with laparoscopically proven PID, the incidence of tubal obstruction increased with successive episodes of PID: **13% after one episode, 35% after two, and 75% after three** (47). **Chlamydia is an important pathogen causing tubal damage and subsequent tubal pregnancy. Chlamydia was cultured from 7% to 30% of patients with tubal pregnancy** (48). Conception is three times as likely to be tubal in women with anti–*Chlamydia trachomatis* titers higher than 1:64 than in those women whose titers were negative (49). Women at risk for chlamydia infections should be diligently tested, treated when infection is present, and counseled about the risk of ectopic pregnancy.

Infertility

The incidence of ectopic pregnancy increases with age and parity, and there is a significant increase in nulliparous women undergoing infertility treatment (38,39,50). Additional risks for infertile women are associated with specific treatments, including reversal of sterilization, ovulation induction, and in vitro fertilization (IVF). Various studies examining risk factors for ectopic pregnancy found that infertility increased the odds of tubal pregnancy at least four times and perhaps as much as 40 times, depending on etiology of infertility (51).

Smoking

Alterations of tubal motility, ciliary activity, and blastocyst implantation are associated with nicotine intake. Cigarette smoking is associated with an increased risk for tubal pregnancy in a dose-dependent fashion. Two classic case-control studies demonstrated this relationship; compared with nonsmokers, smokers of more than 20 cigarettes a day had a relative risk of 3.5, and smokers of up to 10 cigarettes a day had a relative risk of 2.3 (1,52).

Contraceptive Use

By reducing the overall likelihood of pregnancy, all contraceptive use reduces the overall risk of ectopic pregnancy. There is concern that because of the various

mechanisms of action of contraceptives, if a pregnancy were to occur, it might be more likely to be ectopic. In a meta-analysis of 13 studies examining the relationship between contraception and the risk of ectopic pregnancy, there was no increased risk in users of oral contraceptives or barrier methods compared with pregnant controls (53). There is no demonstrated increased risk in users of *depo-medroxyprogesterone* injections, emergency contraceptive pills or etonogestrel implants (54,55). Hormonal and copper-containing IUDs are highly effective at preventing intrauterine and extrauterine pregnancies, with failure rates of 0.2% in the first year of use and 0.7% in the first 5 years of use (56). **In the rare case that women conceive with an IUD in place the pregnancy is more likely to be ectopic.**

Diagnosis

The diagnosis of ectopic pregnancy is complicated by the wide spectrum of clinical presentations from asymptomatic cases to acute abdomen and hemodynamic shock. Until the location of the pregnancy is confirmed, the diagnosis remains a pregnancy of unknown location. The differential diagnosis of a pregnancy of unknown location includes early viable intrauterine pregnancy, early nonviable intrauterine pregnancy, stable ectopic pregnancy and unstable ectopic pregnancy. Making the diagnosis involves combining history and physical examination with clinical findings including laboratory and ultrasound data.

While the management of a ruptured ectopic pregnancy is directed at the primary goal of achieving hemostasis, the management of a pregnancy of unknown location in a stable patient is varied and depends on many patient and pregnancy-specific factors. It is critical to maintain a high degree of suspicion of ectopic pregnancy with pregnancies of unknown location, especially in areas of high prevalence. History and physical examination identify patients at risk, improving the probability of detection of ectopic pregnancy before rupture occurs.

History

The patient's history can be helpful in identifying patients at risk for ectopic pregnancies. Pertinent points in the history include the patient's age, menstrual history, previous pregnancy, infertility history, current contraceptive status, risk factor assessment, and current symptoms.

The classic symptom triad of ectopic pregnancy is pain, amenorrhea, and vaginal bleeding. This symptom group is present in about 50% of patients and is more typical in patients with a ruptured ectopic pregnancy. Abdominal pain is the most common presenting symptom, but the severity and nature of the pain vary widely. There is no pathognomonic pain for an ectopic pregnancy. Pain may be unilateral or bilateral and may occur in the upper or lower abdomen. The pain may be dull, sharp, or crampy

and either continuous or intermittent. With rupture, the patient may experience transient relief of the pain, as stretching of the tubal serosa ceases. Shoulder and back pain, thought to result from peritoneal irritation of the diaphragm may indicate intra-abdominal hemorrhage.

Physical Examination

The physical examination should include measurements of vital signs and examination of the abdomen and pelvis. Frequently, the findings before rupture and hemorrhage are nonspecific and vital signs are normal. The abdomen may be nontender or mildly tender, with or without rebound. The uterus may be slightly enlarged with findings similar to a normal pregnancy (57). Cervical motion tenderness may or may not be present. **An adnexal mass may be palpable in up to 50% of cases, but the mass varies markedly in size, consistency, and tenderness.** A palpable mass may be the corpus luteum and not the ectopic pregnancy. With rupture and intra-abdominal hemorrhage, the patient develops tachycardia followed by hypotension. Bowel sounds are decreased or absent. The abdomen is distended with marked tenderness and rebound tenderness. Cervical motion tenderness is present. Frequently, the findings of the pelvic examination are inadequate as a result of pain and guarding. History and physical examination may or may not provide useful diagnostic information. Additional tests are frequently required to differentiate between early viable intrauterine pregnancy, abnormal intrauterine pregnancy, and suspected ectopic.

Laboratory Assessment

Quantitative β-human chorionic gonadotropin (β-hCG) measurements are the diagnostic cornerstone for ectopic pregnancy. Urine pregnancy tests can detect β-hCG at ≥20 mIU/mL while serum pregnancy tests can detect levels >5 mIU/mL. **a-hCG levels cannot be used to predict gestational age (**58). **a-hCG levels peak at approximately 10 weeks gestation and the average peak level is approximately 100,000 with a wide normal range of variation.** There is the possibility of a phantom β-hCG, in which the presence of heterophile antibodies or proteolytic enzymes causes a low level false-positive serum β-hCG result. These antibodies are large glycoproteins and are not excreted in the urine, resulting in a negative urine pregnancy test. **In the patient with a-hCG levels less than 1,000 mIU/mL, a urine pregnancy test should be performed and confirmatory positive results obtained before instituting treatment** (59).

Single Human Chorionic Gonadotropin Level

A single a-hCG measurement has limited usefulness in the evaluation of a pregnancy of unknown location because there is considerable overlap in values between normal and abnormal pregnancies at a given gestational age. a-hCG levels do not correlate with pregnancy site (60). Many patients with pregnancy of unknown

location are uncertain about their menstrual dates. A single β-hCG level may be useful if negative to exclude the diagnosis of ectopic pregnancy. A single β-hCG level may facilitate the interpretation of ultrasonography when an intrauterine gestation is not visualized. **An a-hCG level greater than the ultrasound discriminatory zone indicates a possible extrauterine pregnancy; however caution must be used with previously defined discrimination zones, as recent research indicates that a much higher a-hCG level should be used for ruling out a normal intrauterine pregnancy** (16,61). Determination of serial β-hCG levels are usually needed to differentiate an ectopic pregnancy from an intrauterine pregnancy failure. Further tests are required for patients in whom ultrasonography examination results are inconclusive and β-hCG levels are below the discriminatory zone.

Serial Human Chorionic Gonadotropin Level

Serial a-hCG levels are usually required when the results of the initial ultrasonography examination are indeterminate (i.e., when there is no evidence of an intrauterine gestation or extrauterine findings consistent with an ectopic pregnancy). Traditionally the β-hCG level was expected to rise at least 66% over 48 hours with an 85% confidence interval, with 15% of normal pregnancies falling outside of this range. About the same number of ectopic pregnancies will have a greater than 66% rise (62). Data indicate that a more conservative cut-off of 53% gives a 99% confidence interval with less than 1% of viable intrauterine pregnancies having a slower rise (63). This data was based on a homogeneous patient population and women with unknown dating (i.e., unclear last menstrual period) were excluded from the study. A more conservative cut-off of greater than or equal to 35% was found in a larger study of over 1,000 ethnically and racially diverse women to adequately predict a viable intrauterine pregnancy and decrease the chance of misclassifying a pregnancy (64). This large study showed that having at least three serial values is helpful, especially if the starting β-hCG level is low. Follow-up research suggests that the expected rise in β-hCG is dependent upon starting β-hCG level. **If the initial a-hCG level is less than 1,500, 1,500 to 3,000, or greater than 3,000 mIU/mL, then the predicted rise at 48 hours is 49%, 40%, and 33%, respectively** (65). Based on these data the traditional 66% should no longer be used in diagnosing ectopic pregnancies. **A cut-off of 53% or even lower to 35% may be more appropriate and decrease the risk of intervening in what may be a viable intrauterine pregnancy.** β-hCG levels alone usually are not enough to make a diagnosis in a pregnancy of unknown location. The entire clinical picture including history, physical examination, and ultrasound findings, combined with β-hCG levels, are needed to make an accurate diagnosis.

If there is a plateau or decline in β-hCG levels, this is usually indicative of a nonviable pregnancy, either intrauterine or extrauterine. The decline in β-hCG levels can be helpful in diagnosing a pregnancy of unknown location. Ectopic pregnancies will

plateau or have a slower rate of decline than spontaneous abortions. Several studies have evaluated the expected decline to develop clinical guidelines. Data support that most spontaneous abortions are expected to decrease 21% to 35% 2 days after presentation and 60% to 84% at 7 days. The drop depends on the starting β-hCG level with faster decline noted with higher starting values of β-hCG (63). An updated model suggested that the range of the drop should be 35% to 50% at 2 days and 66% to 87% at 7 days from the first laboratory test (66). A large study did show that if there is an 85% drop within 4 days or a 95% drop in 7 days the risk of ectopic pregnancy appears to be 0 (67). These expected rates of decline can aid in detecting those women at risk for an ectopic pregnancy and warrant closer follow-up or even intervention, but should be combined with clinical judgment and not be used as absolutes in patient management.

Serum Progesterone

Earlier studies suggested that serum progesterone level could be used to diagnose ectopic pregnancies and identify viable intrauterine pregnancies. However, the level of progesterone in all pregnancies can vary greatly. There are progesterone thresholds that can aid in the evaluation of patient with pregnancy of unknown location. Progesterone levels greater than or equal to 25 ng/mL are associated with viable intrauterine pregnancies as only 1% to 2% of ectopic pregnancies will have levels this high (68). If the ectopic pregnancy does have a level above this threshold it is usually associated with cardiac activity and identifiable on ultrasound. Serum progesterone levels <5 mg/mL are associated with pregnancy failure. Less than 1% of viable intrauterine pregnancies are below this cut-off (69,70).

Other Endocrine Markers

In an effort to improve early detection of ectopic pregnancy various endocrine and protein markers have been evaluated. Useful biomarkers have not been identified for clinical use but further studies are underway.

Ultrasonography

Transvaginal ultrasound is the imaging modality of choice for evaluating the pelvic structures and the location of a newly diagnosed pregnancy (71,72). Transabdominal ultrasonography permits visualization of the pelvis and abdominal cavity and should be included as part of the complete ectopic pregnancy evaluation to detect adnexal masses and hemoperitoneum.

The earliest ultrasound finding of an intrauterine pregnancy is the gestational sac that characteristically has a round, thick echogenic ring surrounding a sonolucent center. As the pregnancy progresses this sac becomes eccentrically located within the endometrial cavity. Although the gestational sac is the first sign of a definitive intrauterine pregnancy it can be mimicked by an intrauterine fluid collection called a pseudogestational sac. Pseudosacs occur in 8% to 29% of patients with ectopic

pregnancy (73,74). This ultrasonographic lucency, centrally located, probably represents bleeding into the endometrial cavity by the decidual cast. Clots within this lucency may mimic a fetal pole.

Historically, identification of the double decidual sac sign (DDSS) is the best method of differentiating true sacs from pseudosacs. The double sac, believed to be the decidua capsularis and parietalis, is seen as two concentric echogenic rings separated by a hypoechogenic space. Although useful, this approach has some limitations in sensitivity and specificity—the DDSS sensitivity ranges from 64% to 95% (75). Pseudosacs may occasionally appear as the DDSS; intrauterine sacs of failed pregnancies may appear as pseudosacs. The DDSS is best observed on transabdominal ultrasound as this is frequently missed with transvaginal ultrasound (16). However, if abdominal ultrasound reveals a DDSS with an empty-appearing gestational sac, a transvaginal ultrasound should be performed as a yolk sac is often visible in this view and is a definitive diagnosis of intrauterine pregnancy.

The appearance of a yolk sac within the gestational sac is diagnostic of an intrauterine pregnancy, while the gestational sac alone is not sufficient because of the risk of misdiagnosis (76). Diagnosing an ectopic pregnancy on transvaginal ultrasound may or may not be straightforward. In the absence of an intrauterine pregnancy, if an adnexal gestational sac with a yolk sac or an embryo is present this is diagnostic of an ectopic pregnancy. However, this finding is the least sensitive sign of ectopic pregnancy, occurring in only 10% to 17% of cases (77).

The recognition of other characteristics of ectopic pregnancy improves ultrasonographic sensitivity. Adnexal rings (fluid sacs with thick echogenic rings) are visualized in less than 50% of ectopic pregnancies (77,78). The adnexal ring may not always be apparent because bleeding around the sac results in the appearance of a nonspecific adnexal mass**. Complex or solid adnexal masses are frequently associated with ectopic pregnancy; however, the mass may represent a corpus luteum, endometrioma, hydrosalpinx, ovarian neoplasm (e.g., dermoid cyst), or pedunculated fibroid** (5,78). The presence of free cul-de-sac fluid is frequently associated with ectopic pregnancy but is not considered evidence of rupture (79). The presence of ***intra-abdominal*** free fluid should raise concern about tubal rupture.

Historically ultrasound findings were correlated with a "discriminatory zone"—the level of β-hCG where an intrauterine pregnancy *should* be visualized. **Discriminatory zones for transvaginal ultrasonography are reported at levels from 1,000 to 2,000 mIU/mL** and vary by institution (15,73,75,77,78,80). **Studies have suggested raising the discriminatory zone to 3,510 mIU/mL in order to avoid false results** for an abnormal pregnancy (61). Discriminatory zones vary according to the expertise of the examiner, capability of the equipment, and pregnancy-related characteristics such as multiples.

Although there are guidelines for a discriminatory zone for intrauterine pregnancy, there is no such zone for ectopic pregnancy. Levels of β-hCG do not correlate with the size of ectopic pregnancy. Regardless of how high the β-hCG level may be, nonvisualization of the pregnancy outside the uterus does not exclude ectopic pregnancy. An ectopic pregnancy may be present anywhere in the abdominal cavity, making ultrasonographic visualization difficult.

Dilation and Curettage

Uterine curettage is performed when the pregnancy is confirmed to be nonviable or is not desired and the location of the pregnancy cannot be determined by ultrasonography. The decision to evacuate the uterus in the presence of a positive pregnancy test must be made with caution to avoid the unintentional disruption of a viable intrauterine pregnancy. Although suction curettage traditionally was performed in the operating room, it can be accomplished under local anesthesia on an outpatient basis. Endometrial sampling methods (e.g., a Novak curettage or Pipelle endometrial sampling device) are accurate in diagnosing abnormal uterine bleeding but their reliability for detecting intrauterine chorionic villi is low and these devices should not be used in the evaluation of a possible ectopic pregnancy (81,82).

It is essential to confirm the presence of trophoblastic tissue as rapidly as possible so that therapy may be instituted. There are many ways this tissue can be evaluated depending on setting of procedure. Traditionally these specimens were sent to pathology for formal evaluation. In this case, the presence of chorionic villi may be assessed rapidly with frozen section analysis, which avoids the waiting period of at least 48 hours for permanent histologic evaluation. Immunocytochemical staining techniques can be used to differentiate intermediate trophoblasts from decidual tissue (83).

More often these simple procedures are performed in an outpatient setting and the ability to immediately evaluate the tissue allows for rapid diagnosis of an intrauterine pregnancy. Surgeons experienced in evaluating tissue immediately after aspiration are at least as accurate as pathologists especially with accurately identifying the presence of the products of conception (84).

After tissue is obtained by curettage, it can be added to saline, in which it will float. Decidual tissue does not float. Chorionic villi are usually identified by their characteristic lacy frond appearance, as demonstrated in **Figure 32-2** above.

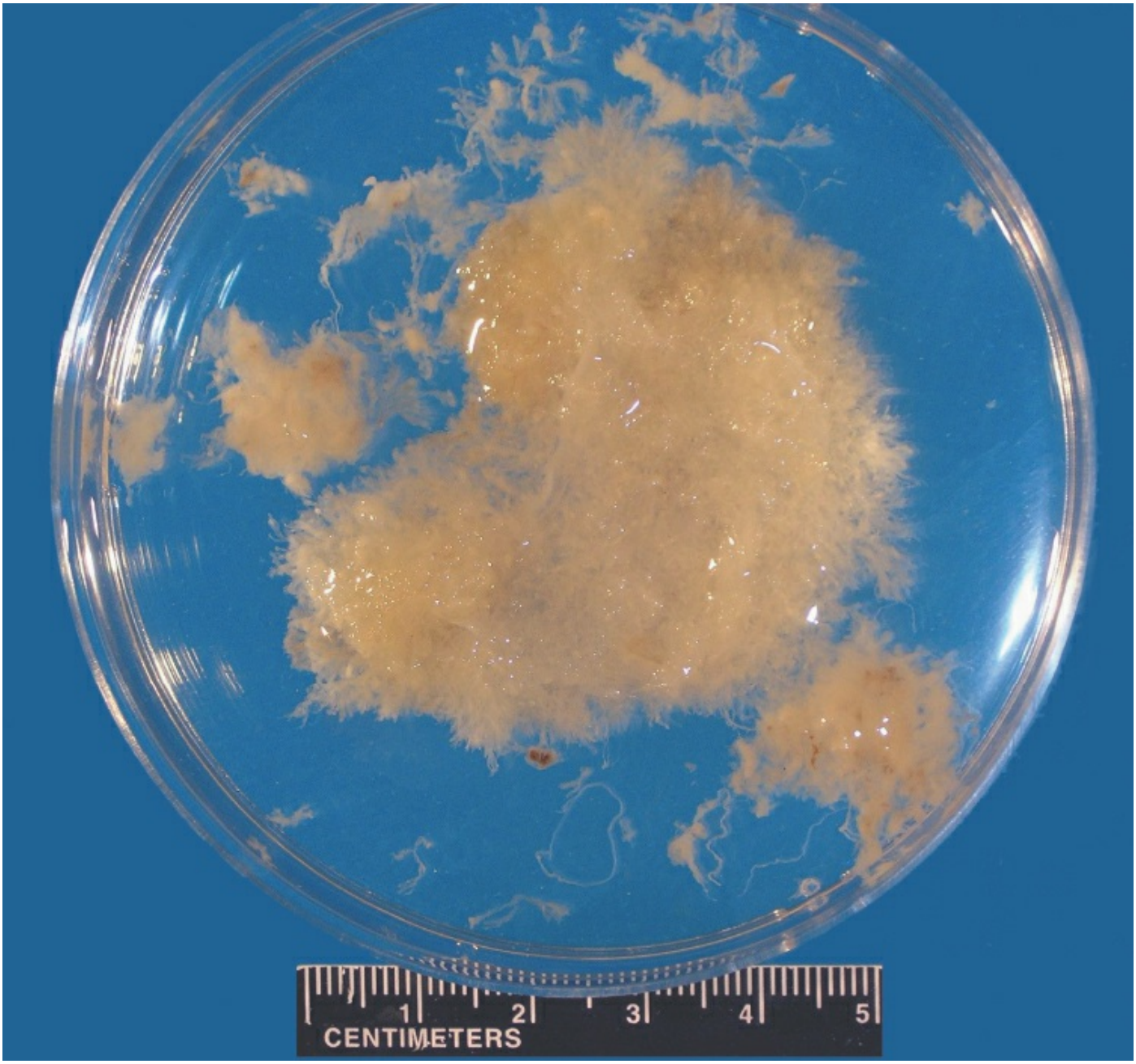


FIGURE 32-2 When floated in saline, chorionic villi are often readily distinguishable as lacy fronds of tissue. (From **Stovall TG, Ling FW.** Extrauterine Pregnancy: Clinical Diagnosis and Management. New York: McGraw-Hill, 1993:186, with permission.)

It is important to identify a gestational sac. Rare villi may be present in uterine aspirations in the presence of interstitial pregnancies, therefore identifying the gestational sac is required. Heterotopic pregnancies are rare but are increasing with advancements in artificial reproductive technologies. If suspicion for a heterotopic pregnancy is high the presence of villi and a gestational sac still warrants further investigation.

If chorionic villi are not confirmed β-hCG levels should be monitored. After evacuation of an abnormal intrauterine pregnancy, the β-hCG level decreases by greater

than 15% within 12 to 24 hours (50). It has been suggested that a fall of ≥50% within 24 hours following manual vacuum aspiration is predictive of an abnormal *intrauterine* pregnancy (85). A borderline fall may represent interassay variability. A repeat level should be obtained in 24 to 48 hours to confirm the decline. If the uterus is evacuated and the pregnancy is extrauterine, the β-hCG level will plateau or continue to increase, indicating the presence of extrauterine trophoblastic tissue.

Culdocentesis

Culdocentesis was historically widely used as a diagnostic technique for ectopic pregnancy. With the use of β-hCG testing and transvaginal ultrasonography, culdocentesis is rarely indicated and is considered obsolete in the evaluation of ectopic pregnancies (86).

Laparoscopy

Traditionally laparoscopy was the gold standard for the diagnosis of ectopic pregnancy. At the time of laparoscopy, the fallopian tubes are easily visualized and evaluated, but the diagnosis of ectopic pregnancy is missed in 3% to 4% of patients who have very small ectopic gestations. The ectopic gestation is seen distorting the normal tubal architecture. With earlier diagnosis, the possibility increases that a small ectopic pregnancy may not be visualized. Pelvic adhesions or previous tubal damage may compromise assessment of the tube. False-positive results occur when tubal dilation or discoloration is misinterpreted as an ectopic pregnancy, in which case the tube can be incised unnecessarily and damaged. With the advances in ultrasound technology, more ectopic pregnancies are being diagnosed earlier allowing for medical interventions and reducing the need for surgical management, thus laparoscopy is no longer considered the gold standard for diagnosis.

Diagnostic Algorithm

The presenting symptoms and physical findings of patients with unruptured ectopic pregnancies are similar to those of patients with normal intrauterine pregnancies (87). History, risk factor assessment, and physical examination are the initial steps in the management of suspected ectopic pregnancy. Patients in a hemodynamically unstable condition should undergo immediate surgical intervention. Patients with a stable, relatively asymptomatic condition may be assessed as outpatients.

There are several potential benefits if the diagnosis of ectopic pregnancy can be confirmed without laparoscopy. First, the anesthetic and surgical risks of laparoscopy are avoided; second, medical therapy becomes a treatment option. Because many ectopic pregnancies occur in histologically normal tubes, resolution without surgery may spare the tube from additional trauma and improve subsequent fertility. Previously, **an algorithm for the diagnosis of ectopic pregnancy without laparoscopy proved to be 100% accurate in a randomized clinical trial** (88,89).

This screening algorithm combined the results of history and physical examination, serial β-hCG levels, vaginal ultrasonography, and dilation and curettage **(Fig. 32-3)**. Serial β-hCG levels are used to assess pregnancy viability, correlated with transvaginal ultrasonography findings and measured serially after a suction curettage. For patients in a stable condition, a treatment decision is never based on a single β-hCG level. After the initial evaluation, the patient is seen again at 48 hours for a repeat β-hCG level. At this time, transvaginal ultrasonography often is repeated so the findings can be correlated with the two β-hCG levels. The algorithm has been updated to account for changes in the new recommendations for a discriminatory zone and expected changes in the β-hCG level with a viable intrauterine pregnancy.

In this algorithm, **transvaginal ultrasonography is used as follows:**

1. **The identification of an intrauterine gestational sac with yolk sac excludes the presence of an extrauterine pregnancy.** If the patient has a β-hCG level of more than 3,510 mIU/mL, and no intrauterine gestational sac is identified, the patient is considered to have an extrauterine pregnancy and can be treated without further testing.
2. **Adnexal gestational sac with a yolk sac or embryo, when seen, definitively confirms the diagnosis of ectopic pregnancy.**
3. **A tubal mass as small as 1 cm can be identified and characterized.**

Suction curettage is used to differentiate nonviable intrauterine pregnancies from ectopic gestations (less than 53%, or even as low as 35%, rise in a-hCG level over 48 hours, an a-hCG level of less than 3,510 mIU/mL, and indeterminate ultrasonography findings). Performance of this procedure avoids unnecessary use of *methotrexate* in patients with abnormal intrauterine pregnancy that can be diagnosed only by evacuating the uterus. An unlikely potential problem with suction curettage is missing either an early nonviable intrauterine pregnancy or combined intrauterine and extrauterine pregnancies.

Treatment

Ectopic pregnancy can be effectively treated medically or surgically. Traditionally, exploratory laparotomy with unilateral salpingectomy was used for diagnosis and treatment for ectopic pregnancies. With techniques available that allow for early detection, including serum quantitative β-hCG levels and ultrasound, more conservative treatment options are available. Minimally invasive surgical techniques and medical management with *methotrexate* are the commonly used treatment options for ectopic pregnancies. **The treatment approach depends on the clinical circumstances, the site of the ectopic pregnancy and the available resources.**

Surgical Treatment

Operative management is the most widely used treatment for ectopic pregnancy. The surgical approach (laparotomy vs. laparoscopy) and procedure (salpingectomy vs. salpingostomy) used to treat ectopic pregnancies depend on the clinical circumstances, available resources, and provider skill level. Each approach and procedure has associated risks and benefits and the treatment employed must be individualized to best meet the needs of the patient and provider.

Laparotomy Versus Laparoscopy

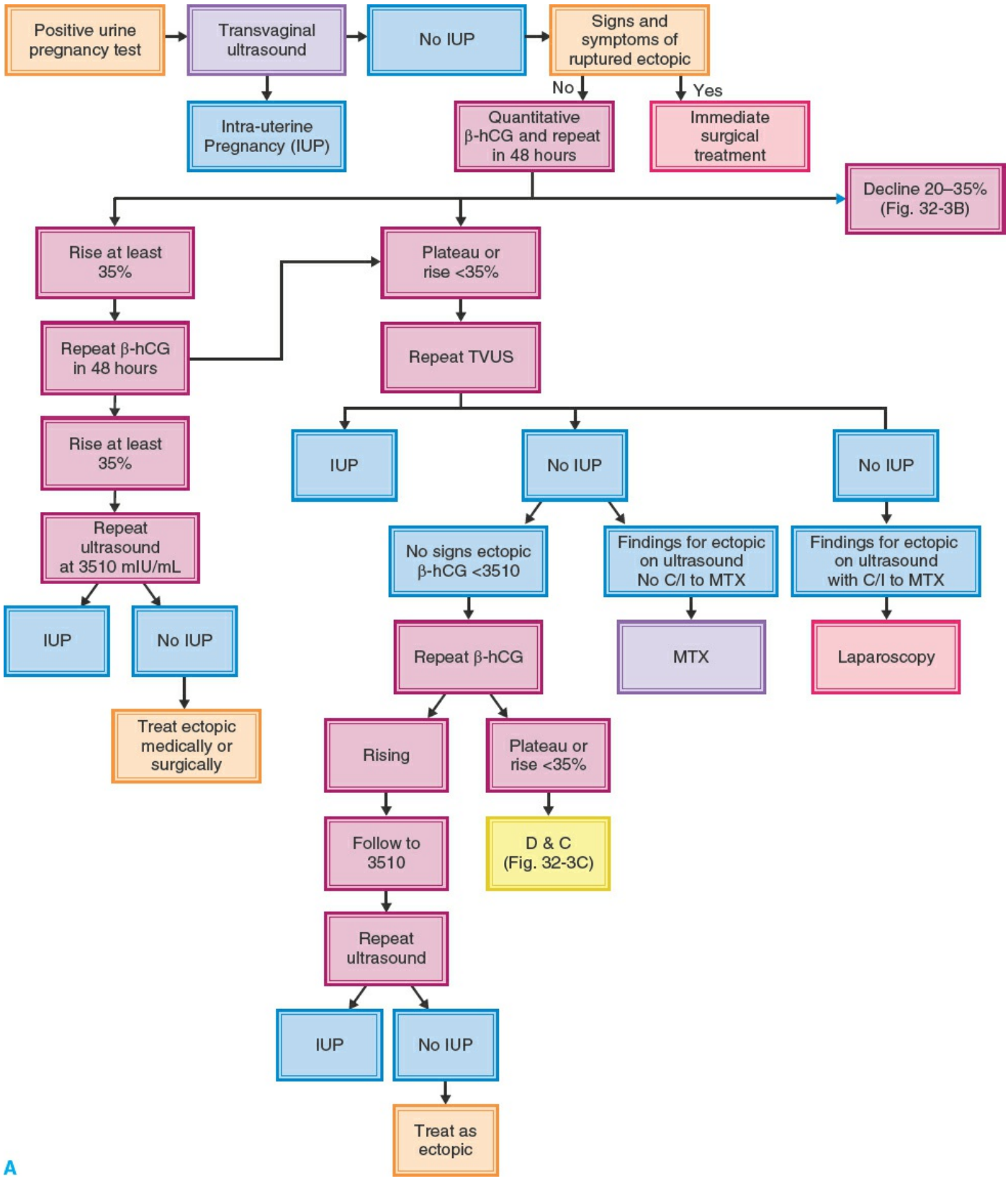
Treatment of an ectopic pregnancy can be accomplished by laparoscopy or laparotomy. The hemodynamic stability of the patient, size and location of the ectopic mass, and the surgeon's expertise all contribute to determining the appropriate surgical approach. **Laparotomy is indicated when the patient becomes hemodynamically unstable and an expedited abdominal entry is required. A ruptured ectopic pregnancy does not necessarily require laparotomy.** If the hemoperitoneum cannot be evacuated in a timely manner, laparotomy should be considered. Surgeon's experience with laparoscopy and the availability of laparoscopic equipment will determine the surgical approach.

In most cases, [3] **laparoscopy is superior to laparotomy for management of ectopic pregnancy. The indications for laparotomy include abdominal pregnancy, extensive abdominal or pelvic adhesive disease, and any other condition making laparoscopy difficult or unsafe.** In a case control study of 50 patients comparing the use of laparoscopy and laparotomy for ectopic pregnancy management, hospital stay was significantly shorter (1.3 ± 0.8 vs. 3.0 ± 1.1 days), operative time was shorter (78 ± 26 vs. 104 ± 27 minutes), and convalescence was shorter (9 ± 8 vs. 26 ± 16 days) in the laparoscopy group (90).

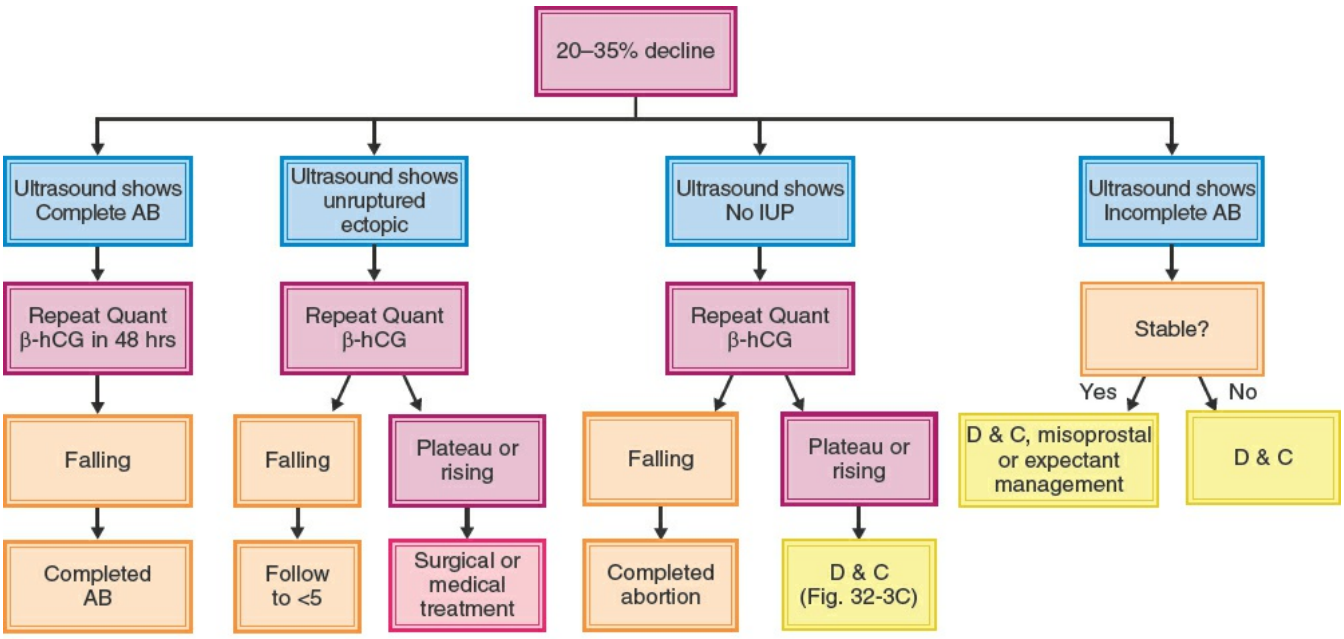
Laparoscopic management was associated with significant cost savings when compared with laparotomy ($4,368 ± $277 vs. $5,090 ± $168). Using a prospective analysis, 105 patients with tubal pregnancy were stratified with regard to age and risk factors and randomized to undergo either laparoscopic management or laparotomy (91). Subsequently, 73 patients underwent second-look laparoscopy to assess the degree of adhesion formation. Patients treated by laparotomy had significantly more adhesions at the surgical site than those treated by laparoscopy, but tubal patency rates were similar. A Cochrane review confirmed these findings and laparoscopic salpingostomy was associated with decreased cost, operative time, blood loss, and hospital stay when compared to salpingostomy at the time of a laparotomy (92).

An alternative to laparoscopy is the use of a mini-laparotomy incision. This approach has the advantage of not requiring laparoscopic equipment and utilizes a smaller incision that should result in decreased postoperative pain and shorter recovery times for patients. A randomized control trial comparing minilaparotomy to laparotomy

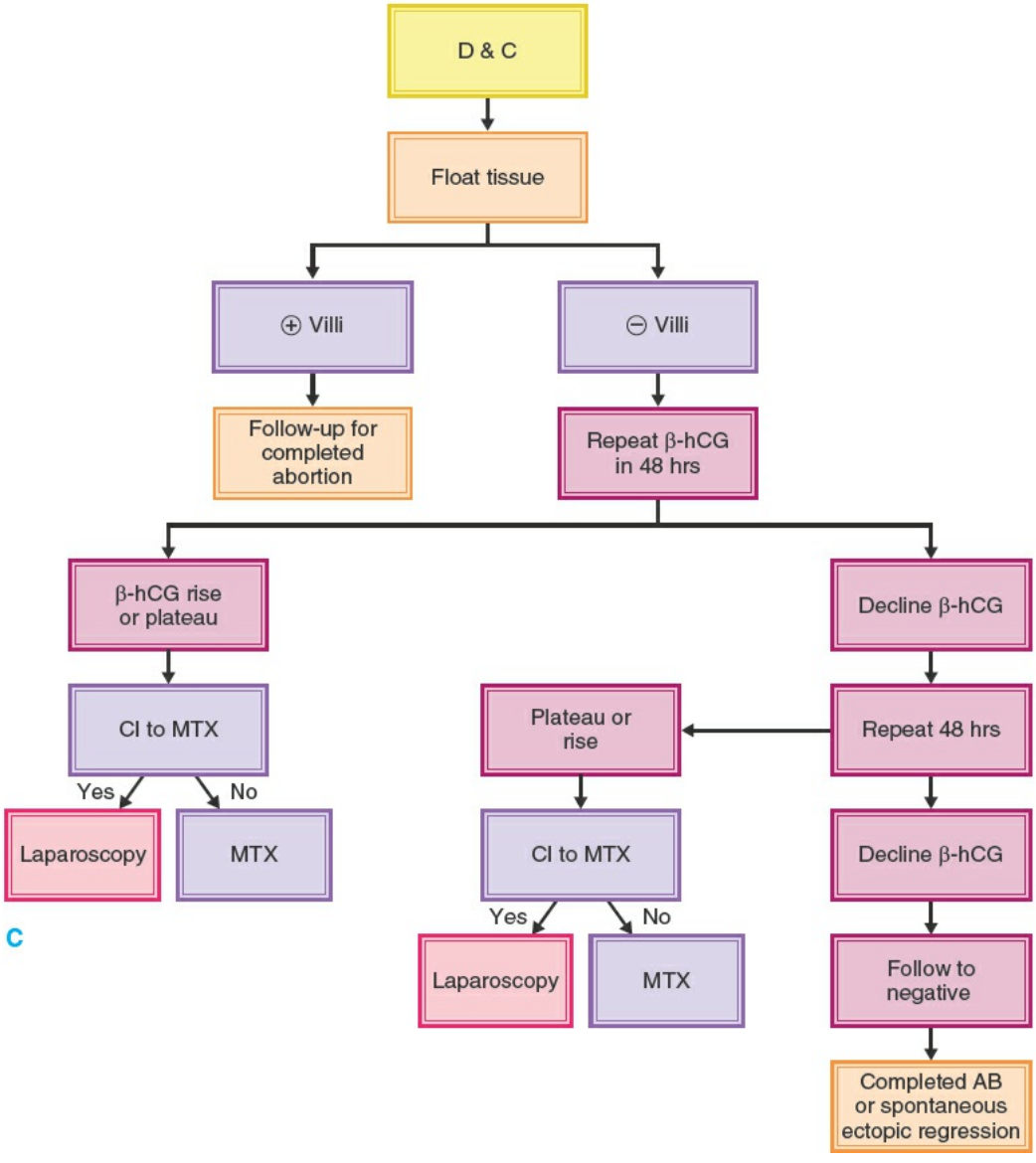
showed decreased complication rates and reduced costs associated with the mini-laparotomy incision with similar success rates in the treatment of the ectopic pregnancy (92,93).


Positive urine pregnancy test
Transvaginal ultrasound
No IUP
Signs and symptoms of ruptured ectopic
No
Yes
Intra-uterine Pregnancy (IUP)
Quantitative β-hCG and repeat in 48 hours
Immediate surgical treatment
Decline 20–35% (Fig. 32-3B)
Rise at least 35%
Plateau or rise <35%
Repeat β-hCG in 48 hours
Repeat TVUS
Rise at least 35%
IUP
No IUP
No IUP
Repeat ultrasound at 3510 mIU/mL
No signs ectopic β-hCG <3510
Findings for ectopic on ultrasound No C/I to MTX
Findings for ectopic on ultrasound with C/I to MTX
IUP
No IUP
Repeat β-hCG
MTX
Laparoscopy
Treat ectopic medically or surgically
Rising
Plateau or rise <35%
Follow to 3510
D & C (Fig. 32-3C)
Repeat ultrasound
IUP
No IUP
Treat as ectopic

A


20–35% decline
Ultrasound shows Complete AB
Ultrasound shows unruptured ectopic
Ultrasound shows No IUP
Ultrasound shows Incomplete AB
Repeat Quant β-hCG in 48 hrs
Repeat Quant β-hCG
Repeat Quant β-hCG
Stable?
Yes
No
Falling
Falling
Plateau or rising
Falling
Plateau or rising
D & C, misoprostal or expectant management
D & C
Completed AB
Follow to <5
Surgical or medical treatment
Completed abortion
D & C (Fig. 32-3C)

B


D & C
Float tissue
⊕ Villi
⊖ Villi
Follow-up for completed abortion
Repeat β-hCG in 48 hrs
β-hCG rise or plateau
Decline β-hCG
CI to MTX
Plateau or rise
Repeat 48 hrs
Yes
No
Laparoscopy
MTX
CI to MTX
Decline β-hCG
Yes
No
Laparoscopy
MTX
Follow to negative
Completed AB or spontaneous ectopic regression

C

FIGURE 32-3 Non-laparoscopic algorithm for diagnosis of ectopic pregnancy. β-hCG, human chorionic gonadotropin; IUP, intrauterine pregnancy; D&C, dilation and curettage.

Salpingectomy Versus Salpingostomy

Multiple studies have been conducted to compare management of ectopic pregnancy with a salpingostomy or salpingectomy. The decision to choose one technique over the other depends on the patient's fertility goals, clinical picture, and the condition of the affected and contralateral fallopian tubes.

Linear salpingostomy can be considered when the patient has an unruptured ectopic pregnancy, wishes to retain her potential for future fertility, and the affected fallopian tube appears otherwise normal. This is particularly important to consider if the contralateral tube appears damaged or has been previously removed.

In a salpingostomy, the products of conception are removed through an incision made into the tube on its antimesenteric border. The procedure can be accomplished with needle-tip cautery, laser, scalpel, or scissors. It can be done with operative laparoscopic techniques or via a laparotomy. Contraindications to a salpingostomy include ruptured fallopian tube, use of extensive cautery to obtain hemostasis, severely damaged tube and recurrent ectopic pregnancy in the same tube. The main risk of salpingostomy is a persistent ectopic pregnancy resulting from failure to remove the entire pregnancy. This was reported in 8% of cases in a recent large open-label study (94). Patients with high starting β-hCG levels, early gestations, and small ectopic pregnancies (<2 cm) are at greater risk of having a persistent pregnancy after a salpingostomy (95). Because of this risk, after salpingostomy, weekly β-hCG levels should be followed to ensure complete resolution of the ectopic pregnancy. β-hCG levels that persist or plateau can usually be treated successfully with a single dose of *methotrexate* (31). Historically, milking the tube to effect a tubal abortion was advocated; if the pregnancy is located within the fimbriae, this technique may be effective. However, when milking was compared with linear salpingostomy for ectopic pregnancies within the ampulla, milking was associated with a twofold increase in the recurrent ectopic pregnancy rate, thus this process is generally not recommended (96).

Reproductive Outcome

Reproductive outcome after ectopic pregnancy is evaluated by determining tubal patency by HSGs, the subsequent intrauterine pregnancy rate, and the recurrent ectopic pregnancy rate. Pregnancy rates are similar in patients treated by either laparoscopy or laparotomy, though a minimally invasive procedure is preferred due to lower overall risks and faster recovery. **Tubal patency on the ipsilateral side after conservative laparoscopic management is about 84%** (97). **In a study of 143 patients followed after undergoing laparoscopic procedures for ectopic pregnancy, the overall intrauterine pregnancy rates after laparoscopic salpingostomy (60%) and**

laparoscopic salpingectomy (54%) were not significantly different (98). However, if the patient had evidence of tubal damage, pregnancy rates (42%) were significantly lower than in those women who did not have tubal damage (79%). In another study, the reproductive outcome of 188 patients followed for a mean of 7.2 years (range 3 to 15 years) was reported after conservation by laparotomy for ectopic pregnancy (99). In randomized controlled trials comparing salpingectomy and salpingostomy, there was no overall difference in future intrauterine pregnancy rates or repeat ectopic pregnancy. However, in cohort studies, salpingostomy is associated with higher rate of repeat ectopic pregnancy (10% vs. 4% with salpingectomy, OR 2.27), but is associated with a slightly higher rate of intrauterine pregnancy (RR 1.24, CI 1.08–1.42) (100).

Medical Treatment

The drug most frequently used for medical management of ectopic pregnancy is *methotrexate,* although other agents have been studied, including potassium chloride (KCl), hyperosmolar glucose, prostaglandins, and *RU-486.* These agents may be given systemically (intravenously, intramuscularly, or orally) or locally (laparoscopic direct injection, ultrasound-guided injection, or retrograde salpingography). Other agents besides *methotrexate* are not recommended for the treatment of ectopic pregnancy because their safety and efficacy are not well-documented.

Methotrexate

Methotrexate is a folic acid analog that inhibits dehydrofolate reductase and thereby prevents synthesis of DNA. *Methotrexate* affects actively growing cells including trophoblastic tissues, malignant cells, bone marrow, intestinal mucosa and respiratory epithelium (101). It is used extensively in the treatment of gestational trophoblastic disease (see Chapter 41). Initially, *methotrexate* was used for the treatment of trophoblastic tissue left *in situ* after exploration for an abdominal pregnancy (102). In 1982, Tanaka et al. treated an unruptured interstitial gestation with a 15-day course of intramuscular *methotrexate and began treatment of ectopic pregnancies with this medication* (103). Multiple studies have documented the safety and efficacy of *methotrexate* therapy for the management of ectopic pregnancies; this is the first-line treatment for many providers. Approximately 35% of patients with ectopic pregnancies are candidates for primary therapy with *methotrexate* (104). *Methotrexate* may be given for the treatment of persistent ectopic pregnancies that fail surgical management.

Candidates for Methotrexate

Medical management of ectopic pregnancies with *methotrexate* is safe and effective, however, not all patients are candidates for this medical therapy. *Methotrexate* therapy can be considered for patients with confirmed, or high suspicion for ectopic pregnancy who are hemodynamically stable with no evidence of rupture. **Table 32-3** documents the absolute contraindications to *methotrexate* therapy including breastfeeding, hepatic,

renal, or hematologic disorders and known sensitivity to *methotrexate*. Relative contraindications to *methotrexate* therapy include gestational sac greater than 4 cm and embryonic cardiac motion on transvaginal ultrasound (Table 32-3). Prior to the administration of *methotrexate*, a patient should have a complete blood count, blood type, liver function tests, electrolyte panel including creatinine, and a chest x-ray if there is any history of pulmonary disease. These studies are usually repeated 1 week after administration of *methotrexate* to evaluate for any potential complications from the therapy (105).

Table 32-3 Contraindications to Medical Therapy

Absolute Contraindications
Intrauterine pregnancy
Hemodynamically unstable
Ruptured ectopic pregnancy
Breastfeeding
Immunodeficiency
Moderate to severe anemia, leukopenia or thrombocytopenia
Known sensitivity to *methotrexate*
Active pulmonary disease
Active peptic ulcer disease
Clinically important hepatic or renal dysfunction
Relative Contraindications
Ectopic pregnancy >4 cm in size by transvaginal ultrasound
Embryonic cardiac motion detected on transvaginal ultrasound
Unable to comply with medical management follow-up
High initial β-hCG concentration (>5,000 mIU/mL)
Refusal to accept blood transfusion

Adapted from The Practice Committee of the ASRM, Medical Treatment of Ectopic Pregnancy, 2013.

Methotrexate Dosing Regimens

Methotrexate is typically given via intramuscular injection but can be administered orally or by intravenous infusion. There are three published regimens for administration of methotrexate: single-dose regimen, a two-dose regimen, and a multidose regimen.

Methotrexate traditionally was administered using a multidose regimen, but single dosing protocols have improved patient compliance and have similar success rates of approximately 90% (92,106). The single-dose protocol also has fewer side effects, however an additional dose of methotrexate may be required in up to 25% of women who receive this treatment (92,106). This second dose is more often required in women with higher starting β-hCG levels.

Methotrexate Single-Dose Regimens

Single-dose regimens were designed to increase patient compliance and simplify the administration of *methotrexate*. This regimen is well studied and safe and effective in the treatment of ectopic pregnancies. The single-dose regimen is detailed in Table 32-4.

Table 32-4 *Methotrexate* Treatment Regimens

Single-Dose Regimen
Administer *MTX* 50 mg/m^2 on day 0
Measure β-hCG level on days 4 and 7
If levels drop by 15%, monitor β-hCG weekly until nonpregnant level
If levels do not drop by 15%, repeat dose of *MTX* and measure β-hCG on days 4 and 7
Multidose Regimen
Administer *MTX* 1 mg/kg IM days 1, 3, 5, 7
Administer *leucovorin* 0.1 mg/kg IM days 2, 4, 6, 8
Measure β-hCG levels on days 1, 3, 5, 7 until 15% decrease between two measurements
Once β-hCG levels drop 15%, stop *MTX* and monitor β-hCG weekly until nonpregnant level
Two-Dose Regimen
Administer *MTX* 50 mg/m^2 on days 0 and 4
Measure β-hCG level on days 4 and 7
If levels drop by 15%, monitor β-hCG weekly until nonpregnant level
If levels do not drop by 15%, repeat dose of *MTX* on days 7 and 11 and measure β-hCG on days 11 and 14. If levels drop 15%, monitor β-hCG weekly until nonpregnant level

MTX, methotrexate; IM, intramuscular; β-hCG, β-human chorionic gonadotropin.
Adapted from The Practice Committee of the ASRM, Medical Treatment of Ectopic Pregnancy, 2013.

Approximately 15% to 20% of patients in the single-dose regimen will require a second dose of *methotrexate* because of persistent β-hCG levels (106,107). The β-hCG level at the time of treatment appears to predict the subsequent success rate of single-

dose therapy. Patients with β-hCG levels greater than 5,000 mIU/mL have a 14.3% chance of treatment failure compared to only 3.7% for women with levels less than 5,000 mIU/mL. **[4] Compared with the multidose protocol, single-dose *methotrexate* is less expensive, patient acceptance is greater because less monitoring is required during treatment, and the treatment results and prospects for future fertility are comparable** (108).

Multidose Regimen

The multidose regimen is outlined in **Table 32-4**. Patients receive 1 mg/kg of *methotrexate* intramuscularly or intravenously on days 1, 3, 5, and 7 with leucovorin 0.1 mg/kg administered on days 2, 4, 6, and 8. As a result of the repeat dosing of *methotrexate*, side effects are more common. The leucovorin helps reduce these side effects and increases patients' tolerance of the treatment. A patient may not require all four doses of *methotrexate* and her β-hCG levels should be monitored on days 1, 3, 5, and 7. If the β-hCG level drops 15% between two measurements, the regimen can be stopped and weekly β-hCG monitoring initiated. If the *methotrexate* is discontinued early, the patient should receive leucovorin after her final dose of *methotrexate* to help reduce potential side effects. If a patient's β-hCG level plateaus or increases, a second round of *methotrexate* and leucovorin can be given 1 week later. Earlier studies indicated approximately 19% will require all four doses, and 17% of women will require only one dose with this regimen (109,110). A **meta-analysis showed 10% of women require only one dose, while nearly 54% will require all four doses** (106).

Methotrexate Two-Dose Regimen

The two-dose regimen was described as a cross between the single- and multidose regimens. Because only 54% require all four doses of the multidose regimen and 15% to 25% will require a second dose in the single-dose regimen, it is reasonable to consider a two-dose regimen of *methotrexate*. The protocol is outlined in **Table 32-4** and involves the administration of *methotrexate* on day 0 and day 4 with monitoring of β-hCG levels on days 4 and 7. If there is less than a 15% drop between the two measures, a repeat administration of *methotrexate* is given on days 7 and 11 and β-hCG levels drawn accordingly. A single study showed an 87% success rate with low complication rates and high patient satisfaction (111).

Effectiveness of Methotrexate

The overall effectiveness of *methotrexate* therapy ranges from 78% to 96% (112). Although the previously mentioned meta-analysis of 26 observational studies including 1,300 women revealed a slightly improved rate of success with multidose therapy, another meta-analysis including two randomized controlled trials showed no difference in success rates between the two regimens. However, the β-hCG levels in both of those studies were less than 3,000 mIU/mL (106,113,114). Systematic reviews have

demonstrated an overall failure rate of at least 14.3% when initial β-hCG is greater than 5,000 mIU/mL compared with a failure rate of less than 4% when the β-hCG is less than 5,000 mIU/mL (108). When comparing *methotrexate* to laparoscopic salpingostomy, the multidose regimen has similar success rates. The single-dose regimen has lower initial success rates. However, after women receive additional doses as needed, the success rates are comparable between laparoscopic salpingostomy and single-dose *methotrexate* protocols (106).

Table 32-5 Initiation of *Methotrexate*: Physician Checklist and Patient Instructions

***Physician* Checklist**
Obtain β-hCG level
Check CBC with differential, liver function tests, creatinine, blood type, and antibody screen
Administer RhoGAM if patient is Rh-negative
Identify unruptured ectopic pregnancy smaller than 4 cm (relative contraindication)
Obtain informed consent
Prescribe $FeSO_4$ 325 mg PO bid if hematocrit is less than 30%
Schedule follow-up appointment on days 4 and 7
Patient Instructions
Refrain from alcohol use, multivitamins containing folic acid, NSAID use and sexual intercourse until β-hCG level is negative
Call your physician if: You experience prolonged or heavy vaginal bleeding The pain is prolonged or severe (lower abdomen and pelvic pain is normal during the first 10–14 days of treatment)

About 4% to 5% of women experience unsuccessful *methotrexate* treatment and require surgery. β-hCG, human chorionic gonadotropin; SGOT, serum glutamic-oxaloacetic transaminase; BUN, blood urea nitrogen; CBC, complete blood count; *RhoGAM*, Rho(D) immune globulin; NSAIDs, nonsteroidal anti-inflammatory drugs; WBC, white blood cell; PO, by mouth; bid, twice daily.

Initiating Methotrexate

Outlined in Table 32-5 is a checklist that should be followed by the physician before initiating *methotrexate*. It includes instructions that are helpful to the patient.

Patient Follow-Up

After intramuscular administration of *methotrexate*, regardless of the dose regimen used, patients are monitored on an outpatient basis with weekly β-hCG levels. These levels need to be monitored until the β-hCG reaches nonpregnant levels. It is possible that tubal rupture may occur even if β-hCG levels are falling. Signs of a tubal

rupture include severe pain, hemodynamic instability, and a drop in hematocrit. Patients who report severe or prolonged pain should be evaluated by measuring hematocrit levels and performing transvaginal ultrasonography. The ultrasound findings during follow-up, although usually not helpful, can be used to provide reassurance that the tube is not ruptured (115). Cul-de-sac fluid is a common finding and the amount of fluid may increase if a tubal abortion occurs. It is not necessary to intervene surgically, unless the patient has a precipitous drop in hematocrit levels or she becomes hemodynamically unstable.

Side Effects

Side effects of *methotrexate* therapy are dose and frequency dependent. The most commonly reported side effects are the gastrointestinal symptoms of nausea, vomiting, stomatitis, and abdominal pain. The frequency of reported side effects ranges from 30% to 40% (106). As a result of these potential effects, women are cautioned against using alcohol and nonsteroidal anti-inflammatory medications during treatment with *methotrexate*. Other side effects include bone marrow suppression, hemorrhagic enteritis, alopecia, dermatitis, elevated liver enzyme levels, and pneumonitis (116). These side effects are usually mild and self-limited; few life-threatening side effects are reported. The risk of all side effects does appear to be higher for multidose regimens. For those patients on prolonged therapy, *leucovorin* can reduce the incidence of these side effects and is included in the "multidose" regimen. Long-term follow-up of women treated with *methotrexate* for gestational trophoblastic disease shows no increase in congenital malformations, spontaneous abortions, or tumors recurring after chemotherapy (117). Treatment of ectopic pregnancy differs from that of gestational trophoblastic disease in that a smaller total dose of *methotrexate* is required and shorter treatment duration is used. Although surgical management of ectopic pregnancy remains the mainstay of treatment worldwide, *methotrexate* treatment is appropriate in those patients who meet the treatment criteria.

Reproductive Outcome

Reproductive function after *methotrexate* treatment can be assessed on the basis of repeat ectopic pregnancy rates, tubal patency, and pregnancy outcome. The risk of subsequent ectopic pregnancy is approximately 10% following either *methotrexate* or salpingostomy (118,119). The tubal patency rates are reported to be higher than 80% in those patients treated with either single-dose or multidose regimens with no difference in rates compared with women treated with salpingostomy. A randomized trial comparing *methotrexate* to laparoscopic salpingostomy showed no difference in tubal patency rates among the two groups, although in this trial patency rates were lower than previously reported at 66% in the salpingostomy group (120). Subsequent spontaneous intrauterine pregnancy rates are similar between those women treated with *methotrexate* versus salpingostomy, with rates ranging from 36% to 64% (121,122). A

Cochrane review comparing interventions for ectopic pregnancy showed no difference in subsequent risk of a repeat ectopic pregnancy and future intrauterine pregnancy rates comparing surgically and medically treated patients. Studies evaluating ovarian reserve after treatment with methotrexate for an ectopic showed no impact on future ovarian reserve (123,124). **[5] Comparison of laparoscopically treated patients with *methotrexate*-treated patients indicates that the two methods have similar reproductive outcomes (92).**

Types of Ectopic Pregnancy

Spontaneous Resolution of Pregnancies of Unknown Location

Some ectopic pregnancies resolve by resorption or by tubal abortion, obviating the need for medical or surgical therapy. The proportion of ectopic pregnancies that resolve spontaneously and the factors that make this more likely are unknown. There are no specific criteria for predicting successful spontaneous resolution of an ectopic pregnancy. A falling β-hCG level is the most common indicator used, but tubal rupture can occur even with falling β-hCG levels. One recent study found that a ratio of β-hCG level at 48 hours compared with initial hCG level of <0.87 predicted a failing pregnancy of unknown location, better than absolute serum β-hCG levels at both of those time periods (125). Patients with low initial levels of β-hCG are generally the best candidates for expectant management, and there is a reported 88% success rate of spontaneous remission with an initial β-hCG level less than 200 mIU/mL (126,127). These patients should be followed with serial β-hCG levels, with a plan to initiate active management if levels plateau or rise or signs suggestive of tubal rupture occur.

Persistent Trophoblastic Tissue

Persistent ectopic pregnancy occurs when a patient underwent conservative surgery (e.g., salpingostomy, fimbrial expression) and viable trophoblastic tissue remains. Histologically, several criteria exist: there is no identifiable embryo, the implantation usually is medial to the previous tubal incision and residual chorionic villi are confined to the tubal muscularis. Peritoneal trophoblastic tissue implants may be responsible for persistence. Diagnosis is made when β-hCG levels plateau after conservative surgery. Risk factors for persistent ectopic pregnancy include the type of surgical procedure, the initial β-hCG level, the duration of amenorrhea, and the size of the ectopic pregnancy, with smaller, earlier pregnancies treated by salpingostomy carrying the highest risk (128). Patients treated with laparoscopic salpingostomy have a higher rate of persistent ectopic pregnancies compared to those treated with salpingostomy at the time of a laparotomy, with an incidence of **persistence after laparoscopic linear salpingostomy ranging from 4% to 15%** (39,92,94).

Management. **Persistent ectopic pregnancy can be treated surgically or**

medically; surgical therapy consists of either repeat salpingostomy or, more commonly, salpingectomy. *Methotrexate* offers an alternative to patients who are hemodynamically stable at the time of diagnosis. *Methotrexate* may be the treatment of choice because the persistent trophoblastic tissue may not be confined to the tube and, therefore, not readily identifiable during repeat surgical exploration (128).

Nontubal Ectopic Pregnancy

The majority of ectopic pregnancies diagnosed are found in the ampulla portion of the fallopian tube and the majority (93%) found within some part of the fallopian tube. Increasingly, more ectopic pregnancies are found in other locations within the abdomen and pelvis. These nontubal ectopic pregnancies are rare but are important to consider as they are associated with more adverse events caused by difficulty and delay in diagnosis and treatment.

Cervical Pregnancy

Diagnosis. **Pregnancy implanted within the cervix is the rarest of all ectopic pregnancies, accounting for less than 1% of all ectopic pregnancies** (1). The cause of cervical ectopic pregnancies is unknown and the rare occurrence prevents identification of known risk factors. The diagnosis may not be suspected until the patient is undergoing suction curettage for a presumed incomplete abortion and hemorrhage occurs. In some cases, bleeding is light, whereas in others there is hemorrhage. These types of ectopic pregnancies are diagnosed and distinguished from ongoing spontaneous abortion mainly with ultrasound findings, and serial β-hCG measurements. Distinguishing a cervical ectopic pregnancy from an incomplete process is often difficult, and many cervical ectopic pregnancies may be misdiagnosed (129). Suggested criteria can be found in Table 32-6. Other potential diagnoses that must be differentiated from cervical pregnancy include cervical carcinoma, cervical or prolapsed submucosal leiomyomas, trophoblastic tumor, placenta previa, and low-lying placenta. An MRI may be helpful in distinguishing between some of these entities if the ultrasound and β-hCG measurements are not clear.

Table 32-6 Ultrasound Criteria for Cervical Pregnancy

1. Gestational sac or placental tissue visualized within the cervix
2. Cardiac motion noted below the level of the internal os
3. No intrauterine pregnancy
4. Hourglass uterine shape with ballooned cervical canal
5. No movement of the sac with pressure from transvaginal probe (i.e., no “sliding sign” that is typically seen with incomplete abortions)

6. Closed internal os

Adapted from **Kung FT, Lin H, Hsu TY, et al.** Differential diagnosis of cervical ectopic pregnancy and conservative treatment with the combination of laparoscopy-assisted uterine artery ligation and hysteroscopic endocervical resection. *Fertil Steril* 2004;81:1642–1649.

Management. **Options for management of cervical ectopic pregnancies include medical treatment with *methotrexate* and surgical dilation and curettage.** The ideal regimen for medical management is unknown and success is reported with both the single- and multidose regimens. More advanced gestations, especially with fetal cardiac activity, may require a combination of multidose *methotrexate* and intra-amniotic/intra-fetal injection of KCl for fetal demise. These injections require skill to avoid rupture of membranes during the procedure. A retrospective study of 62 women with cervical ectopic pregnancies treated in China found that viable pregnancies treated with methotrexate had a higher rate of surgical intervention (43%) than nonviable pregnancies (13%) (130). As this was a retrospective chart review, the authors do not comment on whether some of the additional procedures were planned or if they were a result of methotrexate failure. As with tubal ectopic pregnancies, medical management is appropriate only for those patients who are hemodynamically stable (129).

Preventative surgical management of cervical ectopic pregnancy has been described. If the patient and physician elect to proceed with surgical management, the preoperative preparation should include blood typing and cross-matching, establishment of intravenous access, and detailed informed consent. This consent should include the possibility of hemorrhage that may require transfusion or hysterectomy. In a small study of 6 patients with cervical ectopic in China, all patients were treated with uterine artery embolism (UAE) followed by hysteroscopic endocervical resection (129). Treatment was successful in all six cases without any adjunctive methotrexate treatment and with minimal blood loss (mean 125 mL, range 50 to 250 mL). While this study is small, it suggests the safety of minimally invasive techniques. Patients should be counseled that the fertility effects of undergoing even a temporary UAE are not yet clear.

When a cervical ectopic pregnancy presents with bleeding or if bleeding occurs as part of treatment, various techniques can be used including uterine packing, UAE, lateral cervical suture placement to ligate the lateral cervical vessels, placement of a cerclage, and insertion of an intracervical 30-mL Foley catheter for cervical tamponade. When none of these methods is successful, hysterectomy is required.

Ovarian Pregnancy

Diagnosis. **A pregnancy confined to the ovary accounts for up to 3% of all ectopic pregnancies and is the most common type of nontubal ectopic pregnancy** (1,131). Though the clinical presentation of bleeding, abdominal pain, and positive pregnancy test is similar, ovarian pregnancy is not associated with PID, infertility, or tubal disease

like other ectopic pregnancies (132). The pathology diagnostic criteria were described in 1878 by Spiegelberg, listed in Table 32-7 (133). Ultrasound criteria are difficult as findings are typically a cystic ovarian mass, with a differential of corpus luteum cyst, hemorrhagic cyst, and tubal ectopic pregnancy.

Management. The treatment of ovarian pregnancy has changed. Whereas oophorectomy was advocated in the past, **ovarian cystectomy and/or wedge resection is utilized with success** and successful treatment with *methotrexate* has been reported (134–136).

Abdominal Pregnancy

Abdominal pregnancies are one of the rarest types of ectopic pregnancy, representing 1% to 1.4% of ectopic pregnancies (1,131). They are typically classified as primary or secondary. Pathology criteria for primary abdominal ectopic pregnancy have been established by Studdiford (see Table 32-8) and include normal tubes and ovaries, no evidence of uteroplacental fistula (137). Secondary abdominal pregnancies are more common, thought to result from tubal abortion or rupture or, less often, from subsequent implantation within the abdomen after uterine rupture. Risk factors for abdominal pregnancy include PID, multiparity, endometriosis, assisted reproductive techniques, and tubal damage. The most common area of implantation within the abdomen is the posterior cul-de-sac, and pregnancies have been confirmed in the mesosalpinx, omentum and bowel, liver, spleen, abdominal wall, and within broad ligament (131). **Abdominal pregnancy is associated with high morbidity and mortality, with the risk for death seven to eight times greater than from tubal ectopic pregnancy and 50 times greater than from intrauterine pregnancy**, most likely resulting from later diagnosis.

Table 32-7 Criteria for Ovarian Pregnancy Diagnosis

1. The fallopian tube on the affected side must be intact
2. The fetal sac must occupy the position of the ovary
3. The ovary must be connected to the uterus by the ovarian ligament
4. Ovarian tissue must be located in the sac wall

From **Spiegelberg O.** Casusistik der ovarialschwangerschaft. *Arch Gynaecol* 1878;13:73.

Table 32-8 Studdiford's Criteria for Diagnosis of Primary Abdominal Pregnancy

1. Presence of normal tubes and ovaries with no evidence of recent or past pregnancy
2. No evidence of uteroplacental fistula

3. The presence of a pregnancy related exclusively to the peritoneal surface and early enough to eliminate the possibility of secondary implantation after primary tubal nidation

Adapted from **Anderson PM, Opfer EK, Busch JM, et al.** An early abdominal wall ectopic pregnancy successfully treated with ultrasound guided intralesional methotrexate: A case report. *Obstet Gynecol Int* 2009; Article ID 247452.

Diagnosis. Ultrasound detects only approximately half of all abdominal ectopic pregnancies. Ultrasound features that have been suggested include gestational sac surrounded by loops of bowel, normal-appearing fallopian tubes, and ovaries (138). Differential includes intrauterine pregnancy with retroflexion or distorted by fibroids. When diagnosis is highly suspected, MRI may be helpful in assessing degree of vascular attachment to other abdominopelvic tissues. Abdominal ectopic pregnancies are one of the few ectopic pregnancies that may proceed out of the first trimester. In advanced abdominal pregnancy, the clinical presentation may include painful fetal movement, fetal movements high in the abdomen or sudden cessation of movements. Physical examination may disclose persistent abnormal fetal positioning, abdominal tenderness, a displaced uterine cervix, easy palpation of fetal parts, and palpation of the uterus separate from the gestation. The diagnosis may be suspected when there are no uterine contractions after *oxytocin* infusion.

Management. Because the pregnancy can continue to term, the potential maternal morbidity and mortality are very high. As a result, **surgical intervention is recommended when an abdominal pregnancy is diagnosed.** At surgery, the placenta can be removed if its vascular supply can be identified and ligated, but hemorrhage can occur, requiring abdominal packing that is left in place and removed after 24 to 48 hours. Options for management of hemorrhage include artery embolization. If the vascular supply cannot be identified, the cord is ligated near the placental base, and the placenta is left in place. Placental involution can be monitored using serial ultrasonography and assessment of β-hCG levels. Potential complications of leaving the placenta in place include bowel obstruction, fistula formation and sepsis as the tissue degenerates. There are concerns regarding the use of *methotrexate* treatment in abdominal pregnancies. Specifically, there is theoretically an increased risk of infection and sepsis resulting from the rapid tissue necrosis that occur following *methotrexate* administration. There are reports of successful treatment of abdominal pregnancies with *methotrexate* in patients not considered to be optimal surgical candidates (136,139). There are scattered reports of term abdominal pregnancies. When this occurs, perinatal morbidity and mortality are high, usually as a result of growth restriction and congenital anomalies such as fetal pulmonary hypoplasia, pressure deformities, and facial and limb asymmetry (140).

Interstitial Pregnancy

Diagnosis. **Interstitial pregnancies represent about 2.4% of ectopic pregnancies**

(1). This section of the fallopian tube is relatively thick with an increased capacity to expand prior to rupture. This ability along with increased vascularity of this area may allow these types of ectopic pregnancies to remain asymptomatic for 7 to 16 weeks of gestation (141). However, late presentations are rare; most patients typically present between 6 and 8 weeks of gestation (141). Differential diagnosis includes angular pregnancy, a viable pregnancy that implants within the uterine angle, medial to the ostia. Typically angular pregnancies are asymptomatic unless they end in miscarriages, which occurs approximately 38% of the time (141). In laparoscopy, these can be distinguished as a true interstitial pregnancy appears lateral to the round ligament.

Interstitial pregnancies represent a disproportionately large percentage of fatalities from ectopic pregnancy with a 2.5% mortality rate (142).

Management. These pregnancies were classically treated with laparotomy with cornual resection. Early detection allows for a more conservative management approach in hemodynamically stable patients without evidence of rupture. Medical management with *methotrexate* is well described, with the single- and multidose regimens. Approximately 10% to 20% of patients treated medically will ultimately require surgery and close follow-up is warranted as with all medically managed ectopic pregnancies (141).

Although cornual wedge resection by laparotomy is an acceptable surgical option, minimally invasive techniques exist, including cornual excision, minicornual excision and cornuostomy. Laparoscopic approaches are more widely used and are dependent on surgical skill. Transcervical suction evacuation under laparoscopic or ultrasound guidance has been reported (136,141). The appropriate surgical technique and approach depends on the individual patient presentation and the surgeon's expertise.

Cesarean Scar Ectopic Pregnancy

A pregnancy implanted within the uterine myometrium at the site of a healed cesarean scar is called a cesarean scar pregnancy (CSP). Historically, CSP has been an extremely rare occurrence. However, as cesarean deliveries are becoming more common, incidence has been slowly increasing with estimations among women with prior cesarean deliveries to be up to 1:500 pregnancies (136,143). Because of small numbers, it has not been determined if the number of cesarean deliveries or type of cesarean delivery (e.g., classical or Pfannenstiel incisions) affect risk of CSP.

Diagnosis. Ultrasound is the initial diagnostic tool for CSP, with signs suggestive of CSP including: (1) gestational sac located at the level of the prior scar; (2) surrounding Doppler flow with minimal separation from bladder; (3) outward bulging of the gestational sac within the scar; and (4) negative "sliding organs sign" where the gestational sac does not move with gentle pressure from transvaginal ultrasound (143). CSPs have been separated into two types based on prognosis; type 1 progressing toward uterine cavity; type 2 progressing toward the bladder.

Management. As CSP is quite rare and can present differently based on location and type, there is no management that has proved superior. Early treatment is recommended, as CSP can progress into placental accreta or even uterine rupture if left untreated. Management options include medical management with systemic or local injection of either methotrexate or KCl, surgical management with dilation and curettage with or without hysteroscopy, UAE, or some combination of these approaches. Medical management should only be offered to hemodynamically stable patients. Success rates for methotrexate doses systemically, locally, and combined systemic/local have been reported as 56%, 60%, and 77%, respectively. These cases had a hemorrhage rate of 7% and hysterectomy rate of 3% (143). For surgical management, dilation and curettage under ultrasound guidance had a reported success rate of 76% with a 30% hemorrhage risk and 3% hysterectomy risk (143). Hysteroscopic resection was used with a 62% risk of persistent trophoblastic disease and should be performed in combination with dilation and curettage. A combination of methotrexate followed by dilation and curettage has been reported with success rates up to 86%, hemorrhage risk of 14%, and hysterectomy risk of 4%. UAE can be performed prior to dilation and curettage or even prior to methotrexate therapy to reduce hemorrhage risk. If UAE is not done prophylactically, it can be done in the case of hemorrhage after other treatment options. In some cases, methotrexate was injected into uterine arteries prior to UAE. If used alone, UAE has a reported success rate of 81% with risk of hemorrhage 5%, and risk of hysterectomy 4% (143).

Heterotopic Pregnancy

Heterotopic pregnancy occurs when intrauterine and ectopic pregnancies coexist. The reported incidence is 1:30,000 (35). The diagnosis is often delayed as an intrauterine pregnancy is seen during ultrasonography examination and an extrauterine pregnancy may be overlooked. Patients undergoing ovulation induction with assisted reproductive technology are at risk of ovarian hyperstimulation syndrome (OHSS), which can cause similar ultrasound findings including enlarged ovaries and free fluid in the abdomen and is important to consider in differential diagnosis (144). Serial β-hCG levels are not helpful because the intrauterine pregnancy causes the β-hCG level to rise appropriately. Heterotopic pregnancy is much more common with assisted reproductive technology than spontaneous conception, with possible etiologies including multiple embryo transfers and previous tubal damage (144,145).

Management. The ectopic pregnancy is treated surgically if the intrauterine pregnancy is desired. When the ectopic pregnancy is removed, the intrauterine pregnancy continues in most patients. The rate of spontaneous abortion is higher with approximately one in three ending in miscarriage (145,146). It may be possible to treat the ectopic pregnancy using nonchemotherapeutic medical treatment, such as KCl, by transvaginal or laparoscopically directed injection; however, a reported 55% may

require additional surgical treatment (147).

Multiple Ectopic Pregnancies

Twin or multiple ectopic gestations occur less frequently than heterotopic gestations and may appear in a variety of locations and combinations. Multiple ectopic pregnancies are thought to be rare, but with the advent of assisted reproductive technologies the incidence appears to be rising. A review of bilateral tubal pregnancies reported 242 cases between 1918 and 2007, with 42 cases in the past 10 years alone. Fifty percent of these twin tubal pregnancies were associated with assisted reproductive technologies (148). Another review of 163 cases of tubal ectopic pregnancies had a reported rate of twin tubal pregnancies of 2.4% (149). Although most reports are confined to twin tubal gestations, ovarian, interstitial, and abdominal twin pregnancies have been reported. Management is similar to that of other types of ectopic pregnancy and is somewhat dependent on the location of the pregnancy.

Pregnancy After Hysterectomy

The most unusual form of ectopic pregnancy is one that occurs after vaginal or abdominal hysterectomy (150,151). Such a pregnancy may occur after supracervical hysterectomy because the patient has a cervical canal that may provide intraperitoneal access (149). Pregnancy may occur in the perioperative period with implantation of the already fertilized ovum in the fallopian tube. Pregnancy after total hysterectomy probably occurs secondary to a vaginal mucosal defect that allows sperm into the abdominal cavity. Only case reports are available and management options include surgical removal and systemic methotrexate, depending on location of pregnancy and patient characteristics.

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CHAPTER 33

Recurrent Pregnancy Loss



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Etiology
- Genetic Factors
- Thrombophilias
- Anatomic Abnormalities
- Endocrine Abnormalities
- Maternal Infection
- Immunologic Phenomena
  - *Cellular Immune Mechanisms*
  - *Humoral Immune Mechanisms and Antiphospholipid Syndrome*
- Male Factors
- Other Factors
- Environmental Factors

Preconception Evaluation
- History
- Physical Examination
- Recommended Testing
- Tests with Unproven Utility

Postconception Evaluation

Therapy
- Genetic Abnormalities
- Anatomic Anomalies
- Endocrine Abnormalities
- Infections
- Immunologic Factors
  - *Immunostimulating Therapies: Leukocyte Immunization*
  - *Immunosuppressive Therapies*
  - *Antithrombotic Therapy*
- Psychological Support

Prognosis

KEY POINTS

1 Isolated spontaneous pregnancy loss is common and approximately 15% to 30% of recognized pregnancies end in miscarriage. Recurrent pregnancy loss defined by three or more miscarriages is rare, occurring in 1% of women.

2 Clinical evaluation of a couple with recurrent miscarriage is warranted after two miscarriages caused by similar prevalence of abnormal results for couples with two or three pregnancy losses.

3 The most common cause of first trimester miscarriage is fetal aneuploidy.

4 Evaluation of patients with recurrent miscarriage should include a detailed patient and family history and examination of anatomic, genetic, endocrine, and antiphospholipid syndrome abnormities.

5 Much of the traditionally accepted testing, such as thrombophilia screening and several immunologic screening tests, are not supported by current evidence.

6 At least 50% of couples will have no specific abnormal finding after an evaluation for recurrent miscarriage.

7 After several pregnancy losses, there remains a greater chance of having a viable birth than another miscarriage, even without treatment. Prognosis can improve with treatment of a known underlying etiology.

8 Controversial treatments for recurrent miscarriage, including in vitro fertilization with chromosomal screening of embryos, immunosuppression, and anticoagulation, remain under investigation.

9 Treatment for recurrent pregnancy loss should include close monitoring with β-human chorionic gonadotropin levels and ultrasound, psychological support, and karyotypic analysis of tissues from subsequent miscarriage.

Despite advances in research and technology, recurrent pregnancy loss remains a clinical and emotional challenge for patients and providers. Sporadic miscarriage is the most common complication of pregnancy affecting approximately 1 in 4 couples in their reproductive years. Approximately 70% of human conceptions fail to achieve viability, and an estimated 50% are lost before the first missed menstrual period (1). Studies using sensitive assays for human chorionic gonadotropin (hCG) indicate that the actual rate of pregnancy loss after implantation is 31% (2). **[1]** Miscarriage occurs in 15% to 25% of pregnancies that are clinically recognized before 20 weeks of gestation from last menstrual period (3,4). Traditionally, recurrent miscarriage has been defined as the occurrence of three or more clinically recognized (ultrasound or histopathologic evidence) pregnancy losses before 20 weeks from the last menstrual period (5). Using this definition, recurrent pregnancy loss occurs in approximately 1 in 300 pregnancies (2) and in less than 1% of women (337).

[2] Clinical investigation of pregnancy loss, however, may be initiated after two consecutive spontaneous miscarriages (338). A study of more than 1,000 patients with recurrent pregnancy loss reported no difference in the prevalence of abnormal results for evidence-based and investigative diagnostic tests when the diagnostic workup was initiated after two versus three or more losses (6). If clinical intervention is undertaken

in the form of investigation after two spontaneous miscarriages, approximately 1% of pregnant women will require evaluation (3). Even with a history of recurrent pregnancy loss, a patient is more likely to carry her next pregnancy successfully to term than to miscarry. For patients with a history of recurrent pregnancy loss, the risk of subsequent pregnancy loss is estimated to be 24% after two clinically recognized losses, 30% after three losses, and 40% to 50% after four losses (7). These data make clinical study of recurrent pregnancy loss and its treatment difficult because very large groups of patients must be studied to demonstrate the effects of any proposed therapeutic intervention.

ETIOLOGY

Recurrent pregnancy loss has been attributed to genetic, anatomic, immunologic, endocrine, thrombophilic, and infectious causes but etiology remains under investigation. **[6] Although the exact proportion of patients diagnosed with a particular abnormality varies by study, parental genetic abnormalities (2% to 5%), anatomic issues (10% to 12%), antiphospholipid syndrome (APS) (15%), and other identifiable issues (10%) have been found in couples with recurrent miscarriage. This leaves approximately 50% of couples with a diagnosis of unexplained recurrent miscarriage** (Table 33-1) (3,6,8,338). The lack of abnormal findings in the couple having recurrent pregnancy loss is not surprising given how common fetal aneuploidy is with conception.

[3] At least 60% of preclinical and early clinical pregnancy losses are the result of *de novo* fetal aneuploidy (9). Among women aged 35 or greater who experience recurrent pregnancy loss, spontaneous fetal chromosomal abnormalities are responsible for over 80% of losses (10). This is thought to be the cause of anembryonic pregnancy losses, whereas pregnancy losses occurring after 10 weeks of fetal development are much less likely to derive from fetal aneuploidy. Pregnancy losses resulting from *de novo* fetal aneuploidy, whether early and undocumented or documented through evaluation of chromosomal content in fetal tissues, cloud the results of many published studies. Their presence or absence must be documented in all investigations on recurrent pregnancy loss patients and their potential as a confounding factor discussed. The timing of fetal demise and tissue chromosomal analysis of any collected fetal tissues should be carefully weighed when diagnostic and therapeutic investigations into causes of recurrent pregnancy loss are being considered.

Genetic Factors

Approximately 3% to 5% of recurrent pregnancy loss can be associated with a parental balanced structural chromosome rearrangement and can be diagnosed with blood tests for karyotype for both partners (338). Chromosome rearrangements are most commonly

balanced reciprocal but can include robertsonian translocations, chromosomal inversions, insertions, and mosaicism (11–14). A balanced reciprocal translocation is a rearrangement in chromosomes in which breaks occur in two different chromosomes and the pieces are exchanged so that no genetic material is lost or gained in the process. Balanced rearrangements can only be detected with standard G-banding karyotype. High-density microarray technology and next-generation sequencing can detect smaller deletions and duplications, but are not able to differentiate balanced rearrangements from normal because the total genetic content is the same. When screening parents for chromosome rearrangement, the best test is a metaphase karyotype with G-banding. Embryos from a parent with a balanced translocation with a normal phenotype have either two normal chromosomes or inherit the balanced translocation; however, some embryos can have abnormal chromosome content and lead to babies born with birth defects if they inherit an unbalanced translocation. A robertsonian translocation is a form of chromosomal rearrangement with one of the short-arm chromosomes (13–15) in which there is a loss of part or all of the short arms and fusion of the long arms of the chromosomes. A balanced robertsonian translocation causes no health issues but unbalanced forms can result in trisomies or monosomies that usually result in miscarriage. Some chromosome inversions are benign and do not impact prognosis for patients with recurrent pregnancy loss. However, others may have significant reproductive phenotypes. All patients with balanced chromosome rearrangements should undergo genetic counseling prior to attempting conception to better understand their individual risks.

Neither family history alone nor a history of prior term births is sufficient to rule out a potential parental chromosomal abnormality. Whereas the frequency of detecting a parental chromosomal abnormality is inversely related to the number of previous spontaneous losses, the chance of detecting a parental chromosomal abnormality is increased among couples who have never experienced a live birth (13). Testing for parental karyotopes in couples with recurrent miscarriage is recommended but some argue it has a high cost for discovery of a rare cause for recurrent pregnancy loss with limited treatment options. Proponents of testing indicate it promotes benefits that include permitting patient autonomy in choosing options for treatment and identification of patients at risk for offspring with unbalanced translocations who may have birth defects. A couple with a balanced translocation has a high chance of live birth attempting to conceive via intercourse (339); or they have the option of screening embryos for chromosome arrangements with in vitro fertilization (IVF) (338). Studies to date evaluating the use of IVF with chromosomal screening for couples with recurrent pregnancy loss and translocations do not show a significantly higher chance of success compared to natural conception (235,340). These studies are limited in patient number and use older technology and techniques like fluorescent in situ hybridization (FISH) and single cell day 3 embryo biopsy (235,340). With advancements such as blastocyst

biopsy, alternate chromosome analysis techniques and others, future studies may show a benefit for use of IVF in this population. Based on the existing data, IVF with embryo screening is not strongly recommended for a couple with a balanced translocation and recurrent miscarriage.

Thrombophilias

After combining a known association between the presence of antiphospholipid antibodies, placental dysfunction, and miscarriage with evidence showing subsequent increase in live birth with anticoagulation medications in these patients with recurrent miscarriage (299), attention was turned to investigating inherited thrombophilias as a cause for recurrent pregnancy loss. The clotting cascade is a delicate balance of prothrombotic (see **Fig. 33-1**) and antithrombotic pathways (see **Fig. 33-2**) and dysregulation in either or both of these pathways can cause significant health consequences. Because alterations in coagulation occur naturally in pregnancy with relative maternal hypercoagulability secondary to increases in several procoagulant activities, decreases in select antithrombotic pathways and venous stasis, the delicate balance between pro- and antithrombotic would seem to be even more tenuous throughout gestation (see **Fig. 33-3**). **[5]** Despite the biologic plausibility that patients with recurrent miscarriage would have a higher prevalence of inherited thrombophilia and that anticoagulation of patients with these diagnoses would decrease risk of subsequent miscarriage, the evidence does not support the theories (341).

Table 33-1 Proposed Etiologies and Testing for Recurrent Spontaneous Miscarriage

Proposed Etiology	Proposed Incidence	Testing Supported by Evidence	Controversial Testing	Testing Not Recommended
Embryonic genetic abnormalities	60–80%			
1. Chromosomal imbalance 2. Other genetic defects		Karyotype of pregnancy tissue/ products of conception		
Parental genetic factors	2–5%			
1. Chromosomal 2. Single gene defects 3. Multifactorial		Karyotype for both female and male partners		
Anatomic factors	12–16%			
1. **Congenital** a. Incomplete müllerian fusion or septum resorption b. *Diethylstilbestrol* exposure c. Uterine artery anomalies d. Cervical incompetence 2. **Acquired** a. Cervical incompetence b. Synechiae c. Leiomyomas d. Adenomyosis		Uterine evaluation by hysterosalpingogram, 2D saline sonogram or 3D sonography (with or without saline infusion), office hysteroscopy		
Antiphospholipid syndrome	12–15%	Lupus anticoagulant Anticardiolipin IgG and IgM antibody, anti-β2-glycoprotein IgG and IgM	Testing for other phospholipid antibodies	
Endocrine factors	17–20%			
1. Diabetes mellitus 2. Thyroid disorders 3. Prolactin disorders 4. Luteal phase insufficiency 5. Polycystic ovarian syndrome, including insulin resistance and hyperandrogenism		HbA_{1C} TSH Prolactin	Insulin resistance screening Androgen testing	Endometrial biopsy for luteal phase defect Luteal phase progesterone levels
Infectious factors	7–56%			
1. **Acute infection** 2. **Chronic endometritis**			Cultures in lower genital track and endometrial biopsy for plasma cells	
Immunologic factors other than antiphospholipid syndrome	N/A			
1. Cellular mechanisms a. Suppressor cell or factor deficiency b. Alterations in major histocompatibility antigen expression c. Alterations in cellular immune regulation 1. TH1 immune responses to reproductive antigens (embryo or trophoblast) 2. TH2 cytokine or growth factor deficiency 3. Hormonal-progesterone, estrogen, prolactin, androgen alterations 4. *Tryptophan* metabolism 2. Other humoral mechanisms a. Antithyroid antibodies b. Antisperm antibodies c. Antitrophoblast antibodies d. Blocking antibody deficiency			Anti-thyroid antibodies Other immune cell testing and screening	Anti-sperm antibody testing Circulating natural killer cells, cytokine profiles, blocking antibodies, HLA typing, antipaternal leukocyte antibodies

(*continued*)

Proposed Etiology	Proposed Incidence	Testing Supported by Evidence	Controversial Testing	Testing Not Recommended
Thrombotic factors	N/A			
1. Heritable thrombophilias 2. Antiphopholipid syndrome—see above				Factor V Leiden Prothrombin gene Protein C def Protein S def Antithrombin Homocysteine levels MTHFR (unless strong personal or family history of thrombotic events)
Other factors	N/A			
1. Altered uterine receptivity (integrins, adhesion molecules) 2. Environmental a. Toxins b. Illicit drugs c. Cigarettes and caffeine 3. Placental abnormalities (circumvallate, marginate) 4. Maternal medical illnesses (cardiac, renal hematologic) 5. Male factors 6. Exercise 7. Dyssynchronous fertilization 8. Psychological		Patient history regarding exposures and medical issues	Uterine receptivity testing Sperm testing including DNA fragmentation and aneuploidy	

TH, T helper; MTHFR, methylene tetrahydrofolate reductase; N/A, not applicable.

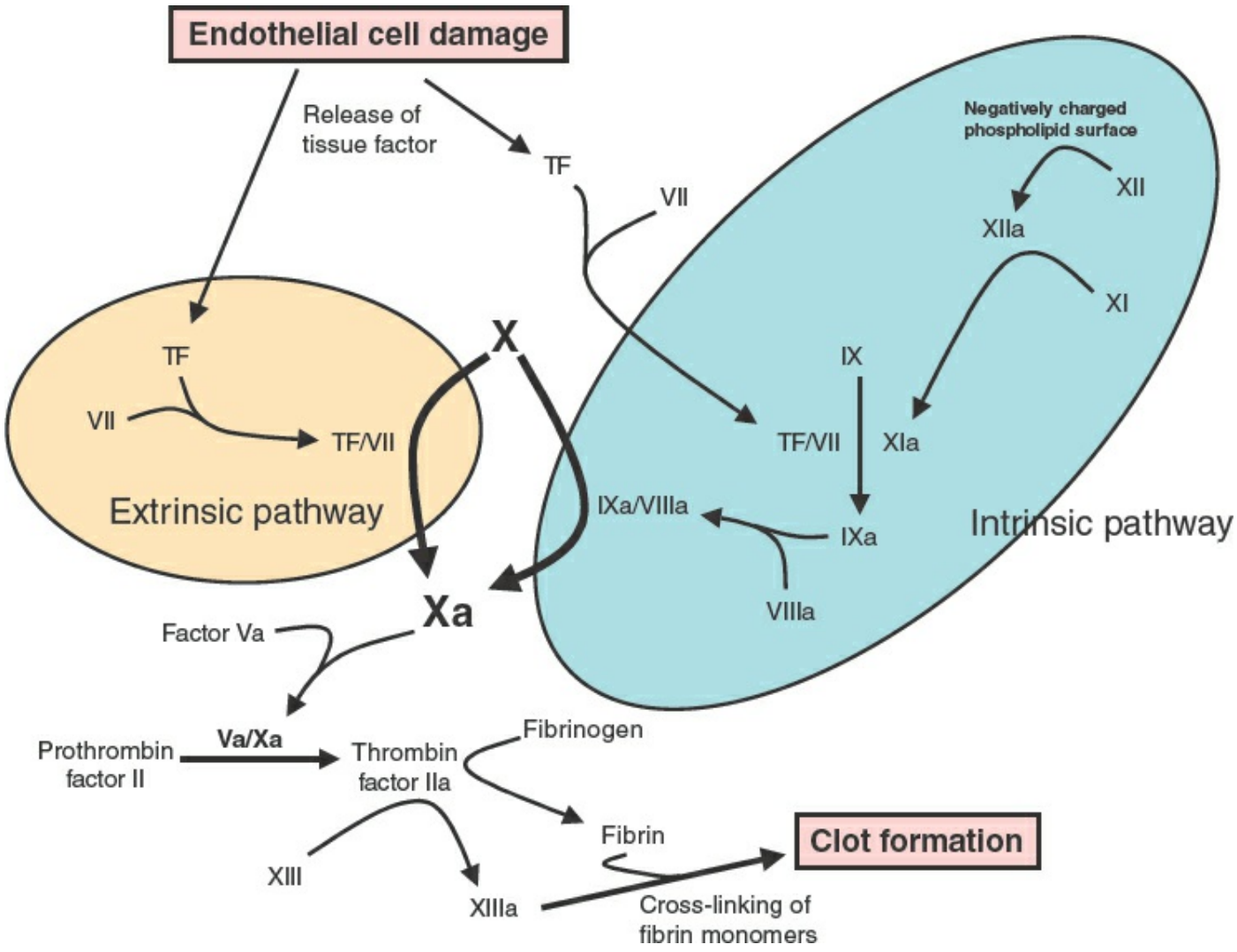


FIGURE 33-1 The clotting cascade. Physiologic clotting is initiated by endothelial cell damage or abnormal exposure of negatively charged phospholipids to serum and blood components. Procoagulant pathways in black are part of the clotting cascade and are prothrombotic. Both lead to activation of cascades of proteolytic enzymes and cleavage of clotting factors. The extrinsic and intrinsic pathways are initiated by distinct mechanisms. They merge at the activation of factor X to form the common pathway. For all coagulation factors, the subscript letter “a” denotes the activated form of the factor.

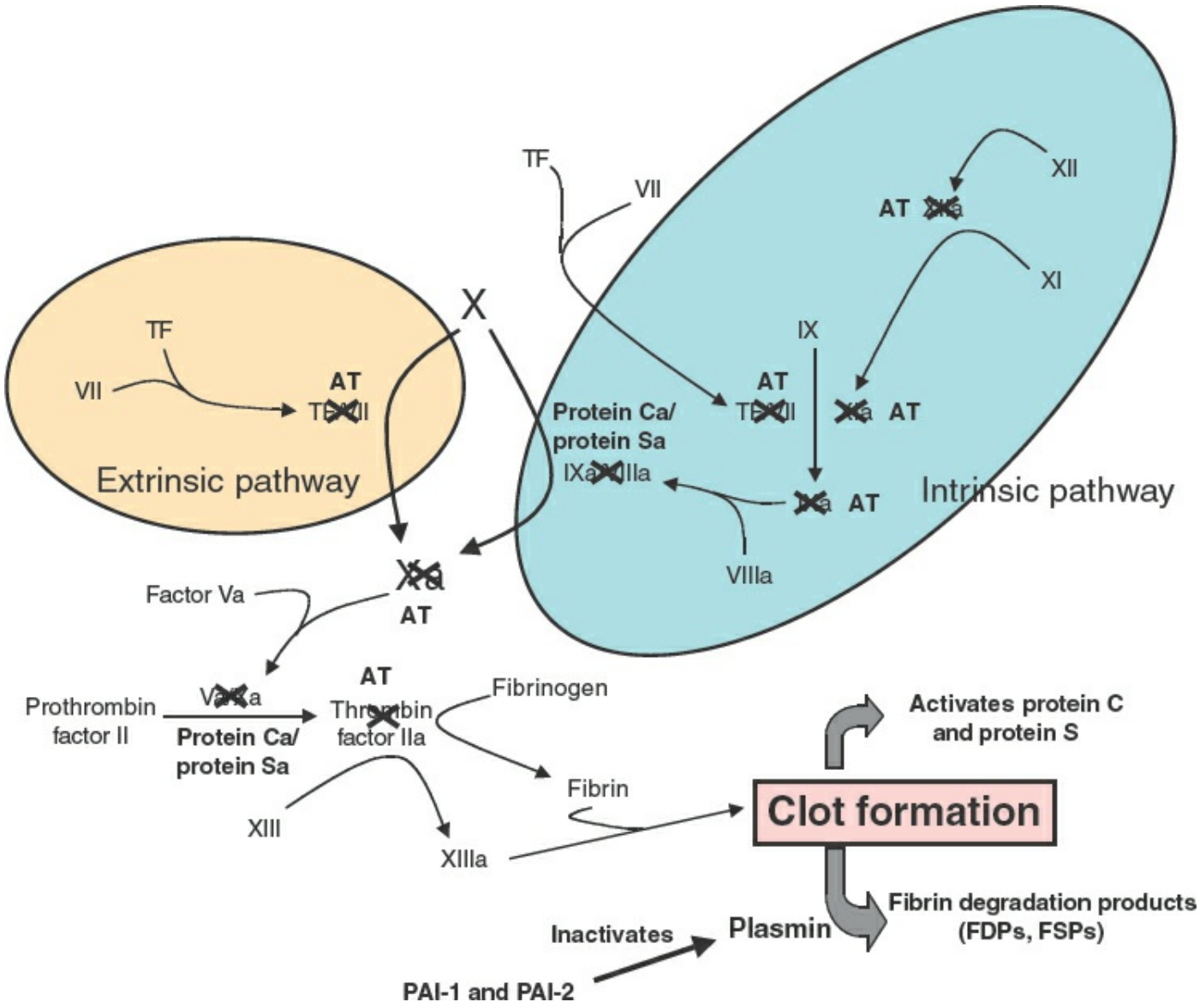


FIGURE 33-2 Physiologic mechanisms that counteract the clotting cascade. The procoagulant cascade is inhibited by several physiologic mechanisms. The balance between pro- and antithrombotic pathways determines the state of coagulability. Antithrombotic mechanisms include the action of antithrombin (AT) and of proteins C and S. The sites of inhibition by these substances are depicted by an "X." Plasminogen activator inhibitors-1 and -2 (PAI-1 and PAI-2) indirectly inactivate plasmin. Plasmin plays an important role in the dissolution of coagulated blood. For all coagulation factors, the subscript letter "a" denotes the activated form of the factor. FSP, fibrin split products; FDP, fibrin degradation products.

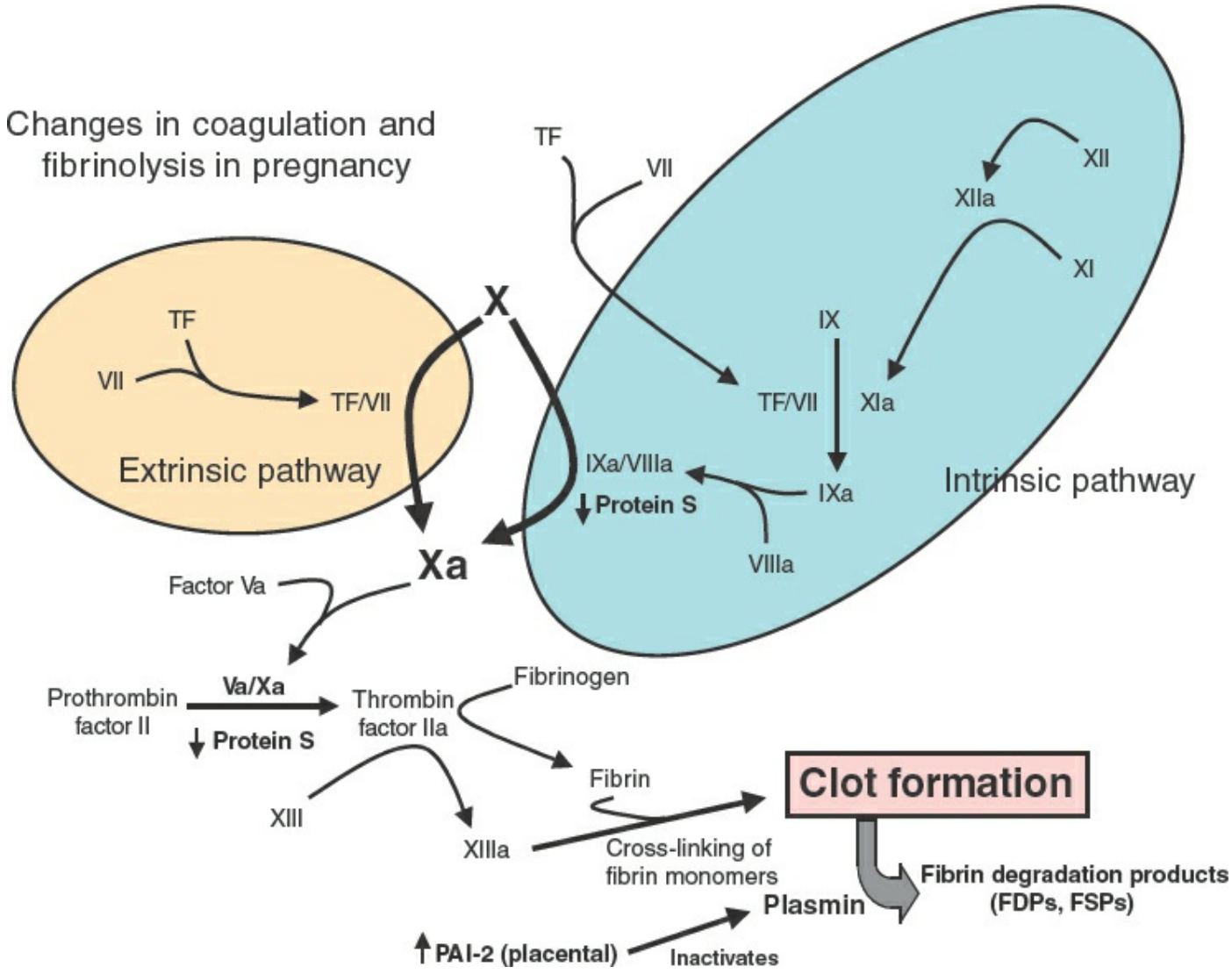


FIGURE 33-3 Alterations coagulation and fibrinolysis during normal pregnancy. Pregnancy is a state of hypercoagulability. Levels of factors VII, VIII, X, and XII are elevated throughout pregnancy, levels of factors II, V, and XIII rise in the first trimester, then return to normal values. The antithrombotic activity mediated by protein S decreases in pregnancy. The placenta produces plasminogen activator inhibitor-2 (PAI-2). For all coagulation factors, the subscript letter "a" denotes the activated form of the factor. FSP, fibrin split products; FDP, fibrin degradation products.

Inherited thrombophilia is a genetic predisposition to venous thromboembolism and traditionally includes factor V Leiden (FVL) mutation, prothrombin gene mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency. It is estimated that up to 15% of the Caucasian population carries an inherited thrombophilic mutation (15). FVL is a clotting protein that works in conjunction with activated factor X to convert prothrombin to thrombin. One comprehensive review shows that carriers for FVL have an increased relative risk of recurrent pregnancy loss (342), however, the absolute risk of miscarriage in this population is low (343). Prothrombin gene mutation results in a deficiency of thrombin and resulting increased concentration of prothrombin in the plasma. Some small studies

have shown a potential association between a mutation in the prothrombin gene and recurrent pregnancy loss but overall recommendations do not support an association with this mutation and any pregnancy complication including miscarriage, intrauterine growth restriction, or preeclampsia (342,343). **Protein S and Protein C in combination are required for factor V and VIII activation and thus deficiency in either can lead to a hypercoagulable state. Patients with protein S or protein C deficiencies may be at slightly higher risk of thrombosis in pregnancy but associations with miscarriage risk have not been definitively demonstrated** (344). **Antithrombin is a small protein that regulates clot formation by inactivating factor Xa and thrombin. Deficiency in this protein leads to high risk of thrombosis and increased risk of miscarriage** (344). Because of its low prevalence (1/2,500), antithrombin deficiency is not recommended for routine screening for recurrent miscarriage in the absence of significant family history of thrombosis (345).

Although not usually considered an inherited thrombophilia, a methylenetetrahydrofolate reductase (MTHFR) mutation may be associated with increased thrombosis risk and some suggest an association with recurrent pregnancy loss. MTHFR is an essential enzyme for folic acid metabolism and is responsible for converting homocysteine to methionine. A mutation in the enzyme may cause increased serum levels of homocysteine that may lead to a hypercoagulable state (see **Fig. 33-4**). There are two predominant mutations (C677T and A1298C) and they are common in certain populations with up to 40% of Caucasian and Hispanic populations being heterozygote for the C677T mutation (346). Some suggest that a mutation leads to lower function of the MTHFR enzyme resulting in higher homocysteine levels and increased risk of thrombosis and miscarriage but the association is controversial (347).

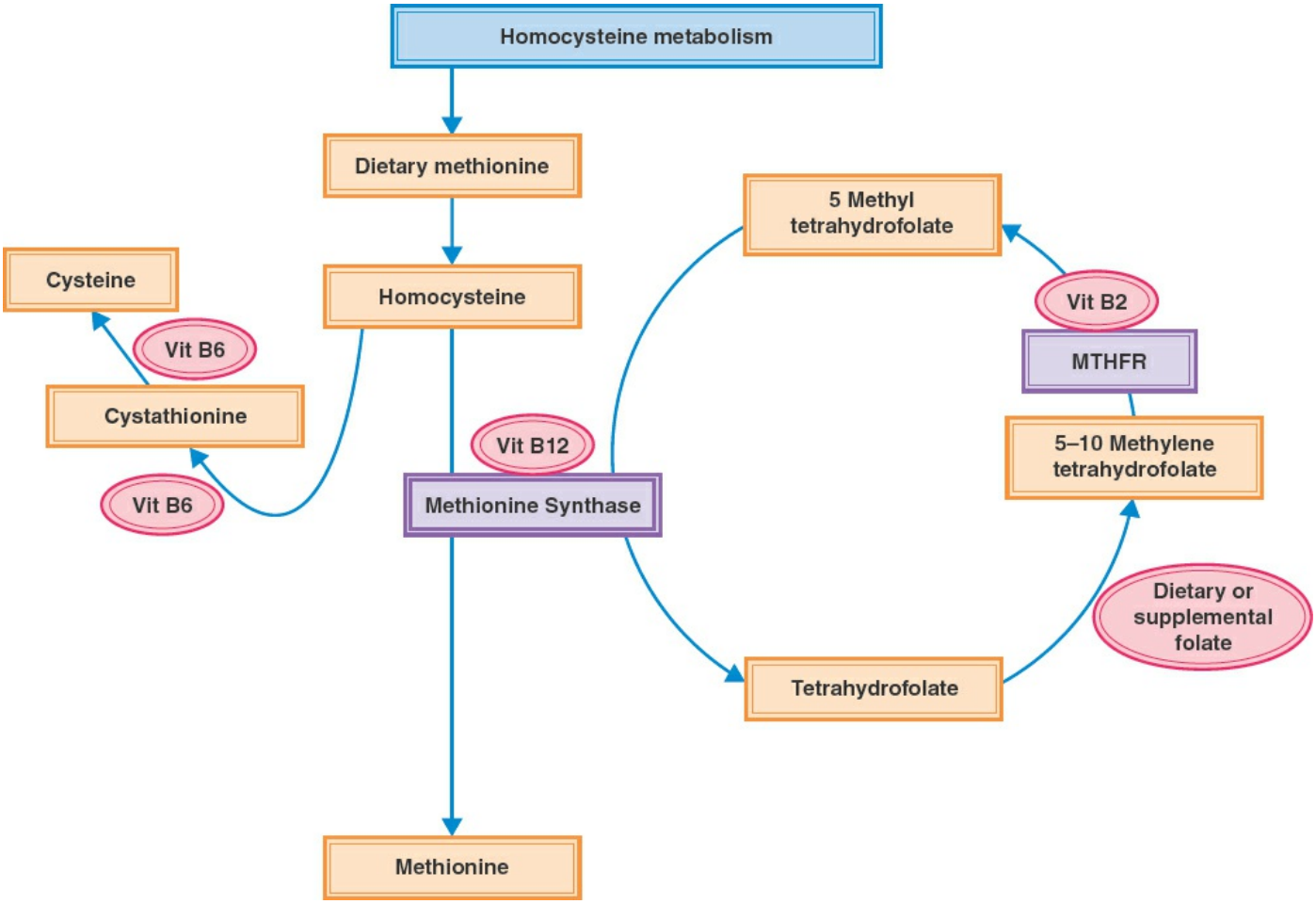


FIGURE 33-4 Homocysteine metabolism. Dietary methionine is metabolized either to cysteine or back into methionine. Homocysteine, a prothrombotic metabolite, is an intermediate in this process. Conversion of homocysteine to methionine requires transfer of a methyl group from 5-methyltetrahydrofolate. The conversion of folate to 5-methyltetrahydrofolate is a multistep process requiring vitamin B_2 as a cofactor for the enzyme, *methylene tetrahydrofolate reductase* (*MTHFR*). Vitamin B_{12} is a required cofactor for the enzyme methionine synthase. Vitamin B_6 is also required for metabolism of sulfur-containing amino acids such as *methionine.*

The proposed mechanistic basis for the association between adverse fetal outcomes and heritable thrombophilias has focused on impaired placental development and function, secondary to venous and/or arterial thrombosis at the maternal–fetal interface. These findings have been noted in the placentas of women with adverse fetal outcomes and known inherited thrombophilias and have been demonstrated in patients with similar outcomes, but lacking inherited thrombophilic risk (18–22). Detractors of placental thrombosis as causal in early pregnancy losses (<10 weeks' gestation) cite an elegant series of experiments demonstrating that maternal blood flow into the intervillous spaces of the human placenta does not occur until approximately 10 weeks of gestation (23–26). Prior to the establishment of intervillous circulation, nutrient transfer from maternal blood to fetal tissues appears to be dependent on transudation that, in turn, relies on flow through the uterine vasculature.

This suggests that maternal or fetal thrombotic episodes in the developing placental vasculature could be equally devastating prior to or after the establishment of intervillous circulation near 10 weeks of gestation. Very early pregnancy losses (biochemical, anembryonic) and known aneuploid fetal losses are unlikely to be altered by the presence of, or treatment for, an underlying thrombophilic state.

[5] Neither the American College of Obstetrician Gynecologists (ACOG) nor the American Society of Reproductive Medicine (ASRM) recommend screening for inherited thrombophilias or MTHFR mutations for patients with recurrent pregnancy loss or any adverse pregnancy outcome (338,345) unless other risk factors are present, such as a history of thrombosis in the patient or a close family member. Despite the lack of evidence and guidelines against routine screening for thrombophilia in recurrent pregnancy loss, many clinicians routinely order these tests (347,348).

Anatomic Abnormalities

Anatomic abnormalities of both the uterine cervix and the uterine body have been associated with recurrent pregnancy loss (28,29). **These anatomic causes may be either congenital or acquired.** During development, the uterus forms via the apposition of a portion of bilateral hollow tubes called the müllerian ducts. The dissolution of the walls of these ducts along their site of apposition allows formation of the intrauterine cavity, the intracervical canal, and the upper vagina. Congenital uterine anomalies may therefore include incomplete müllerian duct fusion, incomplete septum resorption, and uterine cervical anomalies. Although the causes underlying many of the congenital anomalies of the female reproductive tract are unclear, it has been well-documented that prenatal exposure to maternally ingested diethylstilbestrol (DES) results in complex congenital uterine, cervical, and vaginal changes.

Historically, all congenital reproductive tract abnormalities have been linked to isolated spontaneous pregnancy loss and recurrent pregnancy loss, although the presence of an intrauterine septum and prenatal exposure to DES demonstrate the strongest associations (30–32). Women with an intrauterine septum may have as high as a 60% risk for spontaneous miscarriage (33). Uterine septum–related losses most frequently occur during the second trimester (34). If an embryo implants into the poorly developed endometrium overlying the uterine septum, abnormal placentation and resultant first trimester losses may occur (35). The most common uterine congenital anomaly associated with *in utero* DES exposure is hypoplasia, which may contribute to first- or second-trimester pregnancy losses, incompetent cervix, and premature labor (36,37). Congenital anomalies of the uterine arteries may contribute to pregnancy loss via adverse alterations in blood flow to the implanted blastocyst and developing placenta (38).

Acquired anatomic anomalies have likewise been linked to isolated and recurrent

pregnancy losses. These abnormalities include such disparate conditions as intrauterine adhesions, uterine fibroids, and endometrial polyps. Endometrium that develops over an intrauterine synechiae or over a fibroid that impinges in the intrauterine cavity (submucous) may be inadequately vascularized (39). This may promote abnormal placentation for any embryo attempting to implant over such lesions. Although data supporting these concepts are limited, this abnormal placentation may lead to spontaneous pregnancy loss. Less clear is the association between intramural fibroids and recurrent pregnancy loss, but it is suggested that large (≥5 cm) intramural fibroids are associated with pregnancy loss and that removal improves outcomes (see Chapter 11) (32,40).

Endocrine Abnormalities

The endocrinology of normal pregnancy is complex. **Because spontaneous pregnancy is critically dependent on appropriately timed endocrinologic changes of the menstrual cycle, it is not surprising that those endocrine abnormalities that alter pregnancy maintenance may have their effects during the follicular phase of the cycle in which conception occurs, or even earlier.** Modifications in follicular development and ovulation, in turn, may be reflected in abnormalities of blastocyst transport and development, alterations in uterine receptivity to the implanting blastocyst, and improper functioning of the corpus luteum. Endocrinologic factors suggested to be associated with recurrent miscarriage include luteal phase insufficiency, hypersecretion of luteinizing hormone (LH), thyroid disease, and, potentially, insulin resistance and polycystic ovarian syndrome (PCOS), diabetes mellitus, hyperprolactinemia, and decreased ovarian reserve.

Beginning with ovulation and lasting until approximately 7 to 9 weeks of gestation, maintenance of early pregnancy depends on the production of progesterone by the corpus luteum. Normal pregnancies are characterized by a luteal–placental shift at about 7 to 9 weeks of gestation, during which the developing placental trophoblast cells take over progesterone production and pregnancy maintenance (41). Spontaneous pregnancy losses occurring before 10 weeks of gestation may result from a number of alterations in normal progesterone production or utilization. These include failure of the corpus luteum to produce sufficient quantities of progesterone, impaired delivery of progesterone to the uterus, or inappropriate utilization of progesterone by the uterine decidua. Pregnancy failures may occur near the time of the expected luteal–placental shift if the trophoblast is unable to produce biologically active progesterone following demise of the corpus luteum.

Luteal phase insufficiency or luteal phase defects are characterized by inadequate luteal milestones and most likely relate to adverse pregnancy outcome via inadequate or improperly timed endometrial development at potential implantation sites. An elegant

description of abnormalities at the site of implantation, which may be responsible for some cases of recurrent pregnancy loss, describes impaired decidualization of the endometrium as a mechanism for natural selection of human embryos (42). **Luteal phase defect has many causes, some of which are associated with hypersecretion of LH.** Although the mechanism underlying the association of elevated LH levels with recurrent pregnancy loss is incompletely understood, abnormal LH secretion may have direct effects on the developing oocyte (premature aging), on the endometrium (dyssynchronous maturation), or both. Many patients with elevated LH levels also display physical, endocrinologic, and metabolic characteristics of PCOS.

Some studies report ovarian radiologic evidence of PCOS in as many as 40% to 80% of recurrent pregnancy loss patients (43,44). In addition to inappropriately elevated LH levels, PCOS patients are frequently obese and often have elevated circulating androgen levels. Although controversial, both changes have been linked to recurrent pregnancy loss, and elevated androgen levels have been shown to adversely affect markers of uterine receptivity in women with a history of recurrent pregnancy loss (43–46). Many women with PCOS have metabolic alterations in glycemic control characterized by insulin resistance. This too may be directly or indirectly related to adverse pregnancy outcome, and it may explain increases in the rate of spontaneous pregnancy loss among women with type 2 diabetes mellitus (47). Women with overt insulin-dependent diabetes mellitus (IDDM) appear to exhibit a threshold of pregestational glycemic control above which spontaneous pregnancy loss is increased (48,49). Hyperglycemia has been directly linked to embryonic damage (50). In cases of advanced IDDM with accompanying vascular complications, compromised blood flow to the uterus may be mechanistically involved in subsequent pregnancy loss.

Patients with thyroid disease often have concomitant reproductive abnormalities, including ovulatory dysfunction and luteal phase defects. The metabolic demands of early pregnancy mandate an increased requirement for thyroid hormones. It is therefore not surprising that hypothyroidism has been associated with isolated spontaneous pregnancy loss and with recurrent pregnancy loss (51). The definition of hypothyroidism is itself now under scrutiny with many investigators suggesting that cutoff thyroid-stimulating hormone (TSH) values during pregnancy should be less than 2.5 mIU/mL (52). Others have suggested even lower TSH cutoff values (53). Although it has long been debated whether clinically euthyroid patients with antithyroid antibodies have higher rates of miscarriage and recurrent pregnancy loss, thyroid hormone supplementation was shown to reduce miscarriage in infertility patients with positive antithyroid antibodies and otherwise normal TSH levels undergoing IVF (54–60). The mechanism for an association between antithyroid antibody positivity and recurrent pregnancy loss remains unclear; however, these antibodies could be markers of more generalized autoimmunity or may predict an impaired ability of the thyroid gland to respond to the demands of pregnancy.

Elevated prolactin levels have been associated with miscarriage and recurrent miscarriage. Hyperprolactinemia has been associated with ovulatory dysfunction and may result in miscarriage via alterations in the hypothalamic–pituitary– ovarian axis resulting in impaired folliculogenesis, oocyte maturation or luteal phase dysfunction (61–63). One study in patients with hyperprolactinemia and recurrent pregnancy loss showed a higher live birth rate in a subsequent pregnancy after normalization of prolactin levels with a dopamine agonist (63).

Some studies have shown an association between diminished ovarian reserve (DOR) and recurrent miscarriage (64,65). Shahine et al. suggests that this link may result from an association between DOR and increased risk of aneuploid embryos (349). Aneuploidy (chromosomal aberrations) is the most common cause of first trimester miscarriage and women with DOR have a higher percentage of aneuploid embryos compared to age-matched controls in both the recurrent pregnancy loss (349) and the nonrecurrent pregnancy loss patient populations (350). Ovarian reserve testing (early follicular phase follicle stimulating hormone level, estradiol, and anti-müllerian hormone levels) is not currently recommended by ASRM for the evaluation of recurrent miscarriage. DOR can explain higher risk of miscarriage caused by higher risk of aneuploidy and help guide patients regarding the next steps in care. Increasingly, IVF with chromosomal screening of embryos is offered as a treatment option for women with recurrent pregnancy loss (351) but success is minimal in the setting of DOR and may not be higher than success without intervention (352).

Maternal Infection

The association of infection with recurrent miscarriage is among the most controversial and poorly explored of the potential causes for pregnancy loss. **Reproductive tract infection with bacterial, viral, parasitic, zoonotic, and fungal organisms have all been theoretically linked to pregnancy loss; however, mycoplasma, ureaplasma, chlamydia, and a-streptococcus are the most commonly studied pathogens** (66,67). There is data that directly addressed the roles of some of these proposed organisms in recurrent pregnancy loss. One prospective comparison trial involving 70 recurrent pregnancy loss patients reported no elevations in any markers for present or past infection with *Chlamydia trachomatis* when compared with controls (68). In contrast, a very large, prospective trial demonstrated a link between the detection of bacterial vaginosis and a history of second trimester pregnancy loss among 500 recurrent pregnancy loss patients (69). The risk of bacterial vaginosis detection was positively correlated with cigarette smoking in this study.

The etiologic mechanism linking specific organisms to either isolated or recurrent pregnancy loss remains unclear and must certainly differ among infectious organisms. Certain viral organisms, such as herpes simplex virus (HSV)

and human cytomegalovirus (HCMV), can directly infect the placenta and fetus (70,71). The resulting villitis and related tissue destruction may lead to pregnancy disruption. Another theoretic possibility warranting study is that infection-associated–early pregnancy loss may result from immunologic activation in response to pathologic organisms. A large body of evidence supports the role of this mechanism in adverse events later in gestation, such as intrauterine growth restriction, premature rupture of membranes, and preterm birth (72,73). Alternatively, mechanisms that protect the fetus from autoimmune rejection may protect virally infected placental cells from recognition and clearance. This could potentially promote periods of unfettered infectious growth for some of the pathogenic organisms gaining entry to the reproductive tract (74).

Chronic endometritis, defined as the asymptomatic presence of histologically documented plasma cells in an endometrial biopsy, may be associated with recurrent miscarriage. Studies have shown a prevalence of 7% to 13% based on morphologic assessment alone (353,354) and up to 56% in patients with recurrent pregnancy loss (354). Chronic endometritis is associated with previous infections and retained pregnancy tissue and, despite the difficulty of determining cause and effect, treatment with antibiotics shows a higher live birth rate in subsequent pregnancies in some studies (353,354). Endometrial biopsy for chronic endometritis diagnosis and treatment are not recommended by expert groups and larger studies are needed before implementing evaluation and treatment in routine practice.

Immunologic Phenomena

[5] Embryo implantation and pregnancy maintenance is a delicate interaction and balance between maternal and embryonic/fetal immune, hormonal, and coagulation systems. Maternal rejection of paternal antigens and immune system dysfunction as a cause of recurrent miscarriage has been explored extensively but remains controversial (75). Laboratory testing for immune dysfunction can be misleading and the treatments aimed at maternal immunosuppression can have significant side effects. Expert groups have omitted immune testing and recommended against extensive immunosuppression as a treatment for unexplained recurrent miscarriage (338).

A brief review of some of the important concepts in basic immunology is warranted to place testing and treatment discussions in context. **Immune responses classically are divided into innate and acquired responses. Innate responses represent the body's first line of defense against pathogenic invasion.** They are rapid and are not antigen specific. Cell types and mechanisms typically considered vital to innate immunity include complement activation, phagocytosis by macrophage, and lysis by natural killer (NK) and natural killer T (NKT) cells and possibly by TCR γ δ+ T cells. **Acquired immune responses, in contrast, are antigen specific and are largely mediated by T cells and B cells. Acquired responses can be further divided into primary (response**

associated with initial antigen contact) and secondary (rapid and powerful amnestic responses associated with subsequent contact to the same antigen).

Antigen specificity is regulated by two sets of genes in the major histocompatibility complex (MHC), located on chromosome 6 in humans. **MHC class I molecules (human leukocyte antigen [HLA]-A, -B, and -C) are present on the surface of nearly every cell in the human body and are important in defense against intracellular pathogens, such as viral infection and oncogenic transformation.** MHC class I molecules act as important ligands for both the T-cell receptor on CD8+ cytotoxic/suppressor T cells and for a variety of receptors on NK cells (76). **MHC class II molecules (HLA-DR, HLA-DP, and HLA-DQ), in contrast, are present on the surface of a limited number of antigen-presenting cells, including dendritic cells, macrophage and monocytes, B cells,** and tissue-specific cells such as the Langerhans cells in the skin. These molecules are important in defense against extracellular pathogens, such as bacterial invaders. The major ligand for MHC class II is the T-cell receptor on CD4+ T helper cells.

One very important concept in immunology that has particular application to pregnancy is that of immune tolerance. The passage of bone marrow–derived T cells through the fetal thymus during early development has been well described. In this developmental interval, the T cells encounter a process termed thymic education. During thymic education, T cells that express either the CD4 or the CD8 coreceptor are chosen, and autoreactive cells are effectively eliminated. This education promotes T-cell tolerance, allowing selection and survival exclusively of those T cells that recognize nonself and will not react against self (80,81).

Cellular Immune Mechanisms

Three main questions summarize much of the theoretical thinking surrounding pregnancy maintenance and reproductive immunology:

1. Which immune cells populate the reproductive tract, particularly at implantation sites?
2. How do the characteristics of antigen presentation differ at the maternal–fetal interface?
3. What regulatory mechanisms specifically affect reproductive tract immune cells?

Resident Cells: Natural Killer Cells and T Regulatory Cells

Immune cells populating the reproductive tract exhibit many characteristics that distinguish them from their peripheral counterparts. In particular, the human endometrium is populated by T cells, macrophage, and NK-like cells, but very few B cells are present. The relative proportions of these resident cells vary with the menstrual cycle and change dramatically during early pregnancy. Surrounding the time

of implantation, one particular cell type comprises between 70% and 80% of the total endometrial lymphocyte populations (82,83). This cell type is called a variety of names, including decidual granular lymphocytes (DGLs), large granular lymphocytes (LGLs), and decidual NK cells. This heterogeneity of names reflects the fact that this particular cell type differs from similar cells isolated from the periphery, although most believe it to be an NK cell variant. While most peripheral NK cells have low cell surface expression of CD56 ($CD56^{dim}$) and express high levels of CD16, the immunoglobulin receptor responsible for NK-mediated, antibody-dependent cellular cytotoxicity, those in the uterine decidua and at the placental implantation site, are largely $CD56^{bright}$ and $CD16^{dim}$ or CD16− (84). If these unusual endometrial cells are considered NK cells, the implantation site represents the largest accumulation of NK cells in any state of human health or disease. These decidual NK cells display fairly poor cytotoxic function but are robust cytokine secretors (85,86). The balance of activating and inhibitory receptors expressed on their cell surfaces determines their ultimate killing versus secretion patterns (87,88).

The role of NK cells in reproduction and recurrent pregnancy loss is controversial. Some studies show increased levels of CD56 NK cells (those with killer-type activating receptors) in peripheral blood of women with recurrent pregnancy loss compared to controls (89,90) and other studies do not show a difference (355,356). The studies showing a difference may be inherently flawed. Most of the recurrent miscarriage patients included in the study were nulliparous and the controls were multiparous (357); a previous successful pregnancy can induce permanent changes in NK subsets (358). Some studies have shown that a higher level of NK cytotoxicity in the peripheral blood before pregnancy resulted in a higher rate of pregnancy loss (359), while other studies showed similar NK cytotoxicity in recurrent pregnancy loss patients with subsequent pregnancy loss or live birth (360). Results from studies of NK cell levels in endometrial tissues in recurrent miscarriage vary; some showing higher levels of CD56 NK cells in the endometrial tissue from recurrent pregnancy loss patients (94) and others showing lower levels (95). Interpretation of NK cell levels in endometrial tissue can be limited by the inherent variability of levels throughout the different menstrual cycle stages and the questionable testing accuracy using either immunochemistry or flow cytometry (361). A strong argument against using any NK cell testing in the evaluation of recurrent miscarriage patients comes from a large prospective study showing that high NK toxicity before pregnancy did not impact subsequent pregnancy loss rate (362).

A subpopulation of CD4+ T cells has been described that, like all activated lymphocytes, strongly expresses CD25 on their cell surface (77). These CD4+ CD25+ cells are more specifically identified by the intracellular presence of the forkhead box P3 (Fox P3) transcription factor and have been called regulatory T lymphocytes (Treg cells). Treg cells, when activated by autoantigens, can suppress activated inflammatory

cells. They secrete regulatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) (77–79). They may impact avoidance of tissue destruction associated with inflammation and may play a central role in pregnancy maintenance. In pregnant mice and women, these specialized CD4+ cells are systemically expanded in an alloantigen independent fashion and can suppress adverse maternal responses to the fetus (92) and to self (93).

The human decidua contains characteristic immune effector cells. These immune cell populations are reported to be altered in recurrent pregnancy loss patients but not in patients experiencing isolated spontaneous pregnancy losses (91,94–96). Most investigations into whether alterations in these cells (including T cells, decidual NK cells, and NKT cells) determine pregnancy outcome are hampered by insufficient patient numbers to allow meaningful conclusions. **[5]** Further research is needed to understand the role of NK cells and T regulatory cells in reproduction and miscarriage. Expert groups do not recommend testing recurrent pregnancy loss patients for NK cell cytotoxicity or Treg cells and any treatment targeted toward suppression of these immune cells should be conducted only in the setting of a clinical trial.

Antigen Presentation at the Maternal–Fetal Interface

Historically, it was proposed that the implanting trophoblastic allograft could make itself antigenically invisible to avoid immune detection by the maternal host. It could downregulate its expression of the MHC-encoded transplantation antigens (some of which would be of paternal origin) and thereby avoid recognition as nonself. Although immunology studies rendered this theory obsolete, the implanting fetus does utilize this strategy to the extent (97) that placental trophoblast cells do not express MHC class II molecules (98,99). **Unlike nearly every other cell in the human body, trophoblast cells do not express the classical MHC class I transplantation antigens HLA-A and -B.** Rather, a subpopulation of placental cells, specifically the extravillous cytotrophoblast cells, express the classical MHC class I HLA-C products, and the nonclassical HLA-E, -F, and -G products (74,100–104). These extravillous cytotrophoblast cells are of particular interest because they are characterized by remarkable invasive potential (105,106). These cells move from the tips of the anchoring villae of the human placenta, invading deeply into the maternal decidua, and some replace cells within the walls of decidual arterial vessels (105–107). Although the invasive characteristics of extravillous cytotrophoblast may reflect non-MHC–related mechanisms, including well-described integrin switching, the intimate contact of these fetal-derived cells with maternal immune effector cells exposes the fetus to recognition as nonself (108) and it is now apparent that the pregnant woman recognizes and responds to paternally-derived antigens. These responses appear to be essential to pregnancy maintenance but must be tightly regulated.

It is not known why all placental cells downregulate expression of HLA-A and -B,

whereas invasive extravillous cytotrophoblast express HLA-C, -E, and -G. This area of investigation is ripe with hypotheses and study. Because NK cells of the innate immune system recognize and kill cells that express no MHC, the complete downregulation of MHC should cause trophoblast cells to act as targets for those NK cells that are pervasive at sites of implantation (88,97). In addition to possible protection from direct NK cell–mediated killing, the expression of HLA-C, -E, and -G by trophoblast cells may serve a variety of alternate purposes. NK cell receptor–mediated interactions with extravillous cytotrophoblast MHC products modulate cytokine expression profiles at the maternal–fetal interface (85,86). **MHC expression aids in decidual and vascular invasion by the trophoblast, an activity essential for proper placental development** (109). Whereas definitive correlations between placental MHC class I expression patterns and recurrent pregnancy loss remain contentious, trophoblast expression of HLA-G was linked to other disorders of placental invasion, such as preeclampsia (109,110). Genetic mutations at the HLA-G locus have been linked to recurrent pregnancy loss in some, but not all studies (111–114). Soluble or secreted trophoblast MHC products may aid in the development of maternal immune tolerance toward the placenta (115). Soluble HLA-G has been shown to suppress T lymphocyte and NK cell function and to induce the expansion of Treg cells in humans (116).

Aberrant expression of class II MHC determinants, or enhanced expression of MHC class I on syncytiotrophoblast in response to IFN-γ (117) could mediate pregnancy loss by enhancing cytotoxic T cell attack (118). This theory appears unlikely, because the expression of classical MHC antigens does not seem to be induced on aborted tissues from women experiencing one or more pregnancy losses (118). MHC class II genotypes appear to affect susceptibility to a variety of diseases, including diabetes and other autoimmune diseases. **A similar link between MHC class II typing and adverse pregnancy outcome was reported for recurrent pregnancy loss** (119,120).

Regulation of Decidual Immune Cells

The characteristics of the interactions between decidual immune effector cells and the implanting fetus may be determined by factors other than those already mentioned. As might be predicted, these regulatory effects are often targets for investigative efforts, because they may offer more direct insight into potential therapies for immune-mediated disorders of pregnancy maintenance. **Three such regulatory mechanisms will be discussed here: (a) alterations in T helper cell phenotypes; (b) reproductive hormones and immunosuppression; and (c) tryptophan metabolism.**

Antigen-stimulated immune responses involving CD4± T cells can be divided into two major classes: T helper 1 (TH1) responses and T helper 2 (TH2) responses. This subclassification is overly simplified, but it has been useful in broadly defining types of immune responses based on the characteristics of the CD4± cells present, and their associated cytokines. Cytokines are signaling molecules secreted from immune cells that

bind to receptors on other immune cells to either stimulate or inhibit function. TH1 and TH2 immune cells express different cytokines with different functions and studies suggest that successful embryo implantation ultimately occurs in a TH2 dominant environment and that poor pregnancy outcomes may result if the balance favors a TH1 dominant environment (363). Studies have suggested that TH1-type cytokines can be harmful to implanting developing embryo (121,122) and that some patients with recurrent pregnancy loss exhibit a local dysregulation of their T helper cellular immune response to antigens, with typical shifts toward TH1 inflammatory responses at the maternal–fetal interface (123,124). This remains difficult to study and prove given that the dominant immune cell population (TH1 or TH2) is usually determined by peripheral blood levels of cytokines and cytokines display their results at close range. Measurements of cytokines in peripheral blood, endometrial biopsies, or flushing of decidual tissue are subject to technical difficulties and conclusions about cytokines and their role in recurrent pregnancy loss are yet to be determined. TNF-α is one cytokine that can usually be detected easily in the blood with most assays and may be a good marker for inflammation. Studies have shown higher levels of TNF-α in women with recurrent pregnancy loss in early pregnancy (364).

Although many mechanisms are aimed at avoiding maternal immune recognition of the implanting fetus, research in humans and animals indicates that immune responses to fetal antigens are present (126–128)**. Thus, the regulation of this response at the maternal–fetal interface may be critical.** Reproductive hormones have dramatic effects on peripheral cell–mediated immunity, as demonstrated by well-documented and notable gender differences in immune responsiveness (129). The levels of these potentially immunosuppressive hormones are quite elevated in the circulation of pregnant women. The fact that the levels of these hormones at the maternal–fetal interface may be dramatically higher than those in the maternal circulation during pregnancy may help to explain an apparent inconsistency: with some exceptions, overall immune responsiveness during pregnancy appears to change a little, while local modulation at the maternal–fetal interface may be vital (130).

It has been suggested that the immunosuppressive effects of progesterone within the reproductive tract are at least partially responsible for the maintenance of the semiallogeneic implanting fetus (131). In vitro studies have shown that progesterone mediates its suppression of T cell effector function by altering membrane-resident potassium channels and cell membrane depolarization. This action, in turn, affects intracellular calcium signaling cascades and gene expression and may be mediated by nonclassical steroid receptors or may not involve a receptor at all (132–134). Progesterone-mediated changes in T cell gene expression have been associated with the development of TH2-type T helper cell responses and with increased leukemia inhibitory factor (LIF) expression (135). Because a shift in the intrauterine immune environment from TH2 to TH1 has been linked with early spontaneous pregnancy loss,

the elevated intrauterine concentrations of progesterone characteristic of early pregnancy may promote an immune environment favoring pregnancy maintenance (123). To this point, in vitro evidence indicates that progesterone can inhibit mitogen-induced proliferation of and cytokine secretion by CD8+ T cells and can alter the expression of a transcription factor that drives the development of TH1 cells (136,137).

Levels of estrogen rise markedly during pregnancy, and attention has focused on the role of estrogen in immune modulation. A group of animal studies showed that estrogens improve immune responses in males after significant trauma and hemorrhage, suppress cell-mediated immunity after thermal injury, and protect against chronic renal allograft rejection (138–140). In vitro, estrogens appear to downregulate delayed-type hypersensitivity (DTH) reactions and promote the development of TH2-type immune responses, particularly at the elevated estrogen concentrations typical of pregnancy (141,142). In mice, elevations in estrogen have been shown to recruit Treg cells to the uterus (390).

One additional regulatory mechanism proposed for the induction of maternal tolerance to the fetal allograft involves the amino acid tryptophan and its catabolizing enzyme indoleamine 2,3-dioxygenase (IDO). The IDO hypothesis of tolerance in pregnancy rests on data showing that T cells need tryptophan for activation and proliferation (143) and local alterations in tryptophan metabolism at the maternal–fetal interface could either activate or fail to suppress maternal–antifetal immunoreactivity (144). Studies in mice have shown that the inhibition of IDO leads to loss of allogeneic, but not syngeneic, fetuses, and that this effect is mediated by lymphocytes (145). Further support lies in studies demonstrating that hamsters fed diets high in tryptophan have increased rates of fetal wastage (146). Extending this theory to humans requires further investigation. However, the demonstration of IDO expression in human uterine decidua, and the documentation of alterations in serum tryptophan levels with increasing gestational age during human pregnancy support further interest in this potential local immunoregulatory mechanism (147,148).

Humoral Immune Mechanisms and Antiphospholipid Syndrome

Humoral responses to pregnancy-specific antigens exist, and patients with recurrent pregnancy loss can display altered humoral responses to endometrial and trophoblast antigens (123,149). Nevertheless, most literature surrounding humoral immune responses and recurrent pregnancy loss focus on organ nonspecific autoantibodies associated with the antiphospholipid syndrome (APS). Historically, these immunoglobulin-G (IgG) and IgM antibodies were considered to be directed against negatively charged phospholipids. Those phospholipids most often implicated in recurrent pregnancy loss are cardiolipin and phosphatidylserine. However, antiphospholipid antibodies often are directed against a protein cofactor, β2 glycoprotein 1, which assists antibody association with phospholipid (150–154).

Antiphospholipid antibodies were originally characterized solely by prolonged phospholipid-dependent coagulation tests in vitro (activated partial thromboplastin time [aPTT], Russell viper venom time) and by thrombosis in vivo. The association of these antiphospholipid antibodies with thrombotic complications has been termed the APS, and although many of these complications are systemic, some are pregnancy specific—spontaneous miscarriage, stillbirth, intrauterine growth retardation, and preeclampsia (155,156). A reassessment of the criteria used to diagnose APS resulted in additions to the prior Sapporo criteria for diagnosis of APS and continues to include adverse pregnancy outcomes. These criteria, which have been validated clinically, are as follows (156–158):

For a patient to be diagnosed with antiphospholipid syndrome, one or more clinical and one or more laboratory criteria must be present:

Clinical

1. **One or more confirmed episode of vascular thrombosis of any type:**
    - **Venous**
    - **Arterial**
    - **Small vessel**
2. **Pregnancy complications:**
    - **Three or more consecutive spontaneous pregnancy losses at less than 10 weeks of gestation with exclusion of maternal anatomic and hormonal abnormalities and exclusion of paternal and maternal chromosomal abnormalities**
    - **One or more unexplained deaths of a morphologically normal fetus at or beyond 10 weeks of gestation (normal fetal morphology documented by ultrasound or direct examination of the fetus)**
    - **One or more premature births of a morphologically normal neonate at or before 34 weeks of gestation secondary to severe preeclampsia or placental insufficiency**

Laboratory

Testing must be positive on two or more occasions with evaluations 12 or more weeks apart:

1. Positive plasma levels of anticardiolipin antibodies of the IgG or IgM isotype at medium to high levels
2. Positive plasma levels of lupus anticoagulant

3. Anti-β2 glycoprotein-1 antibodies of the IgG or IgM isotype in titers greater than the 99th percentile

The presence of antiphospholipid antibodies (anticardiolipin or lupus anticoagulant) and anti-β2 glycoprotein-1 antibodies during pregnancy is a major risk factor for an adverse pregnancy outcome (150,151,159). In a large series of couples with recurrent pregnancy loss, the incidence of the APS was between 3% and 5% (66). The presence of anticardiolipin antibodies among patients with known systemic lupus erythematosus portends less favorable pregnancy outcomes (160).

Several mechanisms have been proposed by which antiphospholipid antibodies might mediate pregnancy loss (161). Antibodies against phospholipids could increase thromboxane and decrease prostacyclin synthesis within placental vessels. The resultant prothrombotic environment could promote vascular constriction, platelet adhesion, and placental infarction (162–164). Alternatively, in vitro evidence from trophoblast cell lines indicates that IgM action against phosphatidylserine inhibits formation of syncytial trophoblast (165). Syncytialization is required for proper placental function. One study demonstrated that both extravillous cytotrophoblast and syncytiotrophoblast cells synthesize β2 glycoprotein-1, the essential cofactor for antiphospholipid antibody binding (166). Although it gives insight into pathophysiology, the prognostic value of serum levels of specific antibodies against β2 glycoprotein-1 with respect to pregnancy outcome among recurrent pregnancy loss patients is contentious and may be poorer than that of standard anticardiolipin antibodies (167–169). Some have proposed that sera from antibody positive recurrent pregnancy loss patients are particularly adept at inhibiting trophoblast adhesion to endothelial cells in vitro (170). Others noted rapid development of atherosclerosis in the decidual spiral arteries of patients who test positive for antiphospholipid antibodies (171). Still others have demonstrated that levels of the placental antithrombotic molecule—annexin V—are reduced within the placental villa from those women with recurrent pregnancy loss who are antiphospholipid antibody positive (172). However, placental pathologic evidence that supports causal involvement of the antiphospholipid syndrome in pregnancy loss is equivocal. The characteristic lesions for this syndrome (placental infarction, abruption, and hemorrhage) are typically missing in women with antiphospholipid antibodies, and these same pathologic lesions can be found in placentae from women with recurrent miscarriages who do not have biochemical evidence of antiphospholipid antibodies (161,173–175).

One additional group of autoantibodies that have been linked to recurrent pregnancy loss is the antithyroid antibodies. Although the data remain somewhat controversial, several investigators demonstrated an increased prevalence of these antibodies among women with a history of recurrent pregnancy loss, even in the absence of thyroid endocrinologic abnormalities (52,56,57,176–178).

Other antibody-mediated mechanisms for recurrent pregnancy loss have been proposed, including antisperm and antitrophoblast antibodies, and blocking antibody deficiency but none have withstood the test of time.

It is important to suggest during this in-depth discussion of the immune-mediated mechanisms of isolated and recurrent pregnancy loss that pregnancy may not require an intact maternal immune system. Supporting this concept are data showing that agammaglobulinemic animals and women can successfully reproduce (180). Further, viable births occur among women with severe immune deficiencies and in murine models that lack T and B cells (severe combined immunodeficiency [SCID] mice) and those that display a congenital absence of their thymus (nude mice).

[5] Despite the knowledge that most first trimester miscarriages are caused by aneuploidy and that the only immune-related issue recommended for routine evaluation and treatment for recurrent miscarriage by expert groups is APS, providers around the world still test and treat for many different immune issues in couples with recurrent pregnancy loss. Patients and providers feel pressured for answers and interventions in the setting of unexplained recurrent pregnancy loss and immune issues play into the woman's feelings of guilt and worry that there is something wrong with her that is causing her to reject her pregnancy. Immune-related dysfunction in relationship to miscarriage and recurrent pregnancy loss remains up for debate, additional research, and better understanding. Immunosuppressive treatments can result in harm and until more is understood, intervention should be limited to investigations in the setting of Institutional Review Board (IRB)-approved clinical trials.

Male Factors

Most publications that review testing and treatment for recurrent pregnancy loss couples, including this chapter, recommend only a single test for the male partner in the couple—a peripheral blood karyotype. The role of the male partner in the etiology of recurrent pregnancy loss is understudied, but there is a growing body of literature suggesting that the development and validation of novel testing and treatment regimens for the male may prove beneficial (181,182). Detailed peripheral chromosomal testing of men whose partners experienced recurrent pregnancy loss revealed an increased incidence of Y chromosome microdeletions when compared to male partners in fertile and infertile couples (183). Small studies demonstrated that male partners in couples experiencing recurrent pregnancy loss have an increased incidence of sperm chromosomal aneuploidy, particularly sex chromosome disomy, when compared to fertile men (184,365–367). The addition of specialized testing to a standard semen analysis among men in couples with recurrent loss revealed reductions in sperm functional testing (hypo-osmotic swelling, acrosome status, nuclear chromatin decondensation) and increased DNA fragmentation and lipid peroxidation when

compared to fertile men or historical controls (185–187). The latter results suggest that these men may have abnormal levels of reactive oxygen species in their semen or that their sperm cells are particularly sensitive to these compounds. Paternal carriage of the MTHFR C677T mutation and hyperhomocysteinemia were associated with DNA damage and recurrent pregnancy loss (188). A single, small, uncontrolled treatment study using antioxidants among male partners in recurrent pregnancy loss couples who had high levels of sperm DNA damage or semen lipid peroxidation suggested favorable treatment outcomes (186). The only evidence-based recommended test for a male partner in a couple with recurrent pregnancy loss is a peripheral blood karyotype and the other tests and interventions remain under investigation. With more focus on male factor in all aspects of reproduction, more information may surface about the male factor in miscarriage.

Other Factors

It is increasingly evident that the implantation of the blastocyst within the uterine decidua involves an exquisitely scripted crosstalk between embryo and mother. Alterations in this dialogue often result in improper implantation and placental development. For instance, recurrent pregnancy loss has been linked to a dysregulation in the expression patterns of vascular endothelial growth factors (VEGFs) in the developing placenta and their requisite receptors within the maternal decidua (189). Cellular and extracellular matrix adhesion properties may be involved in this dialogue. The concept of uterine receptivity has been emboldened by the description of endometrial integrins and the timing of integrin switching during implantation (190). Others have reported decreased levels of endometrial mucin secretion and reductions in the endometrial release of soluble intercellular adhesion molecule I among women with histories of recurrent pregnancy loss (191,192). Programmed cell death (apoptosis) may play an essential role in normal placental development. Alterations in two important apoptotic pathways—Fas-Fas ligand and bcl2—have been linked to recurrent pregnancy loss and poor pregnancy outcome (75,193).

Environmental Factors

A variety of environmental factors have been linked to sporadic and recurrent early spontaneous pregnancy loss. These are difficult studies to perform, because, in humans, they all must be retrospective and all are confounded by alternative or additional environmental exposures. Nevertheless, the following factors have been linked to pregnancy loss: exposure to medications (e.g., antiprogestogens, antineoplastic agents, anti-inflammatory agents, and inhalation anesthetics), exposure to ionizing radiation, prolonged exposure to organic solvents, and exposure to environmental toxins, especially phthalates, bisphenol-A, and heavy metals (194–197). The latter two

exposures have been demonstrated to have endocrine and immune effects that could lead to poor placentation and subsequent pregnancy loss (198,199). Lathi et al. showed that maternal BPA levels were directly associated with increased risk of miscarriage (368). Associations between spontaneous pregnancy loss and exposures to video display terminals, microwave ovens, high-energy electric power lines, and high altitudes (e.g., flight attendants) are not substantiated (200,201). There is no compelling evidence that moderate exercise during pregnancy is associated with spontaneous miscarriage. Association between stress and miscarriage risk is controversial (369). In the absence of cervical anatomic abnormalities or incompetent cervix, coitus does not appear to increase the risk for spontaneous pregnancy loss (202,203).

Exposure to four particular substances—alcohol, cigarettes, marijuana, and caffeine—deserves specific attention; all have been linked with increased risk of miscarriage through studies with widely varied findings. Although some conflicting data exist, one very large epidemiologic study has shown that **alcohol consumption during the first trimester of pregnancy, at levels as low as three drinks per week, is associated with an increased incidence of spontaneous pregnancy loss** (204–206). **Cigarette smoking has been linked to early spontaneous pregnancy loss;** however, this is not without controversy (207–209). **Alcohol and tobacco intake in the male partner correlates with the incidence of domestic violence, which in turn is associated with early pregnancy loss** (210). **Marijuana has not been shown to necessarily increase the risk of miscarriage in the one study investigating association found in the literature to date** (370)**, however studies have shown poor effects on female** (371) **and male** (372) **fertility and patients should be counseled to refrain until further studies can evaluate risk further.** Evidence adds to a growing body of literature that suggests **consumption of coffee and other caffeinated beverages during early pregnancy is linked to adverse pregnancy outcomes** (207,211). One report casts doubt on the definition of a lower limit for safe use of caffeine in the first trimester of pregnancy (207).

Maintaining a healthy weight may decrease risk of miscarriage as being underweight (373) and overweight (374) have been associated with increased risk of miscarriage. Risk of sporadic and recurrent miscarriage are increased with obesity and etiologic theories include impact on both gamete quality and uterine receptivity in autologous conception (375) and donor egg pregnancies (212).

PRECONCEPTION EVALUATION

[4] Investigative measures that are potentially useful in the evaluation of recurrent spontaneous miscarriage include obtaining a thorough history from both partners, performing a physical assessment of the woman (with attention to the pelvic

examination), and a limited amount of laboratory testing (Table 33-2).

Table 33-2 Investigative Measures Useful in the Evaluation of Recurrent Early Pregnancy Loss

History
1. Pattern, trimester, and characteristics of prior pregnancy losses 2. History of subfertility or infertility 3. Menstrual history 4. Prior or current gynecologic or obstetric infections 5. Signs or symptoms of thyroid, prolactin, glucose tolerance, and hyperandrogenic disorders (including polycystic ovarian syndrome) 6. Personal or familial thrombotic history 7. Features associated with the antiphospholipid syndrome (thrombosis, false positive test for syphilis) 8. Other autoimmune disorders 9. Medications 10. Environmental exposures, illicit and common drug use (particularly caffeine, alcohol, cigarettes, marijuana, and *in utero diethylstilbestrol* exposure) 11. Genetic relationship between reproductive partners 12. Family history of recurrent spontaneous abortion, of obstetric complications, or of any syndrome associated with embryonic or fetal losses 13. Previous diagnostic tests and treatments, including, if available, chromosome testing on products of conception
Physical Examination
1. General physical examination with attention to: a. Obesity b. Hirsutism/acanthosis c. Thyroid examination d. Breast examination/galactorrhea e. Pelvic examination 1. Anatomy 2. Infection 3. Trauma 4. Estrogenization 5. Masculinization
Laboratory
1. Parental peripheral blood karyotype (both partners) 2. Chromosome testing on products of conception 3. Hysterosalpingography, three-dimensional transvaginal sonography, sonohysterography, or office hysteroscopy, followed by hysteroscopy/laparoscopy, if indicated 4. Serum thyroid stimulating hormone level

5. Serum prolactin level
6. Serum HbA_{1c}
7. Antiphospholipid screening
   a. Anticardiolipin antibody levels (IgG and IgM)
   b. Lupus anticoagulant (activated partial thromboplastin time or Russell viper venom)
   c. Anti-β2-glycoprotein-1 antibodies (IgG and IgM)

History

A description of all prior pregnancies, their sequence and whether histologic assessment and karyotype determinations were performed on previously aborted tissues are important aspects of the history. **Approximately 60% of pregnancies lost before 8 weeks of gestation are reported to be chromosomally abnormal; most of these pregnancies are affected by some type of trisomy, particularly trisomy 16** (215,216). **The most common single chromosomal abnormality is monosomy X (45X), especially among anembryonic conceptuses** (217). Aneuploid losses are particularly prevalent among women with recurrent pregnancy loss who are over the age of 35 (8). Research suggests a higher rate of aneuploid miscarriage in recurrent pregnancy loss women with DOR at a younger age (349). Although somewhat controversial, the detection of aneuploidy in miscarriage specimens may be lower when the couple experiencing recurrent miscarriages is euploidic. Alternatively, some investigators have suggested that, because aneuploidy is common among miscarriage specimens from patients experiencing isolated and recurrent spontaneous pregnancy losses, if aneuploidy is documented in fetal tissues from a recurrent pregnancy loss patient, this loss does not affect their prognosis for future pregnancy maintenance (13).

Most women with recurrent pregnancy loss tend to experience spontaneous miscarriage at approximately the same gestational age in sequential pregnancies (218). Unfortunately, the gestational age when pregnancy loss occurs, as determined by last menstrual period, may not be informative, because there is often a 2- to 3-week delay between fetal demise and signs of pregnancy expulsion (219). If patients have had ultrasounds in the first trimester, careful history and detailed record review can reveal a more accurate time of fetal demise than gestational age by last menstrual period or patient's recall. The designation into either primary or secondary categories is not helpful in the diagnosis or management of couples experiencing recurrent miscarriage. Approximately 10% to 15% of couples cannot be classified into either the primary or secondary category because, although their first pregnancy resulted in a loss, it was followed by a term delivery prior to subsequent losses. Expert groups exclude biochemical miscarriages, defined as positive pregnancy test but miscarriage before ultrasound or histopathologic evidence can be obtained, from guidelines. This recommendation is not without controversy. Biochemical miscarriages can be

distressing for patients and providers can feel obligated or unsure about investigating further. Some evidence suggests women with recurrent biochemical miscarriages or a mix of biochemical and clinical miscarriages have similar poor prognosis for subsequent pregnancies (376,377). Investigation is encouraged for recurrent clinical miscarriage (ultrasound or histopathologic evidence) (338) but not biochemical miscarriages.

It is important to glean any history of subfertility or infertility among couples with recurrent pregnancy loss. This is defined as the inability to conceive after 12 months of unprotected intercourse. By definition, 15% of all couples will meet these criteria; this number increases to 33% among couples with recurrent pregnancy losses. Because many pregnancies are lost before or near the time of missed menses, subfertility among recurrent pregnancy loss patients may, in some cases, reflect recurrent preclinical losses. Menstrual cycle history may provide information about the possibility of oligo-ovulation or other relevant endocrine abnormalities in recurrent pregnancy loss patients. A personal and family history of thrombotic events or renal abnormalities may provide vital information. A family history of pregnancy losses and obstetric complications should be addressed specifically. Detailed information about drug and environmental exposure should be obtained.

Physical Examination

A general physical examination should be performed to detect signs of metabolic illness, including PCOS, diabetes, hyperandrogenism, and thyroid or prolactin disorders. During the pelvic examination, signs of infection, DES exposure, and previous trauma should be ascertained. Estrogenization of mucosal tissues, cervical and vaginal anatomy, and the size and shape of the uterus should be determined.

[4] Recommended Testing

[5] Laboratory assessment of couples with recurrent pregnancy losses should include the following:

1. **Chromosome analysis of the products of conception**
2. **Parental peripheral blood karyotyping with banding techniques**
3. **Assessment of the intrauterine cavity with either office hysteroscopy, sonohysterography, three-dimensional transvaginal sonography, or hysterosalpingography, followed by operative hysteroscopy if a potentially correctable anomaly is found** (220)
4. **Thyroid function testing, including serum TSH levels**
5. **Anticardiolipin antibodies, anti-β2 glycoprotein-1 antibodies, and lupus**

anticoagulant testing (aPTT or Russell viper venom testing)

6. **Prolactin**
7. **HbA_{1c}**

Tests with Unproven Utility

A number of laboratory assessment tools are under investigation for use in patients with a history of recurrent pregnancy loss. Results are either too preliminary to warrant unfettered recommendation or studies of their use have been too contradictory to allow final determination of their value.

Tests under investigation with evidence in favor of utilizing:

1. **Evaluation of ovarian reserve using day 3 serum follicle–stimulating hormone, estradiol, and anti-müllerian hormone levels. It appears that decreased ovarian reserve may predict higher risk of aneuploid embryos and miscarriage in all patients, including those with recurrent pregnancy loss** (64,65,349).
2. **Testing for antithyroid antibodies among women with recurrent pregnancy loss remains controversial, but is rapidly gaining support** (52–54,57,176–178). **Investigators have demonstrated an increased prevalence of these antibodies among women with a history of recurrent pregnancy loss, even in the absence of thyroid endocrinologic abnormalities** (53,54,56,177).
3. **Endometrial biopsy for plasma cells/chronic endometritis**

Tests under investigation and the majority of research shows No clinical benefit

a. **Thrombophilia testing (FVL, prothrombin gene mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, homocysteine levels, MTHFR mutation). Once popular for patients with recurrent pregnancy loss, evidence shows limited value in testing and or treatment of thrombophilia testing to prevent miscarriage or poor pregnancy outcome unless patients have a personal or family history of thrombosis**
b. **Testing for peripheral evidence of TH1/TH2 cytokine dysregulation.**
c. **NK cell testing in peripheral blood or endometrium**
d. **Cervical cultures for mycoplasma, ureaplasma, and chlamydia may be considered.**
e. **Testing for serologic evidence of PCOS using LH or androgen values may be useful** (43–46).

Tests not recommended for evaluation in patients with recurrent pregnancy loss:

1. Evaluations that involve extensive testing for serum or site-specific auto- or

alloantibodies (including antinuclear antibodies and antipaternal cytotoxic antibodies) are expensive and unproven. Their use often verifies the statistical tenet that if the number of tests performed reaches a critical limit, the results of at least one will be positive in every patient.
2. Testing for parental HLA profiles is never indicated in outbred populations. Findings that HLA sharing is associated with poor pregnancy outcomes are strictly limited to those specific populations studied, which have very high and sustained levels of marriage within a limited community (179).
3. Use of mixed lymphocyte cultures has not proved useful. Use of other immunologic tests is unnecessary unless these studies are performed, with informed consent, under a specific study protocol in which the costs of these experimental tests are not borne by the couple or their third-party payers.
4. Further work is necessary before suppressor cell or factor determinations, cytokine, oncogene, and growth factor measurements, or embryotoxic factor assessment can be clinically justified.
5. Endometrial biopsy for luteal phase defect

POSTCONCEPTION EVALUATION

Following conception, close monitoring of patients with histories of recurrent pregnancy loss is advised to provide emotional support and to confirm intrauterine pregnancy and its viability. Although controversial, some studies recommend close monitoring in the first trimester of women with a history of recurrent pregnancy loss resulting from a higher incidence of ectopic pregnancy and complete molar gestation in this population (56,222–226). **Determining serum levels of a-hCG may be helpful in monitoring early pregnancy until an ultrasonographic examination can be performed; however, not all failing pregnancies will be preceded by inadequate a-hCG levels** (227). **If used, serum a-hCG levels should be serially monitored from the time of a missed menstrual period until the level is approximately 1,200 to 1,500 mIU/mL, at which time an ultrasonographic scan is performed and blood sampling is discontinued.** Other hormonal determinations are rarely of benefit because levels are often normal until fetal death or miscarriage occurs (228).

If a pregnancy has been confirmed, but clinical follow-up has met newly defined criteria for a failed pregnancy (378), intervention is recommended to expedite pregnancy termination and to obtain tissue for karyotype analysis. **[9] The importance of obtaining karyotypic analysis from tissues obtained after pregnancy demise in a woman experiencing recurrent losses cannot be overemphasized. Results may suggest karyotypic anomalies in the parents and patients report their appreciation of receiving the information** (379). **The documentation of aneuploidy may have**

important prognostic implications and may direct future interventions. Cost analysis has demonstrated that karyotypic analysis is financially prudent among patients with histories of recurrent pregnancy loss (229). Analysis by traditional karyotype fails 20% to 40% of the time because of difficulties in growing cells from products of conception and interpretation of results can be limited as a result of maternal cell contamination (380). Techniques for analysis like comparative genomic hybridization provide results in more than 90% of cases and can differentiate 46XX results from maternal cell contamination (230,380). This technology can be used without fresh samples needed for cell growth and can even be used in specimens that have been in formalin or paraffin (231).

In continuing pregnancies, first trimester screening using cell-free fetal DNA, maternal chemistries, and fetal nuchal lucency measurement or chorionic villus sampling is recommended for obstetrical indications. Amniocentesis may be recommended to assess the fetal karyotype based on prior screening results. In the future, fetal karyotype assessment may be performed using DNA isolated from nucleated fetal erythrocytes in maternal blood (232) or from sampling of the lower genital tract (381).

THERAPY

Advances in the treatment of patients with recurrent pregnancy loss have been slow. Despite a rapid expansion in understanding the molecular and subcellular mechanisms involved in implantation and early pregnancy maintenance, extension of these concepts to prevention of recurrent early pregnancy loss has lagged. Progress toward treatment of most causes of recurrent pregnancy loss has been hampered by a variety of factors. The condition itself has been inconsistently defined. **The results of clinical trials involving recurrent pregnancy loss patients are nearly impossible to compare and evaluate.** Trial design is frequently substandard, with lack of rationale, lack of appropriate control groups, and poor statistical analysis, limiting the ability to draw concrete conclusions from reported results. Epidemiologic data indicate that most patients with a history of recurrent pregnancy loss will, in fact, have a successful pregnancy the next time they conceive (7). For these reasons, with few exceptions, most therapies for recurrent pregnancy loss must be considered experimental. Until further study is completed, treatment protocols involving these therapies should be undertaken only with informed consent and in the setting of a well-designed, double-blind, placebo-controlled clinical trial.

[9] Common but controversial therapeutic options for patients with recurrent pregnancy loss include the use of IVF with preimplantation chromosomal screening of embryos, use of donor oocytes or sperm, antithrombotic interventions, the repair of anatomic anomalies, the correction of any endocrine abnormalities, the

treatment of infections, and a variety of immunologic interventions and drug treatments. Treatment for patients with recurrent miscarriage should include close monitoring of pregnancy, psychological counseling and support, and karyotypic analysis of tissues from subsequent miscarriage.

Genetic Abnormalities

Evidence suggests that, in women with a history of three or more spontaneous pregnancy losses, a subsequent pregnancy loss has a 58% chance of chromosomal abnormality (382). Among women with recurrent pregnancy loss who are age 35 or older, the aneuploidy rate is much higher at 80% (8). Most chromosomal abnormalities identified in miscarriages are autosomal trisomies and considered to result from maternal nondisjunction. Maternal age appears as a consistent and important risk factor for trisomy in most studies. DOR can be associated with higher aneuploidy rate in young women with recurrent pregnancy loss (349). There are several options for patients who suffer from recurrent pregnancy loss who have an identified miscarriage caused by trisomy. The first is to conceive again without any specific change in medical management, as these abnormalities are sporadic and unlikely to recur. Studies examining patients with recurrent pregnancy loss show that women who miscarry chromosomally abnormal conceptions are more likely to achieve a live birth with subsequent pregnancy than those who miscarry chromosomally normal conceptions (13,233). A second treatment option is chromosomal screening of embryos before implantation, commonly referred to as preimplantation genetic screening (PGS), and a third option involves the use of donor gametes.

Because chromosomal abnormalities are the most commonly identified cause of miscarriage, some have argued that the use of chromosomal screening of embryos is indicated for patients with recurrent pregnancy loss. This technique involves biopsying a single cell from a cleavage stage embryo (day 3) or many labs are biopsying several cells from blastocysts (day 5 or 6). Genetic testing can be performed on these cells to determine abnormalities in chromosome number and morphology. Embryos that are diagnosed with genetic abnormalities would be discarded and only those embryos with euploid results considered appropriate for transfer into the uterus. The biopsying of cells from embryos to screen for specific disease causing mutations like cystic fibrosis or sickle cells disease, commonly referred to as preimplantation genetic diagnosis (PGD), is used in many internationally recognized assisted reproductive technology centers, however the use of chromosomal screening via biopsying embryos remains controversial, especially for recurrent pregnancy loss patients.

The use of chromosomal screening of embryos has the potential to reduce the incidence of pregnancy loss arising from a chromosome issue within the embryo. However, definitive studies in this population have not yet been done. The use of this

technology requires the patient to undergo an IVF cycle to obtain embryos for biopsy at significant cost and medical intervention. Although there are several retrospective studies showing reduced miscarriage rates with this technique, several prospective trials using the outcome of successful pregnancy per started cycle fail to show significant benefit (234–244). IVF is invasive and costly and many patients with recurrent pregnancy loss conceive quickly without intervention and have a high likelihood of live birth with their subsequent pregnancy. Therefore, the optimal control group for a study of IVF with chromosomal screening in the recurrent pregnancy loss population is debated. Should it be natural conceptions or IVF without testing of embryos? Finally, the prognosis for a patient with recurrent pregnancy loss does seem to be linked to the chromosome analysis of prior miscarriages. Recurrent pregnancy loss patients who miscarry chromosomally abnormal embryos, seem to have better prognosis than those who miscarry chromosomally normal conceptions, again arguing for expectant management for recurrent pregnancy loss patients with a history of aneuploid loss. On the other hand, patients with poorer prognosis are those who miscarry chromosomally normal embryos and therefore would not benefit from IVF and chromosomal screening of embryos. One intent to treat analysis showed similar pregnancy outcomes in recurrent pregnancy loss patients who chose expectant management compared to those who chose IVF with chromosomal screening (383). The efficacy of chromosomal screening of embryos in the treatment of patients with recurrent pregnancy loss continues to be investigated, and the methods of embryo biopsy and genetic testing continue to evolve (242,243). As these techniques improve and the understanding of aneuploidy and recurrence improves, there may be a subset of recurrent pregnancy loss patients, such as carriers of parental translocations, who might benefit from this intervention. IVF with chromosomal screening of embryos can be considered, but not strongly recommended, for patients with recurrent pregnancy loss.

An additional option for patients with recurrent miscarriage is the use donor eggs or sperm. This treatment is useful for recurrent pregnancy loss patients with specific parental genetic factors and couples with DOR. Patients with robertsonian translocations involving homologous chromosomes have a genetic anomaly which always results in unbalanced gametes, and the use of donor oocyte or donor sperm is recommended. Use of donor gametes among patients with a history of recurrent pregnancy loss can be useful in other cases where couples are at higher risk for unbalanced offspring because one or both prospective parents carries other chromosomal rearrangements, such as reciprocal translocations. In these cases, use of donor gametes was demonstrated to be as effective as its use in matched patients without such a history (245). In all cases of balanced translocations or embryonic aneuploidy, genetic counseling is recommended. Couples with DOR and/or advanced reproductive age have a higher risk of miscarriage, aneuploidy (349), and limited success with IVF with chromosomal screening and therefore should be counseled about

the option of using donor eggs.

Anatomic Anomalies

Hysteroscopic resection represents state-of-the-art therapy for submucous leiomyomas, intrauterine adhesions, and intrauterine septa. Although its efficacy has been debated, this approach appears to limit postoperative sequelae while maintaining improved reproductive outcomes (30,31,245–249). **Use has been safely extended to patients with DES exposure, hypoplastic uteri, and complicated septal anomalies** (30,31,250). Attempts to improve on standard hysteroscopic metroplasty, which is typically performed in the operating room using general anesthesia, often with laparoscopic guidance, are under investigation. Ultrasonographically guided transcervical metroplasty is reported to be safe and effective (246). Ambulatory, office-based procedures, including septum resection under fluoroscopic or ultrasound guidance, are attractive options (247).

For patients with a history of loss secondary to cervical incompetence, placement of a cervical cerclage is indicated. This is usually performed early in the second trimester after documentation of fetal viability. Cervical cerclage should be considered as a primary intervention for women with DES-associated uterine anomalies.

Endocrine Abnormalities

Some investigators have proposed the use of ovulation induction for the treatment of recurrent pregnancy loss (248,249). The theory behind its use in these patients rests on hypotheses that ovulation induction is associated with healthier oocytes. Healthier oocytes, in turn, may decrease the incidence of luteal phase insufficiency through a more receptive hormonal environment, which should result in improved pregnancy maintenance. This approach grossly oversimplifies the mechanisms involved in implantation and early pregnancy maintenance. Until appropriately studied, use of empiric ovulation induction for treatment of unexplained recurrent pregnancy loss should be viewed with caution. Evidence from small studies indicates such use is not effective (248). Still, use of ovulation induction in some subsets of patients with recurrent pregnancy loss could be of benefit. For instance, stimulating folliculogenesis with ovulation induction or luteal phase support with progesterone should be considered for women with luteal phase insufficiency. The efficacy of these therapies, however, is not substantiated (250). Ovulation induction might be beneficial for women with androgen and LH hypersecretion disorders, especially following pituitary desensitization with gonadotropin-releasing hormone agonist therapy (66). This treatment remains controversial because the only large, prospective, randomized controlled trial reports no therapeutic efficacy; none for prepregnancy pituitary

suppression nor for luteal phase progesterone supplementation (251).

Links between PCOS, hyperandrogenism, hyperinsulinemia, and recurrent pregnancy loss make use of insulin-sensitizing agents in the treatment of recurrent pregnancy loss associated with PCOS attractive (43–46). Although further study is needed, there are an increasing number of reports that support its use for this application (252,253). Prepregnancy glycemic control is particularly important for women with overt diabetes mellitus (47,49). Thyroid hormone replacement may be helpful in cases of hypothyroidism. There are data indicating that thyroid hormone therapy may be of some benefit in euthyroid recurrent loss patients with antithyroid antibodies and possibly even in all pregnant women with "euthyroid" TSH levels between 2.5 and 5.0 mIU/L (52–54,177). Use of dopamine agonists to normalize prolactin levels in patients with recurrent pregnancy loss has improved subsequent pregnancy outcomes in limited studies (63), but remains controversial (384). There does not appear to be a place in the medical management of recurrent pregnancy loss for administering bromocriptine to women who do not have a prolactin disorder.

Infections

Empiric antibiotic treatment has been used for couples with recurrent miscarriage but its efficacy is unproven. Elaborate testing for infectious factors among recurrent pregnancy loss patients and use of therapeutic interventions is not justified unless a patient is immunocompromised or a specific infection has been documented (67). For cases in which an infectious organism has been identified, appropriate antibiotics should be administered to both partners, followed by posttreatment culture to verify eradication of the infectious agent before attempting conception.

Chronic endometritis, defined as the asymptomatic presence of histologically documented plasma cells in an endometrial biopsy, may be associated with recurrent miscarriage. In suspected cases of chronic endometritis, it is difficult to determine cause and effect but treatment with antibiotics shows a higher live birth rate in subsequent pregnancies in some studies (353,354). Treatment for chronic endometritis is not recommended by expert groups and larger studies are needed before implementing evaluation and treatment in routine practice.

Immunologic Factors

[5] Immune-mediated recurrent pregnancy loss has received more attention than any other single etiologic classification of recurrent pregnancy loss. Nevertheless, the diagnosis and subsequent treatment of the majority of cases remain unclear (56,118,254–256). **Most therapies for proposed immune-related recurrent pregnancy loss can have harmful side effects and must be considered experimental.**

Immunostimulating Therapies: Leukocyte Immunization

Stimulation of the maternal immune system using alloantigens on either paternal or pooled donor leukocytes has been promoted for patients with immunologic recurrent pregnancy loss, but data do not support its use and side effects can be dangerous. One of the largest trials evaluating the efficacy of leukocyte immunization in patients with unexplained recurrent pregnancy loss is a part of the Recurrent Miscarriage (REMIS) study (258). This investigation was large (over 90 patients per treatment arm), prospective, placebo controlled, randomized, and double blinded. It demonstrated no efficacy for paternal leukocyte immunization in couples with unexplained recurrent pregnancy loss. The best of the meta-analyses definitively rejects use of this therapy in patients with recurrent loss (259). Leukocyte immunization poses a significant risk to the mother and her fetus (231,232,260). Several cases of graft-versus-host disease, severe intrauterine growth retardation, and autoimmune and isoimmune complications have been reported (257,260–264). Alloimmunization to platelets contained in the paternal leukocyte preparation is associated with cases of potentially fatal fetal thrombocytopenia. The routine use of this therapy for recurrent miscarriage is not clinically justified.

Other immunostimulating therapies have been proposed and abandoned. Intravenous preparations consisting of syncytiotrophoblast microvillus plasma membrane vesicles have been used to mimic the fetal cell contact with maternal blood that normally occurs in pregnancy (265). The efficacy of this therapy has not been established (259,265,266). The use of third-party seminal plasma suppositories has been attempted, based on the misconception that TLX was part of an idiotype–anti-idiotype control system (267,268). Third-party seminal plasma suppositories for recurrent miscarriage have no scientifically credible rationale and should not be used.

Immunosuppressive Therapies

Immunosuppressive and other immunoregulating therapies have been advocated for cases in which miscarriage was believed to result from antiphospholipid antibodies or inappropriate cellular immunity toward the implanting fetus. Study design problems, including small numbers of recruited patients, lack of prestratification by maternal age and number of prior losses before randomization, and other methodologic and statistical inaccuracies preclude definitive statements regarding therapeutic efficacy for most of the proposed immunosuppressive approaches.

Intravenous Immunoglobulin

Intravenous immunoglobulins (IVIgs) are composed of pooled samples of immunoglobulins harvested from a large number of blood donors. Studies on the use of IVIg therapy in the treatment of recurrent pregnancy loss are based on the theory that some recurrent pregnancy loss patients have an overzealous immune reactivity to their implanting fetus. IVIgs do have immunosuppressive effects, but the mechanisms

underlying this immune modulation are only partially understood. Based on a large number of relatively small studies using a variety of treatment protocols, there remains no conclusive evidence to suggest that use of IVIg in the treatment of patients with unexplained (and presumed immunologic) recurrent pregnancy loss has any benefit (261,269–273). This includes a recent trial using IVIg in women with secondary recurrent pregnancy loss that was ended early because interim analyses revealed no effect (269). The Cochrane review of immune therapy for recurrent pregnancy loss addressed IVIg therapy and reported that its use did not alter pregnancy outcomes in patients with otherwise unexplained recurrent pregnancy loss (259,266). Improved posttreatment pregnancy rates may be seen, however, when IVIg is used in those specific patients with autoimmune-mediated pregnancy loss associated with APS (274,275). Therapy with IVIgs for recurrent pregnancy loss is expensive, invasive, and time-consuming, requiring multiple intravenous infusions over the course of pregnancy (276). Use of IVIgs for recurrent pregnancy loss is not supported by current evidence and may result in significant side effects such as nausea, headache, myalgias, and hypotension (262). More serious adverse effects include anaphylaxis (particularly in patients with IgA deficiency) (277).

Progesterone

As mentioned earlier, progesterone has known immunosuppressive effects and empiric progesterone supplements for women with a history of recurrent pregnancy loss is a relatively common practice (129–132,136,137). A number of studies using in vitro cellular systems relevant to the maternal–fetal interface have demonstrated that progesterone either inhibits TH1 immunity or causes a shift from TH1- to TH2-type responses that are more favorable for successful pregnancies (136,137,278). Clinical trials evaluating progesterone use in recurrent miscarriage patients show varying results. In 2013, a Cochrane review of multiple studies showed a benefit of progesterone supplementation in women with recurrent pregnancy loss; however, the studies differed in sample size, timing, dose, and type of progesterone supplementation (385). In 2015, Coomarasamy et al. performed a randomized controlled trial of vaginal progesterone in women with three or more first trimester miscarriages. Women were randomized to 400 mg vaginal micronized progesterone twice daily or matched placebo starting with positive pregnancy test but no later than 6 weeks of gestation (386). Similar live birth rates were achieved in the two groups and arguments against routine progesterone use in recurrent pregnancy loss patients could be made despite the late start of progesterone (up to 6 weeks gestation) in some patients. Some research suggests an earlier start to progesterone supplementation is beneficial for outcomes despite the side effects of luteal phase progesterone, including delayed onset of menses, which can be distressing for women trying to conceive (387). Progesterone has been administered intramuscularly and intravaginally for the treatment of recurrent pregnancy loss. It is

thought that vaginal administration may increase local, intrauterine concentrations of progesterone better than systemic administration. Vaginal formulations may provide a better method of attaining local immunosuppressive levels of progesterone while decreasing adverse systemic side effects.

Intralipid Infusion

The relative paucity of inflammatory diseases among the Greenland Inuit population, who consume a diet high in fish oils, led investigators to study the immune modulatory effects of lipid emulsions in total parenteral nutrition preparations for preoperative patients and for burn and trauma victims (279–282). The wide range of demonstrated effects, including lipid preparations that reduced NK cell activity, reduced monocyte proinflammatory cytokine production and increased susceptibility to infection, led investigators to hypothesize, as early as 1994, that lipid infusions might promote an immune environment that would favor pregnancy maintenance (283). Since that time, a small number of publications have addressed the effects of lipid infusions (intralipids) in women with a history of pregnancy loss (284,285). These investigations have demonstrated a decrease in peripheral NK cell activity in women treated with one to three infusions of intralipids. This effect lasted from 4 to 9 weeks after the last infusion (284). The authors did not address NK cell cytokine secretion patterns nor did they assay decidual NK cell function. Despite this paucity of data, intralipid infusions are being administered to recurrent pregnancy loss patients with increasing frequency. The existing data do not support this practice and side effects can include flushing, dizziness, myalgias, nausea, anaphylactic reactions, kidney and liver dysfunction, infection, and thrombosis. Intralipid infusions in recurrent pregnancy loss patients is not recommended clinically and should be administered only under an institutional review board–approved protocol and in a study setting.

TNF-α Inhibition

Interest in the potent proinflammatory cytokine, TNF-α, as a mediator of pregnancy loss came out of the description of the TH1 and TH2 paradigm (125). There have been several publications that link maternal serum TNF-α levels and activating TNF-α gene promoter polymorphisms to recurrent pregnancy loss (286–288). The development of antagonists of TNF-α in the form of blocking antibodies (adalimumab, infliximab) and inhibitory recombinant proteins (etanercept) has permitted successful treatment of several autoimmune disorders, including rheumatoid arthritis, psoriasis, and Crohn disease. Their use has not been associated with universally positive outcomes and may worsen some disorders, including multiple sclerosis (289). These products are associated with rare but worrisome side effects, including liver failure, aplastic anemia, interstitial lung disease, and anaphylaxis (290). Although there exists only a single, small, retrospective, observational, nonrandomly assigned case series that involved treatment of recurrent pregnancy loss patients with inhibitors of TNF-α, these positive

preliminary results have led a growing number of clinics to offer this therapy to patients, often at a significant cost (291). The safety of these compounds in pregnancy has not been appropriately studied and preliminary reports associating exposure to TNF-α inhibitors during early pregnancy to fetal VACTERL syndrome is concerning (292). As with intralipid therapy, use of TNF-**α** inhibition for the treatment of recurrent pregnancy loss should be implemented only under an institutional review board–approved protocol in a study setting and should not generate clinical income.

Other immunoregulating therapies theoretically useful in treating recurrent pregnancy loss include the use of cyclosporine, pentoxifylline, and nifedipine, although maternal and fetal risks with these agents preclude their clinical use. Plasmaphoresis has been used to treat women with recurrent miscarriage and antiphospholipid antibodies (293). Generalized immunosuppression with corticosteroids, such as prednisone, has been advocated during pregnancy for women with recurrent losses and chronic intervillositis and those with recurrent pregnancy loss and APS (294). Although corticosteroids have shown some treatment promise in these patients, maternal and fetal side effects, such as gestational diabetes and intrauterine growth restriction, and the availability of alternative therapies have limited their use (294,295). The efficacy and side effects of prednisone plus low-dose aspirin was examined in a large, randomized, placebo-controlled trial treating patients with autoantibodies and recurrent pregnancy losses. Pregnancy outcomes for treated and control patients were similar; however, the incidence of maternal diabetes and hypertension and the risk of premature delivery were all increased among those treated with prednisone and aspirin (296).

Antithrombotic Therapy

Therapy for patients with recurrent pregnancy losses associated with APS has shifted toward the use of antithrombotic medications. Unlike immunosuppressive treatments, this approach appears to address the effect (hypercoagulability), but not the underlying cause (e.g., genetic, APS) of recurrent pregnancy loss. There are reports that heparin, one typical anticoagulant, may exert direct immunomodulatory effects by binding to antiphospholipid antibodies and may decrease movement of inflammatory cells to sites of alloantigen exposure (297,298). The combined use of low-dose aspirin (75 to 81 mg per day) and subcutaneous unfractionated heparin (5,000 to 10,000 units twice daily) during pregnancy has been best studied among women with APS and appears to be efficacious (299–303). A typical regimen for women with antiphospholipid syndrome would include use of aspirin (81 mg every day) beginning with any attempts to conceive. After pregnancy has been confirmed, 5,000 IU unfractionated sodium heparin is administered subcutaneously twice daily, throughout gestation. Patients using this therapy should be treated in conjunction with a perinatologist because of their increased risks for preterm labor, premature rupture of the membranes, intrauterine growth restriction, intrauterine fetal demise, and preeclampsia. Other potential risks include

gastric bleeding, osteopenia, and abruptio placenta.

Attempts have been made to extend the finding that antithrombotic therapy is efficacious when used to treat patients with APS and recurrent pregnancy loss. These attempts include the use of low–molecular-weight heparins (LMWHs), the use of antithrombotic therapy in non-APS patients with thrombophilia and recurrent pregnancy loss, and even its use among recurrent pregnancy loss patients without thrombophilia (unexplained recurrent losses).

New formulations of heparin, termed LMWHs, have been demonstrated to be superior to unfractionated heparin in the treatment of many clotting disorders (304–306). LMWH has the advantage of an increased antithrombotic ratio when compared with unfractionated heparin. This results in improved treatment of inappropriate clotting with fewer bleeding side effects and LMWH has been associated with a decreased incidence of thrombocytopenia and osteoporosis when compared with its unfractionated counterpart. LMWH has a long half-life and requires less frequent dosing and monitoring, thereby improving patient compliance. **LMWH appears to be safe for use in pregnancy, and has shown promise when combined with low-dose aspirin in the treatment of recurrent pregnancy loss associated with APS** (300,305,307). A few studies have compared the use of unfractionated heparin and aspirin to LMWH and aspirin in the treatment of women with APS and adverse pregnancy outcomes (303,308). The therapies had similar effects in one study (308). A meta-analysis suggested that unfractionated heparin was superior to LMWH, however, there was significant heterogeneity between studies (303).

Anticoagulation for recurrent pregnancy loss patients with thrombophilia but no personal or family history of thrombosis is controversial. Early studies showed efficacy for LMWH treatment for patients with recurrent pregnancy loss associated with other thrombophilias, including activated protein C resistance associated with FVL, mutations in the promoter region of the prothrombin gene, and decreases in protein C and protein S activities (309–311,317). The use of LMWH for this indication appears to have a reassuring safety profile for mother and fetus (307,312,313). Studies and expert groups argue that, despite the biologic plausibility that patients with recurrent pregnancy loss would have a higher chance of inherited thrombophilia and that anticoagulation of patients with these diagnoses would decrease risk of subsequent miscarriage, the evidence does not support the theories (338,341).

The prophylactic use of daily low-dose aspirin has become common practice within the lay public based on its perceived cardiovascular effects combined with its low incidence of side effects. Its sole use in the treatment of recurrent pregnancy loss has likewise gained momentum, and many patients with histories of recurrent loss will either be self-prescribing this therapy or will inquire about its usefulness. There are no good data supporting its use either in patients with heritable thrombophilias or in the general recurrent pregnancy loss population. Although studies are small, the use of low-

dose aspirin alone has not been shown to be effective in the treatment of recurrent pregnancy loss associated with APS (301,314,315). When used in these patients, it should be in combination with unfractionated or LMWH. Large randomized prospective trials examining the empiric use of aspirin alone or in combination with prophylactic doses of heparin have shown no benefit of these therapies in unexplained recurrent pregnancy loss (315). The use of aspirin in early pregnancy has been called into question with reports of an increased incidence of isolated spontaneous pregnancy loss among women who used this medication (213,214). These reports are poorly designed and do not adequately address the level of aspirin exposure 81 mg versus 325 mg. Although reviews have touted the overall safety of aspirin in pregnancy, outside of use in combination with heparin for patients with recurrent pregnancy loss and APS, this medication should be used only with justification in the well-informed patient during early pregnancy (316).

As mentioned previously, vitamins B_6, B_{12}, and folate are important in homocysteine metabolism, and hyperhomocysteinemia is linked to recurrent pregnancy loss in some studies (15,17,27,388). Women with recurrent pregnancy loss and isolated fasting hyperhomocysteinemia should be offered supplemental folic acid (0.4 to 1.0 mg per day), vitamin B_6 (6 mg per day), and possibly vitamin B_{12} (0.025 mg per day) (318–321). Fasting homocysteine levels should be retested after treatment. If levels are normalized or remain only marginally elevated, no further therapy is necessary. Homocysteine levels will predictably decrease during pregnancy.

Treatment of women with recurrent pregnancy loss and an identified inherited or acquired thrombophilia should be based on accompanying history. There are no published large prospective controlled trials examining the benefit of anticoagulation for the prevention of miscarriage in the absence of APS, and, therefore, anticoagulation recommendations for patients with inherited thrombophilias are based on individualized risk of venous thromboembolic events in pregnancy (16).

- **If a venous thromboembolic event occurs during the index pregnancy, posthospitalization management requires therapeutic anticoagulation.**
  UFH: 10,000 to 15,000 U subcutaneous every 8 to 12 hours (monitor to keep aPTT 1.5 to 2.5 times normal) OR
  LMWH: enoxaparin 40 to 80 mg subcutaneous twice a day or dalteparin 5,000 to 10,000 U subcutaneous twice a day). Consider monitoring trough factor Xa levels in the third trimester.
- **If there is a personal history of venous thromboembolic events (particularly in a previous pregnancy or with hormonal contraceptive use) or a strong thrombophilic family history, treat with therapeutic anticoagulation. Thrombotic risk is greatest during the postpartum period.**

- **Anticoagulation should be reinitiated after delivery in doses reflecting predelivery treatment regimens. Postpartum anticoagulation should be continued for 6 to 12 weeks postpartum** (305). Women may continue injectable therapy or transition to oral anticoagulants (e.g., coumarin). Use of heparin or of coumarin derivatives does not prohibit breastfeeding.

Psychological Support

There is no doubt that experiencing isolated and recurrent losses can be emotionally devastating. The risk of major depression is increased greater than twofold among women with spontaneous pregnancy loss; in most women it arises in the first weeks following delivery (322). A caring and empathetic attitude is prerequisite to all healing. Acknowledgment of the pain and suffering couples have experienced because of recurrent miscarriage can be a cathartic catalyst enabling them to incorporate their experience of loss into their lives rather than focusing their lives on their experience of loss (66). **Referrals to support groups and counselors should be offered.** Self-help measures, such as meditation, yoga, exercise, and biofeedback may also be useful.

PROGNOSIS

[7] The prognosis for successful pregnancy depends on the potential underlying cause of pregnancy loss and (epidemiologically) on the number of prior losses. Epidemiologic surveys indicate that the chance of a viable birth even after four prior losses may be as high as 60%. Depending on the study, **the prognosis for successful pregnancy in couples with a cytogenetic etiology for reproductive loss varies from 20% to 80%** (323–325). **Women with corrected anatomical anomalies may expect a successful pregnancy in 60% to 90% of cases** (28,323,326–329). **A success rate higher than 90% has been reported for women with corrected endocrine abnormalities** (324). **Between 70% and 90% of pregnancies reported among women receiving therapy for antiphospholipid antibodies have been viable** (330,331).

Many forms of pre- or postconceptional tests have been proposed to help predict pregnancy outcome (221,332,333,389); **none have been fully substantiated in large, prospective trials. The documentation of fetal cardiac activity on ultrasound may offer prognostic value; however, it appears that its predictions may be greatly affected by any underlying diagnosis.** In one study, the live birth rate following documentation of fetal cardiac activity between 5 and 6 weeks from the last menstrual period was approximately 77% in women with two or more unexplained spontaneous miscarriages (334). It may be important to note that most of the patients in this study had evidence of inappropriate antitrophoblast cellular immunity. Others have shown that 86% of patients with antiphospholipid antibodies and recurrent pregnancy loss had fetal

cardiac activity detected prior to subsequent demise (335). **A prospective, longitudinal, observational study of 325 patients with unexplained recurrent pregnancy losses demonstrated that only 3% of 55 miscarriages occurred following the detection of fetal cardiac activity using transvaginal ultrasonography** (336). The majority of couples with recurrent pregnancy loss will go on to have live birth and reminding patients of this throughout evaluation and treatment can be an invaluable tool for psychological and emotional support through the process.

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SECTION VII

Reproductive Endocrinology & Infertility



CHAPTER 34

Amenorrhea

Valerie L. Baker, Stephanie A. Beall



CHAPTER 35

Endocrine Disorders

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CHAPTER 36

Infertility

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CHAPTER 34

Amenorrhea



Valerie L. Baker, Stephanie A. Beall

Amenorrhea without Secondary Sexual Characteristics
Causes of Primary Amenorrhea
Hypergonadotropic Hypogonadism Associated With Absence of Secondary Sexual Characteristics
Other Causes of Primary Ovarian Failure Without Secondary Sexual Characteristics
Hypogonadotropic Hypogonadism Associated With the Absence of Secondary Sex Characteristics
Genetic Disorders
Other Hypothalamic/Pituitary Dysfunctions
Evaluation of Women With Amenorrhea Associated With the Absence of Secondary Sexual Characteristics
Treatment of Amenorrhea Associated With the Absence of Secondary Sexual Characteristics
Amenorrhea with Secondary Sexual Characteristics and Abnormalities of Pelvic Anatomy
Causes
Outflow and Müllerian Anomalies
Androgen Insensitivity
Ovotesticular Disorder of Sexual Development
Evaluation of Women With Amenorrhea, Normal Secondary Sexual Characteristics, and Suspected Anatomic Abnormalities
Treatment of Women With Amenorrhea, Normal Secondary Sexual Characteristics, and Abnormalities of Pelvic Anatomy
Amenorrhea With Secondary Sexual Characteristics and Normal Pelvic Anatomy
Causes
Polycystic Ovarian Syndrome
Hyperprolactinemia
Primary Ovarian Insufficiency (Premature Ovarian Failure)
Pituitary and Hypothalamic Lesions
Altered Hypothalamic Gonadotropin-Releasing Hormone Secretion
Eating Disorders
Weight Loss and Dieting

Exercise
Stress
Obesity
Other Hormonal Factors
Evaluation for Women With Amenorrhea in the Presence of Normal Pelvic Anatomy and Normal Secondary Sexual Characteristics
Thyroid and Prolactin Disorders
Follicle-Stimulating Hormone Levels
Assessment of the Pituitary and Hypothalamus
Treatment for Women With Amenorrhea in the Presence of Normal Pelvic Anatomy and Normal Secondary Sexual Characteristics
Hirsutism
Ovulation Induction

KEY POINTS

1 Primary amenorrhea is defined as absence of menses at age 13 years when there is no visible development of secondary sexual characteristics or age 15 years in the presence of normal secondary sexual characteristics.

2 Absent or irregular menses may be an indication that a woman has a medical condition that can affect her overall health. The health implications can vary depending on the etiology of the amenorrhea. Therefore, a cause for amenorrhea should be established whenever possible.

3 When gonadal failure occurs in conjunction with primary amenorrhea, it is associated with a high incidence of abnormal karyotype.

4 The most important elements in the diagnosis of amenorrhea include physical examination for secondary sexual characteristics and anatomic abnormalities, measurement of human chorionic gonadotropin (hCG) to rule out pregnancy, serum prolactin and thyroid stimulating hormone (TSH) levels, and assessment of follicle-stimulating hormone (FSH) levels with estradiol to differentiate between hypergonadotropic and hypogonadotropic forms of hypogonadism. It may be helpful to measure anti-müllerian hormone (AMH).

5 Therapeutic measures may include specific therapies (medical or surgical) aimed at correcting the primary cause of amenorrhea, hormone therapy to initiate and maintain secondary sexual characteristics and provide symptomatic relief, treatments to maximize and maintain peak bone mass including hormone therapy, calcium, and vitamin D for women or girls with low circulating estrogen levels, and ovulation induction for patients desiring pregnancy.

6 The anatomic causes of amenorrhea are relatively few, and may be diagnosed by history, physical examination, and imaging.

A complex hormonal interaction must take place in order for normal menstruation to occur. The hypothalamus must secrete gonadotropin-releasing hormone (GnRH) in a pulsatile fashion, which is modulated by neurotransmitters and hormones. The GnRH stimulates secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, which promotes ovarian follicular development and ovulation. A normally functioning ovarian follicle secretes estrogen prior to ovulation. After ovulation, the follicle is converted into a corpus luteum, and progesterone is secreted in addition to estrogen. These hormones stimulate endometrial development and maturation

for embryo implantation. If pregnancy does not occur, estrogen and progesterone secretion decrease and withdrawal bleeding begins. If any of the components (hypothalamus, pituitary, ovary, uterus, and outflow tract) are nonfunctional, bleeding cannot occur.

The mean age of menarche became younger during the previous several decades. Therefore, [1] primary amenorrhea is now defined as the absence of menses by 13 years of age when there is no visible development of secondary sexual characteristics or by 15 years of age in the presence of normal secondary sexual characteristics. The ages defining primary amenorrhea were decreased by 1 year to continue to represent two standard deviations above the mean age of developing secondary sexual characteristics and menses (1). **To detect the cause of primary amenorrhea, it is useful to determine whether secondary sexual characteristics are present (Fig. 34-1). The absence of secondary sexual characteristics indicates that a woman was never exposed to estrogen**. Failure to begin breast development by age 13 always warrants investigation. **[2] Absent or irregular menses may be an indication that a woman has a medical condition that can affect her overall health. The health implications can vary depending on the etiology of the amenorrhea. Therefore, a cause for amenorrhea should be established whenever possible.**

A woman who previously menstruated can develop secondary amenorrhea, which is defined as absence of menstruation for three menstrual cycles or 3 months (2). A woman with regular cycles and a delay of menses of even a week may warrant assessment with a pregnancy test. **It is advisable to evaluate a woman who has fewer than nine cycles per year or cycle length longer than 35 days. With a few exceptions, the causes of primary amenorrhea are similar to the causes of secondary amenorrhea (Fig. 34-2). Therefore, it is important not to overemphasize a distinction between primary and secondary amenorrhea.**

Patients may develop slight alterations in the hypothalamic– pituitary–ovarian axis that are not severe enough to cause amenorrhea but instead cause irregular menses (oligomenorrhea) associated with absent or infrequent ovulation. These patients may bleed excessively during menstruation because estrogen is unopposed. The etiologies of oligomenorrhea overlap with the etiologies of amenorrhea, with the exception that certain anatomic (e.g., absent uterine development) and karyotypic abnormalities (e.g., Turner syndrome), are largely associated with primary amenorrhea.

The World Health Organization (WHO) described three classes of amenorrhea. WHO group I (hypogonadotropic hypogonadism) includes women with no evidence of endogenous estrogen production, normal or low FSH levels, normal prolactin levels, and no lesion in the hypothalamic-pituitary region. WHO group II (normogonadotropic anovulation) is associated with evidence of estrogen

production and normal levels of prolactin and FSH. WHO group III (hypergonadotropic hypogonadism) includes individuals with elevated serum FSH indicating gonadal insufficiency or failure. Not originally included in the classification, a fourth category (hyperprolactinemic anovulation) was added to include women who are anovulatory specifically because of hyperprolactinemia. While not often used clinically, this historic classification system can be helpful in the understanding of the etiology of amenorrhea.

AMENORRHEA WITHOUT SECONDARY SEXUAL CHARACTERISTICS

Disorders associated with hypogonadism may present as primary amenorrhea. **Because breast development is the first sign of estrogen exposure in puberty, patients without secondary sexual characteristics typically have primary, not secondary, amenorrhea** (Fig. 34-1). It is helpful to categorize the causes of amenorrhea in the absence of breast development on the basis of gonadotropin status.

Causes of Primary Amenorrhea

Hypergonadotropic Hypogonadism Associated With Absence of Secondary Sexual Characteristics

Gonadal dysgenesis is a term typically used to describe abnormal development of the gonads, typically resulting in streak gonads. **Gonadal dysgenesis is associated with high levels of LH and FSH** because the gonad fails to produce the steroids and inhibin that would normally feed back to the hypothalamus and pituitary gland to suppress pituitary production of GnRH, LH and FSH. **[3] Karyotypic abnormalities are common in women with primary amenorrhea associated with gonadal failure** (Table 34-1). In one series, approximately 30% of patients with primary amenorrhea had an associated karyotypic abnormality (3). **Turner syndrome (45,X) and its variants represent the most common form of hypergonadotropic hypogonadism in women with primary amenorrhea** (3,4). Other disorders associated with primary amenorrhea include structurally abnormal X chromosomes, mosaicism (e.g., 45,X in some cells and another karyotype such as 46,XX or 46,XXX in other cells), pure gonadal dysgenesis (46,XX and 46,XY individuals with gonadal streaks resulting from lack of gonad development), enzyme deficiencies that prevent normal estrogen production, and gonadotropin-receptor inactivating mutations. Individuals with these conditions have gonadal failure and cannot synthesize ovarian steroids. Gonadotropin levels are elevated because of the lack of negative estrogen feedback on the hypothalamic–pituitary axis. Most patients with these conditions have primary amenorrhea and lack secondary sexual characteristics. Occasionally patients with a

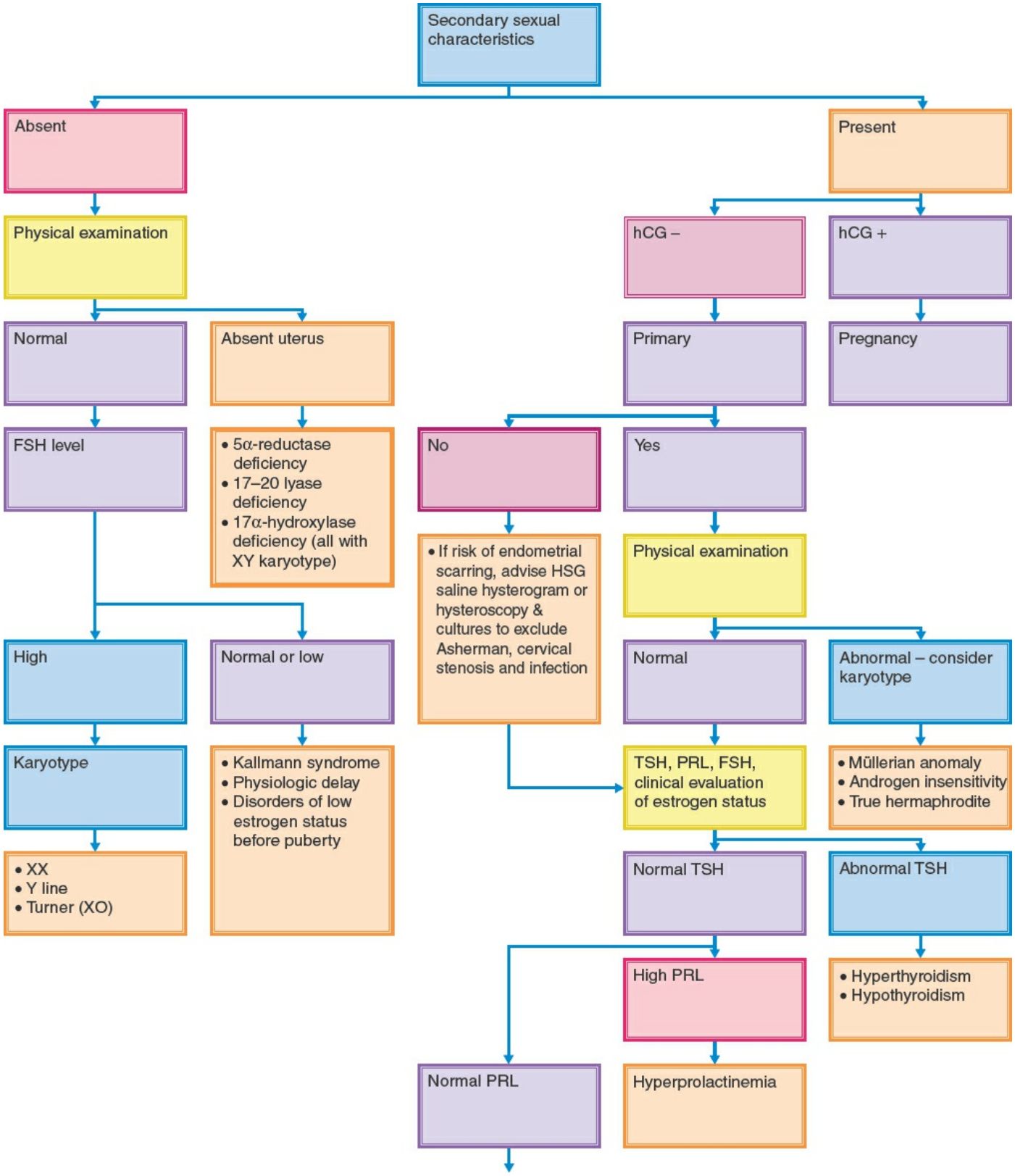
partial deletion of the X chromosome, mosaicism, or pure gonadal dysgenesis (46,XX) may synthesize enough estrogen in early puberty to induce breast development and a few episodes of uterine bleeding and thus have secondary amenorrhea. Ovulation and, occasionally, pregnancy are possible.

Genetic Disorders

Turner Syndrome

Patients with Turner syndrome (45,X) initially have normal ovarian development in utero. Amenorrhea is the result of accelerated atresia of the follicles. The fibrotic ovaries are called streak ovaries.

In addition to gonadal failure, there are associated stigmata with Turner syndrome that include short stature, webbed neck, shield chest, cubitus valgus (increased carrying angle of the arms), low hair line, high-arched palate, multiple pigmented nevi, and short fourth metacarpals (4,5). X inactivation is a process that inactivates most of the genes on one X chromosome. Of the genes on the X chromosome, 20% escape X inactivation, and it is believed that loss of the second copy of these genes in a 45, X patient causes the stigmata associated with Turner syndrome (6). Reports about the relationship between karyotype and dysmorphic features have shown conflicting results, with a general finding of a more severe phenotype associated with monosomy 45X0 compared with a mosaic karyotype (7,8). A Y cell line should be excluded by karyotype, fluorescence *in situ* hybridization, and DNA analysis if necessary (9). Gonadectomy is recommended if a Y cell line is present because of the increased risk of gonadoblastoma and subsequent gonadal germ cell tumors.


Secondary sexual characteristics
Absent
Present
Physical examination
hCG –
hCG +
Normal
Absent uterus
Primary
Pregnancy
FSH level
• 5α-reductase deficiency
• 17–20 lyase deficiency
• 17α-hydroxylase deficiency (all with XY karyotype)
No
Yes
• If risk of endometrial scarring, advise HSG saline hysterogram or hysteroscopy & cultures to exclude Asherman, cervical stenosis and infection
Physical examination
High
Normal or low
Normal
Abnormal – consider karyotype
Karyotype
• Kallmann syndrome
• Physiologic delay
• Disorders of low estrogen status before puberty
TSH, PRL, FSH, clinical evaluation of estrogen status
• Müllerian anomaly
• Androgen insensitivity
• True hermaphrodite
• XX
• Y line
• Turner (XO)
Normal TSH
Abnormal TSH
High PRL
• Hyperthyroidism
• Hypothyroidism
Normal PRL
Hyperprolactinemia

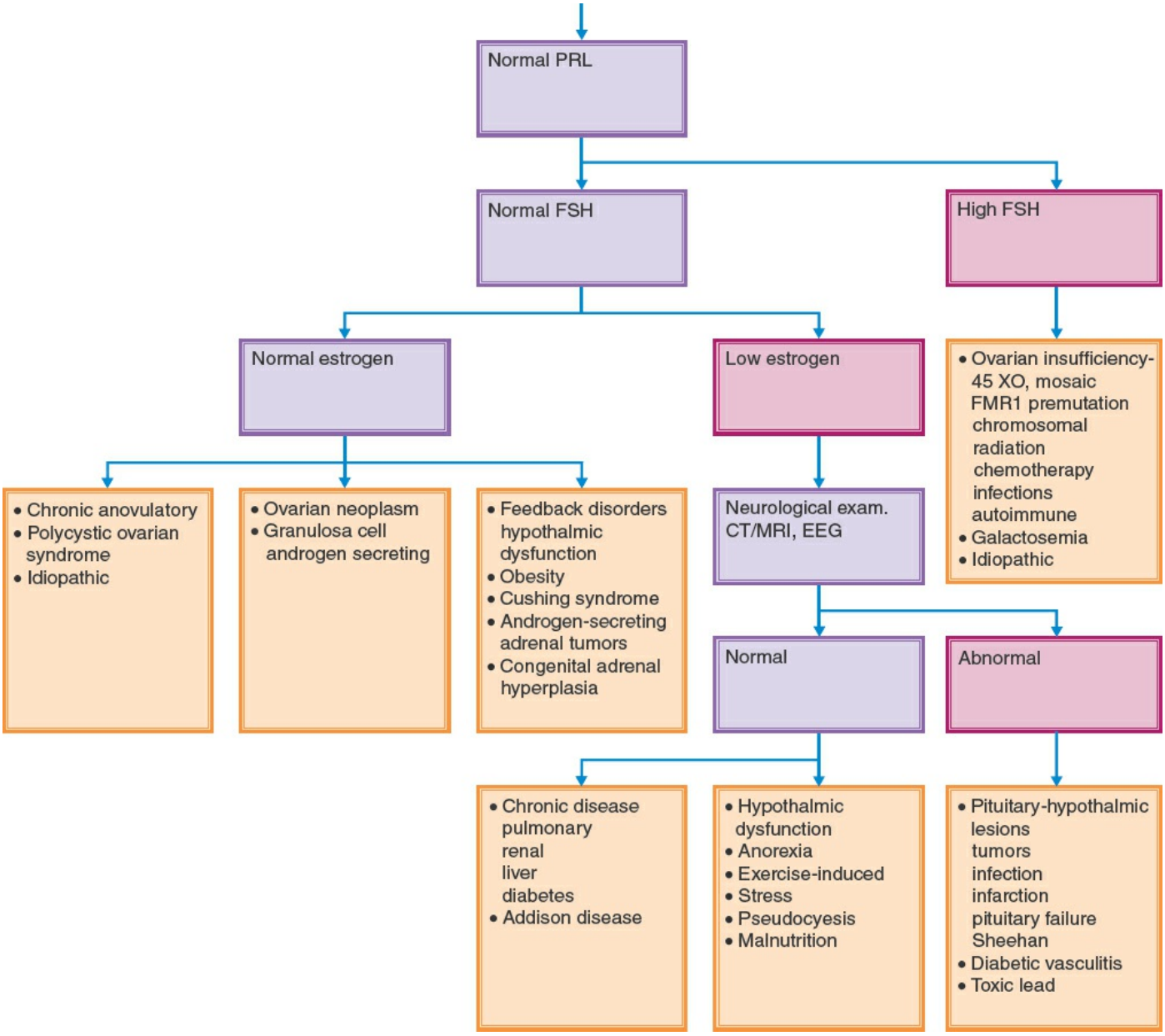


FIGURE 34-1 Decision tree for evaluation of amenorrhea. FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; HSG, hysterosalpingogram; TSH, thyroid-stimulating hormone; PRL, prolactin; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram; SHG, saline hysterogram (also known as saline infusion sonogram).

After the diagnosis of Turner syndrome is confirmed by karyotype, studies should be performed to ensure that cardiac (30% have coarctation of the aorta), renal (especially horseshoe kidney), and autoimmune (thyroiditis) abnormalities are diagnosed and treated. Evaluation should be performed in childhood to identify potential attention-deficit or nonverbal learning disorders. **Women with Turner syndrome should be screened for diabetes mellitus, aortic enlargement, hypertension, and hearing loss throughout their lives** (5,8).

Abnormal X Chromosome

Those 46,XX individuals with partial deletions of the X chromosome have variable phenotypes, probably depending on the amount and location of the missing genetic material. Smaller X chromosome deletions cause distinct features which overlap with features of Turner syndrome, but women with these smaller deletions are not considered to be within the definition of Turner syndrome (8). The pseudoautosomal region of the short arm of the X chromosome escapes X inactivation, thus resulting in two copies remaining transcriptionally active. The effective monosomy created by the deletion of Xp is thought to lead to some of the phenotypic features of Turner syndrome (6). The short stature homeobox (SHOX) gene is located in the distal region of Xp, with deletion directly associated with short stature and skeletal deformities. However, women and girls with a small distal deletion of the short arm of the X chromosome do not appear to be at higher risk for cardiac anomalies or ovarian failure, which are often present in women with Turner syndrome and a 45,X karyotype. Most patients with a ring X have ovarian failure and some phenotypic features similar to Turner syndrome, although some are able to reproduce successfully. These patients differ from those with Turner syndrome in that they are more likely to have intellectual disability. Patients with isochrome of the long arm of the X chromosome (i[Xq]) are similar to XO patients, with the exception that autoimmune disorders are more common. A balanced translocation of the X chromosome to an autosome may lead to gonadal failure (10). Gonadal failure can be caused by the chromosomal break occurring in a gene that is required for ovarian function, abnormal meiosis, or X inactivation of the translocated X and adjacent autosomal genes (6,10). Despite these and other reported associations between karyotype and phenotype, it is important to emphasize that a specific karyotype does not always predict phenotype (8).

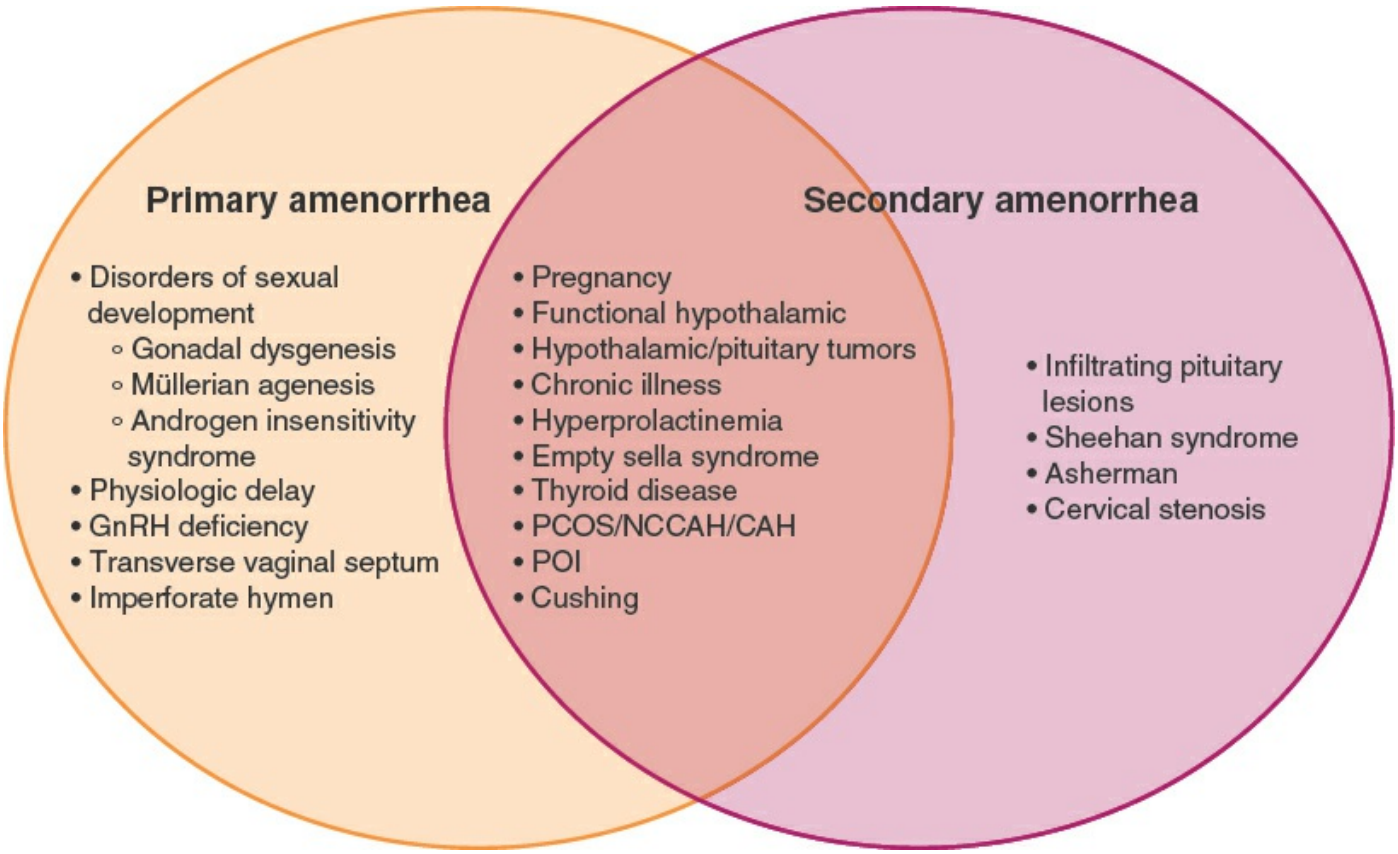


FIGURE 34-2 Schematic illustrating the overlap of the causes of primary and secondary amenorrhea.

Table 34-1 Amenorrhea Associated With a Lack of Secondary Sexual Characteristics

Abnormal pelvic examination
5α-reductase deficiency, 17,20-lyase deficiency, or 17α-hydroxylase deficiency in XY individual
Congenital lipoid adrenal hyperplasia
Luteinizing hormone receptor defect
Hypergonadotropic hypogonadism
Gonadal dysgenesis
Follicle-stimulating hormone receptor defect
Partial deletion of X chromosome
Sex chromosome mosaicism
Environmental and therapeutic ovarian toxins
17α-hydroxylase deficiency in XX individual
Galactosemia
Congenital lipoid adrenal hyperplasia in XX individual

Hypogonadotropic hypogonadism
Physiologic delay
Kallmann syndrome
Central nervous system tumors
Hypothalamic/pituitary dysfunction

Mosaicism

Primary amenorrhea is associated with various mosaic states, the most common of which is 45,X/46,XX (11). The clinical findings in 45,X/47,XXX and 45,X/46,XX/47,XXX are similar to those in 45,X/46,XX and vary in estrogen and gonadotropin production, depending on the number of follicles which ultimately survive in the gonads. When compared with the pure 45,X cell line, individuals with 45,X/46,XX are taller and have fewer abnormalities, although many of those with 45,X/46,XX mosaics are shorter than their peers.

Pure Gonadal Dysgenesis

Individuals who are phenotypically female with sexual infantilism, primary amenorrhea, normal stature, and no karyotypic abnormalities (46,XX or 46,XY) have pure gonadal dysgenesis. The gonads are usually streaks, but there may be some development of secondary sexual characteristics, and a few episodes of uterine bleeding. Pure gonadal dysgenesis in a 46,XY individual (previously known as Swyer syndrome) can occur when mutations in the SRY (sex-determining region gene on the Y chromosome) located at Yp11 result in XY females without proper gonad development (12,13). Mutations in many other genes such as SOX9, DAX1, WT1, and SF1, which affect testicular differentiation and inhibit anti-müllerian hormone production, result in XY pure gonadal dysgenesis (14).

With XX gonadal dysgenesis, the condition is likely to be caused by gene mutations that lead to ovarian insufficiency before pubertal development or after the development of secondary sexual characteristics. Perrault syndrome is a rare autosomal recessive disease with pure gonadal dysgenesis (46,XX) and sensorineural hearing loss (15). XX pure gonadal dysgenesis can be caused by the presence of small Y chromosome fragments in the genome. If Y sequences are present, gonadectomy is recommended.

Mixed Gonadal Dysgenesis

Most patients with mixed gonadal dysgenesis are XY and have ambiguous genitalia with a streak gonad on one side and a malformed testis on the opposite. A small proportion of these patients have mutations in the *SRY* gene.

Rare Enzyme Deficiencies

Congenital Lipoid Adrenal Hyperplasia

Patients with this autosomal recessive disorder are unable to convert cholesterol to pregnenolone, which is the first step in steroid hormone biosynthesis. The initial rate-limiting step in steroidogenesis is the transport of cholesterol from the outer to the inner mitochondrial membrane facilitated by steroidogenic acute regulatory protein (StAR). 48 different mutations have been identified in the StAR (16). Once in the mitochondria, cholesterol is cleaved by the p450scc enzyme. Several cases of p450scc deficiency have been reported (17). These patients present in infancy with hyponatremia, hyperkalemia, and acidosis. Both XX and XY individuals have external female genitalia, however 46 XY patients do not have a uterus and without hormone replacement they will remain sexually infantile. XX patients may acquire secondary sexual characteristics at puberty but develop large ovarian cysts and early ovarian failure (18). Genetic clusters of the disorder are found in the Japanese, Korean, and Palestinian Arab populations. With appropriate mineralocorticoid and glucocorticoid replacement, these patients can survive into adulthood.

17α-Hydroxylase and 17,20-Lyase Deficiency

Mutations in the *CYP17* gene cause abnormalities in the 17α-hydroxylase and 17,20-lyase functions of the protein that is active in the adrenal and gonadal steroidogenic pathways. Over 100 mutations that alter the reading frame of the gene have been associated with combined 17-hydroxylase/17,20-lyase deficiency (19). Patients have either 46,XX or 46,XY karyotypes. The uterus is absent in individuals with 46,XY karyotype, a feature distinguishing them from individuals with the 46,XX karyotype. Individuals with CYP17 mutations have primary amenorrhea, no secondary sexual characteristics, female phenotype, hypertension, and hypokalemia (19). The diminished levels of 17α-hydroxylase that characterize this disorder lead to a reduction in cortisol production, which in turn causes an increase in adrenocorticotropic hormone (ACTH). 17α-hydroxylase is not required for production of mineralocorticoids; thus, excessive amounts of mineralocorticoid are produced, resulting in sodium retention, loss of potassium, and hypertension. **Patients with 17α-hydroxylase deficiency have primordial follicles, but gonadotropin levels are elevated because the enzyme deficiency prevents synthesis of sex steroids.**

Aromatase Deficiency

This very rare autosomal recessive abnormality prevents the affected individual from aromatizing androgens to estrogen (20). This syndrome may be suspected even before birth because most mothers of affected children become virilized during pregnancy. This occurs because the placenta cannot convert the fetal androgens to estrogen and they diffuse into the maternal circulation. At birth, a female child has clitoromegaly and posterior labioscrotal fusion (ambiguous genitalia). At puberty, there is no breast development, primary amenorrhea, worsening virilization, absent growth spurt, delayed

bone age, and multicystic ovaries. The diagnostic hormonal pattern consists of an elevation of FSH, LH, testosterone, and dehydroepiandrosterone sulfate (DHEAS) levels, and undetectable levels of estradiol. Estrogen therapy improves the ovarian and skeletal abnormalities but must be titrated to mimic normal estrogen levels. Estrogen administration should be minimal during childhood and increased at puberty (21).

Galactosemia

In girls, galactosemia often is associated with ovarian failure, but this condition usually is detected by newborn screening programs. A galactose-1-phosphate uridyltransferase level can be measured to assess the patient for galactosemia or carrier status (22).

Rare Gonadotropin Receptor Mutations

Luteinizing Hormone Receptor Mutation

Inactivation of LH receptors is identified in XY patients who have disorders of sexual development (DSD) with primary amenorrhea in the absence of secondary sexual characteristics caused by homozygous premature stop codon, deletions, and missense mutations in the LHR gene located on chromosome 2. The Leydig cells in these individuals are unable to respond to LH, causing Leydig cell hypoplasia. This leads to early testicular failure and prevents masculinization. XX siblings with the same mutations develop normal secondary sexual characteristics but are amenorrheic with elevated LH levels, normal FSH levels, and cystic ovaries (23,24).

Follicle-Stimulating Hormone Receptor Mutation

An autosomal recessive single amino acid substitution in the extracellular domain of the FSH receptor, which prevents FSH binding, was identified in six families in Finland. This condition leads to primary or early secondary amenorrhea, variable development of secondary sexual characteristics, and high levels of FSH and LH (25). A novel homozygous mutation in the FSH receptor gene leading to primary ovarian insufficiency (POI) has been reported (26).

Other Causes of Primary Ovarian Failure Without Secondary Sexual Characteristics

Severe damage to the ovaries before the onset of puberty can lead to ovarian insufficiency and failure to develop secondary sexual characteristics. Ovarian dysfunction can occur in association with irradiation of the ovaries, chemotherapy with alkylating agents (e.g., *cyclophosphamide*), or combinations of radiation and other chemotherapeutic agents (27). Other causes of premature ovarian failure (also known as POI) are more commonly associated with amenorrhea after the development of secondary sexual characteristics, as described below.

Hypogonadotropic Hypogonadism Associated With the Absence of Secondary Sex Characteristics

Primary amenorrhea resulting from hypogonadotropic hypogonadism occurs when the hypothalamus fails to secrete adequate amounts of GnRH or when a pituitary disorder associated with inadequate production or release of pituitary gonadotropins is present.

Physiologic Delay

Physiologic or constitutional delay of puberty is the most common manifestation of hypogonadotropic hypogonadism. Amenorrhea may result from the lack of physical development caused by delayed reactivation of the GnRH pulse generator. Levels of GnRH are functionally deficient in relation to chronologic age but normal in terms of physiologic development.

Kallmann Syndrome

The second most common hypothalamic cause of primary amenorrhea associated with hypogonadotropic hypogonadism is insufficient pulsatile secretion of GnRH (Kallmann syndrome), which has varied modes of genetic transmission. Insufficient pulsatile secretion of GnRH leads to deficiencies in FSH and LH (28). Kallmann syndrome is often associated with anosmia (inability to perceive odors), although a woman may not be aware of her impaired sense of smell. The hypogonadism and anosmia arise because of failure of proper neuronal migration during fetal development.

Other Causes of Gonadotropin-Releasing Hormone Deficiency

Deficiencies in GnRH may be caused by developmental or genetic defects, inflammatory processes, tumors, vascular lesions, or trauma. **Central nervous system (CNS) tumors that lead to primary amenorrhea, the most common of which is craniopharyngioma, are usually extracellular masses that interfere with the synthesis and secretion of GnRH or stimulation of pituitary gonadotropins.** Virtually all of these patients have disorders in the production of other pituitary hormones and LH and FSH (29,30). Prolactin-secreting pituitary adenomas are rare in childhood and more commonly occur after development of secondary sexual characteristics.

Genetic Disorders

5α-Reductase Deficiency

The possibility of 5α-reductase deficiency should be considered in the evaluation of amenorrhea. 5α-Reductase converts testosterone to its more potent form, dihydrotestosterone which is the hormone responsible for triggering masculinization of the male external genitalia during early sexual development (31). Patients with 5α-reductase deficiency are genotypically XY with ambiguous genitalia, frequently experience virilization at puberty, have testes (because of functioning Y chromosomes), and have no müllerian structures as a result of functioning AMH. **Patients with 5α-reductase deficiency differ from patients with androgen insensitivity because they**

do not develop breasts at puberty (Fig. 34-3). These patients have low gonadotropin levels as a result of testosterone levels that are sufficient to suppress breast development and allow normal feedback mechanisms to remain intact. Normal male differentiation of the urogenital sinus and external genitalia do not occur because dihydrotestosterone is required for this development. Normal internal male genitalia derived from the wolffian ducts are present because this development requires only testosterone. Male pattern hair growth, muscle mass, and voice deepening are testosterone dependent.

Gonadotropin-Releasing Hormone Receptor Mutations

Mutations have been identified in the GnRH receptor gene, which lead to abnormal GnRH function (32). Most affected patients are compound heterozygotes, but homozygous autosomal recessive mutations have been identified. The GnRH receptor is a G-protein–coupled receptor. Functional studies show that the mutations cause marked decrease in binding of GnRH to its receptor or prevent second messenger signal transduction. Without a functional signal transduction, FSH and LH are not stimulated and are unable to promote follicular growth. All patients are normosomic.

Follicle-Stimulating Hormone Deficiency

Patients with FSH deficiency usually seek treatment for delayed puberty and primary amenorrhea associated with hypoestrogenism. Patients with this rare disorder are distinguished from other hypoestrogenic patients by having decreased FSH levels and increased LH levels. These patients have low serum androgen levels despite the abnormal LH-to-FSH ratio, indicating that FSH-stimulated follicular development is a prerequisite for thecal cell androgen production. In some of these patients, autosomal recessive mutations in the FSHβ subunit, which impair dimerization of α and β subunits and prevent binding to the FSH receptor, have been identified (33). Pregnancy has been reported after induction of ovulation with injectable gonadotropins (34).

Other Hypothalamic/Pituitary Dysfunctions

Functional gonadotropin deficiency results from malnutrition, malabsorption, weight loss or anorexia nervosa, excessive exercise, chronic disease, neoplasia, and marijuana use, although these conditions are more commonly associated with amenorrhea accompanied by secondary sexual characteristics that developed before the onset of the problem (35,36). **Hypothyroidism, polycystic ovarian syndrome (PCOS), Cushing syndrome, hyperprolactinemia, and infiltrative disorders of the CNS are more commonly associated with amenorrhea in the presence of development of secondary sexual characteristics, but have been reported to lead to amenorrhea accompanied by delayed puberty** (37,38). **Constitutional delay without underlying causes is less common in girls than in boys,**

and the reason for lack of development should be vigorously pursued.

Evaluation of Women With Amenorrhea Associated With the Absence of Secondary Sexual Characteristics

A careful history and physical examination are necessary to appropriately diagnose and treat primary amenorrhea associated with hypogonadism. The physical examination may be particularly helpful in patients with Turner syndrome. A history of short stature but consistent growth rate, a family history of delayed puberty, and normal physical findings (including assessment of smell, optic discs, and visual fields) may suggest physiologic delay. Headaches, visual disturbances, short stature, symptoms of diabetes insipidus, and weakness of one or more limbs suggest CNS lesions (39). Galactorrhea may be seen with prolactinoma, a condition more commonly associated with secondary amenorrhea in the presence of normal secondary sexual characteristics.



FIGURE 34-3 A well-developed patient with complete androgen insensitivity. Note the characteristic paucity of pubic hair and well-developed breasts. (From S**ouhail R, Amine S, Nadia A, et al**. Complete androgen insensitivity syndrome or testicular feminization: Review of literature based on a case report. Pan Afr Med J 2016;25:199. Figure 1 used with permission.)

The diagnostic workup for primary amenorrhea is summarized as follows:

[4] The initial laboratory test should be assessment of serum FSH and LH levels unless the history and physical examination suggest otherwise to differentiate hypergonadotropic and hypogonadotropic forms of hypogonadism. If the FSH level is elevated, a karyotype should be obtained. An elevated FSH level in combination with a 45,X karyotype confirms the diagnosis of Turner syndrome. Partial deletion of the X chromosome, mosaicism, pure gonadal dysgenesis, and mixed gonadal dysgenesis are diagnosed by obtaining a karyotype.

1. **Because of the association with coarctation of the aorta (up to 30%) and thyroid dysfunction, patients with Turner syndrome should undergo echocardiography every 3 to 5 years and thyroid function studies yearly. Cardiac MRI is considered an important component of the cardiac evaluation** (5,8). Patients with Turner syndrome should be evaluated for hearing loss, renal malformations, diabetes, and hypertension.
2. **If the karyotype is abnormal and contains the Y chromosome, as in gonadal dysgenesis, the gonads should be removed to prevent tumors** (14).
3. **If the karyotype is normal and the FSH level is elevated, it is important to consider the diagnosis of 17α-hydroxylase deficiency because it may be a life-threatening disease if untreated.** The characteristic symptoms of 17α-hydroxylase deficiency include hypertension, hypokalemia, and abnormal sexual development. The hormone imbalances include an elevated serum progesterone (>2.0 ng/mL) level, a low to normal 17α-hydroxyprogesterone (10 to 100 ng/mL) level, an elevated serum 11-deoxycorticosterone (100 to 1,000 ng/dL) level, an elevated corticosterone (4,000 to 40,000 ng/dL), and low levels of cortisol, DHEAs, testosterone, and estradiol (19,40). The diagnosis is confirmed with an ACTH stimulation test. After ACTH bolus administration, affected individuals have markedly increased levels of corticosterone and 11-deoxycorticosterone compared with baseline levels and no change in serum 17α-hydroxyprogesterone levels.
4. **If the screening FSH level is low, the diagnosis of hypogonadotropic hypogonadism is established. CNS lesions should be ruled out by imaging using computed tomography (CT) or MRI, especially if galactorrhea, headaches, or visual field defects are identified.** Pituitary adenomas account for over 80% of all sellar and parsellar lesions (41). Rathke cleft cyst, craniopharyngioma, and meningioma are the most common nonadenomatous sellar masses. CNS malignancy and cancer metastases can impact pituitary function and result in hypogonadotropic hypogonadism.
5. **Physiologic delay is a diagnosis of exclusion that is difficult to distinguish from insufficient GnRH secretion.** The diagnosis can be supported by a history suggesting physiologic delay, an x-ray showing delayed bone age, and the absence of

a CNS lesion on CT or MRI scanning.

Treatment of Amenorrhea Associated With the Absence of Secondary Sexual Characteristics

[5] Individuals with primary amenorrhea associated with all forms of gonadal failure and hypergonadotropic hypogonadism need cyclic estrogen and progestogen therapy to initiate, mature, and maintain secondary sexual characteristics. Prevention of osteoporosis is an additional benefit of estrogen therapy:

1. **Therapy is usually initiated with 0.3 to 0.625 mg per day of oral *conjugated estrogens* or 0.5 to 1 mg per day of oral *estradiol*.**
2. **If the patient is short in stature, higher doses should not be used because premature closure of the epiphyses should be avoided.** Most of these patients are of normal height, and higher *estrogen* doses may be used initially and reduced to the maintenance doses after several months.
3. **Estrogen can be given daily in combination with progestogen (*medroxyprogesterone acetate* or *progesterone*) to prevent hyperplasia that could result from unopposed estrogen stimulation of the endometrium in patients with a uterus.** *Medroxyprogesterone* acetate may be administered at a dose of 2.5 mg daily every day of the month or 5 to 10 mg for 12 to 14 days per month. Oral micronized *progesterone* may be administered at a daily dose 100 mg every day of the month or 200 mg daily for 12 to 14 days per month. Cyclic hormone therapy (with 12 to 14 days of *progestogen* per month) more closely mimics the natural menstrual cycle. Progesterone vaginal suppositories may be administered at a dose of 50 mg daily or 100 mg for 12 to 14 days monthly. Progesterone bioadhesive vaginal gel is another option indicated for the treatment of secondary amenorrhea, with a starting dose of 4% (45 mg), and possible increase to 8% (90 mg) for women who have failed to respond to the 4% dose, both used in a cyclic fashion.
4. **Occasionally, individuals with mosaicism and gonadal streaks may ovulate and be able to conceive either spontaneously or after the institution of *estrogen* therapy.**
5. **If 17α-hydroxylase deficiency is confirmed, treatment is instituted with corticosteroid replacement and** estrogen. *Progestogen* should be added to protect the endometrium from hyperplasia.

[5] If possible, therapeutic measures are aimed at correcting the primary cause of amenorrhea:

1. **Craniopharyngiomas may be resected with a transsphenoidal approach or during craniotomy,** depending on the size of the tumor. Studies show similar survival rates with limited tumor removal followed by adjuvant radiotherapy compared to radical gross total resection with an improved quality of life after treatment (42,43).
2. **Germinomas are highly sensitive to radiation and chemotherapy, therefore surgery is rarely indicated** (44).
3. **Prolactinomas and hyperprolactinemia often may respond to dopamine agonists (*bromocriptine* or *cabergoline*)** (45).
4. **Specific therapies are directed toward malnutrition, malabsorption, weight loss, anorexia nervosa, exercise amenorrhea, neoplasia, and chronic diseases.** Logically, it would appear that patients with hypogonadotropic hypogonadism of hypothalamic origin should be treated with long-term administration of pulsatile *GnRH*. This form of therapy is impractical because it requires the use of an indwelling catheter and a portable pump for prolonged periods and there is a lack of availability of this equipment in the United States. The primary focus of treatment should be to correct the underlying problem that is causing the menstrual dysfunction (e.g., malnutrition). **For individuals with anorexia, intensive treatment to achieve weight gain and emotional well-being is preferable to long-term treatment with hormone therapy** (46). If a patient is unable to correct the underlying condition, she may be treated with cyclic *estrogen* and *progestogen* therapy at least until sexual maturity is achieved. When sexual maturation is achieved, hormone therapy can be continued to treat hypoestrogenic symptoms until the underlying disorder leading to amenorrhea can be adequately treated.
5. **Patients with Kallmann syndrome, and patients with other etiologies for hypothalamic amenorrhea, can be treated with hormone replacement.**
6. **If the patient has physiologic delay of puberty, the only management required is reassurance** that the anticipated development will occur eventually.

Individuals whose karyotypes contain a Y cell line (45,X/46,XY mosaicism, or pure gonadal dysgenesis 46,XY) are predisposed to gonadal ridge tumors, such as gonadoblastomas, dysgerminomas, and yolk sac tumors. The gonads of these individuals should be removed when the condition is diagnosed to prevent malignant transformation. There is some evidence that hirsute individuals without Y chromosomes should undergo gonad removal. One patient with hirsutism and the karyotype 45,X was noted to have a streak gonad; the contralateral gonad was dysgenic and contained developing follicles, well-differentiated seminiferous tubules, and Leydig cells. This patient was found to be HY antigen–positive (47).

Clomiphene citrate is often ineffective for inducing ovulation in patients with

hypogonadism who desire pregnancy because such patients are hypoestrogenic. In patients with hypogonadism, ovulation induction with injectable gonadotropins is generally successful. In patients without ovarian function, oocyte donation may be appropriate. **There are reports of death in pregnant patients with Turner syndrome resulting from aortic dissection and rupture** (48,49). Careful counseling and investigation should be undertaken in patients with Turner syndrome before treating them with donated oocytes.

AMENORRHEA WITH SECONDARY SEXUAL CHARACTERISTICS AND ABNORMALITIES OF PELVIC ANATOMY

Causes

Outflow and Müllerian Anomalies

[6] Primary amenorrhea is caused by a congenital abnormality of the female reproductive organs in approximately 20% of cases. Amenorrhea occurs if there is blockage of the outflow tract, if the outflow tract is missing, or if there is no functioning uterus (Table 34-2). Most women with müllerian abnormalities will have normal ovarian function and thus will have normal secondary sexual characteristic development.

Transverse Blockages

Any transverse blockage of the müllerian system will cause amenorrhea. Such outflow obstructions include imperforate hymen, transverse vaginal septum, and absence of the cervix or vagina. Transverse blockage of the outflow tract with an intact endometrium frequently causes cyclic pain without menstrual bleeding in adolescents. The blockage of blood flow can cause hematocolpos, hematometra, or hemoperitoneum, and endometriosis.

Müllerian Anomalies

Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome includes vaginal agenesis with variable development of the uterus accompanied in some cases by renal, skeletal, and auditory abnormalities (50,51). Karyotype is 46,XX. Müllerian agenesis accounts for approximately 10% to 15% of cases of primary amenorrhea (2). Two subtypes are recognized: (1) isolated müllerian aplasia; and (2) müllerian anomaly accompanied by other anomalies which may include renal malformations (such as an absent, pelvic, horseshoe kidney, or double urinary collecting system) skeletal abnormalities, congenital heart defects, and hearing impairment. The exact cause of MRKH syndrome remains largely unknown (52). One study demonstrated a low

prevalence of mutations in two known causative genes (WNT4 and HNF1B), but found copy number variants (CNVs) in certain regions that may be involved (53). Other promising candidate genes and the possibility of epigenetic changes will require further study before any conclusions can be drawn.

Table 34-2 Anatomic Causes of Amenorrhea

Secondary sexual characteristics present
Müllerian anomalies
Imperforate hymen
Transverse vaginal septum
Mayer–Rokitansky–Küster–Hauser syndrome
Androgen insensitivity
Ovotesticular disorder
Absent endometrium
Asherman syndrome
Secondary to prior uterine or cervical surgery
Curettage, especially postpartum
Cone biopsy/ loop electroexcision procedure
Secondary to infections
Pelvic inflammatory disease
Tuberculosis
Schistosomiasis

Absence of Functioning Endometrium

Amenorrhea may occur if there is no functioning endometrium. When the findings of the physical examination are normal, anatomic abnormalities of the uterine cavity should be considered. A congenitally absent endometrium is a rare finding in patients with primary amenorrhea (54). **Intrauterine adhesions, referred to as Asherman syndrome, is more common with secondary amenorrhea or hypomenorrhea**. Adhesions typically result from endometrial trauma during a surgical procedure, but may also result from infection. The most common cause of Asherman syndrome is uterine curettage for pregnancy-related complications (55). Adhesions can develop following myomectomy, curettage of the nongravid uterus, infections related to use of an intrauterine device, tuberculosis, and schistosomiasis. Cervical stenosis resulting from

surgical removal of dysplasia (cone biopsy, loop electroexcision procedure) may lead to amenorrhea.

Androgen Insensitivity

Phenotypic females with complete congenital androgen insensitivity (previously called testicular feminization) have breast development, little or no axillary and pubic hair, and primary amenorrhea (Fig. 34-3) (56). **Genotypically, they are male (XY) but have a defect that prevents normal androgen receptor function, leading to the development of the female external phenotype. The testes, often palpable in the inguinal area or labia, produce müllerian-inhibiting substance that induces the regression of the müllerian structures (fallopian tubes, uterus and upper 1/3 of the vagina). Serum testosterone is in the normal male range.**

The gene for the androgen receptor is located on the X chromosome and inheritance is X-linked recessive. Defects in the androgen receptor gene include complete absence of the gene and mutations that disrupt the binding domains of the receptor. Androgen receptor deficits are diverse and may result from diminished receptor function or concentration. **The diagnosis of this disorder is based on physical examination, serum testosterone concentration, and karyotype. On physical examination, the patients have a blind vaginal pouch, scant or absent axillary and pubic hair, and** breast development at puberty. The breasts, however, have pale areolae and the nipples are immature. At puberty, the conversion of testosterone to estrogen stimulates breast growth. Patients are unusually tall with eunuchoidal tendency (long arms with big hands and feet). The testes should be removed after puberty because of the increased risk of developing testicular cancer (2% to 5%). Research suggests that gonadectomy may be deferred until adulthood because of the low risk of malignancy (57).

Ovotesticular Disorder of Sexual Development

Ovotesticular disorder of sexual development is a rare condition that should be considered as a possible cause of amenorrhea (58). **Both male and female gonadal tissues are present in these patients. Both müllerian and wolffian structures are present and correspond to the ipsilateral gonad.** Genotypes are variable with the majority being 46,XX, with the remaining mosaic and 46,XY. Patients with 46,XX karyotype may menstruate. The external genitalia usually are ambiguous, and breast development frequently occurs in these individuals.

Evaluation of Women With Amenorrhea, Normal Secondary Sexual Characteristics, and Suspected Anatomic Abnormalities

[6] Most congenital abnormalities can be diagnosed by physical examination. In the evaluation of primary amenorrhea, the single most important step is to determine if

the uterus is present. In addition, the vagina and cervix should be examined. Ultrasonography or MRI is useful to identify the müllerian anomaly when the abnormality cannot be found by physical examination. The patient should be examined for skeletal malformations and assessed with intravenous pyelography or renal ultrasound to detect concomitant renal abnormalities.

1. **An imperforate hymen can be differentiated from other transverse blockages by the finding of a perirectal mass that protrudes from the introitus with Valsalva.**
2. **It is difficult to differentiate a transverse septum or complete absence of the cervix and uterus in a female from a blind vaginal pouch in a genotypic male (46,XY) with female sex reversal caused by androgen insensitivity syndrome. Androgen insensitivity is likely when pubic and axillary hair is absent.** To confirm the diagnosis, a karyotype determination should be performed to see whether a Y chromosome is present. In some patients, the defect in the androgen receptor is not complete and virilization occurs.
3. **A congentially absent endometrium is an outflow tract abnormality that cannot be diagnosed by physical examination in a patient with primary amenorrhea.** This abnormality is very rare and is seen in a patient who has normal physical findings (normal vagina, cervix, and uterus), and a normal endocrine evaluation. Although in most cases performance of the progestogen challenge test is not recommended, this test may be of value to confirm the rare diagnosis of congenitally absent endometrium. In this case, progestogen can be administered to a woman who appears to have normal estrogen production (or if estrogen status is questioned, 2.5 mg *conjugated estrogen* or 2 mg *micronized estradiol* can be given for 25 days with 5 to 10 mg of *medroxyprogesterone acetate* added for the last 10 days). Congenital absence of the endometrium is confirmed if no bleeding occurs with this regimen in a patient with primary amenorrhea and no physical abnormalities. Transvaginal ultrasound to assess endometrial thickness may be helpful, with a thickened endometrial lining indicating endometrial response to estrogen. Hysteroscopy with endometrial biopsy should be performed to confirm the diagnosis (54).
4. ***Asherman syndrome* cannot be diagnosed by physical examination. It is diagnosed by performing hysterosalpingography, saline infusion sonography (also known as saline hysterogram), or hysteroscopy.** These tests will show either complete obliteration or multiple filling defects caused by synechiae. If tuberculosis or schistosomiasis is suspected, endometrial cultures should be performed.

Treatment of Women With Amenorrhea, Normal Secondary Sexual Characteristics, and Abnormalities of Pelvic Anatomy

The treatment of congenital anomalies can be summarized as follows:

1. **Treatment of an imperforate hymen involves making a cruciate incision to open the vaginal orifice.** Most imperforate hymens are not diagnosed until a hematocolpos forms. It is unwise to place a needle into a hematocolpos without completely removing the obstruction because a pyocolpos may occur.
2. **If a transverse septum is present, surgical removal is required.** Forty-six percent of transverse septa occur in the upper third of the vagina, and 40% occur in the middle third of the vagina (59). Vaginal dilators should be used to distend the vagina until it is healed to prevent vaginal adhesions and prevent reobstruction (60,61). Patients have a fully functional reproductive system after surgery. Early studies suggested that patients with a repaired complete transverse septum in the middle or upper vagina may have an increased risk of infertility, but other studies have demonstrated normal conception rates following surgical repair (62).
3. **Hypoplasia or absence of the cervix in the presence of a functioning uterus is more difficult to treat than other outflow obstructions.** Previously, a hysterectomy was thought to be required. Conservative laparoscopic uterovaginal anastomosis has been described and is the recommended first-line treatment (63,64). Hysterectomy may be needed if conservative surgery is not successful. Endometriosis is a common finding, and it is questionable whether this condition should be treated initially with surgery or if it will resolve spontaneously after surgical repair of the obstruction. If hysterectomy is needed, the ovaries should be retained to provide the benefits of estrogen and permit the possibility of future childbearing by removing mature oocytes for in vitro fertilization and transfer of embryos to a gestational carrier.
4. **If the vagina is absent or short, progressive dilation is usually successful in making it functional** (60,65,66). If dilation fails or the patient is unable to perform dilation, the McIndoe split thickness graft technique, the Vecchietti procedure, or other surgical approaches may be considered (67–69). The initial use of vaginal dilators is required to maintain a functional vagina.
5. **In patients with complete androgen insensitivity, the testes should be removed after pubertal development is complete to prevent malignant degeneration** (57). In patients with testes, approximately 14% develop a neoplasia, most often a gonadoblastoma. Almost one-half of the testicular neoplasms are malignant (dysgerminomas), but transformation usually does not occur until after puberty (70). In patients who develop virilization and have a XY karyotype, GnRH agonist therapy can be utilized to delay puberty until the individual can develop and determine their gender identity. After puberty the testes should be removed. Bilateral laparoscopic gonadectomy is the preferred procedure for removal of intra-abdominal testes.

6. **Adhesions in the cervix and uterus (Asherman syndrome) can be removed using hysteroscopic resection with scissors or electrocautery** (71,72). It is reasonable to place a pediatric Foley catheter in the uterine cavity for 7 to 10 days postoperatively (along with systemic administration of broad-spectrum antibiotic therapy). A month course of high-dose estrogen therapy with progestogen withdrawal is used to prevent reformation of adhesions. Forty percent to 80% of patients thus treated achieve pregnancy, but complications including miscarriage, preterm labor, placenta previa, and placenta accreta can occur. Cervical stenosis can be treated by cervical dilation.

AMENORRHEA WITH SECONDARY SEXUAL CHARACTERISTICS AND NORMAL PELVIC ANATOMY

Although the complete list of potential causes is long, the most common causes of amenorrhea in women with normal secondary sexual characteristics and normal pelvic examination are pregnancy, PCOS, hyperprolactinemia, thyroid disease, POI (also known as premature ovarian failure), and hypothalamic dysfunction. Pregnancy must be considered in all women of reproductive age with amenorrhea.

Causes

Polycystic Ovarian Syndrome

PCOS is one of the most common endocrine disorders affecting women with a prevalence between 6% and 10%. The syndrome is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic-appearing ovaries (73–75). All definitions of PCOS exclude patients with significantly elevated prolactin, significant thyroid dysfunction, adult-onset congenital adrenal hyperplasia, and androgen-secreting neoplasms from being classified as PCOS. The National Institutes of Health (NIH) 1990 criteria required hyperandrogenism and oligomenorrhea or amenorrhea for the diagnosis for PCOS. **The Rotterdam 2003 criteria required two of three of the following for the PCOS diagnosis: hyperandrogenism, oligomenorrhea or amenorrhea, polycystic ovaries by ultrasound** (76). In 2012, an expert panel workshop at the NIH agreed to utilize the Rotterdam criteria (77). The number of antral follicles to define a polycystic ovary has been debated given the fact that ultrasound is now capable of visualizing small antral follicles accurately (78).

Although insulin resistance and obesity is noted among women with PCOS, it is not included in any of the diagnostic criteria. Insulin resistance is more prevalent in women who are obese with hyperandrogenism and chronic anovulation. Women with PCOS are often subfertile caused by infrequent or absent ovulation. PCOS can have other general

health implications, including increased risk for endometrial hyperplasia and cancer, diabetes, and cardiovascular disease.

Even though **PCOS usually causes irregular bleeding rather than amenorrhea, it remains one of the most common causes of amenorrhea** (2). The etiology of PCOS remains largely unknown.

Not all patients who are hirsute and amenorrheic have PCOS. The possibility of androgen-secreting adrenal tumors or congenital adrenal hyperplasia (79) **should be considered.** Elevations in androgens (e.g., Sertoli–Leydig, hilus, and lipoid cell tumors) and estrogens (e.g., granulosa cell tumors) by ovarian tumors may lead to abnormal menstrual patterns, including amenorrhea. A history of rapid onset of hirsutism is suggestive of a tumor.

Hyperprolactinemia

Hyperprolactinemia is a common cause of anovulation in women. Elevation of prolactin produces abnormal GnRH secretion, which can lead to menstrual disturbances (80). Prolactin levels rise in pregnancy, but typically return to normal within 6 months after delivery in nursing mothers and within weeks in nonnursing mothers. Dopamine release suppresses prolactin secretion. Levels of prolactin can be increased by pituitary adenomas that produce prolactin, by other CNS lesions that disrupt the normal transport of dopamine down the pituitary stalk, and by medications that interfere with normal dopamine secretion (such as antidepressants, antipsychotics including *risperidone, metoclopramide,* some antihypertensives, opiates, and H_2 receptor blockers).

If elevated TSH and elevated prolactin levels are found together, the hypothyroidism should be treated before hyperprolactinemia is treated. Often, the prolactin level will normalize with treatment of hypothyroidism because thyroid-releasing hormone, which is elevated in hypothyroidism, stimulates prolactin secretion.

Primary Ovarian Insufficiency (Premature Ovarian Failure)

POI is suggested as a preferred term for the condition that otherwise was referred to as premature ovarian failure or premature menopause (81,82). Others have suggested premature ovarian insufficiency. POI is defined as the presence of amenorrhea for 4 months or more accompanied by two serum FSH levels in the menopausal range for a woman who is less than 40 years of age. Ovarian "insufficiency" is suggested to be more appropriate than "failure" in part because ovarian function can wax and wane, and function can resume even after it appears that a woman transitioned into menopause. In one large cohort, 24% of women had some resumption of ovarian function after diagnosis of POI (83).

Ovarian insufficiency may be caused by decreased follicular endowment, accelerated follicular atresia, or follicle dysfunction (81). Over 75% of women with POI will have

at least intermittent symptoms including hot flushes, night sweats, and emotional lability (84). Symptoms are uncommon among women with primary amenorrhea who never received estrogen. The incidence of POI has been estimated to be about 1% (85,86).

If the ovary does not develop or stops its hormone production before puberty, the patient will not develop secondary sexual characteristics without exogenous hormone therapy. If ovarian insufficiency begins later in life, the woman will have normal secondary sexual characteristics.

POI clearly compromises the chance of a woman conceiving with autologous oocytes. However, 5% to 10% of women with a diagnosis of premature ovarian failure achieve pregnancy, with approximately 80% of these pregnancies resulting in the delivery of a healthy child (87). It can be difficult to determine which women will be able to conceive. Published studies of testing for ovarian reserve have not specifically focused on the POI populations, and pregnancies may occur with or without treatment despite very unfavorable results for tests of ovarian reserve such as serum FSH, estradiol, and AMH (88). In general, there is no convincing evidence that adjuvant therapies are effective in inducing ovulation for women with premature ovarian failure who no longer respond to gonadotropin therapy (89). Greater understanding of the factors affecting primordial follicle activation may lead to improvements in the success of experimental treatments such as in vitro activation (90–92). Oocyte donation and embryo donation are the only proven effective fertility treatments for women with POI (93).

POI is a heterogeneous disorder with many potential causes (81,94). POI may be caused by sex chromosome disorders, by **fragile X mental retardation 1 (*FMR1*)** premutations, and mutations of single genes (52). Radiation or chemotherapy may lead to POI. The cause of POI may be autoimmune. **The cause remains unknown in a majority of cases** (Table 34-3).

Sex Chromosome and Single Gene Disorders Associated with Primary Ovarian Insufficiency

Absence of one X chromosome (Turner syndrome) is associated with POI, despite normal initial development of the ovaries, because of accelerated atresia of the follicles (95). Although Turner syndrome may often be associated with primary amenorrhea with absence of secondary sexual characteristics, breast development may occur if ovarian function is initially present. Mosaicism of an XO or XY cell line may cause ovarian insufficiency. **Individuals with a 47,XXX karyotype may develop ovarian failure** (96). The most common physical features of 47,XXX are tall stature, epicanthal folds, hypotonia, and clinodactyly.

Table 34-3 Causes of Ovarian Insufficiency or Failure After Development of Secondary Sexual Characteristics

Chromosomal etiology (e.g., Turner mosaic)

FMR1 premutation
Iatrogenic causes: radiation, chemotherapy, surgical damage to ovarian blood supply or removal of ovaries
Infections
Autoimmune-lymphocytic oophoritis
Infections
Galactosemia
Perrault syndrome
Idiopathic (80–90% of cases, includes genetic mutations not detected in routine clinical care)

At least 23 genes are known to have mutations associated with POI and many more are likely to be identified (52,97). However, only two of these genes (*FMR1* and *NR5A1*) account for >3% to 4% of POI patients. A deletion of a portion of the X chromosome may be present in patients with POI. The Xq21-28 region appears to be critical, with several genes in this region identified as the cause of early ovarian insufficiency in humans (*POF1B* gene located at Xq21, the *DIAPH2* gene located at distal Xq21, and the *XPNPEP2* gene located at Xq25 (98,99). Other examples of known mutations are *BMP15* gene (100) and FOXL2 leading to ovarian failure and ptosis (101). An autosomal recessive form of POI is associated with hearing loss in Perrault syndrome (102).

FMR1 *Premutation Carriers*

The most clinically significant gene known to be associated with POI is the *FMR1* gene. Fragile X syndrome, the most common cause of inherited (X-linked) intellectual disability, is caused by inactivation of the *FMR1* gene located on Xq27.3. This inactivation occurs as a result of expansion of a cytosine–guanine–guanine (CGG) triplet repeat of more than 200 copies (103). ***FMR1* premutation carriers (typically defined as greater than 55 but under 200 CGG repeats) may have POI and impaired fertility.** The prevalence of POI in women who carry the ***FMR1*** premutation is estimated to be between 13% and 26%. The risk of having POI appears to increase with increasing premutation repeat size between 59 and 99. It is possible that there is an increased risk of POI among women who carry intermediate-size allele (approximately 41 to 58 repeats), but this is not conclusively proven. The risk plateaus or decreases for women with repeat sizes of 100. Women with full mutations (200 or more CGG repeats) are not at higher risk for POI. It is hypothesized that expression of abnormal *FMR1* mRNA produced by patients with the premutation causes dysfunction in the ovary, which does not occur when the *FMR1* gene is inactivated and not transcribed. The incidence of having a premutation is 0.8% to 7.5%

of women with sporadic POI and up to 13% of women with familial POI.

***FMR1* premutations carried by women are unstable and can expand in the next generation to transmit fragile X syndrome to the male offspring,** especially if women have more than 100 repeats. The smallest repeat to expand to the full mutation in one generation is approximately 59. In contrast to potential expansion in women, the repeat sequence is transmitted from fathers to daughters in a relatively stable manner.

Iatrogenic Causes of Primary Ovarian Insufficiency

Radiation and chemotherapy (especially alkylating agents such as *cyclophosphamide*) may lead to POI (104,105). Other iatrogenic causes of POI include **surgical interference with ovarian blood supply or removal of ovarian tissue which can cause ovarian insufficiency or failure from early loss of follicles.** Ovarian suppression with GnRH agonists has been tried, but has not been clearly proven to preserve fertility (106). Although cigarette smoking decreases the age at which menopause will occur, smoking would not be expected to be the primary cause of amenorrhea occurring before the age of 40. In rare cases, infections have been suggested to be associated with POI.

Autoimmune Disorders

In one series, 4% of women with POI were noted to have steroidogenic cell immunity with lymphocytic oophoritis as the mechanism for follicle dysfunction (107). **Autoimmune lymphocytic oophoritis is associated with a theca cell infiltrate that spares granulosa cells** (108). Ultrasound examination reveals the presence of numerous ovarian follicles, despite elevated serum FSH levels and hypoestrogenism (81). Ovarian antibody testing is not clinically reliable for diagnosing the disorder, as women with biopsy-proven autoimmune oophoritis may have a negative test for ovarian antibody. However, women with autoimmune lymphocytic oophoritis appear to reliably test positive for adrenal antibodies. The most readily available antibody is the 21-hydroxylase antibody. Ideally, antibody to the adrenal gland itself, as assessed by indirect immunofluorescence, is reasonable to test if available. Testing for 21-hydroxylase antibody is strongly recommended for women who are determined to have POI because women who test positive for this antibody are at risk for potentially fatal hypoadrenalism. Signs that suggest a risk for potentially fatal adrenal insufficiency include hyperpigmentation, weakness, nausea, vomiting, diarrhea, and weight loss.

POI may be part of a polyglandular autoimmune syndrome. Antibodies are present in a variable number of patients with POI, depending on the autoimmune studies performed. **Presence of antithyroid antibodies does not confirm that there is an autoimmune cause for POI.**

Galactosemia

Galactosemia is caused by a lack of functional galactose-1-phosphate uridyltransferase

(22). **Galactosemia is a rare cause of POI and is typically diagnosed in childhood prior to presentation with amenorrhea**. Galactose metabolites appear to have toxic effects on ovarian follicles, causing their premature destruction. Although about 90% of women with classic galactosemia develop POI, the pregnancy rate for these women may be higher than for other causes of POI (109).

Pituitary and Hypothalamic Lesions

Hypothalamic Tumors

For normal menstruation to occur, the hypothalamus must be able to secrete GnRH, and the pituitary must be able to respond with production and release of FSH and LH. Tumors of the hypothalamus or pituitary, such as craniopharyngiomas, germinomas, tubercular or sarcoid granulomas, or dermoid cysts, may prevent appropriate hormonal secretion. Patients with these disorders may have neurologic abnormalities, and secretion of other hypothalamic and pituitary hormones may be abnormal. Craniopharyngiomas are the most common tumors. They are located in the suprasellar region and frequently cause headaches and visual changes. The surgical and radiologic treatment of tumors may in itself cause further abnormalities in hormone secretion **(Table 34-4)**.

Table 34-4 Pituitary and Hypothalamic Lesions

Pituitary and hypothalamic
Craniopharyngioma
Germinoma
Tubercular granuloma
Sarcoid granuloma
Dermoid cyst
Pituitary
Nonfunctioning adenomas
Hormone-secreting adenomas
Prolactinoma
Cushing disease
Acromegaly
Infarction
Lymphocytic hypophysitis

Surgical or radiologic ablations
Sheehan syndrome
Diabetic vasculitis

Pituitary Lesions

Hypopituitarism is rare because a large portion of the gland must be destroyed before decreased hormonal secretion affects the patient clinically. The pituitary gland may be destroyed by tumors (nonfunctioning or hormone secreting), infarction, or infiltrating lesions such as lymphocytic hypophysitis, granulomatous lesions, and surgical or radiologic ablations. **Sheehan syndrome is associated with postpartum necrosis of the pituitary resulting from a hypotensive episode that, in its severe form (pituitary apoplexy), presents with the patient in shock.** The patient may develop a localized, severe, retro-orbital headache or abnormalities in visual fields and visual acuity. Patients with a mild form of postpartum pituitary necrosis cannot lactate, lose pubic and axillary hair, and do not menstruate after delivery.

Diabetic vasculitis and sickle cell anemia rarely manifest as pituitary failure. Hypopituitarism is associated with hyposecretion of ACTH and thyroid-stimulating hormone (TSH) and gonadotropins; therefore, thyroid and adrenal function must be evaluated. **If hypopituitarism occurs before puberty, menses and secondary sexual characteristics will not develop.**

Growth hormone (GH), TSH, ACTH, and prolactin are secreted by the pituitary, and the excess production of each by pituitary tumors causes menstrual abnormalities. The menstrual abnormalities are caused by adverse effects of these hormones on the GnRH pulse generator and not by direct effects on the ovary. Prolactinomas are the most common hormone-secreting tumors in the pituitary, as described above.

Altered Hypothalamic Gonadotropin-Releasing Hormone Secretion

Abnormal secretion of GnRH is a common cause of amenorrhea. The term functional hypothalamic amenorrhea implies that correction of causal factors will restore ovulatory function (110). Chronic disease, malnutrition, stress, psychiatric disorders, eating disorders, and exercise inhibit GnRH pulses, thus altering the menstrual cycle (Table 34-5). Other hormonal systems that produce excess or insufficient hormones can cause abnormal feedback and adversely affect GnRH secretion. In hyperprolactinemia, Cushing disease (excess ACTH), and acromegaly (excess GH), excess pituitary hormones are secreted that inhibit GnRH secretion.

Table 34-5 Abnormalities Affecting Release of Gonadotropin-Releasing Hormone

Variable estrogen status[a]
Anorexia nervosa

Exercise induced
Stress induced
Pseudocyesis
Malnutrition
Chronic diseases
Diabetes mellitus
Renal disorders
Pulmonary disorders
Liver disease
Chronic infections
Addison disease
Hyperprolactinemia
Thyroid dysfunction
Euestrogenic states
Obesity
Hyperandrogenism
Polycystic ovary syndrome
Cushing syndrome
Congenital adrenal hyperplasia
Androgen-secreting adrenal tumors
Androgen-secreting ovarian tumors
Granulosa cell tumor
Idiopathic

[a]Severity of the condition determines estrogen status—the more severe, the more likely to manifest as hypoestrogenism.

When the decrease in GnRH pulsatility is severe, amenorrhea results. With less severe alterations in GnRH pulsatility, anovulation and oligomenorrhea can occur. The pulsatile secretion of GnRH is modulated by interactions with neurotransmitters and peripheral gonadal steroids. Kisspeptin plays a critical role in the initiation of GnRH secretion during puberty (110). Endogenous opioids, corticotropin-releasing

hormones (CRH), melatonin, and α-aminobutyric acid (GABA) inhibit the release of GnRH, whereas catecholamine, acetylcholine, and vasoactive intestinal peptide stimulate GnRH pulses. Dopamine and serotonin have variable effects (111).

Decreased leptin levels are associated with hypothalamic amenorrhea, regardless of whether it is caused by exercise, eating disorders, or is idiopathic (112). Leptin is a hormone secreted by adipocytes that is involved in energy hemostasis. Receptors are found in the hypothalamus and bone, making it an excellent candidate for a modulator of menstrual function and bone mass. Levels correlate with nutritional changes and body mass index. Administration of leptin to women with hypothalamic amenorrhea increased levels of LH, estradiol, insulin-like growth factor-1 (IGF-1), and thyroid hormone. Ovulation and increased bone mass occurred in these patients (113). However, weight loss occurring with leptin administration limits the utility of using leptin as a potential therapeutic agent.

Eating Disorders

Anorexia nervosa is an eating disorder that affects many adolescent women. The criteria for diagnosis of anorexia nervosa in the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) include low body weight (defined in a somewhat open-ended fashion as less than minimally normal weight in adults, or less than minimally expected weight in children and adolescents) **and a refusal to maintain a minimally normal or expected weight** (114). **Patients with anorexia may either state the refusal or demonstrate behavior which indicate a refusal to maintain a normal weight.** Patients attempt to maintain their low body weight by food restriction, laxative abuse, and intense exercise. **Anorexia nervosa is a life-threatening disorder with a significant mortality rate** (115). Amenorrhea may precede, coincide, or follow the weight loss. Multiple hormonal patterns are altered. The 24-hour patterns of FSH and LH may show constantly low levels as seen in childhood or increased LH pulsatility during sleep consistent with the pattern seen in early puberty. Hypercortisolism is present despite normal ACTH levels, and the ACTH response to CRH administration is blunted. Circulating triiodothyronine (T_3) is low, yet circulating inactive reverse T_3 concentrations are high. Patients may develop cold and heat intolerance, lanugo hair, hypotension, bradycardia, and diabetes insipidus. They may have yellowish discoloration of the skin resulting from elevated levels of serum carotene caused by altered vitamin A metabolism.

Binge eating is associated with bulimia consisting of vomiting, laxative abuse, and diuretics to control weight. Signs of bulimia include tooth decay, parotid gland hypertrophy (chipmunk jowls), hypokalemia, and metabolic alkalosis.

Weight Loss and Dieting

Weight loss can cause amenorrhea even if weight does not decrease below normal.

Loss of 10% body mass in 1 year is associated with amenorrhea. Some but not all of these women have an underlying eating disorder. Prognosis is good for the return of menses if the patients recover from the weight loss. Dieting without weight loss and changes in diet can lead to amenorrhea (116).

Exercise

In patients with exercise-induced amenorrhea, there is a decrease in the frequency of GnRH pulses, which is assessed by measuring a decreased frequency of LH pulses. These patients are usually hypoestrogenic, but less severe alterations may cause minimal menstrual dysfunction (anovulation or luteal phase defect). The decrease in GnRH pulsatility can be caused by hormonal alterations, such as low levels of leptin or high levels of ghrelin, neuropeptide Y, and corticotrophin-releasing hormone (117). Runners and ballet dancers are at higher risk for amenorrhea than swimmers (118). It was previously suggested that a minimum of 17% body fat is required for the initiation of menses and 22% body fat for the maintenance of menses (119). However, studies suggest that inappropriately low caloric intake during strenuous exercise is more important than body fat (120). **Higher-intensity training, poor nutrition, stress of competition, and associated eating disorders increase an athlete's risk for menstrual dysfunction**. **Osteoporosis may result in stress fractures during training and lifelong increased fracture risk.** Stress fractures most commonly occur in the weight-bearing cortical bone such as the tibia, metatarsal, fibula, and femur. These athletes may fail to reach peak bone mass and have abnormal bone mineralization.

Stress

Stress-related amenorrhea can be caused by abnormalities in neuromodulation in hypothalamic GnRH secretion, similar to those that occur with exercise and anorexia nervosa. Excess endogenous opioids and elevations in CRH secretion inhibit the secretion of GnRH (111). These mechanisms are not fully understood but appear to be the common link between amenorrhea and chronic diseases, pseudocyesis, and malnutrition. Cognitive behavioral therapy has shown some promise in initiating neuroendocrine recovery (121).

Obesity

Most obese patients have normal menstrual cycles, but the percentage of women with menstrual disorders increases for women with obesity compared with women of normal weight. The menstrual disorder is more often irregular uterine bleeding with anovulation rather than amenorrhea. **Obese women have an excess number of fat cells in which extraglandular aromatization of androgen to estrogen occurs. They have lower circulating levels of sex hormone–binding globulin, which allows a larger proportion of free androgens to be converted to estrone. Excess estrogen creates a**

higher risk for endometrial cancer for these women. The decrease in sex hormone–binding globulin allows an increase in free androgen levels, which initially are eliminated by an increased rate of metabolic clearance. This compensatory mechanism diminishes over time, and hirsutism can develop. Frequently, these patients are classified as having PCOS. Alterations in the secretion of endorphins, cortisol, insulin, GH, and IGF-1 may interact with the abnormal estrogen and androgen feedback to the GnRH pulse generator to cause menstrual abnormalities.

Other Hormonal Factors

The secretion of hypothalamic neuromodulators can be altered by feedback from abnormal levels of peripheral hormones. Excesses or deficiencies of thyroid hormone, glucocorticoids, androgens, and estrogens can cause menstrual dysfunction. Excess secretion of GH, TSH, ACTH, and prolactin from the pituitary gland can cause abnormal feedback inhibition of GnRH secretion, leading to amenorrhea. **GH excess causes acromegaly, which may be associated with anovulation, hirsutism, and polycystic-appearing ovaries as a result of stimulation of the ovary by IGF-1. More commonly, GH excess is accompanied by amenorrhea, low gonadotropin levels, and elevated prolactin levels. Acromegaly is recognized by enlargement of facial features, hands, and feet; hyperhidrosis; visceral organ enlargement; and multiple skin tags. Cushing disease is caused by an ACTH-secreting pituitary tumor, which is manifested by truncal obesity, moon facies, hirsutism, proximal weakness, depression, and menstrual dysfunction.**

Evaluation for Women With Amenorrhea in the Presence of Normal Pelvic Anatomy and Normal Secondary Sexual Characteristics

A pregnancy test (urine or serum human chorionic gonadotropin [hCG]) should be performed in a reproductive-age woman who has amenorrhea with normal secondary sexual characteristics and a normal pelvic examination. If the results of the pregnancy test are negative, the evaluation of amenorrhea is as follows:

1. **Clinical assessment of estrogen status**
2. **Serum TSH**
3. **Serum prolactin**
4. **Serum FSH level**
5. **Vaginal ultrasound for assessment of antral follicle count in the ovaries can be considered (may help establish the diagnosis of PCOS or suggest POI)**
6. **[4] Imaging of the pituitary and hypothalamic assessment if prolactin is elevated or if hypothalamic amenorrhea is suspected (particularly if CNS symptoms are present or there is no clear explanation for hypothalamic amenorrhea).**

Assessment of Estrogen Status

The presence of vaginal dryness or hot flashes increases the likelihood of a diagnosis of hypoestrogenism. A serum estradiol level higher than 40 pg/mL is considered indicative of significant estrogen production, but interassay discrepancies often exist and serum estrogen levels can vary greatly on a day-to-day basis for a given woman. Vaginal ultrasound demonstrating a thin endometrium suggests that a patient is hypoestrogenic, unless there is reason to suspect that the patient lacks functional endometrium. A dual-energy x-ray absorptiometry (DEXA) scan to determine bone mineral density should be considered for a patient in whom long-term hypoestrogenism is suspected.

There is little utility in routine performance of a progestogen challenge test to determine the patient's estrogen status. False positives and false negatives are common.

Thyroid and Prolactin Disorders

Consideration should be given to thyroid disorders and hyperprolactinemia in women with amenorrhea because of the relatively common incidence of these conditions.

1. **Sensitive TSH assays can be used to evaluate hypothyroidism and hyperthyroidism.** Further evaluation of a thyroid disorder is required if abnormalities in TSH levels are found. Mild degrees of thyroid dysfunction are unlikely to cause amenorrhea. Given the general health implications of thyroid dysfunction and readily available treatments, routine assessment of TSH is reasonable for women with amenorrhea.
2. **Prolactin is most accurately obtained in a patient who is fasting and who has not had any recent breast stimulation to avoid concluding that a patient is hyperprolactinemic on the basis of a transient prolactin elevation.** If a patient still has some menstrual cycles, it is advisable to obtain the prolactin level in the follicular phase.

Follicle-Stimulating Hormone Levels

Assessment of serum FSH levels is required to determine whether the patient has hypergonadotropic, hypogonadotropic, or eugonadotropic amenorrhea. **A circulating FSH level of greater than 25 to 40 mIU/mL indicated on at least two blood samples is indicative of hypergonadotropic amenorrhea.** Hypergonadotropism implies that the cause of amenorrhea is ovarian insufficiency. The history should establish whether the cause of ovarian insufficiency is chemotherapy or radiation therapy.

Anti-müllerian hormone (AMH) is a circulating biomarker, which correlates with the size of the pool of ovarian follicles (122). AMH is produced by the granulosa cells of preantral and early antral follicles (123). Although it is not formally included in the

diagnosis of POI, AMH becomes undetectable several years before the final menses and thus may aid in the early diagnosis of POI. **AMH levels are low in women with POI and high in women with PCOS.**

If the diagnosis of POI is confirmed, the patient should be tested for:

1. ***FMR1* premutation**
2. **Karyotype**
3. **21-hydroxylase antibody**

FMR1 premutation testing will reveal women at risk for bearing a child with fragile X syndrome, which may be important information for other family members. The goal of the peripheral blood karyotype is to identify an absent or abnormal X chromosome and to identify whether or not any portion of a Y chromosome is present. It is important to identify Y chromosomal material so it may be removed to prevent malignant degeneration. Although commonly suggested that karyotype only be performed if the patient is younger than the age of 30, it should be noted that rare patients with Turner syndrome developed amenorrhea after age 35. In addition, some patients who present older than the age of 30 may have actually had the onset of POI at a younger age but were unaware because of the use of oral contraceptives. Therefore, consideration should be given to performance of karyotype, regardless of the patient's age. Testing for 21-hydroxylase antibody will identify women at risk for adrenal crisis.

If a diagnosis of PCOS is suspected, the patient should have:

1. **Documentation of hyperandrogenism**—either by serum total testosterone and sex hormone binding globulin or free testosterone and/or by presence of physical findings such as acne, hirsutism, and androgenic alopecia.
2. **Serum 17-hydroxyprogesterone to exclude congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency, particularly if the patient is at increased risk**—highest prevalence is among Ashkenazi Jews, Hispanics, Yugoslavs, Native American Inuits in Alaska, and Italians.
3. **If the diagnosis of PCOS is made, the patient should undergo screening for diabetes and a fasting lipid profile**.

Assessment of the Pituitary and Hypothalamus

If the patient is hypoestrogenic and the FSH level is not high, pituitary and hypothalamic lesions should be excluded.

1. **A complete neurologic examination** may help localize a lesion.
2. **Either CT or MRI scanning should be performed** to confirm the presence or absence of a tumor. MRI will identify smaller lesions than CT; if a lesion is too

small for identification by CT, it may be clinically insignificant. MRI offers the advantage of avoiding exposure to x-ray.

3. **The patient's history of weight changes, exercise, eating habits, and body image is an important factor in determining whether anorexia nervosa, malnutrition, obesity, exercise, or stress may be responsible for amenorrhea.**

Patients with certain specific clinical findings should undergo screening for other hormonal alterations:

1. **Androgen levels should be assessed** in any hirsute patient to ensure that adrenal and ovarian tumors are not present and to aid in the diagnosis of PCOS.
2. **Acromegaly** is suggested by coarse facial features, large doughy hands, and hyperhidrosis and **may be confirmed by measuring IGF-1 levels.**
3. In patients with truncal obesity, hirsutism, hypertension, and erythematous striae, **Cushing syndrome should be ruled out** by assessing 24-hour urinary cortisol levels or performing a 1-mg overnight *dexamethasone* suppression test or late night salivary cortisol (124). It is important to confirm that the patient is not taking exogenous glucocorticoid.

Treatment for Women With Amenorrhea in the Presence of Normal Pelvic Anatomy and Normal Secondary Sexual Characteristics

The treatment of nonanatomic causes of amenorrhea associated with normal secondary sexual characteristics varies widely according to the cause. The underlying disorder should be treated whenever possible. Patients who are pregnant may be counseled regarding the options for continued care. **When thyroid abnormalities are detected, thyroid hormone, radioactive iodine, or antithyroid drugs may be administered as appropriate. If hyperprolactinemia is present, treatment may include discontinuation of contributing medications, treatment with dopamine agonists such as *bromocriptine* or *cabergoline,*** and, rarely, surgery for particularly large pituitary tumors. **When POI causes amenorrhea, hormone replacement should be considered to improve quality of life and to prevent osteoporosis** (125). Counseling regarding the risks and benefits of hormone replacement therapy is indicated. Gonadectomy is required when a Y cell line is present.

Surgical removal, radiation therapy, or a combination of both is advocated for treatment of CNS tumors other than prolactinomas. It may be necessary to treat individuals who have panhypopituitarism with various replacement regimens after all the deficits are elucidated. These regimens include estrogen and progestogen replacement for lack of gonadotropins, corticosteroid replacement for lack of ACTH,

thyroid hormone for lack of TSH, and *desmopressin acetate* (*1-deamino-8-D-AVP* [*DDAVP*]) to replace vasopressin.

The treatment of amenorrhea associated with hypothalamic dysfunction depends on the underlying cause:

1. **Hormonally active ovarian tumors are surgically removed (rare).**
2. **Obesity, malnutrition or chronic disease, Cushing syndrome, and acromegaly should be specifically treated.**
3. **Stress-induced amenorrhea may respond to psychotherapy.**
4. **Exercise-induced amenorrhea may improve with moderation of activity and weight gain, when appropriate.** If hypoestrogenism persists, higher doses of estrogen may be needed in these women than in older menopausal women to maintain bone density. In addition, 1,200 to 1,500 mg of calcium and 400 to 800 IU of vitamin D daily are advised. Bisphosphonates do not improve bone density in amenorrheic athletes because it is lack of bone formation rather than increased resorption that causes the osteopenia. In addition, the use of bisphosphonates is not advised because they can be deposited into the bone, and long-term effects, especially during pregnancy, are unknown.
5. **Treatment of eating disorders such as anorexia nervosa generally demands a multidisciplinary approach, with outpatient family-based therapy, the first line particularly for adolescents, and hospitalization reserved for severe cases** (126).
6. **Chronic anovulation associated with PCOS may be treated after identifying the desires of the patient.** Patients may be concerned about their lack of menstruation, not hirsutism, or infertility. **The endometrium of these individuals should be protected from the environment of unopposed estrogen** that accompanies the anovulatory state. Oral contraceptives are a good alternative for those patients who require contraception. For those patients who are not candidates for oral contraceptive use, cyclic administration of progestogen is advised. Progestogen withdrawal will occur if there is an adequate estrogenic environment to induce proliferation of the endometrium, and it is not sufficient to cause withdrawal bleeding in patients who are hypoestrogenic (e.g., those who have amenorrhea associated with anorexia nervosa). Women with PCOS may require treatment for insulin resistance, dyslipidemia, and obesity. Regular periodic screening for diabetes and a lipid panel is recommended for women with PCOS. Reduction in weight in obese women with PCOS leads to improved pregnancy rates, decreases hirsutism, and improves glucose and lipid levels. Insulin-sensitizing medications such as *metformin* and cholesterol-lowering medications such as statins can be considered. Ovulation induction is performed if pregnancy is desired, as described

below.

A common progestogen used to induce withdrawal bleeding and thus protect the endometrium from hyperplastic transformation is *medroxyprogesterone acetate* (10 mg for 12 to 14 days per month). Occasionally, ovulation may occur; therefore, patients should be made aware that pregnancy is possible, and appropriate contraceptive measures should be used. *Medroxyprogesterone acetate* should not be used in early pregnancy. Alternatively, *progesterone* suppositories (50 to 100 mg) or oral *micronized progesterone* (200 mg) can be given for 12 to 14 days per month to protect the endometrium from hyperplasia and induce withdrawal bleeding.

In hypoestrogenic individuals such as those with POI, estrogen replacement must be added to the progestogen for successful menstrual regulation and prevention of osteoporosis. The doses of estrogen needed for relief of symptoms in young women with POI are often higher than those that are used for older menopausal women (127). Women with POI (who would normally still be making hormone if the ovaries were functioning normally) are different from those reaching menopause at a median age of 51. Therefore, data regarding hormone therapy that were collected from women reaching menopause at the median age should not be extrapolated to younger women. Although there are no comparative data and no long-term prospectively collected data regarding hormone therapy for women with POI, **the risks of hormone therapy are likely to be lower and the benefits potentially greater for younger women than for older women reaching menopause after the age of 50** (125).

When chronic anovulation is caused by congenital adrenal hyperplasia, glucocorticoid administration (i.e., *dexamethasone* 0.5 mg at bedtime) is sometimes successful in restoring the normal feedback mechanisms, thereby permitting regular menstruation and ovulation.

Hirsutism

Patients who have oligomenorrhea or amenorrhea resulting from chronic anovulation may have hirsutism. The most common cause of hirsutism and oligo-ovulation is PCOS. After ruling out androgen-secreting tumors and congenital adrenal hyperplasia, treatment may be aimed at decreasing coarse hair growth.

Oral Contraceptives

Oral contraceptives may be effective for hirsutism by decreasing ovarian androgen production and increasing circulating levels of sex hormone–binding globulin, leading to decreased free androgen in the circulation.

Antiandrogens

Spironolactone decreases androgen production and competes with androgens at the androgen receptor. Side effects include diuresis and dysfunctional uterine bleeding. The

use of spironolactone is typically combined with oral contraceptives to avoid irregular bleeding and to prevent pregnancy from occurring while on *spironolactone. Flutamide* is approved by the U.S. Food and Drug Administration (FDA) for adjuvant therapy in prostatic cancer but not specifically for treatment of hirsutism. A low dose of *flutamide* may be effective in treating hirsutism (128). Liver function should be monitored because of the rare complication of hepatotoxicity. *Cyproterone acetate,* a strong progestin and antiandrogen, is used in some countries, but is not available in the United States. It is usually administered in combination with *ethinyl estradiol* in an oral contraceptive and has a high efficacy (129) by decreasing circulating androgen and LH levels, and by inducing antagonism of androgen effects at the peripheral level. *Finasteride,* a 5α-reductase inhibitor, is approved by the FDA for the treatment of benign prostatic hypertrophy (*Proscar*) and male pattern baldness (*Propecia*). It may be effective in treating hirsutism, but with inconsistent results (130).

All antiandrogens are teratogenic as they may lead to feminization of the external genitalia of a male fetus (ambiguous genitalia) if the patient should conceive while taking the medication. Therefore, antiandrogens are typically used in combination with oral contraceptives.

Cosmetic Approaches

Medical treatment can be combined with cosmetic treatment for optimal efficacy (131). *Eflornithine hydrochloride* is a topical cream that is approved by the FDA for use on the face and chin. Improvements in facial hirsutism may be seen in 4 to 8 weeks of twice-daily applications. Short-term options include shaving, chemical depilation, plucking, threading, waxing, and bleaching. Long-term treatments include electrolysis, laser therapy, and intense pulse light therapy.

Ovulation Induction

A large subset of patients with amenorrhea or oligomenorrhea and chronic anovulation seek care because they are unable to conceive. Ovulation induction therapy is generally the treatment of choice for such patients, but pretreatment counseling should be provided in sufficient detail to ensure realistic expectations. The patient should be provided with information regarding the chances of a successful pregnancy (considering age of the patient and treatment modality), potential complications (hyperstimulation and multiple gestation), expense, time, and psychological impact involved in completing the course of therapy. **The selective estrogen receptor modulator, *clomiphene citrate,* is a common first choice for ovulation induction for many patients because of its relative safety, efficacy, oral route of administration, and relatively low cost**. *Clomiphene citrate* is indicated primarily in patients with adequate levels of estrogen and normal levels of FSH and prolactin. It is less effective in hypogonadotropic patients who already have a poor

estrogen supply.

The aromatase inhibitor, *letrozole*, has been demonstrated to be effective for ovulation induction in women with PCOS (132). **In systematic reviews and meta-analyses of randomized trials, ovulation induction with letrozole was found to result in higher pregnancy rate** compared with clomiphene (133,134) and letrozole can be recommended as first-line treatment because of higher ovulation pregnancy and live birth rate (134). However, it should be noted that letrozole is FDA approved only for breast cancer, not for ovulation induction.

As many as 80% of patients can be expected to ovulate after either *letrozole* or *clomiphene citrate* therapy. Contraindications to the use of *clomiphene citrate* or *letrozole* include pregnancy, liver disease, and pre-existing large ovarian cysts. Side effects can include hot flashes. In addition, clomiphene is associated with a risk of visual changes, which generally are viewed as an indication to discontinue subsequent *clomiphene citrate* use. The risk of multiple pregnancy is increased with *clomiphene citrate*. The majority of multiple gestations are twins; triplets and higher order multiple gestations are rare. In a meta-analysis examining use of letrozole for ovulation induction in anovulatory women, letrozole led to a lower rate of multiple pregnancy compared with *clomiphene* (134).

The most commonly recommended treatment regimen for *clomiphene citrate* is 50 mg daily for 5 days, beginning on the 3rd to 5th day of menstrual or withdrawal bleeding. Letrozole is typically prescribed at a starting dose of 2.5 mg or 5 mg daily for 5 days. Cycles may be monitored by measuring midcycle LH levels to assess the hormonal signal for ovulation. Ovulation may be confirmed by measuring midluteal progesterone levels. Ultrasonographic monitoring to assess folliculogenesis may be helpful, especially when *hCG* is used to induce ovulation. Endometrial thinning may be detected with midcycle ultrasound. With these data, it is possible to immediately adjust the dose in the subsequent cycle if a given regimen is ineffective.

Although a large randomized trial demonstrated that *clomiphene* alone is superior to *metformin* alone in achieving live birth in women with PCOS (135), **a meta-analysis suggests that for some patients with PCOS, *metformin* and *clomiphene* combined may increase the likelihood of ovulation compared with *clomiphene* alone** (134). Thinning of the endometrium at midcycle in the face of adequate midcycle estradiol or lack of success with repeated cycles of *letrozole* or *clomiphene* are generally indications to consider injectable gonadotropins.

Women with PCOS who do not ovulate or become pregnant with *clomiphene citrate or letrozole,* and **women with hypogonadotropic hypoestrogenic anovulation, may be candidates for therapy with injectable gonadotropins.** Available preparations include recombinant FSH and LH and products purified from the urine of menopausal women (FSH or FSH–LH combinations). Administration protocols and

dosages vary widely and should be adjusted to individual needs. Safe administration requires careful monitoring of ovarian response with ultrasonography and, in some cases, serial estradiol measurements. In general, gonadotropins are administered at a dose of 37 to 150 IU per day by subcutaneous injection for 3 to 5 days, after which time estradiol and follicular monitoring commence. In most cycles, gonadotropin is administered for 7 to 12 days. Ovulation is triggered by subcutaneous or intramuscular injection of 5,000 to 10,000 IU *hCG* or subcutaneous injection of 250 μg of *recombinant hCG* when the lead follicle reaches 16 to 20 mm in diameter based on ultrasonographic assessments. Ovulation generally occurs approximately 38 to 40 hours after *hCG* administration. Luteal phase support may be provided with the administration of *progesterone* supplementation.

The two major complications associated with induction of ovulation with gonadotropins are multiple pregnancy (10% to 30%) and ovarian hyperstimulation syndrome. The incidence of both of these complications can be reduced but not eliminated by careful monitoring. Cycles complicated by the recruitment of numerous follicles or by high estradiol levels may be canceled by withholding the ovulatory dose of *hCG.* Selected patients may be converted safely to in vitro fertilization. Because severe ovarian hyperstimulation syndrome is life-threatening and may lead to prolonged hospitalization, ovulation induction with gonadotropins generally is performed by experienced practitioners who devote a significant portion of their practice to the treatment of infertility.

Ovulation induction with pulsatile *GnRH* may be effective in patients who have chronic anovulation associated with low levels of estrogen and gonadotropins. For therapy to be successful, a functional ovary and pituitary gland must be present. Patients with ovarian or pituitary failure do not respond to *GnRH* therapy. To be effective, *GnRH* must be administered in a pulsatile fashion, either intravenously or subcutaneously by a programmable pump. Ovulation induction with *GnRH*, as compared with gonadotropins, is associated with a relatively low incidence of ovarian hyperstimulation and multiple births. In addition, the need for appropriate timing of the ovulatory dose of *hCG* is avoided because patients treated with pulsatile *GnRH* have an appropriately timed endogenous LH surge. Disadvantages are mainly related to maintaining the programmable pump and injection site and lack of availability of an appropriate pump in the United States. After ovulation, luteal phase support is necessary and may be provided with *hCG*, *progesterone*, or continuation of the *GnRH* therapy.

For women with overt POI (also known as premature ovarian failure), there is no good evidence to suggest that any treatment can increase the chance of conception with autologous oocytes (87,89). **Treatments that were tried include ovulation induction with *clomiphene* or *gonadotropin,* initial suppression of gonadotropin levels by pretreatment with high-dose estrogen or GnRH agonist**

followed by expectant management or gonadotropin stimulation, standard-dose hormone therapy followed by gonadotropin, and corticosteroid pretreatment followed by gonadotropin. If POI is diagnosed while a patient still has a significant supply of oocytes, fertility preservation could be considered if the patient is not able to consider conception at the time of diagnosis. In most cases, patients with prolonged amenorrhea are not diagnosed at a time when significant numbers of reproductively competent oocytes are present. Fertility preservation is an option for patients about to undergo gonadotoxic chemotherapy (136) or if a patient is known (e.g., based on family history) to be at risk for POI. Either embryos or oocytes can be cryopreserved, but in most cases, oocyte cryopreservation is preferable so that the source of sperm for fertilization of the oocytes can be decided at a future time and/or based on personal feelings about having embryos frozen. Ovarian tissue freezing can be considered if oocyte cryopreservation is not possible, such as when chemotherapy must be initiated immediately.

Patients with POI who desire pregnancy will in most cases have a high chance of having a child with the help of oocyte donation. Oocytes from donors may be harvested after ovulation induction, fertilized with sperm from the intended father or sperm donor, and transferred into the recipient's uterus after the endometrium is appropriately prepared with estrogen and progesterone. Special concern is warranted for women with Turner syndrome who have been reported to have an increased risk of maternal mortality of 2% (49). Rupture of the aorta may occur even if an echocardiogram shows no dilatation (137). In women with Turner syndrome who have a spontaneous pregnancy, the risk of cardiovascular morbidity may be lower (138). It is suggested that all women with Turner syndrome who are considering pregnancy undergo a full cardiac evaluation at a center with expertise in cardiovascular imaging (5,8), and that women with Turner syndrome receive expert consultation regarding whether or not it is safe to consider carrying a pregnancy.

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CHAPTER 35

Endocrine Disorders



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Hyperandrogenism
- Hirsutism
- Polycystic Ovary Syndrome
- Treatment of Hyperandrogenism and PCOS
- Cushing Syndrome
- Congenital Adrenal Hyperplasia
- Androgen-Secreting Ovarian and Adrenal Tumors
- Androgen-Producing Ovarian Neoplasms
- Stromal Hyperplasia and Stromal Hyperthecosis
- Virilization During Pregnancy
- Virilizing Adrenal Neoplasms

Prolactin Disorders
- Prolactin Secretion
- Hyperprolactinemia

Thyroid Disorders
- Thyroid Hormones
- Evaluation
- Autoimmune Thyroid Disease

KEY POINTS

1 Hyperandrogenism (HA) most often presents as hirsutism, which usually arises as a result of androgen excess related to abnormalities of function in the ovary or adrenal glands. By contrast, virilization is rare and indicates marked elevation in androgen levels.

2 The most common cause of HA and hirsutism is polycystic ovarian syndrome (PCOS). The

diagnostic schema for PCOS requires two of three criteria (HA [clinical or biochemical], ovarian dysfunction, and or PCO morphology) and identifies four phenotypes: (1) HA (clinical or biochemical) with ovarian dysfunction and PCO morphology, (2) HA (clinical or biochemical) with ovarian dysfunction, (3) HA (clinical or biochemical) with PCO morphology, (4) ovarian dysfunction and PCO morphology. Caution is recommended in affixing the PCOS diagnosis in adolescence. Patients with PCOS frequently exhibit insulin resistance and hyperinsulinemia.

3 Combination oral contraceptives (OCs) decrease adrenal and ovarian androgen production and reduce hair growth in nearly two-thirds of hirsute patients.

4 Because hyperinsulinemia appears to play a role in PCOS-associated anovulation, treatment with insulin sensitizers may shift the endocrine balance toward ovulation and pregnancy, either alone or in combination with other treatment modalities.

5 Excluding cases that are of iatrogenic or factitious etiology, adrenocorticotropic hormone–independent forms of Cushing syndrome are adrenal in origin. Adrenal cancers are usually very large by the time Cushing syndrome is manifest.

6 Congenital adrenal hyperplasia is an autosomal recessive disorder. Deficiency of 21-hydroxylase is responsible for more than 90% of cases of adrenal hyperplasia resulting from an adrenal enzyme deficiency.

7 Patients with severe hirsutism, virilization, or recent and rapidly progressing signs of androgen excess require careful investigation for the presence of an androgen-secreting neoplasm. Ovarian neoplasms are the most frequent androgen-producing tumors.

8 Elevations in prolactin may cause amenorrhea, galactorrhea, both, or neither. Amenorrhea without galactorrhea is associated with hyperprolactinemia in approximately 15% of women. Normal prolactin levels are found in 50% of women with isolated galactorrhea. Two thirds of women with both galactorrhea and amenorrhea have hyperprolactinemia and one-third will have a pituitary microadenoma.

9 Because levels of thyroid-stimulating hormone (TSH) are sensitive to excessive or deficient levels of circulating thyroid hormone, and because most disorders of hyperthyroidism and hypothyroidism are related to dysfunction of the thyroid gland, TSH levels are used to screen for these disorders. Autoimmune thyroid disorders are the most common thyroid abnormalities in women and represent the combined effects of the multiple antibodies produced. Severe primary hypothyroidism is associated with amenorrhea or anovulation. The classic triad of exophthalmos, goiter, and hyperthyroidism are diagnostic for Graves disease.

The endocrine disorders encountered most frequently in gynecologic patients are those related to disturbances in the regular occurrence of ovulation and accompanying menstruation. The most prevalent of these disorders, polycystic ovary syndrome, is characterized by androgen excess and is often accompanied by insulin resistance. Less common conditions associated with hyperandrogenism, hirsutism and ovulatory dysfunction are also reviewed. Common disorders of the pituitary and thyroid are reviewed in this chapter.

HYPERANDROGENISM

[1] Hyperandrogenism (HA) most often presents as hirsutism. Hirsutism arises as a result of androgen excess related to abnormalities of function in the ovary or adrenal glands, the constitutive increase in expression of androgen effects at the level of the pilosebaceous unit, or both. **By contrast, virilization is rare and indicates marked**

elevations in androgen levels. Virilization commonly is caused by an ovarian or adrenal neoplasm that may be benign or malignant.

Hirsutism

Hirsutism, the most frequent manifestation of androgen excess in women, is defined as excessive growth of terminal hair in a male distribution pattern. This refers particularly to midline hair, side burns, moustache, beard, chest or intermammary hair, and inner thigh and midline lower back hair entering the intergluteal area. The response of the pilosebaceous unit to androgens in these androgen-responsive areas transforms vellus hair (fine, nonpigmented, and short) that is normally present into terminal hair (coarse, stiff, pigmented, and long).

Androgen effects on hair vary in relation to specific body surface regions. Hair that shows no androgen dependence includes lanugo, eyebrows, and eyelashes. The hair of the limbs and portions of the trunk exhibits minimal sensitivity to androgens. Pilosebaceous units of the axilla and pubic region are sensitive to low levels of androgens, such that the modest androgenic effects of adult levels of adrenal androgens are sufficient to result in the substantial expression of terminal hair in these areas. Follicles in the distribution associated with male patterns of facial and body hair (midline, facial, inframammary) require higher levels of androgens, as seen with normal testicular function or abnormal ovarian or adrenal androgen production. Scalp hair is inhibited by gonadal androgens, in varying degrees, as determined by age and genetic determination of follicular responsiveness, resulting in the common frontal–parietal balding seen in some males and in virilized females. **Hirsutism results from increased androgen production and skin sensitivity to androgens. Skin sensitivity depends on the genetically determined local activity of 5α-reductase, the enzyme that converts testosterone to dihydrotestosterone (DHT), the bioactive androgen in hair follicles.**

Hair follicles demonstrate cyclic activity between growth (anagen), involution (catagen), and resting (telogen) phases. The durations of the growth and resting phases vary according to region of the body, genetic factors, age, and hormonal effects. The cycles of growth, rest, and shedding are normally dyssynchronous, but when synchronous, entry into telogen phase in follicles is triggered by major metabolic or endocrine events, such as pregnancy and delivery, or severe illness, and dramatic (although transient) hair loss may occur in the following months (telogen effluvium).

Hirsutism is a relative, rather than absolute, designation. What is normal in one setting may be considered abnormal in others; social and clinical reactions to hirsutism can vary significantly, reflecting ethnic variation in skin sensitivity to androgens and cultural ideals. Androgen-dependent hair (excluding pubic and axillary hair) occurs in only 5% of premenopausal white women and is considered abnormal by white women of North America. In contrast, considerable facial and male pattern hair in other areas

may be more common and more often considered acceptable and normal among groups such as the Inuit and women of Mediterranean background.

Hypertrichosis and Virilization

Two conditions should be distinguished from hirsutism. **Hypertrichosis is the term reserved for androgen-independent terminal hair in nonsexual areas, such as the trunk and extremities.** This may be the result of an autosomal-dominant congenital disorder, a metabolic disorder (such as anorexia nervosa, hyperthyroidism, porphyria cutanea tarda), or medications (e.g., *acetazolamide*, anabolic steroids, *androgenic progestins*, *androgens*, *cyclosporine*, *diazoxide*, dehydroepiandrosterone [DHEA], heavy metals, *interferon*, *methyldopa*, *minoxidil*, *penicillamine*, *phenothiazines*, *phenytoin*, *streptomycin*, *reserpine*, *valproic acid*). **Virilization is a marked and global masculine transformation that includes coarsening of the voice, increase in muscle mass, clitoromegaly (normal clitoral dimensions é standard deviation [SD] are 3.4 + 1 mm width by 5.1 + 1.4 mm length) and features of defeminization (loss of breast volume and body fat contributing to feminine body contour)** (1). Although hirsutism accompanies virilization, **the presence of virilization indicates a high likelihood of more serious conditions that are more common than with hirsutism alone and should prompt evaluation to exclude ovarian or adrenal neoplasm.** Although rare, these diagnoses become likely when onset of androgen effects is rapid and/or sufficiently pronounced to produce the picture of virilization.

The history should focus on the age of onset and rate of progression of hirsutism or virilization. **A rapid rate of progression or virilization is associated with a more severe degree of HA and should raise suspicion of ovarian and adrenal neoplasms or Cushing syndrome.** This is true whether rapid progression or virilization occurs before, during, or after puberty. Anovulation, manifesting as amenorrhea or oligomenorrhea, increases the probability that there is underlying HA. Hirsutism occurring with regular cycles is more commonly associated with normal androgen levels and thus is attributed to increased genetic sensitivity of the pilosebaceous unit and is termed *idiopathic hirsutism.* When virilization is present, anovulation virtually always occurs.

In determining the extent of hirsutism, a sensitive and tactful approach by the physician is mandatory and should include questions regarding the use and frequency of shaving and/or chemical or mechanical depilatories. Typically, clinical evaluation of the degree of hirsutism is subjective. Most physicians arbitrarily classify the degree of hirsutism as mild, moderate, or severe. Objective assessment is helpful, however, especially in establishing a baseline from which therapy can be evaluated. The Ferriman–Gallwey Scoring System for Hirsutism quantitates the extent of hair growth in the most androgen-sensitive sites. It is a scoring scale of androgen-sensitive hair in nine body areas rated on a scale of 0 to 4 (2). A total score higher than 8 is

defined as hirsutism (Fig. 35-1) (3). Although widely used, this scoring system has its limitations, one of which is the fact that the scale does not include the sideburn, buttocks, and perineal areas. Substantial hirsutism may be confined to one or two areas without exceeding the cutoff value in total hirsutism score. This score does not reflect the extent to which hirsutism affects a woman's well-being (3,4).

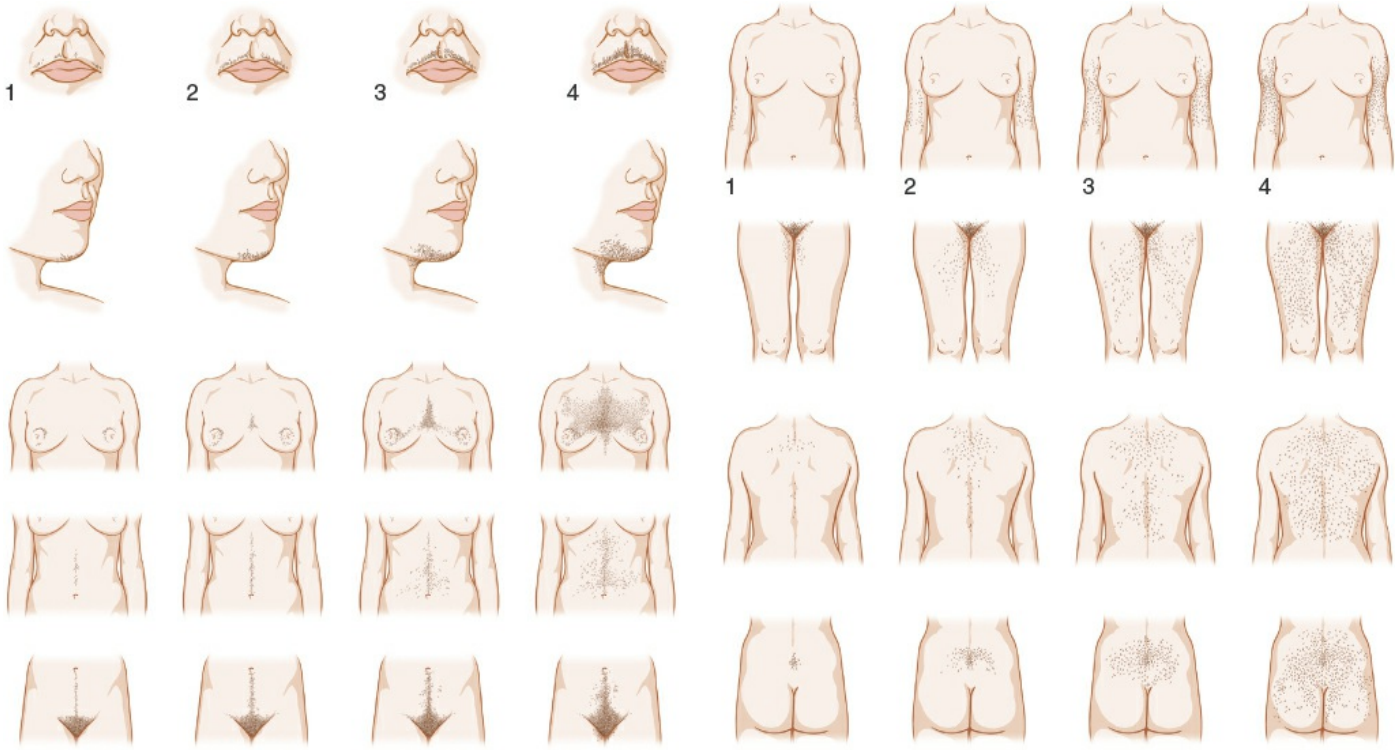


FIGURE 35-1 Ferriman–Gallwey hirsutism scoring system. Each of the nine body areas most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these separate scores are summed to provide a hormonal hirsutism score. (Reproduced from **Hatch R, Rosefield RL, Kim MH, et al**. Hirsutism: implications, etiology, and management. *Am J Obstet Gynecol* 1981;140:815–830. © Elsevier.)

A family history should be obtained to disclose evidence of idiopathic hirsutism, PCOS, congenital or adult-onset adrenal hyperplasia (CAH or AOAH), diabetes mellitus, and cardiovascular disease. A history of drug use should be obtained. In addition to drugs that commonly cause hypertrichosis, anabolic steroids and testosterone derivatives may cause hirsutism and even virilization. During the physical examination, attention should be directed to the presence of obesity, hypertension, galactorrhea, male-pattern baldness, acne (face and back), and hyperpigmentation. With virilization, the presence of an androgen-producing ovarian neoplasm or Cushing syndrome must be considered. In many cases of Cushing syndrome, the patient's presenting symptom is hirsutism which in early stages may masquerade as disorders such as PCOS or AOAH. When considering the possibility of Cushing syndrome, the physician should search for the physical signs of the syndrome. A moon-shaped face, upper body obesity, proximal muscle weakness (difficulty arising from a squatting position), and the development of a

pad of fat between the shoulder blades are particularly notable to patients and diagnosticians considering the diagnosis of Cushing syndrome.

Role of Androgens

Androgens and their precursors are produced by the adrenal glands and the ovaries in response to their respective trophic hormones, adrenocorticotropic hormone (ACTH), and luteinizing hormone (LH) (Fig. 35-2). Biosynthesis begins with the rate-limiting conversion of cholesterol to pregnenolone by side-chain cleavage enzyme. Thereafter, pregnenolone undergoes a two-step conversion to the 17-ketosteroid DHEA along the Δ-5 steroid pathway. This conversion is accomplished by CYP17, an enzyme with 17α-hydroxylase and 17,20-lyase activities. In a parallel fashion, progesterone undergoes transformation to androstenedione in the Δ-4 steroid pathway. The metabolism of Δ-5 to Δ-4 intermediates is accomplished via a Δ-5-isomerase, 3β-hydroxysteroid dehydrogenase (3β-HSD).

Adrenal 17-Ketosteroids

Secretion of adrenal 17-ketosteroids increases prepubertally and independently of pubertal maturation of the hypothalamic–pituitary–ovarian axis. This alteration in adrenal steroid secretion is termed *adrenarche* and is characterized by a dramatic change in the response of the adrenal cortex to ACTH and with preferential secretion of Δ-5 steroids, including 17-hydroxypregnenolone, DHEA, and dehydroepiandrosterone sulfate (DHEAS). The basis for this action is related to the increase in the zona reticularis and in the increased activity of the 17-hydroxylase and the 17,20-lyase enzymes. Independent of the increase in ovarian androgen secretion accompanying puberty, the increase in adrenal androgens owing to adrenarche can account for significant increases in pubic and axillary hair and sweat production by the axillary pilosebaceous units.

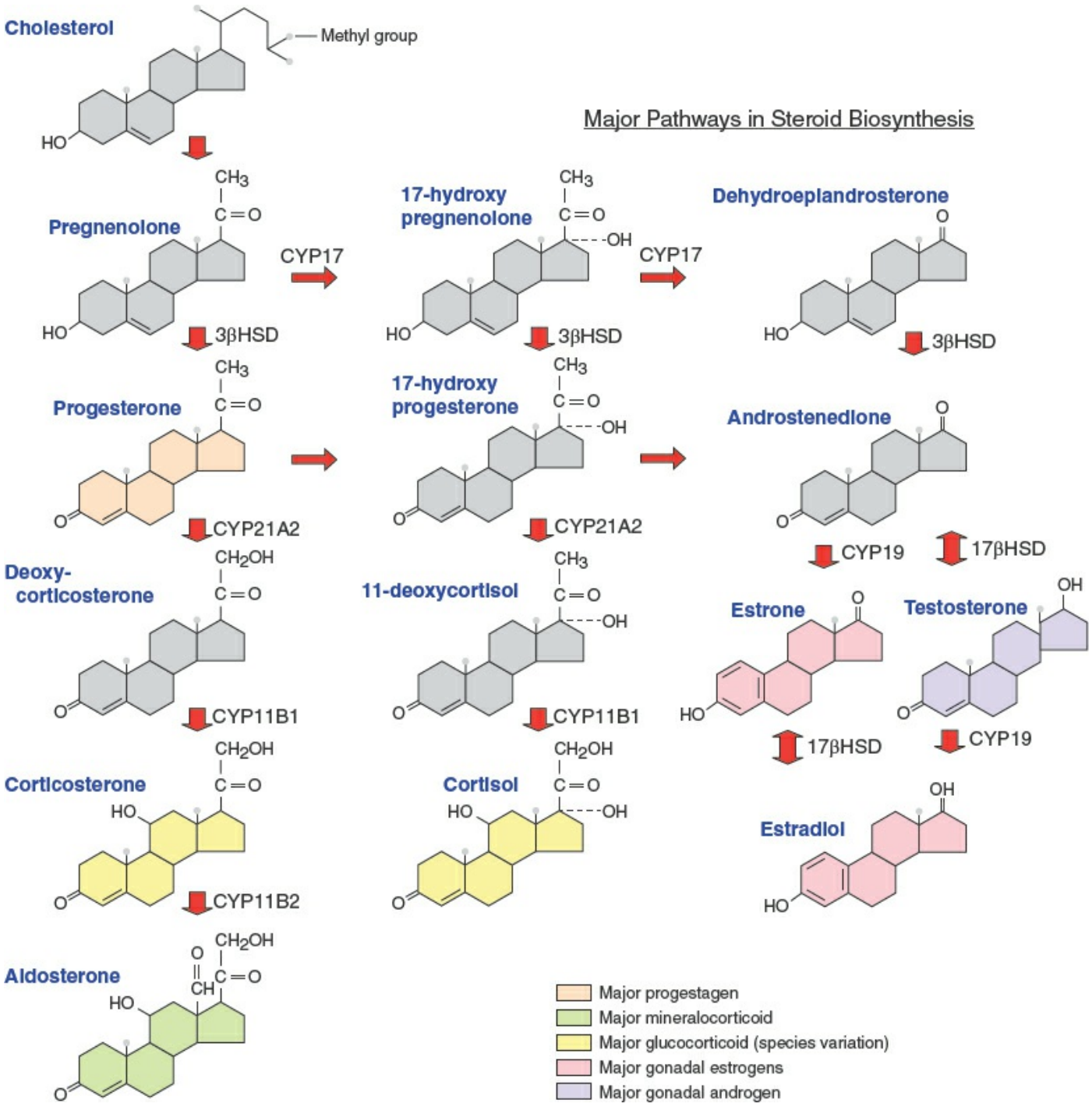


FIGURE 35-2 Major steroid biosynthesis pathway.

Testosterone

Approximately half of a woman's serum testosterone is derived from peripheral conversion of secreted androstenedione and the other half is derived from direct glandular (ovarian and adrenal) secretion. The ovaries and adrenal glands contribute about equally to testosterone production in women. The contribution of the adrenals is achieved primarily through secretion of androstenedione.

Approximately 66% to 78% of circulatory testosterone is bound to sex hormone–

binding globulin (SHBG) and is considered biologically inactive. Most of the proportion of serum testosterone that is not bound to SHBG is weakly associated with albumin (20% to 32%). A small percentage (1% to 2%) of testosterone is entirely unbound or free. **The fraction of circulating testosterone that is unbound by SHBG has an inverse relationship with the SHBG concentration.** Increased SHBG levels are noted in conditions associated with high estrogen levels. Pregnancy, the luteal phase, use of estrogen (including oral contraceptives [OCs]), and conditions causing elevated thyroid hormone levels and cirrhosis are associated with reduced fractions of free testosterone as a result of elevated SHBG levels. Conversely, levels of SHBG decrease and result in elevated free testosterone fractions in response to androgens, androgenic disorders (PCOS, adrenal hyperplasia or neoplasm, Cushing syndrome), androgenic medications (i.e., progestational agents with androgenic biologic activities, such as *danazol*, glucocorticoids, and growth hormones), hyperinsulinemia, obesity, and prolactin.

Laboratory Assessment of Hyperandrogenemia

In hyperandrogenic states, increases in testosterone production are not proportionately reflected in increased total testosterone levels because of the depression of SHBG levels that occurs concomitant with increasing androgen effects on the liver. Therefore, when moderate HA, characteristic of many functional hyperandrogenic states, occurs, elevations in total testosterone levels may remain within the normal range, and only free testosterone levels will reveal the HA. **Severe HA, as occurs in virilization and that results from neoplastic production of testosterone, is reliably detected by measures of total testosterone.** Therefore, in practical clinical evaluation of the hyperandrogenic patient, determination of the total testosterone level in concert with clinical assessment is frequently sufficient for diagnosis and management. When more precise delineation of the degree of HA is desired, measurement or estimation of free testosterone levels can be undertaken and will more reliably reflect increases in testosterone production. These measurements are not necessary in evaluating the majority of patients, but they are common in clinical research studies and may be useful in some clinical settings. Because many practitioners measure some form of testosterone level, they should understand the methods used and their accuracy. Although equilibrium dialysis is the gold standard for measuring free testosterone, it is expensive, complex, and usually limited to research settings. **In a clinical setting, free testosterone levels can be estimated by assessment of testosterone binding to albumin and SHBG.**

Testosterone that is nonspecifically bound to albumin (AT) is linearly related to free testosterone (FT) by the equation:

$$AT = K_a[A] \times FT$$

where AT is the albumin-bound testosterone, K_a is the association constant of albumin for testosterone, and [A] is the albumin concentration.

In many cases of hirsutism, albumin levels are within a narrow physiologic range and thus do not significantly affect the free testosterone concentration. When physiologic albumin levels are present, the free testosterone level can be estimated by measuring the total testosterone and SHBG. In individuals with normal albumin levels, this method has reliable results compared with those of equilibrium dialysis. It provides a rapid, simple, and accurate determination of the total and calculated free testosterone levels as well as the concentration of SHBG.

The bioavailable testosterone level is based on the relationship of albumin and free testosterone and incorporates the actual albumin level with the total testosterone and SHBG. This combination of total testosterone, SHBG, and albumin level measurements —bioavailable testosterone level—can be applied to derive a more accurate estimate of available bioactive testosterone and thus the androgen effect derived from testosterone. Bioactive testosterone determined in this manner provides a superior estimate of the effective androgen effect derived from testosterone (5).

Pregnancy can alter the accuracy of measurements of bioavailable testosterone. During pregnancy, high circulating estradiol levels occupy a large proportion of SHBG binding sites, so that measurement of SHBG levels can overestimate the binding capacity of SHBG for testosterone. Derived estimates of free testosterone, as opposed to direct measure by equilibrium dialysis, are therefore inaccurate during pregnancy. Testosterone measurements in pregnancy are primarily of interest when autonomous secretion by tumor or luteoma is in question, and for these, total testosterone determinations provide sufficient information for diagnosis.

For testosterone to exert its biologic effects on target tissues, it must be converted into its active metabolite, DHT, by 5α-reductase (a cytosolic enzyme that reduces testosterone and androstenedione). Two isozymes of 5α-reductase exist: type 1, which predominates in the skin, and type 2, or acidic 5α-reductase, which is found in the liver, prostate, seminal vesicles, and genital skin. The type 2 isozyme has a 20-fold higher affinity for testosterone than type 1. Both type 1 and 2 deficiencies in males result in ambiguous genitalia, and both isozymes may play a role in androgen effects on hair growth. Dihydrotestosterone is more potent than testosterone, primarily because of its higher affinity and slower dissociation from the androgen receptor. Although DHT is the key intracellular mediator of most androgen effects, measurements of circulating levels are not clinically useful. The relative androgenicity of androgens is as follows: DHT = 300, Testosterone = 100, Androstenedione = 10, DHEAS = 5.

Until adrenarche, androgen levels remain low. Around 8 years of age, adrenarche is heralded by a marked increase in DHEA and DHEAS. The half-life of free DHEA is extremely short (about 30 minutes) but extends to several hours, if DHEA is sulfated. Although no clear role is identified for DHEAS, it is associated with stress, and levels

decline steadily throughout adult life. **After menopause, ovarian estrogen secretion ceases, and DHEAS levels continue to decline, whereas testosterone levels are maintained or may even increase.** Although postmenopausal ovarian steroidogenesis contributes to testosterone production, testosterone levels retain diurnal variation, reflecting an ongoing and important adrenal contribution**.** Peripheral aromatization of androgens to estrogens increases with age, but because small fractions (2% to 10%) of androgens are metabolized in this fashion, such conversion is rarely of clinical significance.

Laboratory Evaluation

The 2008 Endocrine Society Clinical Practice Guidelines suggested testing for elevated androgen levels in women with moderate (Ferriman–Gallwey hirsutism score 9 or greater) or severe hirsutism or hirsutism of any degree when it is sudden in onset, rapidly progressive, or associated with significant acne, obesity, or clitoromegaly. These guidelines suggested against testing for elevated androgen levels in women with isolated mild hirsutism, such as is associated with PCOS, because the likelihood of identifying a medical disorder that would change management or outcome is extremely low (Fig. 35-3) (4).

When laboratory testing for the assessment of hirsutism is indicated, either a bioavailable testosterone level (includes a total testosterone, SHBG, and albumin level) or a calculated free testosterone level (if albumin levels are assumed to be normal) provides the most accurate assessment of the effective androgen effect derived from testosterone. In clinical situations requiring a testosterone evaluation, the addition of 17-hydroxyprogesterone (17-OHP) will screen for adult-onset adrenal hyperplasia, when indicated (Table 35-1). When hirsutism is accompanied by absent or abnormal menstrual periods, assessment of prolactin and thyroid-stimulating hormone (TSH) values is required to diagnose an ovulatory disorder. Hypothyroidism and hyperprolactinemia may result in reduced levels of SHBG and may increase the fraction of unbound testosterone levels, occasionally resulting in hirsutism. In cases of suspected Cushing syndrome, patients should undergo screening with a 24-hour urinary cortisol (most sensitive and specific) assessment or an overnight *dexamethasone* suppression test. For this test, the patient takes 1 mg of *dexamethasone* at 11 pm, and a blood cortisol assessment is performed at 8 am the next day. Cortisol levels of 2 μg/dL or higher after overnight *dexamethasone* suppression require a further workup for evaluation of Cushing syndrome. Elevated 17-OHP levels identify patients who may have AOAH, found in 1% to 5% of hirsute women. The 17-OHP levels can vary significantly within the menstrual cycle, increasing in the periovulatory period and luteal phase, and may be modestly elevated in PCOS. Standardized testing requires early morning testing during the follicular phase.


Hirsutism (adolescent, adult)
Ferriman – Gallwey Score with clinical assessment Figure 35-1, p 890–892
<8
≥9
If moon facies, plethora, striae, dorsoclavicular or supraclavicular fat pads and proximal muscle weakness perform Cushing Syndrome screen
Trial of OCPs, cosmetic and dematologic treatments
No response
Assess for possible PCOS, AOAH, ovarian or adrenocortical tumor
24-hour urinary cortisol
>45 µg/day
Cushing Syndrome Evaluation Tables 35-6 & 35-7 Fig. 37-7, p 907–910
>300 ng/dL
17 OH progesterone bioavailable testosterone (total and free testosterone and SHBG) p 893–896
ACTH stimulation
>1000 ≤10,000 ng/dL
AOAH p 910–912
>10,000 ng/dl CAH p 910–912
Total testosterone >200 ng/dL Free testosterone >6.85 pg/mL
Total Testosterone >80 <150 ng/dL Free testosterone mildly elevated
Total testosterone and 17 OH Progesterone normal
11 Desoxycortisol >7 ng/mL 24 hr urinary cortisol >45 µg/day DHEAS >360 µg/dL Table 35-2
PCOS Figs. 35-4 to 35-6 Table 35-5 p 896–907 Hyperthecosis p 913 HAIR-AN p 900–903 Metabolic syndrome p 900–903
PCOS and Idiopathic hirsutism Figs. 35-4 to 35-6 Table 35-5 p 896–907 Hyperthecosis p 913 HAIR-AN p 900–903 Metabolic syndrome p 900–903
Ovarian or Adrenocorticol Tumor–Androgen Secreting (ACT-AS)
Radiologic consultation and and evaluation
Adrenal androgen secreting tumor usually >1.5 cm and detectable by CT (70–90% sensitivity) Ovarian androgen secreting tumors usually<2cm Selective venous sampling may be required p 912–913

FIGURE 35-3 Evaluation of hirsute women for hyperandrogenism. Evaluation includes more than the assessment of the degree of hirsutism. When hirsutism is moderate (>9) or severe or if mild hirsutism is accompanied by features that suggest an underlying disorder, elevated androgen levels should be ruled out. Disorders to be considered include endocrinopathies, of which PCOS is the most common, and neoplasms. Plasma testosterone is best assessed in the early morning on days 4 to 10 in regularly cycling women. A 17-hydroxyprogesterone is also indicated when symptoms warrant a bioavailable testosterone measurement. *3β-hydroxysteroid dehydrogenase deficiency in severe forms presents with mineralocorticoid and cortisol deficiency. Mild forms are diagnosed with a mean post-ACTH(1-24) stimulation: 17-hydroxypregnenolone/17-hydroxyprogesterone ratio of 11 compared with 3.4 in normals. 11β-hydroxylase deficiency presents with hypertension in the first years of life in two-thirds of patients. The mild form presents with vitalization or precocious puberty without hypertension. Undiagnosed adults demonstrate hirsutism, acne, and amenorrhea. Diagnosis is confirmed with an 11-desoxycortisol level >25 ng/mL 60 minutes after ACTH(1-24) stimulation. ACTH, adrenocorticotropic hormone; AOAH, adult-onset adrenal hyperplasia; DHEAS, dehydroepiandrosterone sulfate; HAIR-AN, hyperandrogenemia, insulin resistance-acanthosis nigricans (see references (2–11,15)).

Table 35-1 Normal Values for Serum Androgens[a]

Testosterone (total)	20–80 ng/dL
Free testosterone (calculated)	0.6–6.8 pg/mL
Percentage free testosterone	0.4–2.4%
Bioavailable testosterone	1.6–19.1 ng/dL
SHBG	18–114 nmol/L
Albumin	3,300–4,800 mg/dL
Androstenedione	20–250 ng/dL
Dehydroepiandrosterone sulfate	100–350 µg/dL
17-Hydroxyprogesterone (follicular phase)	30–200 ng/dL

[a]Normal values may vary among different laboratories. Free testosterone is calculated using measurements for total testosterone and sex hormone–binding globulin, whereas bioavailable testosterone is calculated using measured total testosterone, sex hormone–binding globulin, and albumin. Calculated values for free and bioavailable testosterone compare well with equilibrium dialysis methods of measuring unbound testosterone when albumin levels are normal. Bioavailable testosterone includes free plus very weakly bound (non-SHBG, nonalbumin) testosterone. Bioavailable testosterone is the most accurate assessment of bioactive testosterone in the serum without performing equilibrium dialysis.

According to the Endocrine Society clinical guidelines, patients with morning follicular phase 17-OHP levels of less than 300 ng/dL (10 nmol/L) are likely unaffected. When levels are greater than 300 ng/dL but less than 10,000 ng/dL (300 nmol/L), ACTH testing should be performed to distinguish between PCOS and AOAH. Levels greater than 10,000 ng/dL (300 nmol/L) are virtually diagnostic of congenital adrenal hyperplasia.

Precocious puberty (PP) precedes the diagnosis of adult-onset congenital adrenal hyperplasia in 5–20% of cases. Measurement of 17-OHP should be performed in

patients presenting with PP and a subsequent ACTH stimulation test is recommended if basal 17-OHP is greater than 200 ng/dL. A study using a 200 ng/dL threshold for basal 17-OHP plasma levels to prompt ACTH stimulation testing offered 100% (95% confidence interval [CI], 69 to 100) sensitivity and 99% (95% CI, 96 to 100) specificity for the diagnosis of adult-onset congenital adrenal hyperplasia within the cohort with PP (6).

Because increased testosterone production is not reliably reflected by total testosterone levels, the clinician may choose to rely on typical male pattern hirsutism as confirmation of its presence, or may elect measures that reflect levels of free or unbound testosterone (bioavailable or calculated free testosterone levels). Total testosterone does, however, serve as a reliable marker for testosterone-producing neoplasms. **Total testosterone levels greater than 200 ng/dL should prompt a workup for ovarian or adrenal tumors.**

Although the ovary is the principal source of androgen excess in most of PCOS patients, between 20% and 30% of patients with PCOS will demonstrate elevated levels of DHEAS, particularly when overweight. Measuring circulating levels of DHEAS has very limited diagnostic value, and overinterpretation of DHEAS levels should be avoided (7).

Previously, testing for androgen conjugates (e.g., 3α-androstenediol G [3α-diol G] and androsterone G [AOG] as markers for 5α-reductase activity in the skin) was advocated. Routine determination of androgen conjugates to assess hirsute patients is not recommended, because hirsutism itself is an excellent bioassay of free testosterone action on the hair follicle and because these androgen conjugates arise from adrenal precursors and are likely markers of adrenal and not ovarian steroid production (8).

In the zona reticularis layer of the adrenal cortex, DHEAS is generated by *SULT2A1* (9). This layer of the adrenal cortex is thought to be the primary source of serum DHEAS. DHEAS levels decline as a person ages and the reticularis layer diminishes in size. In most laboratories, the upper limit of a DHEAS level is 350 µg/dL (9.5 nmol/L). A random sample is sufficient because the level of variation is minimized as a result of the long half-life characteristic of sulfated steroids. DHEAS is used as a screen for androgen-secreting adrenocortical tumors (ACT-AS); however, moderate elevations are a common finding in the presence of PCOS, obesity, and stress, which reduces its specificity in testing for ACT-AS (10).

A study of women with ACT-AS (N = 44), compared to women with nontumor androgen excess (NTAE) (N = 102), sheds additional light on the choice of hormones used to screen for an adrenocortical tumor. In the study, the demographics and prevalence of hirsutism, acne, and oligo/amenorrhea were not different. Free testosterone (free T) was the most commonly elevated androgen in ACT-AS (94%), followed by androstenedione (A) (90%), DHEAS (82%), and total testosterone (total T) (76%), and all three androgens were simultaneously elevated in 56% of the cases.

Serum androgen levels became subnormal in all ACT-AS patients after the tumor was removed. In NTAE alone, the most commonly elevated androgen was androstenedione (93%), while all three androgens (T, A, and DHEAS) were elevated in only 22% of the cases. Free testosterone values above 6.85 pg/mL (23.6 pmol/L) had the best diagnostic value for ACT-AS (sensitivity 82%, 95% CI 57% to 96%; specificity 97%, 95% CI 91% to 100%; Table 35-2). The large overlap of androstenedione, testosterone, and DHEAS levels between ACT-AS and androgen excess groups suggests that thoughtful consideration should be employed when choosing hormone studies for this evaluation (11).

The heterogeneity of hormone secretion patterns in the adrenocortical tumor group reveals the complexities of hormone-level screening for adrenocortical tumors: 7 of 44 patients (15.9%) had tumors secreting androgens alone, 2 of 44 (4.5%) had tumors secreting androgens and estrogens, and 28 of 44 (63.6%) had tumors secreting both androgens and cortisol, and 7 of 44 (15.9%) had tumors secreting androgens, cortisol, and estrogens. Compound S or 11-desoxycortisol was increased (≥10 ng/mL or 28.9 nmol/L) in 23 of 27 ACT-AS patients (85%), 20 of 21 patients with malignant tumors, and 3 of 6 patients with apparently benign tumors, although 11-desoxycortisol was normal and inferior to 6 ng/mL (17.3 nmol/L) in 35 of 35 NTAE patients (100%). Youden's index displayed that 11-desoxycortisol level above 7 ng/mL (20.2 nmol/L) has a sensitivity of 89% (95% CI 71% to 98%) and a specificity of 100% (95% CI 90% to 100%) for the detection of ACT-AS (11,12).

Thus, when signs of androgen excess reach the point of virilization or the free testosterone level is above 6.85 pg/mL (23.6 pmol/L), follow-up testing with an 11-desoxycortisol >7 ng/mL, DHEAS >3.6 lg/mL, and 24-hour urinary cortisol >45 lg per day are the most sensitive and specific for the detection of an ACT-AS. Careful consideration of the sensitivity and specificity, diurnal variation, and age-related variation of potentially measureable androgens will aid in choosing the most useful measurements (Table 35-2). Clinically, assessment of androgens is uncommon in routine practice and is performed when hirsutism is sudden in onset, rapidly progressive, or associated with significant acne, obesity, or clitoromegaly. Mild hirsutism associated with clinical findings of PCOS very rarely yields actionable results.

Table 35-2 Sensitivity and Specificity of Basal Hormone Levels in the Evaluation of Female Patients With Androgen-Secreting Adrenocortical Tumors (ACT-AS) and Nontumor Causes of Androgen Excess (NTAE)

	ACT-AS (*n*)	NTAE (*n*)	Sensitivity% (CI)	Specificity% (CI)
Total testosterone >1.25 ng/mL	42	102	60 (45–74)	94 (90–99)
Free testosterone >6.85 pg/mL	17	77	82 (57–96)	97 (91–100)
Androstenedione >4.65 ng/mL	38	99	66 (49–80)	80 (71–87)
DHEAS >3.6 µg/mL	39	97	79 (64–91)	79 (70–87)
17OHP >1.95 ng/mL	36	79	67 (49–81)	86 (76–93)
11-desoxycortisol >7 ng/mL	27	35	89 (71–98)	100 (90–100)

Thresholds were selected using Youden's index, as described in the methods.

CI, 95% confidence intervals.

Reprinted with permission from **d'Alva CB, Abiven-Lepage G, Viallon V, et al.** Sex steroids in androgen-secreting adrenocortical tumors: clinical and hormonal features in comparison with non-tumoral causes of androgen excess. *Eur J Endocrinol* 2008;159:641–647.

Polycystic Ovary Syndrome

PCOS is one of the most common endocrine disorders in women of reproductive age, affecting 5% to 10% of women worldwide. This familial disorder appears to be inherited as a complex genetic trait (13). It is characterized by a combination of HA (either clinical or biochemical), chronic anovulation, and polycystic ovaries. It is frequently associated with insulin resistance (IR) and obesity (14). PCOS receives considerable attention because of its high prevalence and possible reproductive, metabolic, and cardiovascular consequences. **It is the most common cause of HA, hirsutism, and anovulatory infertility in developed countries** (15,16). The association of amenorrhea with bilateral polycystic ovaries and obesity was first described in 1935 by Stein and Leventhal (17). Its genetic origins are likely polygenic and/or multifactorial (18).

Diagnostic Criteria

In an international conference on PCOS organized by the National Institutes of Health (NIH) in 1990, diagnostic criteria for PCOS were based on consensus rather than clinical trial evidence. Their diagnostic criteria recommended clinical and/or biochemical evidence of HA, chronic anovulation, and exclusion of other known disorders. These criteria were an important initial step in standardizing diagnosis and led to a number of landmark randomized clinical trials in PCOS (19).

Since the 1990 NIH-sponsored PCOS conference, evolving perception is that the syndrome may constitute a broader spectrum of signs and symptoms of ovarian dysfunction than those set forth in the original NIH diagnostic criteria. The 2003 Rotterdam Consensus Workshop concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features HA and polycystic ovary (PCO) morphology (Table 35-3).

It is recognized that women with regular cycles, HA, and PCO morphology may be part of the syndrome. It is also recognized that some women with the syndrome will have PCO morphology without clinical evidence of androgen excess, but will display evidence of ovarian dysfunction with irregular cycles. In this new schema, PCOS remains a diagnosis of exclusion with the need to rule out other disorders that mimic the PCOS phenotype (19).

Applying the recommended Rotterdam PCOS Diagnostic Criteria, the presence of two of the three criteria is sufficient to diagnosis PCOS: menstrual cycle anomalies (amenorrhea, oligomenorrhea), clinical and/or biochemical HA, and/or the ultrasound appearance of polycystic ovaries after all other diagnoses are ruled out. [2] This approach results in four phenotypes: (1) HA (clinical or biochemical) with ovarian dysfunction and PCO morphology, (2) HA (clinical or biochemical) with ovarian dysfunction, (3) HA (clinical or biochemical) with PCO morphology, (4) ovarian dysfunction and PCO morphology. This diagnostic approach for PCOS has been ratified by the Endocrine Society (2013) for adult women, but in adolescents the diagnosis should be based on persistent anovulation and clinical or biochemical HA. Other pathologies that can result in a PCOS phenotype include AOAH, adrenal or ovarian neoplasm, Cushing syndrome, hypo- or hypergonadotropic disorders, hyperprolactinemia, and thyroid disease (Fig. 35-4).

All other frequently encountered manifestations offer less consistent findings and therefore qualify only as minor diagnostic criteria for PCOS. They include elevated LH-to-FSH (follicle-stimulating hormone) ratio, IR, perimenarchal onset of hirsutism, and obesity.

Table 35-3 Revised Diagnostic Criteria of Polycystic Ovary Syndrome

1990 Criteria (both 1 and 2)
1. Chronic anovulation
2. Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies
Revised 2003 criteria (2 out of 3)
1. Oligoovulation or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome)

With permission from Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;81:19–25.

Clinical HA includes hirsutism, male pattern alopecia, and acne (19). Hirsutism occurs in approximately 70% of patients with PCOS in the United States and in only 10% to 20% of patients with PCOS in Japan (20,21). A likely explanation for this discrepancy is the genetically determined differences in skin 5α-reductase activity (22,23).

Nonclassic adrenal hyperplasia and PCOS may present with similar clinical features. It is important to measure the basal follicular phase 17-OHP level in all women presenting with hirsutism to exclude the presence of nonclassic congenital adrenal hyperplasia, regardless of the presence of polycystic ovaries or metabolic dysfunction (24).

The menstrual dysfunction in PCOS arises from anovulation or oligo-ovulation and ranges from amenorrhea to oligomenorrhea. Regular menses in the presence of anovulation in PCOS is uncommon, though one report found that among hyperandrogenic women with regular menstrual cycles, the rate of anovulation is 21% (25). **Classically, PCOS is lifelong and characterized by abnormal menses from puberty with acne and hirsutism arising in the teens. It may, however, arise in adulthood, concomitant with the emergence of obesity, presumably because this is accompanied by increasing hyperinsulinemia** (26).

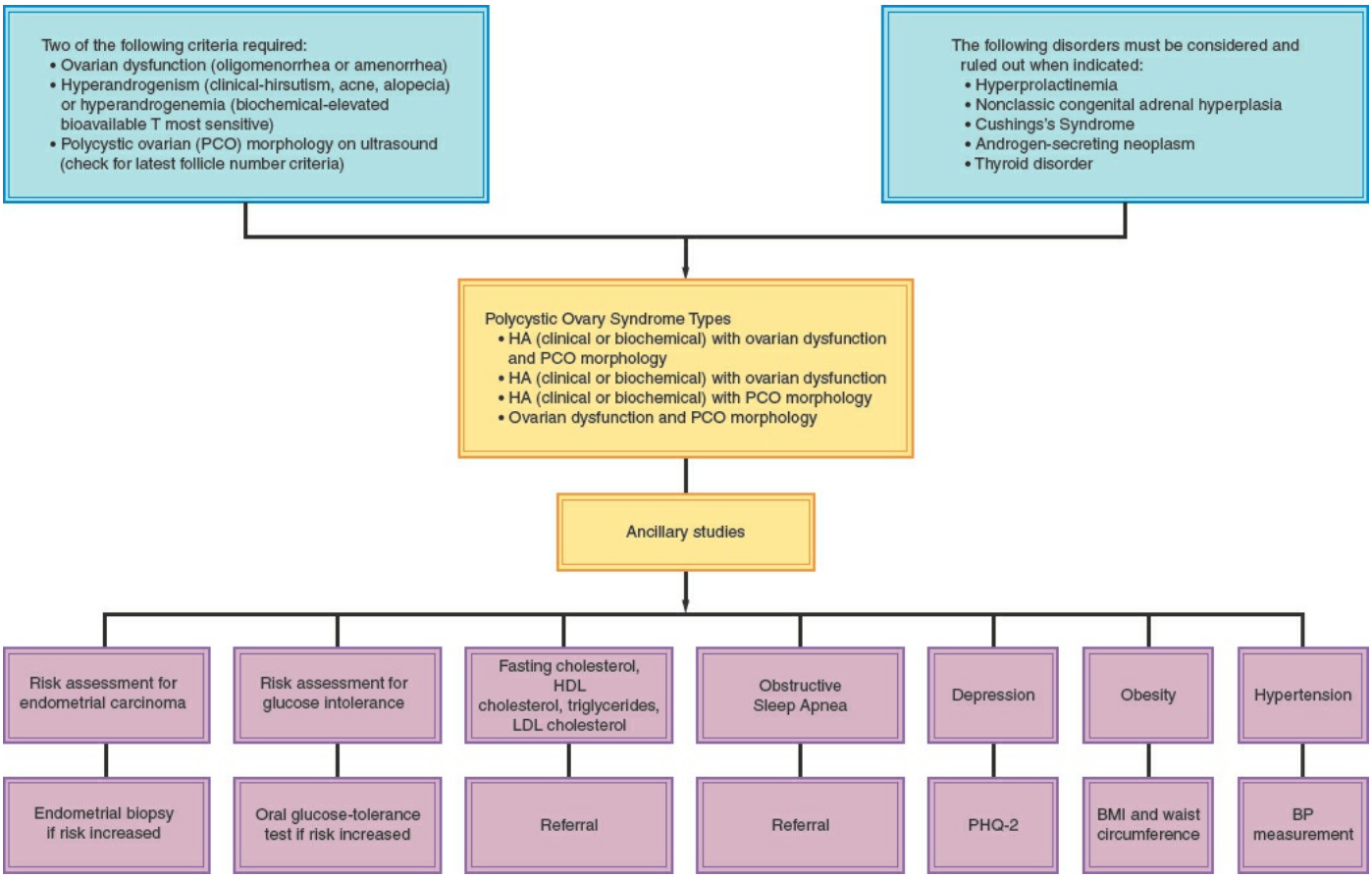


FIGURE 35-4 Diagnostic algorithm for polycystic ovary syndrome. (Modified with permission from

Rosenfield RL. Clinical practice. Hirsutism. *N Engl J Med* 2005;353:2578–2588.)

The sonographic criteria for PCOS morphology requires the presence of 20 or more follicles in either ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL). A single ovary meeting these criteria is sufficient to affix the PCO morphology (27). The appearance of PCO on ultrasound scanning is common. Only a fraction of those with PCO appearance, however, have the clinical and/or endocrine features of PCOS. A PCO appearance is found in about 23% of women of reproductive age, while estimates of the incidence of PCOS vary between 5% and 10% (28). Polycystic appearing ovaries in women with PCOS were not associated with increased cardiovascular disease risk, and were independent of body mass index (BMI), age, and insulin levels (29). An English study demonstrated that without symptoms of PCOS, a PCO appearance alone is not associated with impaired fecundity or fertility (30). Other studies indicate that anti-mullerian hormone (AMH) is a reliable predictor of the small (2 to 9 mm) antral follicle count independent of PCOS or ovarian morphology (31).

Obesity occurs in more than 50% of patients with PCOS. The body fat is usually deposited centrally (android obesity), and a higher waist-to-hip ratio is associated with IR indicating an increased risk of diabetes mellitus and cardiovascular disease (32). Among women with PCOS, there is widespread variability in the degree of adiposity by geographic location and ethnicity. In studies in Spain, China, Italy, and the United States, the percentage of obese women with PCOS were 20%, 43%, 38%, and 69%, respectively (33).

Because increased adiposity, particularly abdominal, is associated with hyperandrogenemia and increased metabolic risk, it is recommended that PCOS patients have a BMI calculation and measurement of waist circumference.

Insulin resistance resulting in hyperinsulinemia is commonly exhibited in PCOS. Insulin resistance may eventually lead to the development of hyperglycemia and type 2 diabetes mellitus (34). About one-third of obese PCOS patients have impaired glucose tolerance (IGT), and 7.5% to 10% have type 2 diabetes mellitus (35). These rates are mildly increased even in nonobese women who have PCOS (10% IGT and 1.5% diabetes), compared with the general population of the United States (7.8% IGT and 1% diabetes) (36,37). **Because of the high risk of IGT and type 2 diabetes mellitus in PCOS, periodic screening of patients to detect early abnormalities in glucose tolerance is recommended (fasting and a 2-hour glucose level using a 75-g oral glucose load).**

Abnormal lipoproteins are common in PCOS and include elevated total cholesterol, triglycerides, and low-density lipoproteins (LDL) and low levels of high-density lipoproteins (HDL) and apoprotein A-I (32,38). According to one report, the most characteristic lipid alteration is decreased levels of $HDL_{2\alpha}$ (39).

Other observations in women with PCOS include impaired fibrinolysis, as shown by elevated circulating levels of plasminogen activator inhibitor (40), an increased incidence of hypertension over the years (which reaches 40% by perimenopause), a greater prevalence of atherosclerosis and cardiovascular disease, and an estimated 7-fold increased risk for myocardial infarction (38,40–43). It is recommended that adolescents and women with PCOS be screened for the following cardiovascular disease risk factors: family history of early cardiovascular disease, cigarette smoking, IGT/T2DM, hypertension, dyslipidemia, obstructive sleep apnea, and obesity (especially increased abdominal adiposity) and manage these when present **(Fig. 35-4)**.

Pathology

Macroscopically, ovaries in women with PCOS are two to five times the normal size. A cross section of the surface of the ovary discloses a white, thickened cortex with multiple cysts that are typically less than a centimeter in diameter. Microscopically, the superficial cortex is fibrotic and hypocellular and may contain prominent blood vessels. In addition to smaller atretic follicles, there is an increase in the number of follicles with luteinized theca interna. The stroma may contain luteinized stromal cells (44).

Pathophysiology and Laboratory Findings

The HA and anovulation that accompany PCOS may be caused by abnormalities in four endocrinologically active compartments: (i) the ovaries, (ii) the adrenal glands, (iii) the periphery (fat), and (iv) the hypothalamus–pituitary compartment **(Fig. 35-5)**.

In patients with PCOS, the ovarian compartment is the most consistent contributor of androgens. Dysregulation of CYP17, the androgen-forming enzyme in both the adrenals and the ovaries, may be one of the pathogenetic mechanisms underlying HA in PCOS (45). The ovarian stroma, theca, and granulosa contribute to ovarian HA and are stimulated by LH (46). This hormone relates to ovarian androgenic activity in PCOS in a number of ways.

1. Total and free testosterone levels correlate directly with LH levels (47).
2. The ovaries are more sensitive to gonadotropic stimulation, possibly as a result of CYP17 dysregulation (45).
3. Treatment with a gonadotropin-releasing hormone (GnRH) agonist effectively suppresses serum testosterone and androstenedione levels (48).
4. Larger doses of a GnRH agonist are required for androgen suppression than for endogenous gonadotropin-induced estrogen suppression (49).

The increased testosterone levels in patients with PCOS are considered ovarian in origin. The serum total testosterone levels are usually no more than twice the upper normal range (20 to 80 ng/dL). However, in ovarian hyperthecosis, values

may reach 200 ng/dL or more (50). The adrenal compartment plays a role in the development of PCOS. Although the hyperfunctioning CYP17 androgen-forming enzyme coexists in the ovaries and the adrenal glands, DHEAS is increased in only about 50% of patients with PCOS (51,52). The hyperresponsiveness of DHEAS to stimulation with ACTH, the onset of symptoms around puberty, and the observation of 17,20-lyase activation (one of the two CYP17 enzymes) are key events in adrenarche that led to the hypothesis that PCOS arises as an exaggeration of adrenarche (50).

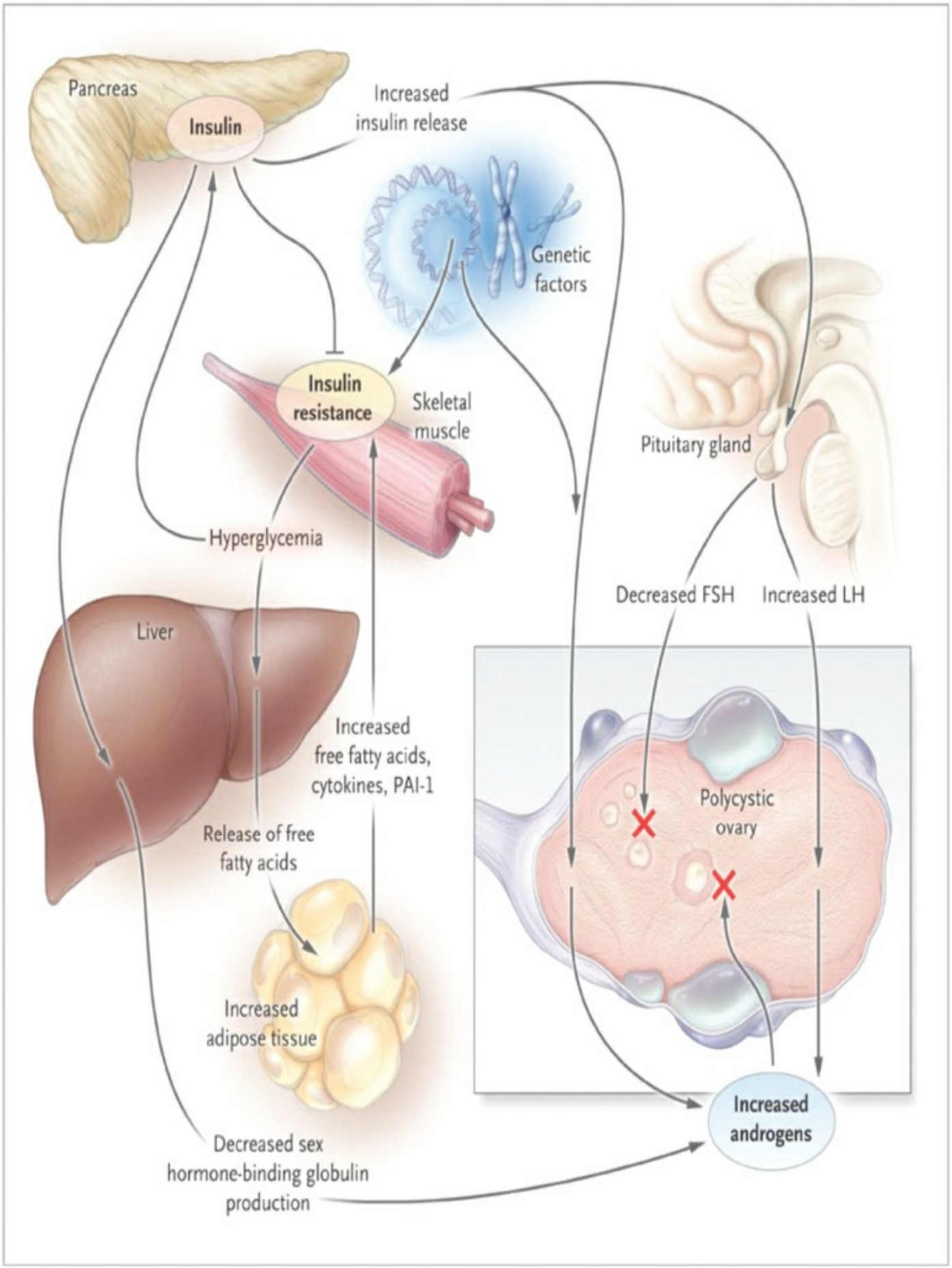

Pancreas
Insulin
Increased
insulin release
Genetic
factors
Insulin
resistance
Skeletal
muscle
Pituitary gland
Hyperglycemia
Decreased FSH
Increased LH
Liver
Increased
free fatty acids,
cytokines, PAI-1
Polycystic
ovary
Release of free
fatty acids
Increased
adipose tissue
Increased
androgens
Decreased sex
hormone-binding globulin
production

FIGURE 35-5 Pathophysiologic characteristics of the polycystic ovary syndrome (PCOS). Insulin resistance results in a compensatory hyperinsulinemia, which stimulates ovarian androgen production in an ovary genetically predisposed to PCOS. Arrest of follicular development (*red "X"*) and anovulation could be caused by the abnormal secretion of gonadotropins such as follicle-stimulating hormone (FSH) or luteinizing hormone (LH) (perhaps induced by hyperinsulinemia), intraovarian androgen excess, direct effects of insulin, or a combination of these factors. Insulin resistance, in concert with genetic factors, may also lead to hyperglycemia and an adverse profile of cardiovascular risk factors. (Modified with permission from **Rosenfield RL**. Clinical practice. Hirsutism. *N Engl J Med* 2005;353:2578–2588.)

The peripheral compartment, defined as the skin and the adipose tissue, manifests its contribution to the development of PCOS in several ways.

1. The presence and activity of 5α-reductase in the skin largely determines the presence or absence of hirsutism (23,24).
2. Aromatase and 17β-hydroxysteroid dehydrogenase activities are increased in fat cells and peripheral aromatization is increased with increased body weight (53,54).
3. With obesity, the metabolism of estrogens, by way of reduced 2-hydroxylation and 17α-oxidation, is decreased and metabolism via estrogen active 16-hydroxyestrogens (estriol) is increased (55).
4. While E2 (estradiol) is at a follicular phase level in patients with PCOS, E1 (**estrone**) levels are increased as a result of peripheral aromatization of androstenedione (56).
5. A chronic hyperestrogenic state, with reversal of the E1-to-E2 ratio, results and is unopposed by progesterone.

The hypothalamic–pituitary compartment also participates in aspects critical to the development of PCOS.

1. An increase in LH pulse frequency relative to those in the normal follicular phase is the result of increased GnRH pulse frequency (57).
2. This increase in LH pulse frequency explains the frequent observation of an elevated LH and LH-to-FSH ratio.
3. FSH is not increased with LH, likely because of the combination of increased gonadotropin pulse frequency and the synergistic negative feedback of chronically elevated estrogen levels and normal follicular inhibin.
4. About 25% of patients with PCOS exhibit mildly elevated prolactin levels, which may result from abnormal estrogen feedback to the pituitary gland. In some patients with PCOS, *bromocriptine* has reduced LH levels and restored ovulatory function (58).

PCOS is a complex multigenetic disorder that results from the interaction between multiple genetic and environmental factors. **Genetic studies of PCOS reported allele sharing in large PCOS patient populations. Linkage studies focused on candidate**

genes, most likely to be involved in the pathogenesis of PCOS, reveal genes grouped into four categories: (i) IR-related genes, (ii) genes that interfere with the biosynthesis and the action of androgens, (iii) genes that encode inflammatory cytokines, and (iv) other candidate genes (59).

In PCOS genome-wide association studies (GWAS), there is evidence for candidate genes related to insulin signaling, FSH receptor, insulin receptor, sexual hormone function, type 2 diabetes (T2D), calcium signaling, interleukin-6, teleomerase activity, gamma-aminobutyric acid (GABA) A receptors, and endocytosis (1q22, 2p16.3, 2p21, 3q26.33, 4p12, 4q35.2, 8q24.2, 9q21.32, 9q33.3, 9q22.32, 11p13, 11q22.1, 12q13.2, 12q14.3, 16p13.3, 16q12.1, 19p13.3, 20q13.2) (60). GWAS in a European PCOS cohort has identified six susceptibility loci mapping to 11q22.1 (*YAP1*), 2p21 (*THADA*), 11p14.1 (*FSHB*), 2q34 (*ERBB4*), 12q21.2 (*KRR1*), and 5q31.1 (*RAD50*). The first four have been confirmed in Han Chinese (61).

Other linkage studies have identified the follistatin, *CYP11A*, *Calpain 10*, *IRS-1* and *IRS-2* regions and loci near the insulin receptor (19p13.3), *SHBG*, *TCF7L2*, and the insulin genes, as likely PCOS candidate genes (62–68). A polymorphic variant, *D19S884*, in *FBN3* was found to be associated with risk of PCOS (69). Using theca cells derived from women with PCOS elevated mRNA levels was noted for *CYP11A, 3BHSD2*, and *CYP17* genes with corresponding overproduction of testosterone, 17-α-hydroxyprogesterone, and progesterone. Despite the characteristically heightened steroidogenesis in POCS, the *STARB* gene was not overexpressed (62). Microarray data using theca cells from PCOS women did not identify any genes near the 19p13.3 locus that were differentially expressed; however, the mRNAs of several genes that map to 19p13.3, including the insulin receptor, p114-Rho-GEF, and several expressed sequence tags, were detected in both PCOS and normal theca cells. Those studies identified new factors that might impact theca cell steroidogenesis and function, including *cAMP-GEFII*, genes involved in all-transretinoic acid (atRA) synthesis signaling, genes that participate in the Wnt signal transduction pathway, and transcription factor GATA6. These findings suggest that a 19p13.3 locus or some other candidate gene may be a signal transduction gene that results in overexpression of a suite of genes downstream that may affect steroidogenic activity (70). Polymorphisms in major folliculogenesis genes, *GDF9*, *BMP15*, *AMH*, and *AMHR2*, are not associated with PCOS susceptibility (71).

Insulin Resistance

Patients with PCOS frequently exhibit IR and hyperinsulinemia. Insulin resistance and hyperinsulinemia participate in the ovarian steroidogenic dysfunction of PCOS. Insulin alters ovarian steroidogenesis independent of gonadotropin secretion in PCOS. Insulin and insulin-like growth factor I (IGF-I) receptors are present in the ovarian stromal cells. A specific defect in the early steps of insulin receptor–mediated signaling

(diminished autophosphorylation) was identified in 50% of women with PCOS (72).

Insulin has both direct and indirect roles in the pathogenesis of HA in PCOS. Insulin in collaboration with LH enhances the androgen production of theca cells. Insulin also inhibits the hepatic synthesis of SHBG, the main circulating protein that binds to testosterone, and thus increases the proportion of unbound or bioavailable testosterone (13).

The most common cause of IR and compensatory hyperinsulinemia is obesity, but despite its frequent occurrence in PCOS, obesity alone does not explain this important association (58). The IR associated with PCOS is not solely the result of HA based on the following:

1. Hyperinsulinemia is not a characteristic of HA in general but is uniquely associated with PCOS (73).
2. In obese women with PCOS, 30% to 45% have glucose intolerance or frank diabetes mellitus, whereas ovulatory hyperandrogenic women have normal insulin levels and glucose tolerance (73). It seems that the associations between PCOS and obesity on the action of insulin are synergistic.
3. Suppression of ovarian steroidogenesis in women with PCOS with long-acting GnRH analogs does not change insulin levels or IR (74).
4. Oophorectomy in patients with hyperthecosis accompanied by hyperinsulinemia and hyperandrogenemia does not change IR, despite a decrease in androgen levels (74,75).

Acanthosis nigricans is a reliable marker of IR in hirsute women. This thickened, pigmented, velvety skin lesion is most often found in the vulva and may be present on the axilla, over the nape of the neck, below the breast, and on the inner thigh (76). **The HAIR-AN syndrome consists of HA, IR, and acanthosis nigricans (AN)** (72,77). These patients often have high testosterone levels (>150 ng/dL), fasting insulin levels of greater than 25 µIU/mL (normal <20 to 24 µIU/mL), and maximal serum insulin responses to glucose load (75 g) exceeding 300 µIU/mL (normal is <160 µIU/m: at 2 hours postglucose load).

Screening Strategies for Diabetes, Insulin Resistance and Metabolic Syndrome

Professional societies collectively recommend that obese women with PCOS and nonobese PCOS patients with risk factors for IR, such as a family history of diabetes, should be screened for metabolic syndrome, including glucose intolerance with an Hgb A1c or oral glucose tolerance test (OGTT) (19). **The standard 2-hour OGTT (75 g) provides an assessment of the degrees of hyperinsulinemia and glucose tolerance and yields the highest amount of information for a reasonable cost and risk** (7). **While an HbA1c test alone provides a diagnosis in the setting of**

uncontrolled chronic hyperglycemia, utilizing an OGTT allows early detection and intervention to prevent complications.

Multiple other testing or screening schemas were proposed to assess the presence of hyperinsulinemia and IR. In one, the fasting glucose-to-insulin ratio is determined, and values less than 4.5 indicate IR. Using the 2-hour GTT with insulin levels, 10% of nonobese and 40% to 50% of obese PCOS women have IGT (2-hour glucose level ê140 but Ä199 mg/dL) or overt type 2 diabetes mellitus (any glucose level >200 mg/dL). Some research studies have utilized a peak insulin level of over 150 lIU/mL or a mean level of over 84 lIU/mL over the three blood draws of a 2-hour GTT as a criterion to diagnose hyperinsulinemia.

The documentation of hyperinsulinemia using either the glucose-to-insulin ratio or the 2-hour GTT with insulin is problematic. When compared with the gold standard measure for IR, the hyperinsulemic–euglycemic clamp, it shows that the glucose-to-insulin ratio does not always accurately portray IR. When hyperglycemia is present, a relative insulin secretion deficit is present. This deficient insulin secretion exacerbates the effects of IR and renders inaccurate the use of hyperinsulinemia as an index of IR. Thus, routine measurements of insulin levels may not be particularly useful.

Although detection of IR, per se, is not of practical importance to the diagnosis or management of PCOS, testing women with PCOS for glucose intolerance is of value because their risk of cardiovascular disease may correlate with this finding. An appropriate frequency for such screening depends on age, BMI, and waist circumference, all of which increase risk.

Interventions

Two-Hour Glucose Tolerance Test Normal Glucose Ranges (World Health Organization criteria, after 75-g glucose load)

- **Fasting: 64 to 128 mg/dL**
- **One hour: 120 to 170 mg/dL**
- **Two hours: 70 to 140 mg/dL**

Two-Hour Glucose Values for Impaired Glucose Tolerance and Type 2 Diabetes (World Health Organization criteria, after 75-g glucose load)

- **Normal (2-hour) <140 mg/dL**
- **Impaired (2-hour) = 140 to 199 mg/dL**
- **Type 2 diabetes mellitus (2-hour) = 200 mg/dL**

Abnormal glucose metabolism may be significantly improved with weight reduction, which may also reduce HA and restore ovulatory function (78). **In obese, insulin-resistant women, caloric restriction that results in weight reduction will reduce the**

severity of IR (a 40% decrease in insulin level with a 10-kg weight loss) (79). This decrease in insulin levels should result in a marked decrease in androgen production (a 35% decrease in testosterone levels with a 10-kg weight loss) (80). Exercise also reduces IR, independent from any associated weight loss, but data on the impact of exercise on the principal manifestations of PCOS are lacking.

In addition to addressing of the increased risk for diabetes, the clinician should recognize IR or hyperinsulinemia as a cluster syndrome called metabolic syndrome or dysmetabolic syndrome X. Recognition of the importance of IR or hyperinsulinemia as a risk factor for cardiovascular disease has led to diagnostic criteria for the metabolic syndrome. The more metabolic syndrome criteria present, the higher the level of IR and its downstream consequences. The presence of three of the following five criteria confirms the diagnosis, and an insulin-lowering agent and/or other interventions may be warranted (19).

Metabolic Syndrome Diagnostic Criteria

- **Female waist >35 in (88 cm)**
- **Triglycerides >150 mg/dL**
- **HDL <50 mg/dL**
- **Blood pressure >130/85 mm Hg**
- **Fasting glucose: 110 to 126 mg/dL**
- **Two-hour glucose from 75-g OGTT: 140 to 199 mg/dL**

Risk factors for metabolic syndrome include nonwhite race, sedentary lifestyle, BMI greater than 25, age over 40 years, cardiovascular disease, hypertension, PCOS, hyperandrogenemia, IR, HAIR-AN syndrome, nonalcoholic steatohepatitis (NASH), and a family history of type 2 diabetes mellitus, gestational diabetes, or IGT.

Long-Term Risks and Interventions

Comprehensive treatment of PCOS addresses reproductive, metabolic, and psychological features.

Metabolic Syndrome

A recent report by the Androgen Excess and PCOS Society concluded that **lifestyle management, either alone or combined with antiobesity pharmacologic and/or surgical treatments, should be used as the primary therapy in overweight and obese women with PCOS** (33). Lifestyle management of obesity in PCOS is multifactorial. Dietary management of obesity should focus on reducing body weight, maintaining a lower long-term body weight, and preventing weight gain. An initial weight loss of

greater than or equal to 5% to 10% is recommended. In obese and overweight women with PCOS, dietary interventions with a resultant weight reduction of more than 5% to less than 15% over the starting body weight is associated with a reduction in either total or free testosterone, adrenal androgens, and improvement in SHBG levels. Metabolic improvements in fasting insulin, glucose, glucose tolerance, total cholesterol, triglycerides, plasminogen activator inhibitor-1, and free fatty acids are reported. Clinically, hirsutism, menstrual function, and ovulation are all improved (33).

Structured exercise improves IR and offers significant benefits in PCOS. The incorporation of structured exercise, behavior modification, and stress management strategies as fundamental components of lifestyle management increases the success of the weight loss strategy **(Table 35-4)**.

Even though lifestyle management strategies should be used as the primary therapy in obese and overweight women with PCOS, they are difficult to maintain long term. Alternative approaches to the treatment of obesity include the use of pharmacologic agents, such as *orlistat*, *sibutramine*, and *rimonabant*, or bariatric surgery (33). The NIH clinical recommendations advise bariatric surgery when BMI is greater than 40 kg/m^2 or greater than 35 kg/m^2 in patients with a high-risk, obesity-related condition after failure of other treatments for weight control (33,81).

Table 35-4 Lifestyle Modification Principles Suggested for Obesity Management in Polycystic Ovary Syndrome (PCOS)

Guidelines for Dietary and Lifestyle Intervention in PCOS
1. Lifestyle modification is the first form of therapy, combining behavioral (reduction of psychosocial stressors), dietary, and exercise management
2. Reduced-energy diets (500–1,000 kcal/day reduction) are effective options for weight loss and can reduce body weight by 7–10% over a period of 6–12 months
3. Dietary plans should be nutritionally complete and appropriate for life stage and should aim for <30% of calories from fat, <10% of calories from saturated fat, with increased consumption of fiber, whole-grain breads and cereals, and fruit and vegetables
4. Alternative dietary options (increasing dietary protein, reducing glycemic index, reducing carbohydrate) may be successful for achieving and sustaining a reduced weight but more research is needed in PCOS specifically
5. The structure and support within a weight-management program is crucial and may be more important than the dietary composition. Individualization of the program, intensive follow-up and monitoring by a physician, and support from the physician, family, spouse, and peers will improve retention
6. Structured exercise is an important component of a weight-loss regime; aim for >30 min/day

Reprinted with permission from **Moran LJ, Pasquali R, Teede HJ, et al.** Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril* 2009;92:1966–1982.

Dyslipidemia is one of the most common metabolic disorders seen in PCOS patients (up to 70% prevalence in a US PCOS population) (82). It is associated with IR and HA in combination with environmental (diet, physical, exercise) and genetic factors. Various abnormal patterns include decreased levels of HDL, elevated levels of triglycerides, decreased total and LDL levels, and altered LDL quality (83,84).

To assess cardiovascular risks and potentially prevent disease in patients with PCOS, multiple professional societies have recommended the following (84):

1. Waist circumference and BMI measurement at every visit, using the National Health and Nutrition Examination Survey method.
2. A complete lipid profile based on the American Heart Association guidelines **(Fig. 35-6)**. If the fasting serum lipid profile is normal, it should be reassessed every 2 years or sooner if weight gain occurs.
3. A 2-hour post-75-g oral glucose challenge measurement in PCOS women with a BMI greater than 30 kg/m^2, or alternatively in lean PCOS women with advanced age (40 years), personal history of gestational diabetes, or family history of type 2 diabetes. An HgbA1c test only provides information on impaired fasting blood glucose levels in the setting of uncontrolled chronic hyperglycemia.
4. Blood pressure measurement at each visit. The ideal blood pressure is 120/80 or lower. Prehypertension should be treated because blood pressure control has the largest benefit in reducing cardiovascular diseases.
5. Regular assessment for depression, anxiety, and quality of life.

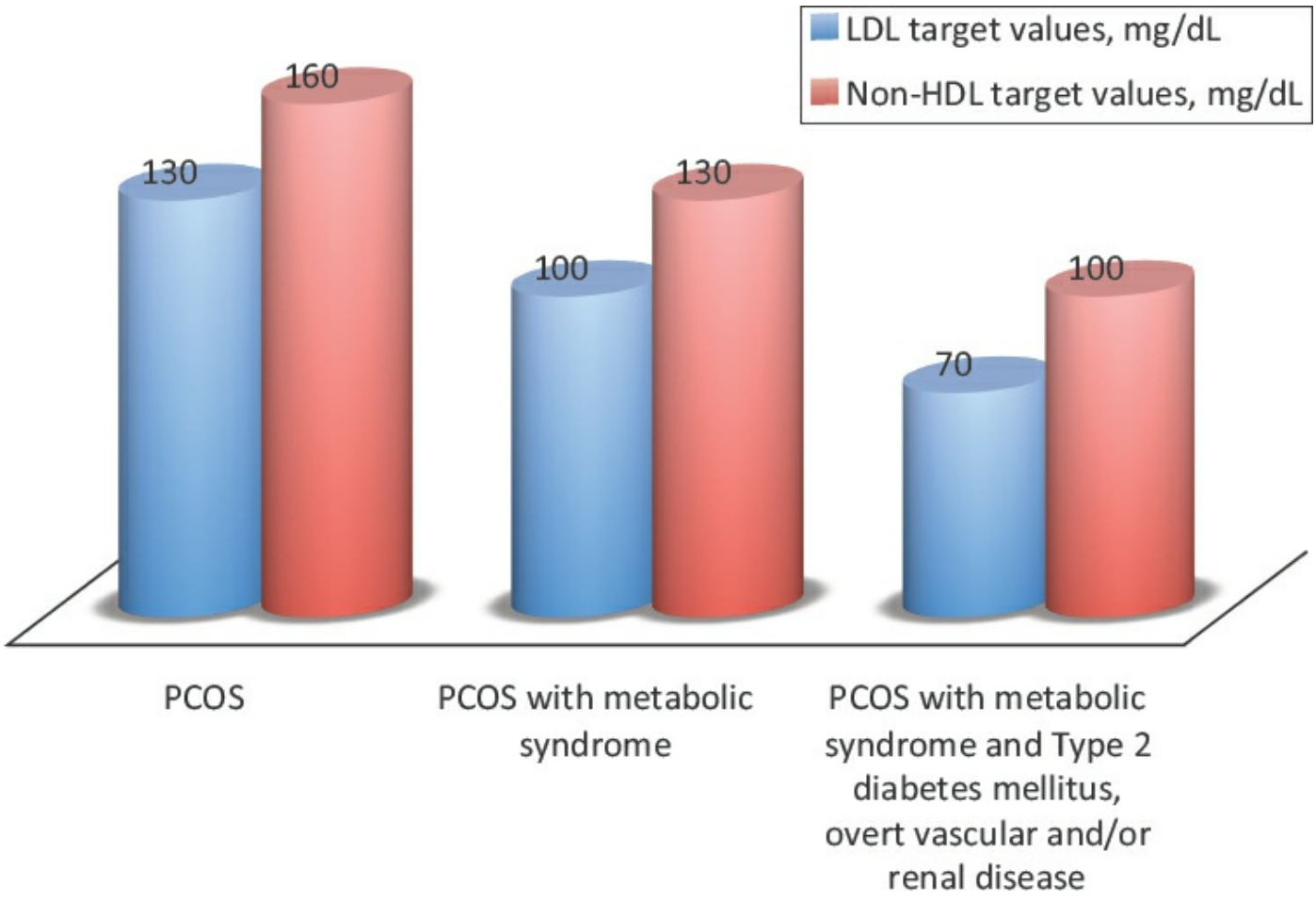


FIGURE 35-6 Lipid guidelines in PCOS to prevent cardiovascular disease risk (values in mg/dL). (Non-HDL = Total cholesterol − HDL, if TG < 400 mg/dL.) (Data for figure derived from **Wild RA, Carmina E, Diamanti-Kandarakis E, et al**. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metab* 2010;95(5): 2038–2049.)

A significant proportion of the population and particularly the obese population have been noted to have inadequate vitamin D levels. Because vitamin D plays a role in many metabolic activities, assessment and supplementation when indicated can be considered.

25-Hydroxy Vitamin D Levels

- Deficient: 8 ng/mL or less (≤20 nmol/L);
- Insufficient: 8 to 20 ng/mL (20 to 50 nmol/L);
- Optimal: 20 to 60 ng/mL (50 to 150 nmol/L; 40 to 50 ng/mL is treatment goal);
- High: 60 to 90 ng/mL (150 to 225 nmol/L);
- Toxic: >90 ng/mL or greater (≥225 nmol/L).

Supplementation Facts

1. The body uses 3,000 to 5,000 IU D_3 per day.
2. In the absence of the sun, 600 IU of D_3 are required to maintain vitamin D levels.
3. D_2 is more rapidly metabolized and is less potent than D_3.
4. Patients receiving 50,000 IU of vitamin D_2 once a week for 8 weeks will usually correct a vitamin D deficiency, and this can be followed by giving 50,000 U of vitamin D_2 once every other week to maintain vitamin D sufficiency.
5. D_3 is more potent and appropriate dosing to correct levels is still under investigation but 600 IU/day is considered a safe intake for adults.

Cancer

In chronic anovulatory patients with PCOS, persistently elevated estrogen levels, which are uninterrupted by progesterone, increase the risk of endometrial carcinoma (85,86). **These endometrial cancers are usually well differentiated, stage I lesions with a cure rate of more than 90%** (see Chapter 37). Endometrial biopsy should be considered in PCOS patients, because they may occasionally harbor these cancers as early as the second decade of life. Abnormal bleeding, increasing weight, and age are factors that should lower the threshold for endometrial sampling. **Prevention of endometrial cancer is a core management goal for patients with PCOS.** If other dimensions of management do not induce regular ovulation (e.g., *clomiphene*, *letrazole*, *or gonadotropins*) or impose continuous progestation influence (e.g., OCs, pregnancy), regular secretory transformation and menstruation should be induced with periodic administration of a progestational agent. Even though the hyperestrogenic state is associated with an increased risk of breast cancer, studies examining the relationship between **PCOS** and **breast** cancer have not always identified a significantly increased risk (86–90). **The risk of ovarian cancer is increased 2-fold to 3-fold in women with PCOS** (86,91).

Depression and Mood Disorders

The clinical features of PCOS, such as infertility, acne, hirsutism, and obesity, promote psychological morbidity. Women with PCOS face challenges to their feminine identity that can lead to loss of self-esteem, anxiety, poor body image, and depression (92).

A study examining the prevalence of depression and other mood disorders in women with PCOS reported a significantly increased prevalence of depression (35% to 40%) when compared with controls (10.7%), after adjusting for BMI, and a family history of depression and/or infertility. Other mood disorders such as anxiety and eating disorders were common in women with PCOS (93). **The high prevalence of depression and other mental health disorders in women with PCOS suggests that assessment and treatment of mental health disorders should be included in the evaluation and management plan** (93). Lifestyle management improves quality of life and depression

in obese and overweight and women with PCOS (92). A simple two-item questionnaire can initiate the conversation (PHQ-2: Little interest or pleasure in doing things 0–3, Feeling down, depressed, or hopeless 0–3).

Treatment of Hyperandrogenism and PCOS

Treatment depends on a patient's goals. Some patients require hormonal contraception, whereas others desire ovulation induction. In all cases where there is significant ovulatory dysfunction, progestational interruption of the unopposed estrogen effects on the endometrium is necessary. This may be accomplished by periodic luteal function resulting from ovulation induction, progestational suppression via contraceptive formulations, or intermittent administration of progestational agents for endometrial or menstrual regulation. **Interruption of the steady state of HA and control of hirsutism usually can be accomplished simultaneously. Patients desiring pregnancy are an exception, and for them effective control of hirsutism may not be possible.** Treatment regimens for hirsutism are listed in Table 35-5. The induction of ovulation and treatment of infertility are discussed in Chapter 36.

Table 35-5 Medical Treatment of Hirsutism

Treatment Category	Specific Regimens
Weight loss	
Hormonal suppression	Oral contraceptives
	Medroxyprogesterone
	Gonadotropin-releasing hormone analogues
	Glucocorticoids
Steroidogenic enzyme inhibitors	Ketoconazole
5α-Reductase inhibitors	Finasteride
Antiandrogens	Spironolactone
	Cyproterone acetate
	Flutamide
Insulin sensitizer	Metformin
Mechanical	Temporary
	Permanent
	Electrolysis

	Laser hair removal

Weight Reduction

Weight reduction is the initial recommendation for patients with accompanying obesity because it promotes health, reduces insulin, SHBG, and androgen levels, and may restore ovulation either alone or combined with ovulation-induction agents (79). **Weight loss of as little as 5% to 7% over a 6-month period can reduce the bioavailable or calculated free testosterone level significantly and restore ovulation and fertility in more than 75% of women** (94). Exercise involving large muscle groups (i.e., thigh) reduces IR and can be an important component of nonpharmacologic, lifestyle-modifying management.

Oral Contraceptives

[3] Combination OCs decrease adrenal and ovarian androgen production and reduce hair growth in nearly two-thirds of hirsute patients (95–98). **Treatment with OCs offers the following benefits:**

1. The **progestin component suppresses LH**, resulting in diminished ovarian androgen production.
2. The **estrogen component increases hepatic production of SHBG**, resulting in decreased free testosterone concentration (99,100).
3. **Circulating androgen levels are reduced**, including those of DHEAS, which to some extent is independent of the effects of both LH and SHBG (32,101).
4. **Estrogens decrease conversion of testosterone to DHT** in the skin by inhibition of 5α-reductase.

When an OC is used to treat hirsutism, a balance must be maintained between the decrease in free testosterone levels and the intrinsic androgenicity of the progestin. Three progestin compounds that are present in OCs (*norgestrel*, *norethindrone*, and *norethindrone acetate*) are believed to be androgen dominant. The androgenic bioactivity of these steroids may be a factor of their shared structural similarity with 19-nortestosterone steroids (102). OCs containing the so-called new progestins (*desogestrel*, *gestodene*, *norgestimate*, and *drospirenone*) have minimized androgenic activity. However, there is limited evidence of clinically measurable differences in outcome resulting from the disparity of in vitro estimates of androgenic potency.

The use of OCs alone may be relatively ineffective (<10% success rate) in the treatment of hirsutism in women with PCOS, **and the OCs may exacerbate IR in these patients** (103,104). Therefore, effective protocols for pharmacologic management of significant hirsutism with OCs usually include coadministration of agents that impede

androgen action.

Medroxyprogesterone Acetate

Oral or intramuscular administration of *medroxyprogesterone acetate* (*MPA*) successfully treats hirsutism (105). It directly affects the hypothalamic–pituitary axis by decreasing GnRH production and the release of gonadotropins, thereby reducing testosterone and estrogen production by the ovary. Despite a decrease in SHBG, total and free androgen levels are decreased significantly (106). **The recommended oral dose for GnRH suppression is 20 to 40 mg daily in divided dosages or 150 mg given intramuscularly every 6 weeks to 3 months in the depot form.** Hair growth is reduced in up to 95% of patients (107). Side effects of the treatment include amenorrhea, bone mineral density loss, depression, fluid retention, headaches, hepatic dysfunction, and weight gain. MPA is not commonly used for hirsutism.

Gonadotropin-Releasing Hormone Agonists

Administration of GnRH agonists may allow the differentiation of androgen produced by adrenal sources from that of ovarian sources (49). GnRH agonists have been shown to suppress ovarian steroids to castrate levels in patients with PCOS (108). Treatment with *leuprolide acetate* given intramuscularly every 28 days decreases hirsutism and hair diameter in idiopathic hirsutism and hirsutism secondary to PCOS (109). Ovarian androgen levels are significantly and selectively suppressed. The addition of OC or estrogen replacement therapy to GnRH agonist treatment (add-back therapy) prevents bone loss and other side effects of menopause, such as hot flushes and genital atrophy. The hirsutism-reducing effect is retained (106,110). Suppression of hirsutism is not potentiated by the addition of estrogen replacement therapy to GnRH agonist treatment (111).

Glucocorticoids

Dexamethasone may be used to treat patients with PCOS who have either adrenal or mixed adrenal and ovarian HA. Doses of *dexamethasone* as low as 0.25 mg nightly or every other night are used initially to suppress DHEAS concentrations to less than 400 μg/dL. **Because *dexamethasone* has 40 times the glucocorticoid effect of cortisol, daily doses greater than 0.5 mg every evening should be avoided to prevent the risk of adrenal suppression and severe side effects that resemble Cushing syndrome.** To avoid oversuppression of the pituitary–adrenal axis, morning serum cortisol levels should be monitored intermittently (maintain at >2 μg/dL). Reduction in hair growth rate was reported, and significant improvement in acne associated with adrenal HA (112).

Ketoconazole

Ketoconazole inhibits the key steroidogenic cytochromes. Administered at a low dose

(200 mg per day), it can significantly reduce the levels of androstenedione, testosterone, and calculated free testosterone (113). It is rarely used for the chronic inhibition of androgen production in women with HA because of the serious risk of adrenocortical suppression and development of adrenal crisis (15).

Spironolactone

Spironolactone is a specific antagonist of aldosterone, which competitively binds to the aldosterone receptors in the distal tubular region of the kidney. It is an effective potassium-sparing diuretic that originally was used to treat hypertension. The effectiveness of *spironolactone* in the treatment of hirsutism is based on the following mechanisms:

1. Competitive inhibition of DHT at the intracellular receptor level (22).
2. Suppression of testosterone biosynthesis by a decrease in the CYP enzymes (114).
3. Increase in androgen catabolism (with increased peripheral conversion of testosterone to estrone).
4. Inhibition of skin 5α-reductase activity (22).

Although total and free testosterone levels are reduced significantly in patients with both PCOS and idiopathic hirsutism (HA with regular menses) after treatment with *spironolactone*, total and free testosterone levels in patients with PCOS remain higher than those with idiopathic hirsutism (HA with regular menses) (115). In both groups, SHBG levels are unaltered. The reduction in circulating androgen levels observed within a few days of *spironolactone* treatment partially accounts for the progressive regression of hirsutism.

At least a modest improvement in hirsutism can be anticipated in 70% to 80% of women using at least 100 mg of *spironolactone* per day for 6 months (116). *Spironolactone* reduces the daily linear growth rate of sexual hair, hair shaft diameters, and daily hair volume production (117). Combination therapy with spironolactone and OCs seems effective via their differing but synergistic activities (15,118).

The most common dose is 50 to 100 mg twice daily. Women treated with 200 mg per day show a greater reduction in hair shaft diameter than women receiving 100 mg per day (119). Maximal inhibition of hirsutism is noted between 3 and 6 months but continues for 12 months. Electrolysis can be recommended 9 to 12 months after the initiation of *spironolactone* for permanent hair removal.

The most common side effect of *spironolactone* is menstrual irregularity (usually metrorrhagia), which may occur in over 50% of patients with a dosage of 200 mg per day (119). Normal menses may resume with reduction of the dosage. Infrequently, other side effects such as mastodynia, urticaria, or scalp hair loss may occur. Nausea and fatigue can occur with high doses (116). Because spironolactone can increase serum

potassium levels, its use is not recommended in patients with renal insufficiency or hyperkalemia. Periodic monitoring of potassium and creatinine levels is suggested.

Return of normal menses in amenorrheic patients is reported in up to 60% of cases (115). Patients must be counseled to use contraception while taking *spironolactone* because it theoretically can feminize a male fetus.

Cyproterone Acetate

***Cyproterone acetate* is a synthetic progestin derived from 17-OHP, which has potent antiandrogenic properties.** The primary mechanism of *cyproterone acetate* is competitive inhibition of testosterone and DHT at the level of the androgen receptor (120). This agent induces hepatic enzymes and may increase the metabolic clearance rate of plasma androgens (121).

A European formulation of *ethinyl estradiol* with *cyproterone acetate* significantly reduces plasma testosterone and androstenedione levels, suppresses gonadotropins, and increases SHBG levels (122). *Cyproterone acetate* shows mild glucocorticoid activity (and may reduce DHEAS levels) (120,123). Administered in a reverse sequential regimen (*cyproterone acetate* 100 mg per day on days 5 to 15, and *ethinyl estradiol* 30 to 50 mg per day on cycle days 5 to 26), this cyclic schedule allows regular menstrual bleeding, provides excellent contraception, and is effective in the treatment of even severe hirsutism and acne (124).

Side effects of *cyproterone acetate* include fatigue, weight gain, decreased libido, irregular bleeding, nausea, and headaches. These symptoms occur less often when *ethinyl estradiol* is added. *Cyproterone acetate* administration is associated with liver tumors in beagles and is not approved by the U.S. Food and Drug Administration (FDA) for use in the United States.

Flutamide

Flutamide, a pure nonsteroidal antiandrogen, is approved for treatment of advanced prostate cancer. Its mechanism of action is inhibition of nuclear binding of androgens in target tissues. Although it has a weaker affinity to the androgen receptor than spironolactone or *cyproterone acetate*, larger doses (250 mg given two or three times daily) may compensate for the reduced potency. *Flutamide* is a weak inhibitor of testosterone biosynthesis.

In a single, 3-month study of *flutamide* alone, most patients demonstrated significant improvement in hirsutism with no change in androgen levels (125). Significant improvement in hirsutism with a significant drop in androstenedione, DHT, LH, and FSH levels was observed in an 8-month follow-up of *flutamide* and low-dose OCs in women who did not respond to OCs alone (126). The side effects of *flutamide* treatment combined with a low-dose OC included dry skin, hot flashes, increased appetite, headaches, fatigue, nausea, dizziness, decreased libido, liver toxicity, and breast

tenderness (127).

In hyperinsulinemic, hyperandrogenemic, nonobese PCOS adolescents on a combination of *metformin* (850 mg per day) and *flutamide* (62.5 mg per day), and the low-dose OC containing *drospirenone*, resulted in a more effective and more efficient reduction in total and abdominal fat excess than was demonstrated by those utilizing an OC with *gestodene* as the progestin (128). The combination of *ethinyl-drospirenone*, *metformin*, and *flutamide* is effective in reducing excess total fat, abdominal fat, and attenuating dysadipocytokinemia in young women with hyperinsulinemic PCOS. The use of the antiandrogen *flutamide* appeared to emphasize effects (129). Many patients taking *flutamide* (50% to 75%) report dry skin, blue-green discoloration of urine, and liver enzyme elevation. Liver toxicity or failure and death are rare but severe side effects of *flutamide* appear to be dose-related (130). The 2008 Endocrine Society clinical practice guidelines do not recommend using *flutamide* as first-line therapy for treating hirsutism. If it is used, the lowest effective dose should be given, and the patient's liver function should be monitored closely (4). *Flutamide* should not be used in women desiring pregnancy.

Finasteride

Finasteride is a specific inhibitor of type 2 5α-reductase enzyme activity, approved in the United States at a 5-mg dose for the treatment of benign prostatic hyperplasia, and at a 1-mg dose to treat male-pattern baldness. In a study in which *finasteride* (5 mg daily) was compared with *spironolactone* (100 mg daily), both drugs resulted in similar significant improvement in hirsutism, despite differing effects on androgen levels (131). Most of the improvement in hirsutism with *finasteride* occurred after 6 months of therapy with 7.5 mg of *finasteride* daily (132). The improvement in hirsutism in the presence of rising testosterone levels is convincing evidence that it is the binding of DHT, and not testosterone, to the androgen receptor that is responsible for hair growth. *Finasteride* does not prevent ovulation or cause menstrual irregularity. The increase in SHBG caused by OCs further decreases free testosterone levels; OCs in combination with *finasteride* are more effective in reducing hirsutism than *finasteride* alone. As with *spironolactone* and *flutamide*, *finasteride* could theoretically feminize a male fetus; therefore, these agents are used only with additional contraception.

Ovarian Wedge Resection

Bilateral ovarian wedge resection is associated with only a transient reduction in androstenedione levels and a prolonged minimal decrease in plasma testosterone (133,134). In patients with hirsutism and PCOS who had wedge resection, hair growth was reduced by approximately 16% (17,135). Although Stein and Leventhal's original report cited a pregnancy rate of 85% following wedge resection and maintenance of ovulatory cycles, subsequent reports show lower pregnancy rates and a concerning

incidence of periovarian adhesions (17,136). Instances of premature ovarian failure and infertility were reported (137).

Laparoscopic Electrocautery

Laparoscopic ovarian electrocautery is used as an alternative to wedge resection in patients with severe PCOS whose condition is resistant to *clomiphene citrate.* In one series, ovarian drilling was achieved laparoscopically with an insulated electrocautery needle, using 100-W cutting current to assist entry and 40-W coagulating current to treat each microcyst over 2 seconds (8-mm needle in ovary) (138). In each ovary, 10 to 15 punctures were created. This led to spontaneous ovulation in 73% of patients, with 72% conceiving within 2 years. Of those who had undergone a follow-up laparoscopy, 11 of 15 were adhesion free. To reduce adhesion formation, a technique that cauterized the ovary in only four points led to a similar pregnancy rate, with a miscarriage rate of 14% (139). Other laparoscopic techniques using laser instead of electrocautery for laparoscopic ovarian drilling were described (140). Most series report a decrease in androgen and LH concentrations and an increase in FSH concentrations (141,142). The beneficial endocrinologic effects of laparoscopic ovarian drilling and the improvement in hirsutism were sustained for up to 9 years in patients with PCOS (143). Unilateral diathermy results in bilateral ovarian activity (144). Further studies are anticipated to define candidates who may benefit most from such a procedure. **The risk of adhesion formation, reduction in AMH and alternative therapies should be discussed during informed consent** (145).

Physical Methods of Hair Removal

Depilatory creams remove hair only temporarily. They break down and dissolve hair by hydrolyzing disulfide bonds. Although depilatories can have a dramatic effect, many women cannot tolerate these irritative chemicals. The topical use of corticosteroid cream may prevent contact dermatitis. *Eflornithine hydrochloride* cream, also known as *difluoromethylornithine* (*DMFO*), irreversibly blocks ornithine decarboxylase (ODC), the enzyme in hair follicles that is important in regulating hair growth. It is effective in the treatment of unwanted facial hair (146). Noticeable results take about 6 to 8 weeks of therapy. Treatment must be continued while inhibition of hair growth is desired, and when the cream is discontinued, hair returns to pretreatment levels after about 8 weeks (4).

Shaving is effective and, contrary to common belief, it does not change the quality, quantity, or texture of hair. However, plucking, if done unevenly and repeatedly, may cause inflammation and damage to hair follicles and render them less amenable to electrolysis. Waxing is a grouped method of plucking in which hairs are plucked out from under the skin surface. The results of waxing last longer (up to 6 weeks) than shaving or depilatory creams (147).

Bleaching removes the hair pigment through the use of *hydrogen peroxide* (usually 6% strength), which is sometimes combined with *ammonia*. Although hair lightens and softens during oxidation, this method is frequently associated with hair discoloration or skin irritation and is not always effective (146).

Electrolysis and laser hair removal are the only permanent means recommended for hair removal. Under magnification, a trained technician destroys each hair follicle individually. When a needle is inserted into a hair follicle, galvanic current, electrocautery, or both used in combination (blend) destroy the hair follicle. After the needle is removed, a forceps is used to remove the hair. Hair regrowth ranges from 15% to 50%. Problems with electrolysis include pain, scarring, and pigmentation. Cost can also be an obstacle (148). Laser hair removal destroys the hair follicle through photoablation. These methods are most effective after medical therapy has arrested further growth.

Insulin Sensitizers

[4] Because hyperinsulinemia appears to play a role in PCOS-associated anovulation, treatment with insulin sensitizers may shift the endocrine balance toward ovulation and pregnancy, either alone or in combination with other treatment modalities.

Metformin (*Glucophage*) is an oral biguanide antihyperglycemic drug used extensively for non–insulin-dependent diabetes. *Metformin* is pregnancy category B drug with no known human teratogenic effect. It lowers blood glucose mainly by inhibiting hepatic glucose production and by enhancing peripheral glucose uptake. *Metformin* enhances insulin sensitivity at the postreceptor level and stimulates insulin-mediated glucose disposal (149).

Metformin has been used extensively to treat oligo-ovulatory infertility, IR, and HA in PCOS patients. *Metformin* has been used to treat PCOS oligo-ovulatory infertility either alone or in combination with dietary restriction, *clomiphene, letrozole*, or gonadotropins. In randomized control studies, *metformin* has been found to improve the odds of ovulation in women with PCOS when compared with placebo (150,151). **A large multicenter, randomized control trial in women with PCOS concluded that *clomiphene* is superior to *metformin* in achieving live births in infertile women with PCOS.** When ovulation was used as the **outcome, the combination of *metformin* and *clomiphene* was superior to either *clomiphene* alone or *metformin* alone** (152). *Metformin* alone compared with placebo increases the ovulation rate in women with PCOS. However, ovulation induction agents such as *clomiphene* or *letrozole* alone are much more effective in increasing ovulation, pregnancy, and live birth rates in women with PCOS than *metformin* alone. There is fair evidence that *metformin* alone does not increase rates of miscarriage when stopped at the initiation of pregnancy and insufficient evidence that *metformin* in combination with other agents used to induce

ovulation increases live birth rates but may improve ovulation rates in *clomiphene*- or *letrazole*-resistant cases (153). The combination of *metformin* and *letrazole* has been shown to be comparable to gonadotropins in pregnancy and live birth rates in *clomiphene*-resistant PCOS patients and superior to other interventions (154). Ovulation induction with *clomiphene* has been associated with a thinner endometrial lining compared with other agents like *letrozole* (155). A recent meta-analysis provided weak evidence that *letrozole* appears to improve live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared with *clomiphene* (156). In women with PCOS, baseline serum AMH levels were higher in those who did not respond to ovulation induction and conversely lower among women who ovulated. Women with higher baseline AMH levels required higher doses of *clomiphene* or *letrozole* to achieve ovulation, suggesting that AMH levels may be a marker of ovarian resistance to ovulation induction (157).

The most common side effects are gastrointestinal, including nausea, vomiting, diarrhea, bloating, and flatulence. Because the drug caused fatal lactic acidosis in men with diabetes and renal insufficiency, **baseline renal function testing is suggested** (158). **The drug should not be given to women with elevated serum creatinine levels** (149).

Concepts regarding the role of obesity and IR or hyperinsulinemia in PCOS suggest that the primary intervention should be recommending and assisting with weight loss (5% to 10% of body weight). A percentage of PCOS patients will respond to weight loss alone with spontaneous ovulation. *Metformin* and lifestyle interventions has been associated with a lower BMI and improved menstruation in women with PCOS compared to lifestyle interventions and placebo over 6 months (159). **In those who do not respond to weight loss alone or who are unable to lose weight, the addition of an insulin sensitizer, after failing the ovulation induction agent alone, may promote ovulation without resorting to injectable gonadotropins.**

A prevailing concern over the increased incidence of spontaneous abortions in women with PCOS and the potential reduction afforded by insulin sensitizers suggests that insulin sensitizers may be beneficial in combination with gonadotropin therapy for ovulation induction or in vitro fertilization (160). Women with early pregnancy loss have a low level of IGF-binding protein-1 (IGFBP-1), and of circulating glycodelin, which has immunomodulatory effects protecting the developing fetus. Use of *metformin* increased levels of both factors, which might explain early findings suggesting that *metformin* use may reduce the high spontaneous abortion rates seen among women with PCOS (161).

A number of observational studies suggested that *metformin* reduces the risk of pregnancy loss (162,163). However, there are no adequately designed and sufficiently powered randomized control trials to address this issue. In the prospective randomized

PPCOS (Pregnancy and PCOS) trial, there was a concerning nonsignificant trend toward a greater rate of miscarriages in the *metformin* only group (162). This trend was not noted in other trials.

There are no conclusive data to support a beneficial effect of *metformin* on pregnancy loss, and the trend toward a higher miscarriage rate in the PPCOS trial, which used extended-release *metformin*, is of some concern (150,152).

The incidence of ovarian hyperstimulation syndrome is reduced with adjuvant *metformin* in PCOS patients at risk for severe ovarian hyperstimulation syndrome (164).

Cushing Syndrome

The adrenal cortex produces three classes of steroid hormones: glucocorticoids, mineralocorticoids, and sex steroids (androgen and estrogen precursors). Hyperfunction of the adrenal gland can produce clinical signs of increased activity of any or all of these hormones. Increased glucocorticoid action results in nitrogen wasting and a catabolic state. This causes muscle weakness, osteoporosis, atrophy of the skin with striae, nonhealing ulcerations and ecchymoses, reduced immune resistance that increases the risk of bacterial and fungal infections, and glucose intolerance resulting from enhanced gluconeogenesis and antagonism to insulin action.

Although most patients with Cushing syndrome gain weight, some lose it. Obesity is typically central, with characteristic redistribution of fat over the clavicles around the neck and on the trunk, abdomen, and cheeks. Cortisol excess may lead to insomnia, mood disturbances, depression, and even overt psychosis. With overproduction of sex steroid precursors, women may exhibit HA (hirsutism, acne, oligomenorrhea or amenorrhea, thinning of scalp hair). Masculinization is rare, and its presence suggests an autonomous adrenal origin, most often an adrenal malignancy. With overproduction of mineralocorticoids, patients may manifest arterial hypertension and hypokalemic alkalosis. The associated fluid retention may cause pedal edema (Table 35-6) (165).

Characteristic clinical laboratory findings associated with hypercortisolism are confined mainly to a complete blood count showing evidence of granulocytosis and reduced levels of lymphocytes and eosinophils. Increased urinary calcium secretion may be present.

Causes

The six recognized noniatrogenic causes of Cushing syndrome can be divided between those that are ACTH dependent and those that are ACTH independent (Table 35-7). The ACTH-dependent causes can result from ACTH secreted by pituitary adenomas or from an ectopic source. The hallmark of ACTH-dependent forms of Cushing syndrome is the presence of normal or high plasma ACTH

concentrations with increased cortisol levels. The adrenal glands are hyperplastic bilaterally. Pituitary ACTH-secreting adenoma, or Cushing disease, is the most common cause of endogenous Cushing syndrome (165). These pituitary adenomas are usually microadenomas (<10 mm in diameter) that may be as small as 1 mm. They behave as though they are resistant, to a variable degree, to the feedback effect of cortisol. Like the normal gland, these tumors secrete ACTH in a pulsatile fashion; unlike the normal gland, the diurnal pattern of cortisol secretion is lost. **Ectopic ACTH syndrome most often is caused by malignant tumors** (166). About one-half of these tumors are small-cell carcinomas of the lung (167). Other tumors include bronchial and thymic carcinomas, carcinoid tumors of the pancreas, and medullary carcinoma of the thyroid.

Ectopic corticotropin-releasing hormone (CRH) tumors are rare and include tumors such as bronchial carcinoids, medullary thyroid carcinoma, and metastatic prostatic carcinoma (167). The presence of an ectopic CRH-secreting tumor should be suspected in patients whose dynamic testing suggests pituitary ACTH-dependent disease but who have rapid disease progression and very high plasma ACTH levels.

The most common cause of ACTH-independent Cushing syndrome is exogenous or iatrogenic (i.e., supraphysiologic therapy with corticosteroids) or factitious (self-induced). Corticosteroids are used in pharmacologic quantities to treat a variety of diseases with an inflammatory component. Over time, such therapy will result in Cushing syndrome. When corticosteroids are taken by the patient but not prescribed by a physician, the diagnosis may be especially challenging. The diagnostic workup for Cushing syndrome focuses on the ability to suppress autonomous cortisol secretion and whether ACTH is elevated or suppressed. According to the Endocrine Society's clinical practice guidelines for the diagnosis of Cushing syndrome, the initial use of one test with high diagnostic accuracy (24-hour urinary free cortisol [UFC], late night salivary cortisol, 1 mg overnight or 2 mg 48-hour *dexamethasone* suppression test) is recommended. The 24-hour UFC should be used to diagnose Cushing syndrome in pregnant women and in patients with epilepsy, whereas the 1-mg overnight *dexamethasone* suppression test, rather than UFC, should be used for initial testing for Cushing syndrome in patients with severe renal failure and adrenal incidentaloma. The 2-mg 48-hour *dexamethasone* suppression test is the optimal test in conditions that are associated with overactivation of the hypothalamic–pituitary–adrenal (HPA) axis: depression, morbid obesity, alcoholism, and diabetes mellitus.

Table 35-6 Overlapping Conditions and Clinical Features of Cushing Syndrome

Symptoms	Signs	Overlapping Conditions
Features that best discriminate Cushing syndrome; most do not have a high sensitivity		

	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and >1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[a]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[a]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[a]	Type 2 diabetes[a]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		
Menstrual abnormalities		
In children, slow growth	In children, abnormal genital virilization	
	In children, short stature	
	In children, pseudoprecocious puberty or delayed puberty	

Features are listed in random order.

[a]Cushing syndrome is more likely if onset of the feature is at a younger age.

Table 35-7 Causes of Cushing Syndrome

Category	Cause	Relative Incidence

ACTH-dependent	Cushing Disease	60%
	Ectopic ACTH-secreting tumors	15%
	Ectopic CRH-secreting tumors	Rare
ACTH-independent	Adrenal cancer	15%
	Adrenal adenoma	10%
	Micronodular adrenal hyperplasia	Rare
	Iatrogenic/factitious	Common

ACTH-dependent Cushing syndrome may be caused by pituitary adenoma, basophil hyperplasia, nodular adrenal hyperplasia, or cyclic Cushing syndrome.
ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

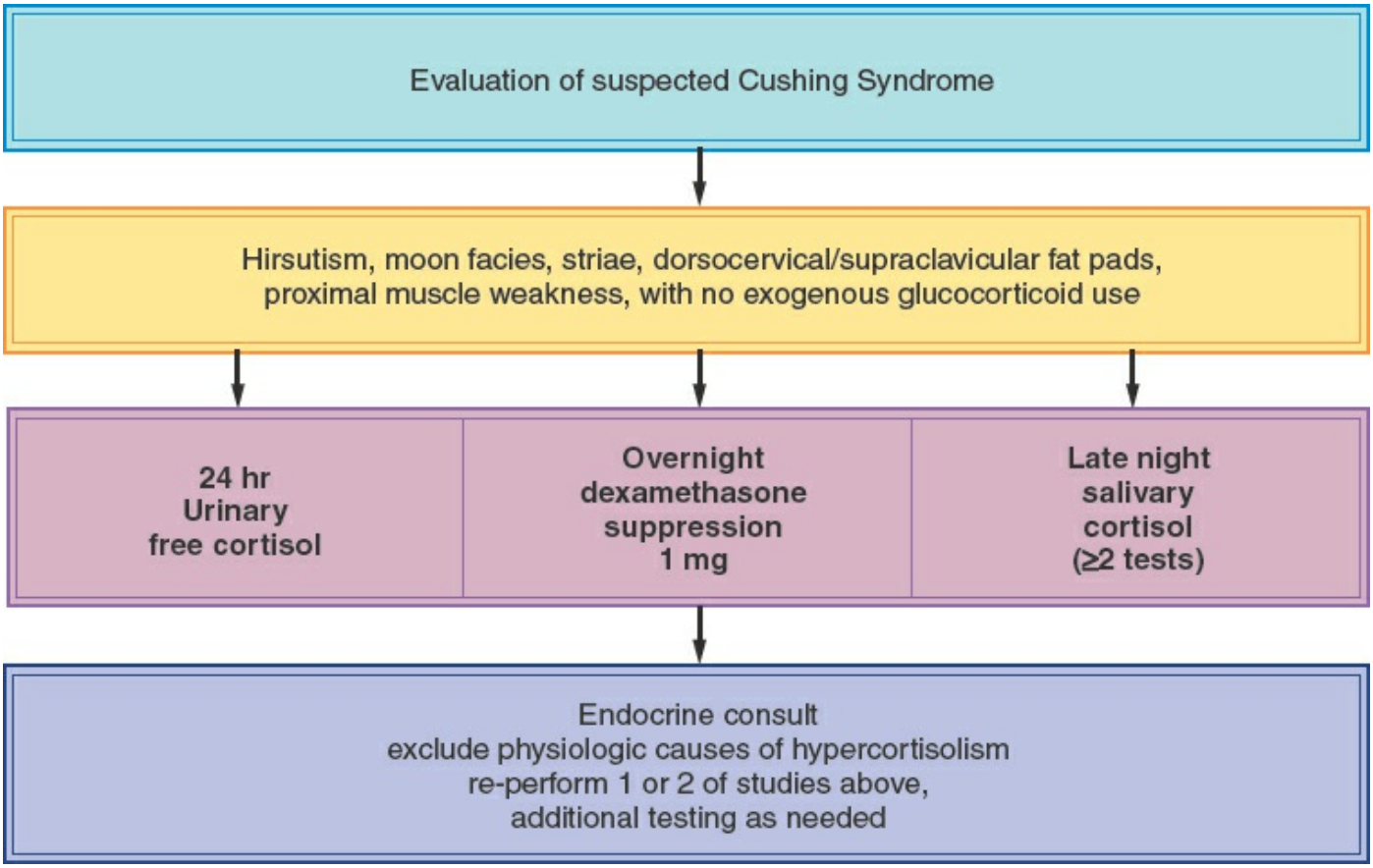


FIGURE 35-7 Algorithm for testing patients suspected of having Cushing syndrome (CS). Diagnostic criteria that suggest Cushing syndrome are a urinary free cortisol (UFC) greater than the normal range for the assay, serum cortisol greater than 1.8 μg/dL (50 nmol/L) after 1 mg dexamethasone (1 mg DST), and a late-night salivary cortisol greater than 145 ng/dL (4 nmol/L). (Based on recommendations from **Nieman LK, Biller BM, Findling JW, et al**. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008;93:1526–1540.)

Patients with an abnormal result should see an endocrinologist and undergo a second test, either one of the above or, in some cases, a serum midnight cortisol or

dexamethasone CRH test. These guidelines are summarized in Figure 35-7 (165).

Treatment of ACTH-Independent Forms of Cushing Syndrome

[5] Excluding cases that are of iatrogenic or factitious etiology, ACTH-independent forms of Cushing syndrome are adrenal in origin. Adrenal cancers are usually very large by the time Cushing syndrome is manifest. This is because the tumors are relatively inefficient synthesizers of steroid hormones. Tumors are larger than 6 cm in diameter and are easily detectable by computed tomography (CT) scanning or magnetic resonance imaging (MRI). Adrenal cancers often produce steroids other than cortisol. Thus, when Cushing syndrome is accompanied by hirsutism or virilization in women or feminization in men, adrenal cancer should be suspected.

An adrenal tumor that appears large and irregular on radiologic imaging is suggestive of carcinoma. In these cases, a unilateral adrenalectomy through an abdominal exploratory approach is preferable. In most malignant tumors, complete resection is virtually impossible. However, a partial response to postoperative chemotherapy or radiation may be achieved. Most patients with malignancy die within 1 year. When administered immediately after surgery, *mitotane* (O,P-DDD, an adrenocorticolytic drug) may be of benefit in preventing or delaying recurrent disease (168). Manifestations of Cushing syndrome in these patients are controlled by adrenal enzyme inhibitors.

Adrenal adenomas are smaller than carcinomas and on average 3 cm in diameter. These tumors are usually unilateral and infrequently associated with other steroid-mediated syndromes. Micronodular adrenal disease is a disorder of children, adolescents, and young adults. The adrenal glands contain numerous small (>3 mm) nodules, which often are pigmented and secrete sufficient cortisol to suppress pituitary ACTH. This condition can be sporadic or familial.

Surgical removal of a neoplasm is the treatment of choice (169,170). If a unilateral, well-circumscribed adenoma is identified by MRI or CT scanning, the flank approach may be the most convenient. The cure rate following surgical removal of adrenal adenomas approaches 100%. Because normal function of the HPA axis is suppressed by autonomous cortisol production, cortisol replacement follows surgery and is titrated downward over several months, during which recovery of normal adrenal function is monitored.

Treatment of Cushing Disease

The main goals of treatment in ACTH-dependent Cushing syndrome are reversal of clinical features, normalization of biochemical changes with minimal morbidity, and long-term control without recurrence (166).

The treatment of choice for Cushing disease is transsphenoidal resection. The remission rate is approximately 70% to 90% and the recurrence rate is 5% to 10% at 5

years and 10% to 20% at 10 years in patients with microadenomas who undergo surgery by an experienced surgeon (171–175). Patients with macroadenoma have lower remission rates (<60%) and higher recurrence rates (12% to 45%) (176–178). Following surgery, transient diabetes insipidus and enduring compromise of anterior pituitary secretion of growth hormone, gonadotropins, and TSH are common (178,179).

Radiation Therapy

Fractionated external beam radiotherapy or stereotactic radiosurgery is used to treat patients with Cushing disease in whom transsphenoidal microsurgery was not successful or in patients who are poor surgical candidates. This therapy can achieve control of hypercortisolemia in approximately 50% to 60% of patients within 3 to 5 years (166,180,181). Hypopituitarism is the most common side effect of pituitary irradiation, and long-term follow-up is essential to detect relapse, which can occur after an initial response to radiotherapy.

High-voltage external pituitary radiation (4,200 to 4,500 cGy) is given at a rate not exceeding 200 cGy per day. Only 15% to 25% of adults show total improvement, but approximately 80% of children respond (179,182).

Medical Therapy

Mitotane can be used to induce medical adrenalectomy during or after pituitary radiation (168). The role of medical therapy is to prepare the severely ill patient for surgery and to maintain normal cortisol levels while a patient awaits the full effect of radiation. Occasionally, medical therapy is used for patients who respond to therapy with only partial remission. Adrenal enzyme inhibitors include *aminoglutethimide*, *metyrapone*, *trilostane*, and *etomidate*.

A combination of *aminoglutethimide* and *metyrapone* may cause a total adrenal enzyme block, requiring corticosteroid-replacement therapy. *Ketoconazole*, an FDA-approved antifungal agent, inhibits adrenal steroid biosynthesis at the side arm cleavage and 11β-hydroxylation steps. The dose of *ketoconazole* for adrenal suppression is 600 to 800 mg per day for 3 months to 1 year (183). *Ketoconazole* is effective for long-term control of hypercortisolism of either pituitary or adrenal origin.

Nelson syndrome results from adenomatous progression of ACTH-secreting cells in patients with Cushing syndrome treated with bilateral adrenalectomy. The macroadenoma that causes this syndrome produces sellar pressure symptoms of headaches, visual field disturbances, and ophthalmoplegia. Extremely high ACTH levels in Nelson syndrome are associated with severe hyperpigmentation (melanocyte-stimulating hormone activity). The treatment is surgical removal or radiation. The offending adenomatous tissue is often resistant to complete surgical removal (184). This syndrome reportedly complicates 10% to 50% of bilateral adrenalectomy cases. Measuring pituitary MRI and ACTH plasma levels at regular intervals after bilateral adrenalectomy will allow detection of the early progression of corticotroph tumors and

the possibility of cure by surgery, particularly with microadenomas (166). Nelson syndrome is less common today because bilateral adrenalectomy is less frequently used as initial treatment.

Congenital Adrenal Hyperplasia

[6] CAH is transmitted as an autosomal recessive disorder. Several adrenocortical enzymes necessary for cortisol biosynthesis may be affected. Failure to synthesize the fully functional enzyme has the following effects:

1. A relative decrease in cortisol production
2. A compensatory increase in ACTH levels
3. Hyperplasia of the zona reticularis of the adrenal cortex
4. An accumulation of the precursors of the affected enzyme in the bloodstream

21-Hydroxylase Deficiency

Deficiency of 21-hydroxylase is responsible for over 90% of all cases of adrenal hyperplasia as a result of adrenal synthetic enzyme deficiency. The disorder produces a spectrum of conditions; CAH, with or without salt wasting, and milder forms that are expressed as HA of pubertal onset (adult-onset adrenal hyperplasia, AOAH). Salt-wasting CAH, the most severe form, affects 75% of patients with congenital manifestations during the first 2 weeks of life and results in a life-threatening hypovolemic salt-wasting crisis, accompanied by hyponatremia, hyperkalemia, and acidosis. The salt-wasting form results from a severity of enzyme deficiency sufficient to result in ineffective aldosterone synthesis. With or without salt-wasting and newborn adrenal crisis, the condition is usually diagnosed earlier in affected female newborns than in males as genital virilization (e.g., clitoromegaly, labioscrotal fusion, and abnormal urethral course) is apparent at birth.

In simple virilizing CAH, affected patients are diagnosed as virilized newborn females or as rapidly growing masculinized boys at 3 to 7 years of age. Diagnosis is based on basal levels of the substrate for 21-hydroxylase, 17-OHP; in cases of congenital adrenal hyperplasia as a result of 21-hydroxylase deficiency and in milder forms of the disorder with manifestations later in life (acquired, late-onset, or adult-onset adrenal hyperplasia), diagnosis depends on basal and ACTH-stimulated levels of 17-OHP.

Patients with morning follicular phase 17-OHP levels of less than 300 ng/dL (10 nmol/L) are likely unaffected. When levels are greater than 300 ng/dL, but less than 10,000 ng/dL (300 nmol/L), ACTH testing should be performed to distinguish between 21-hydroxylase deficiency and other enzyme defects or to make the diagnosis in borderline cases. Levels greater than 10,000 ng/dL (300 nmol/L) are virtually

diagnostic of congenital adrenal hyperplasia.

Nonclassic Adult-Onset Congenital Adrenal Hyperplasia

The nonclassic type of 21-hydroxylase deficiency represents partial deficiency in 21-hydroxylation, which produces a late-onset, milder hyperandrogenemia. Its occurrence depends on some degree of functional deficit resulting from mutations affecting both alleles for the 21-hydroxylase enzyme. Heterozygote carriers for mutations in the 21-hydroxylase enzyme will demonstrate normal basal and modestly elevated stimulated levels of 17-OHP, but no abnormalities in circulating androgens. Some women with mild gene defects in both alleles demonstrate modest elevations in circulating 17-OHP concentrations, but no clinical symptoms or signs.

The hyperandrogenic symptoms of AOAH are mild and typically present at or after puberty. The three phenotypic varieties are as follows (185):

1. Those with ovulatory abnormalities and features consistent with PCOS (39%)
2. Those with hirsutism alone without oligomenorrhea (39%)
3. Those with elevated circulating androgens but without symptoms (cryptic) (22%)

Precocious puberty (PP) reveals late-onset congenital adrenal hyperplasia in 5% to 20% of cases that mainly are caused by nonclassic 21-hydroxylase deficiency.

Measurement of 17-OHP should be performed in patients presenting with PP, and a subsequent ACTH stimulation test is recommended if basal 17-OHP is greater than 200 ng/dL.

The need for screening patients with hirsutism for adult-onset adrenal hyperplasia depends on the patient population. The frequency of some form of the disorder varies by ethnicity and is estimated at 0.1% of the general population, 1% to 2% of Hispanics and Yugoslavs, and 3% to 4% of Ashkenazi Jews (186).

Genetics of 21-Hydroxylase Deficiency

1. The 21-hydroxylase gene is at 6p21.3 amid HLA B and HLA DR genes of the human leukocyte antigen (HLA).
2. The 21-hydroxylase gene is now termed *CYP21*. Its homolog is the pseudogene *CYP21P* (187).
3. Because *CYP21P* is a pseudogene, the lack of transcription renders it nonfunctional. The *CYP21* is the active gene.
4. The *CYP21* gene and the *CYP21P* pseudogene alternate with two genes called *C4B* and *C4A,* both of which encode for the fourth component (C4) of serum complement (187).
5. The close linkage between the 21-hydroxylase genes and HLA alleles has allowed the study of 21-hydroxylase inheritance patterns in families through blood HLA typing (e.g., linkage of HLA-B14 was found in Ashkenazi Jews, Hispanics, and

Italians) (188).

Prenatal Diagnosis and Treatment

Women with congenital and adult-onset forms of the disorder are at a significant risk for having affected infants, owing to the high frequency of 21-hydroxylase mutations in the general population. This presents an important rationale for screening hyperandrogenic women for this disorder when they anticipate childbearing. In families at risk for CAH and in instances where one partner expresses the congenital or adult-onset form of the disease, first-trimester prenatal screening using chorionic villus sampling is advocated (187). The fetal DNA is used for specific amplification of the *CYP21* gene using polymerase chain reaction (PCR) amplification (189). When the fetus is at risk for CAH, maternal *dexamethasone* treatment can suppress the fetal HPA axis and prevent genital virilization in affected females (190). The dose is 20 μg/kg in three divided doses administered as soon as pregnancy is recognized and no later than 9 weeks of gestation. This is done prior to performing chorionic villus sampling or amniocentesis in the second trimester. *Dexamethasone* crosses the placenta and suppresses ACTH in the fetus. If the fetus is determined to be an unaffected female or a male, treatment is discontinued. If the fetus is an affected female, *dexamethasone* therapy is continued.

The practice of prenatal *dexamethasone* treatment for women whose fetuses are at risk for CAH is controversial; seven of eight pregnancies will be treated with *dexamethasone* unnecessarily, albeit briefly, to prevent one case of ambiguous genitalia. The efficacy and safety of prenatal *dexamethasone* treatment is not established, and long-term follow-up data on the offspring of treated pregnancies are lacking (191).

Numerous studies in experimental animal models showed that prenatal *dexamethasone* exposure could impair somatic growth, brain development, and blood pressure regulation. A human study of 40 fetuses at risk for CAH who were treated prenatally with *dexamethasone* to prevent virilization of affected females reported long-term effects on neuropsychological functions and scholastic performance (190,192).

The 2010 Endocrine Society guidelines conclude that prenatal ***dexamethasone*** therapy should be pursued only through institutional review boards' approved protocols at centers capable of collecting sufficient outcome data (193).

11β-Hydroxylase Deficiency

In a small percentage of patients with CAH, hypertension, rather than mineralocorticoid deficiency, develops. The hypertension responds to corticosteroid replacement (194–197). Many of these patients have a deficiency in 11β-hydroxylase (195,196). In most populations, 11β-hydroxylase deficiency accounts for 5% to 8% of the cases of CAH, or 1 in 100,000 births (197). A much higher incidence, 1 in 5,000 to 7,000, was described

in Moroccan Jewish immigrants (197).

Two 11β-hydroxylase isoenzymes are responsible for cortisol and aldosterone synthesis, respectively, CYP11-B1 and CYP11-B2. They are encoded by two genes on the middle of the long arm of chromosome 8 (198–200).

Inability to synthesize a fully functional 11β-hydroxylase enzyme causes a decrease in cortisol production, a compensatory increase in ACTH secretion, and increased production of androstenedione, 11-deoxycortisol, 11-deoxycorticosterone, and DHEA. The diagnosis of 11β-hydroxylase-deficient late-onset adrenal hyperplasia is determined when 11-deoxycortisol levels are higher than 25 ng/mL 60 minutes after ACTH(1-24) stimulation (201).

Patients with 11β-hydroxylase deficiency may present with either a classic pattern of the disorder or symptoms of a mild deficiency. The severe classic form is found in about two-thirds of the patients with mild-to-moderate hypertension during the first years of life. In about one-third of the patients, it is associated with left ventricular hypertrophy, with or without retinopathy, and occasionally death is reported from cerebrovascular accident (194). Signs of androgen excess are common in the severe form and are similar to those seen in the 21-hydroxylase deficiency.

In the mild, nonclassic form, children have virilization or PP but not hypertension. Adult women seek treatment for postpubertal onset of hirsutism, acne, and amenorrhea.

3aβ-Hydroxysteroid Dehydrogenase Deficiency

Deficiency of 3β-HSD occurs with varying frequency in hirsute patients (202,203). The enzyme is found in the adrenal glands and ovaries (unlike 21- and 11-hydroxylase) and is responsible for transforming Δ-5 steroids into the corresponding Δ-4 compounds, a step integral to the synthesis of glucocorticoids, mineralocorticoids, testosterone, and estradiol. In severe forms, cortisol and mineralocorticoids are deficient. The clinical spectrum of 3β-HSD deficiency ranges from the classic salt wasting, hypogonadism, and ambiguous genitalia in males and females, to nonclassic hyperandrogenic symptoms in children and young women (204). In mild forms, elevated ACTH levels overcome these critical deficiencies, and the diagnosis of this disorder relies on the relationship of Δ-5 and Δ-4 steroids. A marked elevation of DHEA and DHEAS in the presence of normal, or mildly elevated, testosterone or androstenedione can suggest the initiation of a screening protocol for 3β-HSD deficiency using exogenous ACTH stimulation (202). Following intravenous administration of a 0.25-mg ACTH(1-24) bolus, within 60 minutes, 17-hydroxypregnenolone levels rise significantly in women with 3β-HSD deficiency, compared with normal women (2,276 ng/dL compared with normal of 1,050 ng/dL). The mean poststimulation ratio between 17-hydroxypregnenolone and 17-OHP is markedly elevated (mean ratio of 11 compared with 3.4 in normal controls and 0.4 in 21-hydroxylase deficiency). The rarity of this disorder indicates that routine screening of hyperandrogenic patients is not justified (202,203).

Treatment of Adult-Onset Congenital Adrenal Hyperplasia

Many patients with congenital AOAH do not need treatment. Glucocorticoid treatment should be avoided in asymptomatic patients with AOAH because the potential adverse effects of glucocorticoids probably outweigh any benefits (191,193).

Glucocorticoid therapy is recommended only to reduce HA for those with significant symptoms. *Dexamethasone* and antiandrogen drugs (both cross the placenta) should be used with caution and in conjunction with OCs in adolescent girls and young women with signs of virilization or irregular menses. When fertility is desired, ovulation induction might be necessary, and a glucocorticoid that does not cross the placenta (e.g., *prednisolone* or *prednisone*) should be used (190).

Many patients, those who are undiagnosed but actually have AOAH, are treated with therapies for ovarian HA and/or PCOS, with progestins for endometrial regulation, *clomiphene*, *letrozole*, or gonadotropins for ovulation induction, or progestins and antiandrogens for control of hirsutism. These therapies may be appropriate, as an alternative to glucocorticoid therapy, even when AOAH is recognized as the cause for the patient's symptoms.

Androgen-Secreting Ovarian and Adrenal Tumors

[7] Patients with severe hirsutism, virilization, or recent and rapidly progressing signs of androgen excess require careful investigation for the presence of an androgen-secreting neoplasm. The two most common sources of androgen-secreting tumors are the adrenal glands and the ovaries. To assess the symptoms, serum and urine tests for androgens and their metabolites should be obtained along with modern abdominal imaging techniques such as CT, MRI, and ultrasound scans (205). In prepubertal girls, virilizing tumors may cause signs of heterosexual PP in addition to hirsutism, acne, and virilization. In patients suspected of harboring an adrenal or ovarian tumor because of rapidly progressing or severe HA, the bioavailable testosterone level (free testosterone level above 6.85 pg/mL; 23.6 pmol/L), followed by an 11-desoxycortisol (above 7 ng/mL; 20.2 nmol/L), DHEAS (>3.6 µg/mL), and a 24-hour urinary cortisol (>45 µg per day) are the most sensitive and specific for the detection of an ACT-AS **(Table 35-2)**. A markedly elevated free testosterone level (2.5 times the upper normal range) is considered typical of an adrenal androgen-secreting tumor, while moderately elevated free testosterone levels are often ovarian in origin. A DHEAS level greater than 800 µg/dL is typical of an adrenal tumor. An adrenal tumor is unlikely when serum DHEAS and urinary 17-ketosteroid excretion measurements are in the normal basal range and the serum cortisol concentration is less than 3.3 µg/dL after *dexamethasone* administration (206). The results of other dynamic tests, especially testosterone suppression and stimulation, are unreliable (207).

A vaginal and abdominal ultrasonographic examination is the first step in the

evaluation of findings suggesting an ovarian neoplasm. Duplex Doppler scanning may increase the accuracy of tumor diagnosis and localization (208).

CT scanning can reveal tumors larger than 10 mm (1 cm) in the adrenal gland but may not help to distinguish among different types of solid tumors or benign incidental nodules (209). In the ovaries, CT scanning cannot help differentiate hormonally active from functional tumors (208,209).

MRI is comparable, if not superior, to CT scanning in detecting ovarian neoplasms, but is neither more sensitive than high-quality ultrasound nor more useful in clinical decision-making when ultrasound identifies a likely neoplasm. Nuclear medicine imaging of the abdomen and pelvis after injection with NP-59 ((131-iodine) 6-beta-iodomethyl-19-norcholesterol), preceded by adrenal and thyroid suppression, may facilitate tumor localization. In the rare circumstances when imaging fails to provide clear evidence for a neoplastic source of excess androgens, selective venous catheterization with measurement of site-specific androgen levels to identify an occult source of for androgen excess may be utilized (210). If all four vessels are catheterized transfemorally, selective venous catheterization allows direct localization of the tumor. Samples are obtained for hormonal analysis, with positive localization defined as a 5:1 testosterone gradient compared with lower vena cava values (211). Under such circumstances, specificity approaches 80%, but this rate should be weighed against the 5% rate of significant complications, such as adrenal hemorrhage and infarction, venous thrombosis, hematoma, and radiation exposure (212).

Androgen-Producing Ovarian Neoplasms

Ovarian neoplasms are the most frequent androgen-producing tumors. Granulosa cell tumors constitute 1% to 2% of all ovarian tumors and occur mostly in adult women (more frequently in postmenopausal than in premenopausal women; see Chapter 39). Usually associated with estrogen production, they are the most common functioning tumors in children and can lead to isosexual PP (213). Patients can present with vaginal bleeding caused by endometrial hyperplasia or endometrial cancer resulting from prolonged exposure to tumor-derived estrogen (214). Total abdominal hysterectomy and bilateral salpingo-oophorectomy are the treatments of choice. If fertility is desired, a more conservative approach involving unilateral salpingo-oophorectomy with careful staging can be performed in women with stage IA (the cancer does not extend outside the involved ovary and a concomitant uterine cancer is excluded) (214). The malignant potential of these lesions is variable. The 10-year survival rates vary from 60% to 90%, depending on the stage, tumor size, and histologic atypia (213).

Thecomas are rare and occur in older patients. In one study, only 11% were androgenic, even in the presence of steroid-type cells (luteinized thecomas) (213). They are unilateral in more than 90% of the cases and rarely malignant. A unilateral salpingo-

oophorectomy is adequate treatment (215).

Sclerosing stromal tumors are benign neoplasms that usually occur in patients younger than 30 years (213). A few cases with estrogenic or androgenic manifestations were reported.

Sertoli–Leydig cell tumors, previously classified as androblastoma or arrhenoblastoma, account for 11% of solid ovarian tumors. They contain various proportions of Sertoli cells, Leydig cells, and fibroblasts (213). Sertoli–Leydig cell tumors are the most common virilizing tumors in women of reproductive age; however, masculinization occurs in only one-third of patients. The tumor is bilateral in 1.5%. In 80% of cases, it is diagnosed at stage IA (213). Sertoli–Leydig cell tumors are frequently low-grade malignancies, and their prognosis is related to their degree of differentiation and stage of disease (216). Treatment with unilateral salpingo-oophorectomy is justified in patients with stage IA disease who desire fertility. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and adjuvant therapy are recommended for postmenopausal women who have advanced-stage disease.

Pure Sertoli cell tumors are usually unilateral. For a premenopausal woman with stage I disease, a unilateral salpingo-oophorectomy is the treatment of choice. Malignant tumors are rapidly fatal (217).

Gynandroblastomas are benign tumors with well-differentiated ovarian and testicular elements. A unilateral oophorectomy or salpingo-oophorectomy is sufficient treatment.

Sex cord tumors with annular tubules (SCTAT) are frequently associated with Peutz–Jeghers syndrome (gastrointestinal polyposis and mucocutaneous melanin pigmentation) (218). Their morphologic features range between those of the granulosa cell and Sertoli cell tumors.

While SCTAT with Peutz–Jeghers syndrome tends to be bilateral and benign, SCTAT without Peutz–Jeghers syndrome is almost always unilateral and malignant in one-fifth of cases (213).

Steroid Cell Tumors

According to Young and Scully, steroid cell tumors are composed entirely of steroid-secreting cells subclassified into stromal luteoma, Leydig cell tumors (hilar and nonhilar), and steroid cell tumors that are not otherwise specific (213). Virilization or hirsutism is encountered with three-fourths of Leydig cell tumors, with one-half of steroid cell tumors not otherwise specific, and with 12% of stromal luteomas.

Nonfunctioning Ovarian Tumors

Ovarian neoplasms that do not directly secrete androgens are occasionally associated with androgen excess, resulting from excess secretion by adjacent ovarian stroma, and include serous and mucinous cystadenomas, Brenner tumors, Krukenberg tumors, benign cystic teratomas, and dysgerminomas (219). Gonadoblastomas arising in the dysgenetic gonads of patients with a Y chromosome are rarely associated with androgen and

estrogen secretion (220,221).

Stromal Hyperplasia and Stromal Hyperthecosis

Stromal hyperplasia is a nonneoplastic proliferation of ovarian stromal cells. Stromal hyperthecosis is defined as the presence of luteinized stromal cells at a distance from the follicles (222). Stromal hyperplasia, which is typically seen in patients between 60 and 80 years of age, may be associated with HA, endometrial carcinoma, obesity, hypertension, and glucose intolerance (222,223). Hyperthecosis is also seen in a mild form in older patients. In patients of reproductive age, hyperthecosis may demonstrate severe clinical manifestations of virilization, obesity, and hypertension (224). Hyperinsulinemia and glucose intolerance may occur in up to 90% of patients with hyperthecosis and may play a role in the etiology of stromal luteinization and HA (76). Hyperthecosis is found in many patients with HAIR-AN syndrome.

In patients with hyperthecosis, levels of ovarian androgens, including testosterone, DHT, and androstenedione, are increased, usually in the male range. The predominant estrogen, as in PCOS, is estrone, which is derived from peripheral aromatization. The E1-to-E2 ratio is increased. Unlike in PCOS, gonadotropin levels are normal (225). Ovaries with stromal hyperthecosis have variable sonographic appearances (226).

Wedge resection for the treatment of mild hyperthecosis was successful and resulted in resumption of ovulation and a pregnancy (227). In cases of more severe hyperthecosis and high total testosterone levels, the ovulatory response to wedge resection is transient (225). In a study in which bilateral oophorectomy was used to control severe virilization, hypertension and glucose intolerance sometimes disappeared (228). When a GnRH agonist was used to treat patients with severe hyperthecosis, ovarian androgen production was dramatically suppressed (229).

Virilization During Pregnancy

Luteomas of pregnancy are frequently associated with maternal and fetal masculinization. This is not a true neoplasm but rather a reversible hyperplasia, which usually regresses postpartum. A review of the literature reveals a 30% incidence of maternal virilization and a 65% incidence of virilized female newborns in the presence of a pregnancy luteoma and maternal masculinization (230–232).

Other tumors causing virilization in pregnancy include (in descending order of frequency) Krukenberg tumors, mucinous cystic tumors, Brenner tumors, serous cystadenomas, endodermal sinus tumors, and dermoid cysts (213).

Virilizing Adrenal Neoplasms

The most common virilizing adrenal neoplasms are adrenal carcinomas. Adrenocortical

carcinomas are rare aggressive tumors that have a bimodal age incidence, with most cases presenting at ages 40 to 50 years (233). Virilization was reported in 20% to 30% of adults with functional adrenocortical carcinoma (234).

When these malignancies virilize, frequently they are associated with elevations in 11-deoxycortisol, cortisol, and DHEAS. These tumors are commonly large and often detectable on abdominal examination. Adrenal tumors that secrete androgens exclusively, whether benign or malignant, are extraordinarily rare (205,235). Modern imaging techniques, such as CT, ultrasonography, MRI, or venous sampling, are extremely useful for distinguishing between an ovarian and an adrenal tumor as a cause of virilization (233).

PROLACTIN DISORDERS

Prolactin was first identified as a product of the anterior pituitary, in 1933 (236). It is found in nearly every vertebrate species. Its presence in humans was long inferred by the association of the syndrome of amenorrhea and galactorrhea in the presence of pituitary macroadenomas, though it was not definitively identified as a human hormone until 1971. The specific activities of human prolactin (hPRL) were defined by the separation of its activity from growth hormone and subsequently by the development of radioimmunoassays (237–239). **Although the initiation and maintenance of lactation is the primary function of prolactin, many studies document roles for prolactin activity within and beyond the reproductive system.**

Prolactin Secretion

There are 199 amino acids within hPRL, with a molecular weight (MW) of 23,000 D **(Fig. 35-8)**. Although human growth hormone and placental lactogen have significant lactogenic activity, they have only a 16% and 13% amino acid sequence homology with prolactin, respectively. In the human genome, a single gene on chromosome 6 encodes prolactin. The prolactin gene (10 kb) has five exons and four introns, and its transcription is regulated in the pituitary by a proximal promotor region and in extrapituitary locations by a more upstream promotor (240).

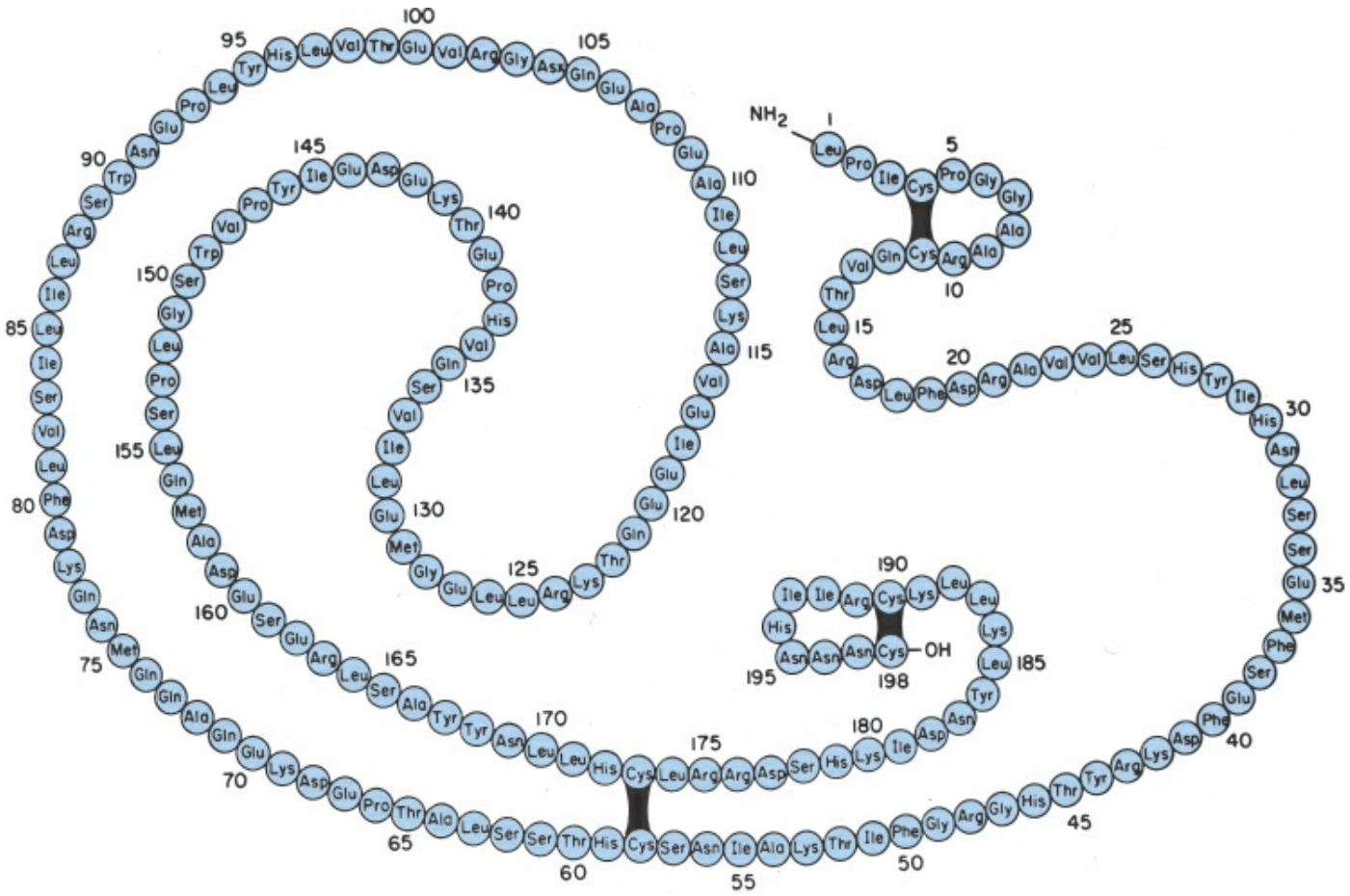


FIGURE 35-8 Amino acid sequence of prolactin. Three cysteine disulfide bands are located within the molecule. (With permission from **Bondy PK**. Rosenberg Leukocyte Esterase: Metabolic Control and Disease. 8th ed. Philadelphia, PA: WB Saunders; 1980.)

In the basal state, three forms are released: a monomer, a dimer, and a multimeric species, called little, big, and big-big prolactin, respectively (241–243). The two larger species can be degraded to the monomeric form by reducing disulfide bonds (244). The proportions of each of these prolactin species vary with physiologic, pathologic, and hormonal stimulation (244–247). The heterogeneity of secreted forms remains an active area of research. Studies indicate that little prolactin (MW 23,000 D) constitutes more than 50% of all combined prolactin production and is most responsive to extrapituitary stimulation or suppression (244,246,247). **Clinical assays for prolactin measure the little prolactin, and in all but extremely rare circumstances, these measures are sufficient to assess diseases of abnormal pituitary production of the hormone.** Prolactin, and its relatives, growth hormone and placental lactogen, do not require glycosylation for most of their primary activities, as is the case for the gonadotropins and TSH. Glycosylated forms are secreted, and glycosylation does affect the bioactivity and immunoreactivity of little prolactin (248–251). It appears that the glycosylated form is the predominant species secreted, but the most potent biologic form appears to be the 23,000-D nonglycosylated form of prolactin (250). Prolactin has over 300 known

biologic activities. Prolactin's most recognized activities include those associated with reproduction (lactation, luteal function, reproductive behavior) and homeostasis (immune responsivity, osmoregulation, and angiogenesis) (252). Despite these many activities, **the only recognized disorder associated with deficiency of prolactin secretion is the inability to lactate.**

To some degree, the physical heterogeneity of prolactin may explain the biologic heterogeneity of this hormone, and although this complicates the physiologic evaluation of prolactin's myriad effects, it is of little importance in the diagnosis and management of hyperprolactinemic states.

In contrast to other anterior pituitary hormones, which are controlled by hypothalamic-releasing factors, prolactin secretion is primarily under inhibitory control mediated by dopamine. **Multiple lines of evidence suggest that dopamine, which is secreted by the tuberoinfundibular dopaminergic neurons into the portal hypophyseal vessels, is the primary prolactin-inhibiting factor.** Dopamine receptors were found on pituitary lactotrophs, and treatment with dopamine or dopamine agonists suppresses prolactin secretion (253–259). The dopamine antagonist *metoclopramide* abolishes the pulsatility of prolactin release and increases serum prolactin levels (255,256,260). **Interference with dopamine transit from the hypothalamus to the pituitary by mass lesions, or blockade of the dopamine receptor as that occurs with antipsychotic and other medications, increases serum prolactin levels.** Thyrotropin-releasing hormone (TRH) causes prolactin release when present at supraphysiologic levels (as in primary hypothyroidism), but does not appear to play an important modulatory role in the normal physiologic regulation of prolactin secretion. GABA and other neurohormones and neurotransmitters also may function as prolactin-inhibiting factors (261–264). Several hypothalamic polypeptides that modulate prolactin-releasing activity are listed in Table 35-8. It appears that dopamine and TRH act as primary controlling neurohormones, while others (i.e., neuropeptide Y, galanin, and enkephalin) act as modulators. It is likely that under differing physiologic conditions (i.e., pregnancy, lactation, stress, aging), a modulator may become a principal regulator of hormone secretion.

The prolactin receptor is a member of the class 1 cytokine receptor superfamily and is encoded by a gene on chromosome 5 (265). Transcriptional regulation of the prolactin receptor is accomplished through three tissue-specific promoter regions: promoter I for the gonads, promoter II for the liver, and promoter III, a generic promoter that includes the mammary gland (266).

Hyperprolactinemia

Physiologic disturbances, pharmacologic agents, or markedly compromised renal function may cause elevations in prolactin levels, and transient elevations occur

with acute stress or painful stimuli. The most common cause of elevated prolactin levels is likely pharmacologic; most patients using antipsychotic medications and many other patients using agents with antidopaminergic properties will exhibit moderately elevated prolactin levels. Drug-related and physiologic conditions resulting in hyperprolactinemia do not always require direct intervention to normalize prolactin levels.

Table 35-8 Chemical Factors Modulating Prolactin Release and Conditions That Result in Hyperprolactinemia

Inhibitory factors
Dopamine
γ-Aminobutyric acid
Histidyl-proline diketopiperazine
Pyroglutamic acid
Somatostatin
Stimulatory factors
b-Endorphin
17b-Estradiol
Enkephalins
Gonadotropin-releasing hormone
Histamine
Serotonin
Substance P
Thyrotropin-releasing hormone
Vasoactive intestinal peptide
Physiologic conditions
Anesthesia
Empty sella syndrome
Idiopathic
Intercourse
Major surgery and disorders of chest wall (burns, herpes, chest percussion)

Newborns
Nipple stimulation
Pregnancy
Postpartum (nonnursing: days 1–7; nursing: with suckling)
Sleep
Stress
Postpartum
Hypothalamic conditions
Arachnoid cyst
Craniopharyngioma
Cystic glioma
Cysticercosis
Dermoid cyst
Epidermoid cyst
Histiocytosis
Neurotuberculosis
Pineal tumors
Pseudotumor cerebri
Sarcoidosis
Suprasellar cysts
Tuberculosis
Pituitary conditions
Acromegaly
Addison disease
Craniopharyngioma
Cushing syndrome
Hypothyroidism
Histiocytosis
Lymphoid hypophysitis

Metastatic tumors (especially of the lungs and breasts)
Multiple endocrine neoplasia
Nelson syndrome
Pituitary adenoma (microadenoma or macroadenoma)
Post-oral contraception
Sarcoidosis
Thyrotropin-releasing hormone administration
Trauma to stalk
Tuberculosis
Metabolic dysfunction
Ectopic production (hypernephroma, bronchogenic sarcoma)
Hepatic cirrhosis
Renal failure
Starvation refeeding
Drug conditions
α-*Methyldopa*
Antidepressants (*amoxapine, imipramine, amitriptyline*)
Cimetidine
Dopamine antagonists (phenothiazines, thioxanthenes, *butyrophenone, diphenylbutylpiperidine, dibenzoxazepine, dihydroindolone, procainamide, metoclopramide*)
Estrogen therapy
Opiates
Reserpine
Sulpiride
Verapamil

Evaluation

Plasma levels of immunoreactive prolactin are 5 to 27 ng/mL throughout the normal menstrual cycle. Samples should not be drawn soon after the patient awakes or after procedures. Prolactin is secreted in a pulsatile fashion with a pulse frequency ranging from about 14 pulses per 24 hours in the late follicular phase to

about 9 pulses per 24 hours in the late luteal phase. There is also a diurnal variation, with the lowest levels occurring in midmorning. Levels rise 1 hour after the onset of sleep and continue to rise until peak values are reached between 5 and 7 am (267,268). The pulse amplitude of prolactin appears to increase from early to late follicular and luteal phases (269–271). Because of the variability of secretion and inherent limitations of radioimmunoassay, an elevated level should always be rechecked. This sample preferably is drawn midmorning and not after stress, previous venipuncture, breast stimulation, or physical examination, all of which transiently increase prolactin levels.

When prolactin levels are found to be elevated, hypothyroidism and medications should first be ruled out as a cause. Prolactin and TSH determinations are basic evaluations in anovulatory infertile women. Infertile men with hypogonadism also should be tested. Likewise, prolactin levels should be measured in the evaluation of amenorrhea, galactorrhea, hirsutism with amenorrhea, anovulatory bleeding, and delayed puberty **(Fig. 35-9)**.

In cases of asymptomatic, incidental hyperprolactinemia, the finding of a macroprolactin elevation will preclude further diagnostic workup and expense as big and big-big prolactin elevations are not associated with adenomas or recognized symptomatology (272).

Physical Signs of Hyperprolactinemia

[8] Elevations in prolactin may cause amenorrhea, galactorrhea, both, or neither. Amenorrhea without galactorrhea is associated with hyperprolactinemia in approximately 15% of women (273–275). The cessation of normal ovulatory processes resulting from elevated prolactin levels is primarily caused by the suppressive effects of prolactin, via hypothalamic mediation, on GnRH pulsatile release (254,273,274,276–284). In addition to causing a hypogonadotropic state, prolactin elevations may secondarily impair the mechanisms of ovulation by causing a reduction in granulosa cell number and FSH binding, inhibition of granulosa cell 17β-estradiol production by interfering with FSH action, and by causing inadequate luteinization and reduced luteal secretion of progesterone (285–290). Other etiologies for amenorrhea are detailed in Chapter 34.

Although isolated galactorrhea is considered indicative of hyperprolactinemia, prolactin levels are within the normal range in nearly 50% of such patients (291–293) **(Fig. 35-9)**. In these cases, whether caused by a prior transient episode of hyperprolactinemia or other unknown factors, the sensitivity of the breast to the lactotrophic stimulus engendered by normal prolactin levels is sufficient to result in galactorrhea. This situation is very similar to that observed in nursing mothers in whom milk secretion, once established, continues and even increases despite progressive normalization of prolactin levels. Repeat testing is occasionally helpful in detecting

hyperprolactinemia. **Approximately one-third of women with galactorrhea have normal menses. Conversely, hyperprolactinemia commonly occurs in the absence of galactorrhea (66%), which may result from inadequate estrogenic or progestational priming of the breast.**

[8] In patients with both galactorrhea and amenorrhea, approximately two-thirds will have hyperprolactinemia; in that group, approximately one-third will have a pituitary adenoma (294). In anovulatory women, 3% to 10% of women diagnosed with PCO disease have coexistent and usually modest hyperprolactinemia (295,296) **(Fig. 35-10)**.

Prolactin and TSH levels should be measured in all patients with delayed puberty. Pituitary abnormalities, including craniopharyngiomas and adenomas, should be considered in all cases of delayed puberty accompanied by low levels of gonadotropins, regardless of whether prolactin levels are elevated. When prolactin-secreting pituitary adenomas are present, the condition of multiple endocrine neoplasia type 1 (MEN-1) syndrome (gastrinomas, insulinoma, parathyroid hyperplasia, and pituitary neoplasia) should be considered, although symptoms of pituitary adenoma are rarely the presenting symptom. Patients who have a pituitary adenoma and a family history of multiple adenomas warrant special attention (297). Prolactinomas are noted in approximately 20% of patients with MEN-1. The *MEN-1* gene is localized to chromosome 11q13 and appears to act as a constitutive tumor suppressor gene. An inactivating mutation results in development of the tumor. It is thought that prolactin-secreting pituitary adenomas that occur in patients with MEN-1 may be more aggressive than sporadic cases (298).

When an elevated prolactin level is documented and medications or hypothyroidism as the underlying cause is excluded, knowledge of neuroanatomy, imaging techniques, and their interpretation is essential to further evaluation (see Chapter 7). **Pituitary hyperprolactinemia is most often caused by a microadenoma or associated with normal imaging findings. These patients can be reassured that the probable course of their condition is benign. Macroadenomas or juxtasellar lesions are less common and require more complex evaluation and treatment, including surgery, radiation, or both.** Levels of TSH should be measured in all patients with hyperprolactinemia **(Fig. 35-9)**.

Imaging Techniques

In patients with larger microadenomas and macroadenomas, prolactin levels usually are higher than 100 ng/mL. However, levels lower than 100 ng/mL may be associated with smaller microadenomas, macroadenomas that produce a "stalk section" effect, and suprasellar tumors that may be missed on a "coned-down" view of the sella turcica. Modest elevations of prolactin can be associated with

microadenomas or macroadenomas, nonlactotroph pituitary tumors, and other central nervous system abnormalities. Imaging of the pituitary gland must be considered when otherwise unexplained and persistent prolactin elevation is present. **In patients with a clearly identifiable drug-induced or physiologic hyperprolactinemia, imaging is not necessary unless accompanied by symptoms suggesting a mass lesion (headache, visual field deficits).** MRI with gadolinium enhancement of the sella and pituitary gland appears to provide the best anatomic detail (299). The cumulative radiation dose from multiple CT scans may cause cataracts, and the "coned-down" views or tomograms of the sella are very insensitive and expose the patient to radiation. For patients with hyperprolactinemia who desire future fertility, MRI is indicated to differentiate a pituitary microadenoma from a macroadenoma and to identify other potential sellar-suprasellar masses. Although rare, when pregnancy-related complications of a pituitary adenoma occur, they occur more frequently in the presence of macroadenomas.

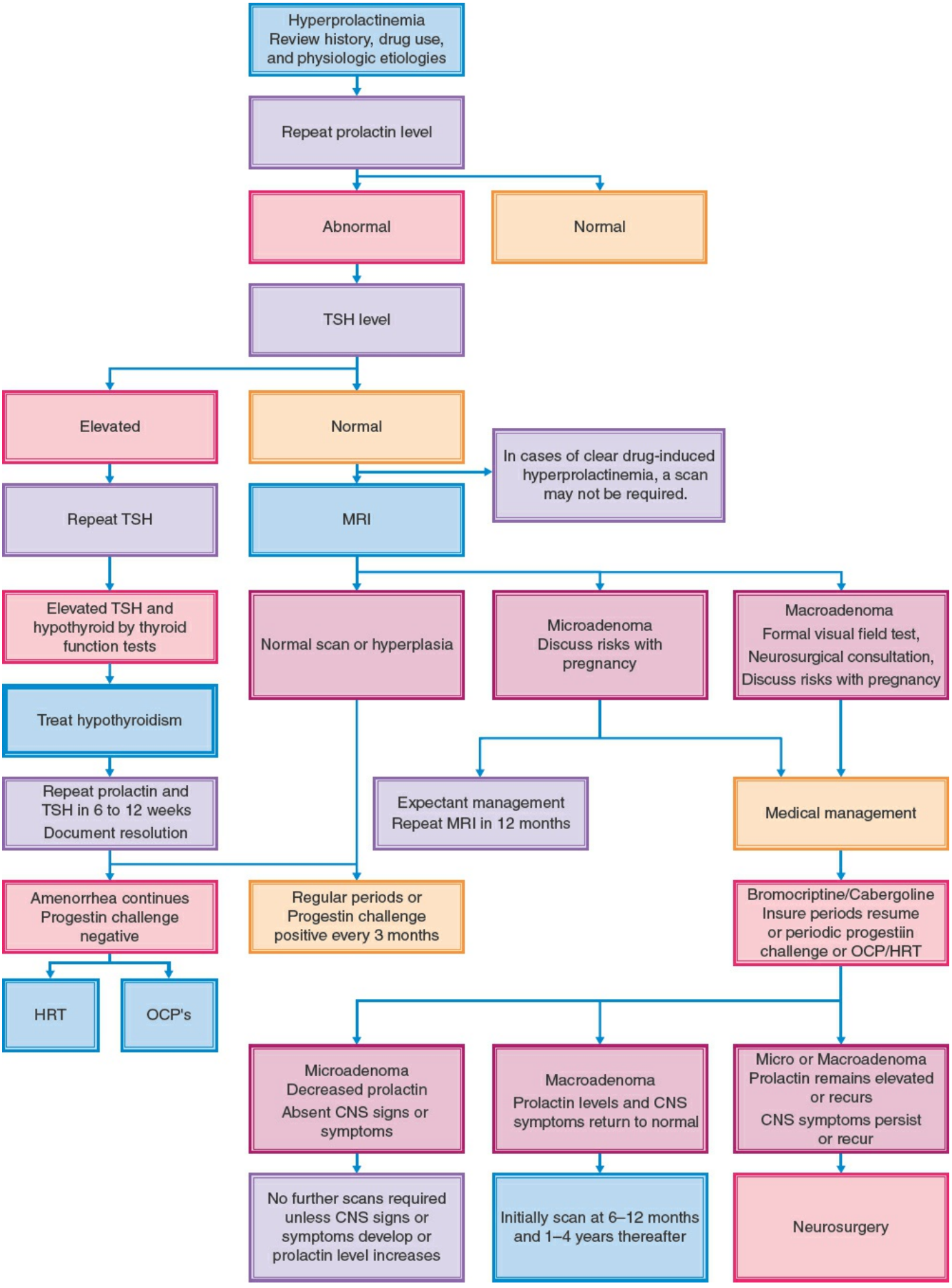

Hyperprolactinemia
Review history, drug use, and physiologic etiologies
Repeat prolactin level
Abnormal
Normal
TSH level
Elevated
Normal
In cases of clear drug-induced hyperprolactinemia, a scan may not be required.
Repeat TSH
MRI
Elevated TSH and hypothyroid by thyroid function tests
Normal scan or hyperplasia
Microadenoma
Discuss risks with pregnancy
Macroadenoma
Formal visual field test,
Neurosurgical consultation,
Discuss risks with pregnancy
Treat hypothyroidism
Repeat prolactin and TSH in 6 to 12 weeks
Document resolution
Expectant management
Repeat MRI in 12 months
Medical management
Amenorrhea continues
Progestin challenge negative
Regular periods or
Progestin challenge positive every 3 months
Bromocriptine/Cabergoline
Insure periods resume or periodic progestiin challenge or OCP/HRT
HRT
OCP's
Microadenoma
Decreased prolactin
Absent CNS signs or symptoms
Macroadenoma
Prolactin levels and CNS symptoms return to normal
Micro or Macroadenoma
Prolactin remains elevated or recurs
CNS symptoms persist or recur
No further scans required unless CNS signs or symptoms develop or prolactin level increases
Initially scan at 6–12 months and 1–4 years thereafter
Neurosurgery

FIGURE 35-9 Workup for hyperprolactinemia. TSH, thyroid-stimulating hormone; MRI, magnetic resonance imaging; CT, computed tomography; HRT, hormone replacement therapy; OCPs, oral contraceptive pills; CNS, central nervous system.

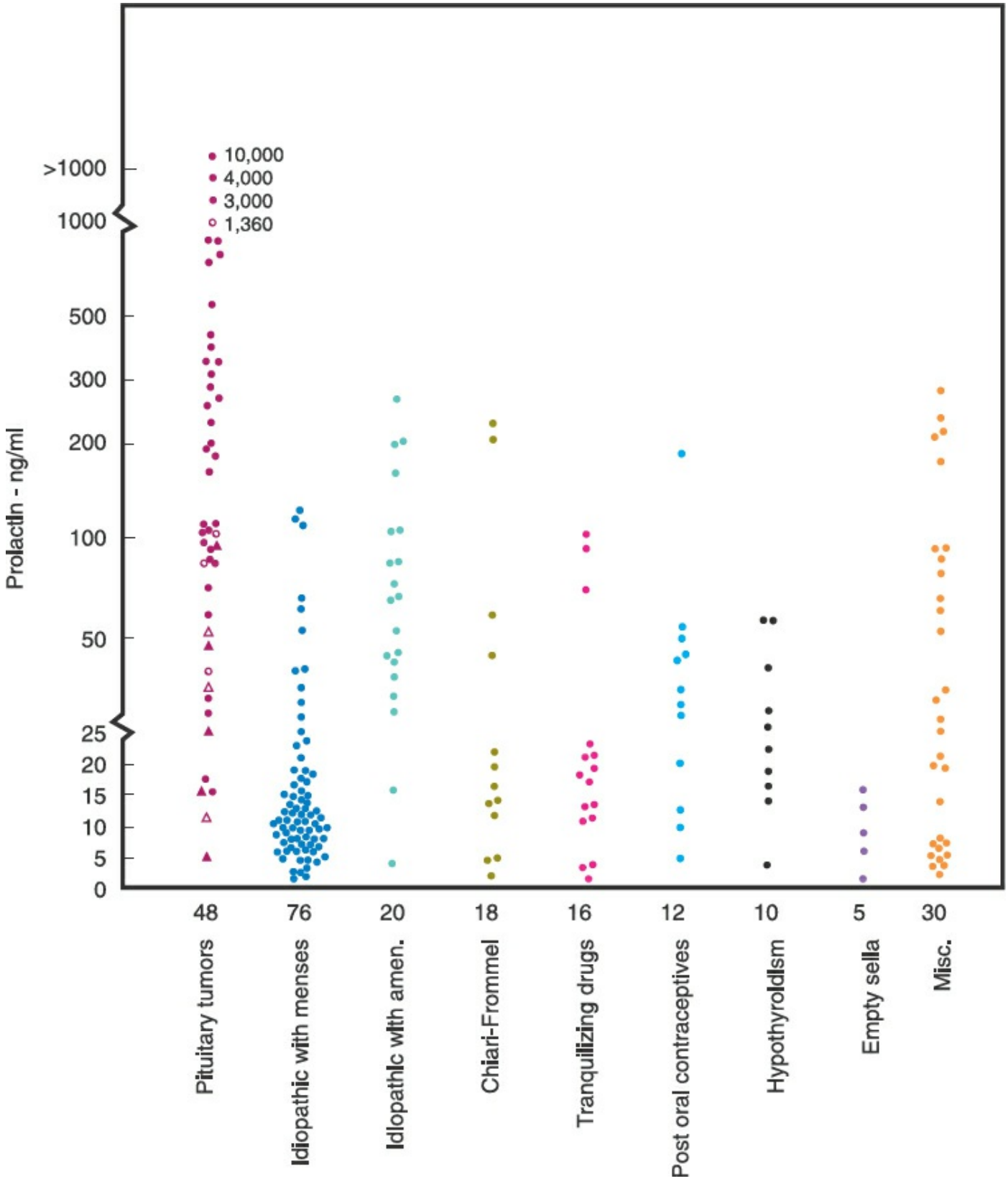


FIGURE 35-10 Prolactin levels in 235 patients with galactorrhea. Among patients with a tumor, open triangles denote associated acromegaly, and solid circles and solid triangles denote previous radiotherapy or surgical resection, respectively. (With permission from **Kleinberg DL, Noel GL, Frantz AG**. Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. *N Engl J Med* 1977;296: 589–600.)

In over 90% of untreated women, microadenomas do not enlarge over a 4- to 6-year period. The argument that medical therapy will prevent a microadenoma from growing is false. While prolactin levels correlate with tumor size, both elevations and reductions in prolactin levels may occur without any change in tumor size. If during follow-up, the prolactin level rises significantly or central nervous system symptoms (headache, visual changes) are noted, repeat imaging may be indicated.

Hypothalamic Disorders

Dopamine was the first of many substances whose production was demonstrated in the arcuate nucleus. Dopamine-releasing neurons innervate the external zone of the median eminence. When released into the hypophyseal portal system, dopamine inhibits prolactin release in the anterior pituitary. **Lesions that disrupt dopamine release can result in hyperprolactinemia**. Such lesions may arise from the suprasellar area, pituitary gland, and infundibular stalk, as well as from adjacent bone, brain, cranial nerves, dura, leptomeninges, nasopharynx, and vessels. Numerous pathologic entities and physiologic conditions in the hypothalamic–pituitary region can disrupt dopamine release and cause hyperprolactinemia.

Pituitary Disorders

Microadenoma

In more than one-third of women with hyperprolactinemia, a radiologic abnormality consistent with a microadenoma (<1 cm) is found. Release of pituitary stem cell growth inhibition via activation or loss-of-function mutations results in cell cycle dysregulation and is critical to the development of pituitary microadenomas and macroadenomas. Microadenomas are monoclonal in origin. Genetic mutations are thought to release stem cell growth inhibition and result in autonomous anterior pituitary hormone production, secretion, and cell proliferation. Additional anatomic factors that may contribute to adenoma formation include reduced dopamine concentrations in the hypophyseal portal system and vascular isolation of the tumor, or both. Recently, the heparin-binding secretory-transforming (*HST*) gene has been noted in a variety of cancers and in prolactinomas (300). **Patients with microadenomas can be reassured of a probable benign course, and many of these lesions exhibit gradual spontaneous regression** (301,302).

Both microadenomas and macroadenomas are monoclonal in origin. Lactotoph adenomas are histologically granulated either sparsely or densely. The sparsely granulated lactotrope adenomas have trabecular, papillary, or solid patterns.

Calcification of these tumors may take the form of a psammoma body or a pituitary stone. Densely granulated lactotrope adenomas are strongly acidophilic tumors and appear to be more aggressive than sparsely granulated lactotrope adenomas. Unusual acidophil stem cell adenomas can be associated with hyperprolactinemia, with some clinical or biochemical evidence of growth hormone excess.

Microadenomas rarely progress to macroadenomas. Six large series of patients with microadenomas reveal that, with no treatment, the risk for progression of microadenoma to a macroadenoma is only 7% (303). Treatments include expectant, medical, or, rarely, surgical therapy. All affected women should be advised to notify their physicians of chronic headaches, visual disturbances (particularly tunnel vision consistent with bitemporal hemianopsia), and extraocular muscle palsies. Formal visual field testing is rarely helpful, unless imaging suggests compression of the optic nerves.

Autopsy and radiographic series reveal that 14.4% to 22.5% of the US population harbor microadenomas, and approximately 25% to 40% stain positively for prolactin (304). Clinically significant pituitary tumors requiring some type of intervention affect only 14 per 100,000 individuals (304).

Expectant Management

In women who do not desire fertility, expectant management can be used for microadenomas and hyperprolactinemia without an adenoma while menstrual function remains intact. Hyperprolactinemia-induced estrogen deficiency, rather than prolactin itself, is the major factor in the development of osteopenia (305). Therefore, **estrogen replacement with typical hormone replacement regimens or hormonal contraceptives is indicated for patients with amenorrhea or irregular menses. Patients with drug-induced hyperprolactinemia can be managed expectantly with attention to the risks of osteoporosis. In the absence of symptoms of pituitary enlargement, imaging may be repeated in 12 months, and if prolactin levels remain stable, less frequently thereafter, to assess further growth of the microadenoma**.

Medical Treatment

Ergot alkaloids are the mainstay of therapy. In 1985, bromocriptine was approved for use in the United States to treat hyperprolactinemia caused by a pituitary adenoma. These agents act as strong dopamine agonists, thus decreasing prolactin levels. Effects on prolactin levels occur within hours, and lesion size may decrease within 1 or 2 weeks. Bromocriptine decreases prolactin synthesis, DNA synthesis, cell multiplication, and overall size of prolactinomas. Bromocriptine treatment results in normal prolactin blood levels or return of ovulatory menses in 80% to 90% of patients.

Because ergot alkaloids, like *bromocriptine*, are excreted via the biliary tree, caution is required when using it in the presence of liver disease. The major adverse effects include nausea, headaches, hypotension, dizziness, fatigue and drowsiness, vomiting,

headaches, nasal congestion, and constipation. **Many patients tolerate *bromocriptine* when the dose is increased gradually, by 1.25 mg (one-half tablet) daily each week until prolactin levels are normal or a dose of 2.5 mg twice daily is reached. A proposed regimen is as follows: one-half tablet every evening (1.25 mg) for 1 week, one-half tablet morning and evening (1.25 mg) during the second week, one-half tablet in the morning (1.25 mg) and a full tablet every evening (2.5 mg) during the third week, and one tablet every morning and every evening during the fourth week and thereafter (2.5 mg twice a day).** The lowest dose that maintains the prolactin level in the normal range is continued (1.25 mg twice daily often is sufficient to normalize prolactin levels in individuals with levels less than 100 ng/mL). Pharmacokinetic studies show peak serum levels occur 3 hours after an oral dose, with a nadir at 7 hours. Because little detectable *bromocriptine* is in the serum by 11 to 14 hours, twice-a-day administration is required. Prolactin levels can be checked soon (6 to 24 hours) after the last dose.

One rare adverse effect of *bromocriptine* is a psychotic reaction. Symptoms include auditory hallucinations, delusional ideas, and changes in mood that quickly resolve after discontinuation of the drug (306).

Many investigators report no difference in fibrosis, calcification, prolactin immunoreactivity, or the surgical success in patients pretreated with *bromocriptine* compared with those not receiving *bromocriptine* (303).

An alternative to oral administration is the vaginal administration of *bromocriptine* tablets, which is well tolerated, and actually results in increased pharmacokinetic measures (307). *Cabergoline*, another ergot alkaloid, has a very long half-life and can be given orally twice per week. Its long duration of action is attributable to slow elimination by pituitary tumor tissue, high-affinity binding to pituitary dopamine receptors, and extensive enterohepatic recirculation.

Cabergoline, which appears to be as effective as *bromocriptine* in lowering prolactin levels and in reducing tumor size, has substantially fewer adverse effects than *bromocriptine*. Very rarely, patients experience nausea and vomiting or dizziness with *cabergoline*; they may be treated with intravaginal *cabergoline* as with *bromocriptine.* A gradually increasing dosage helps avoid the side effects of nausea, vomiting, and dizziness. *Cabergoline* at 0.25 mg twice per week is usually adequate for hyperprolactinemia with values less than 100 ng/mL. If required to normalize prolactin levels, the dosage can be increased by 0.25 mg per dose on a weekly basis to a maximum of 1 mg twice weekly.

Recent studies reveal an increased risk of cardiac valve regurgitation in patients with Parkinson disease who were treated with high doses of *cabergoline* or *pergolide* but not with *bromocriptine* (308,309). Higher doses and a longer duration of therapy were associated with a higher risk of valvulopathy. It is postulated that 5HT2b-receptor

stimulation leads to fibromyoblast proliferation (310). A recent cross-sectional study showed a higher rate of asymptomatic tricuspid regurgitation among *cabergoline*-treated patients compared with untreated patients with newly diagnosed prolactinomas and normal controls (311,312).

The demonstrated relative safety of *bromocriptine* in reproductive-aged women and during more than 2,500 pregnancies suggests *bromocriptine* is the first choice for hyperprolactinemia and micro- and macroadenomas (313).

When *bromocriptine* or *cabergoline* cannot be used, other medications such as *pergolide* or *metergoline* may be used. In patients with a microadenoma who are receiving *bromocriptine* therapy, a repeat MRI scan may be performed 6 to 12 months after prolactin levels are normal, if indicated. Normal prolactin levels and resumption of menses should not be considered absolute proof of tumor response to treatment. Further MRI scans should be performed if new symptoms appear.

Discontinuation of *bromocriptine* therapy after 2 to 3 years may be attempted in a select group of patients who have maintained normoprolactinemia while on therapy (314,315). In a retrospective series of 131 patients treated with *bromocriptine* for a median of 47 months, normoprolactinemia was sustained in 21% at a median follow-up of 44 months after treatment discontinuation (315). Discontinuation of *cabergoline* therapy was successful in patients treated for 3 to 4 years who maintained normoprolactinemia (316). In *cabergoline* discontinuers who met stringent inclusion criteria, a recurrence rate of 64% was noted (317). A meta-analysis involving 743 patients noted sustained normoprolactinemia in only a minority of patients (21%) after discontinuation. Patients with 2 years or more of therapy before discontinuation and no demonstrable tumor visible on MRI had the highest chance of persistent normoprolactinemia (318). Recurrence rates are higher for macroadenomas (as compared to microadenomas or hyperprolactinemia without adenoma) after cessation of either *bromocriptine* or *cabergoline*, warranting a close follow-up with serum prolactin and MRI after cessation of therapy. In patients with macroadenomas, withdrawal of therapy should proceed with caution, as rapid tumor re-expansion may occur.

Macroadenomas

Macroadenomas are pituitary tumors that are larger than 1 cm in size. *Bromocriptine* is the best initial and potentially long-term treatment option, but transsphenoidal surgery may be required. High-dose *cabergoline* therapy was used in *bromocriptine*-resistant or -intolerant macroadenoma patients successfully; however, cautions remain regarding the development of cardiac valve abnormalities (319).

Evaluation for pituitary hormone deficiencies may be indicated. Symptoms of macroadenoma enlargement include severe headaches, visual field changes, and, rarely, diabetes insipidus and blindness. After prolactin has reached normal levels following ergot alkaloid treatment, a repeat MRI is indicated within 6 months to document

shrinkage or stabilization of the size of the macroadenoma. This examination may be performed earlier if new symptoms develop or if there is no improvement in previously noted symptoms. Normalized prolactin levels or resumption of menses should not be taken as absolute proof of tumor response to treatment, particularly with a macroadenoma.

Medical Treatment

Treatment with *bromocriptine* decreases prolactin levels and the size of macroadenomas; nearly one-half show a 50% reduction in size, and another one-fourth show a 33% reduction after 6 months of therapy. Because tumor regrowth occurs in more than 60% of cases after discontinuation of *bromocriptine* therapy, long-term therapy is usually required.

After stabilization of tumor size is documented, the MRI scan is repeated 6–12 months later and, if stable, yearly for several years. This examination may be performed earlier if new symptoms develop or if there is no improvement in symptoms. Serum prolactin levels are measured every 6 months. Because tumors may enlarge despite normalized prolactin values, a reevaluation of symptoms at regular intervals (6 months) is prudent. Normalized prolactin levels or resumption of menses should not be taken as absolute proof of tumor response to treatment (318,320).

Surgical Intervention

Tumors that are unresponsive to *bromocriptine* or that cause persistent visual field loss require surgical intervention. Some neurosurgeons have noted that a short (2- to 6-week) preoperative course of *bromocriptine* increases the efficacy of surgery in patients with larger adenomas (303). Despite surgical resection, recurrence of hyperprolactinemia and tumor growth is common. Complications of surgery include cerebral carotid artery injury, diabetes insipidus, meningitis, nasal septal perforation, partial or panhypopituitarism, spinal fluid rhinorrhea, and third nerve palsy. Periodic MRI scanning after surgery is indicated, particularly in patients with recurrent hyperprolactinemia.

Metabolic Dysfunction and Hyperprolactinemia

Occasionally, patients with hypothyroidism exhibit hyperprolactinemia with remarkable pituitary enlargement caused by thyrotroph hyperplasia. These patients respond to thyroid replacement therapy with reduction in pituitary enlargement and normalization of prolactin levels (321).

Hyperprolactinemia occurs in 20% to 75% of women with chronic renal failure. Prolactin levels are not normalized through hemodialysis but are normalized after transplantation (322–324). Occasionally, women with hyperandrogenemia also have hyperprolactinemia. Elevated prolactin levels may alter adrenal function by enhancing the release of adrenal androgens such as DHEAS (325).

Drug-Induced Hyperprolactinemia

Numerous drugs interfere with dopamine secretion and can be responsible for hyperprolactinemia and its attendant symptoms (Table 35-8). If medication can be discontinued, resolution of hyperprolactinemia is uniformly prompt. If not, endocrine management should be directed at estrogen replacement and normalization of menses for those with disturbed or absent ovulation. Treatment with dopamine agonists may be utilized if ovulation is desired and the drug-inducing hyperprolactinemia cannot be discontinued.

Use of Estrogen in Hyperprolactinemia

In rodents, pituitary prolactin-secreting adenomas occur with high-dose estrogen administration (326). Elevated levels of estrogen, as found in pregnancy, are responsible for hypertrophy and hyperplasia of lactotrophic cells and account for the progressive increase in prolactin levels in normal pregnancy. The increase in prolactin during pregnancy is physiologic and reversible; adenomas are not fostered by the hyperestrogemia of pregnancy. Pregnancy may have a favorable influence on preexisting prolactinomas (327,328). Estrogen administration is not associated with clinical, biochemical, or radiologic evidence of growth of pituitary microadenomas or the progression of idiopathic hyperprolactinemia to an adenoma status (329–332). **For these reasons, estrogen replacement or OC use is appropriate for hypoestrogenic patients with hyperprolactinemia secondary to microadenoma or hyperplasia.**

Monitoring Pituitary Adenomas During Pregnancy

Prolactin-secreting microadenomas rarely create complications during pregnancy. Monitoring of patients with serial gross visual field examinations and funduscopic examination is recommended. If persistent headaches, visual field deficits, or visual or funduscopic changes occur, MRI scanning is advisable. **Because serum prolactin levels progressively rise throughout pregnancy, prolactin measurements are rarely of value.**

For those women who become pregnant while taking bromocriptine to treat a return of spontaneous ovulations, discontinuation of bromocriptine is recommended. This does not preclude subsequent use of *bromocriptine* during the pregnancy to treat symptoms (visual field defects, headaches) that arise from further enlargement of the microadenoma (313,333–335). *Bromocriptine* did not exhibit teratogenicity in animals, and observational data do not suggest harm to pregnancy or fetus in humans.

Pregnant women with previous transsphenoidal surgery for microadenomas or macroadenomas may be monitored with monthly Goldman perimetry visual field testing. Periodic MRI scanning may be necessary in women with symptoms or visual changes. **Breastfeeding is not contraindicated in the presence of microadenomas or**

macroadenomas (313,333–335). The use of *bromocriptine* and presumably other dopaminergic agents that may cause blood pressure elevation during the postpartum period is contraindicated (336–340).

THYROID DISORDERS

Thyroid disorders are 10 times more common in women than men. Approximately 1% of the female population of the United States will develop overt hypothyroidism (341). Even prior to the discovery of the long-acting thyroid stimulator (LATS) in women with Graves disease in 1956, numerous investigations demonstrated a link between these autoimmune thyroid disorders and reproductive physiology and pathology (342).

Thyroid Hormones

Iodide is a critical component of the class of hormones known as thyronines, among which the most important are triiodothyronine (T_3) and thyroxine (T_4). Iodide obtained from dietary sources is actively transported into the thyroid follicular cell for the synthesis of these hormones. The sodium–iodide symporter (NIS) is a key molecule in thyroid function. It allows the accumulation of iodide from the circulation into the thyrocyte against an electrochemical gradient. The NIS requires energy that is supplied by Na-K ATPase, and iodine uptake is stimulated by TSH or thyrotropin. The enzyme thyroid peroxidase (TPO) then oxidizes iodide near the cell-colloid surface and incorporates it into tyrosyl residues within the thyroglobulin molecule, which results in the formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT). T_3 and T_4, formed by secondary coupling of MIT and DIT, are catalyzed by TPO. The membrane-bound, heme-containing oligomer, TPO, is localized in the rough endoplasmic reticulum, Golgi vesicles, lateral and apical vesicles, and on the follicular cell surface. Thyroglobulin, the major protein formed in the thyroid gland, has an iodine content of 0.1% to 1.1% by weight. About 33% of the iodine is present in thyroglobulin in the form of T_3 and T_4, and the remainder is present in MIT and DIT or found as unbound iodine. Thyroglobulin provides a storage capacity capable of maintaining a euthyroid state for nearly 2 months without the formation of new thyroid hormones. The thyroid antimicrosomal antibodies found in patients with autoimmune thyroid disease (ATD) are directed against the TPO enzyme (343,344).

TSH regulates thyroidal iodine metabolism by activation of adenylate cyclase. This facilitates endocytosis as a component of iodide uptake, digestion of thyroglobulin-containing colloid, and the release of thyroid hormones T_4, T_3, and reverse T_3. T_4 is released from the thyroid at 40 to 100 times the concentration of T_3. The concentration of reverse T_3, which has no intrinsic thyroid activity, is 30% to 50% of T_3 and 1% of T_4 concentration. Of thyroid hormones released, 70% are bound by circulating thyroid-binding globulin (TBG). T_4 is present in higher concentrations in the circulating storage pool and has a slower turnover rate than T_3. Approximately 30% of T_4 is converted to

T_3 in the periphery. Reverse T_3 participates in regulation of the conversion of T_4 to T_3. T_3 is the primary physiologically functional thyroid hormone at the cellular level. T_3 binds the nuclear receptor with 10 times the affinity of T_4. Thyroid hormone effects on cells include increased oxygen consumption, heat production, and metabolism of fats, proteins, and carbohydrates. Systemically, thyroid hormone activity is responsible for the basal metabolic rate. It balances fuel efficiency with performance. Hyperthyroid states result in excessive fuel consumption with marginal performance, while hypothyroidism reduces both fuel consumption and performance.

Iodide Metabolism

Normal function of the thyroid gland is dependent on iodine. The World Health Organization recommends 150 µg of iodine per day in women of reproductive age and 250 µg per day is recommended during pregnancy and nursing. Adequate iodination of household salt is defined as salt containing 15 to 40 mg of iodine per kilogram of salt (345).

Optimal iodine intake to prevent disease lies within a relatively narrow range around the recommended daily consumption. Extreme iodine deficiency states are associated with cretinism, goiter, and hypothyroidism, while iodine sufficiency is associated with ATD and reduced remission rates in Graves disease (346).

Risk Factors for Autoimmune Thyroid Disorders

Environmental factors associated with the occurrence of ATDs include pollutants (plasticizers, polychlorinated biphenyls) and exposure to infections such as *Yersinia enterocolitica*, coxsackie B, *Helicobacter pylori*, and hepatitis C (347,348). For reasons not entirely known, women experience a 5- to 10-fold increased incidence of ATD (349). This difference is postulated to be the result of differences in sex steroid hormone levels, differences in environmental exposures, innate differences in female and male immune systems, and inherent chromosomal differences in the sexes (350,351). The immunoglobulins produced against the thyroid are polyclonal, and the multiple combinations of various antibodies consolidate to create the clinical spectrum of ATDs that may affect health and reproductive function.

Evaluation

Thyroid Function

Measurements of free serum T_4 and T_3 are complicated by the low levels of free hormone in systemic circulation, with only 0.02% to 0.03% of T_4 and 0.2% to 0.3% of T_3 circulating in the unbound state (351). Of the T_4 and T_3 in circulation, approximately 70% to 75% is bound to TBG, 10% to 15% attached to prealbumin, 10% to 15% bound

to albumin, and a minor fraction (<5%) is bound to lipoprotein (352,353). Total thyroid measurements are dependent on levels of TBG, which are variable and affected by many conditions such as pregnancy, OC pill use, estrogen therapy, hepatitis, and genetic abnormalities of TBG. Thus, **assays for the measurement of free T_4 and T_3 are more clinically relevant than measuring total thyroid hormone levels.**

There are many different laboratory techniques to measure estimated free serum T_4 and T_3. These methods invariably measure a portion of free hormone that is dissociated from the in vivo protein-bound moiety. This is of little clinical significance assuming the same proportions are measured for all assays and considered in the calibration of the assay (354). The T_3 resin uptake (T_3 RU) test is an example of one laboratory method used to estimate free T_4 in the serum. The T_3 RU determines the fractional binding of radiolabeled T_3, which is added to a serum sample in the presence of a resin that competes with TBG for T_3 binding. The binding capacity of TBG in the sample is inversely proportional to the amount of labeled T_3 bound to the artificial resin. Therefore, a low T_3 RU indicates high TBG T_3 receptor site availability and implies high circulating TBG levels.

The free T_4 index (FTI) is obtained by multiplying the serum T_4 concentration by the T3 RU percentage, yielding an indirect estimate of the levels of free T_4:

$$T_3 \text{ RU\%} \times T_4 \text{ total} = \text{free } T_4 \text{ index.}$$

A high T_3 RU percentage indicates reduced TBG receptor site availability and high FTI and thus hyperthyroidism, whereas a low T_3 RU percentage is a result of increased TBG receptor site binding and thus hypothyroidism. Equilibrium dialysis and ultrafiltration techniques may be used to determine the free T_4 directly. Free T_4 and T_3 may also be determined by radioimmunoassay. Most available laboratory methods used for determining estimations of free T_4 are able to correct for moderate variations in serum TBG but are prone to error in the setting of large variations of serum TBG, when endogenous T_4 antibodies are present, and in the setting of inherent albumin abnormalities (352).

[9] Because most disorders of hyperthyroidism and hypothyroidism are related to dysfunction of the thyroid gland and TSH levels are sensitive to excessive or deficient levels of circulating thyroid hormone, TSH levels are used to screen for these disorders. Thyrotropin or TSH sandwich immunoassays are extremely sensitive and capable of differentiating low-normal from pathologic or iatrogenically subnormal values and elevations. TSH measurements provide the best way to screen for thyroid dysfunction and accurately predict thyroid hormone dysfunction in about 80% of cases (355). Reference values for TSH are traditionally based on the central 95% of values for healthy individuals, and some controversy exists regarding the upper limit of normal.

Values in the upper limit of normal may predict future thyroid disease (354,356). In a longitudinal study, women with positive thyroid antibodies (TPOAbs or TgAbs), the prevalence of hypothyroidism at follow-up was 12.0% (3.0% to 21.0%; 95% CI) when baseline TSH was 2.5 mU/L or less, 55.2% (37.1% to 73.3%) for TSH between 2.5 and 4.0 mU/L, and 85.7% (74.1% to 97.3%) for TSH above 4.0 mU/L (357). Physicians ordering thyrotropin values should be aware of their limitations in the setting of acute illness, central hypothyroidism, and the presence of heterophile antibodies and TSH autoantibodies. In the setting of heterophile antibodies or TSH autoantibodies, TSH values will be falsely elevated (354). In cases of central hypothyroidism, decreased sialylation of TSH results in a longer half-life and a reduction in bioactivity (358,359). TSH levels may be elevated or normal when the patient remains clinically hypothyroid in states of central hypothyroidism, and successful treatment is often associated with low or undetectable TSH levels.

Immunologic Abnormalities

Many antigen–antibody reactions affecting the thyroid gland can be detected. Antibodies to TgAb, the TSH receptor (TSHRAb), TPOAb, the NIS (NISAb), and to thyroid hormone were identified and implicated in ATD states (360). A number of recognized thyroid autoantigens are listed in **Table 35-9**. Antibody production to thyroglobulin depends on a breach in normal immune surveillance (361,362). The prevalence of thyroid autoantibodies in various autoimmune thyroid disorders is shown in **Table 35-10**.

Table 35-9 Thyroid Autoantigens

Antigen	Location	Function
Thyroglobulin (Tg)	Thyroid	Thyroid hormone storage
Thyroid peroxidase (TPO) (microsomal antigen)	Thyroid	Transduction of signal from TSH
TSH receptor (TSHR)	Thyroid, lymphocytes, fibroblasts, adipocytes (including retro-orbital), and cancers	Transduction of signal from TSH
Na^+/I^- symporter (NIS)	Thyroid, breast, salivary or lacrimal gland, gastric or colonic mucosa, thymus, pancreas	ATP-driven uptake of I^- along with Na^+

TSH, thyroid-stimulating hormone; ATP, adenosine triphosphate.

Table 35-10 Prevalence of Thyroid Autoantibodies in Autoimmune Thyroid Disorders

	Hypothyroid		
Antibody	**General**	**Autoimmune**	**Graves**

	Population	Thyroiditis	Disease
Antithyroglobulin (TgAb)	3%	35–60%	12–30%
Antimicrosomal thyroid peroxidase (TPOAb)	10–15%	80–99%	45–80%
Anti-TSH receptor (TSHRAb)	1–2%	6–60%	70–100%
Anti-Na/I symporter (NISAb)	0%	25%	20%

TSH, thyroid-stimulating hormone.

Antithyroglobulin antibodies are predominantly in the noncomplement fixing, polyclonal, immunoglobulin-G (IgG) class. Antithyroglobulin antibodies are found in 35% to 60% of patients with hypothyroid autoimmune thyroiditis, 12% to 30% of patients with Graves disease, and 3% of the general population (363–365). Antithyroglobulin antibodies are associated with acute thyroiditis, nontoxic goiter, and thyroid cancer (360).

Previously referred to as antimicrosomal antibodies, TPO antibodies are directed against TPO and are found in Hashimoto thyroiditis, Graves disease, and postpartum thyroiditis. The antibodies produced are characteristically cytotoxic, complement-fixing IgG antibodies. In patients with thyroid autoantibodies, 99% will have positive anti-TPO antibodies, whereas only 36% will have positive antithyroglobulin antibodies, making anti-TPO a more sensitive test for ATD (365). Anti-TPO antibodies are present in 80% to 99% of patients with hypothyroid autoimmune thyroiditis, 45% to 80% of patients with Graves disease, and 10% to 15% of the general population (364–366). These antibodies can cause artifact in the measurement of thyroid hormone levels. Antithyroid peroxidase (anti-TPO) antibodies are used clinically in the diagnosis of Graves disease, the diagnosis of chronic autoimmune thyroiditis, in conjunction with TSH testing as a means to predict future hypothyroidism in subclinical hypothyroidism, and to assist in the diagnosis of autoimmune thyroiditis in euthyroid patients with goiter or nodules (360).

Another group of antibodies important in ATD bind the TSH receptor (TSHR). The TSHR belongs to the family of G-protein–coupled receptors. TSHRAb are pathogenic and capable of activating (TSI) or blocking (TBI) TSHR functions. TBIs are detectable in two varieties: those that block TSH binding and those that block prereceptor and postreceptor processes. Several investigators have detected such blocking antibodies in patients with primary hypothyroidism and atrophic thyroid glands (367,368). The nomenclature and detection assay of TSHRAb are listed in Table 35-11. Anti-TSH receptor antibodies were reported in 6% to 60% of patients with hypothyroid autoimmune thyroiditis, 70% to 100% of patients with Graves disease, and 1% to 2% of the general population (369–373). Untreated Graves disease patients tested with third-generation immunometric assays are uniformly positive (374). TSHRAb are classified

as binding inhibitory immunoglobulins by competitive binding assays (TBII); and in functional assays: stimulating (TSI)—which possesses capacity to increase cyclic adenosine monophosphate (cAMP) production; blocking (TBI)—which possesses the capacity to reduce TSH effects; and, neutral (TNI)—with no effect on TSH binding or alteration of cAMP levels. A number of competitive and functional assays are available to determine the levels of each antibody type, which, in toto, correlate with severity of disease, extraglandular signs, risk of fetal effects, and chances for remission and recurrence. TSHRAb are used clinically to distinguish postpartum thyroiditis from Graves disease, to predict the risk of fetal and neonatal thyrotoxicosis in women with prior ablative treatment or current thionamide therapy in the setting of Graves disease, and in the diagnosis of euthyroid Graves opthalmopathy (360). These assays will increasingly optimize individual patient testing and treatment (375).

Table 35-11 Nomenclature of Anti-TSH Receptor Antibodies

Abbreviation	Term	Assay Used	Refers To
LATS	Long-acting thyroid stimulator	In vivo assay of stimulation of mouse thyroid	Original description of serum molecule able to stimulate mouse thyroid; no longer used
TSHRAb, TRAb	TSHR antibodies	Competitive and functional assays described below	All antibodies recognizing the TSH receptor (includes TBII (competitive) and TSI, TBI, and TNI (competative) based on assay method)
TBII	TSHR-binding inhibitory immunoglobulin	Competitive binding assays with TSH	Antibodies able to compete with TSH for TSH receptor binding irrespective of biologic activity
TSI (also TSAb)	TSHR-stimulating immunoglobulins	Competitive and functional bioassays of TSH receptor activation	Antibodies able to block TSH receptor binding, induce cAMP production, and nonclassical signaling cascades
TBI (also TSBAb, TSHBAb)	TSHR stimulation-blocking antibodies	Functional bioassays of TSH receptor activation	Antibodies able to block TSH receptor binding, induce cAMP production with ± effects on nonclassical cascades
TNI	TSHR nonbinding immunoglobulin	Binding and functional assays	No TSH binding, no effect on cAMP levels, and variable effects on nonclassical cascades

TSH, thyroid-stimulating hormone.

Antibodies to the NIS are prevalent in a number of thyroid conditions. Anti-NISAbs were detected in 24% of patients with Hashimoto disease and 22% of patients with Graves disease (376). Anti-NISAbs are used experimentally (360).

Autoimmune Thyroid Disease

The most common thyroid abnormalities in women, autoimmune thyroid disorders, represent the combined effects of the multiple thyroid autoantibodies (377). The various antigen–antibody reactions result in the wide clinical spectrum of these disorders. Transplacental transmission of some of these immunoglobulins may affect thyroid function in the fetus. The presence of autoimmune thyroid disorders, particularly Graves disease, is associated with other autoimmune conditions: Hashimoto thyroiditis, Addison disease, ovarian failure, rheumatoid arthritis, Sjögren syndrome, diabetes mellitus (type 1), vitiligo, pernicious anemia, myasthenia gravis, and idiopathic thrombocytopenic purpura. Other factors that are associated with the development of autoimmune thyroid disorders include low birth weight, iodine excess and deficiency, selenium deficiency, parity, OC pill use, reproductive age span, fetal microchimerism, stress, seasonal variation, allergy, smoking, radiation damage to the thyroid, and viral and bacterial infections (378).

Recommendations for Testing and Treatment

Overt and subclinical hypothyroidism are defined as an elevated TSH with a low T_4 and an elevated TSH and normal T_4, respectively, using appropriate patient ranges (nonpregnant and pregnant). A number of professional organizations published various recommendations for thyroid function assessment via a TSH in women. Because of the long interval from development of disease to diagnosis, the nonspecific nature of symptoms, and the potential adverse neonatal and maternal outcomes associated with untreated hypothyroidism in pregnancy, the American Association of Clinical Endocrinologists (AACE) recommended screening women prior to conceiving or at the first prenatal appointment (379,380). The AACE recommended screening for the presence of hypothyroidism in patients with type 1 diabetes mellitus (3-fold increased risk of postpartum thyroid dysfunction and 33% prevalence overall) and patients taking lithium therapy (35% prevalence), and consideration of testing in patients presenting with infertility (>12% prevalence) or depression (10% to 12% prevalence), as these populations are at an increased risk of hypothyroidism (380). **A screening TSH was recommended in women starting at the age of 50 because of the increased prevalence of hypothyroidism in this population** (381). Thyroid function testing at 6-month intervals was recommended for patients taking *amiodarone*, as hyperthyroidism or hypothyroidism occurs in 14% to 18% of these patients (380). Any woman with a history of postpartum thyroiditis should be offered annual surveillance of thyroid function, as 50% of these patients will develop hypothyroidism within 7 years of diagnosis (382). Because there is a high prevalence of hypothyroidism in women with Turner and Down syndromes, an annual check of thyroid function is recommended for these patients (383,384).

Alternatively, the Endocrine Society's clinical practice guidelines regarding the management of thyroid dysfunction during pregnancy and postpartum recommends targeted screening for the following individuals: history of thyroid disorder, family history of thyroid disease, goiter, thyroid autoantibodies, clinical signs or symptoms of thyroid disease, autoimmune disorders, infertility, head and/or neck radiation, and preterm delivery (385). The American Congress of Obstetricians and Gynecologists accepted these recommendations for TSH testing (386). Because of the (i) potentially significant neurologic effects on the fetus and other adverse pregnancy events, (ii) physiologic rise in TBG and the hCG like activity of TSH in pregnancy, and (iii) potential for the targeted screening groups to have overt or subclinical hypothyroidism defined by the reference ranges for pregnancy (TSH <2.5, 3.1, and 3.5 mU/L for the first, second, and third trimesters, respectively), targeted maternal testing for hypothyroidism is encouraged. The targeted screening protocol allows that 30% of subclinical hypothyroidism cases may be missed. According to these recommendations, preconceptionally diagnosed hypothyroid women (overt or subclinical) should have their T_4 dosage adjusted such that the TSH value is less than 2.5 mU/L before pregnancy. The T_4 dosage in women already on replacement will routinely require a dose escalation (30% to 50%) at 4 to 6 weeks gestation in order to maintain a TSH value less than 2.5 mU/L. Pregnant women with overt hypothyroidism should be normalized as rapidly as possible to maintain TSH at less than 2.5 and 3 mU/L in the first, second, and third trimesters, respectively. Euthyroid women with thyroid autoantibodies are at risk of hypothyroidism and should have TSH screening in each trimester. After delivery, hypothyroid women need a reduction in T_4 dosage used during pregnancy. Because subclinical hypothyroidism is associated with adverse outcomes for the mother and the fetus, T_4 replacement is recommended. The American Thyroid Association (ATA) has recommended an alternative approach that states that therapy may be considered for TPO antibody-positive women with TSH concentrations greater than 2.5 mU/L. Treatment is also recommended for TPO antibody-negative women with TSH concentrations greater than 4 mU/L. The ATA does not recommend *levothyroxine* therapy for TPO antibody-negative women with a TSH less than 4.0 mU/L (387).

Hashimoto Thyroiditis

Hashimoto thyroiditis, or chronic lymphocytic thyroiditis, was first described in 1912 by Dr. Hakaru Hashimoto. Hashimoto thyroiditis can manifest as hyperthyroidism, hypothyroidism, euthyroid goiter, or diffuse goiter. High levels of antimicrosomal and antithyroglobulin antibody are usually present, and TSHRAb may also be present (365,388,389). Hashimoto thyroiditis is characterized by a direct T-cell attack on the thyroid gland, leading to thyroiditis and subsequent exposure of thyroid antigens (TPO and thyroglobulin) against which antibodies are produced. Thyroglobulin antibodies (TgAbs) and thyroid peroxidase antibodies (TPOAbs) are commonly associated with a

destructive pattern and are considered diagnostic for this disease. In any iodine-sufficient population, however, the prevalence of TPOAbs and TgAbs is much higher than that of clinical disease, amounting to approximately 15% to 25%, with the highest prevalence found in females and increasing with age. Typically, glandular hypertrophy is found, but atrophic forms are also present. Three classic types of autoimmune injury are found in Hashimoto thyroiditis: (i) complement-mediated cytotoxicity, (ii) antibody-dependent cell-mediated cytotoxicity, and (iii) stimulation or blockade of hormone receptors, which results in hypo- or hyperfunction or growth (Fig. 35-11).

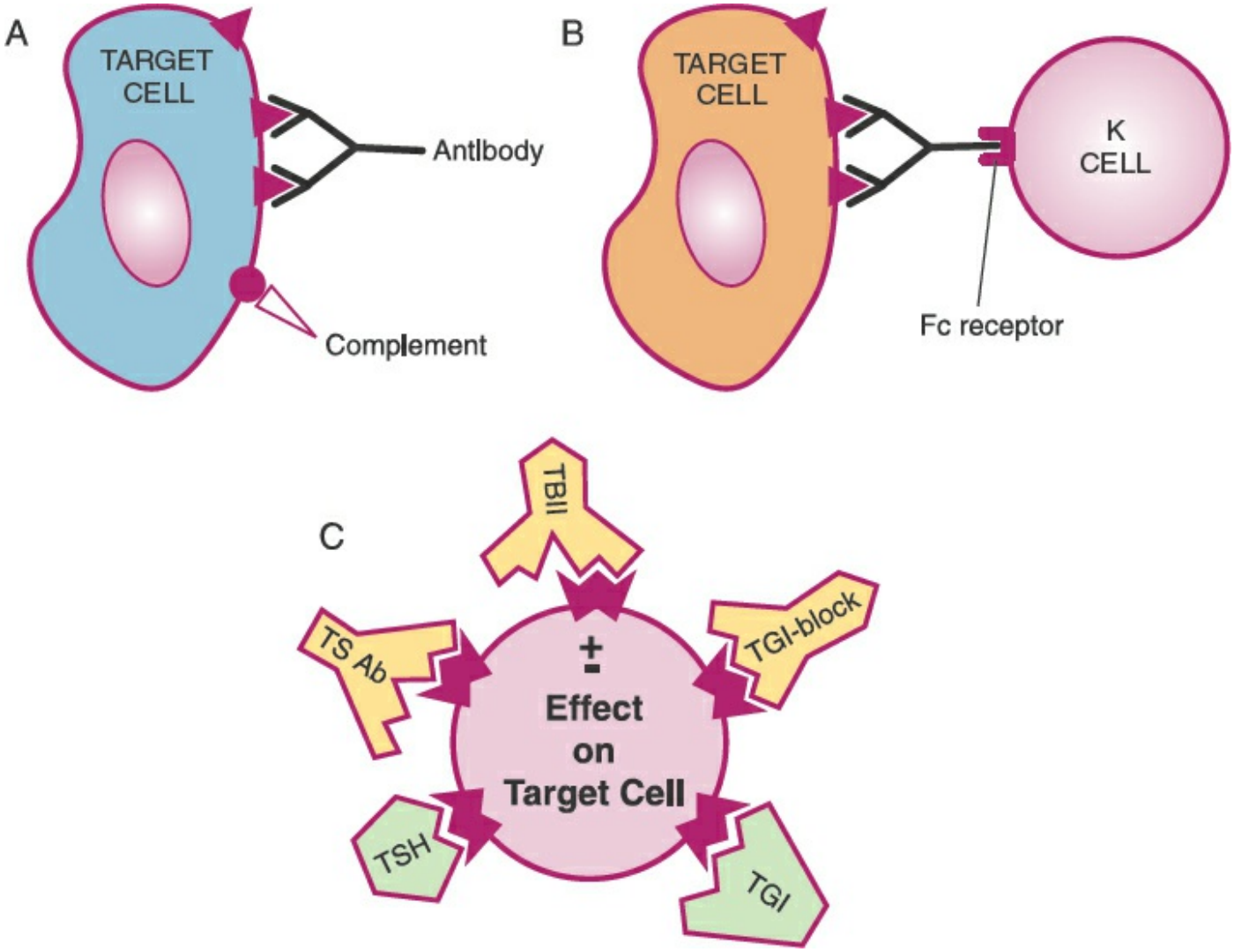


FIGURE 35-11 Types of autoimmune injury found in Hashimoto thyroiditis. **A:** Complement-mediated cytotoxicity, which can be abolished by inactivating the complement system. **B:** Antibody-dependent cell-mediated cytotoxicity (ADCC) function through killer T cells, monocytes, and natural killer cells that have immunoglobulin G fragment receptors. **C:** Stimulation of blockade of hormone receptors leading to hyperfunction or hypofunction or growth, depending on the types of immunoglobulins acting on the target cell. TBII, TSH-binding inhibitor immunoglobulin; TGI, thyroid growth–promoting immunoglobulin; TSAb, thyroid-stimulating antibodies; TSH, thyroid-stimulating hormone. (From IMMUNOLOGICAL OBSTETRICS, edited by W.B. Coulam et al. Copyright © 1992 by W.W. Norton & Company Inc. Used by permission of W. W. Norton & Company, Inc.)

The histologic picture of Hashimoto thyroiditis includes cellular hyperplasia, disruption of follicular cells, and infiltration of the gland by lymphocytes, monocytes, and plasma cells. Occasionally, adjacent lymphadenopathy may be noted. Some epithelial cells are enlarged and demonstrate oxyphilic changes in the cytoplasm (Askanazy cells or Hürthle cells, which are not specific to this disorder). The interstitial cells show fibrosis and lymphocytic infiltration. Graves disease and Hashimoto thyroiditis may cause very similar histologic findings manifested by a similar mechanism of injury.

Clinical Characteristics and Diagnosis of Hashimoto Thyroiditis

Patients with Hashimoto thyroiditis may present with typical symptoms of hypothyroidism or may be relatively asymptomatic. Patients often present with a goiter, which can involve the parietal lobe. At later stages of the disease, hypothyroidism can be found without a goiter. Notable clinical manifestations associated with Hashimoto thyroiditis include fatigue, weight gain, hyperlipidemia, dry hair, dry skin, cold intolerance, depression, menstrual irregularities, bradycardia, and or memory impairment. Hashitoxicosis, the hyperthyroid manifestation of Hashimoto thyroiditis, may occur after a hypothyroid state and development into a euthyroid or hyperthyroid state and is thought to be the result of development of TSH-stimulating antibodies (TSI) associated with Graves disease (380). This variant is estimated to occur in 4% to 8% of patients with Hashimoto thyroiditis. In the setting of Hashitoxicosis, the patient requires frequent follow-up and the potential for adjustments in thyroid supplementation. These patients often become hypothyroid during the course of treatment.

In many cases, an elevated serum TSH is detected during routine screening. Elevated serum anti-TPO antibodies confirm the diagnosis, and free T_4 and T_3 document overt or subclinical hypothyroidism. The sedimentation rate may be elevated, depending on the course of the disease at the time of recognition. Other causes of hypothyroidism should be considered, as listed in **Table 35-12**. Progression from subclinical to clinically overt hypothyroidism is reported to vary from 3% to 20%, with a higher risk noted in patients with goiter or thyroid antibodies (341,390). Treatment of subclinical hypothyroidism is somewhat controversial, but clinical studies suggested treatment of subclinical hypothyroidism is associated with a reduction in neurobehavioral abnormalities, a reduction in cardiovascular risk factors, and an improvement in lipid profile (391,392).

Hashimoto thyroiditis is one of the most frequent autoimmune diseases and has been reported to be associated with gastric disorders in 10% to 40% of patients. About 40% of patients with autoimmune gastritis also present with Hashimoto thyroiditis. Chronic autoimmune gastritis (CAG) is characterized by the partial or complete disappearance of parietal cells leading to impairment of hydrochloric acid and intrinsic factor production. The patients develop hypochlorhydria-dependent iron-

deficient anemia, leading to pernicious anemia, and severe gastric atrophy. This entity is known as polyglandular autoimmune syndrome (393).

Table 35-12 Potential Causes of Hypothyroidism

Primary
Congenital absence of thyroid gland
External thyroid gland radiation
Familial disorders and thyroxine synthesis
Hashimoto thyroiditis
Iodine-131 ablation for Graves disease
Ingestion of antithyroid drugs
Iodine deficiency
Idiopathic myxedema (autoimmune)
Surgical removal of thyroid gland
Secondary
Hypothalamic thyrotropin-releasing hormone deficiency
Pituitary or hypothalamic tumors or disease

Treatment

Thyroxine replacement is initiated in patients with clinically overt hypothyroidism or subclinical hypothyroidism with a goiter. Regression of gland size usually does not occur, but treatment often prevents further growth of the thyroid gland. Treatment is recommended for patients with subclinical hypothyroidism in the setting of a TSH greater than 10 mIU/L on repeat measurements, pregnant patients, a strong habit of tobacco use, signs or symptoms associated with thyroid failure, or patients with severe hyperlipidemia (394). All pregnant patients with an elevated TSH level should be treated with *levothyroxine*. Treatment does not slow progression of the disease. The initial dosage of *levothyroxine* may be as little as 12.5 µg per day up to a full replacement dose. The mean replacement dosage of *levothyroxine* is 1.6 µg/kg of body weight per day, although the dosage varies greatly between patients (380). Aluminum hydroxide (antacids), cholestyramine, iron, calcium, and sucralfate may interfere with absorption. *Rifampin* and *sertraline hydrochloride* may accelerate the metabolism of *levothyroxine*. The half-life of *levothyroxine* is nearly 7 days; therefore, nearly 6 weeks of treatment are necessary before the effects of a dosage change can be evaluated.

Hypothyroidism appears to be associated with decreased fertility resulting from

disruption in ovulation, and thyroid autoimmune disease is associated with an increased risk of pregnancy loss with or without overt thyroid dysfunction (395). A meta-analysis of case–control and longitudinal studies performed since 1990 reveals a possible association between miscarriage and thyroid antibodies with an odds ratio of 2.73 (95% CI 2.20 to 3.40). This association may be explained by a heightened autoimmune state affecting the fetal allograft or a slightly higher age of women with antibodies compared with those without antibodies (0.7 ± 1 year, $p < 0.001$) (396). Studies suggest that early subclinical hypothyroidism may be associated with menorrhagia (397).

Severe primary hypothyroidism is associated with menstrual irregularities in 23% of women, with oligomenorrhea being the most common (396). Reproductive dysfunction in hypothyroidism may be caused by a decrease in the binding activity of SHBG, resulting in increased estradiol and free testosterone as well as from hyperprolactinemia (396). The increase in prolactin levels is the result of enhanced sensitivity of the prolactin-secreting cells to TRH (with elevated TRH seen in primary hypothyroidism) and defective dopamine turnover resulting in hyperprolactinemia (398–401). Hyperprolactinemia-induced luteal phase defects are associated with less severe forms of hypothyroidism (402,403). Replacement therapy appears to reverse the hyperprolactinemia and correct ovulatory defects (404,405).

Combined thyroxine and triiodothyronine therapy is no more effective than thyroxine therapy alone, and patients with hypothyroidism should be treated with thyroxine alone (406). Treatment should target normalizing TSH values, and a daily dose of 0.012 mg up to a full replacement dose of *levothyroxine* (1.6 μg/kg of body weight per day) may be required with dosage dependent on the patient's weight, age, cardiac status, and duration and severity of hypothyroidism (380).

Graves Disease

Graves disease, characterized by exophthalmos, goiter, and hyperthyroidism, was first identified as an association of findings in 1835. A heritable specific defect in immunosurveillance by suppressor T lymphocytes is believed to result in the development of a helper T-cell population that reacts to multiple epitopes of the thyrotropin receptor. This activity induces a B-cell–mediated response, resulting in the clinical features of Graves disease (403). The TSHRAb bind to conformational epitopes in the extracellular domain of the thyrotropin receptor and are uniformly detected in patients with untreated Graves disease (404). Thus, Graves disease is primarily caused by a T-cell abnormality, but the hyperthyroidism associated with the disease is caused by the production of the pathognomonic thyrotropin receptor autoantibodies (TRAbs) produced by B cells.

Graves disease is a complex autoimmune disorder in which several genetic susceptibility loci and environmental factors are likely to play a role in the development of the disease. Human leukocyte antigen and polymorphisms in the

cytotoxic T-lymphocyte antigen 4 (*CTLA-4*) gene were established as susceptibility loci; however, the magnitude of their contributions seems to vary among patient populations and study groups. Additional loci are likely to be identified by a combination of genome-wide linkage analyses and allelic association analyses of candidate genes. The rate of concordance for Graves disease is only 20% in monozygotic twins and even lower in dizygotic twins, consistent with a multifactorial inheritance pattern highly influenced by environmental factors. Linkage analysis identified loci on chromosomes 14q31, 20q11.2, and Xq21 that are associated with susceptibility to Graves disease (407).

Clinical Characteristics and Diagnosis

The classic triad in **Graves disease** consists of exophthalmos, goiter, and hyperthyroidism. The symptoms associated with Graves disease include frequent bowel movements, heat intolerance, irritability, nervousness, heart palpitations, impaired fertility, vision changes, sleep disturbances, tremor, weight loss, and lower extremity swelling. Physical findings may include lid lag, nontender thyroid enlargement (two to four times normal), onycholysis, dependent lower extremity edema, palmar erythema, proptosis, staring gaze, and thick skin. A cervical venous bruit and tachycardia may be noted. The tachycardia does not respond to increased vagal tone produced with a Valsalva maneuver. Severe cases may demonstrate acropachy, chemosis, clubbing, dermopathy, exophthalmos with ophthalmoplegia, follicular conjunctivitis, pretibial myxedema, and vision loss.

Approximately 40% of patients with new onset of Graves disease and many of those previously treated have elevated T_3 and normal T_4 levels. Abnormal T_4 or T_3 results are often caused by protein binding changes rather than altered thyroid function; therefore, assessment of free T_4 and free T_3 is indicated in conjunction with TSH. In Graves disease, the TSH levels are suppressed, and levels may remain undetectable for some time even after the initiation of treatment. Thyroid autoantibodies, including TSI, may be useful during pregnancy to more accurately predict fetal risk of thyrotoxicosis (380). Autonomously functioning, benign thyroid neoplasms that exhibit a similar clinical picture include toxic adenomas and toxic multinodular goiter. A radioactive iodine uptake thyroid scan may help differentiate these two conditions from Graves disease. Rare conditions resulting in thyrotoxicosis include metastatic thyroid carcinoma causing thyrotoxicosis, amiodarone-induced thyrotoxicosis, iodine-induced thyrotoxicosis, postpartum thyroiditis, a TSH-secreting pituitary adenoma, an hCG-secreting choriocarcinoma, struma ovarii, and “de Quervan’s” or subacute thyroiditis (408). Factitious ingestion of thyroxine or desiccated thyroid should be considered in patients with eating disorders. Patients with thyrotoxicosis factitia demonstrate elevated T_3 and T_4, suppressed TSH, and a low serum thyroglobulin level, whereas other causes of thyroiditis and thyrotoxicosis demonstrate high levels of thyroglobulin. **Potential**

causes of hyperthyroidism are listed in Table 35-13.

Treatment

Iodine-131 Ablation

Treatment of women with hyperthyroidism of an autoimmune origin presents unique challenges to the physician who must consider the patient's needs and her reproductive plans. Because the drugs used to treat this disorder have potentially harmful effects on the fetus, special attention must be given to the use of contraception and the potential for pregnancy.

Table 35-13 Potential Causes of Hyperthyroidism

Factitious hyperthyroidism
Graves disease
Metastatic follicular cancer
Pituitary hyperthyroidism
Postpartum thyroiditis
Silent hyperthyroidism (low radioiodine uptake)
Struma ovarii
Subacute thyroiditis
Toxic multinodular goiter
Toxic nodule
Tumors secreting human chorionic gonadotropin (molar pregnancy, choriocarcinoma)

A single dose of radioactive iodine-131 is an effective cure in about 80% of cases and is the definitive treatment in nonpregnant women. Any woman of childbearing age should be tested for pregnancy before undergoing diagnostic or therapeutic administration of iodine. Ablation of a second-trimester fetal thyroid gland and congenital hypothyroidism (cretinism) from treatment during the first trimester were reported (409). Nuclear medicine professionals provide expertise in the administration of the radioactive isotope, and because the effect of the radioactive iodine is not immediate, the endocrinologist continues to provide suppressive medical treatment for 6 to 12 weeks after administration of iodine while the patient remains hyperthyroid. As early as 2 to 3 months after treatment, patients may become hypothyroid and should be supplemented with thyroxine as indicated by serum levels of free thyroid hormone levels (380). TSH testing is not sensitive for predicting thyroid function during this time as changes in TSH lag 2 weeks to several months behind thyroid function changes (380).

Failure to respond to iodine 6 months after treatment may require a repeat treatment with radioactive iodine (408). Postablative hypothyroidism develops in 50% of patients within the first year after iodine therapy and in more than 2% of patients per year thereafter.

A higher rate of miscarriage was noted in women treated with iodine therapy in the year preceding therapy, but there is no reported increase in the rate of stillbirths, preterm birth, low birth weight, congenital malformation, or death after therapy (410). Many thyroidologists and nuclear medicine specialists are willing to allow pregnancy earlier than 1 year after therapy if patients receive replacement therapy with *levothyroxine*.

Thyroid-Stimulating Receptor Antibody in Graves Disease

The level of TSHRAb of the TBII class grossly parallels the degree of hyperthyroidism as assessed by the serum levels of thyroid hormones and total thyroid volume. Studies suggest that the combination of a small goiter volume (<40 mL) and a low TBII level (<30 U/L) results in a 45% chance of remission during the 5 years after completion of a 12- to 24-month course of antithyroid drug therapy (411). In contrast, the overall rate of relapse exceeded 70% in patients with a large goiter volume (>70 mL) and a higher TBII level (>30 U/L). The subgroup of patients with larger goiters and higher TBII levels had less than a 10% chance to remain in remission in the 5 years after treatment. Although it is not necessary for the diagnosis of Graves disease, except in some cases of multinodular goiter, a TSHRAb measurement may be a useful marker of disease severity. Used in combination with other clinical factors, it may contribute to initial decisions regarding treatment. See Table 35-11 for a review of the nomenclature and assay methods for TSHRAb.

Measurements of TSHRAb (TBII category) during treatment with antithyroid drugs are predictive of subsequent outcome. In one series, 73% of TBII-negative patients had remission compared with only 28% of TBII-positive patients who achieved remission after 12 months of antithyroid drug therapy (412). The duration of a course of antithyroid drug therapy may be modified according to the TSHRAb status. In patients whose TSHRAb status became negative and antithyroid drug therapy was discontinued, the relapse rate was 41% compared with a rate of 92% for those patients who remained TSHRAb positive (413). Regardless of the rapidity of the disappearance of TSHRAb, it does seem that antithyroid drug therapy should be maintained for 9 to 12 months to minimize the risk of relapse. TSHRAb status appears to determine, in an inverse relationship, the reduction in thyroid volume after radioactive iodine therapy.

Third-generation TSHRAb assays have been developed, and their utility in evaluation and treatment monitoring is being evaluated. Some patients with Graves disease have or will develop antineutrophil cytoplasmic antibodies (ANCA) after treatment, which may be associated with small-vessel vasculitides, such as Wegener

granulomatosis and microscopic polyangiitis. Smoking appears to be an independent risk factor for relapse after medical therapy and should be considered when planning treatment.

Antithyroid Drugs

Antithyroid drugs of the thioamide class include *propylthiouracil* (*PTU*) and *methimazole*. Low doses of either agent block the secondary coupling reactions that form T_3 and T_4 from MIT and DIT. At higher doses, they also block iodination of tyrosyl residues in thyroglobulin. *PTU* additionally blocks the peripheral conversion of T_4 to T_3. Approximately one-third of patients treated by this approach alone go into remission and become euthyroid (411).

In 2009, the FDA published a warning on the use of *PTU* because of 32 reported cases of serious liver injury associated with its use (414,415). The average daily dose associated with liver failure was 300 mg, and liver failure was reported to occur anywhere from 6 days to 450 days after initiation of therapy (416). Traditionally, *PTU* was the drug of choice to treat hyperthyroidism for the duration of pregnancy because it less readily crosses the placenta, and *methimazole* was associated with an increased risk of choanal atresia and aplasia cutis (417–420). **Because of the case reports of *PTU*-related liver failure and the increased risk of birth defects associated with *methimazole* use during embryogenesis, the FDA and the Endocrine Society recommend *PTU* never be used as first-line medical treatment of hyperthyroidism for nonpregnant patients. It is recommended that its use be limited to pregnant women during the first trimester, situations where surgery or radioactive iodine treatment are contraindicated, and individuals who have developed a toxic reaction to *methimazole*** (414,416). The FDA recommends monitoring patients closely for signs and symptoms of liver injury while taking *PTU*. If liver injury is suspected, *PTU* should be promptly discontinued (414). The ATA recommends an initial dose of 100 to 600 mg per day in three divided doses with a goal to maintain T_4 in the upper limit of normal using the lowest possible dose. Minor reactions such as pruritus affect 3% to 5% of patients treated with thionamide therapy, and antihistamines may eliminate symptoms and allow continued use. Agranulocytosis is a rare and potentially fatal complication of *PTU* and *methimazole* therapy, developing in 0.2% of women treated, and it mandates immediate discontinuation of the drug (417). Agranulocytosis most commonly presents with fever and a sore throat followed by sepsis; the occurrence of fever, sore throat, or a viral-like syndrome should prompt an urgent evaluation.

***Methimazole* is the first-line drug for the treatment of hyperthyroidism, except in the first trimester of pregnancy, as it has been shown to be more effective than *PTU* at controlling severe hyperthyroidism and is associated with higher adherence rates and less toxicity** (421). The ATA recommends initial daily doses of 10 to 40 mg

per day in a single dose. Like treatment with *PTU*, the goal is to maintain a free T_4 level in the upper limits of normal using the lowest possible dose. Free T_4 levels show improvement 4 weeks after therapy, and TSH levels take 6 to 8 weeks to normalize (417). *Methimazole* use in pregnancy is associated with an 18-fold risk of fetal choanal atresia compared with the general population (95% CI 3 to 121) (422). Congenital aplasia cutis was associated with maternal use of *methimazole* during pregnancy; however, it is not known whether the risk (0.03%) is greater than that seen in the general population (423).

Studies suggest a potential role for an intrathyroid *dexamethasone* injection to prevent relapse (424). Other medical therapies include iodide and lithium, both of which reduce thyroid hormone release and inhibit the organification of iodine. Iodide leads to the secondary coupling of T_3 and T_4. Iodide inhibition of thyroid metabolism is only transient, and complete escape from inhibition occurs within 1 to 2 weeks of iodide therapy, making this useful only for acute management of severe thyrotoxicosis (408). *Lithium* may be used when *thionamide* therapy is contraindicated or in combination with *PTU* or *methimazole* (408). To avoid toxicity during treatment, serum lithium levels should be monitored. *Lithium* has been associated with fetal Ebstein anomaly, and iodide has been associated with congenital goiter; these medications should not be used in pregnant women and should be used with caution in women of reproductive age. Because of the complications related to medical therapy of hyperthyroidism, women desiring pregnancy should be counseled to strongly consider surgical treatment or radioactive iodine treatment prior to pregnancy (416).

Breastfeeding and Use of Anti-Thyroid Drugs

Studies have shown that only limited quantities of *PTU* and *methimazole* are secreted in milk, and therefore the neonatal exposure to ATD is minimal and clinically insignificant. Furthermore, a few studies, albeit small scale, have shown normal TFTs and no increased risk of malformations in neonates whose mothers received methimazole in pregnancy (425).

Surgery

Thyroidectomy was used for the treatment of Graves disease but is now rarely used unless there is a suspicion for coexisting thyroid malignancy (380). Potential candidates for surgical intervention include pregnant women refusing or not tolerating antithyroid medical therapy, pediatric patients presenting with Graves disease, or patients who refuse radioactive iodine therapy. Surgery is the most rapid and consistent method of achieving a euthyroid state in Graves disease and avoids the possible long-term risks of radioactive iodine. Surgical intervention may be considered in severe Graves ophthalmopathy. Patients should be rendered euthyroid before a thyroidectomy. The risks of surgery include postoperative hypoparathyroidism, recurrent laryngeal nerve

paralysis, routine anesthetic and surgical risks, hypothyroidism, and failure to relieve thyrotoxicosis.

β-Blockers

Propranolol occasionally is used with or without concurrent antithyroid medications before radioactive iodine or surgery to provide relief of symptoms. Larger and more frequent doses may be required because of a relative resistance to β-adrenergic antagonists in the setting of hyperthyroidism.

Thyroid Storm

Thyroid storm is an acute, life-threatening exacerbation of hyperthyroidism and should be treated as a medical emergency in an intensive care unit setting. Symptoms include tachycardia, tremor, diarrhea, vomiting, fever, dehydration, and altered mental status that may proceed to coma. Patients with poorly controlled hyperthyroidism are most susceptible. Beta-blocker agents, glucocorticoids, *PTU* (the action of which includes inhibition of T_4–T_3 conversion), and iodides are all key elements of therapy.

Hyperthyroidism in Gestational Trophoblastic Disease and Hyperemesis Gravidarum

Because of the weak TSH-like activity of hCG, conditions with high levels of hCG, such as molar pregnancy, may be associated with biochemical and clinical hyperthyroidism. Symptoms regress with removal of the abnormal trophoblastic tissue and resolution of elevated levels of hCG. In a similar fashion, **when hyperemesis gravidarum is associated with high levels of hCG, mild biochemical and clinical features of hyperthyroidism may be seen** (426,427). Gestational trophoblastic disease is reviewed in Chapter 41.

Thyroid Function in Pregnancy

Physicians should be aware of the changes in thyroid physiology during pregnancy. Pregnancy is associated with reversible changes in thyroid physiology that should be noted before diagnosing thyroid abnormalities (see **Fig. 35-12** for pregnancy-associated changes in TBG, total T_4, hCG, TSH, and free T_4) (417). Women with a history of hypothyroidism often require increased thyroxine replacement (25% to 50%) during pregnancy, and patients should have thyroid function tests performed at the first prenatal visit and during each trimester thereafter. Evidence suggests that optimal fetal and infant neurodevelopmental outcomes may require careful titration of replacement thyroxine that meets the frequently increased requirements of pregnancy (428,429). Postpartum, women should return to their prepregnancy dosage of *levothyroxine* and have a follow-up TSH checked 6 weeks postpartum.

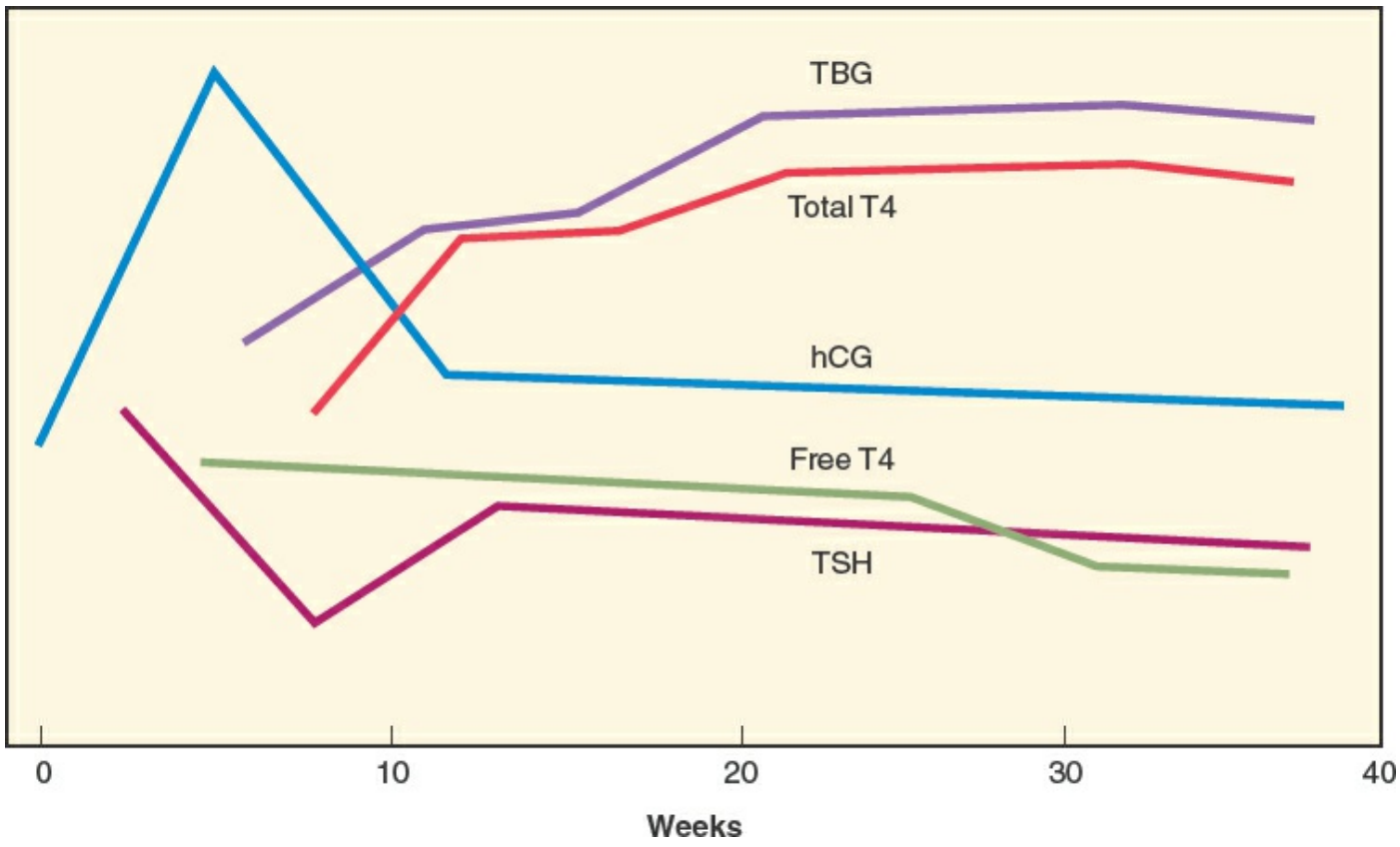


FIGURE 35-12 Pregnancy-associated changes in TSH relative to hCG and free T_4 in relation to TBG. Relative serum concentration changes throughout pregnancy highlighting a fall in TSH associated with an increase in hCG early in pregnancy and a fall in free T_4 as TBG levels rise during pregnancy. hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone; TBG, thyroid-binding globulin total T_4, total thyroxine; free T_4, free thyroxine. (Based on data from **Brent GA**. Maternal thyroid function: interpretation of thyroid function tests in pregnancy. *Clin Obstet Gynecol* 1997;40:3–15.)

Reproductive Effects of Hyperthyroidism

High levels of TSAb (TSI) in women with Graves disease are associated with fetal–neonatal hyperthyroidism (430,431). Despite both the inhibition and elevation of gonadotropins seen in thyrotoxicosis, most women remain ovulatory and fertile (401,432). Severe thyrotoxicosis can result in weight loss, menstrual cycle irregularities, and amenorrhea. An increased risk of spontaneous abortion is noted in women with thyrotoxicosis. An increased incidence of congenital anomalies, particularly choanal atresia and possibly aplasia cutis, can occur in the offspring of women treated with *methimazole* (418,419,422).

Autoimmune hyperthyroid Graves disease may improve spontaneously, in which case antithyroid drug therapy may be reduced or stopped. TSHRAb production may persist for several years after radioactive iodine therapy or radical surgical treatment for hyperthyroid Graves disease. In this circumstance, there is a risk of exposing a fetus to TSHRAb. Fetal–neonatal hyperthyroidism is observed in 2% to 10% of pregnancies occurring in mothers with a current or previous diagnosis of Graves disease, secondary

to the transplacental passage of maternal TSHRAb. This is a serious condition with a 16% neonatal mortality rate and a risk of intrauterine fetal death, stillbirth, and skeletal developmental abnormalities, such as craniosynostosis. Caution against overtreatment with antithyroid medication is warranted, as these medications may cross the placenta in sufficient quantities to induce fetal goiter. Guidelines for TSHRAb testing during pregnancy in women with previously treated Graves disease are found in Table 35-14. Fetal goiters and the associated fetal hypo- or hyperthyroid status were diagnosed accurately in mothers with Graves disease using a combination of fetal ultrasonography of the thyroid with Doppler, fetal heart rate monitoring, bone maturation, and maternal TSHRAb and antithyroid drug status (433).

Postpartum Thyroid Dysfunction

Postpartum thyroid dysfunction is much more common than recognized; it is often difficult to diagnose because its symptoms appear 1 to 8 months postpartum and are often confused with postpartum depression and difficulties adjusting to the demands of the neonate and infant. Postpartum thyroiditis appears to be caused by the combination of a rebounding immune system in the postpartum state and the presence of thyroid autoantibodies. Histologically, lymphocytic infiltration and inflammation are found and anti-TPO antibodies are often present (434,435). The following are criteria for the diagnosis of postpartum thyroiditis: (i) no history of thyroid hormonal abnormalities either before or during pregnancy, (ii) documented abnormal TSH level (either depressed or elevated) during the first year postpartum, and (iii) absence of a positive TSH-receptor antibody titer (Graves disease) or a toxic nodule. A number of studies describe clinical and biochemical evidence of postpartum thyroid dysfunction in 5% to 10% of new mothers (436,437).

Table 35-14 Guidelines for TSHRAb Testing During Pregnancy With Previously Treated Graves Disease

1. In the woman with antecedent Graves disease in remission after ATD treatment, the risk for fetal–neonatal hyperthyroidism is negligible, and systematic measurement of TSHRAb is not necessary. Thyroid function should be evaluated during pregnancy to detect an unlikely but possible recurrence. In that case, TSHRAb assay is mandatory
2. In the woman with antecedent Graves disease previously treated with radioiodine or thyroidectomy and regardless of the current thyroid status (euthyroidism with or without thyroxine substitution), TSHRAb should be measured early in pregnancy to evaluate the risk for fetal hyperthyroidism. If the TSHRAb level is high, careful monitoring of the fetus is mandatory for the early detection of signs of thyroid overstimulation (tachycardia, impaired growth rate, oligohydramnios, goiter). Cardiac echography and measurement of circulatory velocity may be confirmatory. Ultrasonographic measurements of the fetal thyroid have been defined from 20 weeks gestational age but require a well-trained operator, and thyroid visibility may be hindered because of fetal head position. Color Doppler ultrasonography is helpful in evaluating thyroid hypervascularization. Because of the potential risks of fetal–neonatal hyperthyroid cardiac insufficiency and the inability to measure the degree of hyperthyroidism in the mother because of previous thyroid ablation, it may be appropriate to consider direct diagnosis in the fetus. Fetal blood sampling through cordocentesis is feasible as early as 25–

27 weeks gestation with less than 1% adverse effects (fetal bleeding, bradycardia, infection, spontaneous abortion, in utero death) when performed by experienced clinicians. ATD administration to the mother may be considered to treat the fetal hyperthyroidism

3. In the woman with concurrent hyperthyroid Graves disease, regardless of whether it has preceded the onset of pregnancy, ATD treatment should be monitored and adjusted to keep free T_4 in the high-normal range to prevent fetal hypothyroidism and minimize toxicity associated with higher doses of these medications. TSHRAb should be measured at the beginning of the last trimester, especially if the required ATD dosage is high. If the TSHRAb assay is negative or the level low, fetal–neonatal hyperthyroidism is rare. If antibody levels are high (TBII ≥40 U/L or TSAb ≥300%), evaluation of the fetus for hyperthyroidism is required. In this condition, there is usually a fair correlation between maternal and fetal thyroid function such that monitoring the ATD dosage according to the mother's thyroid status is appropriate for the fetus. In some cases in which a high dose of ATD >20 mg/d of methimazole or >300 mg/d of PTU is necessary, there is a risk of goitrous hypothyroidism in the fetus, which might be indistinguishable from goitrous Graves disease. The correct diagnosis relies on the assay of fetal thyroid hormones and TSH, which allows for optimal treatment

4. In any woman who has previously given birth to a newborn with hyperthyroidism, a TSHRAb assay should be performed early in the course of pregnancy

TSHRAb, thyroid-stimulating hormone receptor antibodies; ATD, autoimmune thyroid disease; T_4, thyroxine; TBII, TSH-binding inhibitory immunoglobulin; TSAb, thyroid-stimulating antibody; PTU, propylthiouracil.

Clinical Characteristics and Diagnosis

Postpartum thyroiditis usually begins with a transient hyperthyroid phase between 6 weeks and 6 months postpartum followed by a hypothyroid phase. Only one-fourth of the cases follow this classic clinical picture, and more than one-third have either hyperthyroidism or hypothyroidism alone. Individuals with type 1 diabetes have a 3-fold increased risk of developing postpartum thyroiditis. Women with a history of postpartum thyroiditis in a previous pregnancy have nearly a 70% chance of recurrence in a subsequent pregnancy. Additional risk factors include a family history of thyroid disorders and TPOAb positivity (438). Although psychotic episodes are rare, postpartum thyroid dysfunction should be considered in all women with postpartum psychosis. The thyrotoxic phase may be subclinical and overlooked, particularly in areas where iodine intake is low (439). Unlike patients with Graves disease, those with the hyperthyroidism caused by postpartum thyroiditis have a low level of radioactive isotope uptake. Women with a history of postpartum thyroiditis should be followed closely as they have a 20% risk of permanent hypothyroidism immediately following the onset of thyroiditis, up to a 60% risk of permanent hypothyroidism over the next 5 to 10 years, and up to a 70% risk of postpartum thyroiditis in future pregnancies (440,441).

The absence of thyroid tenderness, pain, fever, elevated sedimentation rate, and leukocytosis helps to rule out subacute thyroiditis (de Quervain thyroiditis). Evaluation of TSH, T_4, T_3, T_3 RU, and antimicrosomal antibody titer confirms the diagnosis.

Treatment

Most patients are diagnosed during the hypothyroid phase and require 6 to 12 months of thyroxine replacement if they are symptomatic (382). Because approximately 60% of women develop permanent hypothyroidism, TSH should be evaluated following discontinuation of replacement therapy.

Rarely, patients are diagnosed during the hyperthyroid phase (442). Antithyroid medications are not routinely used for these women. *Propranolol* may be used for relief of symptoms but should be used with appropriate counseling in nursing mothers.

Antithyroid Antibodies and Disorders of Reproduction

Women who have antithyroid autoantibodies before and after conception appear to be at an increased risk for spontaneous abortion (443,444). Non-organ–specific antibody production and pregnancy loss are documented in cases of antiphospholipid abnormalities (445). The concurrent presence of organ-specific thyroid antibodies and non-organ–specific autoantibody production is not uncommon (445–447). In cases of recurrent pregnancy loss, thyroid autoantibodies may serve as peripheral markers of abnormal T-cell function and further implicate an immune component as the cause of reproductive failure. The clinical implications of these findings in the management of patients with recurrent pregnancy loss are not known. Recurrent pregnancy loss is covered in Chapter 33.

Thyroid Nodules

Thyroid nodules are a common finding on physical examination and are demonstrated by high-frequency ultrasonography in over two-thirds of patients (448). Occasionally such nodules are functional, and clinical and laboratory evaluation should be applied to distinguish these nodules from nonfunctional nodules, which are occasionally malignant. For nonfunctional "cold" nodules, fine-needle biopsy and aspiration are required to rule out malignancy. In the case of indeterminate aspirates, 2% to 20% are malignant; therefore, surgical biopsy is often indicated (449). Molecular diagnosis screening of the *BRAF* mutation improves the diagnosis of cancer on fine-needle aspiration (450).

Turner Syndrome and Down Syndrome

Patients with Turner syndrome (and other forms of hypergonadotropic hypogonadism associated with abnormalities of the second sex chromosome) exhibit a high prevalence of autoimmune thyroid disorders. Approximately 50% of adult patients with Turner syndrome have anti-TPO and antithyroglobulin (anti-TG) autoantibodies. Of these patients, approximately 30% will develop subclinical or clinical hypothyroidism. The disorder is indistinguishable from Hashimoto thyroiditis. A susceptibility locus for Graves disease is noted on chromosome X (451). Because of the increased risk of ATD, it is recommended that women with Turner syndrome are screened with yearly TSH testing starting at the age of 4 (452).

Down syndrome, caused by an extra chromosome 21, is characterized by an atypical

body habitus, mental retardation, cardiac malformations, an increased risk of leukemia, and a reduced life expectancy. The extra chromosome is almost always of maternal origin. Autoimmune thyroid disorders are more common in patients with Down syndrome than in the general population. The gene for autoimmune polyglandular syndrome I (*APECED*) has been mapped to chromosome 21 and is thought to be a transcription factor involved in immune regulation (AIRE). This gene may play a role in the development of ATD in these patients (453). Hashimoto thyroiditis is the most common type of thyroid disease in individuals with Down syndrome. Hypothyroidism develops in as many as 50% of patients older than age 40 with Down syndrome. These clinical syndromes and other evidence suggest part of the genetic susceptibility to Hashimoto thyroiditis may reside on chromosomes X and 21. Because of the increased frequency of hypothyroidism associated with Down syndrome, it is recommended to screen individuals at 6 months, 12 months, and then annually thereafter (384).

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CHAPTER 36

Infertility



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Epidemiology
Initial Assessment
Causes of Infertility
- Impact of Lifestyle on Fertility
- Male Factor
  - *Physiology*
  - *Semen Analysis*
  - *Differential Diagnosis of Male Factor*
  - *Male Age*
  - *Treatment of Male Factor Not due to Azoospermia*
  - *Azoospermia: Classification and Treatment*
- Female Age and Decreased Ovarian Reserve
  - *Decreased Fecundability and Diminished Ovarian Reserve*
  - *Spontaneous Pregnancy Loss*
- Ovulatory Factor
  - *Methods to Document Ovulation*
  - *Polycystic Ovarian Syndrome*
  - *Oral Contraceptive Pretreatment*
- Tubal Factor
  - *Treatment of Tubal Factor Infertility*
- Uterine Factors
  - *Diagnostic Imaging for Uterine Pathology*
  - *Congenital Anomalies of the Uterus*
  - *Acquired Abnormalities of the Uterus*
  - *Luteal Phase Defect and Progesterone Supplementation*
- Pelvic Factor

Endometriosis Infertility
Unexplained Infertility
Proposed Mechanisms for Unexplained Infertility
Treatment of Unexplained Infertility
Assisted Reproductive Technologies (ART) Process
Process of ART
Prevention of Premature Luteinizing Hormone Surge
GnRH Antagonists Fixed Versus Flexible Protocols
Follicular Growth and Stimulation Protocols
Adjunctive Medications
Fertilization by IVF or ICSI
Embryo Transfer
Cryopreservation of Embryos
First Trimester Pregnancy Monitoring
ART Success Rates
National IVF Outcomes Registry
Prediction Models Personalize IVF Success
Cessation of Therapy
Third Party Reproduction
Oocyte Cryopreservation
Complications of Assisted Reproductive Technology
Risks of ICSI
Cycle Cancellation
Oocyte Retrieval
Multiple Gestation
Ectopic and Heterotopic Pregnancy
Ovarian Hyperstimulation Syndrome
Cycle Cancellation
Adjunctive Medications
Embryo Cryopreservation
In vitro Oocyte Maturation
Risk of Cancer After Fertility Therapy
Stress
Neonatal and Child Development
Preimplantation Genetic Diagnosis and Screening
Preimplantation Genetic Screening
Preservation of Fertility in Cancer Patients

KEY POINTS

The physician's initial encounter with an infertile couple is the most important one because it sets the tone for subsequent evaluation and treatment. Factors from either or both partners may contribute to difficulties in conceiving. Therefore, it is important to understand male and female reproductive physiology and consider all possible diagnoses before pursuing invasive treatment.

1 The main causes of infertility include male factor, decreased ovarian reserve, ovulatory disorders (ovulatory factor), tubal injury, blockage, or paratubal adhesions (including endometriosis with evidence of tubal or peritoneal adhesions), uterine factors, systemic conditions (including infections or chronic diseases such as obesity, autoimmune conditions, or chronic renal failure), cervical and

immunologic factors, and unexplained factors (including endometriosis with no evidence of tubal or peritoneal adhesions).

2 Basic investigations that should be performed before starting any infertility treatment are semen analysis, confirmation of ovulation, and documentation of tubal patency. Ovarian reserve screening is often performed.

3 Male factor is the only cause of infertility in 20% of infertile couples, but it may be a contributing factor in as many as 50% of cases. Within this category are same sex female couples desiring to conceive; they would not necessarily be considered traditionally infertile, but they would need donor sperm. Treatment of reversible anatomic, endocrine or infectious causes of subfertility, such as varicocele repair, cessation of suppressive medications or toxic behaviors, and treatment of sexually transmitted diseases and thyroid disorders, may be efficacious. Intrauterine insemination (IUI) is the best studied and most widely practiced of all the insemination techniques. Intracytoplasmic sperm injection (ICSI) has allowed couples with male factor infertility to achieve assisted reproductive technology (ART) pregnancy outcomes that are comparable with those of couples with nonmale factor infertility using conventional in vitro fertilization (IVF) treatment.

4 An association between the age of the woman and reduced fertility has been well-documented. The decline in fecundability begins in the early 30s and accelerates during the late 30s and early 40s. Chemotherapeutics may hasten loss of ovarian reserve and may prompt fertility preservation counseling. Similar counseling should be undertaken for male cancer patients.

5 Disorders of ovulation account for about 30% to 40% of all cases of female infertility. These disorders are generally among the most easily diagnosed and most treatable causes of infertility.

6 The most common cause of oligo-ovulation and anovulation—both in the general population and among women presenting with infertility—is polycystic ovarian syndrome (PCOS).

7 Tubal and peritoneal factors account for 30% to 40% of cases of female infertility. Cervical factor is estimated to be a cause of infertility in no more than 5% of infertile couples. Uterine pathologies contribute to infertility in as many as 15% of couples seeking treatment. Leiomyomas have not been shown to be a direct cause of infertility. If the evaluation is negative (i.e., unexplained) then superovulation with IUI may be considered, though with less success than ART.

8 ART techniques include gametes from autologous or third-party sources, IVF, ICSI using ejaculated or surgically retrieved sperm that is either fresh or cryopreserved, gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), oocyte and embryo cryopreservation, and use of gestational carriers. Because of improved success rates associated with IVF embryo transfer, the performance of GIFT and ZIFT has declined dramatically. Embryo screening using morphokinetic methods, PGD, and PGS are also utilized.

9 Multiple gestation, especially higher-order multiple gestation, is a serious complication of infertility treatment and has tremendous medical, psychological, social, and financial implications.

10 Other complications of ART can occur, but stress is the most common reason for patients to discontinue fertility therapy. Improved protocols can minimize ovarian hyperstimulation syndrome (OHSS) risks, and recent studies have not shown an increased risk for breast, uterine, or ovarian cancer secondary to medications used for superovulation in the treatment of infertility. Although concerns have been raised about congenital abnormalities in offspring, absolute risk seems to be low.

11 Information on the Society for Assisted Reproductive Technology (SART) and registered ART clinics are accessible by the public at https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2015. The Centers for Disease Control (CDC) by law collects ART data and this is publicly available at ftp://ftp.cdc.gov/pub/Publications/art/ART-2015-Clinic-Report-Full.pdf#page=4.

Assessing the scope of infertility is hampered in part by the lack of standardized definitions (1). Infertility is variably defined as no pregnancy with unprotected intercourse for 1 year (2) or 2 years (1). This condition may be further classified as

primary infertility, **in which no previous pregnancies have occurred, and** ***secondary infertility,*** **in which a prior pregnancy, although not necessarily a live birth, has occurred** (3). **About 90% of couples should conceive within 12 months of unprotected intercourse** (4). **The term subfertility is often used interchangeably with infertility** (5). **Fecundability refers variously to the probability of pregnancy per cycle or to the number of cycles to achieve a pregnancy** (6). **Fecundity refers to the probability of achieving a live birth** (7). **The diagnosis of impaired fecundity has been proposed to include couples with ê36 months without conception or physical inability or difficulty in having a child** (7).

EPIDEMIOLOGY

The prevalence of infertility in the United States has been variously estimated from 7.4% (8) **to 15.5%** (9) **depending on the methodologic approach used.** However, utilization of infertility services in the United States remains low at 17% or 6.9 million women aged 25 to 44 from 2006 to 2010 with higher utilization noted among women age ≥30, non-Hispanic Whites, and higher socioeconomic strata (10).

INITIAL ASSESSMENT

The physician's initial encounter with an infertile couple is the most important one because it sets the tone for subsequent evaluation and treatment. **It cannot be overemphasized that in partnered patients, infertility is a problem of the couple.** The presence of the partner, beginning with the initial evaluation, involves him or her in the therapeutic process. **[1]** This essential involvement demonstrates the physician's receptivity to the partner's needs and those of the patient, allowing both members of the couple an opportunity to ask questions and voice any concerns.

[2] **The physician should obtain a complete medical, surgical, and urologic/gynecologic history from both partners.** Specifically, information regarding menstrual cycle regularity, pelvic pain, and previous pregnancy outcomes is important. Risk factors for infertility, such as a history of pelvic inflammatory disease (PID) or pelvic surgery, should be reviewed. A history of intrauterine exposure to diethylstilbestrol (DES) is significant. In addition, a review of systems relevant to pituitary, adrenal, and thyroid function is useful. Questions regarding galactorrhea, hirsutism, and changes in weight are particularly relevant. A directed history, including developmental defects such as undescended testes, past genital surgery, infections (including mumps orchitis), previous genital trauma, and medications should be obtained from the male partner. A history of occupational exposures that might affect the reproductive function of either partner is important, as is information about coital

frequency, dyspareunia, and sexual dysfunction. Finally, information should be obtained on any family history of infertility, premature ovarian failure, congenital physical or intellectual impairments, and hereditary conditions relevant to preconception planning, such as cystic fibrosis, thalassemia, and Tay–Sachs disease.

[1] The initial interview provides the physician with the opportunity to assess the emotional impact of infertility on the couple. It gives the physician a chance to emphasize the emotional support available to the couple as they proceed with the diagnostic evaluation and suggested treatments. In most cases, referral to a trained social worker or psychologist may be beneficial.

The physical examination of the woman should be thorough, with attention given to height, weight, body habitus, hair distribution, thyroid gland, and pelvic examination. Referral of the male partner to a urologist for examination often is beneficial if historic information or subsequent evaluation suggests an abnormality. This initial encounter provides an opportunity to outline the general causes of infertility and discuss subsequent diagnostic and treatment plans (**Figs. 30-1** to **30-3**).

[3] The basic investigations that should be performed before starting any infertility treatment are semen analysis, confirmation of ovulation, and documentation of tubal patency (**Figs. 36-1** **to** **36-3**). If a patient with severe systemic illness such as renal failure, liver failure, or cancer wishes to conceive, careful preconception assessment and counseling is advisable because the risks of fertility treatment and pregnancy can be substantial.

CAUSES OF INFERTILITY

The main causes of infertility include:

1. **Male factor**
2. **Decreased ovarian reserve**
3. **Ovulatory factor**
4. **Tubal factor**
5. **Uterine factor**
6. **Pelvic factor**
7. **Unexplained**

The relative prevalence of the different causes of infertility varies widely among patient populations (Table 36-1). Worldwide, male factor accounts for 51.2% (11) and tubal blockage for 25% to 35% (12) of infertility and subfertility (conception after attempting for 1 year). In Europe, ovulatory dysfunction accounts for 21% to 32%, male factor 19% to 57%, tubal factor 14% to 26%, unexplained 8% to 30%, endometriosis 4% to 6%, and combined male and female factors 34.4% of infertility (13–15). **[4]**

Male factor is the only cause of infertility in about 20% of infertile couples, but it may be a contributing factor in as many as 50% of cases (15–17). Very few couples have absolute infertility, which can result from congenital or acquired irreversible loss of functional gametes in either partner or the absence of reproductive structures in either partner. **[2]** Spontaneous conception is less likely to occur with age >42, infertility duration >4 years, severe endometriosis, or severe tubal disorder (18), so patients with those features should be strongly encouraged to consider treatment rather than expectant management.

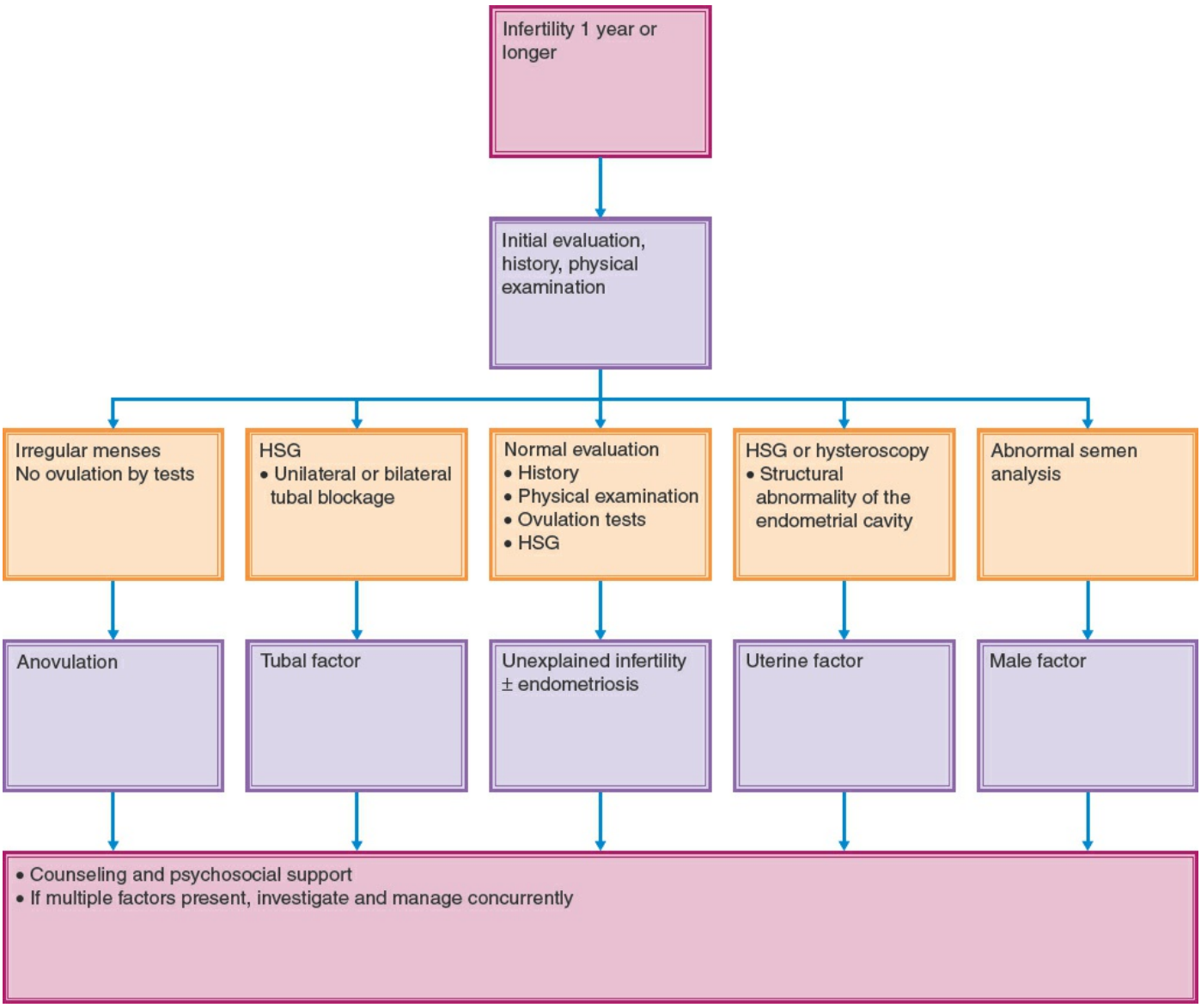


FIGURE 36-1 Diagnostic and treatment algorithm: Infertility. HSG, hysterosalpingography. (From **Yao M.** *Clinical management of infertility*. ©2000 The Advisory Board Company. All rights reserved. Used with permission.)

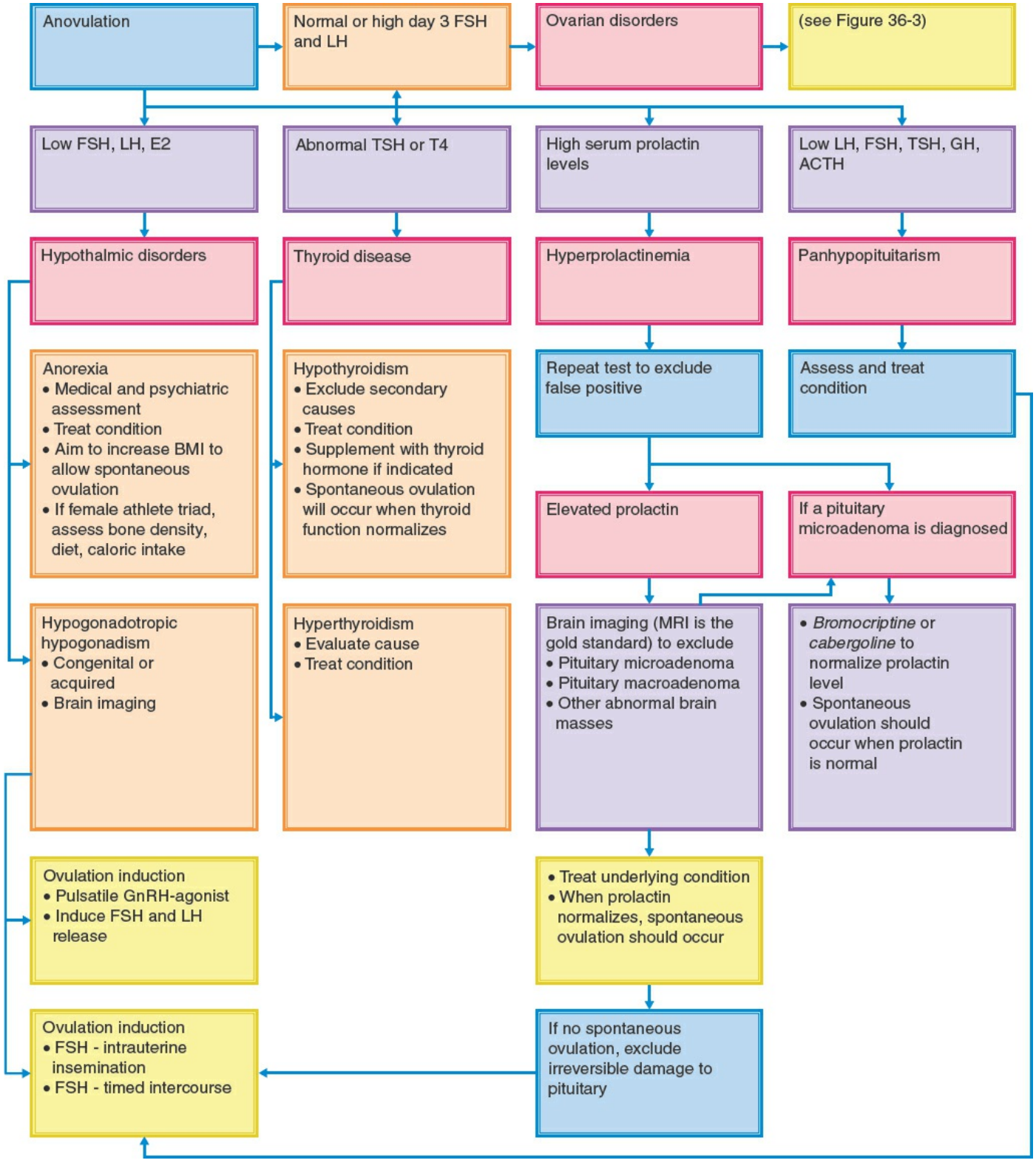


FIGURE 36-2 Diagnostic and treatment algorithm: Anovulation. FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; TSH, thyroid-stimulating hormone; T4, thyroxine; GH, growth hormone; ACTH, adrenocorticotropic hormone; BMI, body mass index; MRI, magnetic resonance imaging; GnRH, gonadotropin-releasing hormone. (From **Yao M.** *Clinical management of infertility*. ©2000 The Advisory Board Company. All rights reserved. Used with permission.)

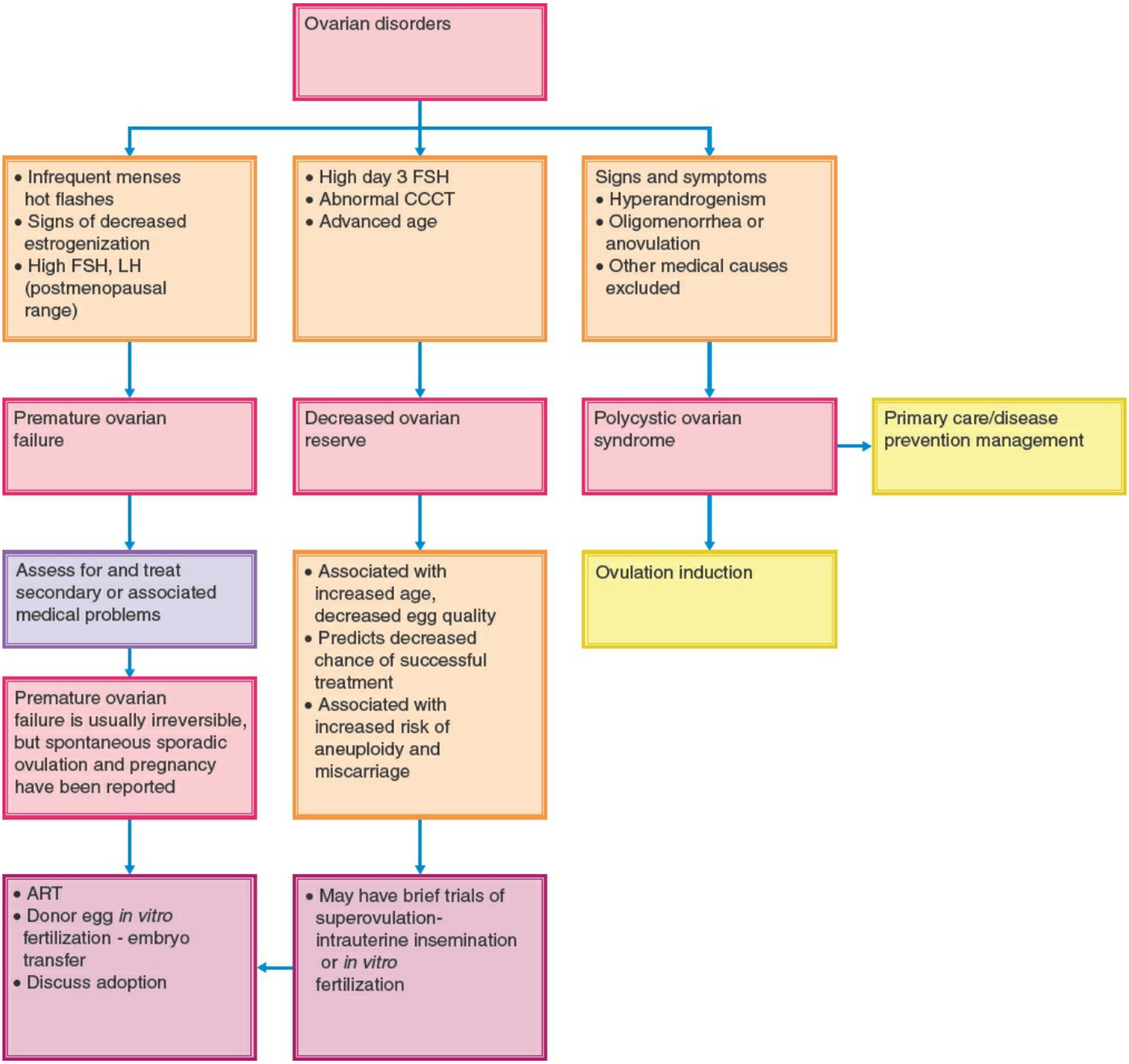


FIGURE 36-3 Diagnostic and treatment algorithm: Ovarian disorders. FSH, follicle-stimulating hormone; LH, luteinizing hormone; CCCT, clomiphene citrate challenge test; ART, assisted reproductive technology. (From **Yao M.** *Clinical management of infertility*. ©2000 The Advisory Board Company. All rights reserved. Used with permission.)

Impact of Lifestyle on Fertility

[2] Women with class II obesity particularly when partnered with similarly obese men experience longer time to pregnancy compared to normal-weight couples, and female obesity is associated with lower pregnancy rates with IVF compared to normal-weight women (21–23). Potential etiologies for obesity-associated infertility include disrupted hypothalamic–pituitary–ovary axis, diminished fertilization rate, and impaired

endometrial gene receptivity. In mildly obese body mass index (BMI) <35 kg/m^2 women randomized to weight loss of ~20 pounds versus no weight loss, IVF live birth rates did not significantly differ, but spontaneously conceived live birth rates were higher in the weight-loss group (24). Obese men have higher rates of hypogonadotropic hypogonadism and sperm DNA or mitochondrial damage compared to normal-weight men (25,26). Substance (drug and alcohol) use in men is discussed in "Male Factor." A survey of 12,800 women in the United States undergoing IVF revealed that nearly a quarter of them consumed alcohol, 7% smoked, and two-thirds used caffeine during treatment (27). Studies report that compared to nonsmokers, maternal and paternal tobacco smokers have lower live birth rates with intercourse (28), lower pregnancy rates using donor IUI (29) and partner IUI (30), and higher rates of IVF cycle cancellation prior to oocyte retrieval even among female former smokers (31). Reassuringly, maternal low to moderate daily intake of alcohol (<12 g) and caffeine (<200 mg) in the 1 year prior to ART did not impact ART outcomes (32).

[2] TABLE 36-1 Causes of Infertility

Relative Prevalence of the Etiologies of Infertility (%)	
Male factor	17–28
Both male and female factors	8–39
Female factor	33–40
Unexplained infertility	8–28
Approximate Prevalence of the Causes of Infertility in the Female (%)	
Ovulatory dysfunction	21–36
Tubal or peritoneal factor	16–28
Miscellaneous causes	9–12
Prevalence of etiologies of infertility (1,15,19,20)	

Male Factor

The concept of a global decline in sperm counts is controversial (33,34). A decline in sperm density has been observed in the United States, Europe, and Australia, while decreased motility and semen volume have been reported in India (33). Given that decreases in sperm parameters have been noted in fertile men (35) and in U.S. sperm donors (36), the clinical relevance for fecundability is unknown. However, one simulation model has suggested that if sperm concentrations decline by 21% to 47%, fecundability would decrease by 7% to 15% (37).

Physiology

Spermatogenesis

The male reproductive tract consists of the testis, epididymis, vas deferens, prostate, seminal vesicles, ejaculatory duct, bulbourethral glands, and urethra. **Gonadotropin-responsive cells in the testes include Leydig cells (the site of androgen synthesis) and Sertoli cells, which line the seminiferous tubules (the site of spermatogenesis)** (38). **The [1] pituitary gland secretes luteinizing hormone (LH), which stimulates the synthesis and secretion of testosterone by the Leydig cells, and follicle-stimulating hormone (FSH), which acts with testosterone on the Sertoli cells to stimulate spermatogenesis (38).** In [1] humans, a new cohort of spermatogonia enter the maturation process every 16 days, and the development from spermatogonia stem cells to the mature sperm cells takes about 75 days (39). Spermatogonia undergo mitotic division to give rise to spermatocytes (38). These diploid spermatocytes subsequently undergo meiosis to produce haploid spermatids, which contain 23 (rather than 46) chromosomes (38). Maturation of spermatids is called spermiogenesis and involves condensation of the nucleus, formation of the flagellum, and the formation of the acrosome (a structure derived from the Golgi complex covering the tip or head of the sperm nucleus) (40). The resultant spermatozoa are released into the seminiferous tubule lumen and enter the epididymis, where they continue to mature and become progressively more motile during the 2 to 6 days that is required to traverse this tortuous structure and reach the vas deferens (41).

Sperm Transport

[1] During ejaculation, mature spermatozoa are released from the vas deferens along with fluid from the prostate, seminal vesicles, and bulbourethral glands (42). The released semen is a gelatinous mixture of spermatozoa and seminal plasma; however, this thins out 20 to 30 minutes after ejaculation. This process, called liquefaction, is the direct result of proteolytic enzymes within the prostatic fluid (42). **[1] Following ejaculation, the released spermatozoa must undergo capacitation to become competent to fertilize the oocyte** (43). Capacitation occurs within the cervical mucus and involves removal of inhibitory mediators such as cholesterol from the sperm surface, tyrosine phosphorylation, and calcium ion influx, all of which allow the sperm to recognize additional fertilization cues during travel through the female reproductive tract (43). After the sperm reach the tubal isthmus they are slowly released into the ampulla, further reducing the number of sperm that reach the oocyte (43). Sperm transport from the posterior vaginal fornix to the fallopian tubes occurs within 2 minutes during the follicular phase of the menstrual cycle (44).

Fertilization

[1] As the capacitated sperm near and pass through cumulus cells surrounding the

oocyte, hydrolytic enzymes are released from the acrosome via exocytosis in a process called the acrosome reaction (43). Capacitation and the acrosome reaction can be induced in vitro (40,43). Following the acrosome reaction, the sperm binds to and penetrates the zona pellucida (the extracellular coat surrounding the oocyte). This allows fusion of the sperm with the plasma membrane of the oocyte, an event that promotes changes in the oocyte that prevent entry by additional sperm (43). **As the first sperm penetrates, cortical granules are released (the cortical reaction) from the oocyte into the perivitelline space. This stops the oocyte's zona pellucida from binding new sperm and inhibits penetration by previously bound sperm, further reducing the possibility of polyspermy** (45).

Recreational, Iatrogenic, and Environmental Male Reproductive Toxins

Decreased sperm concentration and motility have been noted in areas of the United States with heavy agriculture and pesticide use (35), but occupational exposures have not been linked to infertility (46). **[4] Alcoholism negatively affects all semen analysis parameters** (47,48) **and either smoked** (48,49) **or chewed tobacco** (50) **is associated with decreased sperm density and motility.** Compared to nonusers, marijuana used greater than once per week was associated with diminished sperm concentration and count by nearly 30% (51). Concurrent use of other illicit substances such as cocaine further decreased sperm quantity and negatively impacted motility (51). Certain medications may reduce sperm numbers or function or may cause ejaculatory dysfunction (Table 36-2). **Vaginal lubricants such as Astroglide, KY Jelly, saliva, and olive oil inhibit sperm motility in vitro, while no adverse effects are seen with hydroxethyl cellulose (Pre-Seed), mineral oil, or canola oil** (44). **[4]** However, Astroglide and KY do not appear to affect fecundability in noninfertile couples engaging in procreative intercourse (52).

[1] TABLE 36-2 Drugs that Can Impair Male Fertility

Impaired spermatogenesis—sulfasalazine, methotrexate, nitrofurantoin, colchicine, chemotherapy
Pituitary suppression—testosterone injections, gonadotrophin-releasing hormone analogs
Antiandrogenic effects—cimetidine, spironolactone
Ejaculation failure—a blockers, antidepressants, phenothiazines
Erectile dysfunction—b blockers, thiazide diuretics, metoclopramide
Drugs of misuse—anabolic steroids, cannabis, heroin, cocaine

From **Hirsh A.** Male infertility. *BMJ* 2003;327:669–672, with permission.

Semen Analysis

[3] The basic semen analysis measures semen volume, sperm concentration, sperm motility, and sperm morphology (42). Recently revised, the normal values suggested by the World Health Organization (WHO) in 2010 are listed with the previously published guidelines in Table 36-3 (42,53). Both criteria were developed using fertile men whose semen parameters were in the lowest 5th centile of the group studied, but values above the reference ranges do not guarantee male fertility. Because infertile men were not used to develop the criteria, values below the cutoffs may not necessarily indicate infertility (42). However, significant deviations from the reference limits are generally classified as male factor infertility (17). Given regional differences between laboratories and in semen quality, laboratories are encouraged to develop their own reference ranges (42). Typically, semen is assessed manually, but computer-aided sperm analysis (CASA) may be used (42). Limitations of CASA include a lack of standardization among instruments, an inability to differentiate intact from nonintact sperm, possible bias from artifacts during preparation, and a paucity of studies on fertility outcomes in large populations (42).

Abstinence

[3] Previous recommendations for prolonged abstinence time up to 7 days (42) **have little supporting evidence, and likely there is benefit to shorter abstinence duration regardless of baseline parameters. [1]** The epididymis stores the equivalent of three ejaculations (41), and therefore short abstinence is unlikely to significantly deplete sperm quantity in most men. A retrospective United States study of 1939 oligozoospermic subfertile men found that >2 days abstinence was associated with more samples with >20 M total motile counts and higher ejaculate volume but no statistically significant impact on concentration, motility, or morphology (54). With >5 days of abstinence, oligozoospermic men had reduced total motile sperm count and normal morphology (55). Although longer abstinence >2 days in normozoospermic men increased sperm concentration and total count, it was globally detrimental with respect to lower ejaculate volume, total and progressive motility, viability, and tail morphology (54). With prolonged abstinence >10 days, even normozoospermic men will have reduced total motile sperm count and reduced proportions of sperm with normal morphology (55), as sperm overflow into the urethra and are flushed out into the urine (42). Prolonged epididymal storage with heightened oxidative stress negatively affects quality in terms of elevated sperm DNA fragmentation (54), and may explain the improved pregnancy rates associated with shortening abstinence times to ≤2 days prior to specimen collection for intrauterine insemination (IUI) (56).

[3] TABLE 36-3 Semen Analysis Terminology and Normal Values

Terminology (42)	
Normozoospermia	All semen parameters normal

Oligozoospermia	Reduced sperm numbers Mild to moderate: 5–20 million/mL Severe: <5 million/mL
Asthenozoospermia	Reduced sperm motility
Teratozoospermia	Increased abnormal forms of sperm
Oligoasthenoteratozoospermia	Sperm variables all subnormal
Azoospermia	No sperm in semen
Aspermia (anejaculation)	No ejaculate (ejaculation failure)
Leucocytospermia	Increased white cells in semen
Necrozoospermia	All sperm are nonviable or nonmotile

Normal Semen Analysis—World Health Organization (42)		
	1992 Guidelines	**2010 Guidelines**
Volume	>2 mL	≥1.5 mL
Sperm concentration	>20 million/mL	≥15 million/mL
Sperm motility	>50% progressive or >25% rapidly progressive	≥32% progressive
Morphology (strict criteria)	>15% normal forms	≥4% normal forms
White blood cells	<1 million/mL	<1 million/mL
Immunobead or mixed antiglobulin reaction test	<10% coated with antibodies	<50%

Terminology from **Hirsh A.** Male infertility. *BMJ* 2003;327:669–672, with permission.

Specimen Collection

The specimen should be obtained by masturbation and collected in a clean container kept at ambient temperature (42). **[3]** The patient should report any loss of the specimen, particularly the first portion of the ejaculate, which contains the highest sperm concentration (42). Collection may be performed either at home or in a private room near the laboratory (42). The sample should be taken to the laboratory within one-half to one hour of collection to prevent dehydration and degradation (42). **If masturbation into a container is not possible, condoms specially designed for semen analysis should be used rather than latex condoms which are toxic to sperm** (42). **Intercourse to collect the sample is discouraged because of contamination risk** (42).

[3] Even when the specimen is obtained under optimal circumstances, interpretation of the results of the semen analysis is complicated by variability within the same individual and overlap in infertile and fertile reference semen parameters (42). Semen parameters may vary widely from one man to another and among men with proven fertility (42). **In many circumstances, several specimens are necessary to verify an abnormality** (42).

Sperm Volume and pH

The lower limit of normal semen volume is ê1.5 mL and the pH should be ê7.2 (42). These parameters are affected mainly by the balance between the acidic secretions of the prostate gland and the alkaline fluid from the seminal vesicles (42). Low volume along with pH <7 suggests obstruction of the ejaculatory ducts or absence of the vas deferens (42). **[3]** Difficulties with collection, retrograde ejaculation, or androgen deficiency can contribute to low volume (42). Consider further workup with urine voided immediately after ejaculation in patients with documented low semen volume <1 mL, after verifying with the man that no spill occurred during collection (17). Calculate the total sperm in the urine divided by the (total sperm in urine plus total sperm in ejaculate) multiplied by 100. A value >7.1% to 8.3% will be found in patients with partial retrograde ejaculation (57).

High volumes >5 mL suggest inflammation of the accessory glands (42).

Sperm Concentration

Sperm concentration or density is defined as the number of sperm per milliliter in the total ejaculate (42). **[3] The normal lower limit is ê 15 million/mL, revised from ê 20 million/mL (42,53).** Only intact sperm are counted in determining sperm concentration (42). Fifteen percent to 20% of infertile men are azoospermic (no sperm) and 10% have a density of <1 million/mL (42,58).

Sperm Motility and Viability

Sperm motility is the percentage of progressively and total (progressive plus nonprogressive) motile sperm in the ejaculate (42). **[3] The normal lower limit is ê 32%, which was revised from ê 50% (42,53). Viability should be at least 58% (42).** Progressive motility refers to movement either linearly or in a large circle regardless of speed. Nonprogressive motility describes sperm that display only small movements/twitching or no movement at all (immotile) (42). Assessments of speed of progression, either rapid or slow, have been removed from the revised guidelines as a result of difficulty in unbiased measurement of this parameter (42). A reduction in sperm motility is referred to as asthenozoospermia (42). Leukocytes can impair sperm motility through oxidative stress (42). When many immotile sperm are present or when progressive motility is <40% viability studies should be performed (42). Viable immotile sperm may have flagellar defects while the presence of nonviable immotile

sperm (necrozoospermia) suggests epididymal pathology (42). **[3]** Viable sperm have intact plasma membranes, which will not stain (dye exclusion) but will swell in hypoosmotic solutions (hypoosmotic swelling test) (42). Sperm motility *in-vitro* is decreased in the presence of women's serum neutrophils, which release extracellular "traps" that enmesh sperm in filaments elaborated by these inflammatory cells.

Sperm Morphology

Morphology testing assesses anatomic malformations of the sperm. **[3] The lower limit for normal morphology is ê 4% using strict criteria, a change from previous guidelines using a more lenient assessment and a cutoff of ê 30% (42,53).** Assessment of sperm morphology involves fixing and staining a portion of the specimen (42). The strict Tygerberg criteria were introduced by Kruger et al. in 1986 to assess sperm morphology (42,59,60). Using this system, the entire spermatozoon—including the head, midpiece, and tail—is assessed, and even mild abnormalities in head forms are classified as abnormal (42). Most sperm from normal men exhibit minor abnormalities when subjected to Tygerberg standards (42). An abnormality of sperm morphology is known as teratozoospermia, and these sperm have poor fertilizing potential and may have abnormal DNA (42). Low strict sperm morphology <9% was a better discriminator for infertility than either count or motility in a large cross sectional multicenter study (61). A disadvantage to any morphology assessment is that reproducibility may be hampered by the subjective nature of the assessment (42).

Round Cells, Bacteria, and Leukocytes

[3] Round cells include immature germ cells and leukocytes (42). The prevalence of round cells in a large IVF cohort was 5.4%, of which 73% were found to be immature germ cells (62). Immature germ cell elevation is associated with lower sperm concentration and normal morphology, compromised sperm DNA integrity, lower fertilization, and higher pregnancy loss rates with Intracytoplasmic sperm injection (ICSI) (62), while leukocytes (predominantly neutrophils) are associated with inflammation (42). Leukocytes can be distinguished by positive peroxidase staining, and normal leukocyte concentrations should be <1 million/mL (42). However, the prognostic significance of leukocytes in the semen is controversial; even low levels can be associated with reactive oxygen species and sperm DNA damage, but their presence has inconsistent effects on IVF/ICSI outcomes (42,62–64). Bacteriospermia prevalence among infertile men is ~50%, with detection rates likely affected by semen collection technique and specific test parameters, and prevalence is not necessarily associated with leukocytospermia; it may represent asymptomatic colonization without an inflammatory response (62,65). The most common pathogens associated with bacteriospermia are *Chlamydia trachomatis* (41.4%), *Ureaplasma urealyticum* (15.5%), and *Mycoplasma hominis* (10.3%), with *M. hominis* and *U. urealyticum* having higher prevalence in men with leukocytospermia compared to those without (65).

Antisperm Antibodies

Antisperm antibodies are often associated with sperm agglutination, may be present in seminal plasma, on sperm surfaces and in maternal serum, and risk factors include history of ductal obstruction, prior genital infection, testicular trauma, and prior vasectomy reversal (17). Using the immunobead test, washed spermatozoa are exposed and assessed for binding to labeled beads (42). In the mixed agglutination reaction, human red blood cells sensitized with human IgG are mixed with partner's semen (42). Spermatozoa that are coated with antibodies form mixed agglutinates with the red blood cells (42).**[3]** Antisperm antibody testing is limited by the lack of specific antibody binding, which is important because only a subset of antibodies is thought to have cytotoxic or agglutinating effects (66). Although the presence of antisperm antibodies has typically been managed with ICSI, it is uncertain whether that treatment is beneficial (66), and antibody testing would not be indicated if ICSI were a priori planned (17).

Postcoital Testing

[3] The purpose of the postcoital test, in which the cervical mucus is microscopically examined shortly after intercourse during the periovulatory cycle phase, is to assess the effect of cervical mucus on sperm viability and function (2). The test is considered positive if one or more progressively moving sperm per high power field is observed, negative if no sperm or only nonprogressive or immotile sperm are seen (3). However, its prognostic value and impact on management are limited by poor specificity, poor reproducibility, or controversial interpretation of the results (2). Nevertheless, a large recent study of infertile couples with <3 years of infertility from the Netherlands found that a positive postcoital test was associated with improved spontaneous pregnancy rates compared to negative test results, while a negative postcoital test was associated with improved IUI and IVF pregnancy rates compared to positive test results (3).

Sperm DNA Integrity

[3] Sperm DNA fragmentation has been associated with impaired pregnancy rates during IVF and is associated with an elevated risk of miscarriage, perhaps related to paternal age with its associated increase in double strand DNA damage (67). Sperm DNA fragmentation does not appear to correlate with blastocyst aneuploidy in a small study (68). Sperm chromatin structure assays, terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick end labeling (TUNEL) assays, sperm chromatin dispersion tests, and single gel electrophoresis assays have varying thresholds for DNA damage diagnosis and varying positive predictive values (PPVs) for pregnancy with assisted reproduction; TUNEL assay results have the best correlation (67). These tests reflect the aggregate sperm DNA integrity of a heterogeneous sperm population rather than an individual fertilizing sperm, which limits the utility of this testing in the context of fertility treatment (67). **[3]** Nonetheless it may add etiologic information particularly in otherwise unexplained cases, and may prompt

recommendations for reducing sperm DNA damage with interventions such as antioxidant supplementation (67).

Epigenetic Sperm DNA Assessment

Epigenetics is the next frontier in sperm functional biology assessment, and epigenetic changes may be acquired transgenerationally or from conditions such as obesity (69). In couples with unexplained infertility, poor embryo development during IVF and men with abnormal semen analysis parameters, the sperm exhibit genome-wide alterations in genome packaging (i.e., histone modifications) and DNA methylation using chip microarrays as compared to those from fertile men (70,71). Assessment is available with the Episona test, but similar limitations as with the sperm integrity assays exist, including lack of applicability to the individual fertilizing sperm, and uncertainty as to treatments. In the case of obesity, weight loss may ameliorate epigenetic sperm changes through remodeling (69).

Differential Diagnosis of Male Factor

An underlying etiology for male factor was found using diagnostics in two-thirds of infertile men (72). Table 36-4 lists the differential diagnoses for male factor infertility (73). Several groups have attempted to assess the distribution of male infertility diagnoses; two such distributions are shown in Table 36-5 (74,75). The first is the result of a WHO study of 7,057 men with complete diagnoses based on the WHO standard investigation of the infertile couple (74). The figures include data from cases in which the male partner was normal and the presumed cause of the couple's infertility was a female factor. The second distribution is the result of a study of 425 subfertile male patients (74). Although the two studies represent different populations (one is from a study of couples, the other from a urologic practice) and differ in their distribution of male infertility diagnoses, idiopathic male factor and varicocele predominate. Other anatomic and endocrine causes occur less frequently. Particularly among men with oligozoospermia, 75% of cases were idiopathic (16). Factors which definitively lead to male infertility include secondary hypogonadism, genetic causes, seminal tract obstruction, oncologic disease therapies, and severe sexual dysfunction, while plausible causative factors include congenital urogenital anomalies and acquired testicular damage (unilateral cryptorchidism, testis cancer, and orchitis) (16). **[2]** Although not considered as primary etiologies for male factor infertility, varicocele, leukocytospermia, obesity, and uncontrolled chronic disease are more prevalent in infertile compared to fertile men (16). Same sex female couples or single women without a male partner who desire pregnancy may be considered as part of this category.

Male Age

[2] Men have reportedly fathered children into their 90s, but pregnancy rates are decreased with paternal age ê 40 to 45 and particularly ê age 50 (76). Increasing

paternal age is associated with a higher frequency of disomic sex chromosomes and structural chromosomal abnormalities in the sperm (76). With respect to the offspring, paternal age confers higher rates of autosomal dominant diseases such as achondroplasia and craniosynostosis and somewhat higher rates of trisomy 21 (76). In mice, offspring of older fathers have decreased survival (77). Increased paternal age is associated with recurrent pregnancy loss (78). Psychiatric conditions such as schizophrenia have been associated with increased paternal age, but this may reflect trends of men with psychiatric conditions to delay fathering children until later ages rather than *de-novo* genetic mutations (79).

[2] TABLE 36-4 Etiologic Factors in Male Infertility

Pretesticular	**Testicular**
Endocrine	***Genetic***
Hypogonadotropic hypogonadism	Klinefelter syndrome
Coital disorders	Y chromosome deletions
Erectile dysfunction	Immotile cilia syndrome
Psychosexual	***Congenital***
Endocrine, neural, or vascular	Cryptorchidism
Ejaculatory failure	***Infective (orchitis)***
Psychosexual	***Antispermatogenic agents***
After genitourinary surgery	Heat
Neural	Chemotherapy
Drug related	Drugs (especially testosterone)
Posttesticular	Irradiation
Obstructive	***Vascular***
Epididymal	Torsion
Congenital	Varicocele
Infective	***Immunologic***
Vasal	***Idiopathic***
Genetic: cystic fibrosis	
Acquired: vasectomy	

Epididymal hostility	
Epididymal asthenozoospermia	
Accessory gland infection	
Immunologic	
Idiopathic	
Postvasectomy	

From **De Kretser DM.** Male infertility. *Lancet* 1997;349:787–790, with permission.

Treatment of Male Factor Not due to Azoospermia

Medical treatment of reversible infectious or endocrine causes of male subfertility, such as sexually transmitted diseases and thyroid disorders, tends to be efficacious (80). Although injections of exogenous FSH have been reported to improve pregnancy rates, the benefit is less clear for clomiphene citrate, an estrogen antagonist at the hypothalamus and pituitary that promotes gonadotropin release (80). **[4] Exogenous testosterone is not recommended in the treatment of male subfertility because of negative feedback inhibition at the pituitary that results in reduced intratesticular testosterone and decreased spermatogenesis** (81). The prevalence of men receiving prescribed testosterone replacement therapy is 7% to 9%, of whom one-third have normal or supraphysiologic testosterone levels prior to treatment and half do not receive appropriate follow-up (81,82). Antioxidant food supplements have been evaluated (80). **[4]** Glutathione, carnitine, and vitamin E do not appear to affect semen parameters, but administration of zinc and folic acid were associated with improved sperm concentration and morphology (83). The diagnosis and treatment of azoospermia (no sperm on semen analysis) will be discussed separately from other forms of male factor infertility.

Varicocele Repair

A varicocele is an abnormal dilation of the veins within the spermatic cord (16). Clinically palpable varicoceles are present in 13.5% of men who recently fathered a pregnancy and 31% of men with otherwise idiopathic oligozoospermia (16). The pathophysiologic effects of a varicocele appear to be mediated by an associated rise in testicular temperature, reflux of toxic metabolites from the left adrenal or renal veins, or higher reactive oxygen species (84,85). **[4] While treatment is associated with improved semen parameters in some studies, it is not clear whether varicocele repair improves fertility** (84,86,87). Treatment via surgery or percutaneous embolization is typically considered if the varicocele is palpable and the semen analysis is abnormal, and may allow some couples to use IUI instead of in vitro fertilization (IVF) (88) and improve IVF outcomes in the setting of oligozoo or

azoospermia (89). Complications of treatment include infection, varicocele persistence, recurrence, and hydrocele formation (84).

[4] TABLE 36-5 Frequency of Some Etiologies in Male Factor Infertility

Cause	Percentage	Cause	Percentage
No demonstrable cause	48.5	Varicocele	37.4
Idiopathic abnormal semen	26.4	Idiopathic	25.4
Varicocele	12.3	Testicular failure	9.4
Infectious factors	6.6	Obstruction	6.1
Immunologic factors	3.1	Cryptorchidism	6.1
Other acquired factors	2.6	Low semen volume	4.7
Congenital factors	2.1	Semen agglutination	3.1
Sexual factors	1.7	Semen viscosity	1.9
Endocrine disturbances	0.6	Other	5.9
Total	**103.9[a]**		**100**

[a]More than 100% because of multiple factors.

From **The ESHRE CAPRI Workshop Group.** Male sterility and subfertility: guidelines for management. *Hum Reprod* 1994;9:1260–1264; and **Burkman LJ, Cobbington CC, Franken DR, et al.** The hemizona assay (HZA): Development of a diagnostic test for the binding of human spermatozoa to the human hemizona pellucida to predict fertilization potential. *Fertil Steril* 1988;49:688–697, with permission.

Artificial Insemination

Artificial insemination has mainly been used to treat unexplained infertility (usually combined with superovulation) and male factor infertility (including same sex female couples). **[4] All artificial insemination procedures involve the placement of whole semen or processed sperm into the female reproductive tract, which permits sperm–ovum interaction in the absence of intercourse.** The placement of whole semen into the vagina as a mode of fertility treatment is now rarely performed except in cases of severe coital dysfunction. All the common forms of artificial insemination involve processed sperm obtained from the male partner or a donor. Many techniques for artificial insemination have been described, but only intracervical (ICI) and IUI have been routinely employed.

Insemination Processing

During and after intercourse, seminal fluid usually is prevented from reaching the intrauterine cavity and intra-abdominal space by the cervical barrier. **[4] The**

introduction of seminal fluid past this barrier may be associated with pelvic infection and severe uterine cramping or anaphylactoid reactions, possibly mediated by seminal factors such as prostaglandins (90). Thus, protocols for processing whole semen include the washing of specimens to remove seminal factors and to isolate pure sperm (90). Additional processing may include centrifugation through density gradients, sperm migration protocols, and differential adherence procedures (90). Finally, phosphodiesterase inhibitors, such as pentoxiphylline, have been used during semen processing to enhance sperm motility, fertilization capacity, and acrosome reactivity for IVF procedures (83,91).

Intrauterine Insemination

IUI is the best studied and most widely practiced of all the insemination techniques. It involves placement of approximately 0.3 to 0.5 mL of washed, processed, and concentrated sperm into the intrauterine cavity by transcervical catheterization (90). **[4]** Patients should remain immobile for approximately 15 minutes following the procedure (92). It is difficult to identify an optimal protocol or definitively determine pregnancy rates with IUI because of patient and protocol heterogeneity, with multifactorial influences on pregnancy rates including couple age, fertility diagnosis, stimulation type, and insemination timing relative to ovulation (93). **Ideally, the partner's total motile sperm count in the IUI specimen should be ê5 million** (94–96) **or ê10 million** (97), **although a French study found similar pregnancy rates with all values ê1 million** (98). Pregnancy rates with semen meeting those thresholds have been reported to be 10.5% per cycle (97) and 38% after 4 to 6 cycles (96). Delivery rates (17% vs. 8%) are higher when ≥2 follicles ≥15 mm are present as compared to 1 follicle, particularly when GnRH antagonists are employed (98). Although teratozoospermia using older criteria has been associated with IUI failure (94), low strict normal morphology of 2% to 4% has not been found to be predictive of IUI failure as compared to morphology >4% in two recent retrospective studies (99,100), but effects of more severe teratozoospermia on IUI outcomes remain nebulous. No benefit has been found with respect to double IUI versus single IUI during a single cycle (101). The technique of fallopian tube sperm perfusion (FSP) has been proposed to improve IUI pregnancy rates, whereby the washed sperm is instilled slowly over several minutes through an inflated balloon catheter to prevent reflux, but has not been found in a large randomized trial (102) or in a 2013 Cochrane systematic review (103) to be associated with improved pregnancy rates. Unexplained infertility and IUI will be discussed separately later in this chapter.

Timing of IUI

IUI typically is performed 24 hours following the LH surge (104). However, given data that ovulation can occur much later than this, it is not surprising that no differences in

pregnancy rates were found when IUI was performed between 24 and 60 hours following the LH surge (105). IUI pregnancy rates doubled when human chorionic gonadotropin (hCG) trigger was used instead of natural LH surge (98). **[4]** Although timing of IUI is typically performed 36 hours following hCG administration to coincide with follicle rupture, no significant differences in pregnancy or live birth rates are seen whether IUI is performed at 24 or 36 hours following the hCG trigger (106).

Donor IUI

For men with azoospermia, couples with significant male factor infertility who do not desire ART, and women without a male partner who are seeking pregnancy, therapeutic donor insemination offers an effective option (107). In earlier prospective randomized or crossover trials, IUI was shown to be superior to ICI for donor insemination (108). The success rates with ICI are lower than those with IUI, particularly when using frozen sperm (90,108–110). Women receiving donor sperm because of same sex partnership or being single had natural cycle IUI ongoing pregnancy rates that were similar to ICI at 10% per cycle and 40% cumulative over six treatment cycles (111). Lesbian women who achieved a live birth required a (mean ± SD) 3 ± 1.1 donor IUI cycles to conceive (112). **[4]** In patients younger than 30 years of age who have no other infertility factors, delivery rates approach 90% after 12 cycles of IUI treatment with frozen sperm (113), so patients who do not conceive within 6 to 12 months should be assessed for female factors and encouraged to terminate treatment or proceed with alternative forms of therapy. The concomitant use of clomiphene citrate or human menopausal gonadotropin (hMG) for controlled ovarian hyperstimulation (COH) did not result in higher fecundity rates in these patients (113). **[4] Psychological counseling should be offered because of the potential repercussions of using donor gametes** (107). Higher pregnancy rates have been demonstrated when donor IUI is performed 1 day after natural cycle serum LH rise (20%) compared to those randomized to 2 days postrise (11%) (114).

Donor Sperm Screening

Although the use of fresh donor semen is associated with higher pregnancy rates than the use of frozen specimens (115,116), both the Centers for Disease Control and Prevention (CDC) and the American Society for Reproductive Medicine recommend the use of frozen samples (107). **This recommendation stems from the increasing incidence of human immunodeficiency virus (HIV) infection in the general population and the lag time between HIV infection and seroconversion** (107). Semen donors are screened for HIV infection, hepatitis B, hepatitis C, syphilis, gonorrhea, chlamydia, and cytomegalovirus infections, all of which may be transmitted through semen (107). All cryopreserved samples are quarantined for 6 months, and the donor is retested for HIV before clinical use of the specimen (107). Donors are likewise questioned about any family history of genetically transmitted disorders, including both mendelian (e.g., hemophilia, Tay–Sachs disease, thalassemia, cystic fibrosis, congenital adrenal

hyperplasia, Huntington disease) and polygenic/multifactorial conditions (e.g., mental retardation, diabetes, heart malformation, spina bifida) (107). **[1]** Those with a positive family history of these conditions are eliminated as donor candidates (107).

Intracytoplasmic Sperm Injection

ICSI in the United States has been utilized for 93% of ART cycles for male factor infertility to achieve pregnancy outcomes that are comparable with those of couples with nonmale factor infertility using conventional IVF treatment (117). **[9]** The technique involves direct injection of a live sperm into the oocyte, thereby theoretically bypassing limitations imposed by sperm motility and defects in capacitation, the acrosome reaction, and/or sperm binding the zona pellucida (117). This microsurgical procedure involves stripping the aspirated cumulus complex of all surrounding granulosa cells, inserting a single viable sperm into the cytoplasm (ooplasm) of the oocyte that optimally is metaphase II (117) though less mature oocytes may still be considered for injection (118). ICSI should be offered if the semen analysis shows <2 million motile sperm, <5% motility, or if surgically recovered sperm is used (58), though there is wide latitude for utility depending on use of semen normal value thresholds (119). **[9]** Higher pregnancy rates have been noted with fresh when compared to frozen specimens and with ejaculated when compared to surgically retrieved sperm (58). **Success rates are affected by the age of the female partner and oocyte quality** (58). **[9]Nonmale factor indications for ICSI are contentious** (120) **but are utilized in 66.9% of United States ART cases** (117) **and with much higher frequency worldwide, and include teratozoospermia** (121), **unexplained infertility, previous fertilization failure with conventional IVF, diminished ovarian reserve, fertility preservation, and the fertilization of oocytes before preimplantation genetic diagnosis (PGD)** (117).

Risks of ICSI

Oocyte degeneration following ICSI is a relatively common occurrence with rates ranging from 5% to 19% (122). Prior reports have not supported the idea that oocyte degeneration is a function of technician skill; though, it is suggested that inherent oocyte quality, ovarian stimulation itself, unexpected random technical problems, or mechanical removal of cumulus and corona cells may contribute to this phenomenon (122). **While accumulated data indicate that there is an overall increased risk of congenital abnormalities with ART, ICSI does not appear to be associated with a higher risk compared to conventional IVF** (123). **[11]** The prevalence of sex chromosome abnormalities and translocation appears to be slightly higher with ICSI versus IVF; however, it is unclear whether these relate to the ICSI procedure or inherent gamete defects, as men with abnormal semen parameters have higher rates of sperm aneuploidy (124). There may be an increased risk of imprinting disorders with ICSI

(125). Although prior studies have not found an association with impaired intellectual or motor development among ICSI children, one study reported a higher incidence of autism when ICSI was used compared with IVF (126). **In the setting of specific genetic abnormalities such as Y chromosome microdeletions, abnormal karyotypes, cystic fibrosis mutations or congenital absence of the vas deferens, genetic counseling should be offered to address the possible risk of infertility or other abnormalities in the offspring** (124).

Azoospermia: Classification and Treatment

[4] Azoospermia describes the absence of spermatozoa in the ejaculate and is found in 1% of all men (127) **and up to 15% to 20% of infertile men** (58,127). Causes are categorized into pretesticular (nonobstructive), testicular (nonobstructive), and posttesticular (includes obstructive and nonobstructive) etiologies, but in some cases the condition is idiopathic (58).

Pretesticular Azoospermia

Pretesticular azoospermia from organic causes is relatively rare and results from gonadotropin deficiency, which leads to loss of spermatogenesis (58,127,128). The physician should perform a full endocrine history that includes information on puberty and growth and check for low serum levels of LH, FSH, and testosterone (58,127,128). Prolactin levels and pituitary imaging are indicated in cases of hypogonadotropic hypogonadism (58). **[4] Hormonal treatment includes pulsatile GnRH, hCG, and exogenous gonadotropins** (58,127,128). The best predictors of good response are postpubertal onset of gonadotropin deficiency and testicular volume >8 mL (58). **Iatrogenic azoospermia commonly results from medical testosterone use.** Treatment includes discontinuation of exogenous testosterone and recovery therapy with medications such as clomiphene citrate, hCG, and/or follicle stimulating hormone (FSH) with frequent follow-up semen analyses and endocrine labs (81). Azoospermia recovers to a median concentration of 6.5 million/mL 4.5 months following cessation of testosterone use; full recovery of sperm quantity was more likely in those men who used testosterone for less than 1 year, while those use who used it for several years were unlikely to recover (81).

Testicular Azoospermia

Gonadal failure is the hallmark of testicular azoospermia. Causes of this condition may be genetic, acquired (e.g., radiation therapy, chemotherapy, testicular torsion, varicocele, or mumps orchitis), or developmental (e.g., testicular maldescent) (58,127,128). Testicular atrophy is often present (58,127,128). Because of the low chance of obtaining sperm, testicular biopsy is generally not recommended with hypergonadotropic hypogonadism (elevated levels of LH and FSH with low serum

levels of testosterone) and consideration should be given to using donor sperm (58,127,128). Diagnostic testicular biopsies may be indicated in the setting of normal hormonal testing (58,127,128). If sperm are present in diagnostic testing, consideration can be given to using surgically retrieved spermatozoa for ICSI (58,127,128). If no sperm are present, consideration can be given to correcting acquired conditions such as varicocele, which may restore sperm to the ejaculate to permit ICSI or spontaneous pregnancy (129,130). **[4] Chromosomal abnormalities by peripheral karyotype testing are present in about 7% of infertile, 5% of oligospermic, and 10% to 15% of azoospermic men** (131). Sex chromosome aneuploidies such as Klinefelter syndrome (47,XXY) encompass two-thirds of these infertility-associated chromosome abnormalities (131). Microdeletions in the Y chromosome have been identified in 10% to 20% of men with idiopathic azoospermia or severe oligospermia with concentration <5 million/mL **(Table 36-6)** (131). These microdeletions can be transmitted to the male offspring, who may suffer from infertility (131). Therefore, screening for genetic causes is indicated in nonacquired cases of testicular azoospermia so that genetic counseling can be provided before treatment (124). The two most commonly implicated candidate gene families are the RNA-binding motif (*RBM*) and the "deleted in azoospermia" (*DAZ*) families, but microdeletions at various loci on the Y chromosome have been described (131,132). For example, microdeletions in Yq11.23 can occur in one or more of three regions: *AZFa* (proximal), *AZFb* (central), and *AZFc* (distal) (131).

[4] TABLE 36-6 Genetics and Male Infertility

Clinical Diagnosis	Genetic Tests	Most Common Defects	Incidence (%)
Congenital bilateral absence of vas deferens (CBAVD)	Cystic fibrosis (CFTR gene)	ΔF508, R117H	66
Nonobstructive azoospermia	Karyotype	47, XXY AZFa, AZFb[a], AZFc	15–30 10–15
Severe (<5 M/mL) oligozoospermia	Karyotype Translocation Y chromosome microdeletions	47, XXY Partial AZFb, AZFc	1–2 0.2–0.4 7–10

[a]AZFb the most severe (DAZ gene—deleted in azoospermia) causes the most severe defects of spermatogenesis; AZFc causes the mildest defects of spermatogenesis

CFTR, cystic fibrosis transmembrane conductance regulator; AZF, azoospermia factor.

From **Hirsh A.** Male infertility. *BMJ* 2003;327:669–672, with permission.

Posttesticular Azoospermia

Posttesticular or obstructive etiologies are associated with normal gonadotropin and testosterone levels and are present in up to 40% of azoospermic men (58,127).

Ejaculatory dysfunction is associated with oligospermia or aspermia but rarely azoospermia (127). **[4] Obstructive causes include congenital absence or obstruction of the vas deferens or ejaculatory ducts, acquired obstruction of these ducts, or ductal dysfunction, including retrograde ejaculation** (58,127). In the congenital bilateral absence of the vas deferens (CBAVD) or hypogonadism, men with low-volume ejaculate should have a postejaculatory urinalysis to check for retrograde ejaculation, which is associated with diabetics and surgery to the bladder or prostate (58,128). Sperm may be isolated from the neutralized urine of men with retrograde ejaculation and processed for insemination or for ART (42). Transrectal ultrasound (US) may be of use to diagnose ejaculatory duct obstruction or unilateral vasal agenesis (to demonstrate contralateral atresia) but is generally not needed for CBAVD (127). **[3] Renal imaging is necessary when either unilateral or bilateral vasal absence is diagnosed as a result of the 10% to 25% incidence of renal agenesis** (127). Most men with CBAVD will also have seminal vesicle agenesis, so they will almost all have low semen volume, pH, and low fructose (127). Spermatogenesis can be expected to be normal in CBAVD, so diagnostic biopsy is generally not indicated (133). In some cases, testicular biopsy may be indicated to differentiate between testicular and posttesticular causes (127). At least two-thirds of men with CBAVD have mutations of the cystic fibrosis transmembrane conductance regulator *(CFTR)*gene (127). **[3] However, because many CFTR mutations are undetectable, CBAVD patients should be assumed to have a mutation and thus testing of the female partner's carrier status should be performed** (127).

Vasectomy Reversal and Treatment of Obstructive Azoospermia

Vasectomy can be reversed effectively using microsurgical vasovasostomy or vasoepididymostomy. The latter technique can be used for epidydimal obstructions (134). Patency and subsequent pregnancy rates after vasectomy reversal approach are 100% and 80% respectively (135). Pregnancy typically occurs within 24 months of reversal (135). **[4] Rates of patency and pregnancy vary inversely with the length of time from vasectomy, particularly for reversal procedures performed after ê15 years** (134,135). Although 60% of reversal patients develop antisperm antibodies, these do not appear to affect fecundability (135). Following surgery, periodic semen analyses can identify reobstruction, which can range from 3% to 21% depending on which segments were anastomosed (135). For those patients with azoospermia 6 months after reversal, the procedure is considered a failure and testicular sperm aspiration with ICSI could be considered (135). However, repeat vasovasostomy is associated with patency rates of 75% and pregnancy rates of 43% (135).

Surgical Sperm Recovery for Intracytoplasmic Sperm Injection

Among the many surgical methods for sperm recovery, the most widely described are

microsurgical epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), testicular sperm extraction (TESE), and percutaneous testicular sperm fine-needle aspiration (TESA, also called fine needle aspiration, or FNA) (133). Both MESA and TESE are open surgical procedures performed with an operating microscope and general or regional anesthesia, whereas the percutaneous procedures need only local anesthesia (133). The optimal method for surgical sperm recovery has not been determined and certainly varies based on patient history (133). **[9]** Hematoma risk appears to be low regardless of method (133). Testicular atrophy is a rare complication of TESE and TESA even when biopsies are obtained from multiple testicular sites (133).

With obstructive azoospermia, pregnancy rates using sperm retrieval and ICSI are 24% to 64% and outcomes using either frozen thawed or fresh sperm are comparable (133). Because MESA allows for diagnosis and possible reconstruction of ductal pathology and usually yields very large numbers of sperm, sperm cryopreservation and avoidance of repeat surgery may be possible (133). If repeat sperm retrievals are needed, the minimum interval between procedures is 3 to 6 months to allow for adequate healing (134). Surgical sperm retrieval in the setting of nonobstructive azoospermia is addressed in the "Testicular Azoospermia" section.

Female Age and Decreased Ovarian Reserve

Decreased Fecundability and Diminished Ovarian Reserve

Most women will experience an age-related decline in fecundability that is physiologic rather than pathologic. **[9]** **This decline begins in the early 30s and accelerates during the late 30s and early 40s, reflecting declines in oocyte quantity and quality, commonly referred to as ovarian reserve** (136). Attribution of age-related decline of fecundability to ovarian reserve is supported by research findings among women using a wide range of methods to conceive, including natural conception, donor sperm through IUI for male factor infertility, use of donor egg in IVF, and age-related declines in IVF success rates when using a woman's own eggs. Among populations that do not practice contraception, fertility peaks at age 20, declines somewhat at age 32, steeply declines after the age of 37, and is rare after age 45 (136). Female partners of azoospermic husbands who received donor IUI had cumulative pregnancy rates over 12 cycles of 74% (age <31 years), 62% (age 31 to 35), and 54% (age >35) (137). Chronologic aging of the endometrium does not seem to play an appreciable role in reduced fertility, given the excellent (~40% to 60%, depending on whether frozen oocytes were utilized) live birth rates using donor oocytes regardless of recipient age (138,139). These examples of reproductive aging relate to the decline of the stock of primordial follicles, established early in fetal life, to near zero at menopause (140). **[5]** "Diminished ovarian reserve" has been variously defined based on age, biochemical parameters, sonography,

poor follicular response to ovarian stimulation, and number of oocytes retrieved during IVF (141). The prevalence of diminished ovarian reserve diagnoses in a U.S. IVF cohort increased to 26% in 2011, but the diagnosis has not consistently predicted IVF or pregnancy outcomes (141). Etiologies attributed to prematurely diminished ovarian reserve include iatrogenic (i.e., cytotoxic agents, radiation, and surgical removal of reproductive tissues), pelvic endometriosis or adhesions, immunologic, and genetic factors. **[5]** Although premature ovarian failure/menopause prior to age 40 has been associated with an increased number of premutation-level trinucleotide repeat lengths in the ***FMR1*** gene, a similar increase has not been consistently confirmed in premenopausal diminished ovarian reserve women (142,143).

Spontaneous Pregnancy Loss

[5] Reproductive aging is associated with abnormalities in the oocyte meiotic spindles that lead to chromosome alignment errors and increase rates of conceptus aneuploidies, particularly trisomies (136). This serves to increase the risk for spontaneous pregnancy loss and thereby decrease live birth rates in older women (136,144). A large study based on the Danish national registry estimated the rates of clinically recognized spontaneous pregnancy loss for various age groups to be 13.3% (12 to 19 years), 11.1% (20 to 24 years), 11.9% (25 to 29 years), 15.0% (30 to 34 years), 24.6% (35 to 39 years), 51.0% (40 to 44 years), and 93.4% (>45 years) (145). Using sensitive hCG assays in women during their reproductive years, 22% of all pregnancies were found to be lost before they could be clinically diagnosed (146).

Ovarian Reserve

[1] Ovarian reserve refers to the size of the nongrowing, or resting, primordial follicle population in the ovaries. This ovarian reserve, in turn, presumably determines the number of growing follicles and the "quality" or reproductive potential of their oocytes (144). Although ovarian reserve and fecundability decrease with aging, they may not be consistently reflected by a woman's chronologic age because ovarian reserve does not decline at the same pace at a given age for all women. The prognostic value of anti-mullerian hormone (AMH) levels and antral follicle count (AFC) among IVF patients, independent of age, has established them as standard ovarian reserve tests (147–150).

Serum Anti-Mullerian Hormone

AMH is produced by the granulosa cells of preantral and small antral follicles (151,152). The serum level of AMH in women with normal cycles declines with age (151) and becomes undetectable after menopause (153). **[3] Unlike other serum markers, AMH can be measured at any time in the menstrual cycle** (153) **and levels are best interpreted using age-specific reference ranges** (154). Evolving assay platforms from Diagnostic Systems Laboratories to Beckman Coulter AMH Generation

II (154), modifications to the generation II assay protocol (155) and further use of automated platforms (156) limits interpretation of serial AMH results. In women engaging in procreative intercourse without a history of infertility, AMH level does not correlate with monthly fecundability regardless of age at least in the short term (6 to 12 months) (6,157). **[5]** Anti-mullerian hormone was found to be a good predictor of both excessive (>3.5 ng/mL) and poor (<1 ng/mL) IVF stimulation response and is strongly correlated to the AFC (152,153,158).

Antral Follicle Count

Using transvaginal US in the early follicular phase, all 2 to 10 mm ovarian follicles are counted and the total for both ovaries is called the basal AFC (140). The AFC correlates very well with chronologic age in normal fertile women and appears to reflect what remains of the primordial follicular pool (140). Decreases in AFC with age are gradual rather than sudden (159). **[3] A total AFC <4 is predictive of poor response and higher cancellation rates with IVF** (160,161).

With the use of machine learning, IVF success prediction models using AMH and/or AFC can be used together with age and other clinical factors such as BMI, reproductive history, and clinical infertility diagnoses, to provide highly accurate IVF live birth probabilities. **[3]** For example, the use of AMH and/or AFC reclassified over 60% of patients to have higher IVF live birth probabilities and over 10% of patients found to have lower probabilities compared to the age-control model (150). Some providers use other ovarian reserve tests in addition to AMH and AFC.

Serum Day 3 FSH

[5] As women age, FSH physiologically rises in the early follicular phase (cycle day 3), with levels of 5.74 IU/L at ages 35 to 39 and 14.34 IU/L at ages 45 to 59 (162). In a study of 181,536 IVF cycles in the United States, a basal FSH ≥12 constituted the 90th centile of the dataset and was selected as the threshold for elevated level (141). Higher levels are seen after unilateral oophorectomy (162). In women in their 40s, levels >20 IU/L are predictive of menopause (162). Because the incidence of abnormal values is lower in younger women, testing is typically performed for women aged 35 or older (162). In subfertile women with an FSH ≥8 IU/L, spontaneous pregnancy rates decrease by 7% per unit of FSH increase, with a 40% reduction at 15 IU/L and 58% at 20 IU/L (163). FSH levels vary widely by assay, laboratory, and population (164). Basal FSH ≥12 mIU/mL has a PPV of 30.9% when used alone and 48% when combined with female age ≥40 years for predicting cycle cancellation for poor response or fewer than four oocytes obtained at retrieval, such that IVF therapy should not necessarily be withheld from patients diagnosed with diminished ovarian reserve (141). Compared to women with normal levels, elevated basal serum (>10 mIU/mL) did not affect monthly fecundability in women aged 30 to 44 without a history of infertility attempting to conceive spontaneously, regardless of age (157).

Basal Estradiol Level

Basal day 3 FSH is often combined with estradiol (E2) testing. E2 levels on day 3 reflect follicular growth rather than the number of antral follicles (151). Elevations in FSH and decreases in inhibin B (see below) that accompany aging result in advanced follicular growth at the end of the preceding luteal phase. In response, early follicular E2 levels are typically higher in older women and in women with advanced reproductive aging (140).

Clomiphene Citrate Challenge Test

Clomiphene citrate is thought to have antiestrogenic effects on the hypothalamic–pituitary axis, resulting in a decrease in E2-mediated suppression of FSH production by the pituitary (165). **The clomiphene citrate challenge test (CCCT) involves the measurement of serum FSH and E2 on day 3 of the menstrual cycle, and again on day 10 after administration of clomiphene citrate (100 mg orally each day) from days 5 to 9** (165). **[3]** The CCCT has been reported to be more sensitive than basal FSH alone in identifying poor response to exogenous gonadotropins, but others report that the predictive values of the tests do not differ substantially (164,165).

Serum Inhibin B

Serum inhibin B is secreted by ovarian granulosa cells starting at the preantral follicle stage and therefore reflects the size of the growing follicular cohort (152). Reduced inhibin B levels are seen with aging even in normal fertile women (151). Inhibin B alone has poor predictive value for ovarian response (152,164) but improves the predictive value when added to the CCCT (165). Unlike basal testing, levels of inhibin B measured on the 5th day of ovarian stimulation were predictive of live birth following IVF/ICSI (166).

Options for Diminished Ovarian Reserve

[5] Treatments of diminished ovarian reserve include autologous IVF, use of donor oocytes or embryos, and adoption. Multiple stimulation protocols have been proposed for autologous IVF in poor responders including judicious use of gonadotropins with LH activity, estrogen pretreatment, use of GnRH antagonists during and prior to ovarian stimulation, microdose flare GnRH agonists, and selective estrogen receptor modulators such as clomiphene and letrozole along with gonadotropin injections (167,168). All have varying degrees of success, but counseling for diminished ovarian reserve patients in whom donor gametes are not of interest must include disclosure that per-cycle pregnancy rates are low, particularly in older women (169), such that multiple IVF cycles may be necessary and the prognosis may be poor or futile. However, isolated case reports of success do provide some hope in this regard (170,171), so it may be appropriate to offer autologous therapy to motivated, well-counseled patients.

Adjuncts During Autologous IVF

[5] Adjunctive autologous IVF therapies include androgens such as DHEA and testosterone, growth hormone, Coenzyme Q-10 (CoQ10), vitamin D, and omega-3 fatty acids. Pretreatment of women with diminished ovarian reserve for 2 to 5 months with dehydroepiandrosterone (DHEA; 25 mg three times daily) has been described to improve oocyte yield and pregnancy rates with IVF in case series (172–174). Putative mechanisms for this action include increasing serum concentrations of insulin-like growth factor 1 (IGF-1), which may potentiate gonadotropic effects on the follicle, and providing the ovary with additional prohormone for additional ovarian steroidogenesis (174). Pretreatment with DHEA led to higher ovarian volumes and AFCs in women with premature ovarian insufficiency (175), however some prospective cohort and randomized trials have not found statistically significant improvements for stimulation parameters or pregnancy rates in poor (176,177) or normal responders (178). A similar rationale has prompted the use of transdermal testosterone 10 to 12.5 mg for 14 to 28 days pretreatment or during stimulation with varied results in terms of number of oocytes retrieved and pregnancy rate (179,180). A Cochrane review of 17 randomized controlled trials found moderate quality evidence of live birth benefit for DHEA and testosterone in poor responders (181).

Growth hormone, by enhancing the granulosa cell response to gonadotropins through increases in local IGF-1 production, has been found to improve pregnancy and live birth rates for poor responders in some meta-analyses including the Cochrane database (182–184). Suggested dosing for growth hormone is 2.5 mg subcutaneously from day 6 of stimulation to day of trigger (182). The cost of growth hormone may be prohibitive for some patients; it is generally not covered by insurance for off-label use, and such use may be restricted by the 1990 Anabolic Steroids Control Act (185).

Nutritional supplementation may provide important adjunctive benefits. CoQ10 is found in higher concentrations in follicular fluid of oocytes that produce good quality embryos by morphokinetic assessment and pregnancies (186). Oocytes and early embryos obtain energy solely from CoQ10-mediated mitochondrial oxidative phosphorylation which allows proper oocyte maturation and fertilization, but aging diminishes CoQ10 production mitochondrial oxidative phosphorylation (187). These changes can be reversed by CoQ10 supplementation in mice and humans (188). Women randomized to 600 mg of daily CoQ10 for 2 months prior and during their IVF cycle had a nonstatistically significant increase in good quality embryos and embryo euploidy compared to the placebo group (187). Omega-3 fatty acids such as those found in fish oil extends reproductive lifespan in murine models, and this may be through effects on the pituitary. Normal-weight reproductively healthy women taking 4 g of eicosapentaenoic acid and docosahexaenoic acid daily for 4 weeks had reduced baseline and GnRH-stimulated serum FSH levels (189). Vitamin D deficiency has been inconsistently associated with AMH levels and AFC, so it is difficult to derive clinical recommendations for vitamin D supplementation solely for the indication of diminished

ovarian reserve (190). Supplementation for vitamin D deficient patients has produced inconsistent outcomes with respect to pregnancy rates in the context of IVF (191,192).

Ovulatory Factor

[6] Ovulatory factor accounts for 30% to 40% of all cases of female infertility (193). Initial diagnoses among women with ovulatory factor infertility may include anovulation (complete absence of ovulation) or oligo-ovulation (infrequent ovulation). **[1]** Menstrual history may be suggestive if oligomenorrhea, amenorrhea, polymenorrhea, or dysfunctional uterine bleeding are present (193). Menstrual dysfunction is present in 18% to 20% of the general population (194). **Figure 36-4** shows the fluctuations of E2, progesterone, FSH, and LH in a normal, 28-day ovulatory cycle. **The normal length of the menstrual cycle in reproductive-age women varies from 21 to 35 days, with a mean of 27 to 29 days** (195). Most of the variability in cycle length occurs during the follicular phase (196) but the luteal phase, often considered to be fixed at 14 days, can range from 7 to 19 days (197). **[1]** Even women with regular monthly menses may have anovulation (194), although the presence of moliminal symptoms such as premenstrual breast swelling, bloating, and mood changes are much more suggestive of ovulatory cycles (194). **[3]** In women with absent or infrequent ovulation, serum FSH, prolactin, and thyroid-stimulating hormone (TSH) testing should be performed (193).

Methods to Document Ovulation

The "Fertile Window"

[1] The fertile window is the 6-day interval ending on the day of ovulation, and does not extend past ovulation (44,196). Sperm can survive for up to 6 days in well-estrogenized cervical mucus, but the egg may be fertilizable for less than a day (196). Daily intercourse during this window may increase the probability of conception (44,196). **[1]** The average woman is fertile between days 10 and 17 of the menstrual cycle, but many women can conceive outside of this range (197). **[4]** Therefore, if timed intercourse (TI) is too cumbersome, intercourse two to three times weekly throughout the menstrual cycle will likely result in at least some of those occasions falling within the fertile window (198). Duration of abstinence prior to the fertile window has not been established, although one author suggests 5 days (196).

Basal Body Temperature

This inexpensive method involves daily recording of oral or rectal temperature using a basal body temperature (BBT) thermometer before the patient arises, eats, or drinks (199). The secretion of progesterone following ovulation causes a temperature increase of about 0.5° to 1°F over the baseline temperature of 97° to 98.8°F that is typically recorded during the follicular phase of the menstrual cycle (199). Ovulation is assumed

after 3 consecutive days of raised temperatures (199). Charting of daily BBTs produces a characteristic biphasic pattern in women with ovulatory cycles (199). [1] **Limitations to BBT include its inability to prospectively predict ovulation and its frequent false negative results** (200). Smoking and irregular sleep patterns can interfere with accurate BBT testing (199).

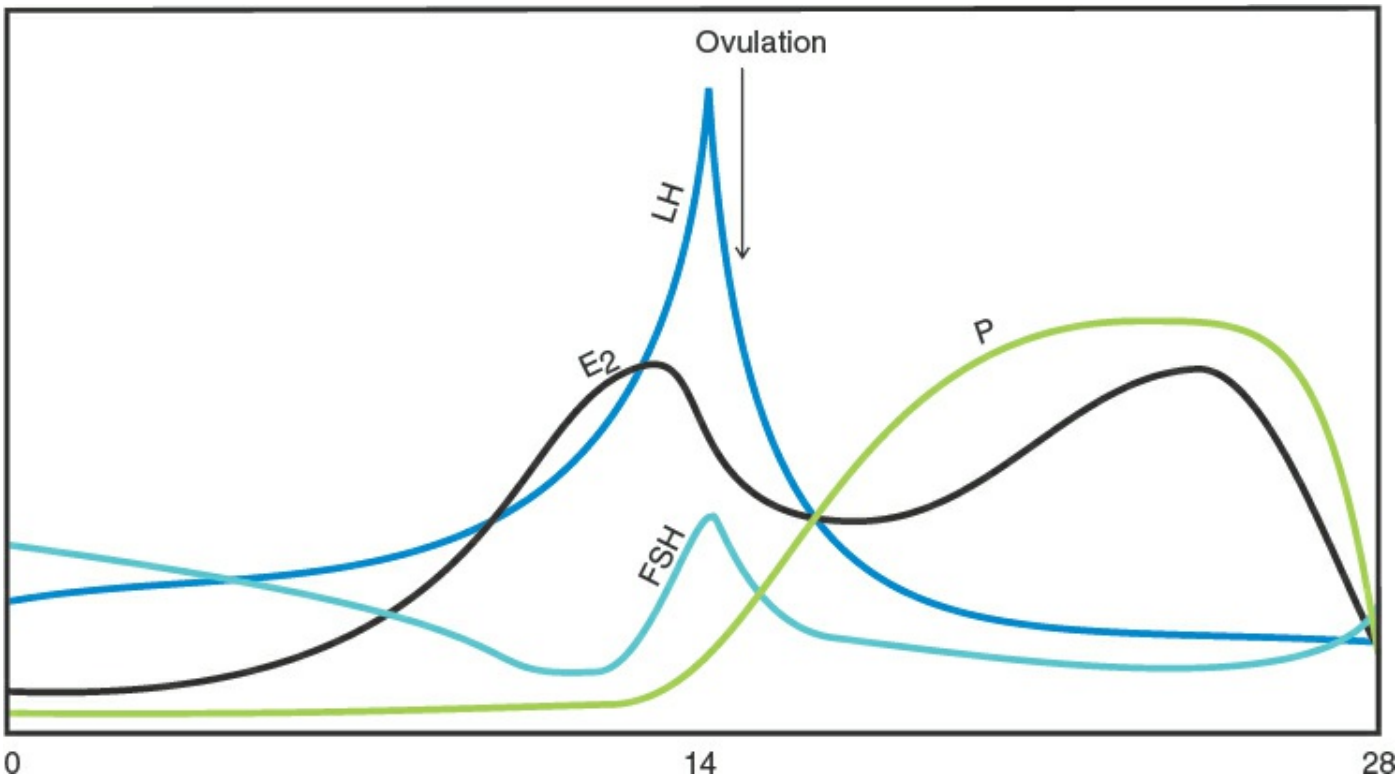


FIGURE 36-4 Relative hormonal fluctuations in a normal, ovulatory, 28-day menstrual cycle.

Cervical Mucus

During the fertile window, cervical secretions at the vaginal introitus are slippery and clear, while secretions at other times of the menstrual cycle are dry and sticky (44,199). [1] The volume of cervical mucus peaks 2 to 3 days prior to ovulation, thus identifying higher day-specific probabilities of conception (44).

Luteinizing Hormone Monitoring

At a mean time of 2 hours following the peak of the serum LH surge, urinary LH can be detected (201). Commercially available kits for documenting the LH surge are generally accurate, quick, convenient, and relatively inexpensive enzyme-linked immunosorbent assays (ELISA) that use 35 to 50 mIU/mL as their threshold for detection (201,202). **When the LH surge is detected, ovulation may occur within the next 48 hours** (44,201,202). The positive predictive and negative predictive values for these kits have been described to be 92% (201) and 95% (203), respectively. Because the duration of the surge may be <12 hours, twice daily testing may increase detection rates (202).

However, the 2 days of highest probability of conception are the day of and the day prior to the LH surge, so this may lead to abstaining from intercourse during a potentially fertile time (196). False positive rates occur in 7% of cycles (44,204), which may reflect urinary clearance of unsustained premature LH surges (200). **[1]** The tests cannot be used in patients with irregular cycles (196).

Midluteal Serum Progesterone

When used to document ovulation, serum progesterone measurement should coincide with peak progesterone secretion in the midluteal phase (typically on days 21 to 23 of an ideal 28-day cycle or 7 days following the LH surge) (193). **The lower limit of progesterone levels in the luteal phase varies among laboratories, but a level above 3 ng/mL (10 nmol/L) typically confirms ovulation** (193). **Interpretation of isolated luteal phase measurements of serum progesterone is complicated by the frequent pulses that characterize the secretion of this hormone** (193). **[1]** Although ovulatory levels are often considerably higher than 3 ng/mL, low midluteal serum levels of progesterone are not necessarily diagnostic of anovulation (193).

Ultrasound Monitoring

Ovulation is characterized by a decrease in the size of a monitored ovarian follicle and by the appearance of fluid in the cul-de-sac using transvaginal US (193). **[6]** **Follicles reach a preovulatory diameter of 17 to 19 mm in spontaneous cycles or 19 to 25 mm for clomiphene-induced cycles** (205,206). A combination of LH testing and US can be used, with LH kit testing starting when the US-measured follicle size reaches 14 mm (200). Ten percent of the cycles of normally fertile women may have a luteinized unruptured follicle, whereby progesterone is released and the luteal phase progresses normally without visible signs of follicle rupture when daily USs are performed from cycle days 10 to 20 (207). This incidence is increased to 25% in women with unexplained infertility (207). **Because of the inconvenience and expense of serial measurements, US monitoring should be reserved for patients who fail less expensive methods for detecting ovulation or for certain types of ovulation induction** (193).

Polycystic Ovarian Syndrome

[7] The most common cause of oligo-ovulation and anovulation—in the general population and among women presenting with infertility—is PCOS (208). The diagnosis of PCOS is determined by exclusion of other medical conditions such as pregnancy, hypothalamic–pituitary disorders, or other causes of hyperandrogenism, for example, androgen-secreting tumors or nonclassical congenital adrenal hyperplasia *and* the presence of two of the following conditions (209):

- **Oligo-ovulation or anovulation (manifested as oligomenorrhea or**

amenorrhea)

- **Hyperandrogenemia (elevated levels of circulating androgens) or hyperandrogenism (clinical manifestations of androgen excess)**
- **Polycystic ovaries detected by US**

Documentation of elevated serum LH: FSH ratios and hyperinsulinemia are not required for either diagnosis or treatment of PCOS (208,209). Patients with PCOS should be counseled and screened regarding potential metabolic disease and obstetric complications prior to fertility treatment (208).

Ovulation Induction in Women With Polycystic Ovarian Syndrome

Despite the use of similar medications, the indications and goals of ovulation induction should be distinguished from those of superovulation. The goal of ovulation induction refers to the therapeutic restoration of the release of one egg per cycle in a woman who either has not been ovulating regularly or has not been ovulating at all (205). **In contrast, the explicit goal of superovulation for women with unexplained infertility is to cause more than one egg to be ovulated, thereby increasing the probability of conception** (205). **Overall, 60% to 85% of women with PCOS will ovulate when treated with clomid or letrozole. [6] Of the women who ovulate, 15% to 20% will be pregnant per cycle and 50% will be pregnant by 6 months of treatment** (210–212).

Weight Loss

Obesity in PCOS patients is associated with poor infertility treatment outcomes (208,213–215), although the impact on pregnancy loss rates is less clear (208,213,216). **[7] Given that even a 5% weight loss may improve pregnancy rates, weight loss should be encouraged in all overweight and obese infertility patients** (208). In general, lifestyle modification is the first-line therapy, followed by pharmacologic treatment and weight-loss surgery (208). Lifestyle recommendations include a decrease in daily caloric consumption by 500 kcal and regular physical exercise, although the optimal regimen for the latter is unknown (208,217). Weight-loss interventions should be undertaken prior to attempting conception in patients with excess body weight (208).

Ovulation Induction Agent Pharmacology (Clomiphene Citrate [Clomid, Serophene], Letrozole [Femara], Anastrozole [Arimidex])

Clomiphene citrate is a weak synthetic estrogen that mimics the activity of an estrogen antagonist when given at typical pharmacologic doses for the induction of ovulation (205). It is cleared through the liver and excreted into the stool, with 85% clearance in 6 days (205). **[7] A functional hypothalamic–pituitary–ovarian axis is usually required for appropriate clomiphene citrate action** (205). More specifically, clomiphene citrate is thought to bind and block estrogen receptors in the hypothalamus

for prolonged periods, thereby decreasing the normal ovarian–hypothalamic estrogen feedback loop (205). This blockade increases GnRH pulsatility, leading to increased pituitary secretion of gonadotropins which promote ovarian follicular development (205). Letrozole and anastrozole are potent, reversible nonsteroidal aromatase inhibitors that have been used off-label for the treatment of patients with anovulatory infertility since 2001 (218). Letrozole is administered orally and cleared by the liver with a shorter half-life (48 hours) than clomiphene citrate (2 weeks). By reducing ovarian E2 secretion, letrozole disrupts E2's negative feedback effect on pituitary gonadotropin release. The consequent rise in FSH promotes ovarian follicular development.

Ovulation Induction Outcomes

Ovulation induction is first-line treatment for anovulatory infertility (219). Over the course of 6 months, clomiphene is associated with 49% ovulation, 23.9% pregnancy, and 22.5% live birth rates in women with anovulatory infertility (213). **[7]** **Clomiphene effectiveness is decreased by obesity, increased age, and hyperandrogenic states** (213,220,221). Side effects of clomiphene citrate include vasomotor flushes, mood swings, breast tenderness, pelvic discomfort, and nausea (205). In a minority of individuals, the antiestrogenic effects of clomiphene citrate at the level of the endometrium or the cervix may have adverse effects on fertility (205). In the presence of visual abnormalities, clomiphene citrate should be discontinued promptly (205). Multiple gestation rates with clomiphene citrate are approximately 8%, most of which are twins (205). Though historically clomiphene citrate has been the drug of choice for the treatment of women with PCOS-associated anovulation, current evidence suggests that letrozole results in higher ovulation and live birth rates compared with clomiphene, particularly for obese (BMI >30) women. In a multicenter trial of 750 women with PCOS-associated infertility randomizing to letrozole (2.5 mg) or clomiphene citrate (50 mg) from cycle day 3 to 7 for up to five cycles, the cumulative live birth rate was significantly higher in the letrozole arm (27.5% vs. 19.1%; RR 1.44, 95% CI 1.10–1.87) (222). Twin pregnancy rates were similar in the letrozole (3.4%) and clomiphene (7.4%) groups (222). A subsequent meta-analysis of six trials comparing clomiphene and letrozole for ovulation induction in anovulatory women with PCOS observed higher live birth rates with letrozole (OR 1.79; 95% CI 1.38–2.31) (223). Side effects with letrozole include dizziness and fatigue. **[7]** Although concerns have been raised regarding possible associations between fetal congenital anomalies and the use of aromatase inhibitors, no such increase was observed when letrozole was compared to clomiphene (224).

Ovulation Induction Dosing

Letrozole is supplied in 2.5 mg tablets, and the typical starting dose is 2.5 mg per day. Clomiphene citrate drug is supplied in 50 mg tablets; the usual starting dosage is 50

mg/day, but patients who are very sensitive may respond to 12.5 to 25 mg/day (205). Either agent is typically begun within the first 5 days after the onset of a spontaneous or progesterone-induced menses and is continued for 5 days (i.e., treatment on days 3 to 7 or 5 to 9 of the menstrual cycle) (205). Prior to initiating letrozole, patients should be counseled that ovulation induction represents an off-label use of the drug. Given the pregnancy category X designation of both clomiphene and letrozole, care should be taken to ensure that the patient is not pregnant prior to administration of these agents. If ovulation does not occur at the initial dosage of 2.5 mg letrozole or 50 mg *clomiphene citrate,* the dosage is increased in each subsequent cycle by 2.5 mg or 50 mg per day, respectively (205). **Seventy-four percent of women will ovulate with 100 mg/day** (205), **the maximum dose approved by the U.S. Food and Drug Administration** (209). However, some patients need higher doses, which have been safely given up to 250 mg/day (205). A stair-step method increases the dose within a single cycle without intervening menses if no follicular response is documented by US 4 to 5 days after the last dose (225). **[7]** Ovulation induction treatment should be limited to six ovulatory cycles or 12 total cycles (205,226,227).

Monitoring Ovulation Induction Therapy

If preovulation monitoring is not performed, patients should be instructed to have intercourse every 2 to 3 days following the last day of therapy and check serum progesterone weekly × 5 weeks before inducing a withdrawal bleed or increasing the dose of the ovulation induction agent (213). **Although no clear advantage has been demonstrated for any ovulation monitoring technique, regular contact should be maintained with patients to review response to therapy** (205). The urinary LH surge may be detected 5 to 12 days after treatment is completed (205). When clomiphene or letrozole is given on cycle days 5 to 9, the surge typically occurs on cycle days 16 to 17 and can be confirmed by midluteal serum progesterone testing 7 days later (205). With US monitoring, treatment should be withheld if large cysts are seen on baseline testing (205). Following ovulation induction use, follicles typically reach a preovulatory diameter of 19 to 25 mm by US, but may be as large as 30 mm (205,206). **[7]** A combination of LH testing and US can be used, with LH kits starting when the largest US-measured follicle reaches 14 mm in diameter (200).

Human Chorionic Gonadotropin

If a dominant follicle develops, but there is no spontaneous LH surge, hCG can be used to induce final follicular maturation (205), with ovulation occurring approximately 40 hours following administration (228). **Although administration of hCG at mid-cycle does not** appear to improve conception chances in most infertility patients using clomiphene citrate (104,229,230), **it may be useful for patients with known ovulatory dysfunction** (229) **or for IUI.** **[7]** The medication may be derived from urine (5,000 to

10,000 international units intramuscularly) or manufactured with recombinant technology (250 µg subcutaneously, equivalent to 5,000 to 6,000 IU urinary) (228).

Insulin Sensitizers

Insulin resistance contributes to the pathogenesis of PCOS. Metformin is an oral biguanide that is approved for the treatment of noninsulin-dependent diabetes and has been used in PCOS to increase the frequency of spontaneous ovulation (231). Metformin acts by several mechanisms, including inhibition of gluconeogenesis in the liver and increasing the uptake of glucose in the periphery (231). **Although the literature is conflicting, larger studies have suggested that the live birth rate with metformin alone (7.2%) is lower than that achieved with clomiphene, and overall the combination does not confer additional benefit over clomiphene alone** (213,232). Subgroups of patients including those who are obese may benefit from combination therapy, however (220,233). Though prepregnancy use of metformin does not appear to reduce miscarriage rate, there is insufficient evidence to recommend metformin use during pregnancy to reduce the risk of miscarriage (234). Risks of metformin include gastrointestinal upset and rare lactic acidosis, so it should be avoided in settings of hepatic/renal dysfunction and prior to surgery or use of contrast radiologic dye (231). Reported effective doses include 500 mg three times daily (231), 850 mg twice daily (231), and 1,000 mg twice daily (213). The medication is best tolerated when started at the lowest dose and increased gradually. Extended release formulations are associated with less gastrointestinal upset (213). **Because regular ovulation may not occur with metformin alone, patients may need medications to induce withdrawal bleeding to reduce the risk of continued anovulation and endometrial hyperplasia** (208). **[7] The use of thiazolidinediones, including the PPAR-f agonists, *rosiglitazone* and *pioglitazone*, for ovulation induction in PCOS patients has become less widespread as a result of their association with weight gain and, in the case of *rosiglitazone*, increased cardiovascular risk** (208).

Dexamethasone

Adjunctive oral dexamethasone may improve ovulation rates in patients resistant to clomiphene alone (219). These improvements have been reported even in the absence of adrenal hyperandrogenemia (235,236), so the mechanism of action remains unclear. Dose regimens have included 0.5 mg × 5 days starting on day of clomiphene (237), 0.5 mg × 6 weeks prior to starting clomiphene (238), and 2 mg × 10 days starting on day of clomiphene (235,236).

Oral Contraceptive Pretreatment

[7] Administration of oral contraceptives (OCs) × 2 months prior to beginning a cycle of clomiphene may improve ovulation and pregnancy rates in clomiphene-resistant patients, perhaps by improving a pre-existing hyperandrogenic environment (219,239).

Gonadotropin Therapy

Anovulatory PCOS patients who fail to ovulate or conceive with oral agents may be considered for ovulation induction with exogenous gonadotropin injections (240). For women with clomiphene-resistant PCOS, treatment with gonadotropins results in ovulation rates of 43% to 83% and pregnancy rates of 21% to 29% (241–243). Evening medication administration allows for morning monitoring and mid-day decision-making. Monitoring involves serum E2 levels and transvaginal US measurements of follicle development. Typical protocols monitor at baseline, 4 to 5 days after treatment initiation, and every 1 to 3 days until follicular maturation. Expected follicle growth is 1 to 2 mm daily after achieving 10 mm diameter (240). **Given the goal of promoting growth of a single mature follicle, low initial gonadotropin doses of 37.5 to 75 international units (IU)/day are generally recommended, with increases in doses by 50% of the previous dose after 7 days if no follicle >10 mm is observed** (208,240). Typical treatment duration is 7 to 12 days, but some patients require longer medication regimens for adequate stimulation (240). The maximum required gonadotropin dose seldom exceeds 225 IU per day (240). Ovulation triggering with hCG is recommended for gonadotropin cycles and is used when 1 to 2 follicles are 16 to 18 mm diameter and the E2 level per dominant follicle is 150 to 300 pg/mL (240). Ovulation is expected 24 to 48 hours after the hCG trigger. GnRH agonists such as leuprolide (500-µg subcutaneously) can be used to trigger ovulation to minimize risks associated with ovarian hyperstimulation syndrome, but require progesterone supplementation following administration (240). Intercourse should be recommended within 24 to 48 hours of ovulation triggering or IUI 24 to 36 hours after triggering (240). Testing for pregnancy is performed within 15 to 16 days after ovulation triggering and the cycle reviewed if pregnancy testing is negative. **[7]** Gonadotropin dosage in future cycles should be altered if the prior response was inadequate or excessive.

Gonadotropin Preparations

Several gonadotropin preparations are available. hMG is derived from human urine and includes approximately equivalent FSH and LH (derived from hCG) activity of 75 IU each (228). Formulations of hMG and FSH can be administered either subcutaneously or intramuscularly (228). FSH-only preparations may be derived either from urine or via recombinant methods, and are packaged either as lyophilized powder or premixed liquid cartridges/pens (228). Except for highly purified urinary FSH, which has an FSH activity of 82.5 IU per ampule, all other products contain 75 IU of gonadotropin when supplied in ampules (228). **All preparations of FSH are highly purified, with minimal to no batch to batch variation and a high level of safety regardless of the derived source** (228). Despite being differentially marketed as follitropin alpha and beta, these recombinant FSH preparations still contain combinations of 1 alpha and 1 beta glycoprotein chain. Rather, they differ in their posttranslational modifications and

processes for purification (228). [7] For PCOS patients, FSH alone appears to be sufficient in the gonadotropin preparation, although hMG is not harmful (Table 36-7) (240). Contraindications to gonadotropin therapy are listed in Table 36-8.

Gonadotropin Outcomes

Cumulative live birth rates are similar when gonadotropins are compared to clomiphene for ovulation induction when the goal is monofollicular ovulation and a maximum of six ovulatory cycles is similarly recommended (208). [7] **When compared to other anovulatory patients, PCOS patients using gonadotropins are at higher risk for multiple gestations (36%), ovarian hyperstimulation syndrome (4.6%), and cycle cancellation (10%) as a result of their high numbers of baseline antral follicles** (208,212,240). Cancellation should be strongly considered in patients who reach E2 levels of 1,000 to 2,500 pg/mL, have ≥3 follicles ≥16 mm, or ≥2 follicles ≥16 mm plus ≥2 follicles ≥14 mm (208). Sequential use of gonadotropins and either clomiphene or aromatase inhibitors has been associated with lower gonadotropin requirements and lower cancellation rates and treatment duration without compromising pregnancy rates. The addition of aromatase inhibitors is associated with a lower number of dominant follicles and lower maximum E2 levels (244–246).

[8] TABLE 36-7 Relative and Absolute Contraindications of Gonadotropins for the Treatment of Infertility in Women

Trade Name	Name of Compound	Source	Amount of FSH per Ampule	Amount of LH Activity per Ampule	Route of Administration
Menopur (Ferring Pharmaceuticals, Inc.)	Menotropin urinary hMG	Highly purified	75 IU	75 IU (from ~10 units HCG)	SC
Follistim (Merck)	Follitropin	Recombinant FSH beta	75 IU[a]	None	SC
Gonal-F (EMD Serono)	Follitropin	Recombinant FSH alpha	75 IU[a]	None	SC

[a]Also available in pen formulation.

FSH, follicle-stimulating hormone; LH, luteinizing hormone; hMG, human menopausal gonadotropin; IM, intramuscularly; SC, subcutaneously; N/A, not applicable.

Surgical Treatment

For clomiphene resistant patients, surgical ovarian drilling has been performed as an alternative to the outdated ovarian wedge resection to decrease ovarian androgen-producing tissue and to promote ovulation without the risk of multiple pregnancy seen with gonadotropin administration (208,247). Drilling 3 to 15 puncture sites per ovary is typically performed via laparoscopy using electrocautery/diathermy (248–251) or laser (252–254), although transvaginal US-guided (255,256) and vaginal hydrolaparoscopy (257) procedures have been reported. Successful drilling has been performed with the harmonic scalpel (252). Within 12 months after ovarian drilling, cumulative ovulation, clinical pregnancy, and live birth rates are 52%, 26% to 48%, and 13% to 32%, respectively (247). **These outcomes are similar to those using gonadotropins, but**

ovarian drilling carries a lower multiple gestation rate (247). Outcomes are not significantly different when diathermy versus laser are used for drilling (247), but they are compromised with patient age >35 years or basal FSH >10 mIU/mL (249). **[7]** The risks of ovarian drilling include surgical complications, adhesions, recurrence of anovulation, and a theoretical risk of ovarian failure (247,258).

[8] TABLE 36-8 Relative and Absolute Contraindications of Gonadotropins for the Treatment of Infertility in Women

1. Primary ovarian failure with elevated follicle-stimulating hormone levels
2. Uncontrolled thyroid and adrenal dysfunction
3. An organic intracranial lesion such as a pituitary tumor
4. Undiagnosed abnormal uterine bleeding
5. Ovarian cysts or enlargement not caused by polycystic ovary syndrome
6. Prior hypersensitivity to the particular gonadotropin
7. Sex hormone–dependent tumors of the reproductive tract and accessory organs
8. Pregnancy

Adapted from **Physicians' desk reference.** *Micromedex (R) Healthcare Series Vol. 107.* Thompson PRD and Micromedex Inc., 1974–2004.

Ovulation Induction for Other Anovulatory Disorders

Hyperprolactinemia

Hyperprolactinemia can be associated with oligomenorrhea or amenorrhea and should be evaluated with a pituitary MRI to exclude macroadenoma or other intracranial pathology (259). **[6] Dopamine agonists are first-line agents in symptomatic patients with hyperprolactinemia to restore ovulation** (259). Bromocriptine normalizes prolactin levels and induces ovulation in 80% to 90% of patients (260). It is taken two to three times daily, and most patients will respond to a total dose <7.5 mg daily (260). Side effects can be significant and include nausea, vomiting, postural hypotension, and headache (260). For this reason, bromocriptine is begun with a low dose of 1.25 mg (half of a 2.5-mg tablet) daily with food in evenings and prolactin level can be repeated 2 weeks later to adjust the dose as appropriate (261). The 1.25-mg dose may be adequate for those with prolactin level <50 ng/mL, while those <100 ng/mL may need 2.5 mg daily (261). In patients unable to tolerate oral administration, bromocriptine has been used vaginally 5 mg daily (262). Cabergoline has similarly high efficacy and the advantage of a 0.25 mg twice-weekly dosing schedule and fewer side effects (260). **[6]** In a review of over 700 cases of cabergoline use at the time of conception, the risk of miscarriage and malformations was no higher than the baseline rate in the general

population (263).

Hypogonadotropic Hypogonadism

[6] Anovulation in the presence of low serum LH, FSH, and E2 levels defines hypogonadotropic hypogonadism and reflects dysfunction within the hypothalamic–pituitary axis (259). Causes of hypogonadotropic hypogonadism, including craniopharyngiomas, pituitary adenomas, arteriovenous malformations, or other central space-occupying lesions, should be excluded using magnetic resonance imaging (259). Stress, extreme weight loss, anorexia, excessive exercise, and low BMI are all associated with functional hypothalamic suppression, so good nutrition and optimal body weight should be encouraged to restore ovulation (259,264). Leptin is a hormone produced by peripheral adipocytes that reflects energy stores and is deficient in women with diet or exercise-induced amenorrhea (265). Exogenous leptin has been reported to restore ovulation in these women (265,266). **Other conditions of hypothalamic dysfunction, such as congenital hypothalamic failure (Kallmann syndrome), can be treated using pulsatile GnRH therapy or gonadotropins. In these patients, FSH and LH should be administered** (259,267). Pulsatile GnRH agonist therapy (25 ng/kg every 60 to 90 minutes) simulates normal physiology and offers some advantages over gonadotropin injections, including fewer multiple gestations and less ovarian hyperstimulation syndrome (OHSS) while maintaining excellent pregnancy rates (267).

Hypothyroidism

The prevalence of hypothyroidism among mid-reproductive aged women is 2% to 4% and is mostly caused by autoimmune factors (268). Menstrual abnormalities, including those from anovulation, are present in 23% to 68% of overtly hypothyroid women and can be corrected with levothyroxine replacement (268). **The presence of antithyroid antibodies (even if euthyroid) are associated with increased rates spontaneous pregnancy loss and lower live birth rates** (269). However, among euthyroid Chinese women with elevated thyroid peroxidase antibodies, levothyroxine supplementation 25 to 50 mcg daily did not affect miscarriage or live birth rates with IVF in a 2017 randomized trial (270). **[2]** In any case, because even very mild or subclinical hypothyroidism can have adverse effects on fetal brain development and subsequent intelligence quotient, it is prudent to screen and treat women with thyroid hormone abnormalities before commencing infertility treatment (268).

Tubal Factor

Tubal factor accounts for 25% to 35% of infertility (12). Noninfectious causes for tubal factor include tubal endometriosis, salpingitis isthmica nodosa, tubal polyps, tubal spasm, and intratubal mucous debris (12). **[8] The incidence of tubal infertility has been reported to be 8%, 19.5%, and 40% after one, two, and three episodes of**

PID, respectively (271). Live birth rates are negatively affected by the severity of a single episode of PID (272). *C. trachomatis* and *Neisseria gonorrhoeae* are common pathogens associated with PID and infertility (273). *M. hominis* and *U. urealyticum* have been implicated in PID but their contribution to infertility is less clear (273). Many patients with documented tubal damage have no history of PID and are presumed to have had subclinical chlamydial infections (274,275).

Hysterosalpingography

Hysterosalpingography (HSG) is performed after menses but prior to ovulation between cycle days 7 and 12 to avoid potential pregnancy and take advantage of the thinner proliferative phase endometrium (276). The patient is typically premedicated 30 to 60 minutes prior to the procedure with ibuprofen or related medication (276). Lidocaine injected intracervically may provide further pain relief (277). With the patient in the dorsal lithotomy position, **either a metal cannula or a balloon catheter is inserted through the cervix and past the internal cervical os. [3] Contrast dye is injected under fluoroscopy to visualize the uterine cavity, fallopian tube architecture, and tubal patency** (276,278). Certain disease processes, such as salpingitis isthmica nodosa, have a characteristic appearance on HSG, with honeycombing as a result of contrast-filled diverticular projections (279). Compared to laparoscopy, HSG has a sensitivity and specificity of 65% and 83% for the diagnosis of tubal patency (280). By flushing inspissated mucus and debris, the HSG procedure may have therapeutic value, particularly with use of oil-based contrast. A large multicenter RCT that randomized 1,119 women to oil- or water-based contrast found a significantly higher live birth rate after use of oil-based contrast at HSG (38% vs. 28%; RR 1.38, 95% CI 1.17–1.64) (281).

Hysterosalpingography Risks

Although use of oil-based contrast is thought to carry potential risk of intravasation-associated oil embolism, this complication has not been observed in large prospective studies (282). Patients should be screened for and pretreated with glucocorticoids if iodine allergy is found (278). The risk of PID after HSG is 0.3% to 3.1% overall but is >10% in the setting of hydrosalpinges (283,284). **Therefore, HSG should be avoided in the setting of known hydrosalpinges and/or current or suspected PID** (276,284). The role of routine antibiotic prophylaxis for HSG is controversial (285), but in high-risk patients doxycycline could be considered. Recommended dosing is 100 mg twice daily, beginning the day before HSG and continuing for 3 to 5 days. If prophylaxis is not used and hydrosalpinges are noted on examination, postprocedure doxycycline treatment is recommended. Other rare complications of HSG include vascular intravasation, cervical laceration, uterine perforation, hemorrhage, vasovagal reactions, severe pain, and allergic response to the contrast dye (276).

Sonohysterography

Many infertility practices routinely use sonohysterography to assess tubal patency because it can be performed in a typical fertility clinic and involves no ionizing radiation exposure for patient or staff. **[3]** This advantage over HSG is at least partially offset by an inability to accurately define tubal architecture when performed using standard 2D approaches. The use of contrast media during sonohysterography is preferred to improve accuracy in documenting fallopian tubal patency, but these contrast agents are not available in the United States. As a substitute, the use of agitated saline (air-saline) during sonohysterography provides good negative predictive value when compared to HSG or laparoscopy (286). Large studies comparing the sensitivity and specificity of sonohysterography and HSG in the detection of tubal occlusion are not available.

Chlamydia Serology

Chlamydia antibody testing appears to have comparable sensitivity and specificity to HSG, but does not localize pathology and testing has no therapeutic benefit (279). It has been proposed that positive serologies in the setting of normal HSG should still prompt laparoscopy to rule out peritubal adhesions (275).

Laparoscopy

[3] Laparoscopy is considered the gold standard for diagnosing tubal and peritoneal disease (287). It allows visualization of all pelvic organs and permits detection and potential concurrent treatment of intramural and subserosal uterine fibroids, peritubal and periovarian adhesions, and endometriosis (287). Abnormal findings on HSG can be validated by direct visualization on laparoscopy using chromopertubation, which involves the transcervical installation of a dye such as indigo carmine to directly visualize tubal patency and fimbrial architecture (287). **[3] Even laparoscopy has been reported to have a false positive rate of 11% for proximal tubal occlusion when resected tubal segments are examined pathologically** (288).

Other Diagnostic Modalities

Falloposcopy is used in conjunction with hysteroscopy and allows direct fiberoptic visualization of tubal ostia and intratubal architecture for identification of tubal ostial spasm, abnormal tubal mucosal patterns, and even intraluminal debris causing tubal obstruction (288,289). Instrumentation availability and technical complications, including tubal perforation, limit its routine use (289).

Treatment of Tubal Factor Infertility

[8] As success rates for ART continue to improve, the indications for surgical approaches in the treatment of tubal infertility have become increasingly limited (290). Surgery can be effective in several situations and may be the optimal approach in some

patients.

Proximal Tubal Occlusion

Proximal tubal catheterization and cannulation performed either via HSG or hysteroscopy can restore tubal patency in up to 85% of obstructions, although the reocclusion rate approaches 30% (12). **The best candidates for proximal tubal catheterization/cannulation have suspected muscle spasm, stromal edema, amorphous debris, mucosal agglutination, or viscous secretions, while nonresponders include those with luminal fibrosis, failed tubal reanastomosis, fibroids, congenital atresia, or tuberculosis** (12). Occlusion caused by salpingitis isthmica nodosa, endometriosis, synechiae, salpingitis, and cornual polyps will only occasionally respond to catheterization/cannulation (12). Catheterization involves passage of a soft catheter into the tubal ostia, while cannulation passes a guidewire through the ostia and injects contrast media or colored dye (12,279). Tubal perforation, typically minor, occurs in 1.9% to 11% of cases (12,279,288). **Catheterization under fluoroscopy during HSG is referred to as selective salpingography** (291). **Visualization of patency with the hysteroscopic approach can be accomplished using laparoscopy** (12) **or US** (288). Ongoing pregnancy rates following proximal tubal catheterization/cannulation are 12% to 44% regardless of hysteroscopic or HSG approach (12). If occlusion persists or recurs, IVF is usually recommended. Microsurgical tubocornual anastomosis is an option with small studies reporting pregnancy rates of up to 68% (12). This procedure is typically performed via laparotomy and involves excision of the tubal isthmus, followed by reimplantation of the residual tube into a new opening made through the uterine cornua (279).

Distal Tubal Occlusion (Excluding Sterilization or Hydrosalpinx)

[8] Distal tubal disease and occlusion are causal in 85% of all tubal infertility and can be secondary to a variety of inflammatory conditions including infection, endometriosis, or prior abdominal or pelvic surgery (279,292). Patients younger than 35 years of age with mild distal tubal disease, normal tubal mucosa, and absent or minimal pelvic adhesions are the best candidates for corrective microsurgery (292). IVF should be considered for older patients or those with diminished ovarian reserve, combined proximal and distal tubal disease, severe pelvic adhesions, tubal damage that is not amenable to reconstruction, or additional infertility factors (292,293). Fimbrioplasty involves lysis of fimbrial adhesions or dilation of fimbrial phimosis, whereas salpingostomy (also known as salpingoneostomy) involves the creation of a new tubal opening in an occluded fallopian tube (292). In well-selected patients, pregnancy rates are reported to be 32% to 42.2%, 54.6% to 60%, 30% to 34.6%, and 55.9% for adhesiolysis, fimbrioplasty, salpingostomy, and nonsterilization-related anastomosis, respectively (279,292). **As a group, these procedures are associated**

with a 7.9% rate of subsequent ectopic pregnancy (292).

Sterilization Reversal

Twenty percent of women express regret following sterilization, and 1% to 5% of those will request reversal (294), **often as a result of a change in marital status** (293). The technique for sterilization reversal involves microsurgical dissection of the occluded ends of the fallopian tube followed by a layered reapposition of the proximal and distal tubal segments (293). Surgical approaches include minilaparotomy, laparoscopy (293), and robotic-assisted laparoscopy (294). Pregnancy rates following microsurgical tubal reanastomosis for sterilization reversal are 55% to 81%, with most pregnancies occurring within 18 months of surgery (293). Ectopic pregnancy rates following the procedure are generally <10% but may approach 18% (292,295). **The main predictors of success are age <35 years** (293,295), **isthmic–isthmic or ampulo-ampullar anastomosis** (295), **final anastomosed tubal length >4 cm** (293), **and less destructive sterilization methods such as rings or clips** (293,295). Unlike vasectomy reversal, the length of time between fallopian tubal sterilization and reversal does not seem to affect outcome (293). **[8]** IVF should be considered ***in lieu*** of sterilization reversal for older patients or those with diminished ovarian reserve, severe pelvic adhesions, additional infertility factors or prior unsuccessful reanastomosis (292,293).

Hydrosalpinx

Distal occlusion may lead to fluid buildup in the fallopian tube causing a hydrosalpinx (279). Hydrosalpinx fluid impedes embryo development and implantation (279). A meta-analysis of 14 studies and 1,004 patients with hydrosalpinges concluded that IVF pregnancy rates were significantly lower in the presence of hydrosalpinges (296). **[9] Salpingectomy for hydrosalpinx prior to IVF significantly improves both pregnancy and live birth rates when compared to IVF performed with the fallopian tubes *in situ*** (297,298), **although laparoscopic tubal occlusion appears to be a reasonable alternative** (299). There is significantly less outcome data on the use of transvaginal needle drainage and salpingostomy for treatment of hydrosalpinges prior to IVF (279).

Uterine Factors

[8] Pathologies within the uterine cavity are the sole cause of infertility in as many as 15% of couples seeking treatment (300) **and are diagnosed in >50% of infertile patients** (300). Therefore, the evaluation of the couple with infertility should consistently include an assessment of the endometrial cavity. Uterine cavity abnormalities include endometrial polyps, endometrial hyperplasia, submucous myomas, intrauterine synechiae, and congenital uterine anomalies (301).

Diagnostic Imaging for Uterine Pathology

Hysteroscopy

[3] Hysteroscopy is considered the gold standard for uterine cavity evaluation because it permits direct visualization (300–302). The procedure involves insertion of an endoscope through the cervical canal into the uterine cavity and instillation of distention media to facilitate visualization (300–302). **Diagnostic hysteroscopy may be performed in the office using a small-diameter hysteroscope and saline distention, often without need for anesthesia** (301). To optimize visualization of the endometrial cavity and avoid performing the procedure during early pregnancy, hysteroscopy is typically scheduled during the early- to mid-follicular phase of the cycle (300). Disadvantages to the procedure include poor visualization when uterine bleeding is present and the inability to evaluate structures outside the uterine cavity, including those in the myometrium and adnexa (300). Office hysteroscopy is reported to have 72% sensitivity for cavity abnormalities when compared to operative hysteroscopy using general anesthesia (300).

Hysterosalpingogram

Insofar as it allows assessment of tubal and uterine pathology, HSG ("Tubal Factors") is a reasonable initial imaging technique to use in the basic infertility evaluation (301). Hysterosalpingogram shows the general configuration of the uterine cavity and indicates endometrial lesions as filling defects or irregularities of the uterine **[3]** wall (301). **Excessive contrast may lead to false negative findings** (301), **which may account for the 50% sensitivity of HSG compared to hysteroscopy for endometrial polyps** (302). Inability to discriminate air bubbles, mucous, and debris from true intracavitary pathology may account for HSG's high false positive rate when compared with hysteroscopy (301,302). Other drawbacks include patient discomfort, use of iodinated contrast, and radiation exposure (301).

Transvaginal Ultrasound

Compared to hysteroscopy, standard 2D transvaginal US has a 75% PPV and 96.5% negative predictive value for intracavitary polyps but a 0% PPV for intrauterine adhesions (302). Similar to HSG, it has a sensitivity of 44% for uterine malformations (302).

Sonohysterography

Saline infusion sonography (SIS), synonymous with sonohysterography, involves the transcervical instillation of saline, often via a balloon catheter, during transvaginal US to distend the uterine cavity and delineate the endometrium (303). As with office hysteroscopy and HSG, SIS is performed during the follicular phase of the cycle and anesthesia is typically not required (303). Endometrial polyps appear as hyperechogenic pedunculated lesions, submucous fibroids have mixed echogenicity, and adhesions contain densely echogenic and cystic areas (303). **Compared to**

hysteroscopy, SIS has 100% sensitivity, specificity, positive and negative predictive values for uterine polyps (302). As a result of the smaller volume of distention media used, SIS is generally better-tolerated than HSG or hysteroscopy (300,303). Another advantage of SIS is the ability to evaluate the adnexa, and the myometrium for fibroids or adenomyosis. When combined with 3D technology, SIS is particularly good at assessing the overall uterine contour and delineating congenital anomalies such as septate uteri (303). Standard SIS has a somewhat lower sensitivity of 77.8% in detecting uterine congenital anomalies when compared to hysteroscopy, but this is higher than 2D transvaginal US or HSG (302). **[3]** Hysterosalpingogram and SIS perform similarly for intrauterine adhesions, each having approximately 50% PPV and >90% negative predictive value (302).

Magnetic Resonance Imaging (MRI)

Although transvaginal US, HSG, SIS, and hysteroscopy may suggest congenital uterine anomalies, pelvic MRI is considered the gold standard for imaging and is particularly useful for diagnosing rudimentary uterine horns (304). Pelvic MRI has the best sensitivity and specificity for intramural and submucous myomas compared to pathologic examination (305), and is especially useful for large or multiple fibroids (306). **[3]** MRI has been suggested as a tool to differentiate fibroids from adenomyosis, but routine use over US is not recommended (306,307).

Congenital Anomalies of the Uterus

Congenital uterine anomalies occur in 3% to 4% of women. This increases to 5% to 10% in women with early pregnancy loss and up to 25% in those with second and third trimester pregnancy losses (304). During female embryonic development the paired paramesonephric or mullerian ducts elongate toward each other and fuse in the midline. This is followed by resorption of the intervening septum to form the upper vagina, cervix, uterus, and fallopian tubes by week 20 of gestation (308). Failure of any of these steps leads to absent uterine development or development of unicornuate, bicornuate, arcuate, didelphys, or septate uteri (308). **Because of the proximity of the paramesonephric ducts to the urinary system, renal anomalies often coexist with mullerian anomalies. Appropriate urologic imaging should be performed whenever a mullerian anomaly is diagnosed** (304,308). **[2] Uterine anomalies are more closely associated with pregnancy wastage and poor obstetric outcomes than infertility, as the prevalence of congenital uterine defects is generally similar among fertile and infertile women** (304). The exception to this is mullerian agenesis. Patients with mullerian agenesis can have genetically related children only through use of IVF and a gestational carrier (304). The arcuate uterus is the mildest congenital uterine anomaly and typically live birth rates are comparable to those in women with normal uteri (304). **Surgical uterine repair to improve obstetric outcomes remains controversial for**

most anomalies. [8] However, rudimentary uterine horns require removal on diagnosis and hysteroscopic metroplasty of the septate uteri significantly reduces the rates of pregnancy loss, but not infertility (304,309). The number of reproductive-age patients presenting with *in utero* exposure to DES is declining rapidly and will continue to decline, as the substance was banned in 1971 (304). Women whose mothers were exposed to DES have higher rates of uterine malformations (e.g., T-shaped uterus) and associated obstetric complications (304).

Acquired Abnormalities of the Uterus

Leiomyomas

Leiomyomas, also called myomas or fibroids, are benign monoclonal uterine myometrial tumors that affect 25% to 45% of all reproductive-age women; this number is even higher in African Americans (310). The mechanisms by which fibroids cause infertility are unknown, but may involve altered uterine contractility, impaired gamete transport, or endometrial dysfunction (311). Among women with infertility and uterine leiomyomas, pregnancy rates are primarily affected by leiomyoma location (305,311). **[8] Subserosal fibroids do not appear to affect fertility or obstetric outcomes, while cavity-distorting intramural, noncavity-distorting >5 cm, and submucosal myomas are associated with lower implantation and live birth rates** (305,311,312).

Myomectomy

In women desiring fertility who require treatment for fibroids, myomectomy is the preferred approach and uterine artery embolization is relatively contraindicated (311). **Removal of cavity-distorting intramural and submucous myomas is generally recommended prior to proceeding with infertility treatment** (305,311). **[8] The utility of surgical removal of noncavity-distorting intramural fibroids is unknown** (305,311,312). Myomectomy can be performed hysteroscopically (306), via laparotomy (310,313), laparoscopically (alone [310,314], with robotic assistance [313,314]), or vaginally (315). Hysteroscopic removal is generally preferred for small submucous fibroids (306), while use of the other methods generally depends on patient preference, operator skill, or the presence of other pelvic pathologies (310,313,314). The utility of pretreatment with GnRH agonists prior to surgery is debatable. GnRH agonists may shrink larger fibroids (5 to 6 cm) enough to allow hysteroscopic resection (306) and may decrease the risk of intraoperative blood loss and postoperative anemia (310). **Fluid overload and uterine perforation are the most common complications of hysteroscopic myomectomy** (306), **while bleeding and adjacent organ injury are more often associated with alternative approaches** (310). Fibroids that are located low on the uterus and posteriorly are less amenable to laparoscopic resection (310). Transmyometrial approaches raise concern for uterine rupture during pregnancy, although this risk appears to be very low (310).

Endometrial Polyps

The incidence of asymptomatic endometrial polyps among women with infertility has been reported to range from 6% to 8% (316,317) but may be as high as 32% (318). Risk factors for polyp development include obesity, unopposed estrogen exposure, and polycystic ovary syndrome (319). The mechanisms by which endometrial polyps may impair fertility are incompletely described, but may relate to disordered endometrial receptivity (319). One report localized 32% of endometrial polyps in infertile women to the posterior uterine wall, indicated that 40.3% of patients had multiple polyps, and stated a 6.9% hyperplasia rate (320). Polypectomy is generally performed via curettage, blind avulsion, or hysteroscopic removal (318). **[8] Although the efficacy of polypectomy prior to infertility treatment has not been clearly established** (318), **a prospective randomized trial showed a 2.1-fold higher rate of pregnancy among women who underwent the procedure prior to IUI** (321). Higher pregnancy rates have been noted for polyps removed from the uterotubal junction when compared to those removed from other locations (320). Smaller nonrandomized studies provide conflicting data on the negative fertility effects of polyps <1.5 to 2 cm (320,322,323).

Intrauterine Synechiae or Asherman Syndrome

Severe trauma to the basalis layer of the endometrium with subsequent tissue bridge formation leads to intrauterine synechiae or Asherman syndrome (324). Symptoms of severe disease include amenorrhea, menstrual irregularities, spontaneous abortion, and recurrent pregnancy loss (324). **[1] The causes of intrauterine adhesions are often iatrogenic, with patients typically reporting intraoperative or postoperative complications of uterine evacuations for incomplete pregnancy loss, pregnancy termination, or postpartum hemorrhage** [1] (324). Myomectomy, hysterotomy, diagnostic curettage, cesarean section, tuberculosis, caustic abortifacients, and uterine packing are less common causes in Western countries (324). In developing countries, Asherman syndrome caused by genital tuberculosis is quite common (325). **Hysteroscopic resection of synechiae is the preferred treatment to restore fertility in women with Asherman syndrome. Patients with genital tuberculosis have a very poor prognosis** (324–326). Postoperative prevention of adhesion reformation disease may involve estrogen therapy alone × 1 month or in combination with intraoperative placement of an intrauterine device (such as a small Malecot catheter or pediatric Foley catheter) for 1 to 2 weeks (324,326). There is no standard regimen for estrogen therapy, but oral conjugated estrogens 2.5 mg daily overlapping with progestin (324) or E2 valerate 2-mg injections daily (326) have been suggested.

Luteal Phase Defect and Progesterone Supplementation

Mechanisms

The luteal phase is normally characterized by progesterone secretion by the corpus

luteum and appropriate endometrial secretory transformation that allow for embryonic implantation in the endometrium and support of early pregnancy for the first 7 to 8 weeks of gestation (327,328). **Luteal phase deficiency (LPD) is a condition in which endogenous progesterone is not sufficient to maintain a functional secretory endometrium during the implantation window** (329,330) **and is thought to account for 4% of infertility** (329). Proposed mechanisms for LPD include inadequate production of progesterone following ovulation (331), improper GnRH pulsatility causing insufficient gonadotropin production during the LH surge (329,330), and inadequate endometrial responsivity to progesterone (329). **Assisted reproductive technologies (ARTs) or gonadotropin ovulation induction medications may induce iatrogenic LPD via disruption of granulosa cells from follicular aspiration and suppression of endogenous LH secretion through a combination of supraphysiologic E2 levels and GnRH agonist/antagonist therapy** (328,331).

Diagnosis

Diagnostic criteria for LPD have been variably defined, but have included a low mid-luteal phase serum progesterone level, a BBT rise lasting less than 11 days, and a shortened luteal phase of less than 14 days (332). Unfortunately, the characteristic pulsatile secretion of progesterone during the luteal phase of the menstrual cycle combines with wide temporal variations (even within a 60- to 90-minute time span) to make interpretation of mid-luteal progesterone levels difficult (327). **Similar rates of shortened luteal phase are found in fertile and infertile women and there is significant variability of luteal phase length from cycle to cycle in an individual woman** (330). **The notion of a universal optimal duration of progesterone to achieve embryo implantation has been questioned** (333). **[1] There is significant interobserver variability in pathologic interpretation of endometrial biopsies from infertile women** (334) **and out-of-phase biopsy results poorly discriminate between fertile and infertile women** (335).

Treatment

[8] Progesterone therapy is considered standard practice during ART cycles, but is more controversial during non-ART fertility treatments (336,337). When used, progesterone supplementation can be administered via oral, vaginal, or intramuscular routes, with highest serum levels associated with daily 50- to 100-mg intramuscular progesterone (336,337). Most products are delivered in oil, and caution should be used to ascertain the presence of sesame or peanut allergies. Vaginal micronized progesterone, 200 to 600 mg daily in divided doses, is associated with the highest endometrial concentrations of progesterone. The side effects of this delivery route can include vaginal discharge and irritation. Other vaginal preparations include a once-daily gel and a 100-mg insert that is given two to three times daily. As a result of erratic

absorption and decreased bioavailability, oral micronized progesterone is less effective for progesterone supplementation (336). **There remains no consensus regarding the superiority of vaginal versus intramuscular administration.** When hCG is used for trigger, hCG levels peak at the time of egg retrieval, followed by a rise in serum progesterone levels that peak 5 days postretrieval and then decline (336). There are no differences in pregnancy or live birth rates when progesterone is initiated on the same day following retrieval versus 1 day after retrieval (338). A systematic 2015 review indicated lower pregnancy rates when progesterone support was administered prior to hCG-triggered egg retrieval or delayed until 6 days postretrieval, and suggested an initiation window for intramuscular progesterone of postegg retrieval day 0 to day 3 postretrieval (336). This initiation window is consistent with descriptions of luteal phase support during GnRH-agonist–triggered cycles (339). Because of the more rapid endometrial advancement compared to intramuscular route, delayed vaginal progesterone administration until 48 hours postretrieval has been advocated, but better-quality randomized trials are needed before drawing definitive conclusions (336). **[9]** Though the optimum duration of supplementation has not been determined, progesterone is typically continued until 8 to 10 weeks of gestation (336,337). Intravaginal luteal phase supplemental progesterone may increase pregnancy rates in women with PCOS treated with letrozole (340). **[8]** A 2017 systematic review and meta-analysis indicated a benefit for unexplained infertility using primarily vaginal progesterone initiated 0 to 2 days post-IUI in cycles using clomiphene alone or with gonadotropins with 1 live birth for every 11 patients treated (337).

Pelvic Factor

Endometriosis

Endometriosis affects 6% to 10% reproductive age women (341) but is present in 25% to 50% women with unexplained infertility (287). **[8]** It is characterized by the presence of endometrial glands and stroma located outside of the uterine cavity and is found primarily on the peritoneum, ovaries, and rectovaginal septum (341). Fecundability rates in affected patients are estimated at 2% to 10% per month (342). Possible mechanisms for infertility among women with endometriosis include anatomic distortion from adhesions or fibrosis and the impact of chronic inflammation on gametes, embryos, tubal fimbria, and eutopic endometrium (341,342). Laparoscopic visualization and histologic confirmation of biopsied lesion(s) remains the gold standard for the diagnosis of endometriosis. **[8]** The disease is staged laparoscopically according to the Revised American Society for Reproductive Medicine's classification, with stage III to IV (moderate-severe) characterized by ovarian endometriomas, dense tubal or ovarian adhesions, and/or cul-de-sac obliteration (341). Vaginal US has excellent specificity for endometriomas and other deep disease (343). It is unclear whether the mere presence of

endometriosis negatively affects IVF outcomes. Endometriosis patients have similar rates of embryonic aneuploidy (344) and live birth with ARTs (345,346) as compared to unaffected patients. **[9]** However, more severe disease (stages III and IV) and previous endometriosis surgery are associated with fewer oocytes retrieved and reduced pregnancy/live birth rates (by 30% to 40%) compared to patients without endometriosis (345,346).

Endometriosis Infertility

Management

Hormonal suppression of endometriosis typically has minimal benefit for endometriosis-related infertility (341,347). For minimal to mild disease, laparoscopic ablation appears to significantly improve pregnancy rates when compared to diagnostic laparoscopy alone as evidenced by a large randomized trial reporting 31% (treated) versus 17% (untreated) pregnancy rates (348,349). A subsequent meta-analysis supported the effectiveness of laparoscopic treatment in stages I to II endometriosis-associated infertility (341,342,350,351). **[8]** **Number needed to treat analysis suggests that eight laparoscopies involving treatment of mild or minimal endometriosis would need to be performed for each pregnancy gained.** A Cochrane review found moderate evidence in favor of particularly excisional laparoscopic treatment of minimal-mild endometriosis for spontaneous pregnancy in the 9 to 12 months postoperatively (183,347). Although removal of endometriomas may be indicated prior to IVF, when they would interfere with oocyte retrieval (349), endometrioma resection during IVF/ICSI treatment is associated with decreased ovarian function in up to 13% of cases (352,353), reduced quantity of dominant follicles, and fewer retrieved oocytes compared to unoperated patients in a meta-analysis of 2,649 IVF cycles (354). Furthermore, 40% of endometriomas recur postoperatively (349). **[8]** Therefore, IVF is considered a reasonable first-line therapy for endometriosis-associated infertility because of the short time to pregnancy and avoidance of surgery (290). Sclerotherapy, whereby the endometrioma is drained via transvaginal puncture and a sclerotic agent such as ethanol is instilled into the cyst cavity, was associated with higher numbers of retrieved oocytes and similar pregnancy rates as compared to laparoscopic management, in a meta-analysis of 18 studies, and may be an alternative to surgery (345).

Adhesions

Adhesions may result from sharp, mechanical, or thermal injury, infection, radiation, ischemia, desiccation, abrasion, or foreign body reaction (355). Adhesiolysis improves pregnancy rates by 12% at 1 year and by 29% at 2 years in infertile women with adnexal adhesions (355). Use of adhesion barriers reduces adhesion formation following laparoscopy and laparotomy, but there is no consistent evidence for

improvement in pregnancy rates (355,356).

Unexplained Infertility

Thirty percent of couples are diagnosed with unexplained infertility, in which the basic infertility evaluation reveals normal semen parameters, evidence of ovulation, patent fallopian tubes, and no other obvious cause of infertility (357). **Patients with unexplained infertility may feel reassured that even after 12 months of attempting, 20% will conceive in the following 12 months and over 50% in the following 36 months** (4). In couples with good prognostic factors of female age <30, <24 months of infertility, and a previous pregnancy in the same partnership (4), unexplained infertility may merely reflect the lower extreme of normal fertility (357). It is likely that technology is limited in terms of diagnosing all causes for infertility (357). **[2]** The utility of evaluations other than basic testing in an infertile couple has yet to be proven (358).

Proposed Mechanisms for Unexplained Infertility

Luteinized Unruptured Follicle Syndrome

This condition involves luteinization of a follicle that has failed to rupture and release its oocyte, leading to a normal menstrual cycle but infertility (207). It is thought to occur in up to 25% of patients with unexplained infertility, more than twice the incidence in fertile women (207). The diagnosis may justify the use of IVF whereby follicles are aspirated and oocytes are retrieved and fertilized in vitro.

Immunologic Factors

The impact of the immune system on reproductive function is an area of intense study and debate. Among the potential immune causes of reproductive failure are imbalances in the T-lymphocyte population. By increasing the secretion of anti-inflammatory T_H2 cytokines and inhibiting the secretion of proinflammatory T_H1 cytokines, progesterone shifts the balance to T_H2 dominance to support embryo implantation and early pregnancy (359). The absence of a reliable screening test for T_H1:T_H2 balance has handicapped studies designed to influence the balance toward improved outcomes. Although serum antiphospholipid antibodies and antithyroid antibodies are more prevalent among patients with unexplained infertility than among fertile women (360), the presence of antiphospholipid antibodies has not been found to adversely affect IVF outcomes, so screening is discouraged (361). Furthermore, a randomized double-blinded placebo controlled trial found no difference in *in vitro* fertilization-embryo transfer (IVF-ET) live birth rate with administration of heparin 5,000 units SC and aspirin 100 mg daily in patients with detectable antiphospholipid antibodies (362). The relationship of thyroid antibodies and reproductive outcomes are discussed in the

Ovulatory Factor section.

Unexplained infertility has been associated with antisperm antibodies (363), described further in the Male Factor section. Uterine natural killer cells (UNKs) account for over 70% of leukocytes in the secretory endometrium and appear to play a primary role in regulating early placentation (364). UNKs express specialized cell surface receptors known as killer cell immunoglobulin receptors (KIRs), encoded by highly polymorphic genes classically divided into inhibitory (KIR A) and activating (KIR B) haplotypes (365). The ligand for KIRs is the highly polymorphic HLA-C molecule expressed by extravillous trophoblast cells. In a study of 668 euploid single embryo transfers with annotation of maternal KIR and embryonic HLA-C haplotypes, maternal KIR haplotype was found to influence the risk of pregnancy loss and the HLA-C ligands modified the risk (366). High-risk combinations such as KIR A/homozygous C2 resulted in a 51% increase in the risk of pregnancy loss with euploid embryo transfer (366). **[2]** These studies support a potential role for immune factors contributing to unsuccessful implantation and pregnancy.

Infection

C. trachomatis and related clinical and subclinical infections have been discussed in the "Tubal Factor" section. No consistent associations have been reported between chlamydial species, *M. hominis* and unexplained infertility in men or women (275,367,368). *U. urealyticum* and *Mycoplasma genitalium* may be of more concern (369). Prophylactic doxycycline (100 mg twice daily for 4 weeks) given to infertile couples improved pregnancy rates only among couples in whom the male partner cleared ureaplasma infections (370). Antimicrobial prophylaxis is often given for ART, but it is not clear the extent to which clearance of these organisms improves pregnancy rates (369,371). Chronic endometritis is an inflammatory condition characterized by the presence of plasma cells in the endometrium found in 56.8% of patients with unexplained infertility, 57.6% of patients with repeat implantation failure, and 42.3% of women with endometriosis (372–374). A significantly higher rate of spontaneous pregnancies and live births were observed in patients successfully treated with antibiotics as compared to patients with persistent endometritis after antibiotics (374). **[8]** Although the uterine cavity has classically been designated to be sterile, different bacterial communities have been detected that appear to influence implantation following IVF embryo transfer (375).

Undiagnosed Pelvic Pathology

[8] Following a negative infertility workup, laparoscopy has been proposed to evaluate for peritubal adhesions that may distort tubo-ovarian relationships and endometriosis (376,377) but there is a lack of consensus as to the frequency of these abnormalities and many practitioners will forego laparoscopy ***in lieu*** of empiric fertility treatment in such patients. In young patients, laparoscopy may be cost-effective compared to fertility

therapy (378).

Occult Male or Oocyte Factors

[2] Occult male factor, such as impaired sperm DNA integrity (see Male Factor), despite normal semen analysis and oocyte factors, such as premature zona hardening, mitochondrial dysfunction, and/or aberrant spindle formation have been suggested as putative mechanisms for unexplained infertility (379).

Treatment of Unexplained Infertility

Historically, unexplained infertility was often treated with superovulation using clomiphene, letrozole, or gonadotropins in a stepwise approach, combined with IUI (e.g., CC/IUI, letrozole/IUI, and FSH/IUI), followed by ART. However, a randomized clinical trial (the FASTT trial) showed that for patients aged 21 to 39, CC/IUI and FSH/IUI were inferior compared to IVF based on their lower ongoing pregnancy rates (CC/IUI 7.6%, FSH/IUI 9.8%, and IVF 30.7%), a shorter time-to-pregnancy period and higher costs (380). These results are consistent to those reported by Guzick et al. in which the per-cycle pregnancy rates are 9% for gonadotropins/IUI, 4% for superovulation, or 5% for IUI alone (381). **Meta-analysis of 1,159 participants with unexplained infertility involving seven randomized controlled trials of CC alone or CC/IUI indicated no improvement in pregnancy or live birth rates when compared to no treatment or placebo** (227). Another review of over 3,000 patients showed that CC or CC/IUI or TI were similar to expectant management (382). Therefore, CC/IUI or FSH/IUI is not the treatment of choice for unexplained infertility (383,384). Similarly, in the Forty and Over Treatment Trial (FORT-T trial), patients aged 38 to 42 were found to have higher live birth rates from IVF than from CC/IUI or FSH/IUI (385). **[9]** **Despite research findings supporting the use of IVF as first-line treatment for unexplained infertility, superovulation/IUI treatments have continued to be widely used,** presumably because they are less expensive than IVF on a per-cycle basis and in some countries, superovulation/IUI may be much more accessible than IVF. (Risks with clomiphene, letrozole, and non-ART gonadotropins, and gonadotropin preparations, are discussed in the "Ovulatory Factor" section.)

ART options for unexplained infertility include conventional IVF, split IVF/ICSI, and ICSI, depending on whether the patient and her provider accept the risk of failed fertilization. The use of ICSI or splitting sibling oocytes between IVF and ICSI has been proposed as an approach to unexplained infertility patients to diagnose and treat underlying occult male or oocyte factors (379,386). **While ICSI is often suggested or recommended to patients with unexplained infertility to minimize the occurrence of failed fertilization caused by occult male or oocyte factors** (379,386), **IVF and ICSI have comparable pregnancy or live birth rates in patients with unexplained infertility** (386,387).

For young couples with unexplained infertility, especially those with a desire to have more than one child, diagnostic laparoscopy may be a good option for the evaluation and possible treatment of endometriosis (378,388).

Superovulation (Controlled Ovarian Hyperstimulation) with IUI

Unlike ovulation induction, in which the goal is to stimulate the release of a single oocyte in anovulatory women, the explicit goal of superovulation (for non-ART or ART purposes) is to cause more than one egg to be ovulated, thereby increasing the probability of conception in women with unexplained infertility (205). **[8] In most superovulation protocols, a baseline scan is performed on day 2 of the menstrual cycle to assess AFC and the presence or absence of ovarian cysts. Baseline estrogen and progesterone levels are typically obtained on this day** (389). **Starting daily doses in superovulation cycles are higher for clomiphene (100 mg × 5 days) and gonadotropins (150 to 300 IU daily) than those used for ovulation induction** (152,381,389). **Superovulation with clomiphene is otherwise conducted as described above for ovulation induction. When gonadotropins are used in normal responders with unexplained infertility, FSH doses of 225 IU and 300 IU lead to similar outcomes with IVF** (152). The maximal gonadotropin dosage is typically 450 IU per day because higher dosages do not increase ovarian response (389). **In most superovulation protocols, gonadotropins are started on day 2 or 3 of menses** (381,389,390). **The starting dose of gonadotropins is maintained each day until cycle day 6 or 7 (stimulation day 4 or 5), when the serum E2 level and transvaginal US are first measured to document ovarian response** (152,381,390). **Gonadotropin dosage is increased by 50 to 100 IU per day every 2 to 4 days until a response is evident** (391). **E2 levels typically double every 48 hours, with follicle growth of 1.7 mm daily after 10-mm diameter is reached** (392). **Triggering of ovulation typically occurs when at least 2 follicles have reached an average diameter of ê17 to 18 mm and the endometrial thickness is ê8 mm** (152,381,390,393–395). **For non-ART cycles,** patients should receive counseling about the risk of high-order multiple gestation and offered the option for **cancellation** for **E2 levels 1,000 to 2,500 pg/mL, for ê3 follicles ê16 mm, or for ê2 follicles ê16 mm plus ê2 follicles ê14 mm** (208). **In a randomized trial, previously untreated couples with unexplained infertility** had similar cumulative live birth rates using three cycles of gonadotropin/IUI compared to a single cycle of IVF (5).

Cost-Effectiveness

According to computerized decision-tree modeling, laparoscopy followed by expectant management for unexplained infertility may be cost-effective when compared to no intervention, non-ART treatment, or IVF (378). Given that 15 gonadotropin/IUI cycles are needed to produce one additional pregnancy when compared to ICI alone (357), IVF

seems a reasonable option. **[8]** In Massachusetts, where insurance companies are required to cover infertility treatment, the cost-effectiveness of IVF in the treatment of unexplained infertility was determined (380). Couples were randomized to accelerated treatment with three cycles of clomiphene citrate/IUI followed by up to six cycles of IVF if no pregnancy occurred (n = 256) versus conventional treatment with clomiphene/IUI × 3 cycles, then injectable gonadotropins/IUI × three cycles, then IVF × six cycles (n = 247) (380). Median time to pregnancy was 8 months in the accelerated versus 11 months in the conventional treatment groups. The authors used an average cost per cycle with clomiphene/IUI of $500, with gonadotropin/IUI of $2,500, and assuming IVF costs were <$17,749/cycle. They reported that the accelerated treatment protocol resulted in a savings of $2,624 per couple and lowered the per delivery charges by $9,856 compared to conventional treatment regimens (380). **The study concluded that couples with unexplained infertility who have not achieved pregnancy after three cycles of clomiphene/IUI should proceed directly to IVF** (380).

Assisted Reproductive Technologies (ART) Process

Process of ART

ARTs include IVF, ICSI, gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), cryopreserved embryo transfers, and the use of donor oocytes (396). Because of improved success rates associated with IVF embryo transfer, the performance of GIFT and ZIFT has declined in the United States (396), so this review will focus primarily on IVF and ICSI. **Both processes involve the following:**

- **Prevention of a premature LH surge**
- **Follicle growth**
- **Pretreatment**
- **Adjunctive medications**
- **Oocyte maturation/ovulation triggering**
- **Oocyte retrieval**
- **Luteal support**
- **Fertilization by IVF or ICSI**
- **In vitro embryo culture**
- **Transfer of fresh embryos**
- **Cryopreservation surplus embryos**
- **First trimester pregnancy monitoring**

Baseline Ovarian Cysts

[9] Prior to beginning therapy, a baseline US may be performed on cycle day 2 or 3

during menses (or following GnRH agonist suppression) to confirm an optimally thin (<4 mm) endometrium and quiescent ovaries. With clomiphene citrate cycles, the presence of ovarian cysts on a baseline scan was associated with decreased rates of ovulation but not of pregnancy, although cyst size was not predictive of response (397). Ovarian cysts on baseline evaluation have been associated with decreased pregnancy rates in ovulation induction cycles employing gonadotropins (398). In IVF patients, **functional (estrogen-producing) cysts are seen in 9.3% of women following GnRH agonist suppression** (399). Although nonfunctional ovarian cysts up to 5.3 cm did not affect IVF outcomes (400), functional ovarian cysts (mean diameter 2 cm and baseline E2 180 pg/mL) have been associated with increased gonadotropin requirements (dosing and duration), higher cancellation rates, fewer retrieved oocytes, poorer embryo quality, and lower pregnancy rates per cycle (9.6% vs. 29.7% in cyst-free cycles) (399). Ovarian cysts >20 mm that are seen on the baseline scan tend to resolve spontaneously within 1 to 2 months and OC administration does not appear to hasten their resolution (401). However, OC or progesterone/progestin pretreatment prior to GnRH agonist cycles is associated with decreased risk of cyst formation (402,403). Functional cyst aspiration prior to gonadotropin stimulation, which is commonly performed to expedite initiation of treatment, did not improve IVF outcomes in one large study (399). US-guided transvaginal cyst aspiration prior to IVF stimulation led to similar pregnancy outcomes as use of antagonist for cyst resolution though prestimulation antagonist was associated with slightly longer duration and dose of stimulation (404).

Prevention of Premature Luteinizing Hormone Surge

LH Surge and Premature Luteinization

[9] Without GnRH agonist or antagonist suppression **(Fig. 36-5)**, LH surges occur in IVF cycles as a result of high E2 levels in the early follicular phase. This, in turn, results in a lower oocyte yield and reduced pregnancy rates (405). **Spontaneous ovulation prior to oocyte retrieval is reported to occur in 16% of nonsuppressed IVF cycles** (406). The premature LH rise typically occurs after 5 to 7 days of stimulation (405). **[9] In contrast, premature luteinization is a somewhat misleading term that refers to a rise in serum progesterone (cutoffs vary from 0.8 to 2 ng/mL) observed on the day of hCG administration and occurs in the setting of low LH levels secondary to gonadotropin-suppressive medications** (407). The incidence of premature luteinization has been estimated at 6% to 7% when the progesterone cut-off level is set at >1.5 ng/mL (408), but it may be as high as 35% (407). Mechanisms underlying premature luteinization may include: incomplete pituitary desensitization, increased granulosa cell receptor sensitivity to LH secondary to aggressive COH or innately poor responders, and/or the presence of multiple follicles each producing a normal amount of progesterone consistent with the late follicular phase (407,408). Although the literature on this subject remains inconsistent, the negative effects of

premature luteinization (409), have been attributed to endometrial advancement rather than oocyte or embryo dysfunction (407,408). Methods proposed to address premature luteinization have included earlier triggering with hCG, less aggressive stimulation protocols, cryopreservation of embryos (freeze all) (408) and administration of the antiprogestin mifepristone at the time of hCG (410).

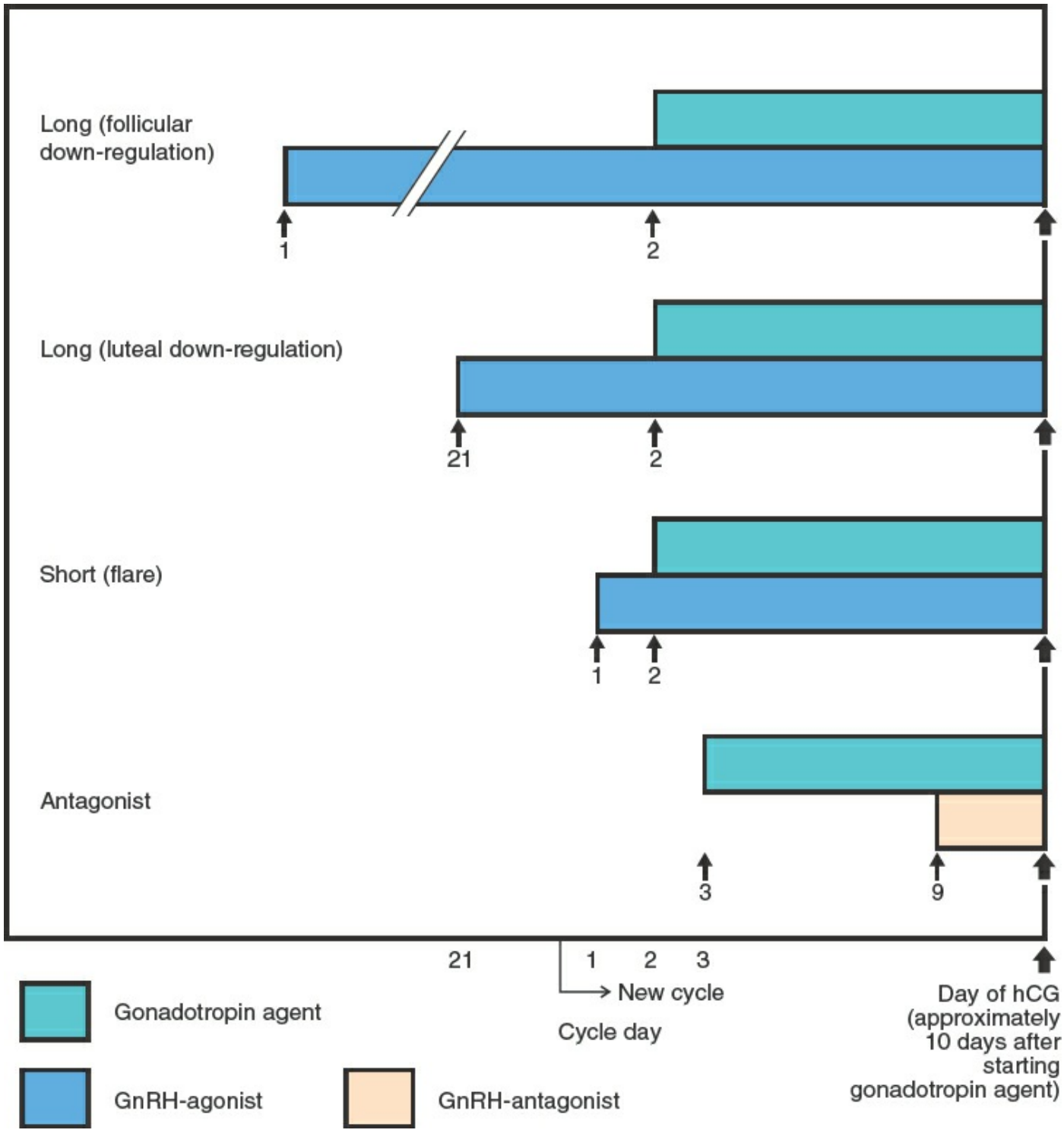


FIGURE 36-5 In vitro fertilization protocols using gonadotropin-releasing hormone (GnRH) agonist or antagonist with gonadotropins in controlled ovarian hyperstimulation. hCG, human chorionic gonadotropin.

GnRH Agonists

Native GnRH is rapidly degraded in the circulation (411). Commercial preparations of GnRH agonists consist of decapeptides similar to GnRH but for modification at two amino acid residues, which increase the half-life and receptor binding affinities (411). **Over the course of 10 to 14 days, agonists initially bind to and upregulate pituitary GnRH receptor activity, leading to a "flare response" of increased gonadotropin secretion. [9] This is followed by receptor desensitization (depleted gonadotropin pools along with rapid uncoupling of the GnRH receptor from its regulatory protein and loss of signal transduction) which suppresses circulating levels of pituitary gonadotropins and, with high doses and prolonged use, eventually decreases GnRH receptor numbers** (389,405,411–413). Therefore, prolonged use of GnRH agonists induces a menopause-like state characterized by low E2 levels and accompanied by common side effects such as hot flashes and moodiness (389). The flare effect may cause ovarian cyst formation as described in the "Unexplained Infertility" section of this chapter (389). GnRH agonists are commercially available for either depot or daily use and can be administered intranasally (buserelin and nafarelin) or by intramuscular or subcutaneous injection (leuprolide, triptorelin, or buserelin). Intranasal preparations have lower absorption rates when compared to injectable agonists and are associated with milder suppression (414). Typical starting daily doses of leuprolide are 1 mg, 0.5 mg, or 25 mcg (microdose) (412).

GnRH Agonist Protocols

Some of the more commonly used ART medications and protocols are summarized in Figure 36-5 and Table 36-7. [9] In the "long protocol," a GnRH agonist is started in the luteal phase (day 21) of the previous cycle. This diminishes the GnRH agonists flare effect and suppresses endogenous FSH and dominant follicle selection to promote synchronous follicular growth (405). **After 10 to 14 days of GnRH agonist administration, a pelvic US and E2 level are used to confirm suppression and gonadotropin stimulation begins. The GnRH agonist is continued (the dose may be halved or unchanged) throughout the cycle until the hCG trigger** (405,412).**Mean serum progesterone levels on the day of hCG administration using the long protocol are reportedly 0.84 ng/mL** (408). **[9] The long protocol provides for better oocyte yields and pregnancy rates in normal responders when compared with shorter protocols that use later administration or early cessation of agonists** (405). **Shorter protocols using lower GnRH agonist doses have been advocated for poor responders in whom excessive suppression may be undesirable, perhaps because of direct negative effects of the agonist on the ovary** (412). **Long protocols, particularly those using single-dose depot rather than daily GnRH agonist formulations** (415), **are associated with higher gonadotropin dose and**

duration, which themselves have been associated with lower pregnancy rates (416,417). Alternatively, GnRH microdose flare protocols have been developed that may improve oocyte yield in poor responders. Microdose flare regimens involve pretreatment with 14 to 21 days of combination OCs. Four days following the cessation of the OC pills, a microdose (25-mcg leuprolide) of agonist is added in the early follicular phase to take advantage of the agonist flare effect. Gonadotropin stimulation is initiated 1 to 2 days later while continuing the agonist (412).

GnRH Antagonists

GnRH antagonists (cetrorelix and ganirelix) were developed by modifying the GnRH decapeptide at six positions. They compete with endogenous GnRH for binding to pituitary GnRH receptors (411). **[9] Because they have no agonistic activity, GnRH antagonists lead to almost immediate suppression of FSH and LH and do not require the additional time for pituitary downregulation that characterizes the GnRH agonists** (411). With prolonged use, GnRH antagonists downregulate GnRH receptors (411). The only delivery method available for GnRH antagonist is subcutaneous injection, although orally active agents are in development (413). GnRH antagonists can be given as 0.25 mg daily doses or as a single 3-mg dose with no differences in outcomes (413). The time between daily injections should not exceed 30 hours (389). With single-dose regimens, avoidance of multiple injections is attractive but additional small doses starting 4 days after initial dose are required in 10% of cycles (413). **Use of GnRH antagonists in ART protocols is typically begun on days 4 to 7 of stimulation. [9] This timing balances the risk for premature LH surges with the need for initiation of endogenous FSH-mediated follicular recruitment and endogenous E2 production prior to administration** (389,405,413).

GnRH Antagonists Fixed Versus Flexible Protocols

Several GnRH antagonist protocols have been developed for use in ART cycles. **Fixed protocols involve starting the antagonist on days 4, 5, 6, or 7 of stimulation regardless of follicular response** (389,395,405,413). Flexible protocols were developed to reduce gonadotropin stimulation dose and duration (405). **In flexible protocols, varying thresholds have been described for antagonist initiation. [9] These include addition of the antagonist when the leading follicle has reached 12 to 16 mm in average diameter or when the E2 level has risen above 600 pg/mL** (390,394,405,412,413). When flexible protocols are used, pregnancy rates are similar when antagonist is initiated on days 4 or 5 of stimulation but drop significantly when antagonist is initiated after day 6. This suggests that rapid follicular growth may be more important in preventing LH surges and improving pregnancy rates than the day the antagonist is initiated (390). Fixed initiation of a GnRH antagonist on day 6 of

stimulation has been associated with higher pregnancy rates when compared to flexible protocols in one meta-analysis involving four randomized trials, however **the true superiority of one approach over the other remains to be defined** (390,412,413). **Diminished E2 levels can be expected following GnRH antagonist administration, but this does [9] not appear to affect follicular growth** (395). **Dose increases in exogenous FSH** (389,412) **or LH** (412,413) **do not appear to be necessary.**

GnRH Agonists Compared With Antagonists

Because there is no pituitary desensitization period required when GnRH antagonists are used in ART, cycles can begin more quickly than those that employ GnRH agonists (389). **Antagonists are associated with lower duration of stimulation, lower stimulation dose, and reduced rates of ovarian hyperstimulation syndrome** (418). **Antagonists are often used in the absence of pretreatment with OCPs. Initiation of antagonist cycles relies on the start of spontaneous menses often making scheduling easier for GnRH agonist cycles** (419). **Study and protocol heterogeneity make it difficult to detect consistent differences in IVF pregnancy outcomes after GnRH agonist and [9] antagonist cycles** (418,420). **A Cochrane review of 27 randomized controlled trials indicated that, while the number of good quality transferred embryos produced are similar, clinical pregnancy rates are higher by 4.7% in agonist compared to antagonist cycles. They concluded that for every 21 couples, 1 additional pregnancy would be gained by using a GnRH agonist protocol** (418). **The number of oocytes retrieved and the live birth rates also favored agonist usage** (418).

Follicular Growth and Stimulation Protocols

Follicular Recruitment

Primordial follicles are 0.03 mm in size and reach the point of ovulation only after 150 days (five menstrual cycles) during which they grow into preantral (primary and secondary follicles), early antral, small antral, and large antral follicles (421,422). The resting follicle pool includes primordial and preantral follicles (421). Resting follicles continuously enter either growth or apoptotic phases from birth until menopause, a process which is gonadotropin independent (421). After 90 days, activated resting follicles contain a fluid-filled antrum, marking their responsiveness to gonadotropins and are referred to as early antral follicles of 0.2- to 0.5-mm size (421,423). Over the next 70 days these early antral follicles grow into 2 mm small antral follicles, with this slow pace of growth mediated by AMH (421). Small antral follicles size 2 to 5 mm, which are recruitable and gonadotropin dependent, begin to slowly enlarge in the late luteal phase of the cycle preceding ovulation while concurrently LH-induced theca cell androgen production increases (421,424). In the early follicular phase during the menses of a natural cycle, the follicle that will ultimately become dominant has a

diameter of 5 to 8 mm (425). Growth of the follicle to 10 mm indicates selection, with the next largest follicle typically 8 mm (424,425). When the antral follicle grows beyond 10 mm, follicular AMH decreases and FSH induces the appearance of LH receptors on the granulosa cells (414). **[1]** At that point, somewhat contrary to the 2-cell-2-gonadotropin model, LH can exert FSH-like actions on the granulosa cell, including stimulation of aromatase with associated intrafollicular decreasing androgen and increasing E2 levels (414,421). **With complete absence of endogenous LH, such as that seen with hypothalamic hypogonadism, exogenous FSH produces fewer preovulatory follicles, inadequate E2, lower ovulation rates, and thinner endometrium when compared to ovaries stimulated with agonist downregulation and exogenous hMG (FSH and LH)** (414). **[6]** Therefore, in the setting of normal hypothalamic function, it seems likely that even with suppressive therapy, enough endogenous LH is present to synergize with exogenous FSH to provide adequate stimulation for recruitment (414).

Follicular Waves and Timing of Stimulation

The above referenced 2 to 5 mm small antral follicles develop synchronously, cyclically, in cohorts, or "waves," during each menstrual cycle (423). The emergence of a wave is detectable ultrasonographically when the lead follicle reaches 4 to 6 mm, which occurs in association with at least two follicles reaching ≥6 mm (423). The wave is considered major (ovulatory) when over the next ~2 days the lead follicle is ≥10 mm and exceeds other follicles by ≥2 mm, while in minor (anovulatory) waves the largest follicle is <10 mm and is similar size to other follicles (423,425,426). In major waves of unstimulated cycles, the nonovulated follicles become atretic, while in minor waves all follicles in the cohort become atretic (426). The majority of unstimulated human menstrual cycles have two waves of follicular development (423,425). In two-wave cycles, the first wave is minor and has been variously described to occur the day before ovulation (423,425) or the day after ovulation (426), with progesterone elevations facilitating follicle atresia (426). **[1]** The second wave (in two-wave cycles) is major and occurs 14 to 15 days after ovulation (or the day after menses onset) (423,425,426). Of the 32% of menstrual cycles with three waves, most of those involved two minor waves occurring the day of ovulation and 12 to 13 days after ovulation (or 1 day prior to menses onset) and one major wave occurring 17 days after ovulation (or 6 days after menses onset) (423,425). However, 19% of the three-wave cycles had three major waves occurring at each of the same time points (425). For simplification, day 1 of menses (if onset occurred in evening then day 1 is considered to be the next day) will likely correspond to the emergence of the ovulatory wave in women with two waves, while day 1 of menses will correspond to emergence of an anovulatory wave in women with three waves (423).

Synchronization of Follicle Growth

A small randomized trial in 2012 found women who began stimulation on cycle day 1 of spontaneous menses had two additional follicles ≥15 mm at time of trigger compared to the group starting stimulation on cycle day 4; nonsignificant trends favoring the day 1 start were observed for cycle cancellation rates, number of total and mature oocytes retrieved (423). **[9]** During the hormone-free interval on combination OC pills, the dominant follicles emerged at the 4 to 5 mm diameter ~3 to 5 days after pill cessation (427) providing support for the practice of starting gonadotropin stimulation at this time. **These findings are intriguing and suggest a path toward greater synchrony during stimulation.** Based upon findings in cows, one group hypothesized that in women, aspirating the dominant follicle at ~ menstrual cycle day 6 to 7 should induce emergence of a new wave 2 days later at which point gonadotropin stimulation can begin to precisely synchronize the follicle cohort (426). Pharmacologic induction of wave emergence has been proposed to include high-dose E2 (i.e., a single 8-mg E2V injection) followed immediately by 5 days of progesterone 100 mg daily given at any time of the cycle to induce luteolysis and suppress FSH to regress the dominant follicle (426). Upon cessation of the progesterone, a new wave should begin with serum FSH surge at which point gonadotropin stimulation can start; the authors suggest that OCs would not affect wave dynamics but a citation is not given (426).

Monitoring and Timing of Trigger

Monitoring during ART is helpful to detect the synchronous growth of dominant follicles, though practitioners vary in specific monitoring elements. **[9]** Survey respondents of consistently high-performing United States IVF clinics all used both E2 and US follicle size for stimulation monitoring, and 40% to 50% additionally measured progesterone and LH during the stimulation, with monitoring performed four to six times during the stimulation (428); however, a Cochrane study in 2014 found that US monitoring alone without serum testing may be reasonable for monitoring (429).

In one report, women who were predicted to be normal responders using 225 to 300 IU of FSH required 11 days of stimulation, had 11 to 13 follicles ≥15 mm on the day of hCG trigger, had a peak E2 level of approximately 2,100 pg/mL, and had 10 to 11 oocytes retrieved, of which 82% to 83% were mature (152). **[9]** The optimal level of E2 at the time of hCG administration is between 70 and 140 pg/mL per oocyte or follicle (393). Oocytes have been recovered from follicles with US mean diameters between 13 and 24 mm corresponding to fluid volumes of >1 mL and ≤7 mL, with optimal recovery rates for 3 mL (430). In a worldwide survey of IVF practices, of which 18% were in the United States, the majority administered trigger when 2 to 3 lead follicles (81% of respondents) reached an US mean diameter of 16 to 20 mm (92% of respondents) (431). High-performing United States IVF clinics administer trigger after a mean of 9 to 10 days of stimulation, when at least two lead follicles reach mean diameter ≥18 mm, with that study reporting a range of 17 mm to >20 mm (428). See the

"Superovulation" section of "Unexplained Infertility" for additional information on gonadotropin stimulation.

Follicle Stimulating Hormone Versus Human Menopausal Gonadotropin

Concern has been raised that exogenous LH might be needed to address the sudden decrease in endogenous LH that is associated with GnRH antagonist use and the possible excess endogenous LH suppression in long GnRH agonist protocols (414). In a 2010 survey of high-performing United States clinics none chose an FSH-only protocol for young normal responders (428). An analysis of >21,000 IVF/ICSI cycles that used antagonist suppression performed in 15 Latin American countries found hMG and LH protocols were associated with fewer oocytes retrieved, while pregnancy and live birth rates as compared to FSH-only protocols were not statistically significantly different (432). **[9]** This suggests that less expensive **FSH-only protocols may be reasonable in unselected women** (432). The authors did acknowledge, however, that the hMG and LH treated women were older and had higher rates of ovarian insufficiency than the FSH-only patients (432), so **individualizing protocols given extremes of age and ovarian response is appropriate.** In support of individualized protocols is a study showing hMG in women with elevated AMH >5.2 ng/mL is associated in agonist and antagonist protocols with fewer instances of retrieving >15 oocytes and higher fresh transfer live birth rates as compared to FSH only, although OHSS rates were similar (433). Higher androgen and lower progesterone levels on the day of hCG trigger are observed when hMG is used for stimulation rather than FSH alone, indicating a more favorable endocrine profile with hMG (433,434). The ratio of LH to FSH must be evaluated cumulatively over the entire stimulation rather than just at the beginning, as there appears to be a "sweet spot" of 0.3 to 0.6 for the lowest risk of serum progesterone premature elevation ≥1.5 ng/mL (434).

Stimulation Dose and Optimal Number of Retrieved Oocytes

Concerns have been raised about premature luteinization and lower pregnancy rates with higher-dose FSH stimulation protocols (408); each additional 100 IU of gonadotropins has been associated with a 2% lower rate of clinical pregnancy and live birth (416), and 300 units daily FSH did not increase number of retrieved oocytes or live birth rate compared to 225 units in a randomized controlled trial of "normal responders" (435). A possible explanation stems from comparative evaluations of unstimulated cycles in which the dominant follicle contains higher follicular E2, androgen, AMH, and LH concentrations compared to those measured in stimulated dominant follicles and may indicate follicle quality is inversely proportional to quantity (436,437). Therefore reduced-dose stimulation to obtain <8 or ≤4 oocytes using clomiphene citrate 50 to 100 mg for either 5 days or more extended durations through the day of trigger along with gonadotropin doses of 75 to 150 units ranging from a few days to longer duration have been described (437–439). A meta-analysis of >300

minimal stimulation cycles found that a median of five oocytes retrieved was optimal for pregnancy and live birth rates (417). These protocols are less expensive and multiple cycles may be noninferior in terms of live birth rates to higher-dose protocols (440).

Higher-stimulation doses are understood to be a function of patient characteristics (genetically determined ovarian sensitivity to gonadotropins or age-related aneuploidy) rather than exerting a direct adverse effect on IVF outcome and a more nuanced portrait of different ovarian reserve categories is needed in order to draw conclusions between dose and outcome (441). **[9] Other publications provide compelling support for protocols that regardless of responder status aim for increased retrieved oocytes in a single retrieval cycle and has led some to disavow previous rationales for minimal stimulation** (437,442). Sixty percent of high-performing United States IVF centers in 2010 reported that for a young normal responder with healthy BMI they would use a relatively high-starting gonadotropin dose of 300 units per day (428). There appears to be no benefit of exceeding a total daily gonadotropin dose of 450 IU in any patient (389). A previous trial indicating no benefit with higher gonadotropin doses was notable for nonsignificant trends to higher age, higher BMI, lower AMH, and lower antral count in the high FSH dose compared to the lower-dose group (435). A randomized trial of minimal stimulation versus conventional higher-dose stimulation in 564 first cycles with women age <39 found that while minimal stimulation was associated with 49% cumulative (over 6 months) live birth rates, the conventional stimulation live birth rates were significantly higher at 63% (439). In fresh oocyte donor cycles, recipient live birth rates were maximized when >10 oocytes were retrieved (443); each 3.4 mature (M2) oocytes were associated with 1 euploid embryo (444). Among oocyte donors, embryo aneuploidy rates increased with decreased ovarian sensitivity (i.e., gonadotropin doses per oocyte increased) but increased overall gonadotropin doses were not associated with aneuploidy (444). In autologous cycles 15 to 20 oocytes was optimal for fresh transfer live birth (445,446). **[9]** Higher numbers of oocytes 15 to 25 were associated with more usable blastocysts and >1 live birth from a single autologous IVF cycle and each additional oocyte was associated with an 8% increase in the chance for >1 live births (446). The likelihood of a single autologous retrieval leading to live birth over subsequent fresh and frozen/thaw transfers was highest with >15 retrieved oocytes in a randomized trial of >1,000 women allocated to either antagonist or long agonist suppression (447). A second retrospective paper reporting on >1,000 women who underwent a single retrieval cycle similarly found that >15 oocytes retrieved was associated with the highest cumulative live birth rates with single embryo transfer compared with fewer numbers of oocytes (448). In >400,000 autologous IVF cycles, increased number of oocytes >10 were associated with a 3% lower miscarriage rate compared to cycles with <4 oocytes even after adjusting for age (449). In poor responders of mean age 38 with AFC 5 to 6 and AMH

0.7 ng/mL, those randomized to high gonadotropin doses had nearly 10% lower cycle cancellation rates, 8% lower rates of no oocytes retrieved, two additional mature oocytes retrieved (4.8 vs. 2.7), more embryos available for transfer (2.7 vs. 1.8), and a nonsignificant trend to higher pregnancy rate per initiated cycle (438). Oocyte donors in whom ≥17 oocytes were obtained had 2 to 3 additional euploid embryos per retrieval cycle compared to cycles with <17 oocytes, and aneuploidy rate did not increase with gonadotropin dose (444). **Although minimal stimulation protocols by design are simpler with less up-front medication and freezing services which may contribute to cost, these should be weighed against the advantages of protocols that aim for safely maximizing per-cycle live birth efficiency** (442). Caution should be exercised when deciding whether to prolong stimulation duration to obtain additional embryos when trigger-day serum progesterone levels are >1.49 or >2 ng/mL as these thresholds correlate respectively with fewer morphologically top-quality blastocyst or day 3 embryos.

Pretreatment

[9] Combined OCs are commonly taken for 14 to 28 days prior to GnRH analogs to ease cycle scheduling (419), **synchronize follicular development** (450), **further prevent LH surges** (450), **reduce the incidence of ovarian cysts** (450), **and reduce cancellation rates caused by hyperstimulation** (451). Patients can begin OCs anytime between days 1 and 5 of menses (450). For antagonist cycles, COH begins 2 to 5 days after OCs (irrespective of menses) (419). During long GnRH agonist protocols, the agonist overlaps the final 5 days of OC use, followed by initiation of COH on the second or third day of withdrawal bleeding (402,451). Microdose flare protocols involve pretreatment with 14 to 21 days of OC, followed 4 days later by a microdose of agonist. COH typically starts 1 to 2 days later (412). **The progestins norethindrone acetate 10 mg orally daily, medroxyprogesterone acetate 10 mg orally daily, or a single intramuscular dose of progesterone (not specified) can be used in place of an OC in ART cycles. Recommended duration and the timing of treatment initiation vary widely. A duration of 5 to 20 days and initiation anytime between days 1 and 19 of menses have been reported** (450). Four mg of daily micronized 17β E2 or E2 valerate, has been used *in lieu* of OCs in ART cycles, with initiation between cycle days 15 and 21 and a duration of 10 to 15 days (450). OC pretreatment for antagonist cycles has been shown to increase the duration and number of medication doses during stimulation. There is "moderate quality" evidence from a recent Cochrane review for reduced ongoing pregnancy and live birth rates with a possible improvement in pregnancy loss rates (403). However, OC pretreatment during GnRH agonist cycles is associated with higher pregnancy rates than those in cycles without pretreatment (402). Progestin and E2 pretreatment do not conclusively affect live birth rates in either agonist or antagonist cycles (403). They may be useful to synchronize stimulated follicle

growth (see “Follicular Growth and Stimulation Protocols”).

Adjunctive Medications

Prenatal vitamins should be given to all infertility patients beginning at least 1 month prior to initiation of infertility treatment. Low-dose aspirin 80 to 100 mg daily commencing at downregulation and given for variable durations (up to 13 weeks gestation or if recurrent loss to 38 weeks) is commonly used during IVF regimens to improve ovarian stimulation response and endometrial implantation. In some recurrent loss patients low-dose aspirin is given in conjunction with heparin (452). A 2016 Cochrane review of “low to moderate quality” RCT evidence comprising >2,600 patients found no evidence of benefit for routine IVF use in terms of pregnancy, miscarriage, or live birth (453). Aspirin use confers a fourfold increased risk (50% vs. 13.6% in nonusers) of first trimester subchorionic hemorrhage in non-IVF and IVF pregnancies, which was not observed with heparin use (452). These findings prompted the authors to discontinue the use of aspirin in routine infertility and IVF patients, reserving it for antiphospholipid syndrome and recurrent loss patients. They will discontinue the aspirin if subchorionic bleeding is detected (452). Glucocorticoids given to women during the peri-implantation period may improve pregnancy rates in women undergoing IVF (rather than ICSI). A Cochrane study found this result of marginal statistical significance and did not observe improvement in terms of pregnancy or live birth rates for glucocorticoids given to an overall sample of 1,800 patients. More study is needed before recommendations to specific subgroups (i.e., autoantibodies, unexplained infertility, or recurrent implantation failure [RIF]) (454). In 2015 one group discontinued their routine use of oral doses of methylprednisolone (16 mg daily) and doxycycline (100 mg twice daily) for 4 days commencing either on the day of oocyte retrieval or 4 days prior to frozen ET, because they did not find that these medications statistically beneficial in terms of pregnancy, miscarriage, or live birth rates regardless of whether ICSI and assisted hatching were performed (455). Metformin may limit OHSS in PCOS patients (456). An updated Cochrane review found that metformin improved clinical pregnancy rates with IVF, but showed no conclusive benefit for live birth rates (457).

Physiology of Oocyte Maturation

Prior to maturation, oocytes are arrested in the prophase stage of meiosis I, also known as the germinal vesicle stage (458,459). Meiosis I oocytes must reach at least the early antral follicle stage to respond to FSH and be competent to resume meiosis (460). *In vivo*, LH receptors on the follicle are induced by FSH during later stages of follicular development (460). Therefore, only fully grown oocytes respond to the LH surge *in vivo* to begin the cytoplasmic and nuclear maturation that are required for developmental progression toward the metaphase stage of meiosis II. At this point, the developmentally competent oocyte will extrude the first polar body, the oocyte–cumulus complex will

detach from the ovarian wall (461), ovulation will occur, and fertilization is possible (458–460).

Trigger During ART Cycles

Because spontaneous LH surges occur inconsistently during non-ART gonadotropin cycles and are suppressed in ART cycles, hCG has been used to trigger ovulation. In combination with its long half-life, the homology between hCG and LH (identical α subunits) permits cross-reactivity with the LH receptor and induction of final oocyte maturation and ovulation (462). **[9]** hCG is derived from urine (5,000 to 10,000 IU intramuscularly) or through recombinant technology (250 µg subcutaneously, equivalent to 5,000 to 6,000 IU of intramuscular urinary product) (228). The half-life of hCG is 2.32 days, compared to 1 to 5 hours for LH (462). **Ovulation is typically triggered when at least 2 follicles are ê17 to 18 mm in average diameter (but <24 mm) and the endometrial thickness is ê8 mm** (152,381,390,393–395,463). Similar clinical outcomes have been noted when 5,000 IU or 10,000 IU of urine-derived hCG (464) and urinary or recombinant preparations (463,465) are used for triggering. If there is concern for OHSS, GnRH agonists can substitute for hCG to trigger ovulation in antagonist protocols.

Oocyte Retrieval

Oocyte retrieval is performed via transvaginal US–guided needle puncture into each follicle and aspiration of follicular fluid. Either general anesthesia or intravenous conscious sedation may be used (466). Prophylactic antibiotics such as ceftriaxone are recommended at the time of retrieval (467). The vaginal prep can be performed either with sterile saline alone or with povidone-iodine and vigorous saline flushing (468,469). **The highest oocyte yield is obtained when oocyte retrieval is performed 36 to 37 hours after the hCG injection** (463). Earlier retrieval (35 hours) is associated with a much lower oocyte yield, and later retrieval risks ovulation. Spontaneous follicular rupture appears to occur at a mean of 38.3 hours following hCG administration (463).

Luteal Support

The rationale and regimens for luteal phase support with progesterone are discussed in the "Uterine Factor" section. Luteal phase E2 supplementation is not necessary for fresh embryo transfers unless GnRH agonist trigger is utilized (339,470,471). In the case of GnRH agonist trigger, E2 0.1-mg patches starting 1-day postretrieval coadministered with intramuscular progesterone has been proposed to offset corpus luteum dysfunction (339). **[9]** Luteal support with low-dose hCG 1,000 to 1,500 units given at egg retrieval and again up to 5 days postretrieval has been used successfully (339).

Fertilization by IVF or ICSI

Following semen collection and sperm processing (described in the "Male Factor" section), sperm are incubated in media for 3 to 4 hours to promote sperm capacitation and the acrosome reaction. Before fertilization, retrieved oocytes are cultured in media. Conventional IVF involves insemination concentrations of 100,000 to 800,000 motile sperm/mL per oocyte with each oocyte in a small droplet of media under oil (11,472,473). **[9]** For every three cycles done for severe male factor, the use of ICSI prevents one case of fertilization failure when compared to conventional IVF (11). The indications for, procedure, and risks of ICSI are discussed under "Male Factor."

In Vitro Embryo Culture

Embryo Development

Initial embryo development is typically assessed 15 to 20 hours after insemination or ICSI, when fertilization is characterized by the presence of two pronuclei and the extrusion of the second polar body (11,473,474). **[9]** Embryos are examined again for cleavage after 24 to 30 hours of culture (11). The first embryo cleavage occurs approximately 21 hours after fertilization, and subsequent divisions occur every 12 to 15 hours up to the 8-cell stage on the 3rd day of embryo development (475). Compaction to form the 16-cell morula occurs on the 4th day of embryo development,

and differentiation of the inner cell mass and trophectoderm to form a blastocyst (containing a fluid-filled area called a blastocoel) is completed by the 5th to 6th days (476,477).

Culture Environment

Prior to compaction, while the embryo is under genetic control of the oocyte, it uses a pyruvate-based metabolism. It requires at least a few amino acids, and prefers a relatively oxygenated environment (though much lower than atmospheric oxygen) similar to that found in the fallopian tube (475,478). **After compaction, glucose and amino acid needs increase, the embryonic genome is activated, and metabolism requires a very low oxygen environment similar to that found in the uterus** (475,478). Supplementation of culture media with hyaluron and albumin is beneficial in the postcompaction period (475). Culture media systems are classified as either single or sequential. Single culture media was developed to provide all the necessary nutrients required (day 1 through day 5/6) in a single media formulation, reducing stress on the embryo by keeping a stable environment and allowing any embryo-generated autocrine/paracrine factors to remain (479). Single culture media uses stable dipeptide glutamine to avoid toxic ammonium buildup from the breakdown of amino acids (479). Sequential culture media systems were designed to mimic the changing metabolic and nutritional requirements of the developing embryo by culturing embryos in media designed for the cleavage-stage embryo (days 1 to 3) and on day 3 switching to culture media designed to support blastocyst development. **Although both culture systems have advantages, there is insufficient evidence to recommend one over the other, particularly as to whether any benefit of increased blastocyst development translates into improved pregnancy or live birth rates** (479).

Extended Culture to Blastocyst

Although precompaction human embryos can survive when placed in the uterus, the uterine cavity is a nonphysiologic location for them and there is greater uterine pulsatility during this period that may cause the embryos to be expelled (480). **Therefore, the blastocyst stage represents a more physiologic time for embryo transfer** (480). Because nearly 60% of morphologically normal cleavage embryos, but only 30% of blastocysts, are chromosomally abnormal, extended culture allows for better selection of embryos with improved quality (480,481). Notably, if a patient is a carrier of a balanced translocation, nearly 80% of cleavage embryos and 60% of blastocysts may be chromosomally abnormal (482). The euploidy rate of blastocysts is higher with completed development by postretrieval day 5 compared to day 6 or day 7.

Blastocyst Versus Cleavage Transfer Outcomes

Comparisons involving equal numbers of transferred embryos demonstrate that fresh blastocyst transfer is associated with up to 10% higher pregnancy rate and up

to 13% higher live birth rate than cleavage-stage transfer, which can be helpful information if considering elective single embryo transfer. Drawbacks to extended culture include the small possibility that no embryos will survive to fresh blastocyst transfer and a 23% reduction in women having additional embryos for cryopreservation. However, ovarian reserve with AMH >1 ng/mL strongly positively influences the presence of supernumerary blastocysts available for cryopreservation. Monozygotic twinning rates may be higher with blastocyst culture, although this has not been a consistent finding.

Criteria for Extended Culture

There are no established guidelines or criteria that determine when to utilize extended culture (483). Varying suggestions include: maternal age ≤42 with ≥ five 2-pronuclear (2PN) stage embryos on postretrieval day 1; maternal age of ≤40 and ≥ three good-quality day 3 embryos having 4 to 10 cells with <15% fragmentation; maternal age of ≤41 to 42 and ≥ four good-quality day 3 embryos having 4 to 10 cells with <15% fragmentation; and age <37 with ≥4 morphologically good embryos on day 3 or ≥4 embryos with 6 cells and <10% fragmentation (474,476,483).

Embryo Transfer

Embryo Morphology

[9] Embryo morphology guides the choice of embryo for transfer. Pronuclear embryos are assessed by their distribution and number of nucleoli, the position of the second polar body relative to the first, and cleavage rates (abnormal rates are too fast, too slow, or arrested) (477). Preferred cleavage-stage embryos have a normal developmental pattern characterized by early cleavage on day 1, 4 cells on day 2, and 8 cells on day 3. Embryo fragmentation should be ≤10%, the blastomere size should be regular and there should be no multinucleation (474). The Gardner and Schoolcraft system for scoring blastocysts uses a scale from 1 (worst) to 6 (best), with grades 1 to 3 indicating growth of the blastocele until it completely fills the embryo. Grade 4 blastocysts are expanded with a larger blastocele volume and a thinning zona pellucida. The trophectoderm in a grade 5 blastocyst is starting to hatch though the zona and the grade 6 blastocyst has completely escaped or hatched from the zona (473). The inner cell mass is graded A–C based on tightness and cellularity (A is best), and the trophectoderm is assessed from A–C based upon cohesiveness and cellularity (A is best) (473). Conventional embryo morphology grading remains the most common methodology in choosing embryos to transfer but it has limitations. In order to assess development and morphology of embryos, handling of the embryos and removing them from the controlled environment of the incubator is required. This exposure leads to differences in oxygen levels, temperature and pH which may have adverse effects on the development of the embryos (484). Understandably conventional morphology

assessment is limited to specific points in time to avoid repeated exposure to the atmospheric environment (484). Time-lapse imaging has been developed by installing a camera in the incubator allowing for continuous undisturbed evaluation of the embryos. In addition to the ability to assess morphology at multiple time points, morphokinetic monitoring, which assesses the rate at which embryos reach developmental events, can be accomplished with time-lapse imaging. Prior results of randomized studies comparing clinical outcomes of time-lapse monitoring versus conventional morphology have been mixed (484–486). Although there appears to be a potential benefit in the application of time-lapse imaging, more high-quality, well-designed randomized control trials need to be performed before any definitive conclusions can be drawn (484–486).

Number of Embryos to Transfer

Multiple gestation pregnancies increase complications for mothers and fetuses, so guidelines have been developed to minimize this adverse outcome (487). **[10] Single embryo transfer should be the standard if an embryo is euploid regardless of the age of the patient or stage of the embryo** (487). Single embryo transfer is recommended for patients <age 38 undergoing a fresh cycle, if they have had a prior live birth or there is an expectation that at least one high-quality embryo will be available for cryopreservation (487). Patients < age 38 undergoing frozen embryo transfer (FET) should have a single embryo transferred if vitrified blastocysts are available, if it is the patient's first FET, or if the patient had a previous live birth (487). In all other cases, transfer of embryos should be limited to two embryos in women under the age of 35. In older women, the maximum number of transferred cleavage-stage embryos should be: 3 in women aged 35 to 37, 4 in women aged 38 to 40, and 5 in women >40 years of age (487). Because of their high implantation potential, no more than three blastocysts should be transferred to any woman regardless of her age (487). **[10]** Limits on the number of embryos transferred when the embryos were created from donor oocytes should be based on the age of the donor, rather than the recipient (487).

Transfer Procedure

[9] The goal of transcervical embryo transfer is to atraumatically deliver the embryos to an optimal intrauterine location for implantation. Prior to performing the embryo transfer the cervix and vagina are cleansed using media or saline. The utility of removing remaining cervical mucus appears to be beneficial in improving live birth and clinical pregnancy rates (488). Embryo transfer can be accomplished using a number of transcervical techniques. Direct transfer is performed by loading the transfer catheter with embryo(s) and transferring immediately without a trial transfer. Trial transfer permits assessment of the cervical canal prior to performing the actual transfer. Trial transfer can be combined with an afterload technique if the trial transfer is difficult. The outer sheath of the trial transfer catheter is left in place while removing the inner catheter and a new inner transfer catheter loaded with the embryo(s) is threaded through

the trial catheter sheath into the uterus. Afterload technique can be planned and utilized intentionally without a trial transfer. Transabdominal US should be utilized to assess the endometrial cavity and other pelvic structures prior to and during the transfer to assure deposit of the embryo(s) in the upper or middle area of the uterine cavity but no closer than 1 cm from the fundus (488). **[9] Implantation is more likely when using a soft catheter and when fundal contact is avoided** (488). When the embryos are deposited, the entire catheter should be removed immediately as there does not appear to be any benefit in delaying catheter withdrawal (488). After the transfer, the catheter is checked for retained embryos. If present, retained embryos should be immediately retransferred as there is no detriment in pregnancy rates (488). When the embryo transfer is completed, the patient may leave immediately without a period of bed rest (488). Although intrauterine infections decrease pregnancy rates, the efficacy of antibiotic administration at the time of transfer is not supported (488).

Cryopreservation of Embryos

Embryo cryopreservation at the pronuclear, cleavage, and blastocyst stages has permitted multiple transfer cycles from a single oocyte retrieval. Because transfer of cryopreserved embryos is less expensive than a second fresh cycle, overall fertility treatment costs can be optimized. Techniques for embryo cryopreservation include slow freezing and rapid freezing or vitrification. Slow freezing protocols use lower concentrations of cryoprotectants but are more time-consuming when compared to vitrification, which uses high-concentration cryoprotectants for rapid cooling and is less expensive (489). Embryo thawing is accomplished by brief exposure to air and warm water followed by rehydration (490). Although pregnancy rates for frozen embryo transfer (FET) cycles using the two cryopreservation methods are similar, vitrification is associated with higher postthaw embryo survival (93% vs. 76% with slow freezing) (489). **[9] Favorable postthaw embryo survival rates after vitrification has contributed to the increasing success of FET, with live birth rates that are no different than fresh embryo transfer** (491). The success of FET has led to a growing trend toward freezing entire embryo cohorts for transfer at a later date. This strategy has the added advantage of greatly reducing the risk of ovarian hyperstimulation syndrome with reassuring perinatal and obstetric outcomes (492). Although a number of studies report a favorable live birth rate per transfer when using a freeze-all strategy compared with fresh transfer, cumulative birth rates have not been shown to be different (493). Particularly in PCOS patients, a freeze-all strategy with subsequent warmed embryo transfer improved live birth rates compared to fresh transfer, though an increase in preeclampsia and singleton infant birth weight were noted. Well-designed randomized controlled trials are needed before recommending routine use of a freeze-all strategy (493).

Endometrial Preparation for Frozen Embryo Transfer

When FET is combined with a recipient's natural cycle, no exogenous treatment is given and transfer is timed to spontaneous ovulation, performed 7 days following detection of the serum LH surge (333). [9] In medicated FET cycles, E2 supplementation begins in the early follicular phase and is continued for up to 13 to 15 days prior to initiating progesterone (490). Multiple E2 preparations have been described for use in FET cycles, but none have been proven superior (494). Transvaginal US is used to assess endometrial thickness during estrogen therapy and estrogen administration continues until an optimal thickness of ≥6.5 to 8 mm is reached (333,490). Progesterone supplementation begins 48 to 72 hours prior to transfer when cleavage-stage embryos are used and 6 to 7 days prior to transfer when blastocysts will be thawed (490,494) unless different progesterone timing is indicated (333). Several progesterone preparations have been described for use in FET cycles, but none have been proven superior ("Uterine Factor") (494). **Medicated FET cycles offer control and flexibility of transfer timing while maintaining low cancellation rates; however, adequate pituitary suppression may not always be achieved** (495). [9] **A GnRH agonist may be used in conjunction with medicated FET cycles as an added measure to prevent premature LH surges that may adversely affect endometrial maturation** (495). Coordination between the embryo and endometrium is critical to successful implantation (333). For some women, this remains elusive resulting in RIF defined as failure of at least three IVF cycles in which one or two morphologically high-grade embryos are transferred (333). **Prior studies of the transcriptome of the endometrium have shown the ability to accurately catalog the endometrium in all phases of the menstrual cycle and have challenged the assumption that the window in which the endometrium is receptive to embryo implantation is universal in all women** [9] (333). **The Endometrial Receptivity Array (ERA©, Igenomix) has been developed to address the optimal window of implantation in patients with RIF** through the use of a molecular diagnostic tool (333). While the initial reproductive outcomes applying the ERA© in patients with RIF have been promising, more studies incorporating a larger population are needed to validate these results (496).

First Trimester Pregnancy Monitoring

hCG including the a subunit can be detected in spent culture media from the 2PN-stage onward. The production of hCG by the blastocyst can be detected in the serum as early as 7 days posttransfer, and serum quantitative hCG levels may be obtained 11 to 14 days following embryo transfer (490,497). [9] **A serum threshold of 200 mIU/mL of hCG measured 12 days after transfer is 92% and 80% predictive of ongoing pregnancies for day 3 and day 5 embryos respectively, with levels normally rising approximately 40% per day** (497). **If normally rising hCG levels are detected, transvaginal US is planned at 6 to 7 weeks of gestation to determine the**

location of the pregnancy, the number of gestational sacs, and pregnancy viability (497). **[9] In those at high risk for ectopic pregnancy, early diagnosis using serial hCG and US examinations are important to reduce the risk of a ruptured ectopic pregnancy and to improve the success of medical management** (498). **These patients may benefit from transvaginal US at 5.5- to 6-weeks gestation as a gestational sac should become visible in a normal pregnancy during this time** (498). **When concern arises as to pregnancy viability, serial US findings of growth arrest with fetal pole length <20 mm at time of fetal demise correlate with aneuploidy of conceptus.**

[12] TABLE 36-9 Live Birth Rates from IVF Cycles Using Patient's Own Eggs and Uterus

		Age Years					
	All Ages	<35	35–37	38–40	41–42	>42	
Singleton	–	31.9%	24.7%	16.7%	8.7%	2.8%	
Twin		8.8%	6.0%	3.3%	1.2%	0.3%	
Higher-order multiple	–	0.2%	0.1%	0.1%	0.0%	0%	0
All live births	–	40.4–41.4%	30.3–31.5%	19.6–20.6%	9.4–10.4%	2.7–3.4%	n/a

IVF (in-vitro fertilization) 2015 outcomes (139).

ART SUCCESS RATES

IVF can be a highly effective treatment for many patients, but fewer than 200,000 IVF cycles are performed per year. The low IVF utilization rates are thought to be a result of the high cost of IVF and low retention rates among patients after an unsuccessful first IVF cycle. Providers have recommended counseling patients to consider IVF as a course of treatment, if needed, in order to maximize each patient's probability of having a live birth from IVF (499). A patient's decision to pursue medical treatment for infertility is often impacted by personal, financial, and medical factors. The provider's role is to establish the clinical diagnoses, discuss the risks and benefits of various treatment options, and recommend treatment. If the treatment options include COH and IVF (such as in unexplained infertility), providers would typically counsel the patients about the success rates of IUI (with clomid or gonadotropins) and IVF in the context of the patient's clinical data and diagnoses. Patients who are paying out-of-pocket for IVF treatment can benefit from a thorough discussion about the cost of each treatment option in the context of the per-cycle cost and the number of treatments that may be needed for each option. **[1]** Because the latter is directly related to the patient's per-cycle treatment success, understanding the relationship between the personalized IVF success probability and potential cost of IVF can help patients plan and maximize their chances of having a live birth (baby). Public reporting of each IVF center's success rates has been available for more than two decades. There have been significant efforts to

incorporate predictive modeling and technology to provide patient-centric probabilities of IVF success based on each patient's own health data.

National IVF Outcomes Registry

Since 1992, all clinics performing ART in the United States have been required to submit IVF cycle data and outcomes annually to the CDC via the National Assisted Reproductive Technology Surveillance System (NASS) which publishes reports of IVF outcomes analyses (500–504). The Society for Assisted Reproductive Technology (SART) via the Clinic Outcome Reporting System (CORS) publishes a summary of each registered ART clinic's IVF outcomes at https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2015 (139). For most purposes, ART cycles using ICSI and IVF are combined and analyzed as IVF cycles because their success rates are similar. IVF success rates, largely dependent on maternal age, are conventionally summarized from NASS/CDC and SART/CORS in an age-based format as shown in Table 36-9. SART asks that its reports not be used to compare IVF centers, presumably because success rates can be impacted by patient demographics and clinical attributes which vary among IVF centers. SART has been reporting, since 2014, the parameter of cumulative live birth rate, which reflects the chance of achieving a live birth after a fresh or FET within a year of cycle initiated for egg retrieval (139). **[12]** This allows tracking individual outcomes over time, accounting for fresh and frozen transfers stemming from the retrieval (139).

Prediction Models Personalize IVF Success

The ability to provide highly accurate and personalized probabilities of IVF success benefits the individual patient and gives providers insight about prognostic groups and profiles in their patient population. IVF success prediction models are not new, but the use of machine learning to develop and validate prediction models has dramatically improved model performance as defined by prediction accuracy, the ability to rank patients based on the difference in success probabilities using area-under-the-curve (AUC) in a receiver-operating curve analysis, and the percentage of patients who would receive a significantly different probability compared to conventional age-based prognostic classification (505).

Of the clinical data available prior to treatment, the patient's age is a key predictor of COH or IVF success and accounts for over 50% of relative importance of quantifiable predictors of IVF success (150,505,506). However, many other clinical predictors—ovarian reserve, BMI, reproductive history, clinical diagnoses, sperm parameters, total amount of gonadotropins used, oocyte parameters, and embryo scores—impact and predict treatment success. Fertility providers are interested in using data and technology to improve the patient's experience by offering personalized IVF success prognostics.

First, providers should define their goals. The intended goal of the prediction model determines the types of clinical predictors to be used by the model. For example, a prediction model that aims to inform a patient's decision to do her first IVF cycle should not use clinical predictors that can only be known after she starts IVF, such as the amount of gonadotropin used or oocyte and embryo parameters (150,506). A prediction model that aims to inform a patient's decision to do eSET should use clinical predictors —such as the number of blastocysts—that are available up to the day of embryo transfer (507).

When choosing a prediction model, it is important to consider whether the dataset used to develop and test the model reflects the patient population to which the model will be applied. Specifically, several researchers continue to raise the concern that a model developed and tested in one center may not have the same performance or accuracy when applied to another center, or rigorous steps may be required to test and recalibrate the model (508–511). This problem can be partially addressed by using a prediction model developed from data pooled from multiple centers or the national registry, though the applicability of the model to each individual center still needs to be tested (506,512–514). Alternatively, center-specific prediction models can be developed and tested based on each center's own data (150,505,507,515).

Cessation of Therapy

Patients must be accurately informed of estimated success rates and reasonable expectations for all therapeutic interventions (516). Patients with a very poor prognosis have a 2% to 5% chance of achieving a live birth with fertility therapy and those with a futile prognosis have a ≤1% chance (516). Refusing or limiting therapy may be justified if the risk of intervention outweighs the potential benefits (516).

Third Party Reproduction

When gametes and/or the ability to gestate a pregnancy are compromised through circumstances or disease, other reproductive options can be considered. **These include use of donor sperm ("Male Factor"), donor oocytes, donor embryos, a gestational carrier, or a combination of these approaches.** In contrast to donor gametes (sperm or oocytes), the decision to donate embryos is typically made after the embryos have been generated and there is a known surplus. A gestational carrier receives and gestates birth embryos created from the intended mother's oocytes. Patients who choose to utilize a gestational carrier may have irreparable uterine factor infertility or suffer from medical conditions that contraindicate pregnancy. In true surrogacy, the birth mother is also the genetic mother but not the mother who will raise the child. Legal and psychosocial counseling are suggested for all parties embarking on any form of third party reproduction.

Donor Oocyte

[9] Patients with premature ovarian insufficiency, poor oocyte quality, poor ovarian response to stimulation, or failed fertilization or implantation after multiple ART cycles may be candidates to receive donated oocytes. A female same-sex couple may choose to have one partner undergo IVF and place the resulting oocytes fertilized with donor sperm into the other partner (517). With carefully selected donors using nonfrozen oocytes, live birth rates per cycle of donor oocyte IVF are 50% to 60% or higher regardless of the recipient's age (138,139). Recipients must be aware that advanced recipient age is associated with higher risk for preeclampsia, diabetes, and cesarean section (518). Oocyte donors must endure all the interventions and risks of the ART process, except for embryo transfer and luteal support. Because of the intensity of therapy and the potential infectious disease and genetic risks for donor, recipient, and the resulting offspring, oocyte donors must be screened for infectious and heritable disorders similar to those performed for sperm donors ("Male Factor"), and undergo meticulous informed consent and a comprehensive psychosocial evaluation (519). Oocyte donors may be anonymous or known to the recipient (519). Oocyte recipients undergo endometrial preparation as described in the "ART Process" section, which may be synchronized with the donor for a fresh transfer **(Fig. 36-6)** or may be dissociated from the donor retrieval if using cryopreserved oocytes or embryos. Other topics, such as methods for donor recruitment and financial compensation for the donor are challenging issues (520).

Oocyte Cryopreservation

Historically, oocyte donation was restricted to the use of fresh oocytes, requiring coordination between the donor and recipient (519). **[9]** **With the continued evolution of cryopreservation technology, oocyte cryopreservation is a viable alternative and is no longer considered an experimental technique** (519). Oocyte cryopreservation techniques have resulted in excellent oocyte survival after vitrification and warming (519). Subsequent fertilization and pregnancy rates have been similar to patients undergoing IVF/ICSI with fresh oocytes (519), though live birth rates may be somewhat reduced (139). The utilization of cryopreserved oocytes has the potential to offer greater flexibility in pregnancy timing, more choices in the selection of a donor, and reduced cost (519). Multiple applications of this technology have been proposed to include fertility preservation in patients receiving gonadotoxic therapies, patients with genetic conditions, patients who are unable to cryopreserve embryos, and patients who want to electively defer childbearing (519). Oocytes can be cryopreserved when there is insufficient sperm for fertilization at the time of oocyte retrieval (519). Although preliminary data on perinatal outcomes are reassuring, more data are needed before routine oocyte cryopreservation and universal donor oocyte banking can be

recommended (519).

Complications of Assisted Reproductive Technology

Risks of ICSI

Risks of ICSI are detailed in "Male Factor."

Cycle Cancellation

Criteria for cycle cancellation vary; high-performing United States clinics reported a threshold of ≤3 follicles (up to <5 follicles) (428). **[9] Cycle cancellation in normal responders occurred in up to 6% of the cycles as a result of inadequate response and 1.5% of cycles for excessive response** (152), **and risk increases with older age and lower ovarian reserve** (416). In 0.2% to 7% of retrievals, no oocytes will be obtained (461). Two proposed explanations include human error during the administration of hCG and early oocyte atresia despite normal follicular response (461).

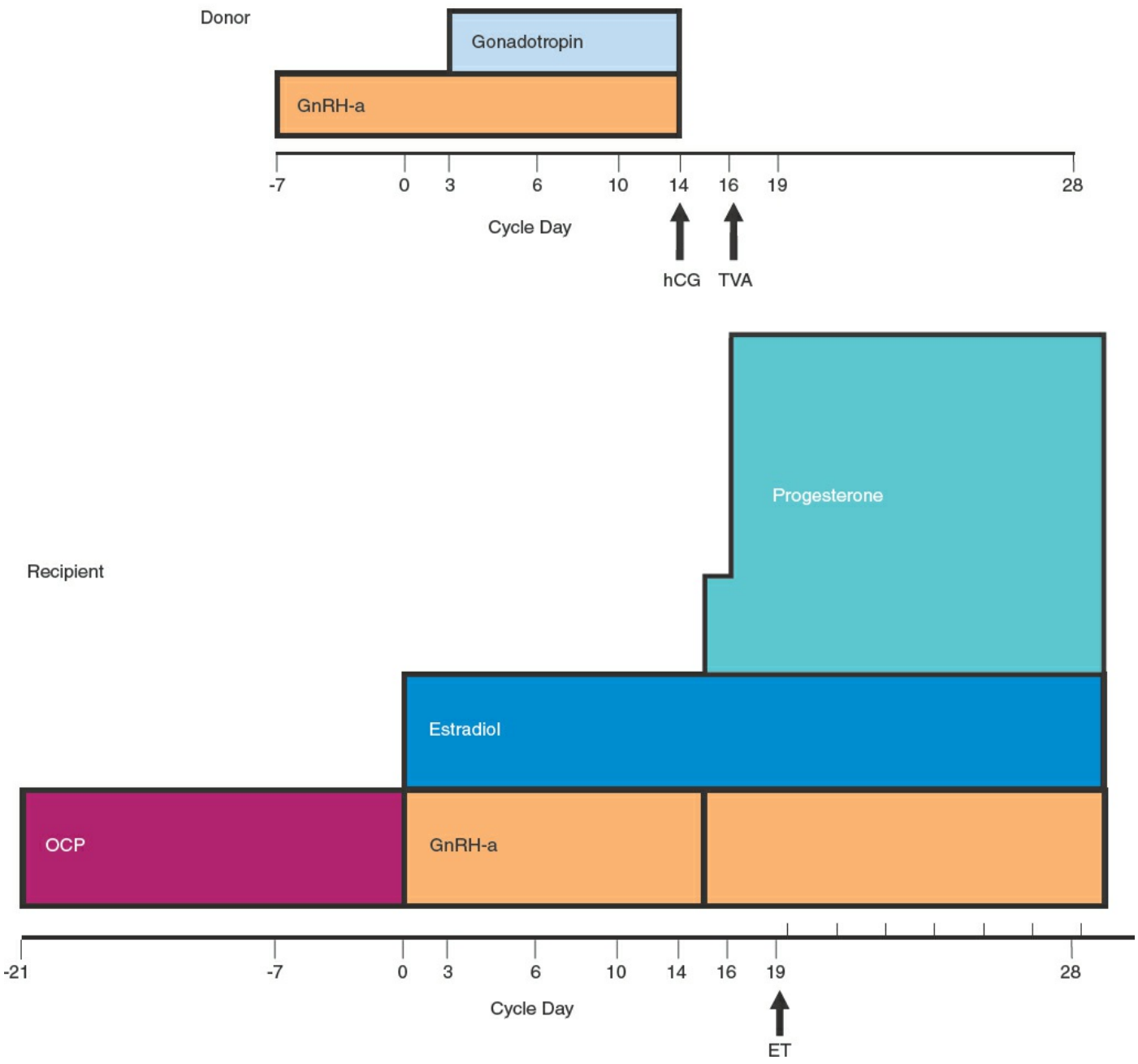


FIGURE 36-6 Regimens of ovarian stimulation and hormone replacement used to synchronize the development of ovarian follicles in the oocyte donor and the endometrial cycle in the recipient. hCG, human chorionic gonadotropin; OCP, oral contraceptive pill; GnRH-a, gonadotropin releasing hormone agonist; TVA, ultrasound-guided transvaginal aspiration of oocytes. (Adapted from **Chang PL, Sauer MY**. Assisted reproductive techniques. Stenchever MA, ed. Atlas of Clinical Gynecology, Mishell DR, ed. Reproductive Endocrinology. Vol. 3. Philadelphia, PA: Current Sciences Group; 1998, with permission.)

Oocyte Retrieval

The risks of oocyte retrieval include bleeding requiring transfusion, injury to adjacent structures requiring laparotomy, formation of a pelvic abscess leading to loss of reproductive function despite prophylaxis, and risks related to anesthesia (521).

Multiple Gestation

As the majority of ART cycles involve the transfer of more than one embryo, multiple gestation occurs at higher rates than for spontaneous conception (3%). This has social, medical, emotional, and financial ramifications (501,522). **[10]** **Although the majority of complications of multiple gestations occur with high-order (ê3) multiples, twins have increased risks for low birth weight, preterm birth, and neurologic deficits when compared to singletons** (522,523). **[10]** Despite this, 20% of infertile patients view multiple pregnancy as a desired outcome (501). Because most patients lack insurance coverage for IVF, patients may push their physicians to take greater risks when deciding on the number of embryos to transfer (501). The multiple pregnancy risk is higher in patients under the age of 35 who are undergoing IVF since their embryos are typically of better quality and implantation rates are higher, but multiple pregnancy can occur at any reproductive age (138,139). With increasing adherence to guidelines suggesting limitations on the number of embryos to transfer in a given ART cycle and improved implantation rates that allow single embryo transfer, the multiple infant live birth rate has decreased in most age groups from 2006 through 2015, occurring in 24% in women aged <35, 23% aged 35 to 37, and 20% age 38 to 40 (138). However, the multiple live birth rate increased in that same time period slightly to 18% aged 41 to 42 and 12% aged >42 (138). **[10]** Most multiple pregnancies arising from ART are dizygotic, but monozygotic twinning occurs in 3.2% of IVF cycles (compared to a background rate of 0.4%) (501). Concerns have been raised that monozygotic twinning might increase after blastocyst culture, but this finding has not been consistent (476,524).

Selective Reduction

Ten percent of multifetal pregnancies spontaneously lose at least one gestational sac during the first trimester. This loss rate increases to 21% in women >35 years of age (525). The spontaneous reduction rate to twins or singletons is much higher for triplets (14%) (526) than for quadruplets (3.5%) **[10]** (525). **Selective pregnancy termination or multifetal reduction may be an option for some patients in whom spontaneous reduction does not occur by 11 to 13 weeks** (527). This involves first karyotyping each fetus through transabdominal chorionic villous sampling to preferentially reduce those that are abnormal, then injecting potassium chloride into the heart of the targeted fetus (527). Although selective reduction carries a 3% to 7% risk of losing the entire pregnancy when performed prior to 19 weeks, this is still lower than the 15% chance of

spontaneously losing an entire triplet pregnancy (523,527). Selective fetal reduction is typically considered for triplet or higher pregnancies, but even reduction from twins to singletons may have benefits (523).

Ectopic and Heterotopic Pregnancy

ART pregnancies effectively bypass the fallopian tubes to achieve pregnancy but ectopic pregnancy (implantation outside the uterus) is still possible. Historically rates of ectopic pregnancy were higher in ART when compared to spontaneous conception, although data have shown **[11]** rates of ectopic pregnancy in ART to be similar to the general population rate of 2% (528). **The absence of an intrauterine pregnancy on transvaginal US evaluation in conjunction with a maternal serum hCG level above a threshold of 1,500 to 2,500 mIU/mL suggests an abnormal gestation** (498). This threshold or discriminatory zone is individualized to each institution depending on the characteristics of the hCG assay used and clinical expertise. A more conservative discriminatory zone decreases the risk of incorrectly diagnosing an ectopic pregnancy and terminating a viable pregnancy (498). **[11]** This is especially important in multiple gestation which will produce higher hCG levels at an earlier stage (498). Heterotopic pregnancy involves concurrent intrauterine and ectopic pregnancy, usually within the tube (529) but ovarian implantations have been reported (530). **[11]** The incidence of heterotopic pregnancy, which is extremely rare in spontaneous conceptions, is notably higher after IVF treatment with an incidence as high as 1% (529). Risk factors for heterotopic pregnancy include multiple gestation, smoking, previous tubal surgery, and prior PID, in addition to ART (529). As with standard ectopic pregnancies, pain and bleeding are the most common presenting findings with heterotopic pregnancies (529). Heterotopic pregnancies are most often diagnosed in the first 5 to 8 weeks of gestation using laparoscopy or laparotomy (529). **Only 26% of heterotopic cases can be diagnosed with transvaginal US, possibly because of difficulties in sonographic interpretation in the presence of concomitant ovarian hyperstimulation** (529). After treatment of a heterotopic gestation with laparoscopy, laparotomy, or US-guided injection of potassium chloride into the extrauterine pregnancy, the overall delivery rate for the intrauterine pregnancy is nearly 70% (529).

Ovarian Hyperstimulation Syndrome

OHSS is a medical complication that is completely iatrogenic and unique to stimulatory infertility treatment (531). **Its symptoms are the result of ovarian enlargement and fragility, extravascular fluid accumulation, and intravascular volume depletion** (532). Proposed mechanisms for the characteristic fluid shifts that accompany OHSS include increased protein-rich fluid secretion from the stimulated ovaries, increased renin and prorenin within follicular fluid, and increased capillary permeability mediated by angiotensin (532). **[11]** **Vascular endothelial growth factor**

(VEGF), whose expression in granulosa cells and serum is augmented by hCG, and a variety of other inflammatory cytokines have been implicated in the pathogenesis of this disease (532). Two distinct patterns of OHSS onset have been described. Early OHSS occurs 3 to 7 days following the hCG trigger and is associated with the administration of exogenous hCG (533). **[11]** Late-onset disease occurs 12 to 17 days after the hCG trigger; it is the result of endogenous hCG secretion from the pregnancy and tends to be more severe with multiple gestation (533). Pregnancy outcomes are inconsistently affected by the presence of OHSS, with higher rates of biochemical losses but similar rates of clinical losses when compared to patients without OHSS (533).

Severity Classification

[11] A RCT (534) described mild, moderate, and severe OHSS classifications considering criteria from Golan (531) and Navot (535) as follows: mild OHSS (grade 1 to 2) is associated with abdominal distention and discomfort with grade 2 including nausea, vomiting or diarrhea accompanied by ovary diameter of at least 5 mm. Moderate or grade 3 includes grade 2 plus sonographic subclinical ascites near the liver or in the pelvis if pocket >9 mm. Severe OHSS (grade 4 to 5) is associated with grade 3 plus clinical ascites, hydrothorax, or dyspnea, with grade 5 including hemoconcentration, renal insufficiency or oliguria, elevated transaminases, venous thromboembolism, or respiratory distress syndrome.

Risk Factors

Mild OHSS occurs commonly in both stimulated non-ART and ART cycles, but severe disease is rare in non-ART cycles (536). Severe disease is more common with ART, occurring in 5% of antagonist and nearly 9% of agonist protocols (534). Polycystic ovary syndrome, polycystic ovarian morphology with attendant elevated anti-mullerian hormone levels (>3.36 ng/mL), and previous episodes of OHSS are major risk factors for the disease (532,534,536,537). E2 concentrations of >3,500 pg/mL and >6,000 pg/mL at the time of hCG trigger were associated with severe OHSS in 1.5% and 38% of patients, respectively (536). More than 20 preovulatory follicles were associated with a 15% incidence of severe OHSS (536). When 20 to 29 oocytes were collected at retrieval, 1.4% of patients developed severe OHSS; this rose to 22.7% with ≥30 oocytes (536).

Management

If outpatient management is appropriate, the patient should be instructed to limit her activity, to weigh herself daily, and to monitor her fluid intake (at least 1 L/day of mostly electrolyte-balanced fluid) and output (532). Daily follow-up by telephone or visit is important and the patient should be reassessed if she notes worsening of the symptoms or if her weight gain increases to more than 2 lb per day (532). **Indications**

for hospitalization include inability to tolerate oral hydration, hemodynamic instability, respiratory compromise, tense ascites, hemoconcentration, leukocytosis, hyponatremia, hyperkalemia, abnormal renal or liver function, and decreased oxygen saturation (532). Fluid intake and urine output need to be carefully measured, and admission to an intensive care setting can be considered if the patient has hyperkalemia, renal failure, respiratory failure, or thromboembolic disease (532). Although IV fluids may worsen ascites, they are essential to correct hypovolemia, hypotension, electrolyte abnormalities and oliguria (532). Albumin 25% can be dosed 50 to 100 mg IV every 4 to 12 hours if further intravascular volume expansion is needed (532). Diuretics can be considered to improve weight gain and oliguria only after hypovolemia has been corrected (532). Thromboembolic prophylaxis should be given (532). Single or repeated transvaginal or transabdominal US–guided paracentesis may relieve pain, hydrothorax, or persistent oliguria (532). **[11]** Rapid large-volume fluid removal can be considered, as compensatory fluid shifts are unlikely to occur in this typically young healthy population, so long as the patient is carefully monitored (532).

OHSS Prevention

No method will prevent OHSS completely, but recognition of high-risk patients is the first step in decreasing that risk (538). PCOS, elevated AMH (>3.4 ng/mL), high peak E2 (>3,500 pg/mL), multifollicular development (≥25 follicles), or a high number of oocytes retrieved (≥24 oocytes) are associated with an elevated risk of OHSS (538).

COH and GnRH Analogs

Careful gonadotropin stimulation for monofollicular development is discussed under "Ovulatory Factor." **For ART, stimulation protocols for high-risk patients include lower initial COH doses of 150 IU to 225 IU and GnRH antagonists for LH surge prevention, which reduce the total dosage and duration of gonadotropin stimulation** (534). **[11]** GnRH antagonists when introduced following oocyte retrieval appear to accelerate regression of severe early OHSS without any adverse effects on pregnancy and live birth rates (539).

Ovulation Triggering

Decreasing the dose of hCG to reduce the incidence of OHSS is controversial (538). **GnRH agonists can be used instead of hCG during antagonist cycles to induce an endogenous LH surge. The very short half-life of endogenous LH may reduce the incidence and/or severity of OHSS** (538). As GnRH agonist triggers are associated with lower pregnancy rates, it may be a preferable option for patients who are not planning a fresh embryo transfer (538). **[11]** For those wanting to continue with a fresh cycle, low-dose hCG coadministered with a GnRH agonist trigger may prevent the lower pregnancy rates observed when a GnRH agonist is used alone (538).

Coasting

Coasting may be considered when E2 levels are >4,500 pg/mL and/or there are 15 to 30 mature follicles present (537). **During coasting, gonadotropin stimulation is withheld and E2 levels are checked daily** (537). An initial rise of E2 is typically observed within the first 48 hours of the coast, but the levels should subsequently plateau or decrease (540). The patient may be triggered when serum E2 levels fall to <3,500 pg/mL (537). **[11]** If GnRH agonists are used for initial LH surge suppression, switching to an antagonist during the coast has been associated with improved outcomes (537).

Cycle Cancellation

[11] Cycle cancellation may be recommended if there are >30 mature follicles, the coast duration is >4 days, or if E2 levels rise to >6,500 pg/mL during coasting (537,540).

Adjunctive Medications

The adjunctive use of metformin is associated with decreased OHSS rates in PCOS patients (541). Aspirin and calcium use appear to decrease the risk of OHSS as separate adjuncts (538). Evidence suggests that the use of letrozole following hCG triggering is effective in preventing moderate to severe early-onset OHSS (542). **Cabergoline, a dopamine agonist that inhibits VEGF production, decreased OHSS rates when given at 0.5 mg daily for 8 days from the day of hCG administration** (538,543). **Long-term use of cabergoline should be avoided as it may be associated with valvular heart disease** (537,540,544). **[11]** The benefit of albumin administration in decreasing rates of OHSS is unclear (538).

Embryo Cryopreservation

[11] Cryopreservation of all embryos without transfer appears to reduce late-onset OHSS although early-onset OHSS may still occur (540). With improved freezing techniques, live birth rates following frozen/thaw transfers are similar to fresh transfer (491). More information on embryo cryopreservation can be found in the "ART Process" section.

In vitro Oocyte Maturation

In vitro oocyte maturation (IVM) completely obviates the need to stimulate the ovaries with gonadotropins. During IVM cycles, immature follicles are aspirated following hCG administration, and the retrieved oocytes are grown in vitro until they mature. Mature oocytes are fertilized by insemination or ICSI (545). Randomized trials are still needed to further evaluate this technique (545). IVM is considered an experimental procedure and should only be performed in specialized centers (546). Randomized trials are still needed to further evaluate this technique before it can be recommended as an alternative to conventional ART techniques (547).

Risk of Cancer After Fertility Therapy

Infertility by itself is a predisposing factor for ovarian cancer and breast cancer (548). **Although treatments that promote incessant ovulation and elevated estrogen levels offer biologic plausibility for further increased cancer risk, data regarding the impact of infertility therapy on malignancy are inconsistent and limited by methodologic issues** (548). The practice committee for the American Society of Reproductive Medicine completed an analysis of accumulated data of prior studies addressing the potential risk of cancer with fertility drug use (548). No association between fertility drug use and an increased risk of invasive ovarian cancer, breast cancer, or endometrial cancer could be established when evaluating the available data (548). Although several studies have shown a small absolute risk of borderline ovarian tumors there is a lack of consistent evidence that any particular fertility drug increases the risk of borderline ovarian tumors (548). When considering other cancers, there does not appear to be a risk of invasive thyroid cancer, colon cancer, or cervical cancer (548). **[11]** There is insufficient evidence to determine if there is an increased risk of melanoma or lymphoma (548).

Stress

Stress, as manifested by anxiety or depression, is thought to be increased among women experiencing infertility (549). **Stress is the most common reason for patients, even those with insurance coverage, to terminate fertility treatment** (550). **[11]** Although the preponderance of the evidence suggests that stress does not adversely affect IVF outcome, additional studies are needed before any conclusions can be made (551–553). If psychological disorders are present, treatment should be offered regardless of fertility status.

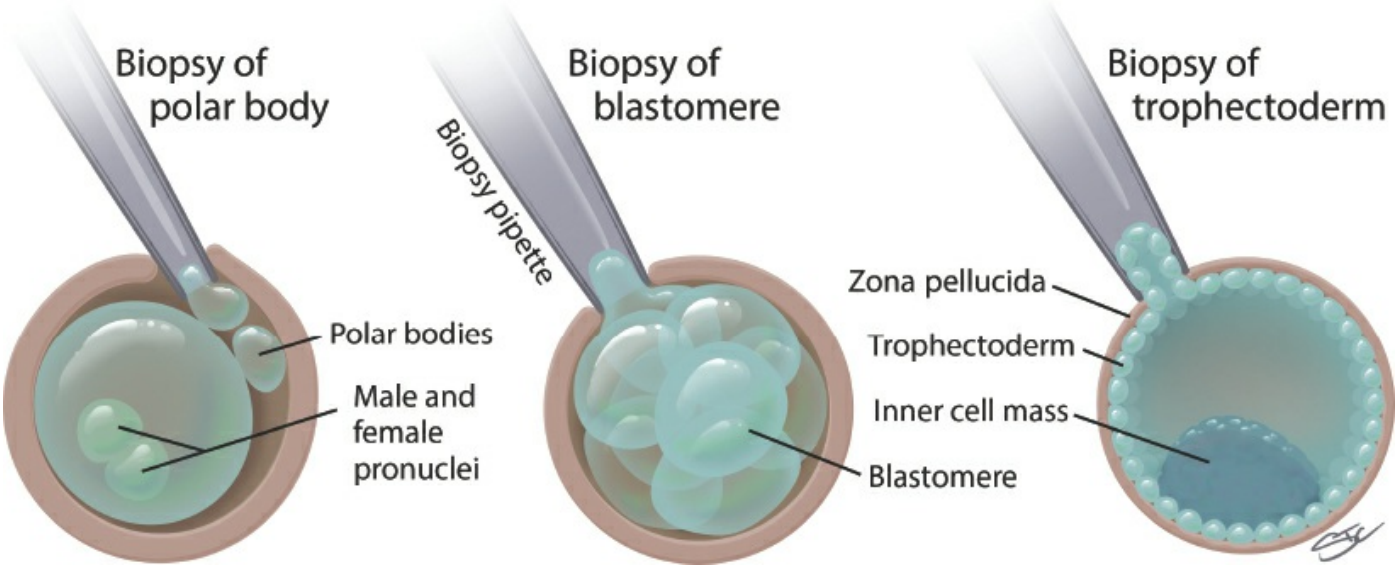
Neonatal and Child Development

With the ever-growing number of births resulting from ART, it is important to consider potential perinatal risks and long-term childhood outcomes. Multifetal gestation and its subsequent effect on maternal and fetal morbidity and mortality represent the most significant risk of ART (554). Risks of multiple gestation include preterm birth, low birth weight, small for gestational age, congenital anomalies, and perinatal mortality. These risks appear to have an independent association with IVF regardless of fetal number (554). The risk of negative long-term outcomes of children born after IVF are primarily associated with inherent risks of multiple gestation pregnancies. When multiple gestation is excluded the risk is uncertain and underscores the need for further studies (554). **[10]** **The most important step in mitigating neonatal and long-term** pediatric risk associated with IVF is continued emphasis on elective single embryo transfer (487). Patients should have a thorough history and physical performed, addressing any health problems or inherited conditions that could impact future

pregnancy (554).

Preimplantation Genetic Diagnosis and Screening

[9] The primary indication for PGD is to improve the chances of having healthy infants in families at high risk for a specific genetic disease (555). Following embryo biopsy, genetic testing can be performed on a blastomere (cell from day 3 embryo), polar body, or on blastocyst trophectoderm prior to transferring the embryo (556) **(Fig. 36-7)**. Data favor biopsy at the blastocyst stage over the cleavage stage (557). Aneuploidy in embryos most commonly affects chromosomes X, Y, 13, 14, 15, 16, 18, 21, and 22 (556). Fluorescence *in situ* hybridization (FISH) is a technique that assesses aneuploidy, translocation, other structural chromosomal defects, and sex chromosome content (556). FISH is technically limited by the number of distinct chromosomes that can be evaluated, giving the technique an inherently high false negative rate. Newer genetic technologies have been developed that have the ability to assess the entire genome using array comparative genomic hybridization (aCGH), single nucleotide polymorphism (SNP) arrays, and next-generation sequencing (NGS) (558). **[9]** One-quarter of the cases of PGD are performed for single gene disorders, most commonly myotonic dystrophy, Huntington disease, cystic fibrosis, fragile X syndrome, spinal muscular atrophy, tuberous sclerosis, Marfan syndrome, thalassemia and sickle cell anemia (556). Because polymerase chain reaction (PCR) is required for single gene disorder diagnosis, ICSI is performed during ART to avoid contamination from sperm bound to the zona pellucida (556). **[9]** PGD can be used for HLA tissue matching in an effort to produce a child whose cord blood or stem cells could help an existing affected child (556). Disadvantages to PGD include decreased postbiopsy embryo survival, requirements for extended culture with an associated possibility that no embryos will be available for transfer or cryopreservation, false positive and false negative testing results, and controversies regarding disposition of nontransferred embryos (555,556).



[9] FIGURE 36-7 Embryo biopsy procedure. A small opening is made in the zona pellucida and depending on the stage of embryonic development the removal of a polar body (fertilized or unfertilized oocyte), blastomere (cleavage stage 8 cell), or trophectoderm (blastocyst) is performed.

Preimplantation Genetic Screening

PGD is not synonymous with PGS, which is performed in couples without known chromosomal anomaly, mutation, or other genetic abnormalities (555). **[9] PGS focuses on identifying euploid embryos for transfer, with the goal of increasing implantation rates and decreasing miscarriage rates** (558). **[10]** When embryos are known to be euploid, single embryo transfer is universally recommended to decrease the risk of multiple gestation (487). Available genetic testing platforms for PGS are the same as those used in PGD and will equally detect whole chromosome aneuploidy. Newer genetic technologies **(Figs. 36-8** to **36-11)** have added more genetic capabilities to include assessment of segmental aneuploidy, mosaicism, and mitochondrial DNA (mtDNA) copy number (558). Work on mtDNA has suggested that it may have value as a potential biomarker of embryo viability (559). Earlier studies indicated that elevated mtDNA content is associated with implantation failure, although data have not corroborated these findings, suggesting the need for further evaluation of the technology (559–562). Although it seems intuitive that replacing only euploid embryos should improve pregnancy and live birth rates in patients with advanced age, recurrent pregnancy loss, or implantation failure, study outcomes have not been consistent (555,556,563–566). A significant challenge to the application of PGS is chromosomal mosaicism **(Figs. 36-12** and **36-13)**, which arises from mitotic errors during embryo development, and has raised concerns of how well the biopsy sample represents the embryo as a whole, and whether subsequent embryonic self-correction can restore euploidy (567). Mosaic embryos can be considered potentially viable but should be deprioritized for transfer compared to embryos with nonmosaic euploid results as a

result of limited data on neonatal outcomes, diminished implantation, pregnancy, and live birth rates and higher miscarriage risk (568,569). **[9]** Mosaicism involving two or more chromosomes and/or higher amount of aneuploidy (involving more affected cells) could be considered for transfer (568,569) but one study suggests they be further deprioritized compared to embryos with single mosaic chromosome and/or lower degrees of aneuploidy (569). **[11]** Thorough genetic and physician counseling is necessary for the patient to proceed with testing embryos using PGD/PGS and to understand the results if PGS/PGD is performed, in order for an informed decision to be made regarding whether and which embryos to transfer.

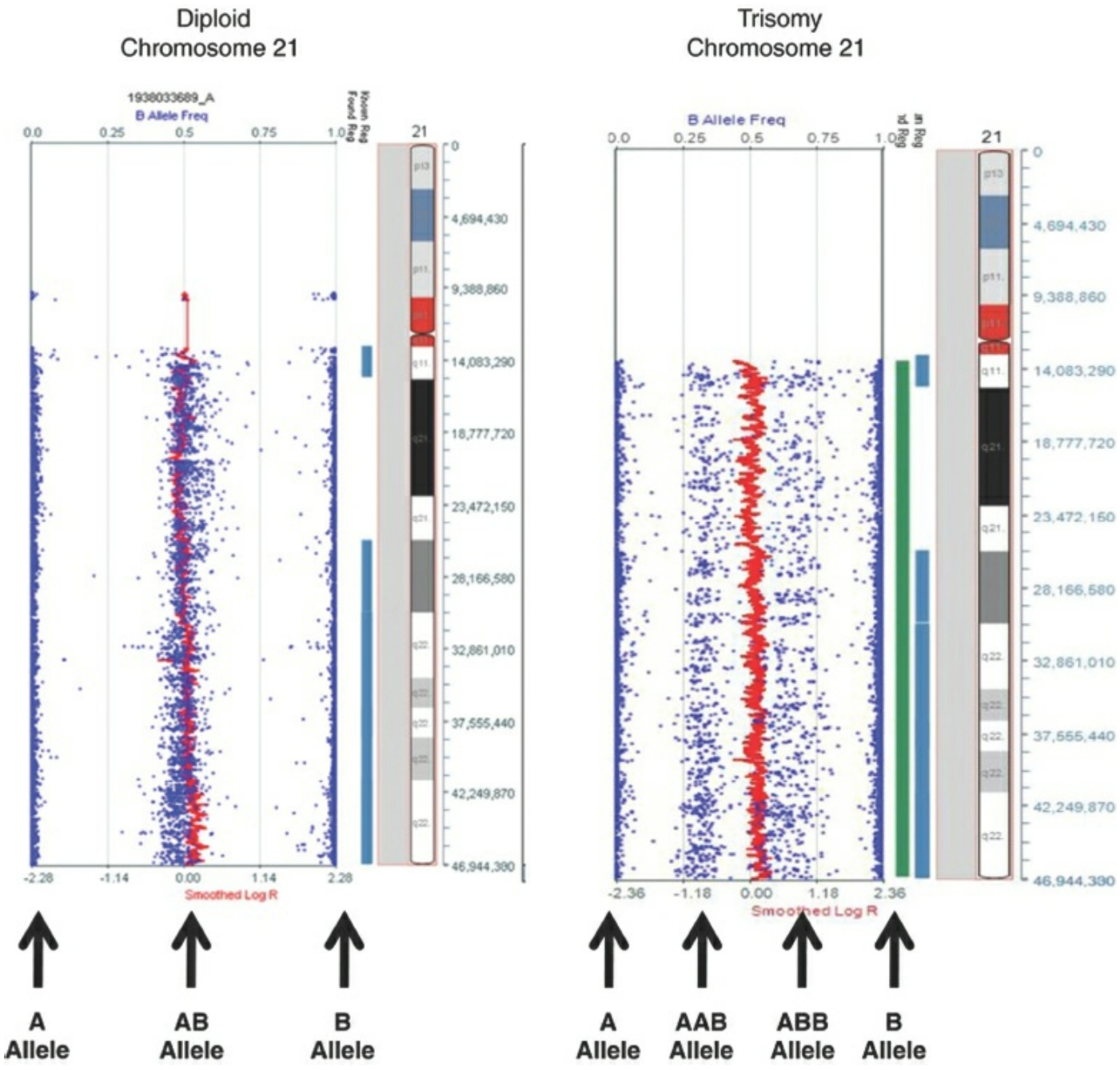


FIGURE 36-8 Detection of abnormalities with different PGS platforms. Using single nucleotide

polymorphisms (SNP), diploid chromosome 21 is seen on the left, trisomy 21 on the right. (Adapted with permission from **Brezina et al.** [558].)

Preservation of Fertility in Cancer Patients

Improved cancer treatments such as chemotherapy, surgery, and radiotherapy have greatly enhanced survival, such that many cancer survivors contemplate parenthood (570). Unfortunately, those life-saving treatments can diminish fertility potential in men and women (570). Cancer itself does not usually affect oocytes, but certain chemotherapeutic drugs or radiation damage may adversely affect ovarian reserve and uterine function, particularly in older women (570). **[5] If time allows, prior to commencement of cancer treatment, women can undergo an ART cycle with embryo or oocyte cryopreservation, although ovarian tissue preservation and in vitro maturation of oocytes remain experimental** (546). Fertility sparing treatments may be considered in certain situations including radical trachelectomy for cervical cancer, progestin therapy *in lieu* of hysterectomy for uterine cancer, and unilateral oophorectomy for some ovarian tumors (570). Ovarian function may be preserved when ovarian transposition is performed prior to radiation therapy (546). It is unclear whether ovarian suppression with GnRH analogs during chemotherapy or radiation is protective and it is still considered investigational (546). In men, cancer directly affects gametogenesis and cancer treatments cause more fertility damage when given at younger ages (570). **[5] Semen and sperm cryopreservation prior to cancer treatment, when feasible, is the standard fertility preservation method in men** (546).

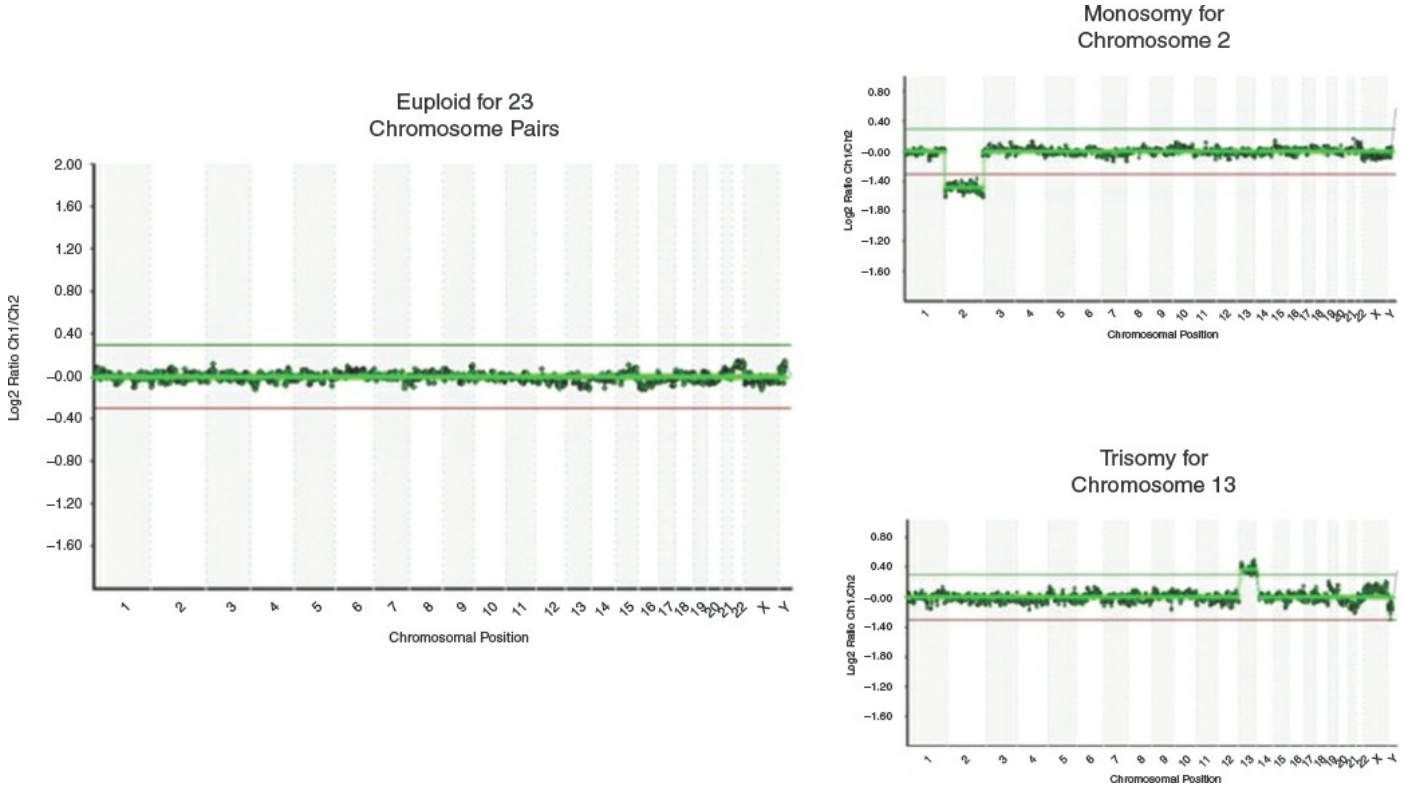


FIGURE 36-9 Detection of abnormalities with different PGS platforms. Using **comparative genomic hybridization (CGH)**, the left panel indicates euploid/diploid results with a relatively equal ratio of green/red fluorescence in all 23 pairs of chromosomes. The top right shows chromosome 2 monosomy with downward deviation indicating a relative lack of green, as compared to red, signal intensity. The bottom right shows chromosome 13 trisomy with upward deviation indicating a relative increase of green, as compared to red, signal intensity. (Adapted with permission from **Brezina et al.** [558].)

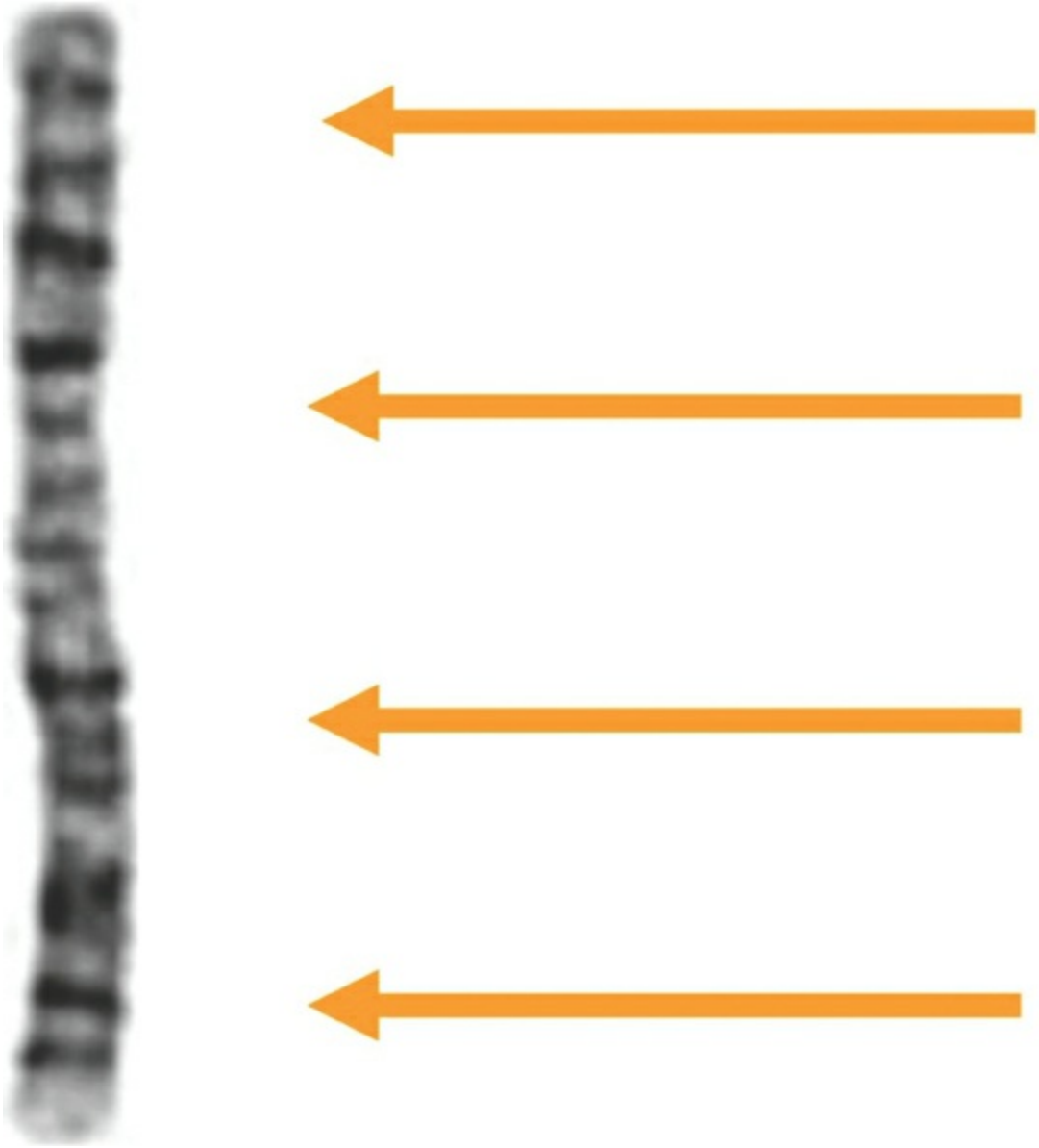


FIGURE 36-10 qPCR. Detection of abnormalities with different PGS platforms. This depicts the low number of regions of a given chromosome evaluated by quantitative PCR (qPCR). **(**Adapted with permission from **Brezina et al.** [558].)

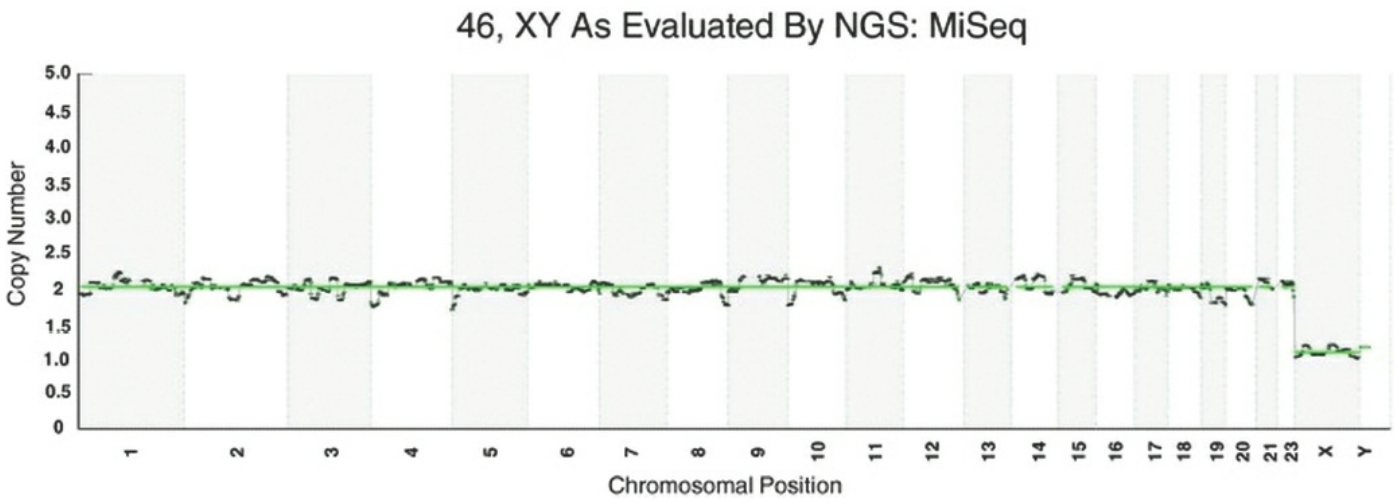


FIGURE 36-11 NGS. Detection of abnormalities with different PGS platforms. This depicts a euploid (diploid) 46XY embryo using next-generation sequencing (NGS), sequenced using MiSeq (Illumina). (Adapted with permission from **Brezina et al.** [558].)

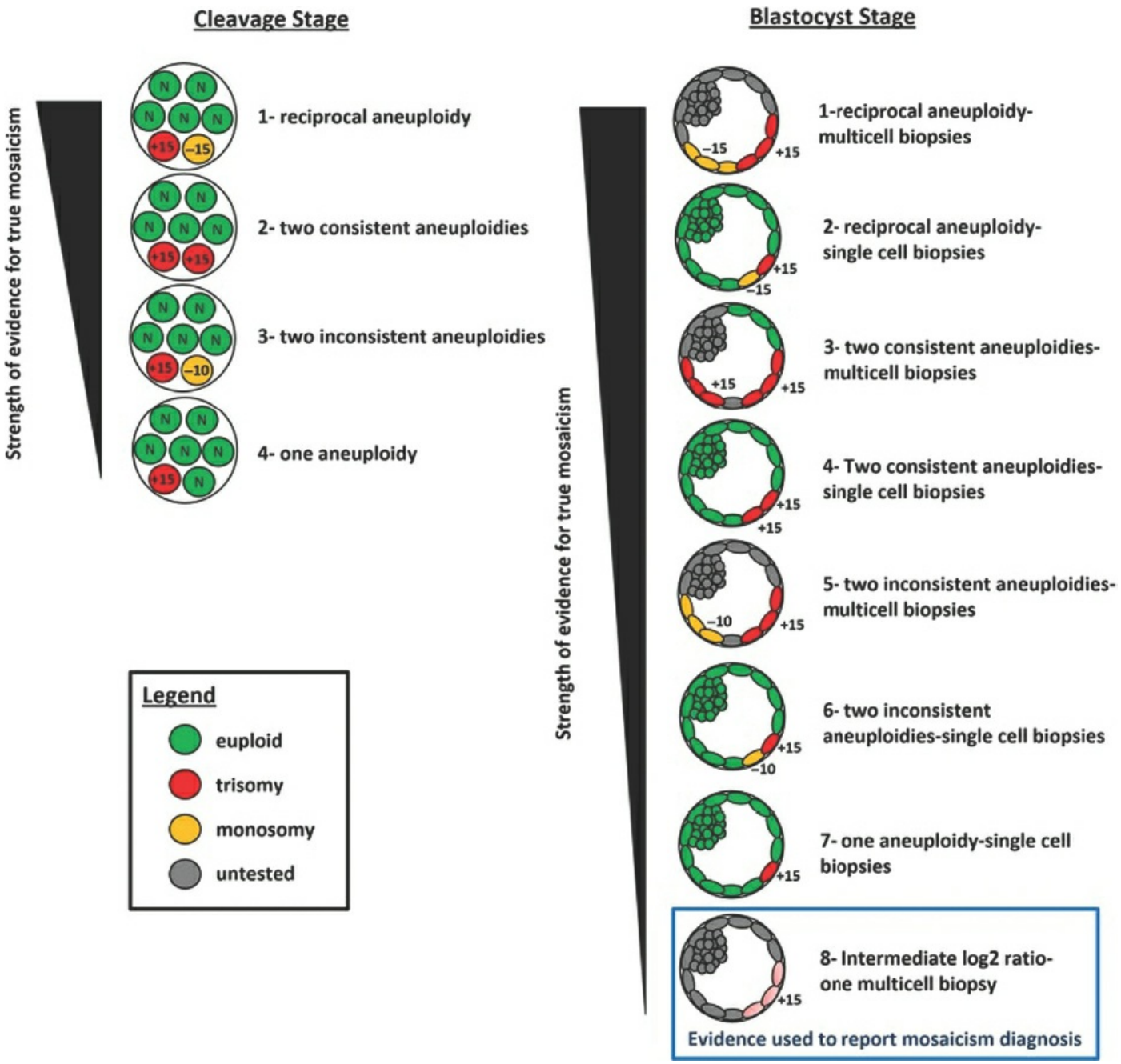


FIGURE 36-12 Embryonic chromosomal mosaicism. Permutations at cleavage and blastocyst stage. **(**Adapted with permission from **Capalbo et al.** [567].)

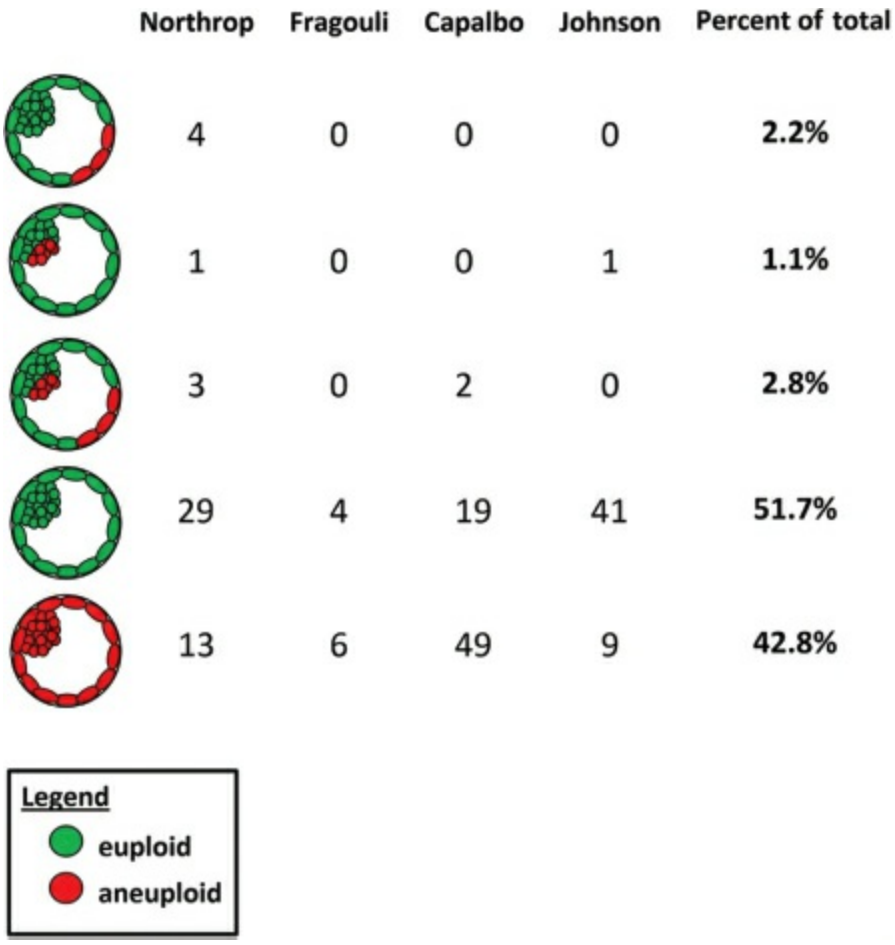


FIGURE 36-13 Embryonic chromosomal mosaicism. Mosaicism between inner cell mass and trophectoderm in disaggregated embryos. (Adapted with permission from **Capalbo et al.** [567].)

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SECTION VIII

Gynecologic Oncology



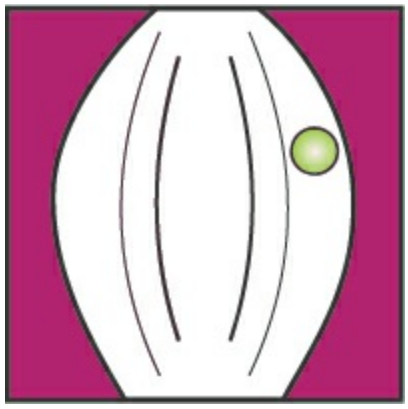
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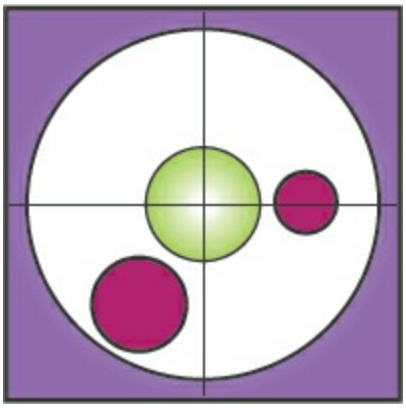
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CHAPTER 37

Uterine Cancer



Sean C. Dowdy, Gretchen E. Glaser, John R. Lurain

Epidemiology and Risk Factors
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Fertility-Sparing Treatment of Endometrial Hyperplasia and Cancer
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KEY POINTS

1 The most common risk factors for the development of endometrial carcinoma are related to prolonged, unopposed estrogen stimulation.

2 Office endometrial aspiration biopsy is the accepted first step in evaluating a woman with abnormal uterine bleeding or suspected endometrial pathology.

3 Serous and clear cell endometrial carcinomas make up less than 10% of endometrial cancers, yet account for more than one-half of all endometrial cancer deaths.

4 Most patients with endometrial cancer should undergo surgical staging, including hysterectomy, bilateral salpingo-oophorectomy, and peritoneal cytology. Lymph node assessment is necessary for most patients, but may be omitted in patients with negligible risk of lymphatic spread.

5 The most important adverse prognostic variables in endometrial cancer are advancing patient age, nonendometrioid or grade 3 histology, deep myometrial invasion, lymph-vascular invasion, large tumor size, cervical extension, lymph node metastasis, and intraperitoneal spread.

6 Postoperative adjuvant radiotherapy and chemotherapy in selected patients with endometrial cancer decreases the risk of local vaginal/pelvic recurrence and improves disease-free survival.

7 Overall 5-year survival rate in endometrial cancer is approximately 75%.

8 Radiotherapy is the best treatment option for patients with isolated local–regional recurrences who have not received prior radiation. Isolated vaginal recurrences may be salvaged in up to 80% of patients.

9 Uterine sarcomas are, in general, the most malignant group of uterine tumors and differ from endometrial cancers with regard to risk factors, diagnosis, clinical behavior, pattern of spread, and management.

Endometrial carcinoma is the most common malignancy of the female genital tract, accounting for almost one-half of all gynecologic cancers in the United States. In 2018, an estimated 63,230 new cases and 11,350 cancer-related deaths are anticipated (1). Endometrial carcinoma is the fourth most common cancer, ranking behind breast, lung, and colorectal cancers, and the sixth leading cause of death from malignancy in women. Overall, about 2.8% of women develop endometrial cancer during their lifetimes. Although endometrial carcinoma usually presents as early-stage disease and often is managed without radical surgery or radiotherapy, deaths from endometrial carcinoma rose by about 2% per year from 2010 to 2014. **Endometrial cancer is a disease that occurs primarily in postmenopausal women and is increasingly virulent with advancing age. The definite role of estrogen in the development of most endometrial cancers is established. Any factor that increases exposure to unopposed estrogen increases the risk for endometrial cancer.**

EPIDEMIOLOGY AND RISK FACTORS

There appear to be two pathogenetic types of endometrial cancer (2). **Type I, accounting for about 75% to 85% of cases, occurs in younger, perimenopausal women with a history of exposure to unopposed estrogen, either endogenous or exogenous.** In these women, tumors begin as hyperplastic endometrium and progress to carcinoma. These "estrogen-dependent" tumors tend to be better differentiated and have a more favorable prognosis than tumors not associated with hyperestrogenism. **Type II endometrial carcinoma occurs in women without estrogenic stimulation of the endometrium.** These spontaneously occurring cancers are not pathologically associated with endometrial hyperplasia, but may arise in a background of atrophic endometrium. They are less differentiated and associated with a poorer prognosis than estrogen-dependent tumors. These "estrogen-independent" tumors tend to occur in older, postmenopausal, thin women and are present disproportionately in African American and Asian women. Over the past decade, molecular genetic studies showed that these two tumor types evolve via distinct pathogenetic pathways (3) (see Types I and II Endometrial Carcinoma: Molecular Aberrations, below).

Several risk factors for the development of endometrial cancer have been identified, **[1] most of which are related to prolonged, unopposed estrogen stimulation of the**

endometrium (Table 37-1) (3–5). Nulliparous women have two to three times the risk of parous women. Infertility and a history of irregular menses as a result of anovulatory cycles (prolonged exposure to estrogen without sufficient progesterone) increase risk. Natural menopause occurring after age 52 years increases the risk for endometrial cancer 2.4-fold compared with women who experienced menopause before 49 years of age, probably as a result of prolonged exposure of the uterus to progesterone-deficient menstrual cycles. **The risk of endometrial cancer is increased 1.5 times for overweight and more than 2.5-fold for obese women** (resulting from excess estrone as a result of conversion of adrenally derived androstenedione by aromatization in peripheral fat) (6). The obesity epidemic in Western countries, together with growing rates of insulin resistance and metabolic syndrome, is expected to increase the incidence of endometrial cancer in coming years.

Table 37-1 Risk Factors for Endometrial Cancer

Characteristic	Relative Risk
Nulliparity	2–3
Late menopause	2.4
Obesity	
21–50 lb overweight	3
>50 lb overweight	10
Diabetes mellitus	2.8
Unopposed *estrogen* therapy	4–8
Tamoxifen therapy	2–3
Atypical endometrial hyperplasia	8–29
Lynch II syndrome	20

Other factors leading to long-term estrogen exposure, such as polycystic ovary syndrome and functioning ovarian tumors, are associated with an increased risk for endometrial cancer. Menopausal *estrogen* therapy without *progestins* increases the risk of endometrial cancer four- to eightfold. This risk increases with higher doses and with more prolonged use and can be reduced to essentially baseline levels by the addition of at least 10 days of *progestin treatment* (7). The use of the antiestrogen *tamoxifen* for treatment of breast cancer is associated with a two- to threefold increased risk for the development of endometrial cancer, although this finding is confounded by the apparent greater risk of endometrial cancer in women who have breast cancer, with or without treatment with *tamoxifen* (5). Analysis of diabetes mellitus is confounded by obesity,

but is thought to be associated with a modest increase in endometrial cancer risk even after adjusting for other factors (8). **Women with Lynch II syndrome (previously referred to as hereditary nonpolyposis colorectal cancer syndrome, or HNPCC), a cancer susceptibility syndrome with germline mutations in mismatch repair genes *MLH1, MSH2,* and *MSH6,* have a 40% to 60% lifetime risk for endometrial and colon cancer** (9). Other medical conditions, such as hypertension and hypothyroidism, are associated with endometrial cancer, but a causal relationship has not been confirmed.

ENDOMETRIAL HYPERPLASIA

Endometrial hyperplasia represents a spectrum of morphologic and biologic alterations of the endometrial glands and stroma, ranging from an exaggerated physiologic state to carcinoma *in situ.* **Clinically significant hyperplasias usually evolve within a background of proliferative endometrium as a result of protracted estrogen stimulation in the absence of progestin influence.** Endometrial hyperplasias are important clinically because they may cause abnormal bleeding, be associated with estrogen-producing ovarian tumors, result from hormonal therapy, and precede or occur simultaneously with endometrial cancer.

The classification scheme endorsed by the International Society of Gynecological Pathologists is based on architectural and cytologic features and long-term studies that reflect the natural history of the lesions (10) **(Table 37-2)**. Architecturally, hyperplasias are either simple or complex, differentiated by complexity and crowding of the glandular elements. **Simple hyperplasia** is characterized by dilated or cystic glands with round to slightly irregular shapes, an increased glandular-to-stromal ratio without glandular crowding, and no cytologic atypia. **Complex hyperplasia** has architecturally complex (budding and infolding) crowded glands, with less intervening stroma without atypia. **Atypical hyperplasia refers to cytologic atypia and can be categorized as simple or complex, depending on the corresponding glandular architecture.** Criteria for cytologic atypia include large nuclei of variable size and shape that have lost polarity, increased nuclear-to-cytoplasmic ratios, prominent nucleoli, and irregularly clumped chromatin with parachromatin clearing **(Fig. 37-1)**.

Table 37-2 Classification of Endometrial Hyperplasias

Type of Hyperplasia	Progression to Cancer (%)
Simple (cystic without atypia)	1
Complex (adenomatous without atypia)	3
Atypical	

Simple (cystic with atypia)	8
Complex (adenomatous with atypia)	29

From **Kurman RJ, Kaminski PF, Norris HJ**. The behavior of endometrial hyperplasia: a long term study of "untreated" hyperplasia in 170 patients. *Cancer* 1985;56:403–412, with permission.

The risk of endometrial hyperplasia progressing to carcinoma is related to the presence and severity of cytologic atypia. Kurman et al. retrospectively studied endometrial curettings from 170 patients with untreated endometrial hyperplasia followed for a mean of 13.4 years (11). They found that **progression to carcinoma occurred in 1% of patients with simple hyperplasia, 3% of patients with complex hyperplasia, 8% of patients with atypical simple hyperplasia, and 29% of patients with atypical complex hyperplasia.** Most of the hyperplasias seemed to remain stable (18%) or regress (74%). **As many as 25% to 43% of patients with atypical hyperplasia detected in an endometrial biopsy or curettage specimen will have an associated, usually well-differentiated, endometrial carcinoma detected during hysterectomy (**12). Marked cytologic atypia, a high mitotic rate, and marked cellular stratification are features of atypical endometrial hyperplasia most often associated with the finding of an undiagnosed carcinoma at hysterectomy.

Fertility-Sparing Treatment of Endometrial Hyperplasia and Cancer

Younger patients with endometrial cancer tend to have disorders such as polycystic ovarian syndrome, chronic anovulation, and infertility, indicative of exposure to intrinsic estrogen excess (13). Lesions in this age group are usually well differentiated and of endometrioid subtype with the potential to regress with oral or localized progestational therapy. Although standard treatment for all endometrial cancer is hysterectomy and staging, nonsurgical treatment with hormonal therapy may be an option for appropriately selected women desiring to preserve fertility. Surrogate staging techniques, such as magnetic resonance imaging (MRI), may be employed to evaluate the depth of myometrial invasion or identify extrauterine disease, although low sensitivity has the potential for underdiagnosis (14,15).

High regression rates for endometrial cancer and atypical hyperplasia following treatment with *progestin* therapy are extensively documented (16–20). Relatively small cohorts of patients and reports of hormone failure suggest caution when counseling patients for conservative management (21). A comprehensive review of hormonal treatment of grade 1endometrial cancer, including 27 articles with a combined total of 81 patients, included treatment with a variety of progestational agents. The overall response rate was 76% (62/81) and the median time to regression was 12 weeks (22). The recurrence rate was 24% among responders; nearly all recurrences occurred within 1 year of diagnosis. Only 1 month of progestational treatment was required to achieve a

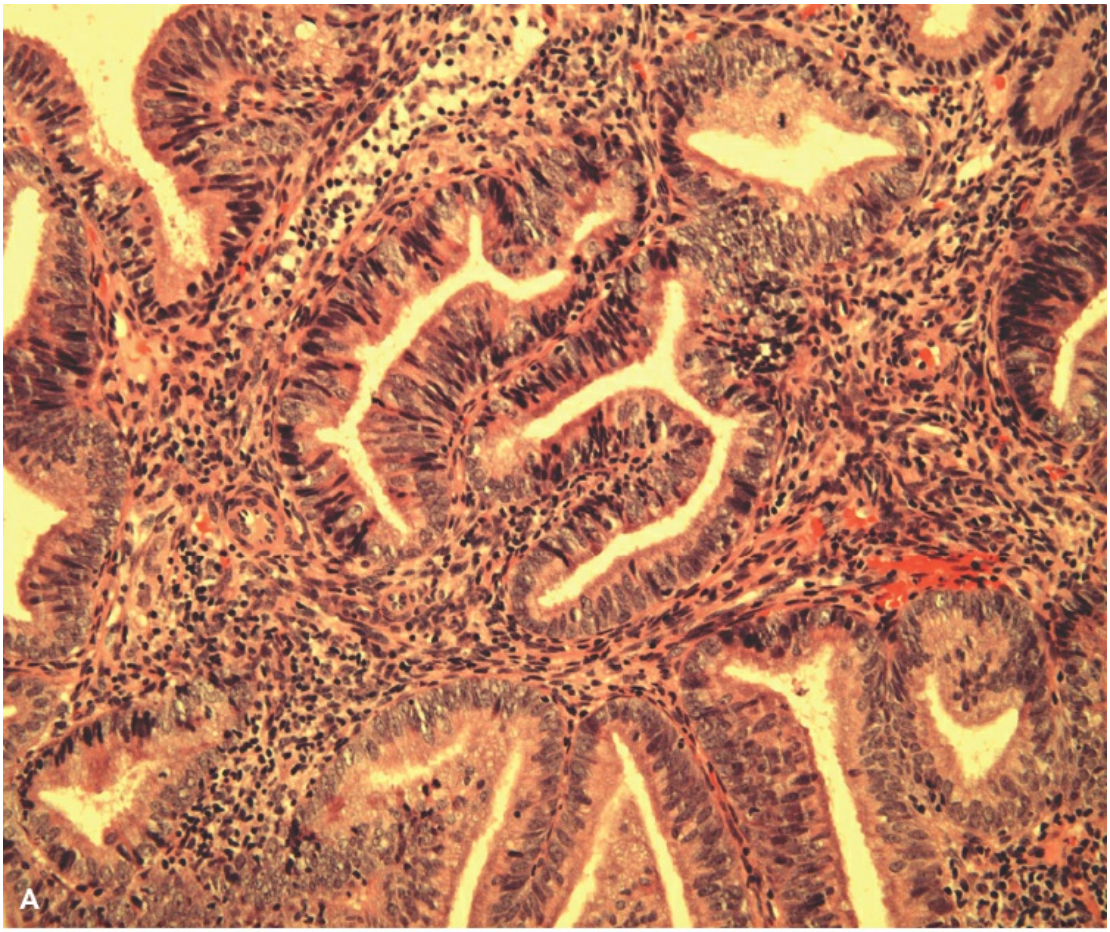
response in the 76% of patients without recurrence. Twenty patients achieved pregnancy following treatment. It is important to note that 24% (19/81) of the original cohort never responded to treatment, and only 68% had any documented follow-up endometrial sampling. Progestational therapy can successfully treat disease while preserving fertility for patients with atypical hyperplasia and well-differentiated presumed stage I endometrial cancer. Appropriate patient selection and exclusion criteria remain undefined. Patients must be counseled that failure to identify recurrence or extension of disease during progestational treatment may lead to a delay in definitive surgery and ultimately a compromised prognosis (18).

Continuous *progestin* therapy with *megestrol acetate* (40 to 160 mg per day) is probably the most reliable treatment for reversing complex or atypical hyperplasia, recognizing that higher doses may be associated with reduced compliance secondary to side effects. No clear consensus exists for an optimal follow-up interval. Therapy should be continued for at least 3 to 6 months, and endometrial biopsy should be performed to assess response. **Periodic endometrial biopsy or transvaginal ultrasonography is advisable in patients being monitored on progestin therapy for atypical hyperplasia because of the presence of undiagnosed cancer in at least 25% of cases and the high recurrence rate after treatment with progestins.** In this setting the use of progesterone should be considered a temporary, rather than long-term, treatment. **For women with atypical complex hyperplasia who no longer desire fertility, hysterectomy is recommended.**

ENDOMETRIAL CANCER SCREENING IN THE GENERAL POPULATION

Screening for endometrial cancer should not be undertaken because of the lack of an appropriate, cost-effective, and acceptable test that reduces mortality. **Routine Papanicolaou (Pap) testing is inadequate, and endometrial cytologic assessment is too insensitive and nonspecific to be useful in screening for endometrial cancer, even in a high-risk population.** Transvaginal ultrasonographic examination of the uterus and endometrial biopsy are too expensive to be employed as screening tests.

Screening for endometrial cancer or its precursors may be justified for certain high-risk women, such as members of families with hereditary nonpolyposis colorectal cancer (23). Women taking *tamoxifen* receive no benefit from routine screening with transvaginal ultrasonography or endometrial biopsy (24,25). Similarly, there is insufficient evidence to recommend screening for endometrial cancer in women because of a history of unopposed estrogen therapy, late menopause, nulliparity, infertility or failure to ovulate, obesity, diabetes, or hypertension (26).


A

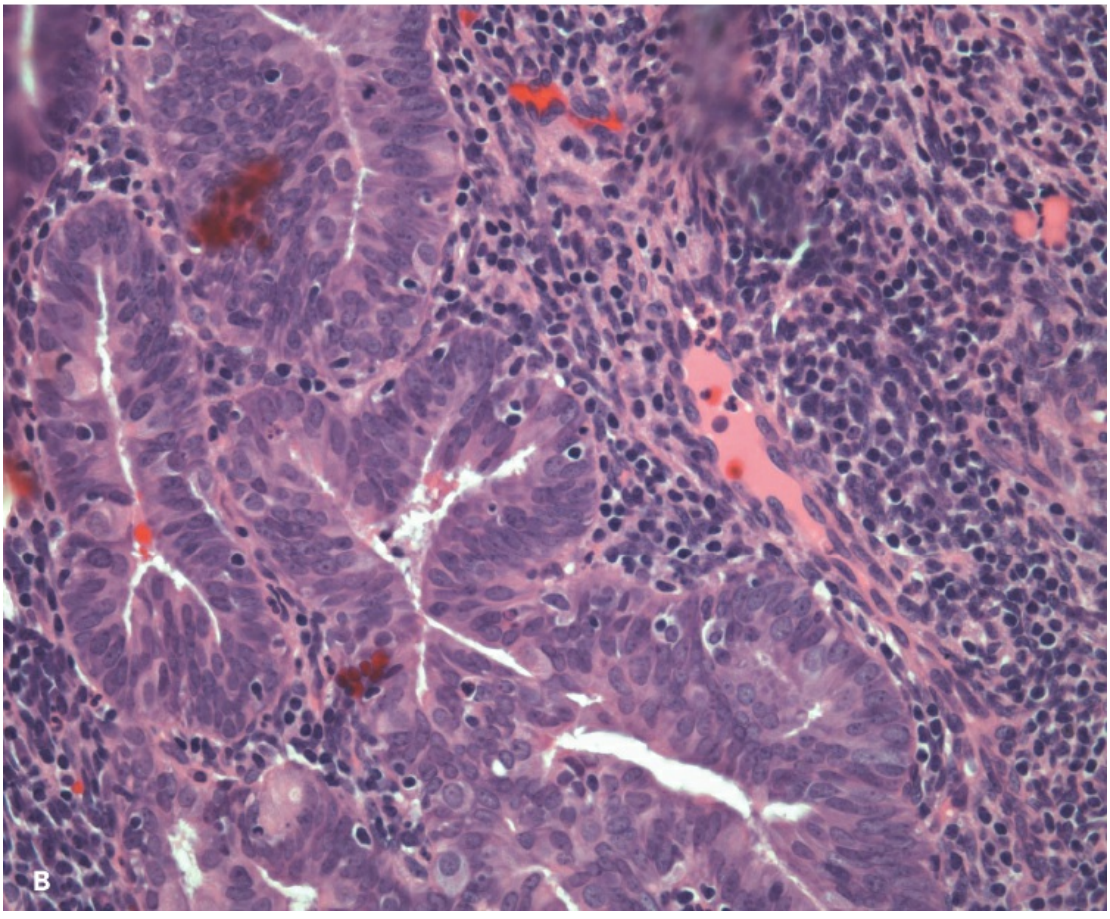

B

FIGURE 37-1 Atypical hyperplasia (complex hyperplasia with severe nuclear atypia) of endometrium. **A:** The proliferative endometrial glands reveal considerable crowding and papillary infoldings. The endometrial stroma, although markedly diminished, can still be recognized between the glands. **B:** Higher magnification demonstrates disorderly nuclear arrangement and nuclear enlargement and irregularity. Some contain small nucleoli. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

Most patients with endometrial cancer present with abnormal perimenopausal or postmenopausal uterine bleeding when the tumor is still confined to the uterus. Application of an appropriate and accurate diagnostic test in this situation usually results in early diagnosis and a high cure rate with timely treatment. It is important to recognize that the workup of abnormal uterine bleeding should include endometrial biopsy even in premenopausal patients, as 5% of cases are in women under the age of 40.

Surveillance and Prevention in Patients at High Risk

Most endometrial carcinomas are sporadic, but at least 10% of cases have a hereditary basis (27,28). Two genetic models were described in the development of familial endometrial cancer: Lynch II syndrome and patients with a predisposition for endometrial cancer alone, both of which are inherited in an autosomal dominant fashion (29). The majority of studies focused on the increased incidence of endometrial cancer associated with Lynch II syndrome, a highly penetrant disorder (80% to 85%) (30). Lynch II syndrome is caused by an inherited mutation in one of the following mismatch repair genes: *hMSH2, hMLH1, PMS1, PMS2,* or *hMSH6* (31). The disorder is characterized by early age (average age younger than 45 years) at onset of neoplastic lesions in a variety of tissues, including the colon, uterus, stomach, ureters, ovaries, and skin (30,32). The lifetime risk of endometrial cancer in women with Lynch II syndrome is 32% to 60% and the lifetime risk of ovarian cancer is 10% to 12% (33,34). Colorectal cancer is less prevalent in women with Lynch II syndrome than in men, whose risk approaches 100%. In a study of 1,763 patients from 50 Lynch II syndrome families in the Finnish Cancer Registry, the cumulative incidence of colorectal cancer in women was 54% by age 70, while the cumulative incidence of endometrial cancer was 60%, supporting surveillance (9,33,35). No effective screening method has been identified for patients at increased risk for ovarian cancer.

The Mallorca group, composed of experts in the treatment of hereditary gastrointestinal cancers from nine countries, recommended the following endometrial cancer surveillance strategy for patients with Lynch II syndrome: annual pelvic examination, transvaginal ultrasound, and endometrial biopsy beginning at 35 to 40 years of age (36). These recommendations are by expert opinion only, and it is unknown whether these interventions are cost-effective or will impact mortality from endometrial or ovarian cancer in patients with Lynch II syndrome. An attractive alternative to early

detection is prophylactic surgery after completion of childbearing (37). A multi-institutional, matched case-control study found that prophylactic hysterectomy with bilateral salpingo-oophorectomy is an effective primary prevention strategy in women with Lynch II syndrome. No woman with hysterectomy and bilateral salpingo-oophorectomy developed endometrial, ovarian, or peritoneal carcinoma during the period of follow-up. In contrast, endometrial cancer developed in 33% and ovarian cancer in 5% of women who did not undergo prophylactic surgery (34).

Recognizing that 3% to 5% of endometrial cancers can be attributed to Lynch syndrome, a new diagnosis of endometrial cancer represents an opportunity to identify patients with germline mutations. Clinical screening using protocols such as the Amsterdam or Bethesda criteria has been used in the past, but the use of molecular tumor testing has been shown to improve the rate of Lynch II detection (38). For example, in 2007 the Society of Gynecologic Oncology developed clinical practice guidelines to identify women who may benefit from germline Lynch testing. Bruegl et al. attempted to validate these guidelines in an unselected cohort of patients with endometrial cancer and reported poor sensitivity (32.6%, 95% confidence interval [CI] 19.2%–48.5%), showing that a majority of Lynch II patients were missed using this criteria. They went on to show that universal screening was ultimately more cost effective than the SGO model (39). Another study by Goverde et al. found universal testing in endometrial cancer patients under age 70 was cost-effective (6,668 British pounds/life year gained) as a result of the prevention of colorectal cancer in index patients and their relatives (40). Performing immunohistochemistry for *MLH1*, *MSH2*, *MSH6*, and *PMS2* expression is one cost effective model that is available in most laboratories. Recognizing that loss of *MLH1* is most often caused by hypermethylation, such analyses should be completed to appropriately triage patients to germline testing (41).

There are rare reports of pedigrees in which family members are affected by endometrial cancer alone, and genetic studies have not found a germline mutation associated with site-specific endometrial cancer (29,42,43). A population-based study of endometrial cancer and familial risk in younger women (Cancer and Steroid Hormone, or CASH, Study Group) reported that a history of endometrial cancer in a first-degree relative increased the risk of endometrial cancer by nearly threefold (odds ratio of 2.8; 95% CI, 1.9%–4.2%) (44). A significant association was found with colorectal cancers, with an observed odds ratio of 1.9 (95% CI, 1.1%–3.3%). The presence of Lynch II syndrome families within the cohort may explain the latter association, but a family history of endometrial cancer was an independent risk factor for endometrial cancer, after adjusting for age, obesity, and number of relatives (44).

Endometrial cancer and breast cancer share some of the same reproductive and hormonal risk factors such as nulliparity and exposure to unopposed estrogen (4,45,46). However, a familial association between breast and endometrial cancer is uncertain

(46). Although it has been posited that patients with *BRCA* mutations were at elevated risk for endometrial cancer (in addition to breast and ovarian cancer), this increase in risk may be present only in those patients with a personal history of breast cancer who are taking *tamoxifen* (47).

ENDOMETRIAL CANCER

Clinical Features

Symptoms

Endometrial carcinoma most often occurs in women in the sixth and seventh decades of life, at an average age of 60 years; 75% of cases occur in women older than 50 years of age. **About 90% of women with endometrial carcinoma have vaginal bleeding or discharge as their only presenting symptom.** Most women recognize the significance of postmenopausal bleeding and seek medical consultation within 3 months. Some women experience pelvic pressure or discomfort indicative of uterine enlargement or extrauterine disease spread. Bleeding may not have occurred because of cervical stenosis, especially in older patients, and may be associated with hematometra or pyometra, causing a purulent vaginal discharge. This finding is often associated with a poor prognosis (48). **Less than 5% of women diagnosed with endometrial cancer are asymptomatic.** In the absence of symptoms, endometrial cancer is usually detected following an abnormal Pap test, discovery of cancer in a uterus removed for some other reason, or evaluation of an abnormal finding on a pelvic ultrasonography examination or computed tomography (CT) scan obtained for an unrelated reason. Women who are found to have malignant cells on Pap test are more likely to have other poor prognostic factors (49).

Abnormal perimenopausal and postmenopausal bleeding should always be taken seriously and be properly investigated, no matter how minimal or nonpersistent. Causes may be nongenital, genital extrauterine, or uterine. Nongenital tract sites should be considered based on the history or examination, including testing for blood in the urine and stool. Invasive tumors of the cervix, vagina, and vulva are usually evident on examination, and any abnormalities should be biopsied. Traumatic bleeding from an atrophic vagina may account for up to 15% of all causes of postmenopausal vaginal bleeding. This diagnosis can be considered if inspection reveals a thin, friable vaginal wall, but the possibility of a uterine source of bleeding must first be eliminated.

Possible uterine causes of perimenopausal or postmenopausal bleeding include endometrial atrophy, endometrial polyps, *estrogen* therapy, hyperplasia, and cancer (50,51) (Table 37-3). Uterine leiomyomas should never be accepted as a cause of postmenopausal bleeding. **Endometrial atrophy is the most common endometrial finding in women with postmenopausal bleeding, accounting for 60% to 80% of**

such bleeding. Women with endometrial atrophy usually were menopausal for about 10 years. **Endometrial biopsy often yields insufficient tissue or only blood and mucus, and usually bleeding ceases after biopsy.** Endometrial polyps account for 2% to 12% of postmenopausal bleeding. Polyps are often difficult to identify with office endometrial biopsy or curettage. Hysteroscopy, transvaginal ultrasonography, or both, may be useful adjuncts in identifying endometrial polyps. Unrecognized and untreated polyps may be a source of continued or recurrent bleeding, leading eventually to unnecessary hysterectomy.

Estrogen therapy is an established risk factor for endometrial hyperplasia and cancer. **The risk for endometrial cancer is four to eight times greater in postmenopausal women receiving unopposed *estrogen* therapy, and the risk increases with time and higher *estrogen* doses.** This risk can be decreased by the addition of a *progestin* to the *estrogen,* either cyclically or continuously. Endometrial biopsy should be performed as indicated to assess unscheduled bleeding or annually in women not taking a *progestin.* **Endometrial hyperplasia occurs in 5% to 10% of patients with postmenopausal uterine bleeding.** The sources of excess estrogen should be considered, including obesity, exogenous estrogen, or an estrogen-secreting ovarian tumor. **Less than 10% of patients with postmenopausal bleeding have endometrial cancer.**

Table 37-3 Causes of Postmenopausal Uterine Bleeding

Cause of Bleeding	Percentage
Endometrial atrophy	60–80
Estrogen replacement therapy	15–25
Endometrial polyps	2–12
Endometrial hyperplasia	5–10
Endometrial cancer	10

Premenopausal women with endometrial cancer invariably have abnormal uterine bleeding, which is often characterized as menometrorrhagia or oligomenorrhea, or cyclical bleeding that continues past the usual age of menopause. The diagnosis of endometrial cancer must be considered in premenopausal women if abnormal bleeding is persistent, recurrent or if obesity or chronic anovulation is present.

Signs

Physical examination seldom reveals any evidence of endometrial carcinoma, although **obesity is a commonly associated constitutional factor.** Special attention should be given to the more common sites of metastasis. Peripheral lymph nodes should be

assessed carefully. Abdominal examination is usually unremarkable, except in advanced cases in which ascites or hepatic or omental metastases may be palpable. On gynecologic examination, the vaginal introitus and suburethral area, and the entire vagina and cervix, should be carefully inspected and palpated. Bimanual rectovaginal examination should be performed specifically to evaluate the uterus for size and mobility, the adnexa for masses, the parametria for induration, and the cul-de-sac for nodularity.

Diagnosis

[2] Office endometrial aspiration biopsy is the accepted first step in evaluating a patient with abnormal uterine bleeding or suspected endometrial pathology. The diagnostic accuracy of office-based endometrial biopsy is 90% to 98% when compared with subsequent findings at dilation and curettage (D&C) or hysterectomy (52).

The narrow plastic cannulas are relatively inexpensive, often can be used without a tenaculum, cause less uterine cramping (improving patient acceptance), and are successful in obtaining adequate tissue samples in more than 95% of cases. If cervical stenosis is encountered, a paracervical block can be performed, and the cervix can be dilated. Premedication with an antiprostaglandin agent can reduce uterine cramping. Complications following endometrial biopsy are exceedingly rare; uterine perforation occurs in only 1 to 2 cases per 1,000. Endocervical curettage may be performed at the time of endometrial biopsy if cervical pathology is suspected. **A Pap test is an unreliable diagnostic test because only 30% to 50% of patients with endometrial cancer have abnormal Pap test results (**53).

Hysteroscopy and D&C should be reserved for situations in which cervical stenosis or patient tolerance does not permit adequate evaluation by aspiration biopsy, bleeding recurs after a negative endometrial biopsy, or the specimen obtained is inadequate to explain the abnormal bleeding. Hysteroscopy is more accurate in identifying polyps and submucous myomas than endometrial biopsy or D&C alone (54).

Transvaginal ultrasonography may be a useful adjunct to endometrial biopsy for evaluating abnormal uterine bleeding and selecting patients for additional testing (55). Transvaginal ultrasonography, with or without endometrial fluid instillation (sonohysterography), may be helpful in distinguishing between patients with minimal endometrial tissue whose bleeding is related to perimenopausal anovulation or postmenopausal atrophy and patients with significant amounts of endometrial tissue or polyps who are in need of further evaluation. The finding of an endometrial thickness greater than 4 mm, a polypoid endometrial mass, or a collection of fluid within the uterus requires further evaluation. Although most studies agree that an endometrial thickness of less than 5 mm in a postmenopausal woman is consistent with atrophy, more

data are needed before ultrasonography findings can be considered to eliminate the need for endometrial biopsy in a patient with symptoms (56).

Pathology

The histologic classification of carcinoma arising in the endometrium is shown in Table 37-4 (10,57).

Endometrioid Adenocarcinoma

The endometrioid type of adenocarcinoma accounts for about 80% of endometrial carcinomas. These tumors are composed of glands that resemble normal endometrial glands; they have columnar cells with basally oriented nuclei, little or no intracytoplasmic mucin, and smooth intraluminal surfaces **(Fig. 37-2)**. As tumors become less differentiated, they contain more solid areas, less glandular formation, and more cytologic atypia. The well-differentiated lesions may be difficult to separate from atypical hyperplasia.

Table 37-4 Classification of Endometrial Carcinomas

Endometrioid adenocarcinoma Variants Villoglandular or papillary Secretory With squamous differentiation
Mucinous carcinoma
Papillary serous carcinoma
Clear cell carcinoma
Squamous carcinoma
Undifferentiated carcinoma
Mixed carcinoma

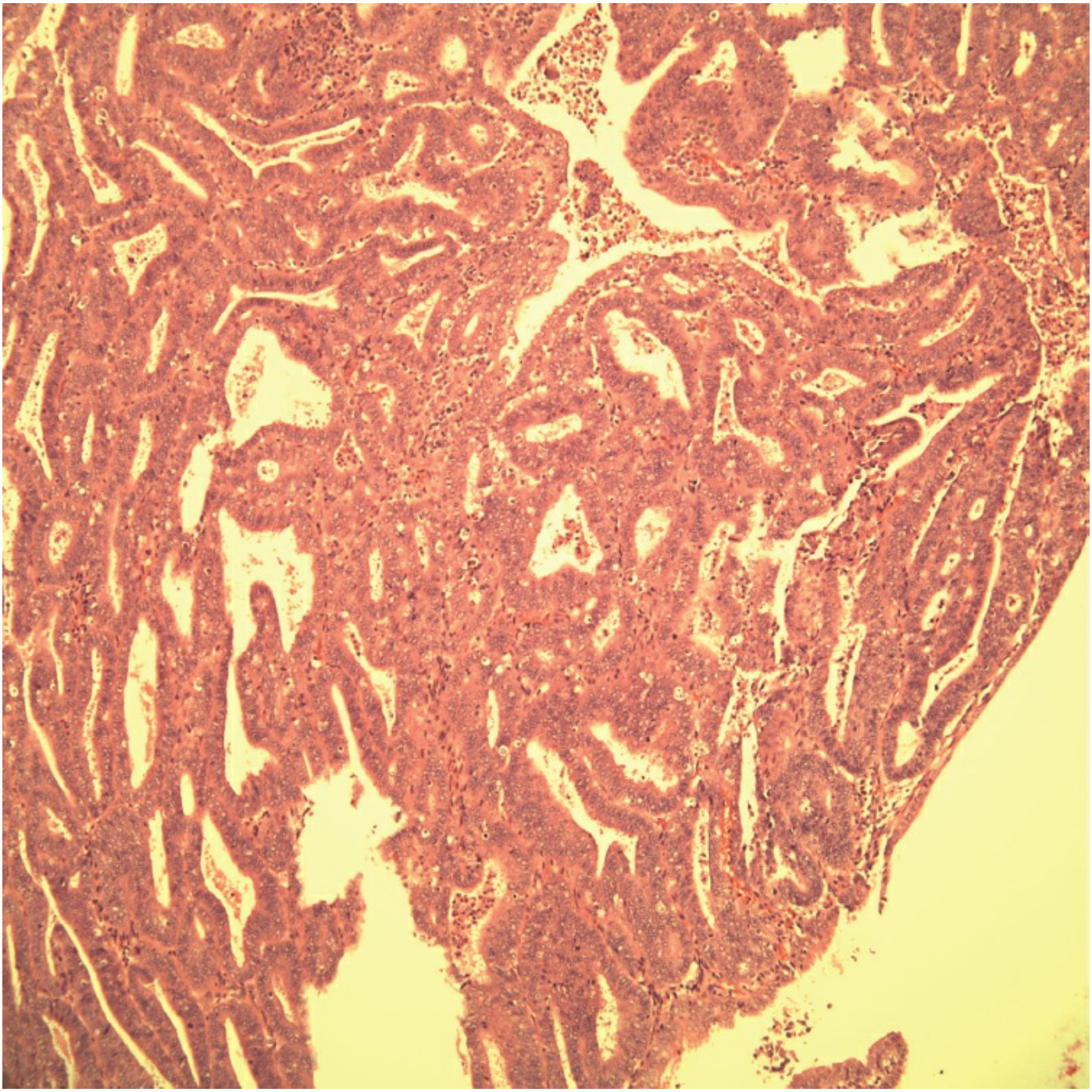


FIGURE 37-2 Well-differentiated adenocarcinoma of endometrium. The glands and complex papillae are in direct contact with no intervening endometrial stroma, the so-called back-to-back pattern. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

Criteria that indicate the presence of invasion and are used to diagnose carcinoma are desmoplastic stroma, back-to-back glands without intervening stoma, extensive papillary pattern, and squamous epithelial differentiation. These changes, with the exception of the infiltrating pattern with desmoplastic reaction, require an area of involvement equal to or exceeding one-half of a low-power microscopic field (LPF) (>1 LPF; 4.2 mm in diameter) (58,59).

The differentiation of a carcinoma, expressed as its grade, is determined by architectural growth pattern and nuclear features (Table 37-5). In the International Federation of Gynecology and Obstetrics (FIGO) grading system proposed in 1989, tumors are grouped into three grades: *grade 1,* 5% or less of the tumor shows a solid growth pattern; *grade 2,* 6% to 50% of the tumor shows a solid growth pattern; and *grade 3,* more than 50% of the tumor shows a solid growth pattern. The presence of notable nuclear atypia that is inappropriate for the architectural grade increases the tumor grade by one.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component. This FIGO system is applicable to all endometrioid carcinomas, including its variants, and to mucinous carcinomas. In serous and clear cell carcinomas, nuclear grading takes precedence; however, most investigators believe that these two carcinomas should always be considered high-grade lesions, making grading unnecessary.

Table 37-5 FIGO Definition for Grading of Endometrial Carcinoma

Histopathologic Degree of Differentiation:
G1 <5% nonsquamous or nonmorular growth pattern
G2 6–50% nonsquamous or nonmorular growth pattern
G3 >50% nonsquamous or nonmorular growth pattern
Notes on Pathologic Grading:
Notable nuclear atypia, inappropriate for the architectural grade, raises a grade 1 (G1) or grade 2 (G2) tumor by one grade
In serous adenocarcinoma, clear cell adenocarcinoma, and squamous cell carcinoma, nuclear grading takes precedence
Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component

FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obst* 2009;105:103–104.

About 15% to 25% of endometrioid carcinomas have areas of squamous differentiation (Fig. 37-3). In the past, tumors with benign-appearing squamous areas were called *adenoacanthomas,* and tumors with malignant-looking squamous elements were called *adenosquamous carcinomas.* It is recommended that the term *endometrial carcinoma with squamous differentiation* be used to replace these two designations because the degree of differentiation of the squamous component parallels that of the glandular component, and the behavior of the tumor is largely dependent on the grade of

the glandular component (60).

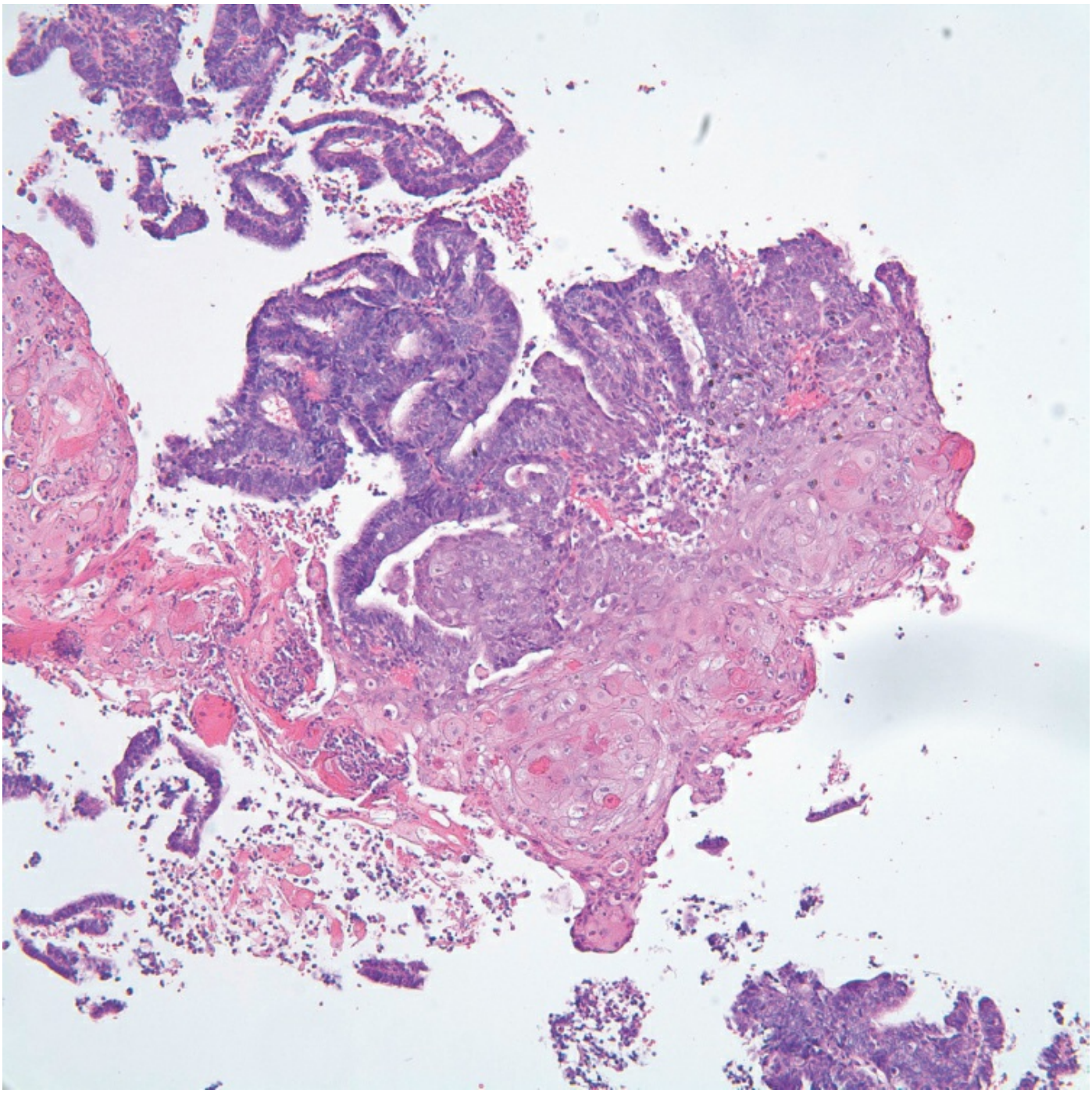


FIGURE 37-3 Adenocarcinoma with squamous differentiation of endometrium. This lesion is also classified as adenoacanthoma. Squamous cells with eosinophilic cytoplasm and distinct cell borders form solid clusters in the lumina of neoplastic glands. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

A *villoglandular* configuration is present in about 2% of endometrioid carcinomas (61). In these tumors, the cells are arranged along fibrovascular stalks, giving a papillary appearance but maintaining the characteristics of endometrioid cells.

The villoglandular variants of endometrioid carcinomas are always well-differentiated lesions that behave like the regular endometrioid carcinomas, and they should be distinguished from serous carcinomas. ***Secretory carcinoma*** **is a rare variant of endometrioid carcinoma that accounts for about 1% of cases (**62). It occurs mostly in women in their early postmenopausal years. The tumors are composed of well-differentiated glands with intracytoplasmic vacuoles similar to early secretory endometrium. These tumors behave as regular well-differentiated endometrioid carcinomas and have an excellent prognosis. Secretory carcinoma may be an endometrioid carcinoma that exhibits progestational changes, but a history of progestational therapy is rarely elicited. Secretory carcinoma must be differentiated from clear cell carcinoma because both tumors have predominately clear cells. These two tumors can be distinguished by their structure: secretory carcinomas have uniform glandular architecture, uniform cytology, and low nuclear grade, whereas clear cell carcinomas have more than one architectural pattern and a high nuclear grade.

Mucinous Carcinoma

About 5% of endometrial carcinomas have a predominant mucinous pattern in which more than one-half of the tumor is composed of cells with intracytoplasmic mucin (63). Most of these tumors have a well-differentiated glandular architecture; their behavior is similar to that of common endometrioid carcinomas, and the prognosis is good. It is important to recognize mucinous carcinoma of the endometrium as an entity and to differentiate it from endocervical adenocarcinoma. Features that favor a primary endometrial carcinoma are the merging of the tumor with areas of normal endometrial tissue, presence of foamy endometrial stromal cells, presence of squamous metaplasia, or presence of areas of typical endometrioid carcinoma.

Serous Carcinoma

About 3% to 4% of endometrial carcinomas resemble serous carcinoma of the ovary and fallopian tube (64). Most often, these tumors are composed of fibrovascular stalks lined by highly atypical cells with tufted stratification **(Fig. 37-4)**. Psammoma bodies are frequently observed.

[3] ***Serous carcinomas,*** **also referred to as** ***uterine papillary serous carcinomas,*** **are considered high-risk lesions.** The first description in 1982 noted that this entity usually occurred in elderly, hypoestrogenic women who presented with advanced-stage disease and accounted for up to one-half of deaths from endometrial carcinoma (64). Since then, several reports documented the aggressive nature and poor prognosis of serous carcinomas.

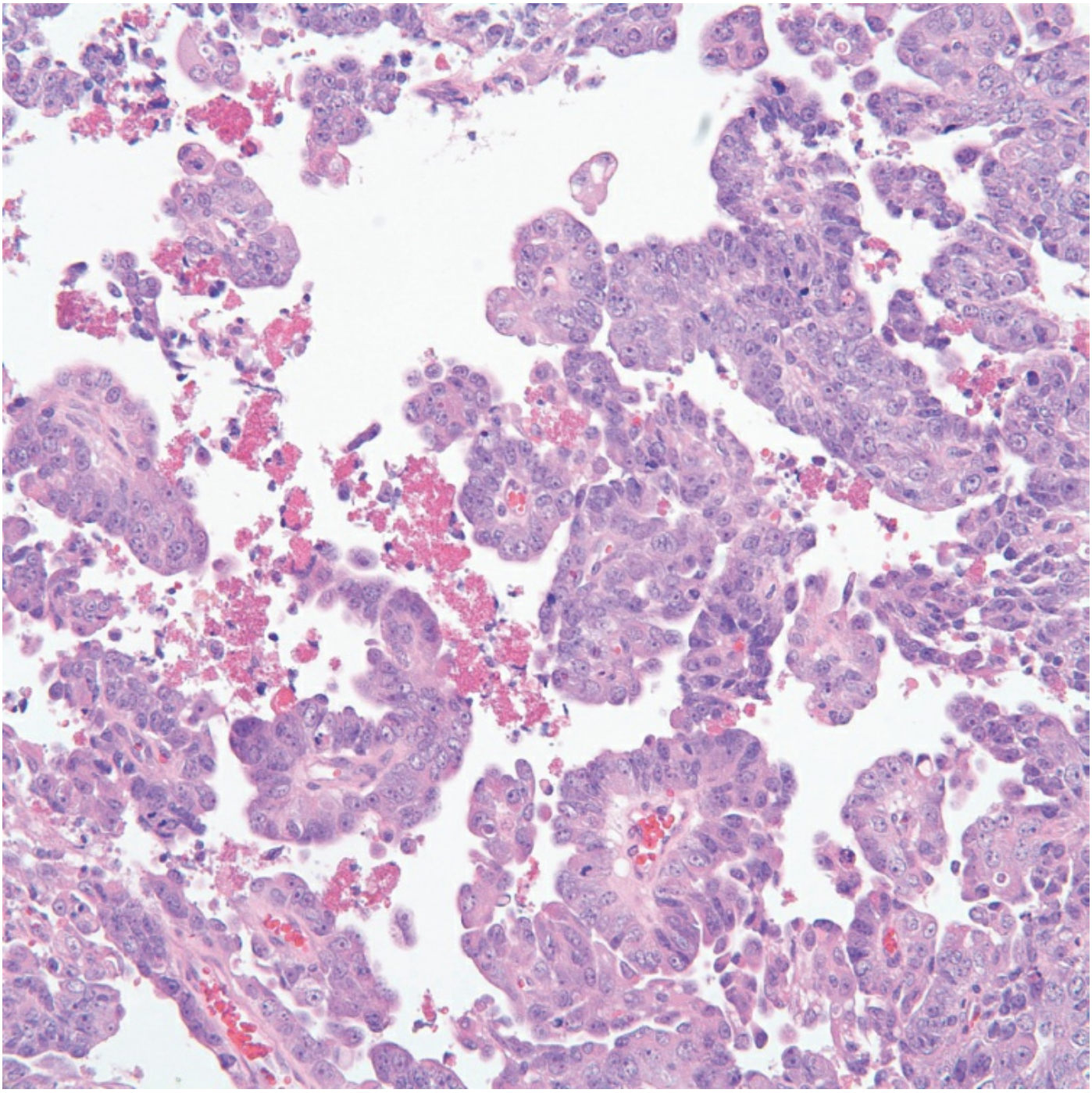


FIGURE 37-4 Serous carcinoma of endometrium. Branching papillae are supported by delicate fibrovascular cores and lined with columnar cells with moderate nuclear atypism, multiple nucleoli, and mitotic figures. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

They are commonly admixed with other histologic patterns, but mixed tumors behave as aggressively as pure serous carcinomas. Even patients with a very small proportion of serous features (5%) remain at high risk of recurrence (65). Serous carcinomas are often associated with lymph–vascular space and deep myometrial invasion. The presence of lymph node metastases, positive peritoneal cytology, and intraperitoneal

tumor does not necessarily correlate with increasing myometrial invasion. **Even when these tumors appear to be confined to the endometrium or endometrial polyps without myometrial or vascular invasion, they behave more aggressively than endometrioid carcinomas and have a propensity to spread intra-abdominally, simulating the behavior of ovarian carcinoma.** In one series, 37% of patients with serous carcinomas of the endometrium confined to a polyp demonstrated extrauterine disease when subjected to exploration and surgical staging (66).

A multi-institutional review of 206 patients with surgical stage I and II serous carcinomas demonstrated recurrence in 21% (65). Substage and treatment with platinum-based chemotherapy were associated with improved overall survival. Survival of surgically staged patients without myometrial invasion or extrauterine disease is between 89% and 100%, suggesting that observation may be appropriate in select patients, particularly in elderly patients with comorbidities (67). However, stage I patients, particularly those with myometrial invasion, remain at high risk of peritoneal and vaginal recurrence. Therefore, platinum-based chemotherapy and vaginal brachytherapy should be considered in these patients (67–69).

Surgical treatment of advanced disease is no different from the endometrioid subtype, consisting of complete extirpation of visible disease (68). In one investigation from the Mayo Clinic, cytoreduction to microscopic residual was associated with a median overall survival of 51 versus 12 months for those patients with any residual (70). Postoperative treatment of advanced disease in the United States consists of chemotherapy and pelvic radiation, with or without para-aortic radiation. The Gynecologic Oncology Group (GOG) study GOG184 included serous carcinomas and randomized patients to *carboplatin* and *paclitaxel* versus *cisplatin, doxorubicin (Adriamycin),* and *paclitaxel* together with tumor volume–directed radiation (71). The former regimen demonstrated similar outcomes with less toxicity. Limited data suggest that delivering radiation "sandwiched" with chemotherapy improves progression-free and overall 3-year survival rates (72). Ongoing studies are evaluating the role of chemotherapy alone for these tumors, especially because of the high rate of peritoneal dissemination and recurrences. It remains unknown whether radiation improves survival when added to chemotherapy.

Clear Cell Carcinoma

Clear cell carcinoma accounts for less than 5% of all endometrial carcinomas (73). Clear cell carcinoma usually has a mixed histologic pattern, including papillary, tubulocystic, glandular, and solid types. The cells have highly atypical nuclei and abundant clear or eosinophilic cytoplasm. Often, the cells have a hobnail configuration arranged in papillae with hyalinized stalks **(Fig. 37-5)**.

Clear cell carcinoma characteristically occurs in older women and like serous carcinoma is considered a poor prognosticator. Traditionally clear cell carcinoma was

associated with very poor outcomes with overall survival rates varying from 33% to 64%. A multi-institutional review of 99 patients with uterine clear cell carcinoma documented only one recurrence (vaginal) in the 22 patients without extrauterine disease subjected to thorough surgical staging (74). Considering all 49 patients with stage I or II disease (regardless of the extent of staging), only one hematologic failure was noted. These data argue against the use of systemic therapy in patients with clear cell carcinoma limited to the pelvis, while the 10% vaginal cuff failure suggests that vaginal brachytherapy alone may be sufficient treatment. In contrast, others argued for systemic treatment of patients with stage I disease (75).

Complete surgical staging is important because 52% of patients with clinical stage I clear cell carcinoma have metastatic disease. Patients who undergo a complete cytoreduction appear to have improved progression-free and overall survivals compared to women left with residual disease following surgery (74). Postoperative therapy for patients with advanced disease is platinum based (75).

Squamous Carcinoma

Squamous carcinoma of the endometrium is rare. Some tumors are pure, but most have a few glands. To establish primary origin within the endometrium, there must be no connection with or spread from cervical squamous epithelium. Squamous carcinoma often is associated with cervical stenosis, chronic inflammation, and pyometra at the time of diagnosis. This tumor has a poor prognosis, with an estimated 36% survival rate in patients with clinical stage I disease (76).

Simultaneous Tumors of the Endometrium and Ovary

Synchronous endometrial and ovarian cancers are the most frequent simultaneously occurring genital malignancies, with a reported incidence of 1.4% to 3.8% (77,78). **Most commonly, the ovarian and endometrial tumor are well-differentiated endometrioid adenocarcinomas of low stage, resulting in an excellent prognosis.** Patients often are premenopausal and present with abnormal uterine bleeding. The ovarian cancer usually is discovered as an incidental finding and is diagnosed at an earlier stage because of the symptomatic endometrial tumor, leading to a more favorable outcome. Up to 29% of patients with endometrioid ovarian adenocarcinomas have associated endometrial cancer. If more poorly differentiated, nonendometrioid histologic subtypes are present, or if the uterine and ovarian tumors are histologically dissimilar, the prognosis is less favorable. Immunohistochemical studies, flow cytometry, and assessment of molecular DNA patterns to detect loss of heterozygosity (LOH) may be helpful in distinguishing between metastatic and independent tumors, but the differential diagnosis can usually be determined by conventional clinical and pathologic criteria.

Pretreatment Evaluation

After establishing the diagnosis of endometrial carcinoma, the next step is to evaluate the patient thoroughly to determine the best and safest approach to management of the disease. A complete history and physical examination are of utmost importance. Patients with endometrial carcinoma are often elderly and obese with a variety of medical problems, such as diabetes mellitus and hypertension, which complicate surgical management. Any abnormal symptoms, such as bladder or intestinal symptoms should be evaluated.

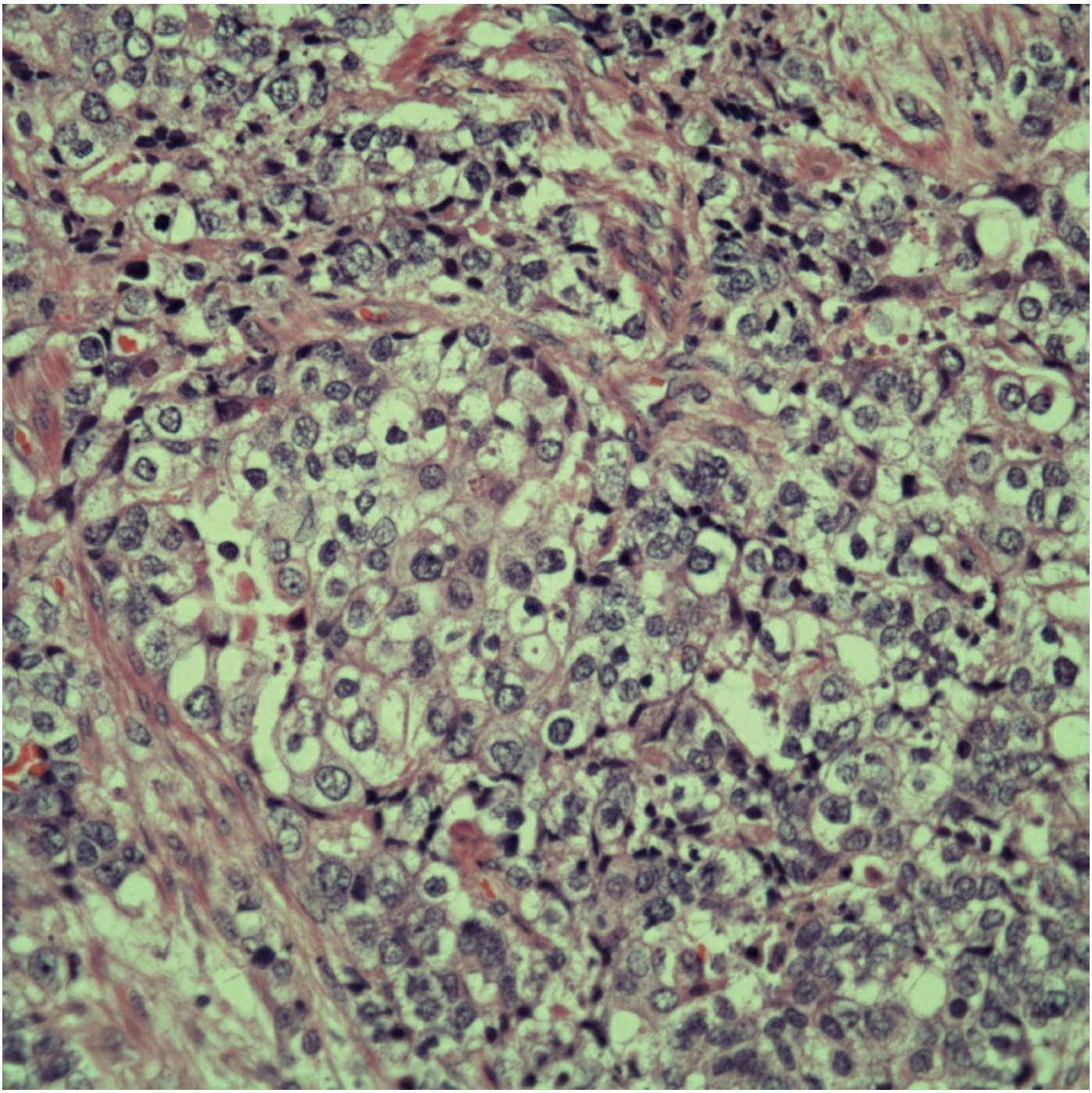


FIGURE 37-5 Clear cell adenocarcinoma of the endometrium. Back-to-back glands lined by polygonal to columnar cells with distinct cell membrane, abundant granular to clear cytoplasm, and variably sized nuclei (including binucleated and multinucleated forms) with prominent nucleoli (magnification ×400). (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

On physical examination, attention should be directed to enlarged or suspicious lymph nodes, including the inguinal area, abdominal masses, and possible areas of cancer spread within the pelvis. Evidence of distant metastasis or locally advanced disease in the pelvis, such as gross cervical involvement or parametrial spread, may alter the treatment approach.

Chest radiography should be performed to exclude pulmonary metastasis and to evaluate the cardiorespiratory status of the patient. Other routine preoperative studies should include electrocardiography, complete blood and platelet counts, and blood type and screen. Other preoperative or staging studies are neither required nor necessary for most patients with endometrial cancer. **Studies such as cystoscopy, colonoscopy, intravenous pyelography, and barium enema are not indicated unless dictated by patient symptoms, physical findings, or other laboratory tests (**79). CT scanning of the abdomen and pelvis may be considered in patients with type II uterine cancer to determine if minimally invasive surgery is appropriate. Stage IV disease is usually clinically evident based on patient symptomatology and clinical examination. Ultrasonography and MRI can be used to assess myometrial invasion preoperatively with a fairly high degree of accuracy (80,81). This information may be of use in planning the surgical procedure with regard to whether lymph node sampling should be undertaken.

Serum CA125, an antigen that is elevated in the blood of 80% of patients with advanced epithelial ovarian cancers, is elevated in most patients with advanced or metastatic endometrial cancer. In one study, 78% of endometrial cancer patients with lymph node metastases had an elevated preoperative CA125 level (82). Preoperative measurement of serum CA125 may help determine the extent of surgical staging and, if elevated, may be useful as a tumor marker in assessing response to subsequent therapy (83,84).

Clinical Staging

Clinical staging, according to the 1971 FIGO system, should be performed only in patients who are deemed not to be surgical candidates because of their poor medical condition or the degree of disease spread (85). The current FIGO staging is surgical, which has supplanted the old clinical system. With improvements in preoperative and postoperative care, anesthesia administration, and surgical techniques, almost all patients are medically suitable for operative therapy. A small percentage of patients will not be candidates for surgical staging because of gross cervical involvement,

parametrial spread, invasion of the bladder or rectum, or distant metastasis.

Surgical Staging

Widely accepted management of endometrial cancer consists of hysterectomy, [4] removal of remaining adnexal structures, and appropriate surgical staging in patients considered at risk for extrauterine disease (86,87). Surgical staging has been recommended for patients with endometrial cancer since 1988 (87). In spite of this general recommendation, the incorporation of a systematic pelvic and para-aortic lymphadenectomy in all patients is not universally accepted (88,89). This recommendation became more controversial after the publication of two large prospective randomized trials that failed to demonstrate improved outcomes for patients who underwent pelvic lymphadenectomy (90,91). These two studies show differences in their design: in the ASTEC trial all women with clinical stage I were included without exclusion criteria, whereas the Italian study excluded women with stage IA and IB grade 1 tumors, and nonendometrioid malignancies. In the Italian study, systematic nodal dissection was performed, as opposed to pelvic node sampling in the ASTEC trial (median number of lymph nodes harvested 30 vs. 12, respectively). The studies share characteristics that could lead to misinterpretation of their results. The percentage of nodal positivity is low in both studies (13% and 9%), suggesting that regardless of differences in exclusion criteria, low-risk cases were included in both studies, thus diluting possible (if any) therapeutic benefit of lymphadenectomy. Neither study used the information derived from lymphadenectomy to target postoperative treatment (i.e., to spare patients with negative nodes from radiotherapy or to target postoperative treatment to the metastatic areas), thus eliminating a potential benefit.

GOG33 demonstrated that patients with absent or superficial myometrial invasion have a low probability of lymphatic metastases (92)**, and this risk approaches zero for patients with endometrioid grade 1 or 2 disease, superficial myometrial invasion, and tumor diameter less than 2 cm** (93). An observational study reported a significant survival benefit of para-aortic lymphadenectomy in patients at intermediate or high risk of recurrence (based on presence of histologic grade 3 or deep myometrial invasion, or lymphovascular invasion, or evidence of spread outside of the uterine corpus), compared to patients who had hysterectomy with pelvic lymphadenectomy but without para-aortic lymphadenectomy. This benefit was not observed in patients with low-risk endometrial cancer (94). The Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) study identified patients with stage IC, grade 3 endometrial carcinoma as being at high risk of early distant spread and death when treated with hysterectomy only (no staging), followed by pelvic external beam radiation therapy. These patients had a 31% risk of distant recurrence (89). Patients with the greatest potential to benefit from surgical staging are those with risk

factors such as histologic grade 3, deep myometrial invasion, or lymphovascular invasion (see Surgical Treatment for a discussion of sentinel lymph node biopsy).

In summary, surgical staging should (a) identify patients with disseminated disease who are at high risk of recurrence; (b) target postoperative treatment; (c) reduce the number of patients potentially requiring postoperative treatment when the provided information is used appropriately (avoiding the risk of morbidity without reasonable benefit); and (d) possibly eradicate lymphatic disease. In spite of these potential benefits in high-risk patients, prospective randomized data demonstrating a survival advantage or reduction in overall morbidity resulting from a potential reduction of adjuvant treatment are not available.

Table 37-6 Carcinoma of the Endometrium (2008)

Stage I[a]	Tumor confined to the corpus uteri
IA[a]	No or less than half myometrial invasion
IB[a]	Invasion equal to or more than half of the myometrium
Stage II[a]	Tumor invades cervical stroma, but does not extend beyond the uterus[b]
Stage III[a]	Local and/or regional spread of the tumor
IIIA[a]	Tumor invades the serosa of the corpus uteri and/or adnexae[c]
IIIB[a]	Vaginal and/or parametrial involvement[c]
IIIC[a]	Metastases to pelvic and/or para-aortic lymph nodes[c]
IIIC1[a]	Positive pelvic nodes
IIIC2[a]	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV[a]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA[a]	Tumor invasion of bladder and/or bowel mucosa
IVB[a]	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

[a]Either G_1, G_2, or G_3.

[b]Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

[c]Positive cytology has to be reported separately without changing the stage.

FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obst* 2009;105:103–104.

The FIGO published the updated surgical staging system for endometrial cancer

(Table 37-6) (95). In comparison with recommendations from 1988, the new system introduces the following changes: (a) former stages IA and IB are combined; (b) former stage IIA was eliminated so that only the presence of cervical stroma involvement is considered stage II disease; (c) peritoneal cytologic findings positive for endometrial cancer are no longer a criterion for disease upstaging (although FIGO still recommends the collection of peritoneal washing, recognizing the predictive value of positive cytologic findings when combined with other poor prognosis factors); and (d) stage IIIC was divided into IIIC1 and IIIC2 in accordance with the absence or presence of positive para-aortic nodes. The presence of parametrial disease is now formally recognized as stage IIIB disease.

Prognostic Variables

Although disease stage is the most significant variable affecting survival, [5] a number of other individual prognostic factors for disease recurrence or survival are known, including tumor grade, histopathology, depth of myometrial invasion, patient age, and surgical-pathologic evidence of extrauterine disease spread (**Tables 37-7** and **37-8**). Other factors, such as **tumor size, peritoneal cytology, hormone receptor status, flow cytometric analysis, and oncogene perturbations, are implicated as having prognostic importance.**

Table 37-7 Surgical-Pathologic Findings in Clinical Stage I Endometrial Cancer

Surgical-Pathologic Finding	Percentage of Patients
Histology	
Adenocarcinoma	80
Adenosquamous	16
Other (papillary serous, clear cell)	4
Grade	
1	29
2	46
3	25
Myometrial invasion	
None	14
Inner third	45
Middle third	19

Outer third	22
Lymph–vascular space invasion	15
Isthmic tumor	16
Adnexal involvement	5
Positive peritoneal cytology	12
Pelvic lymph node metastasis	9
Aortic lymph node metastasis	6
Other extrauterine metastasis	6

Modified from **Creasman WT, Morrow CP, Bundy BN, et al.** Surgical pathologic spread patterns of endometrial cancer. *Cancer* 1987;60:2037–2041, with permission.

Age

In general, younger women with endometrial cancer have a better prognosis than older women. Two reports observed no deaths related to disease in patients with endometrial cancer diagnosed before 50 years of age (96,97). Another series demonstrated a 60.9% 5-year survival rate for patients older than 70 years of age, compared with 92.1% survival rate for patients younger than 50 years of age (98). Decreased survival was associated with an increased risk for extrauterine spread (38% vs. 21%) and deep myometrial invasion (57% vs. 24%) for these two groups. **[7]** The GOG reported 5-year survival rates of 96.3% for patients 50 years of age or younger; 87.3% for patients 51 to 60 years; 78% for patients 61 to 70 years; 70.7% for patients 71 to 80 years; and 53.6% for patients older than 80 years (99).

Increased risk for recurrence in older patients was related to a higher incidence of grade 3 tumors or unfavorable histologic subtypes; however, age appears to be an independent prognostic variable. Increasing patient age appears to be independently associated with disease recurrence in endometrial cancer (100,101). In one study, the mean age at diagnosis of patients who had recurrence or died of disease was 68.6 years, compared with 60.3 years for patients without recurrence. For every 1 year increase in age, the estimated rate of recurrence increased 7%. None of the patients younger than 50 years of age developed recurrent cancer, compared with 12% of patients aged 50 to 75 years and 33% of patients older than 75 years (102).

Histologic Type

Nonendometrioid histologic subtypes account for about 10% of endometrial cancers and carry an increased risk for recurrence and distant spread (103–105). In a retrospective review of 388 patients treated at the Mayo Clinic for endometrial cancer, 52 (13%) had an uncommon histologic subtype, including 20 adenosquamous,

14 serous, 11 clear cell, and 7 undifferentiated carcinomas. In contrast to the 92% survival rate among patients with endometrioid tumors, the overall survival for patients with one of these more aggressive subtypes was only 33%. At the time of surgical staging, 62% of the patients with an unfavorable histologic subtype had extrauterine spread of disease (103).

Histologic Grade

Histologic grade of the endometrial tumor is strongly associated with prognosis (86,92,102,106–108). In one study, recurrences developed in 7.7% of grade 1 tumors, 10.5% of grade 2 tumors, and 36.1% of grade 3 tumors. Patients with grade 3 tumors were in excess of five times more likely to have a recurrence than were patients with grades 1 and 2 tumors. The 5-year disease-free survival rates for patients with grades 1 and 2 tumors were 92% and 86%, respectively, compared with 64% for patients with grade 3 tumors (149). Another study reported similar results, noting recurrences in 9% of patients with grades 1 and 2 tumors compared with 39% of patients with grade 3 lesions (107). Increasing tumor anaplasia is associated with deep myometrial invasion, cervical extension, lymph node metastasis, and both local recurrence and distant metastasis.

Table 37-8 Prognostic Variables in Endometrial Carcinoma

Age
Histologic type
Histologic grade
Myometrial invasion
Lymph–vascular space invasion
Isthmus–cervix extension
Adnexal involvement
Lymph node metastasis
Intraperitoneal tumor
Tumor size
Peritoneal cytology
Hormone receptor status
DNA ploidy/proliferative index
Genetic/molecular tumor markers

Tumor Size

Tumor size is a significant prognostic factor for lymph node metastasis and survival in patients with endometrial cancer (93,109,110). One report determined tumor size in 142 patients with clinical stage I endometrial cancer and found lymph node metastasis in 4% of patients with tumors 2 cm or smaller, in 15% of patients with tumors larger than 2 cm, and in 35% of patients with tumors involving the entire uterine cavity (108). Tumor size better defined an intermediate-risk group for lymph nodes metastasis (i.e., patients with grade 2 tumors with less than 50% myometrial invasion). Overall, these patients had a 10% risk for lymph node metastasis, but there was no nodal metastasis associated with tumors 2 cm or smaller, compared with 18% when tumors were larger than 2 cm. Five-year survival rates were 98% for patients with tumors 2 cm or smaller, 84% for patients with tumors larger than 2 cm, and 64% for patients with tumors involving the whole uterine cavity (109).

Hormone Receptor Status

Estrogen receptor and progesterone receptor levels are prognostic indicators for endometrial cancer independent of grade in several studies (111–114). Patients whose tumors are positive for one or both receptors have longer survival times than patients whose carcinomas lack the corresponding receptors. Even patients with metastasis have an improved prognosis with receptor-positive tumors (112). Progesterone receptor levels appear to be stronger predictors of survival than estrogen receptor levels, and the higher the absolute level of the receptors, the better the prognosis.

DNA Ploidy and Proliferative Index

About two-thirds of endometrial adenocarcinomas have a diploid DNA content as determined by flow cytometric analysis (113,115–118). **The proportion of nondiploid tumors increases with stage, lack of tumor differentiation, and depth of myometrial invasion.** In several studies, DNA content was related to clinical course of the disease, with death rates reported to be higher in women whose tumors contained aneuploid populations of cells. The proliferative index is related to prognosis.

Myometrial Invasion

Because access to the lymphatic system increases as cancer invades into the outer one-half of the myometrium, increasing depth of invasion is associated with increasing likelihood of extrauterine spread and recurrence (92,107,119). The association of depth of myometrial invasion with extrauterine disease and lymph node metastases was reported (92). Of patients without demonstrable myometrial invasion, only 1% had pelvic lymph node metastasis, compared with patients with outer one-third myometrial invasion who had 25% pelvic and 17% aortic lymph node metastases. Deep

myometrial invasion (>50% for all stages; ≥66% for stage I) is the strongest predictor of hematogenous recurrence (120). Survival decreases with increasing depth of myometrial invasion. In general, patients with noninvasive or superficially invasive tumors have an 80% to 90% 5-year survival rate, whereas those with deeply invasive tumors have a 60% survival rate. The most sensitive indicator of the effect of myometrial invasion on survival is distance from the tumor–myometrial junction to the uterine serosa. Patients with tumors that are less than 5 mm from the serosal surface are at much higher risk for recurrence and death than those with tumors greater than 5 mm from the serosal surface (121).

Lymph–Vascular Space Invasion

Lymph–vascular space invasion (LVSI) appears to be an independent risk factor for recurrence and death from all types of endometrial cancer (92,122,123). The overall incidence of LVSI in early endometrial cancer is about 15%, although it increases with increasing tumor grade and depth of myometrial invasion. One study reported LVSI in 2% of grade 1 tumors and 5% of superficially invasive tumors, compared with 42% of grade 3 tumors and 70% of deeply invasive tumors (124). LVSI was demonstrated to be a strong predictor of lymphatic dissemination and lymphatic recurrence (125). Another study reported deaths in 26.7% of patients with clinical stage I disease with LVSI, compared with 9.1% of those without LVSI (126). Likewise, an 83% 5-year survival rate was reported for patients without demonstrable LVSI, compared with a 64.5% survival rate for those in whom LVSI was present (181). Using multivariate analysis, LVSI correlated significantly with survival of patients with stage I endometrial adenocarcinomas in another report (123).

Isthmus and Cervix Extension

The location of the tumor within the uterus is important. Involvement of the uterine isthmus, cervix, or both, is associated with an increased risk for extrauterine disease, lymph node metastasis, and recurrence. Cervical stromal invasion was a strong predictor of lymphatic dissemination and lymphatic recurrence, especially for pelvic lymph nodes (125). One study reported that if the fundus of the uterus alone was involved with tumor, there was a 13% recurrence rate, whereas if the lower uterine segment or cervix was involved with occult tumor, there was a 44% recurrence rate (105). A subsequent GOG study found that tumor involvement of the isthmus or cervix without evidence of extrauterine disease was associated with a 16% recurrence rate and a relative risk of 1.6 (86). Patients with cervical involvement tended to have higher-grade, larger, and more deeply invasive tumors, undoubtedly contributing to the increased risk for recurrence.

Peritoneal Cytology

Several historical reports noted increased recurrence rates and decreased survival rates

and, on this basis, recommended treatment for positive cytology (127,128). Most of the studies included patients with other evidence of extrauterine disease spread and were performed without appropriate multivariate analysis and with patients who were incompletely staged. The GOG study critically analyzed 1,180 clinical stages I and II endometrial cancer patients in whom appropriate surgical and pathologic staging was performed (86). Considering only the 697 patients for whom peritoneal cytology status and adequate follow-up were available, 25 (29%) of 86 patients with positive cytology developed recurrence, compared with 64 (10.5%) of 611 patients with negative cytology. They noted that 17 of the 25 recurrences in the positive cytology group were outside the peritoneal cavity.

In contrast to these reports, an equal number of studies found no significant relationship between malignant peritoneal cytology and an increased incidence of disease recurrence in the absence of other risk factors such as extrauterine disease (128–130). Patients with positive peritoneal cytology as the only site of extrauterine disease (i.e., no adnexal or uterine serosal invasion) and without poor prognosticators (i.e., myometrial invasion more than 50%, nonendometrioid histologic subtype, grade 3, lymph-vascular space invasion, cervical invasion) have a very favorable outcome with an absence of extra-abdominal recurrences (131). These patients have an associated 5-year survival of 98% to 100% even when not treated with adjuvant therapy (99,142). Patients with positive cytology in addition to poor prognostic factors demonstrate a high rate (47%) of distant extra-abdominal failure and may potentially benefit from systemic chemotherapy. **Positive peritoneal cytology seems to have an adverse effect on survival only if the endometrial cancer has spread to the adnexa, peritoneum, or lymph nodes, not if the disease is otherwise confined to the uterus (**132). These considerations led to the omission of cytology as a factor impacting stage in the FIGO 2009 staging criteria.

The following conclusions may be reached regarding the prognostic implications of positive peritoneal cytology:

1. **Positive peritoneal cytology is associated with other known poor prognostic factors.**
2. **Positive peritoneal cytology in the absence of other evidence of extrauterine disease or poor prognostic factors has no significant effect on recurrence and survival.**
3. **Positive peritoneal cytology, when associated with other poor prognostic factors or extrauterine disease, increases the likelihood for distant and intra-abdominal disease recurrence and has a significant adverse effect on survival.**
4. **Use of several different therapeutic modalities has not resulted in any proven benefit to patients with endometrial cancer and positive peritoneal cytology.**

Stage IIIA: Adnexal or Uterine Serosal Involvement

Most patients with stage IIIA disease have other poor prognostic factors that place them at high risk for recurrence. One series described treatment of all patients with serosal or adnexal invasion (or both) with whole-abdomen radiotherapy. Failures were observed outside the abdomen in 100% of patients with full-thickness myometrial invasion or uterine serosal invasion, and in 20% to 25% of cases in the presence of isolated adnexal invasion (86,133). These patients may benefit from postoperative systemic chemotherapy.

Lymph Node Metastasis

Lymph node metastasis is the most important prognostic factor in clinical early-stage endometrial cancer. Of patients with clinical stage I disease, about 10% will have pelvic and 6% will have para-aortic lymph node metastases. Patients with lymph node metastases have almost a sixfold higher likelihood of developing recurrent cancer than patients without lymph node metastases. One study reported a recurrence rate of 48% with positive lymph nodes, including 45% with positive pelvic nodes and 64% with positive aortic nodes, compared with 8% with negative nodes. **The 5-year disease-free survival rate for patients with lymph node metastases was 54%, compared with 90% for patients without lymph node metastases (**99). One series examined patients with lymph node metastases in addition to other extrauterine sites of disease (vagina, uterine serosa, positive peritoneal cytology, adnexal invasion). The recurrence rates were 67% (41% extranodal) for those with lymphatic dissemination versus 32% (5% extranodal) for those with other sites of extrauterine disease spread (131).

Intraperitoneal Metastases

Extrauterine metastasis, excluding peritoneal cytology and lymph node metastasis, occurs in about 4% to 6% of patients with clinical stage I endometrial cancer. Gross intraperitoneal spread is highly correlated with lymph node metastases; one study noted that 51% of patients with intraperitoneal tumor had positive lymph nodes, whereas only 7% of patients without gross peritoneal spread had positive nodes (92). Extrauterine spread other than lymph node metastasis is significantly associated with tumor recurrence. Another study found that 50% of patients with extrauterine disease developed recurrence, compared with 11% of patients without extrauterine disease, making recurrence almost five times more likely in patients with extrauterine disease spread. The 5-year disease-free survival rate for patients with nonlymphatic extrauterine disease was 50%, compared with 88% in other patients (99). Predictors of peritoneal relapse include stage IV disease or stage II or III disease with two or more of the following risk factors: cervical invasion, positive peritoneal cytology, positive lymph nodes, and nonendometrioid histology (134).

Types I and II Endometrial Carcinoma: Molecular Aberrations

Based on their etiologic and pathologic features, sporadic endometrial cancer is classified into two subtypes (2,87). Type I (endometrioid histology) represents the majority of lesions (approximately 80%), which are mostly low grade, estrogen receptor positive, associated with hyperestrogenism, and arise from atypical complex hyperplasia (135). Hyperestrogenism may be attributed to obesity with peripheral conversion of androgens to estrogens, anovulation, or exposure to excessive exogenous estrogen (87,136–138). Obesity, polycystic ovarian syndrome, *tamoxifen* use, and unopposed *estrogen* use are all associated with increased risk of endometrial cancer. Other associated findings include late onset of menopause, nulliparity, diabetes mellitus, and hypertension. The molecular basis for the progression from hyperplasia to invasive endometrial carcinoma as a result of hyperestrogenism remains unknown because the involvement of only a minority of factors is reproducible (139). In contrast, type II endometrial cancer (serous, clear cell carcinoma) appears to be unrelated to high estrogen levels and often develops in nonobese women. Type II cancers arise from its precursor, endometrial intraepithelial carcinoma (EIC) adjacent to an atrophic endometrium background in relatively older women (140). Distinct molecular changes are associated with these two subtypes. Common genetic changes in endometrioid endometrial cancer include mutations in *PTEN* (141–144), or β-catenin genes (145). In contrast, type II cancers frequently demonstrate alterations in HER2/*neu,* p53, p16, E-cadherin, and loss of LOH (146). These distinct molecular alterations underscore prognostic differences. Type I endometrial cancer is limited to the uterus in 70% of cases with a 5-year survival greater than 85%. Type II endometrial cancer displays a more aggressive clinical course and a poor prognosis; even in tumors with little or no myometrial invasion, more than one in three patients will have extensive extrauterine spread with complete surgical staging, resulting in an overall survival of 20% (66,70,73,147).

Inactivation of the *PTEN* tumor–suppressor gene is one of the earliest aberrations observed in endometrial cancer precursors and is the most common genetic defect in type I cancers, observed in up to 83% of tumors (141). Tumors with *PTEN* mutations tend to be well differentiated and minimally invasive (148). Approximately 20% of sporadic endometrioid cancers demonstrate a molecular phenotype referred to as microsatellite instability (MSI) (149,150). Microsatellites are short segments of repetitive DNA bases scattered throughout the genome. MSI describes the accumulation of sequence changes in these DNA segments that occur because of the inactivation of intranuclear proteins that comprise the mismatch repair system (151). Inactivation of *MLH1*, a component of the mismatch repair system, is a common event in type I endometrial cancer. This alteration occurs through hypermethylation of CpG islands in the gene promoter, a process known as epigenetic silencing (152,153). This is in contrast to colon cancer, in which MSI and inactivation of the mismatch repair genes

occurs through mutations in mismatch repair genes, including *hMSH2, hMLH1, PMS1, PMS2,* or *hMSH6* (31). MSI and abnormal methylation of *MLH1* are early events in endometrial carcinogenesis and are described in precancerous lesions (154,155). Mutations in codons 12 or 13 of the K-ras oncogene are reported in 10% to 20% of endometrial adenocarcinomas (156). The presence of mutations of K-ras appears to be an independent unfavorable prognostic factor (157,158).

Chromosomal instability with extensive genomic derangements is commonly found in type II endometrial cancers (159). The most frequent genetic alteration is TP53 mutation, present in about 90% of serous carcinomas (160,161). In contrast to endometrioid carcinoma, MSI is rare (<5%), as are K-ras and *PTEN* mutations (144,162). Other genetic alterations that occur more frequently in serous compared to endometrioid carcinomas are inactivation of p16 (45%) and overexpression and gene amplification of HER2/*neu* oncogene (45% and 70%, respectively) (160,163). HER-2/*neu* overexpression is related to diminished, progression-free survival (164,165). E-cadherin, an oncogene responsible for cell-to-cell adhesion that seems to play a critical role in initiation and progression of endometrial neoplasia, is absent or reduced in 62% to 87% of cases. Loss of E-cadherin is often associated with advanced stage and LOH in both serous and clear cell carcinomas (166,167).

Surgical Treatment

The most common current protocol for surgical management of endometrial cancer includes peritoneal cytology, hysterectomy and bilateral salpingo-oophorectomy, and surgical staging. In patients with nonendometrioid cancer, omentectomy along with appendectomy and peritoneal biopsies may be performed. The need to perform lymphadenectomy continues to evolve from complete pelvic and para-aortic lymphadenectomy historically, to lymphadenectomy based on risk factors for dissemination, to the increasingly common use of sentinel lymph node biopsy (168,169). The National Comprehensive Cancer Network (NCCN)® states that lymph node assessment can be performed using either strategy (170).

Selective lymphadenectomy based on a surgical algorithm is determined by histology, tumor grade, tumor size, extent of myometrial invasion, and presence of extra-uterine disease. Lymphadenectomy is omitted altogether for patients without endometrioid tumors measuring less than 2 cm in size and less than 50% myometrial invasion. The decision to administer postoperative radiation, chemotherapy, or both, is predicated on the final results of pathologic examination of the surgical specimen and cytology, according to previously described criteria (168).

Sentinel lymphadenectomy is performed using a standardized cervical injection of indocyanine green and fluorescence imaging in patients with clinical stage I endometrial cancer of all histologies and grades. Identified sentinel lymph nodes are evaluated using

hematoxylin, eosin, and immunohistochemistry staining. A multicenter trial showed a 97.2% sensitivity and negative predictive value of 99.6% for the sentinel lymph node technique (171). Patients with macrometastases in sentinel lymph nodes are treated according to previous algorithms (172). Adjuvant therapy for low-volume sentinel lymph node metastases is still under debate (173).

Vaginal Hysterectomy

Vaginal hysterectomy may be considered for patients with endometrial cancer and multiple morbidities and in some circumstances may be preferable to radiation therapy alone. Vaginal hysterectomy with bilateral salpingo-oophorectomy alone may be acceptable treatment for patients with low-risk tumors (endometrioid, grade 1 or 2, <50% myometrial invasion, and tumor diameter <2 cm). In one report, a 94% survival rate was found in 56 patients with clinical stage I endometrial carcinoma treated by vaginal hysterectomy, with or without postoperative radiotherapy (mostly brachytherapy). Three-fourths of these patients had grade 1 lesions (174). Other groups have reported excellent outcomes for patients treated with vaginal hysterectomy with curative intent (175,176).

Laparoscopic Management

Advances in endoscopic technologies and power sources allowed application of a laparoscopic approach to the management of endometrial cancer. Since 1992, there were multiple reports documenting the feasibility of laparoscopically assisted vaginal hysterectomy with bilateral salpingo-oophorectomy and laparoscopic lymphadenectomy for staging and treatment of patients with endometrial cancer (177–180). These early studies demonstrated no differences in lymph node counts, estimated blood loss, and recurrence or survival rates with laparoscopy versus laparotomy, whereas decreased perioperative morbidity, longer operating times, shorter hospital stays, and earlier return to work were associated with laparoscopy.

Although the literature has isolated case reports of port site metastases, there are few data documenting the incidence. Martinez et al. analyzed 1,216 patients with endometrial and cervical cancer and showed that the port site metastasis rate was less than 0.5%; no port site metastases occurred after excluding patients with peritoneal disease (181).

A large prospective study by GOG randomized patients to laparoscopy versus laparotomy for the primary treatment of patients with endometrial cancer (182). Over 2,500 patients were enrolled, 1,696 to laparoscopy and 920 to laparotomy. Consistent with early reports, patients randomized to laparoscopy had shorter hospital stay (52% more than 2 days vs. 94% in the laparotomy group), less blood loss, and fewer postoperative complications (14% vs. 21%). The rate of intraoperative complications was similar, and the operative time was longer in the laparoscopy cohort. There was no difference in lymph node counts, and stage distribution was identical between groups. A

follow-up quality-of-life investigation of the same cohorts revealed improved Functional Assessment of Cancer Therapy–General (FACT-G) scores, better physical functioning, better body image, less pain and its interference with quality of life, and an earlier resumption of normal activities and return to work over the 6-week recovery period in the laparoscopic group (183). Although the differences were modest and negligible by 6 months, the analysis was performed as per intention to treat. Of concern was the 24% rate of conversions in the laparoscopic cohort; only 4% were converted because of advanced disease. Improvements in laparoscopic equipment and surgical technique have drastically decreased this conversion rate to 2.4% in a subsequent trial (184).

The use of extraperitoneal laparoscopic staging for para-aortic lymphadenectomy was reported in a prospective investigation of 293 patients with endometrial cancer (185). The extraperitoneal approach greatly improved exposure by circumventing handling of the small bowel and was successful in over 90% of unselected patients up to a BMI of 51. There was no difference in lymph node counts, all dissections were performed to the level of the renal veins, and significant improvements in blood loss, postoperative complications, and length of stay were noted compared to the laparotomy group. If full para-aortic lymphadenectomy is necessary in an obese patient, the extraperitoneal approach offers the most reliable method to consistently perform a thorough dissection.

Robotic-assisted surgery gained popularity for endometrial cancer treatment (see Chapter 28). Improved instrumentation and visualization allow minimally invasive surgery to be performed by surgeons with less laparoscopic experience, and in patients, particularly obese patients, who otherwise might not be candidates for minimally invasive surgery. In one report limited to obese patients with endometrial carcinoma, the robotic approach offered reduced operating times, less blood loss, higher lymph node yields, and shorter hospital stays compared to laparoscopy (186).

When not limited to obese patients, robotic-assisted surgery appears to offer the same benefits as laparoscopy in regards to postoperative morbidity and convalescence compared to laparotomy, but with shorter operative times (187). Long-term survival in patients treated with laparoscopy for their endometrial cancer show comparable outcomes, and can be expected to apply to robotic surgery, as it is simply an advanced laparoscopic tool. A GOG trial showed three-year recurrence rates of 11.4% with laparoscopy versus 10.2% with open surgery, and 5-year survival was 90% in both arms (188).

Radical Hysterectomy

Radical hysterectomy, with removal of the parametria and upper vagina, and bilateral pelvic lymphadenectomy, does not improve survival of patients with clinical stage I disease compared with extrafascial hysterectomy and bilateral

salpingo-oophorectomy alone (189–191). Radical hysterectomy increases intraoperative and postoperative morbidity and should not be performed for treatment of apparent early endometrial cancer. In the presence of demonstrable invasion of the cervix, a modified extrafascial hysterectomy may be performed. This may improve outcomes and decrease the risk of local recurrences, especially if postoperative local radiation is not planned in younger patients (192).

Radiation Therapy as Primary Treatment

Primary surgery followed by individualized radiation therapy is the most widely accepted treatment for early-stage endometrial cancers. About 5% to 15% of endometrial cancer patients have severe medical conditions that render them unsuitable for surgery (86). These patients tend to be elderly and obese with multiple chronic or acute medical illnesses, such as hypertension, cardiac disease, diabetes mellitus, and pulmonary, renal, and neurologic diseases.

Several series show that radiotherapy is effective treatment for patients with inoperable endometrial cancer (Table 37-9) (193,194). One reported on the treatment of 120 patients with clinical stage I and 17 patients with clinical stage II endometrial cancer with radiation alone, 85% of whom received only intracavitary radiation. Because of the high incidence of death caused by intercurrent illness in this group of patients, the 5- and 10-year overall survival rates were only 55% and 28%, respectively, compared with disease-specific survival rates of 87% and 85%, respectively. There was no difference in disease-specific survival rates between patients with stage I and II disease. Intrauterine cancer recurred in 14% of patients, and extrauterine pelvic disease recurred in 3%. The authors treated 15 patients with stage III and IV disease, usually with a combination of external-beam and intracavitary radiation therapy, yielding a 5-year disease-specific survival rate of 49%. Five patients (3%) had serious late complications of radiation therapy (194).

Although it is generally agreed that intracavitary radiation is necessary to achieve adequate local control, the indications for external-beam radiation therapy in the primary treatment of endometrial cancer are less well defined. Patients with cervical involvement and known or suspected extrauterine pelvic spread undoubtedly would benefit from external-beam radiation therapy. Theoretically, external-beam radiation could sterilize microscopic nodal disease and possibly increase the radiation dose to deep myometrial or subserosal uterine disease, which may receive an insufficient dose from intracavitary radiation alone. A correlation between tumor grade and recurrence was noted in several reports. One found that the 5-year progression-free survival rate for medically inoperable patients with clinical stage I disease treated with radiotherapy alone was 94% for grade 1, 92% for grade 2, and 78% for grade 3 tumors (193).

The decision to treat a patient who has endometrial cancer with radiation alone must include a careful analysis of the relative risks and benefits of surgery. Although

radiation alone can produce excellent survival and local control, it should be considered for definitive treatment only if the operative mortality rate is estimated to exceed the 10% to 15% risk for uterine recurrence that is expected with radiation treatment alone.

Table 37-9 Review of Recent Series of Endometrial Carcinoma Treated with Radiation Alone

Author	Year	Stage	No. of Patients	Local Recurrence Rate (%)	Disease-Specific Survival Rate (%)[a]	Major Complication Rate (%)[a]
Landgren et al.	1976	I–II	124	22	68	7
		III–IV	26	42	22	
Abayomi et al.	1982	I–II	50	26	78	15
		III–IV	16	—	10	
Patanaphan et al.	1985	I–II	42	14	64	2
		III–IV	10	60	20	
Jones and Stout	1986	I–II	146	22	61	4
		III–IV	14	79	14	
Varia et al.	1987	I–II	73	21	43	10
Wang et al.	1987	I–II	41	22	76	5
Grigsby et al.	1987	I	69	9	88	16
Taghian et al.	1988	I–II	94	6	70	17
		III–IV	10	10	27	
Lehoczky et al.	1991	I	171	20	75	0
Kupelian et al.	1993	I–II	137	14	85	3
		III–IV	15	32	49	

[a]For all stages combined.

From **Kupelian PA, Eifel PJ, Tornos C, et al.** Treatment of endometrial carcinoma with radiation therapy alone. *Int J Radiat Oncol Biol Phys* 1993;27:817–824, with permission.

Patterns of Metastatic Dissemination: Implications for Postoperative and Disease-Based Adjuvant Treatment

Endometrial cancer is commonly diagnosed early in its natural history with approximately 80% of patients presenting with stage I disease. Nevertheless, approximately one of every three women who die of endometrial cancer was considered to have early locoregional disease at primary diagnosis. The majority of treatment failures and the accompanying compromised longevity probably result from the failure to recognize sites of occult extrauterine dissemination at primary diagnosis. Traditional postoperative therapy (modality based) for high-risk endometrial cancer is external-beam radiotherapy that is frequently supplemented with vaginal brachytherapy. This approach improves local control but not survival in early-stage disease (88,195).

Understanding the different pathways of metastatic dissemination of endometrial cancer and their predictive factors allows the development of an individualized model for target-based therapeutic approaches to the predicted site(s) of failure. The natural

history of epithelial corpus cancer includes four potential routes of metastasis: (a) contiguous extension (mainly to the vagina); (b) hematogenous dissemination; (c) lymphatic embolization; and (d) exfoliation with intraperitoneal spread. On the basis of regression analysis, independent pathologic risk factors predictive of the four routes of metastatic spread were identified:

1. **Contiguous extension: histologic grade 3 and lymph-vascular space invasion are proven predictors of vaginal relapse in stage I endometrial cancer (**196).
2. **Hematogenous: deep myometrial invasion is the strongest predictor of hematogenous recurrence (>50% for all stages and ê66% for stage I) (**119,120).
3. **Lymphatic: lymphatic failure is more likely to occur when cervical stroma involvement or positive lymph nodes are present (**125).
4. **Peritoneal: predictors of peritoneal relapse are: (a) stage IV disease; or (b) stage II or III disease with two or more of the following risk factors: cervical invasion, peritoneal cytologic results positive for endometrial cancer, positive lymph nodes, and nonendometrioid histologic findings (**134).

Patients with the risk factors summarized in Table 37-10 account for 35% of the overall population with endometrial cancer, but 89% of the observed hematogenous, lymphatic, and peritoneal relapses. Importantly, 46% of the patients considered at risk subsequently experienced a recurrence in one or more of the three sites, compared with only 2% of patients not judged to be at risk based on these criteria (p <0.001). The identification of subgroups of patients at risk for the different patterns of recurrence would allow postoperative treatment targeted to the predicted areas of tumor dissemination. The recurrence sites predicted by risk factors would presuppose different adjuvant treatment strategies. Patients at risk for hematogenous or peritoneal recurrence would potentially benefit from systemic cytotoxic treatment, while patients at risk for lymphatic or vaginal recurrence would potentially benefit from radiation treatment directed at areas at risk.

Table 37-10 Rates of Recurrence at 5 Years According to the Different Risk Categories for 915 Patients

Risk Category	Recurrence at 5 Years (%)
Hematogenous	
All stages	
Myometrial invasion ≤50%	4
Myometrial invasion >50%	28
Stage I (negative lymph nodes)	

Myometrial invasion <66%	2
Myometrial invasion ≥66%	34
Lymphatic	
No risk factors	2
CSI and/or positive lymph nodes	31
Peritoneal	
Stage IV disease	63
Stage II–III disease and ≥2 risk factors[a]	21
Stage I–III disease and ≤1 risk factor[a]	1
Overall[b]	
Not at risk[c]	2
At risk[c]	46

[a]CSI, nonendometrioid histologic subtype, positive lymph nodes, or positive result on peritoneal cytologic evaluation.

[b]Excluding vaginal recurrences.

[c]For at least one of the three categories of recurrence (i.e., hematogenous, lymphatic, or peritoneal).
CSI, cervical stromal invasion.
From **Mariani A, Dowdy SC, Keeney GL, et al.** High-risk endometrial cancer subgroups: Candidates for target-based adjuvant therapy. *Gynecol Oncol* 2004;95:120–126.

MODALITIES OF POSTOPERATIVE TREATMENT

Observation

Patients with grades 1 and 2 lesions without myometrial invasion or any of the above risk factors (Table 37-10) have an excellent prognosis and require no postoperative therapy. In a GOG study, there were no recurrences and a 100% disease-free 5-year survival rate in the 91 patients in this category, 72 of whom received no additional treatment after hysterectomy (86). Other investigators reported equally favorable results with only surgical therapy in similar patients (197).

Vaginal Vault Radiation

Vaginal brachytherapy is an attractive alternative to external radiation therapy (ERT). High-dose rate (HDR) brachytherapy is well tolerated with low rates of severe or chronic complications. Vaginal control rates with the more convenient, better-tolerated HDR brachytherapy are comparable to control rates with the lengthier low-dose rate

(LDR) brachytherapy. Pearcey and Petereit established the HDR dosing of 21 Gy to 5-mm depth in three fractions as the standard brachytherapy dose, providing local control rates of 98% to 100% (198). Additional retrospective data demonstrate 96% to 98% vaginal control rates with HDR in high-risk early-stage endometrial cancer (199,200). Retrospective data suggest that the vaginal relapse rate after brachytherapy averages 4% to 5% (Table 37-11) and this is similar to the 5-year vaginal failure rate of 3.5% reported among the highest-risk patients who received ERT in PORTEC-1 (88,199,201,202).

Table 37-11 Recurrence in High-Risk, Comprehensively Staged, Early-Stage Endometrial Cancer after Adjuvant Vaginal Brachytherapy Alone (No Pelvic ERT)

Author (Ref.)	No. of Patients	Lymphadenectomy Performed	Postoperative Vaginal Brachytherapy	No. of Recurrences *N* (%)
Orr et al. (287)	115	+	+	6 (5.2)
Mohan et al. (288)	28	+	+	2 (7)
Chadha et al. (289)	38	+	+	3 (7.9)
Fanning (201)	66	+	+	2 (3)
Horowitz et al. (199)	102	+	+	10 (9.8)
Straughn et al. (290)	56	+	+	0 (0)
Solhjem et al. (202)	100	+	+	0 (0)
Total	505			23 (4.6)[a]

[a]Includes 18 distant (78% of all recurrences), 3 vaginal (13%), 1 isolated pelvic sidewall (4.3%), 1 unknown site (4.3%).

ERT, external radiation therapy.

PORTEC-2 randomized patients with apparent uterine-confined endometrial cancer at high risk for recurrence (>60 years of age with grade 1 or 2, stage IB and grade 3, stage IA; or any age, any grade IIA with <50% myometrial invasion), to pelvic ERT (46 Gy, in 23 fractions) versus vaginal brachytherapy (21 Gy in three HDR fractions or 30 Gy LDR, to a depth of 0.5 cm). At 3 years, there was no difference in vaginal failure rates (0.9% for vaginal brachytherapy, 2% for pelvic ERT; $p = 0.97$). There was a higher rate of nonvaginal pelvic relapse in the brachytherapy group (3.6%) compared to the ERT group (0.7%; $p = 0.03$), however, the absolute difference was small and there was no difference in overall survival (203). The difference between nonvaginal pelvic recurrences may be a reflection of unrecognized lymph node metastases at the time of initial surgery treated with ERT. One concern regarding PORTEC-2 is that there was not a surgery-only control in the study. However, the highest-risk endometrial cancer subgroup in PORTEC-1 (patients >60 years of age with grade 3 or deeply invasive

grade 1 or 2, all stage I) was similar to the cohort included in PORTEC-2 and the locoregional recurrence rate in patients who did not receive adjuvant ERT in PORTEC-1 was 18% (88).

Grade 3 histology and lymph-vascular invasion are proven predictors of vaginal relapse in stage I endometrial cancer. Patients with these risk factors are the most likely group to benefit from vaginal vault brachytherapy (196). Although vaginal recurrences can be successfully treated and controlled in up to 81% of cases, the addition of vaginal brachytherapy to the initial surgical intervention can significantly reduce the risk of such recurrences (204).

External Pelvic Radiation

Radiation therapy traditionally was suggested to patients who were deemed to have intermediate or high risk of recurrence, according to grade and depth of myometrial invasion. Several retrospective studies and large, randomized trials did not show an overall survival benefit for intermediate- and high-risk patients with stage I endometrial cancer (or occult IIA endometrial cancer according to the 1988 FIGO staging) who received adjuvant pelvic radiotherapy.

[6] The PORTEC trial tested the role of postoperative pelvic radiation therapy for presumed stage I endometrial cancer in 714 patients. Eligibility criteria were stage IB, grades 1 to 2, and stage IA, grades 2 to 3; patients with stage IA, grade 3, were only 10% of the study population, and lymph node biopsies and peritoneal cytology were not required. Local–regional recurrences developed in 14% of the surgery group, compared with 4% of the postoperative pelvic radiation group. Overall, the 5-year survival rate was no different between the two groups (85% vs. 81%, respectively) (88). These results were confirmed by GOG99, a prospective, randomized investigation of surgery alone (including lymphadenectomy to the level of the inferior mesentery artery in some patients) versus surgery plus adjuvant pelvic radiation in intermediate-risk endometrial cancer (stages IA to IIB occult). Of 392 patients accrued to the study, more than 80% were actually low-risk patients (90.6% stage I, 81.6% grades 1 to 2, 82% <50% myometrial invasion). Disease recurrence was reduced by 58% ($p = 0.007$) with the use of postoperative pelvic radiation. After 2 years, the cumulative recurrence rate was 12% in the group with no postoperative treatment compared with 3% in the group that received pelvic radiation. The pelvic failure rate was 8.9% in the surgery-alone group compared with 1.6% in the postoperative pelvic radiation group. **Overall survival rates were not significantly improved in patients receiving postoperative pelvic radiation compared with those treated only with surgery (92% vs. 86%, respectively)** (259). **The intergroup ASTEC/EN.5 trial provided further confirmation that external-beam radiation therapy in patients at intermediate to high risk of recurrence has no significant effect on overall survival** (205).

Postoperative whole-pelvis external-beam radiation usually involves the delivery

of 4,500 to 5,040 cGy in 180 cGy daily fractions over 5 to 6 weeks to a field encompassing the upper one-half of the vagina inferiorly, the lower border of the L4 vertebral body superiorly, and 1 cm lateral to the margins of the bony pelvis. The dose of radiation at the surface of the vaginal apex usually is boosted to 6,000 to 7,000 cGy by a variety of techniques. The most frequently reported side effects are gastrointestinal, usually abdominal cramps and diarrhea, although more serious complications such as bleeding, proctitis, bowel obstruction, and fistula can occur and may require surgical correction. The urinary system may be affected in the form of hematuria, cystitis, or fistula. The overall complication rate ranges from 25% to 40%; and the rate of serious complications requiring surgical intervention is about 1.5% to 3%.

External-beam pelvic radiation does not appear to impact survival in patients with high-risk stage I endometrial cancer. Patients with extrauterine pelvic disease, including adnexal spread, parametrial involvement, and pelvic lymph node metastases, in the absence of extrapelvic disease, are likely to benefit from postoperative pelvic radiation.

Extended-Field Radiation

Patients with histologically proven para-aortic node metastases or patients at risk for para-aortic disease, but without surgical evaluation, are candidates for extended-field radiation therapy. The entire pelvis, common iliac lymph nodes, and para-aortic lymph nodes are included within the radiation field. The para-aortic radiation dose is limited to 4,500 to 5,000 cGy. **Extended-field radiotherapy appears to improve survival in patients with endometrial cancer who have positive para-aortic lymph nodes** (86,206).

Five-year survival rates of 47% and 43% were reported for patients with surgically confirmed isolated para-aortic lymph node metastases and for those with para-aortic and pelvic lymph node metastases, respectively, using postoperative extended-field radiation. In one report, only one case of severe enteric morbidity occurred in 48 patients, a complication rate of 2% (207). In a GOG study, 37 of 48 patients with positive para-aortic nodes received postoperative para-aortic radiation, 36% of whom remained tumor free at 5 years (86). A comparison of patients with positive para-aortic nodes treated with *megestrol acetate* alone versus *megestrol acetate* and extended-field radiation showed that the survival rate in the patients receiving extended-field radiation was significantly better: 53% versus 12.5%, respectively (208). In another study of 18 patients with positive para-aortic nodes, 5-year survival rates were 67% for microscopic nodal disease and 17% for gross nodal disease (209).

Whole-Abdomen Radiation

Whole-abdomen radiation therapy (WART) was historically reserved for patients with stages III and IV endometrial cancer. It was also considered for patients with serous or carcinosarcomas, which have a propensity for upper abdominal recurrence (210–213). WART is rarely used since the publication of GOG122, which showed favorable progression free and overall survival in advanced endometrial carcinoma with chemotherapy as opposed to WART (see section on "Chemotherapy") (214). The recommended dose to the whole abdomen is 3,000 cGy in 20 daily fractions of 150 cGy, with kidney shielding at 1,500 to 2,000 cGy, along with an additional 1,500 cGy to the para-aortic lymph nodes and 2,000 cGy to the pelvis. Gastrointestinal side effects, including nausea, vomiting, and diarrhea, sometimes make it necessary to interrupt therapy, but it is rare for patients to discontinue treatment because of these symptoms. Hematologic toxicity can be expected to occur during whole-abdomen radiation, but it is usually mild. The incidence of late complications, mainly chronic diarrhea and small bowel obstruction, is low (5% to 10%).

Progestins

Because most endometrial cancers have estrogen and progesterone receptors, and *progestins* were used successfully to treat metastatic endometrial cancer, postoperative adjuvant *progestin* therapy attempted to reduce the risk of recurrence. This therapy is attractive because it provides systemic treatment and has few side effects. Unfortunately, **several large randomized, placebo-controlled studies failed to identify a benefit for adjuvant *progestin* therapy (**215,216).

Chemotherapy

Adjuvant cytotoxic chemotherapy was studied in a few trials. The GOG treated 181 patients who had poor prognostic factors with postoperative radiation and randomly assigned patients to receive no further therapy or *doxorubicin* chemotherapy. After 5 years of observation, there was no difference in recurrence rates between the two groups (217).

The GOG122 trial compared whole-abdominal radiotherapy versus systemic chemotherapy (eight cycles of *doxorubicin* and *cisplatin*) in 388 patients with stage III or IV disease who underwent maximal surgical resection of disease to less than 2 cm. Its results showed a significant advantage of chemotherapy on 5-year survival (214). Patients who received chemotherapy had a 13% improvement in 2-year progression-free survival (50% vs. 46%) and an 11% improvement in overall 2-year survival (70% vs. 59%) compared with patients treated with whole-abdomen radiation. This study was the first to suggest an improvement in outcome for use of adjuvant chemotherapy compared with radiation, but toxicity was more prevalent with chemotherapy. Patients with gross residual disease were assigned to the radiation arm, almost guaranteeing failure; and overall, 55% of patients experienced a recurrence or progression during the

study period (218). GOG184 randomized 552 patients with advanced disease to six cycles of *cisplatin* and *doxorubicin* with or without *paclitaxel* following surgical debulking and radiotherapy. Side effects were more pronounced with the three-drug regimen, and recurrence-free survival (RFS) at 36 months was no different between arms (62% vs. 64% for the three-drug regimen). The investigation was closed to patients with stage IV disease during the trial, but subgroup analysis suggested a 50% reduction in recurrence or death in the 57 patients with gross residual disease who received *cisplatin, doxorubicin,* and *paclitaxel* (71).

The PORTEC-3 trial and GOG258 investigated the combination of chemotherapy and radiotherapy in advanced or high-risk endometrial cancer. PORTEC-3 is investigated overall survival and failure-free survival of patients with high-risk and advanced stage endometrial carcinoma treated after surgery with chemoradiation followed by chemotherapy versus pelvic radiation alone (219). **The results of the large randomized trial showed that the addition of 4 cycles *carboplatin* and *paclitaxel* chemotherapy to standard external-beam radiotherapy resulted in a statistically significant improvement of progression-free survival (75.5% vs. 68.6%, HR = 0.71) with no significant benefit to overall survival (81.8% vs. 76.7%, HR = 0.76). The investigators recommended that women with high-risk endometrial cancer should be individually counseled about this combined treatment, and that continued follow-up is needed to evaluate long-term survival.**

GOG258 compared chemoradiation followed by chemotherapy versus chemotherapy alone in advanced endometrial cancer (220). The open-label randomized phase III trial compared treatment with *cisplatin* and tumor volume-directed radiation followed by *carboplatin* and *paclitaxel* for four cycles (C-RT) versus *carboplatin* and *paclitaxel* treatment for six cycles (CT). The preliminary analysis showed that combined modality regimen did not increase RFS in patients with optimally debulked stage III/IVA endometrial carcinoma (HR 0.9, 95% CI [0.74,1.1]). C-RT reduced the rate of local recurrence compared to CT. The estimates for 5-year overall survival are 70% for the C-RT arm versus 73% for the CT arm, and long-term survival and quality-of-life data to be reported as the data mature.

Regarding the use of chemotherapy in high-risk populations with early-stage endometrial cancer, the European Organisation for Research and Treatment of Cancer, along with the Nordic Society of Gynecologic Oncology, presented the results of a collaborative trial comparing external radiotherapy versus chemoradiotherapy in patients with stages I or II or IIIC1 (positive pelvic nodes only) and one of the following characteristics: grade 3 or myometrial invasion greater than 50%, DNA aneuploidy, or clear cell or serous histologic type. Performance of a systematic lymphadenectomy was optional. A total of 375 patients were enrolled over a 10-year period and the study was closed early because of slow recruitment. The hazard ratio for progression-free survival was 0.58 (95% CI, 0.34%–0.99%) in favor of

chemoradiation after a median follow-up of 3.5 years (221).

The Japanese GOG randomized patients to pelvic radiotherapy versus platinum-based chemotherapy in patients with stage IB to IIIC endometrial cancer and myometrial invasion greater than 50%. Assessment of para-aortic nodal status was performed in only 29% of cases. The investigators found no differences between the two experimental arms in terms of progression-free survival and overall survival. A subgroup analysis of 120 patients with either (a) stage IB tumor and age greater than 70 years or grade 3 endometrioid adenocarcinoma; or (b) stage II or IIIA tumor (positive cytologic findings) showed that chemotherapy was associated with significantly improved disease-free and overall survival rates (222).

The benefits achieved with combined chemoradiation, identification of the best chemotherapeutic regimen, and the identification of subgroups of patients who may benefit from these treatments deserves further investigation.

Clinical Stage II

Endometrial cancer involving the cervix either contiguously or by lymphatic spread has a poorer prognosis than disease confined to the corpus (192,223–226). Preoperative assessment of cervical involvement is difficult. **Endocervical curettage has relatively high false-positive (50% to 80%) and false-negative rates.** Histologic proof of cancer infiltration of the cervix or presence of obvious tumor on the cervix is the only reliable means of diagnosing cervical involvement, although ultrasonography, hysteroscopy, or MRI may show cervical invasion.

The relatively small number of true stage II cases in reported series and the lack of randomized, prospective studies preclude formulation of a definitive treatment plan. **Three areas must be addressed in any treatment plan:**

1. **For optimal results, the uterus should be removed in all patients.**
2. **Because the incidence of pelvic lymph node metastases is about 36% in stage II endometrial cancer, any treatment protocol should include treatment of these lymph nodes.**
3. **Because the incidence of disease spread outside the pelvis to the para-aortic lymph nodes, adnexal structures, and upper abdomen is higher than in stage I disease, attention should be directed to evaluating and treating extrapelvic disease.**

Two approaches usually were used in the treatment of clinical stage II disease:

1. **Radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy**
2. **Combined radiation and surgery (external pelvic radiation and intracavitary**

radium or cesium followed in 6 weeks by total abdominal hysterectomy and bilateral salpingo-oophorectomy)

An initial radical surgical approach to treatment of clinical stage II endometrial cancer has the advantage of collecting accurate surgical-pathologic information. Conversely, many patients with endometrial cancer are elderly and obese and have medical problems that make this approach unsuitable. Reported results are no better than those with combined radiation and less radical surgical therapy (192). The use of radical hysterectomy may be limited to patients with anatomic problems that prevent optimum dosimetry or other conditions that conflict with the use of radiation therapy.

The most common, traditional approach to the management of clinical stage II endometrial cancer is to use external and intracavitary radiation followed by extrafascial hysterectomy. This combined approach resulted in 5-year survival rates of 60% to 80%, with severe gastrointestinal or urologic complications occurring in about 10% of patients (224,227,228). Patients who have medically inoperable disease are usually treated with external-beam radiation and one or two intracavitary insertions. Compared with combined radiation and surgery, the results with radiation alone are diminished, but about 50% of patients are long-term survivors **(Table 37-9)** (195).

Another method of management of clinical stage II endometrial cancer that is gaining favor is an initial surgical approach followed by radiation. This method is based on the difficulty in establishing the preoperative diagnosis of cervical involvement in the absence of a gross cervical tumor, the evidence that radiation is equally effective when given after hysterectomy, and the high incidence of extrapelvic disease when the cervix is involved. An extrafascial hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings for cytology, and resection of grossly enlarged lymph nodes are performed. Modified radical or radical hysterectomy can be considered to obtain free margins. These procedures are followed by appropriate pelvic or extended-field external and intravaginal radiation, depending on the results of surgical staging. Excellent results were reported using this treatment scheme (225,229,230).

Clinical Stages III and IV

Clinical stage III disease accounts for about 7% to 10% of all endometrial carcinomas (231–233). Patients usually have clinical evidence of disease spread to the parametria, pelvic sidewall, or adnexal structures; less frequently, there is spread to the vagina or pelvic peritoneum. **Treatment for stage III endometrial carcinoma must be individualized, but initial operative evaluation and treatment should be considered because of the high risk for occult lymph node metastases and intraperitoneal spread when disease is known to extend outside of the uterus into the pelvis.** In the presence of an adnexal mass, the initial impetus for surgery is to determine the nature of

the mass. Surgery is performed to determine the extent of disease and to remove the bulk of the disease if possible. This procedure should include peritoneal washings for cytologic examination, removal of bulky para-aortic and pelvic lymph nodes, biopsy or excision of any suspicious areas within the peritoneal cavity, and omentectomy and peritoneal biopsies. Except in patients with bulky parametrial disease, total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed. **The goal of surgery is eradication of all macroscopic disease because this finding is of major prognostic importance in the management of patients with clinical stage III disease.** Postoperative therapy can be tailored to the extent of disease.

Results of therapy depend on the extent and nature of disease. A 5-year survival rate of 54% was reported for all patients with stage III disease; however, the survival was 80% when only adnexal metastases were present, compared with 15% when other extrauterine pelvic structures were involved (231). Patients with surgical-pathologic stage III disease have a much better survival rate (40%) than those with clinical stage III disease (16%) (234). Patients who are treated with combined surgery and radiation fare better than patients who receive radiation therapy alone (233).

Stage IV endometrial adenocarcinoma, in which tumor invades the bladder or rectum or extends outside the pelvis, makes up about 3% of cases (233–236). **Treatment of stage IV disease is patient dependent but usually involves a combination of surgery, radiation therapy, and systemic hormonal therapy or chemotherapy.** One objective of surgery and radiation therapy is to achieve local disease control in the pelvis to provide palliative relief of bleeding, discharge, and complications involving the bladder and rectum. In one report, control of pelvic disease was achieved in 28% of 72 patients with stage IV disease treated with radiation alone or in combination with surgery, *progestins,* or both (235). **Several reports noted a positive impact of cytoreductive surgery on survival, the median survival being about three times greater with optimal cytoreduction (18 to 34 months vs. 8 to 11 months, respectively) (**235,236). Pelvic exenteration may be considered in the very rare patient in whom disease is limited to the bladder, rectum, or both (237,238).

Chemotherapy

In cases of advanced disease, chemotherapy with *carboplatin* and *paclitaxel* is now standard treatment (254–258). GOG209 demonstrated *carboplatin* and *paclitaxel* to be not inferior to the combination of *paclitaxel, doxorubicin,* and *cisplatin*, and the toxicity and tolerability profile favored *carboplatin* and *paclitaxel* (256). In a retrospective study, the overall response rate to combination *carboplatin* and *paclitaxel* in patients with either advanced or recurrent endometrial cancer was 43%, but only 5% achieved a complete response and the median survival was 13.2 months (255).

Single-agent chemotherapy options include *paclitaxel*, albumin-bound *paclitaxel, docetaxel, carboplatin, cisplatin, doxorubicin, liposomal doxorubicin*, and *topotecan*.

When single-agents are used as first-line therapy, response rates range from 21% to 36%.

Recurrent Disease

About 15% of patients treated for early (stage I and II) endometrial cancer develop recurrent disease (239,240). In contrast, recurrent disease is detected in up to 50% of patients with advanced (stage III and IV) endometrial cancer (241). More than 50% of recurrences develop within 2 years and about 75% occur within 3 years of initial treatment. The distribution of recurrences is dependent in large part on the type of primary therapy, that is, surgery alone versus surgery plus local or regional radiotherapy. Vaginal and/or pelvic recurrences comprise over 50% of all recurrences in patients treated with surgery alone. Approximately 70% of recurrences in patients treated with combined surgery and radiotherapy (vaginal or external beam) are extrapelvic, most commonly lung, abdomen, lymph nodes (aortic, supraclavicular, inguinal), liver, brain, and bone (242,243).

At the time of diagnosis of recurrent endometrial cancer, approximately one-third of patients are asymptomatic and are only discovered to have recurrent cancer on routine surveillance examinations or radiologic studies. Almost one-half of patients found to have lung metastases on follow-up chest imaging are asymptomatic. Approximately 90% of patients with metastases at other sites have symptoms related to the site of recurrence (244).

Patients with isolated vaginal recurrences fare better (70% 3-year survival) than those with pelvic recurrences (8% 3-year survival), or distant metastases (14% 3-year survival) (240). Patients who initially have well-differentiated tumors or who develop recurrent cancer more than 3 years after the primary therapy tend to have an improved prognosis (245,246).

Surgery

A small subset of patients with isolated recurrent endometrial cancer may benefit from surgical intervention (247). A search for distant recurrences is obligatory, as such patients with metastatic disease are best treated with chemotherapy, unless there is an isolated pulmonary metastasis which may be amenable to excision. Recurrent disease isolated to the central pelvis following radiation is rarely seen. Selected patients with such a recurrence may be candidates for pelvic exenteration (248,249) although morbidity is high and survival rates are low. There is some evidence that radical pelvic resection in conjunction with intraoperative radiation may cure some patients, albeit with a high complication rate (250). Cytoreductive surgery for abdominal pelvic recurrences may be a treatment option for patients where complete gross surgical resection seems possible (251) **(Fig. 37-6)**.

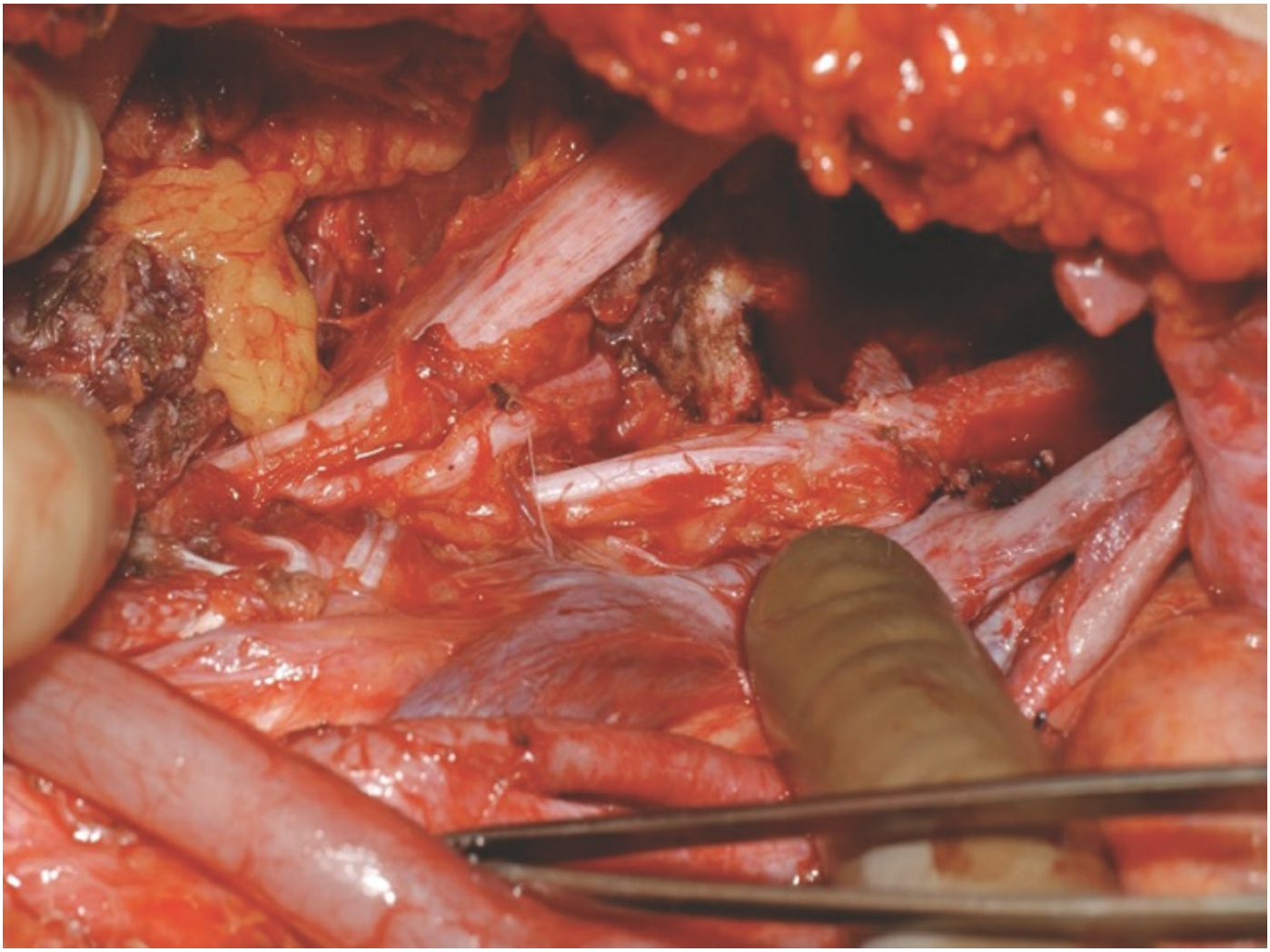


FIGURE 37-6 Radical pelvic sidewall resection. Photo taken of a patient with a left pelvic sidewall recurrence following resection of psoas muscle and bony ilium. Structures from lower to upper aspect of the photo (medial to lateral) include ureter, internal and external iliac artery, common iliac vein, lumbosacral trunk, obturator nerve (sacrificed), and femoral nerve. The cut edge of the psoas muscle is seen at left. (Provided by Sean C. Dowdy, MD, Mayo Clinic.)

Table 37-12 Carcinoma of the Endometrium: Stage Distribution and Actuarial Survival by Stage (Surgical and Clinical)

	Patients Treated		Survival	
Stage	*N*	Percent	3-Year	5-Year
Surgical				
I	3,996	70	92	87
II	709	12	82	76
III	758	13	66	59
IV	231	4	23	18
Clinical				
I	232	61	63	54
II	64	16	53	41
III	54	14	30	23
IV	33	8	12	12
Total	6,260	100	82	76

Adapted from **Creasman WT, Odicino F, Maisonneuve P, et al.** Carcinoma of the corpus uteri. FIGO Annual Report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45–86, with permission.

Patients with recurrent endometrial cancer are frequently elderly, overweight, and have numerous comorbidities thereby increasing operative and postoperative morbidity and mortality. Patients who are most often helped by surgical approaches to recurrent disease are younger, have well-differentiated endometrial tumors, have a longer time from original treatment to recurrence, and have negative margins or no gross residual disease after surgery (246,247).

Radiation Therapy

[8] Radiotherapy is the best treatment option for patients with isolated local–regional recurrences who have not received prior radiation (239,252,253). The best local control and subsequent cure are achieved by a combination of external pelvic radiation therapy followed by vaginal brachytherapy to deliver a total tumor dose of at least 6,000 cGy. Patients with low-volume disease limited to the pelvis (most of which is contained in the vagina) have the best outcomes. Retrospective studies have shown complete remission rates after salvage radiotherapy for isolated vaginal relapse to be 40% to 80% in previously nonirradiated patients compared to 10% to 25% in patients who have received prior irradiation. Patients who undergo radiation for pelvic extension of disease have much lower reported survival rates of 0% to 26%. Factors associated with improved survival and control of pelvic disease in patients with locally recurrent endometrial cancer who receive radiotherapy include initial low-grade endometrioid histology, younger age at recurrence, recurrent tumor size 2 cm or less, time from initial treatment to recurrence of more than 1 year, vaginal versus pelvic

disease, and use of vaginal brachytherapy.

Chemotherapy

The standard chemotherapy for recurrent metastatic endometrial cancer is the same as that for advanced stage disease, that is, combination chemotherapy with *carboplatin* and *paclitaxel* (257,258). However, there are no randomized controlled trials comparing *carboplatin* and *paclitaxel* in the recurrent setting.

When single agents are used as second-line treatment, response rates range from 4% to 27%; *paclitaxel* being the most active in this setting. *Temsirolimus* and *bevacizumab* may be appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic therapy, although response rates are low at 4% and 13.5%, respectively (259). Studies have indicated that patients with programmed death ligand 1 (PD-L1) positive tumors and those with MMR-deficient (dMMR) or microsatellite instability high (MSI-H) endometrial cancer may respond to programmed death receptor-1 (PD-1) blockade with *pembrolizumab* (260,261). (See **Tables 37-12** and **37-13**.)

Table 37-13 Surgically Staged Endometrial Cancer: Actuarial 5-Year Survival Rate (%) by Histologic Grade and Stage (1988 Staging Criteria)

	Grade		
Stage	**1**	**2**	**3**
IA	93	90	69
IB	90	93	84
IC	89	81	63
IIA	91	78	57
IIB	78	75	58
IIIA	79	69	44
IIIB	77	40	21
IIIC	61	61	44
IVA	—	—	19
IVB	35	27	7

Adapted from **Creasman WT, Odicino F, Maisonneuve P, et al.** Carcinoma of the corpus uteri. FIGO Annual Report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45–86, with permission.

Table 37-14 Response to Progestin Therapy in Advanced or Recurrent Endometrial Cancer

Author (Ref.)		Progestin	No. of Patients	Response Rate (%)
Piver et al. (291)	*HPC*	1,000 mg/week IM	51	14
	MPA	1,000 mg/week IM	37	19
Podratz et al. (292)	*HPC*	1–3 g/week IM	33	9
	MA	320 mg/day PO	81	11
Thigpen et al. (293,294)	*MPA*	150 mg/day PO	219	14
		200 mg/day PO	138	26
		1,000 mg/day PO	140	18

HPC, hydroxyprogesterone caproate (Delalutin); MPA, medroxyprogesterone acetate (Provera, Depo-Provera); MA, megestrol acetate (Megace); IM, intramuscular; PO, oral.

Hormonal Therapy

Hormonal therapy is an excellent management option for patients with asymptomatic recurrent endometrial cancer, especially for those who have low-grade, hormone receptor positive tumors (244,246). Progestin therapy, either megestrol acetate 80 mg twice daily or medroxyprogesterone acetate 50 to 100 mg three times daily, is recommended when radiation therapy, surgery, or both, are not feasible for treatment of localized recurrent cancer or in nonlocalized disease. Progestins have reported response rates ranging from 15% to 25%. Higher response rates are observed with well-differentiated tumors, expression of ER/PR receptors, longer disease-free interval, and location and extent of extrapelvic, especially pulmonary, metastatic disease. Progestin therapy should be given for at least 2 to 3 months before assessing response, and continued for as long as disease is static or in remission. In the presence of a relative contraindication to high-dose progestin therapy (e.g., prior or current thromboembolic disease, severe heart disease, or inability to tolerate progestin therapy), tamoxifen 20 mg twice daily is recommended, yielding response rates of about 10% to 20%. An alternating regimen of progestin and tamoxifen or an aromatase inhibitor may be substituted for a progestational agent, but response rates may be lower and toxicity higher. Failure to respond to hormonal therapy is an indication for initiation of chemotherapy. (See Table 37-14.)

UTERINE SARCOMA

Uterine sarcomas are relatively rare tumors arising from mesenchymal tissues of the uterus, including the uterine muscle and endometrial stroma. They account for approximately 3% of all uterine malignancies (262). In general, [9] uterine sarcomas are some of the most malignant uterine tumors and differ from endometrial carcinomas with regard to diagnosis, clinical behavior, pattern of spread, and management (265).

Classification and Staging

The two most common histologic types of uterine sarcoma are leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS), which make up approximately 60% and 20% of uterine sarcomas, respectively (Table 37-15). Rarer subtypes of malignant mesenchymal tumors that occur in the uterus are undifferentiated uterine sarcoma (UUS), adenosarcoma, and perivascular epithelioid cell neoplasm (PEComa) (264–266). Carcinosarcomas, also known as malignant mixed müllerian tumors (MMMT), were previously categorized and included in uterine sarcoma treatment algorithms, but are thought to represent high-grade carcinomas with mesenchymal metaplasia (267).

Staging of uterine sarcomas had previously been based on the FIGO staging system for endometrial adenocarcinomas. Recognition of the unique spread pattern and clinical behavior of uterine sarcomas required an independent staging system for each histologic type that was developed for LMS and ESS in 2009 (**Tables 37-16** and **37-17**) (268).

Endometrial Stromal Sarcoma

ESSs occur primarily in perimenopausal women between ages 45 and 50 years, with approximately one-third occurring in postmenopausal women. There is no apparent relationship to parity or associated diseases, and these tumors are rare in African American women. The most frequent symptom is abnormal uterine bleeding; abdominal pain, and pressure caused by an enlarging uterus occur less often, and some patients do not have any symptoms. Pelvic examination usually reveals regular or irregular uterine enlargement, sometimes associated with rubbery parametrial induration. The diagnosis may be determined by endometrial biopsy, but the usual preoperative diagnosis is uterine leiomyoma (267).

ESSs are composed of cells resembling normal endometrial stroma in the proliferative phase. They are divided into two types based on histologic criteria, such as cellular atypia, mitotic activity, and vascular invasion: low-grade ESS and high-grade ESS including undifferentiated sarcoma. Molecular profiling supports dividing these endometrial sarcomas into low- and high-grade entities based on histopathology and clinical behavior and outcomes (266).

Low-grade ESS is distinguished microscopically by mitotic rates of less than 10 MF/10 HPF, slight nuclear atypia, minimal necrosis, and presence of estrogen and progesterone receptors; myometrial and lymph–vascular invasion are common. Up to one-half of these tumors harbor a *JAZF1–SUZ12* gene fusion, which correlates with lower-grade, earlier-stage tumors and may be helpful in diagnosing these tumors and differentiating them from higher-grade endometrial stroma sarcomas (266,269).

Table 37-15 Classifications of Uterine Sarcomas

I. Pure nonepithelial tumors

A. Homologous
1. Endometrial stromal tumors
a. Low-grade stromal sarcoma
b. High-grade or undifferentiated stromal sarcoma
2. Smooth muscle tumors
a. Leiomyosarcoma
b. Leiomyoma variants
1. Cellular leiomyoma
2. Leiomyoblastoma (epithelioid leiomyoma)
c. Benign metastasizing tumors
1. Intravenous leiomyomatosis
2. Benign metastasizing leiomyoma
3. Disseminated peritoneal leiomyomatosis
B. Heterologous
1. Rhabdomyosarcoma
2. Chondrosarcoma
3. Osteosarcoma
4. Liposarcoma
II. Mixed epithelial–nonepithelial tumors
A. Malignant mixed müllerian tumor
1. Homologous (carcinosarcoma)
2. Heterologous
B. Adenosarcoma

Modified from **Clement P, Scully RE**. Pathology of uterine sarcomas. In: Coppleson M, ed. *Gynecologic oncology: Principles and Practice*. New York: Churchill-Livingston, 1981, with permission.

Low-grade ESSs are found to extend beyond the uterus in 40% of cases at the time of diagnosis, but the extrauterine spread is confined to the pelvis in two-thirds of these cases. Upper abdominal, pulmonary, and lymph node metastases are less common. Recurrences occur in almost one-half of cases at an average interval of 5 years after initial therapy and local recurrence is more common than distant metastasis. These tumors tend to have protracted clinical courses (263–267,269,270).

Optimal initial therapy for patients with low-grade ESS consists of surgical excision of all grossly detectable tumors. Total hysterectomy should be performed. The fallopian tubes and ovaries should be removed because of the propensity for tumor extension into the parametria, broad ligaments, adnexal structures, and the possible stimulating effect of estrogen on tumor cells if the ovaries are retained. The relatively low rate of lymph node metastasis in the absence of gross lymph node involvement or extrauterine disease suggests that lymph node dissection is not necessary. Pelvic irradiation is recommended for inadequately excised or locally recurrent pelvic disease. Owing to the indolent nature of the disease, cytotoxic chemotherapy is unlikely to be beneficial. Hormonal therapy with an aromatase inhibitor or progestin yields response rates close to 50% in patients with recurrent or metastatic disease. Recurrent or metastatic lesions may be amenable to surgical excision. Prolonged survival and cure are common even after the development of recurrent or metastatic disease with the overall 5-year survival exceeding 90% (263–267,270).

High-grade ESS and UUS are highly malignant neoplasms, although the prognosis is poorer for the latter. Histologically, both exhibit greater than 10 MF/10 HPF, necrosis, significant cytologic pleomorphim, and prominent myometrial and lymph–vascular invasion. UUS, by definition, lacks recognizable morphologic or immunohistochemical evidence of smooth muscle or endometrial stromal differentiation. Higher-grade ESSs have been found to have a unique genetic rearrangement *YWHAE–FAM22A/B* which correlates with a more aggressive clinical behavior (266,269).

Table 37-16 FIGO Staging for Uterine Endometrial Stromal Sarcoma and Adenosarcoma

Stage	Definition	
I	Tumor limited to uterus	IA: tumor limited to endometrium/endocervix with no myometrial invasion IB: ≤½ myometrial invasion IC: >½ myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis	IIA: adnexal involvement IIB: involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)	IIIA: one site IIIB: more than one site IIIC: metastasis to pelvic and/or para-aortic lymph nodes
IV		IVA: tumor invades bladder and/or rectum IVB: distant metastasis

Prat J. FIGO staging for uterine sarcomas. *Int J Gynecol Obstet* 2009;104:177–178.

Table 37-17 FIGO Staging for Uterine Leiomyosarcoma

Stage	Definition	
I	Tumor limited to uterus	IA: <5 cm IB: >5 cm
II	Tumor extends beyond the uterus, within the pelvis	IIA: adnexal involvement IIB: involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)	IIIA: one site IIIB: more than one site IIIC: metastasis to pelvic and/or para-aortic lymph nodes
IV		IVA: tumor invades bladder and/or rectum IVB: distant metastasis

Prat J. FIGO staging for uterine sarcomas. *Int J Gynecol Obstet* 2009;104:177–178.

Treatment of high-grade ESS and UUS should consist of total hysterectomy and bilateral salpingo-oophorectomy. The poor therapeutic results with surgery alone, suggest that adjuvant radiation therapy, chemotherapy, or both, should be used in combination with surgery, however, there is no data to support this. These tumors are not responsive to hormonal therapy. The 5-year disease-free survival rate for these tumors is 25% (263–267,270).

Uterine tumor resembling ovarian sex-cord tumor (UTROSCT) is a rare variant of ESS, which contains elements resembling ovarian sex-cord tumors. Immunohistochemically, these tumors express calretinin, inhibin, CAM5.2, and progesterone receptor; positive staining for calretinin and at least one of the other markers confirms the diagnosis of UTROSCT. The mean age of diagnosis is 52. The most common presenting symptom is abnormal uterine bleeding. Although some of these tumors are large and have infiltrative margins, almost all behave benignly. Endometrial stromal tumors with sex-cord–like elements (ESTSCLE) tend to behave more aggressively with larger tumors, more extrauterine metastases, and a higher rate of recurrence (271).

Leiomyosarcoma

The median age for women with LMS is 54 (range 43 to 63) years, and premenopausal women have a better survival. This malignancy has no relationship with parity, and the incidence of associated diseases is not as high as in endometrial carcinomas. African Americans have a higher incidence and a poorer prognosis than women of other races. A history of prior pelvic radiation can be elicited in about 4% of women with uterine LMS. The incidence of sarcomatous change in benign uterine leiomyomas is reported to be between 0.13% and 0.81%, and most uterine LMSs are unassociated with pre-existing leiomyomas (272–276).

Presenting symptoms, which are usually of short duration (mean = 6 months) and not

specific to the disease, include vaginal bleeding, pelvic pain or pressure, and awareness of an abdominal mass. The principal physical finding is the presence of a pelvic mass. The diagnosis should be suspected if pelvic pain accompanies an enlarging uterus, especially in a postmenopausal woman. Endometrial biopsy, although not as useful as in ESSs or carcinomas, may establish the diagnosis in as many as one-third of cases if the lesion is submucosal. MRI, especially contrast-enhanced MRI, may be more diagnostic than ultrasound or CT in differentiating LMSs and smooth muscle tumors of uncertain malignant potential (STUMP) from leiomyomas (275).

Pathologically, the number of mitoses in uterine smooth muscle tumors has traditionally been considered the most reliable indicator of malignant behavior. Tumors with less than 5 MF/10 HPF behave in a benign fashion and tumors with more than 10 MF/10 HPF are frankly malignant, while tumors with 5 to 10 MF/10 HPF-termed STUMP have a less predictable behavior. In addition to mitotic index greater than 10, other histologic indicators used to classify uterine smooth muscle tumors as malignant are severe cytologic atypia, infiltrating borders, coagulative tumor cell necrosis, and presence of vascular invasion (266,277) **(Fig. 37-7)**. Gross presentation of the tumor at the time of surgery is an important prognostic indicator. Tumors greater than 5 cm, with infiltrating rather than pushing borders, and extension beyond the uterus have a poorer prognosis. The pattern of tumor spread is usually through the myometrium, into pelvic blood vessels and lymphatics, contiguously to pelvic structures and intra-abdominally, and distantly (most often the lungs). Reported survival rates for women with uterine LMS range from 20% to 63% (mean 47%). Younger women with stage I disease do best, while older women and those with advanced disease do least well (272–276).

Surgery is the mainstay of treatment for uterine LMS. For women with uterine-confined disease, total hysterectomy is recommended, optimally avoiding intra-operative morcellation which may increase recurrence and death in women with previously undiagnosed uterine LMS (275,278). Bilateral salpingo-oophorectomy should be done in postmenopausal women and in women with gross extrauterine disease. Preservation of the ovaries in premenopausal women does not increase the risk of recurrence. Retroperitoneal lymphatic spread is rare in women with early-stage disease and lymphadenectomy is not associated with a survival advantage. In women with disease spread outside the uterus, complete cytoreductive surgery or metastasectomy (especially in the lungs) may improve survival (272–276).

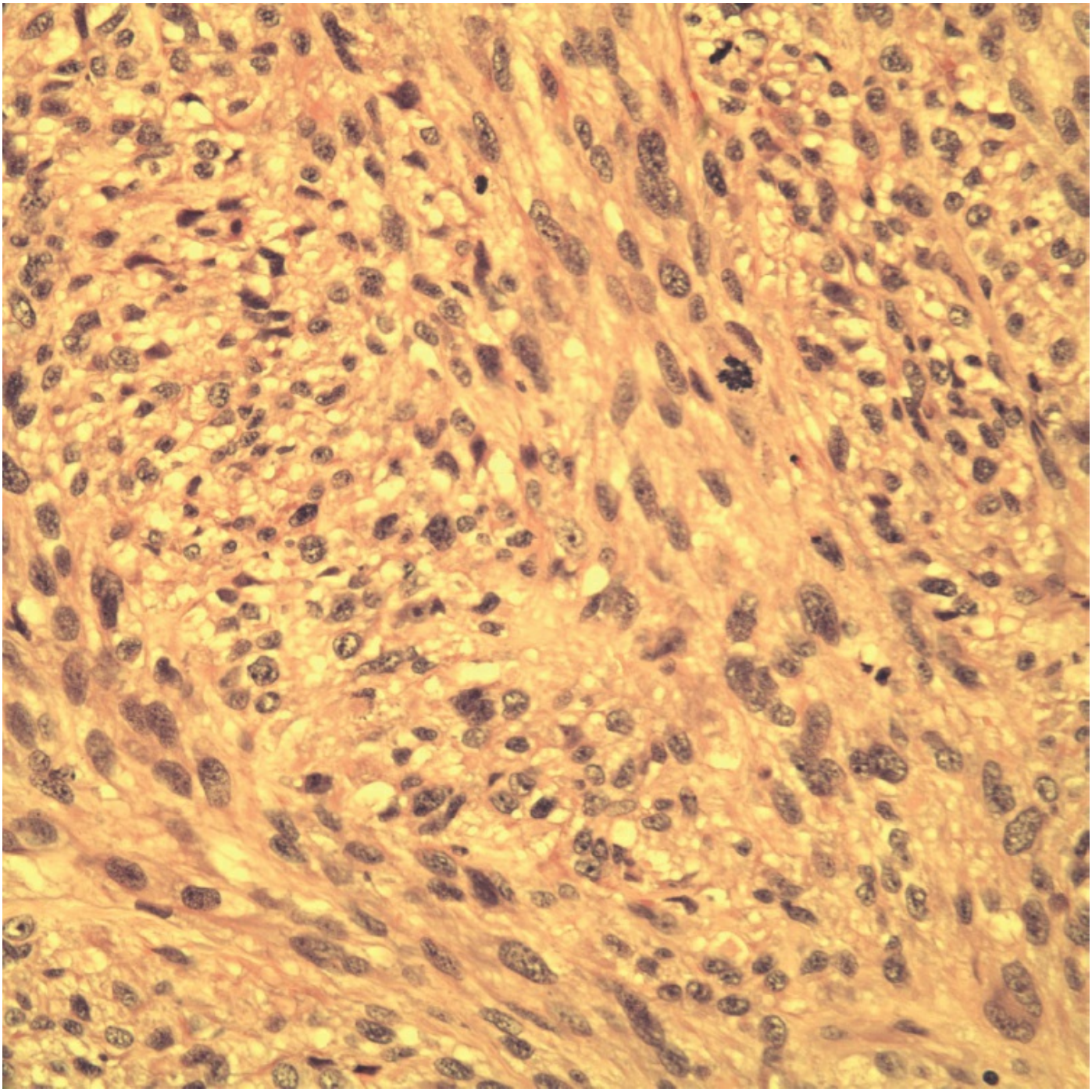


FIGURE 37-7 Leiomyosarcoma of the uterus. Interlacing bundles of spindle cells have fibrillar cytoplasm, irregular and hyperchromatic nuclei, and multiple mitotic figures. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

Radiation therapy does not improve outcomes for women with uterine LMS. Data from a phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) comparing adjuvant postoperative pelvic radiation therapy to observation only for women with early-stage uterine LMS found no differences in overall survival or recurrence rates (279). This lack of benefit of adjuvant postoperative radiotherapy was supported by results from a Surveillance,

Epidemiology, and End Results (SEER) database (280). Therefore, postoperative adjuvant radiation therapy is not recommended for completely-resected, early-stage disease.

Chemotherapy is indicated and increases survival in patients with advanced LMS. Several single agents, such as *dacarbazine, doxorubicin, epirubicin, eribulin, gemcitabine, ifosfamide, liposomal doxorubicin, pazopanib, temozolomide*, and *trabectedin* have been shown to have some activity in treating advanced or metastatic LMSs yielding response rates of 15% to 25%, and *doxorubicin* is the most active. Combination chemotherapy with *gemcitabine/docetaxel* or *doxorubicin/ ifosfamide +/– dacarbazine* has yielded response rates of 53% and 30%, respectively, in advanced uterine LMS, however, median time to progression is usually less than 6 months and survival less than 2 years (259). A phase II trial of the combination of *doxorubicin/olaratumab* versus single-agent *doxorubicin* for the treatment of soft tissue sarcomas including LMSs found the combination to be superior with a median progression-free survival of 6.6 versus 4.1 months and a median overall survival of 26.5 versus 14.7 months, respectively (281). Adjuvant postoperative chemotherapy for early-stage uterine LMS has failed to improve survival or lower the 40% to 70% risk of recurrence, despite its increasing use (282).

Five other clinical pathologic variants of uterine smooth muscle tumors deserve special comment: myxoid LMS, epithelioid LMS, intravenous leiomyomatosis, benign metastasizing uterine leiomyoma, and disseminated peritoneal leiomyomatosis (266,277).

Myxoid LMS is characterized grossly by a gelatinous appearance and apparent circumscribed border. Microscopically, the tumors have a myxomatons stroma and extensively invade adjacent tissue and blood vessels. The mitotic rate may be low (0 to 2 MF/10 HPF), which belies their aggressive behavior and poor prognosis (283). Surgical excision by hysterectomy is the mainstay of treatment. The low mitotic rate and abundance of intracellular myxomatous tissue suggest that these tumors would not be responsive to radiation therapy or chemotherapy.

Epithelioid LMS often forms large fleshy intrauterine masses, commonly associated with hemorrhage. They exhibit a microscopic pattern of epithelioid differentiation consisting of round cells with eosinophilic and granular or clear cytoplasm growing in sheets, nests, or cords in addition to cytologic atypia, increased mitotic activity (>5MF/10 HPF), and tumor cell necrosis. These tumors must be distinguished from placental site trophoblastic tumors and epithelioid trophoblastic tumors. Epithelioid LMSs are aggressive tumors with a prognosis similar to myxoid LMSs, with a propensity for late recurrences. Hysterectomy is the only treatment proven to be of any benefit (277).

Intravenous leiomyomatosis is characterized by the growth of histologically benign smooth muscle into venous channels within the broad ligament and then into uterine and

iliac veins. The intravascular growth takes the form of visible, worm-like projections that extend from a myomatous uterus into the parametria toward the pelvic sidewalls. It may be confused with low-grade stromal sarcoma. Symptoms are related to the associated uterine myomas. Most women are in the late fifth and early sixth decades of life. The prognosis is excellent, even when tumor is left in pelvic vessels. Late local recurrences can occur, and deaths from extension into the inferior vena cava or metastases to the heart have been reported. Estrogen may stimulate the proliferation of these intravascular tumors. Treatment should be total hysterectomy with bilateral salpingo-oophorectomy and excision of any extrauterine tumor when technically feasible. Antiestrogen therapy is appropriate if residual tumor remains after surgery (277).

Benign metastasizing uterine leiomyoma is a rare condition in which a histologically benign uterine smooth muscle tumor acts in a somewhat malignant fashion and produces benign metastasis, usually to the lungs or lymph nodes. In most instances, intravenous leiomyomatosis is not apparent. The metastasizing myomas are capable of growth at distant sites, whereas the intravenous tumors spread only by direct extension within blood vessels. Experimental and clinical evidence suggests that these tumors are stimulated by estrogen. Removing the source of estrogen, by oophorectomy or withdrawal of exogenous estrogen, or by treatment with an antiestrogen or a gonadotropin agonist has an ameliorating effect. Surgical treatment should consist of total hysterectomy, bilateral salpingo-oophorectomy, and resection of pulmonary metastases, if possible (284).

Disseminated peritoneal leiomyomatosis is a rare clinical entity characterized by benign smooth muscle nodules scattered throughout the peritoneal cavity. This condition probably arises as a result of metaplasia of subperitoneal mesenchymal stem cells to smooth muscle, fibroblasts, myofibroblasts, and decidual cells under the influence of estrogen and progesterone. Most reported cases occurred in 30- to 40-year-old women who are or were recently pregnant or who have a long history of oral contraceptive use. Intriguing features of this disease are its grossly malignant appearance, benign histology, and favorable clinical outcome. Intraoperative diagnosis requires frozen-section examination. Extirpative surgery, including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and excision of as much gross-tumor as possible, may be indicated in menopausal women. Removal of the source of excess estrogen and treatment with progestins or antiestrogens has resulted in regression of unresected tumor masses. Almost all women have a good prognosis (285).

Adenosarcoma

Adenosarcoma consists of an admixture of benign-appearing neoplastic glands and a sarcomatous stroma. It accounts for only about 5% of all uterine sarcomas. Most patients present with postmenopausal uterine bleeding, and the disease is diagnosed or

suspected on endometrial sampling. Most adenosarcomas are well circumscribed and are limited to the endometrium or superficial myometrium. Standard treatment is total hysterectomy and bilateral salpingo-oophorectomy; routine lymph node dissection is not indicated. Because recurrences, mostly in the form of local pelvic or vaginal disease, are reported to occur in up to 40% to 50% of cases, adjuvant postoperative vaginal brachytherapy or pelvic radiation has been recommended. There is little evidence for the use of adjuvant chemotherapy or hormonal therapy. Survival is mainly impacted by the presence or absence of sarcomatous overgrowth, which is found in about 30% of cases. Overall 5-year survival is reported to be 70% to 80% without sarcomatous overgrowth versus 50% to 60% with sarcomatous overgrowth (286).

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CHAPTER 38

Cervical and Vaginal Cancer



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Cervical Cancer
- **Epidemiology and Risk Factors**
- **Evaluation**
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  - *Histologic Appearance of Invasion*
- **Staging**
  - *Additional Staging Modalities*
- **Pathology**
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Staging
Etiology
Screening
Symptoms
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Pathology
Treatment
Sequelae
Survival

KEY POINTS

1 Human papillomavirus (HPV) infection is the causal agent of cervical cancer.

2 Screening programs are effective at decreasing the incidence of cervical cancer. Vaccines help decrease the incidence of cervical cancer.

3 The most common histologic type of cervical cancer is squamous, and the relative and absolute incidence of adenocarcinoma is increasing. Both histologies are caused by HPV infection.

4 Cervical cancer is clinically staged, although modern radiographic modalities such as computed tomography, magnetic resonance imaging, ultrasound, or positron emission tomography, if available, may be beneficial for individual treatment planning. The staging system has been updated in 2018.

5 Treatment of cervical cancer is based on stage of disease. Early-stage disease (stages I to IIA) can be treated with either radical surgery or radiation therapy. Advanced stage disease (stages IIB to IV) is best treated with chemoradiation, including brachytherapy.

6 Vaginal cancer is a rare disease with many similarities to cervical cancer. Radiation therapy is the mainstay of treatment for most patients; however, select patients may be treated with radical surgery.

7 Minimally invasive radical hysterectomy. Laparoscopic and robotic radical hysterectomies were being performed with larger degree of frequency in highly selected patients world wide.

Cervical cancer ranks as the third most common gynecologic neoplasm in the United States, behind cancer of the uterine corpus and ovary, mainly as a result of the effectiveness of screening programs. **Worldwide, cervical carcinoma continues to be a significant health care problem. In developing countries, where health care resources are limited, cervical carcinoma is the second most frequent cause of cancer death in women.** Because cervical cancer is preventable, it is imperative that gynecologists and other primary health care providers for women be familiar with vaccination programs, screening techniques, diagnostic procedures, and risk factors for cervical cancer and management of preinvasive disease. Vaginal cancer is a rare tumor that shares an epidemiology and risk factor profile that is similar to cervical cancer.

CERVICAL CANCER

Epidemiology and Risk Factors

Invasive cancer of the cervix is considered a preventable disease because it has a long preinvasive state, cervical cytology screening programs are available, and the treatment of preinvasive lesions is effective. In spite of the preventable nature of this disease, the CDC reported 12,578 new cases of invasive cervical cancer resulting in 4,115 deaths in the United States in 2014 (1). This data are similar to the 2011 statistics, with only a slight decrease (1,2). Nationally, the lifetime probability of developing cervical cancer is 1:128. Although screening programs in the United States are well established, it is estimated that 30% of cervical cancer cases will occur in women who have never had a Papanicolaou (Pap) test. In developing countries, this percentage approaches 60% (3). Nevertheless, the worldwide incidence of invasive disease is decreasing, and cervical cancer is being diagnosed earlier, leading to better survival rates (2,4). The mean age for cervical cancer in the United States is 47 years, and the distribution of cases is bimodal, with peaks at 35 to 39 years and 60 to 64 years of age (2).

There are numerous risk factors for cervical cancer: young age at first intercourse (younger than 16 years), multiple sexual partners, cigarette smoking, race, high parity, low socioeconomic status, and chronic immune suppression. The relationship to oral contraceptive use was debated. Some investigators proposed that use of oral contraceptives might increase the incidence of cervical glandular abnormalities; however, this hypothesis was not consistently supported (5,6). **[1]** Many of these risk factors are linked to sexual activity and exposure to sexually transmitted diseases. Infection with the herpes virus was thought to be the initiating event in cervical cancer; however, infection with human papillomavirus (HPV) was determined

to be the causal agent in the development of cervical cancer, with herpes virus and *Chlamydia trachomatis* likely acting as cofactors. The role of human immunodeficiency virus (HIV) in cervical cancer is mediated through immune suppression (5). The Centers for Disease Control and Prevention described cervical cancer as an acquired immune deficiency syndrome (AIDS)–defining illness in patients infected with HIV (7).

[1] The initiating event in cervical dysplasia and carcinogenesis is infection with HPV. HPV infection was detected in up to 99% of women with squamous cervical carcinoma. HPV is the causative agent in both squamous and adenocarcinoma of the cervix, but the respective tumors may have different carcinogenic pathways (8). There are more than 100 different types of HPV, more than 30 of which can affect the lower genital tract. There are 15 high-risk HPV subtypes; two of the high-risk subtypes, 16 and 18, are found in up to 70% of cervical carcinomas. The mechanism by which HPV affects cellular growth and differentiation is through the interaction of viral E6 and E7 proteins with tumor suppressor genes p53 and Rb, respectively. Inhibition of p53 prevents cell cycle arrest and cellular apoptosis, which normally occurs when damaged DNA is present, whereas inhibition of Rb disrupts transcription factor E2F, resulting in unregulated cellular proliferation (9). Both steps are essential for the malignant transformation of cervical epithelial cells. Initially, there were two HPV vaccines, the quadrivalent *Gardasil* and the bivalent *Cervarix*, approved by the U.S. Food and Drug Administration (FDA). Both protect against HPV subtypes 16 and 18. **[2]** The efficacy of *Gardasil* was 97% to 100% for preventing cervical intraepithelial neoplasia (CIN) grades 2 and 3 caused by HPV 16 or 18 in females who were not previously infected with either HPV 16 or 18 before vaccination; however, efficacy was only 44% in those who were infected prior to vaccination (10). Recently, the FDA has approved a third HPV vaccine, Gardasil-9, which protects against the four subtypes of the quadrivalent vaccine plus an additional five high-risk subtypes (HPV 31/33/45/52/58). In a head-to-head, immunoresponse trial, the 9-valent HPV vaccine showed non-inferior anti-HPV 6/11/16/18 antibody response (11). The efficacy of the 9-valent vaccine in preventing CIN 2,3, VIN 2 or 3, and VAIN 2 or 3 was 97% in the HPV-naïve patient population (12). Long-term data for superior efficacy in HPV 31/33/45/52/58-related clinical outcomes is still pending. The FDA also extended the recommended age indication for Gardisil-9 to include men and women ages 9 to 45. Because these vaccines do not protect against all HPV subtypes, vaccinated women need to continue to receive cervical cancer screening according to published guidelines.

Evaluation

Vaginal bleeding is the most common symptom occurring in patients with cancer of the cervix. Most often, this is postcoital bleeding, but it may occur as irregular or postmenopausal bleeding. Patients with advanced disease may present with a

malodorous vaginal discharge, weight loss, or obstructive uropathy. In asymptomatic women, cervical cancer is most commonly identified through evaluation of abnormal cytologic screening tests. The false-negative rate for Pap tests in the presence of invasive cancer is up to 50%, so a negative Pap test should never be relied on in a symptomatic patient (13).

Initially, all women suspected of having cervical cancer should have a general physical examination performed to include evaluation of the supraclavicular, axillary, and inguinofemoral lymph nodes to exclude the presence of metastatic disease. On pelvic examination, a speculum is inserted into the vagina, and the cervix is inspected for suspicious areas **(Fig. 38-1)**. The vaginal fornices should be closely inspected. With invasive cancer, the cervix is usually firm and expanded, and these features should be confirmed by digital examination. Rectal examination is important to help establish cervical consistency and size, particularly in patients with endocervical carcinomas. Rectal examination is the only way to determine cervical size if the vaginal fornices have been obliterated by menopausal changes or by the extension of disease. Parametrial extension of disease is best determined by the finding of nodularity beyond the cervix on rectal examination.

When obvious tumor growth is present, a cervical biopsy is usually sufficient for diagnosis. If gross disease is not present, a colposcopic examination with cervical biopsies and endocervical curettage is warranted. If the diagnosis cannot be established conclusively with colposcopy and directed biopsies, which may be the case with adenocarcinoma, cervical conization may be necessary.

Colposcopic Findings of Invasion

Colposcopic examination is mandatory for patients with suspected early invasive cancer based on cervical cytology and a grossly normal-appearing cervix. Colposcopic findings that suggest invasion are (i) abnormal blood vessels, (ii) irregular surface contour with loss of surface epithelium, and (iii) color tone change. Colposcopically directed biopsies may permit the diagnosis of frank invasion and thus avoid the need for diagnostic cone biopsy, allowing treatment to be administered without delay. If there is debate about the depth of invasion based on the cervical biopsies, and if the clinical stage may be upstaged to stage IA2 or IB1, the patient should undergo a conization. In the presence of a large cervical biopsy specimen showing invasion greater than 3 mm, or two biopsy specimens separated by 7 mm showing invasive cervical carcinoma, therapy should proceed without delay, and the patient could undergo radical surgery or radiation therapy.

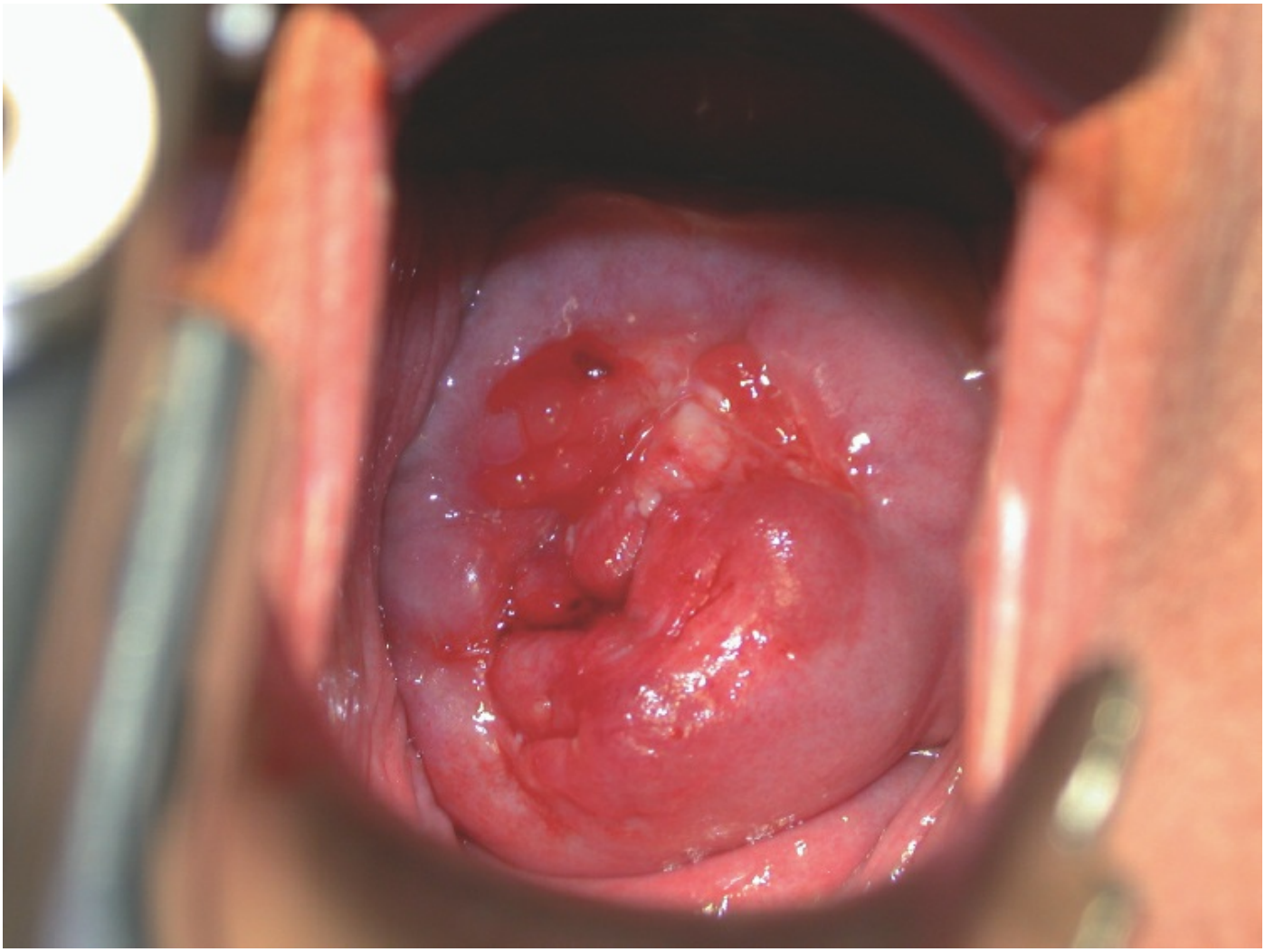


FIGURE 38-1 Gross appearance of cervical cancer on examination.

Abnormal Blood Vessels

Abnormal vessels may be looped, branched, or reticular. **Abnormal looped vessels are the most common colposcopic finding and arise from the punctated and mosaic vessels present in CIN.** As the neoplastic growth process proceeds and the need for oxygen and nutrition increases, angiogenesis occurs as a result of tumor and local tissue production of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and other cytokines, resulting in the proliferation of blood vessels and neovascularization. Punctate vessels push out over the surface of the epithelium in an erratic fashion, producing the looped, corkscrew, or J-shaped pattern of abnormal vessels characteristic of invasive disease. Abnormal blood vessels arise from the cervical stroma and are pushed to the surface as the underlying cancer invades. The normally branching cervical stromal vessels are best observed over nabothian cysts. In this area, the branches are generally at acute angles, with the caliber of vessels becoming smaller after branching, much like the arborization of a tree. The abnormal branching blood vessels seen with cancer tend to form obtuse or

right angles, with the caliber sometimes enlarging after branching. Sharp turns, dilations, and luminal narrowing characterize these vessels. The surface epithelium may be lost in these areas, leading to irregular surface contour and friability.

Abnormal reticular vessels represent the terminal capillaries of the cervical epithelium. Normal capillaries are best seen in postmenopausal women with atrophic epithelium. When cancer involves this epithelium, the surface is eroded, and the capillary network is exposed. These vessels are very fine and short and appear as small comma-shaped vessels without an organized pattern. They are not specific to invasive cancer; atrophic cervicitis may also have this appearance.

Irregular Surface Contour

Abnormal surface patterns are observed as tumor growth proceeds. The surface epithelium ulcerates as the cells lose intercellular cohesiveness secondary to loss of desmosomes. Irregular contour may occur as a result of papillary characteristics of the lesion. **This finding can be confused with a benign HPV papillary growth on the cervix. For that reason, biopsies should be performed on all papillary cervical growths to avoid missing invasive disease.**

Color Tone

Color tone may change as a result of increasing vascularity, surface epithelial necrosis, and in some cases, production of keratin. The color tone is yellow-orange rather than the expected pink of intact squamous epithelium or the red of the endocervical epithelium.

Adenocarcinoma

Adenocarcinoma of the cervix does not have a specific colposcopic appearance. All of the aforementioned blood vessels may be seen in these lesions. Because adenocarcinomas tend to develop within the endocervix, endocervical curettage is required as part of the colposcopic examination, and traditional screening methods are less reliable (13).

Histologic Appearance of Invasion

Cervical conization is required to assess correctly the depth and the linear extent of involvement when microinvasion is suspected. Early invasion is characterized by a protrusion of malignant cells from the stromal–epithelial junction. This focus consists of cells that appear better differentiated than the adjacent noninvasive cells and have abundant pink-staining cytoplasm, hyperchromatic nuclei, and small-to-medium–sized nucleoli (14). **These early invasive lesions form tonguelike processes without measurable volume and are classified as International Federation of Gynecology and Obstetrics (FIGO) stage IA1.** With further progression, more tonguelike processes and isolated malignant cells appear in the stroma, followed by a proliferation

of fibroblasts (desmoplasia) and a bandlike infiltration of chronic inflammatory cells **(Fig. 38-2)**. **With increasing depth of invasion, lesions occur at multiple sites, and the growth becomes measurable by depth and linear extent. Lesions that are less than 3 mm in depth are classified as FIGO stage IA1. Lesions that are 3 to 5 mm or more in depth and up to 7 mm in linear extent are classified as FIGO stage IA2** (15). As the depth of stromal invasion increases, so does the risk of capillary lymphatic space involvement. Dilated capillaries, lymphatic spaces, and foreign-body multinucleated giant cells containing keratin debris are often seen in the stroma.

The depth of invasion should be measured with a micrometer from the base of the epithelium to the deepest point of invasion. **Depth of invasion is a significant predictor for the development of pelvic lymph node metastasis and tumor recurrence. Although lesions that have invaded 3 mm or less rarely metastasize, patients in whom lesions invade between 3 and 5 mm have positive pelvic lymph nodes in 3% to 8% of cases** (16). The significance of the cutoff at 3 mm is not identified completely; it was postulated that small capillary–lymphatic spaces at this level are incapable of facilitating the transport of malignant cells. Uneven shrinkage of tissue by fixative often creates space between the tumor nests and the surrounding fibrous stroma, simulating vascular lymphatic invasion **(Fig. 38-2)**. Therefore, suspected vascular–lymphatic involvement with invasion of less than 3 mm should be interpreted with care. A lack of endothelial lining indicates that the space is a fixation artifact rather than true vascular invasion.

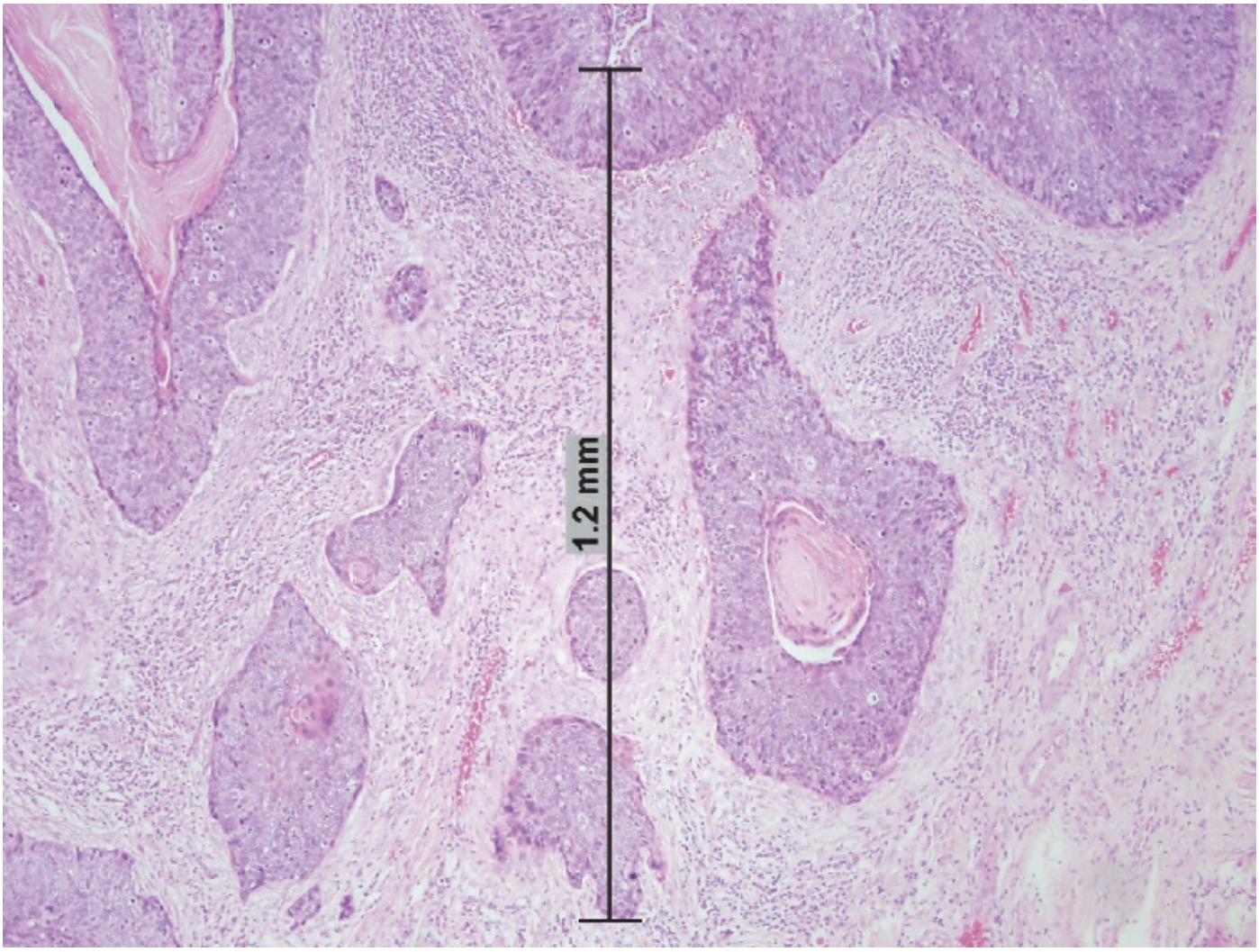


FIGURE 38-2 Microinvasive squamous carcinoma. Multiple irregular tonguelike processes and isolated nests of malignant cells are seen, some surrounded by clear spaces, simulating capillary lymphatic invasion. This is an artifact caused by tissue shrinkage. The depth of stromal invasion is measured from the basement membrane of the overlying cervical intraepithelial neoplasia (CIN). In this case, it is 1.2 mm.

Staging

The FIGO staging system was updated in 2018 to include imaging and pathologic findings and is presnted in Table 38-1 and **Figure 38-3**. The old 2008 FIGO clinical staging system is shown in Table 38-2. The FIGO staging system is applicable to all histologic types of cervical cancer. The reported data presented in this chapter are based on the 2008 staging system.

When there is doubt concerning the stage to which a cancer should be allocated, the earlier stage should be selected. After a stage is assigned and treatment is initiated, the stage must not be changed because of subsequent findings. The upstaging of patients during treatment will produce an erroneous perception of improvement in the results of treatment of low-stage disease. Following is a breakdown of the incidence of cervical cancer by the clinical staging system at diagnosis: 38%,

stage I; 32%, stage II; 26%, stage III; and 4%, stage IV (4,16,17).

In the 2018 staging system, horizontal spread is no longer considered in stage IA, only the depth of invasion is used. Stage IB is now divided into 3 stages, Stages IB1, IB2, and IB3. Stage IB1 denotes lesions that are <2 cm in greatest dimension, reflecting advances fertility-sparing procedures that are now recommended for selected patients with these smaller tumors. Last, Stage III has added a stage with substages to reflect pelvic and paraaortic lymph node metastasis; this is due to the worsening of outcomes when lymph node metastasis is present. See Table 38-1 for the revised 2018 FIGO staging system.

Table 38-1 FIGO Staging of Carcinoma of the Cervix Uteri (2018)

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall

IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower staging should be assigned.

[a]Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.

[b]The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

From **Bhatla N, Berek JS, Cuello Frede M, et al.** FIGO Committee Report. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynecol Obstet* 2019:1–7.

Additional Staging Modalities

Various investigators used lymphangiography, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and positron emission tomography (PET) in an attempt to improve the accuracy of clinical staging (18–28). **These modalities suffer from poor sensitivity and high false-negative rates.** Evaluation of the para-aortic lymph nodes with lymphangiography is associated with a false-positive rate of 20% to 40% and a false-negative rate of 10% to 20% (18–20). Overall, lymphangiography has a sensitivity of 79% and specificity of 73% (23). CT has poor sensitivity (34%) but excellent specificity (97%) (24). The accuracy of CT scanning is 80% to 85%; the false-negative rate is 10% to 15%, and the false-positive rate is 20% to 25% (19–21). Ultrasound has a high false-negative rate (30%), low sensitivity (19%), but high specificity (99%) (22). Early data showed that MRI results were comparable to those of CT scanning, a finding confirmed on meta-analysis (24,25). **A systematic review comparing CT scan with MRI showed that MRI is significantly more sensitive with equivalent specificity.** MRI has excellent sensitivity

on T2-weighted images for the detection of parametrial disease (26).

PET scans are increasingly being utilized alone or in conjunction with CT or MRI to detect metastatic disease. Studies suggest that PET may be more useful than other imaging techniques for the detection of extrapelvic disease, with comparable or better sensitivity and specificity (27). A meta-analysis of 72 studies found PET (75%, 98%) to have superior sensitivity and specificity compared with CT (58%, 92%) and MRI (56%, 93%) for the detection of lymph node metastases (28). PET scans may be better predictors of eventual treatment outcome. Although these studies show promise for the use of PET scans in detecting metastases, its sensitivity in detecting pelvic nodal disease may be limited (29). Integrated PET/CT imaging may prove more sensitive than PET alone, especially for the detection of pelvic adenopathy.

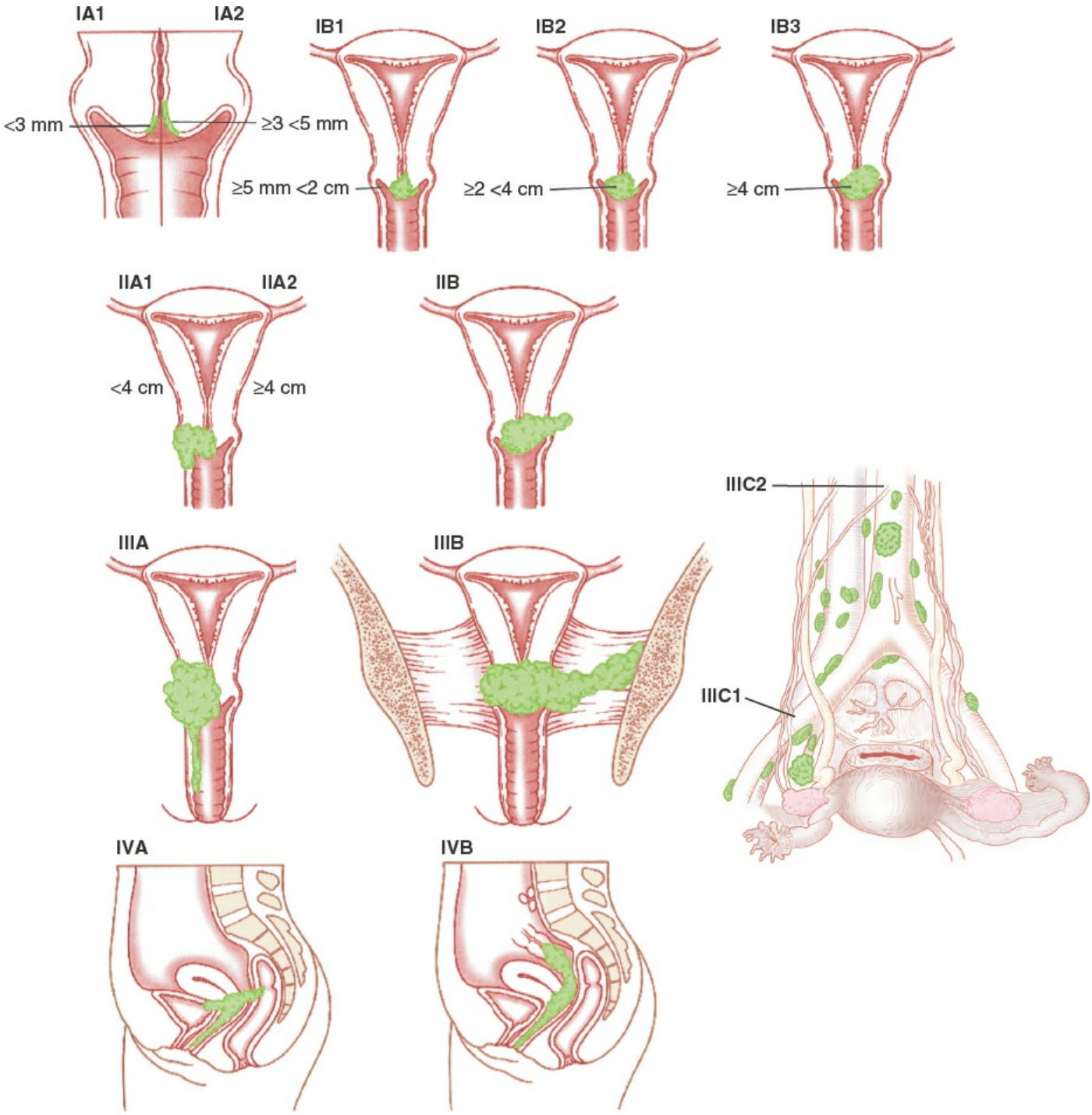


FIGURE 38-3 FIGO Cervical Cancer Staging (2018). (Adapted from **Benedet J, Odicino F, Maisonneuve P, Beller U, Creasman W, Heintz A, Ngan H, and Pecorelli S.** Carcinoma of the cervix uteri. *International Journal of Gynecology & Obstetrics*. 2003;83:41–78.)

When abnormalities are noted on CT, MRI, or PET, radiographic-guided fine-needle aspirations (FNA) can be performed to confirm metastatic disease and individualize treatment planning. [4] The FIGO 2018 staging system incorporates imaging and pathologic measurements in determining the size and extent of the primary tumor and the presence of pelvic and para-aortic metastasis.

The accuracy of clinical staging is limited, and surgical evaluation, although not practical or feasible in all patients, can more accurately identify metastatic disease (30).

Pathology

Squamous Cell Carcinoma

Invasive squamous cell carcinoma is the most common variety of invasive cancer in the cervix. [3] Histologically, variants of squamous cell carcinoma include **large cell keratinizing, large cell nonkeratinizing, and small cell types** (31). Large cell keratinizing tumors consist of tumor cells forming irregular infiltrative nests with laminated keratin pearls in the center. Large cell nonkeratinizing carcinomas reveal individual cell keratinization but do not form keratin pearls **(Fig. 38-4)**. The category of small-cell carcinoma includes poorly differentiated squamous cell carcinoma and small-cell anaplastic carcinoma. If possible, these two tumors should be differentiated. The former contains cells that have small-to-medium-sized nuclei and more abundant cytoplasm than those of the latter. The designation of small-cell anaplastic carcinoma should be reserved for lesions resembling oat cell carcinoma of the lung. Small-cell anaplastic carcinoma infiltrates diffusely and consists of tumor cells that have scanty cytoplasm, round to oval small nuclei, coarsely granular chromatin, and high mitotic activity. The nucleoli are absent or small. **Immunohistochemistry or electron microscopy can differentiate the small-cell neuroendocrine tumors.** Patients with the large cell type of carcinoma, with or without keratinization, have a better prognosis than those with the small-cell variant. Small-cell anaplastic carcinomas behave more aggressively than poorly differentiated squamous carcinomas that contain small cells. Infiltration of parametrial tissue and pelvic lymph node metastasis affect the prognosis.

Table 38-2 FIGO Clinical Staging of Carcinoma of the Cervix Uteri (2008)

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA[a]
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension

Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney[b]
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

[a]All macroscopically visible lesions, even those with superficial invasion, are allotted to stage IB carcinomas. Invasion is limited to a measured stroma invasion with a maximal depth of 5.0 mm and a horizontal extension greater than 7.0 mm. Depth of invasion should not be greater than 5 mm taken from the base of the epithelium of the original tissue squamous or glandular. The depth of invasion should always be reported in millimeters, even those cases with “early minimal stromal invasion” (~1 mm). The involvement of vascular/lymphatic spaces should not change stage allotment.

[b]On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to another cause.

FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Obstet Gynecol* 2009;105:103–104.

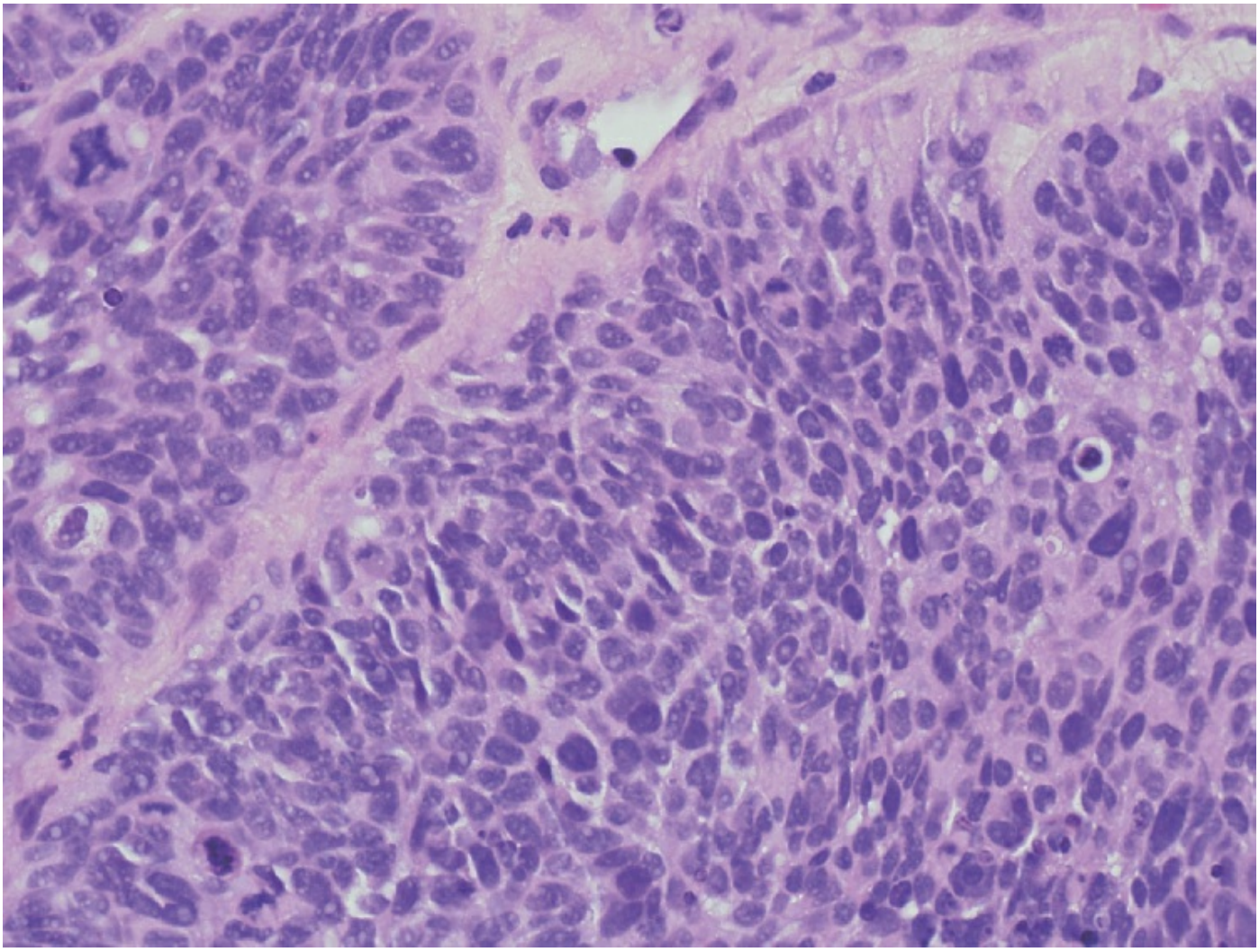


FIGURE 38-4 Invasive squamous cell carcinoma, large cell nonkeratinizing type. Tumor cells form irregular nests and have abundant eosinophilic cytoplasm and distinct cell borders indicative of squamous differentiation.

Other less common variants of squamous carcinoma include **verrucous carcinoma** and **papillary (transitional) carcinoma.** Verrucous carcinomas may resemble giant condyloma acuminatum, are locally invasive, and rarely metastasize. Papillary carcinomas histologically resemble transitional cells of the bladder and may have more typical squamous cell invasion at the base of the lesion. Papillary carcinomas behave and are treated in a manner similar to traditional squamous cell cancers, except that late recurrences were noted.

Adenocarcinoma

There are an increasing number of cervical adenocarcinomas reported in women in their 20s and 30s. [3] Although the total number of cases of adenocarcinoma is relatively stable, this disease is appearing more frequently in young women, especially as the number of cases of invasive squamous cell carcinoma decreases.

Older reports indicated that 5% of all cervical cancers were adenocarcinomas, whereas newer reports show a proportion as high as 18.5% to 27% (32–34). Much of this proportional increase is related to a decreasing incidence of squamous carcinoma secondary to screening programs (which are less accurate at identifying preinvasion adenocarcinoma), greater exposure to oral contraceptives, and a greater exposure to HPV (5,6).

Adenocarcinoma in situ (AIS) is believed to be the precursor of invasive adenocarcinoma, and it is not surprising that the two often coexist (35). In addition to AIS, intraepithelial or invasive squamous neoplasia occurs in 30% to 50% of cervical adenocarcinomas (36). A squamous intraepithelial lesion may be observed colposcopically on the ectocervix, and the coexistent adenocarcinoma often is higher in the cervical canal.

Patients with AIS who are treated with conization should undergo close clinical follow-up. Endocervical curettage, often used in surveillance, may miss residual or invasive disease, and false-negative rates as high as 50% were reported (37). In addition, skip lesions not resected at the time of conization may be present. For these reasons, hysterectomy should be considered the standard therapy for patients who have completed their childbearing. In two reports, patients with negative cone biopsy margins were followed conservatively, with few requiring repeat surgical procedures (38,39). Because cervical AIS tends to affect women during their reproductive years, a thorough discussion of risks and benefits should take place, and treatment should be individualized.

Adenocarcinoma of the cervix is managed in the same manner used for squamous cell carcinoma. Adenocarcinoma was believed to be associated with a worse prognosis and outcome when compared with squamous cell carcinoma. A study of 203 women with adenocarcinoma and 756 women with squamous carcinoma supported this assertion (33). This study showed 5-year survival rates of 90% versus 60%, 62% versus 47%, and 36% versus 8% for stages I, II, and III, respectively. Although some attributed these rates to a relative resistance to radiation, they are more likely a reflection of the tendency of adenocarcinomas to grow endophytically and to be undetected until a large volume of tumor is present. Adenocarcinomas may be detected by cervical sampling, but less reliably so than squamous carcinomas. A definitive diagnosis often requires cervical conization. When adjusted for tumor size, it appears that there is no difference in prognosis between the two histologic subtypes. In a Gynecologic Oncology Group (GOG) review of patients treated with concurrent *cisplatin* chemotherapy with radiotherapy, survival was equivalent among squamous, adenocarcinoma, and adenosquamous carcinoma subgroups (40).

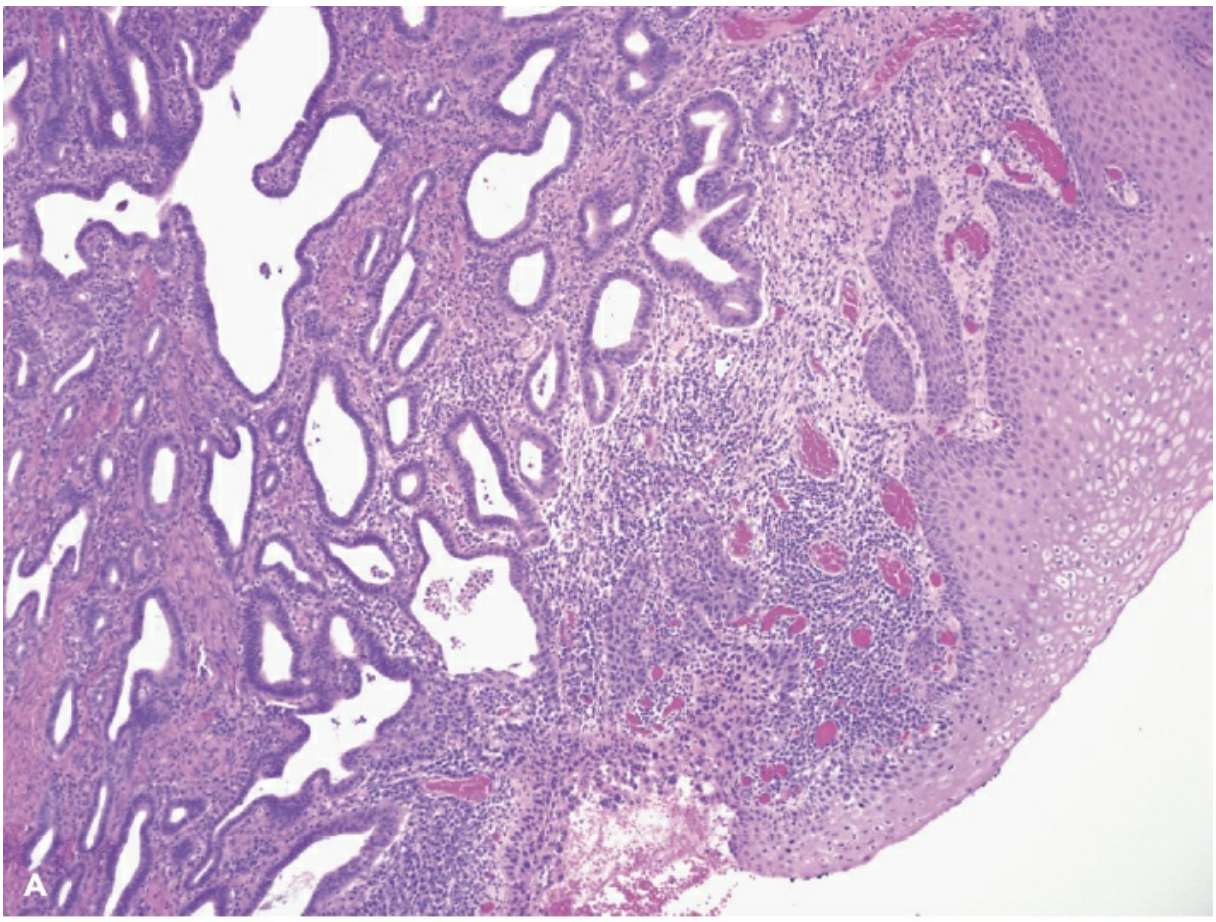
The clinical features of stage I adenocarcinomas are well studied (33,41,42). These studies identified size of tumor, depth of invasion, grade of tumor, and age of the patient as significant correlates of lymph node metastasis and survival. When matched with

squamous carcinomas for lesion size, age, and depth of invasion, the incidence of lymph node metastases and the survival rate appear to be the same (41,42). **Patients with stage I adenocarcinomas can be selected for treatment according to the same criteria as for those with squamous cancers** (42).

The choice of treatment for bulky stages I and II tumors is controversial. Some advocated treatment with radiation alone, whereas others support radiation plus extrafascial hysterectomy (43–45). In 1975, Rutledge et al. reported an 85.2% 5-year survival rate for all patients with stage I disease treated with radiation alone and an 83.8% survival rate for those who had radiation plus surgery (44). The central persistent disease rate was 8.3%, compared with 4% for those who had radiation plus surgery. In stage II disease, the 5-year survival rate was 41.9% for radiation alone and 53.7% for radiation plus surgery. **A subsequent report revealed no significant difference in survival among patients treated with radiation alone or radiation plus extrafascial hysterectomy** (46).

Invasive adenocarcinoma may be pure **(Fig. 38-5A,B)** or mixed with squamous cell carcinoma. Within the category of pure adenocarcinoma, the tumors are quite heterogeneous, with a wide range of cell types, growth patterns, and differentiation (33). **About 80% of cervical adenocarcinomas consist predominantly of the endocervical type cells with mucin production. The remaining tumors are populated by endometrioid cells, clear cells, intestinal cells, or a mixture of more than one cell type. By histologic examination alone, some of these tumors are indistinguishable from those arising elsewhere in the endom etrium or ovary.** Within each cell type, the growth patterns and nuclear abnormalities vary according to the degree of differentiation. In well-differentiated tumors, tall columnar cells line the well-formed branching glands and papillary structures, whereas pleomorphic cells tend to form irregular nests and solid sheets in poorly differentiated neoplasms. The latter may require mucicarmine and periodic acid–Schiff (PAS) staining to confirm their glandular differentiation.

In a retrospective review of GOG trials of chemoradiation for cervix carcinoma, treatment with radiation alone was associated with worse overall survival (OS) in adenocarcinoma and adenosquamous carcinoma when compared with squamous carcinoma. In contrast, treatment with *cisplatin*-based chemoradiation was associated with similar progression-free and OS between the adenocarcinoma and squamous groups (40).


A

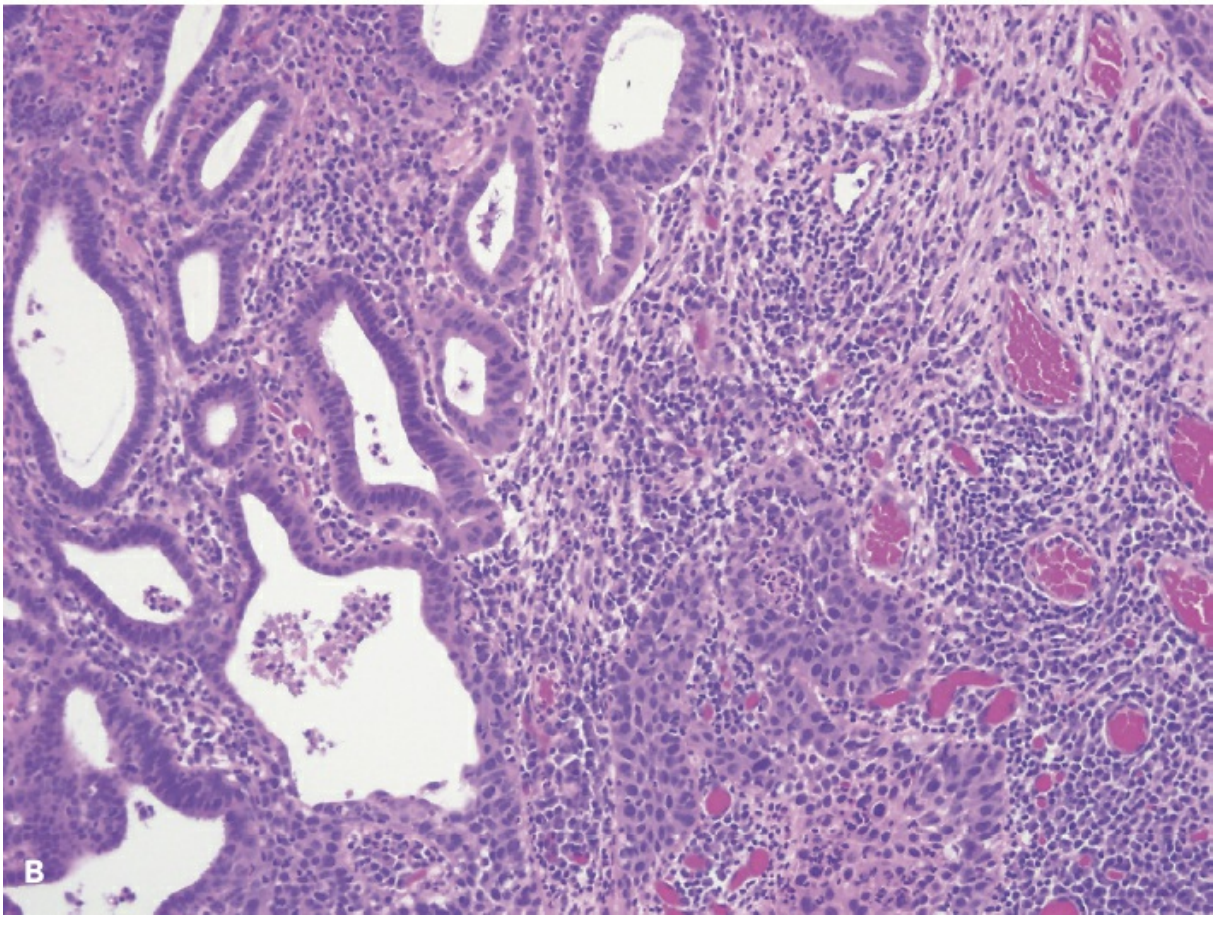

B

FIGURE 38-5 Invasive adenocarcinoma of the cervix, well differentiated. **A:** Irregular glands are lined with tall columnar cells with vacuolated mucinous cytoplasm resembling endocervical cells. **B:** Nuclear stratification, mild nuclear atypism, and mitotic figures are evident in higher power.

There are several special variants of adenocarcinoma. **Minimal deviation adenocarcinoma (adenoma malignum)** is an extremely well-differentiated form of adenocarcinoma in which the branching glandular pattern strongly simulates that of the normal endocervical glands. The lining cells have abundant mucinous cytoplasm and uniform nuclei (47,48). Because of this, the tumor may not be recognized as malignant in small biopsy specimens, thereby causing considerable delay in diagnosis. Special immunohistochemical staining may be required to establish the diagnosis. Earlier studies reported a dismal outcome for women with this tumor, but other studies found a favorable prognosis if the disease is detected early (49). Although rare, similar tumors were reported in association with endometrioid, clear, and mesonephric cell types (50).

An entity described as **villoglandular papillary adenocarcinoma** deserves special attention (51). It primarily affects young women, some of whom are pregnant or users of oral contraceptives. Histologically, the tumors have smooth, well-defined borders, are well differentiated, and are either in situ or superficially invasive. Follow-up information is encouraging. None of these tumors recurred after cervical conization or hysterectomy, and no metastasis was detected among women undergoing pelvic lymphadenectomy. This tumor appears to have limited risk for spread beyond the uterus.

Adenosquamous Carcinoma

Carcinomas with a mixture of malignant glandular and squamous components are known as **adenosquamous carcinomas.** Patients with adenosquamous carcinoma of the cervix were reported to have a poorer prognosis than those with pure adenocarcinoma or squamous carcinoma but a review of patients treated with *cisplatin*-based chemoradiation has shown no difference in survival among the three groups (52).

In mature adenosquamous carcinomas, the glandular and squamous carcinomas are readily identified on routine histologic evaluation and do not cause diagnostic problems. **In poorly differentiated or immature adenosquamous carcinomas, glandular differentiation can be appreciated only with special stains, such as mucicarmine and PAS.** In one study, 30% of squamous cell carcinomas demonstrated mucin secretion when stained with mucicarmine (50). These squamous cell carcinomas with mucin secretion have a higher incidence of pelvic lymph node metastases than do squamous cell carcinomas without mucin secretion, and they are similar to the signet-ring variant of adenosquamous carcinoma (50,53).

Glassy cell carcinoma is recognized as a poorly differentiated form of adenosquamous carcinoma (53). Individual cells have abundant eosinophilic, granular, ground-glass cytoplasm, large round to oval nuclei, and prominent nucleoli. The stroma

is infiltrated by numerous lymphocytes, plasma cells, and eosinophils. Approximately half of these tumors contain glandular structures or stain positive for mucin. The poor diagnosis of this tumor is linked to understaging and resistance to radiotherapy.

Other variants of adenosquamous carcinoma include **adenoid basal carcinoma** and **adenoid cystic carcinoma.** Adenoid basal carcinoma simulates the basal cell carcinoma of the skin (54). Nests of basaloid cells extend from the surface epithelium deep into the underlying tissue. Cells at the periphery of tumor nests form a distinct parallel nuclear arrangement, so-called peripheral palisading. An "adenoid" pattern occasionally develops, with "hollowed-out" nests of cells. Mitoses are rare, and the tumor often extends deep into the cervical stroma.

Adenoid cystic carcinoma of the cervix behaves much like such lesions elsewhere in the body. The tumors tend to invade into the adjacent tissues and metastasize late, often 8 to 10 years after the primary tumor was removed. Like other adenoid cystic tumors, they may metastasize directly to the lung. The pattern simulates that of the adenoid basal tumor, but there is a cystic component, and the glands of the cervix are involved (54). Mitoses may be seen but are not numerous.

Sarcoma

The most important sarcoma of the cervix is **embryonal rhabdomyosarcoma,** which occurs in children and young adults. The tumor has grapelike polypoid nodules, known as botryoid sarcoma, and the diagnosis depends on the recognition of rhabdomyoblasts. **Leiomyosarcomas** and **mixed mesodermal tumors** involving the cervix may be primary but are more likely to be secondary to uterine tumors. **Cervical adenosarcoma** is described as a low-grade tumor with a good prognosis (55).

Malignant Melanoma

On rare occasions, melanosis is seen in the cervix. **Malignant melanoma** may arise de novo in this area. Histopathologically, it simulates melanoma elsewhere, and the prognosis depends on the depth of invasion into the cervical stroma.

Neuroendocrine Carcinoma

The classification of neuroendocrine cervical carcinoma includes four histologic subtypes: **(i) small cell, (ii) large cell, (iii) classical carcinoid,** and **(iv) atypical carcinoid** (56). Neuroendocrine tumors of the cervix are rare, and treatment regimens are based on small case series of patients.

Small-cell (neuroendocrine type) carcinoma of the cervix is aggressive in nature and is similar to cancer arising from the bronchus (57). The hallmark of neuroendocrine tumors is their aggressive malignant behavior with the propensity to metastasize. At the time of diagnosis, it is usually disseminated, with bone, brain, liver, and bone marrow being the most common sites of metastases. In one study of 11 patients

with disease apparently confined to the cervix, a high rate of lymph node metastasis was noted (58). Pathologically, the diagnosis is aided by the finding of neuroendocrine granules on electron microscopy and by immunoperoxidase studies that are positive for a variety of neuroendocrine proteins such as calcitonin, insulin, glucagon, somatostatin, gastrin, and adrenocorticotropic hormone (ACTH). In addition to the traditional staging for cancer of the cervix, these patients should undergo bone, liver, and brain scanning, bone marrow aspiration, and biopsy to evaluate the possibility of metastatic disease. Therapy consists of surgery, chemotherapy, and radiation. Because patients with early-stage disease have distant metastases, multimodal therapy is recommended. The main active chemotherapeutic agent is *etoposide*.

Local therapy alone gives almost no chance of cure of small-cell carcinoma. Regimens of combination chemotherapy improved the median survival rates in small-cell bronchogenic carcinoma, and these regimens are used for treatment of small-cell carcinoma of the cervix. Combination chemotherapy may consist of *vincristine*, *doxorubicin*, and *cyclophosphamide* (*VAC*) or *VP-16* (*etoposide*) and *cisplatin* (*EP*) (59). Patients must be monitored carefully because they are at high risk for developing recurrent metastatic disease (60).

Patterns of Spread

Cancer of the cervix spreads by (i) direct invasion into the cervical stroma, corpus, vagina, and parametrium; (ii) lymphatic metastasis; (iii) blood-borne metastasis; and (iv) intraperitoneal implantation. The incidence of pelvic and para-aortic nodal metastasis is shown in Table 38-3.

The cervix is commonly involved in cancer of the endometrium and vagina. The latter is rare, and most lesions that involve the cervix and vagina are designated cervical primaries. Consequently, the clinical classification is that of cervical neoplasia extending to the vagina, rather than vice versa. Endometrial cancer may extend into the cervix by three modes: direct extension from the endometrium, submucosal involvement by lymph vascular extension, and multifocal disease. The latter is most unusual, but occasionally a focus of adenocarcinoma may be seen in the cervix, separate from the endometrium. This lesion should not be diagnosed as metastasis but rather as multifocal disease. Malignancies involving the peritoneal cavity (e.g., ovarian cancer) may be found in the cul-de-sac and extend directly into the vagina and cervix. Carcinomas of the urinary bladder and colon occasionally extend into the cervix. Cervical involvement by lymphoma, leukemia, and carcinoma of the breast, stomach, and kidney is usually part of the systemic pattern of spread for these malignancies. Isolated metastasis to the cervix in such cases may be the first sign of a primary tumor elsewhere in the body.

Table 38-3 Incidence of Pelvic and Para-Aortic Lymph Node Metastasis by Stage Based on FIGO Clinical Staging (2008)

Stage	No. of Patients	Positive Pelvic Nodes (%)	Positive Para-Aortic Nodes (%)
IA1 (≤3 mm)	179[a]	0.5	0
IA2 (>3–5 mm)	84[a]	4.8	<1
IB	1,926[b]	15.9	2.2
IIA	110[c]	24.5	11
IIB	324[c]	31.4	19
III	125[c]	44.8	30
IVA	23[c]	55	40

[a]References: (77,111,118,121,122,170).

[b]References: (17,77,79,94,95,98–102,189).

[c]References: (17,18,95,98,99,103,150).

Treatment Options

The treatment of cervical cancer is similar to the treatment of any other type of malignancy in that both the primary lesion and potential sites of spread should be evaluated and treated. The therapeutic modalities for achieving this goal include primary treatment with surgery, radiotherapy, chemotherapy, or **[5]** chemoradiation. **While radiation therapy can be used in all stages of disease, surgery is limited to patients with stages I to IIA disease. The 5-year survival rate for stage I cancer of the cervix is approximately 85% with either radiation therapy or radical hysterectomy.** A study using the National Cancer Institute's Surveillance Epidemiology and End Results data by an intent-to-treat analysis showed that patients in the surgery arm had an improved survival when compared with patients in the radiation arm (61). Optimal therapy consists of radiation, or surgery alone, to limit the increased morbidity that occurs when the two treatment modalities are combined. Recent improvements in the treatment of cervical carcinoma include adjuvant chemoradiation in patients discovered to have high-risk cervical carcinoma after radical hysterectomy and in patients with locally advanced cervical carcinoma.

Surgery

There are advantages to the use of surgery instead of radiotherapy, particularly in younger women for whom conservation of the ovaries is important. Chronic bladder and bowel problems that require medical or surgical intervention occur in up to 8% of

patients undergoing radiation therapy (62). Such problems are difficult to treat because they result from fibrosis and decreased vascularity. This is in contrast to surgical injuries, which usually can be repaired without long-term complications. Sexual dysfunction is less likely to occur after surgical therapy than radiation, because of vaginal shortening, fibrosis, and atrophy of the epithelium associated with radiation. Surgical therapy shortens the vagina, but gradual lengthening can be brought about by sexual activity. The epithelium does not become atrophic because it responds either to endogenous estrogen or to exogenous estrogens if the patient is postmenopausal.

Radical hysterectomy is reserved for women who are in good physical condition. Advanced chronologic age should not be a deterrent. With improvements in anesthesia, elderly patients withstand radical surgery almost as well as their younger counterparts (63). **It is prudent not to operate on lesions that are larger than 4 cm in diameter because these patients will require postoperative radiation therapy.** When selected in this manner, the urinary fistula rate is less than 2%, and the operative mortality rate is less than 1% (64,65). A summary of the management of cervical cancer is presented in Table 38-4.

If radiation therapy is needed, transposing the ovaries out of the planned radiation field may preserve ovarian function. Although transposition provides some protection, studies suggest that normal ovarian function is preserved in fewer than 50% of patients (66,67). Metastasis to the ovaries occurs in 0.9% of cases of early-stage cervical cancer, so preservation of the ovaries, particularly with adenocarcinoma, may confer a small recurrence risk (68).

Cone Biopsy of the Cervix

Cone biopsy of the cervix serves a diagnostic and therapeutic role in cervical cancer. The procedure is indicated to confirm the diagnosis of cancer, and to definitively treat stage IA1 disease when preservation of fertility is desired. For effective treatment, there must be no evidence of lymph–vascular space invasion, and both endocervical margins and curettage findings must be negative for cancer or dysplasia. Because stage IA1 cancers have less than a 1% risk of lymph node metastasis, lymphadenectomy is not necessary. If the endocervical margin or curettage is positive for dysplasia or malignancy, further treatment is necessary because these findings are strong predictors of residual disease. For squamous cell carcinoma, the risk of residual disease is 4% if both the endocervical margin and curettage are negative for dysplasia or malignancy, 22% if the endocervical margin alone is positive, and 33% if both are positive (69). In cases of AIS, the status of the cone margins is particularly important, with residual preinvasive and invasive disease noted in up to 25% and 3%, respectively, of cases with negative margins, and up to 80% and 7%, respectively, in cases with positive margins (70,71).

Table 38-4 Management of Invasive Cancer of the Cervix by Stage

Stage	Disease	Treatment[a]
IA1	<3 mm - LVSI	Conization or Extrafascial Hyst
	<3 mm + LVSI	Modified Rad Trachel **or** Modified Rad Hyst + pelvic lymph **or** SLN
IA2	≥3 mm <5 mm	Modified Rad Trachel **or** Modified Rad Hyst + pelvic lymph **or** SLN
IB1	≥5 mm <2 cm	Mod Rad/Rad Trachel **or** Mod Rad/Rad Hyst + pelvic lymph **or** SLN
IB2	≥2 cm <4 cm	Rad Hyst + pelvic lymph
IB3	≥4 cm	Chemoradiation, pelvic field
IIA1	<4 cm + upper vagina	Rad Hyst + pelvic lymph **or** chemoradiation
IIA2	≥4 cm + upper vagina	Chemoradiation, pelvic field
IIB	+ Parametria not to pelvic wall	Chemoradiation, pelvic field
IIIA	+ Lower vagina	Chemoradiation, pelvic field
IIIB	+ Pelvic wall or hydronephrosis	Chemoradiation, pelvic ± extended field
IIIC1	+ Pelvic lymph nodes	Chemoradiation, pelvic ± extended field
IIIC2	+ Para-aortic lymph nodes	Chemoradiation, pelvic + extended field + systemic chemotherapy
IVA	+ Adjacent pelvic organs	Chemoradiation, pelvic + extended field **or** pelvic exenteration
IVB	+ Distant organs	Systemic chemotherapy ± radiation, pelvic or modified field

LVSI, lymphvascular space invasion; Mod, modified; Rad, radical; Trachel, trachelectomy; Hyst, hysterectomy; lymph, lymphadenectomy; SLN, sentinel lymph node biopsy in selected cases.

[a]Treatment recommendations must be individualized based on the patient's status and specific disease variables.

Simple (Extrafascial) Hysterectomy

Type I hysterectomy is an appropriate therapy for patients with stage IA1 tumors without lymph–vascular space invasion who are not desirous of future fertility. In such cases, lymphadenectomy is not recommended. If lymph-vascular space invasion is found, a type II modified radical hystectormy with pelvic sentinel lymph node biospy or lymphandectomy is appropriate.

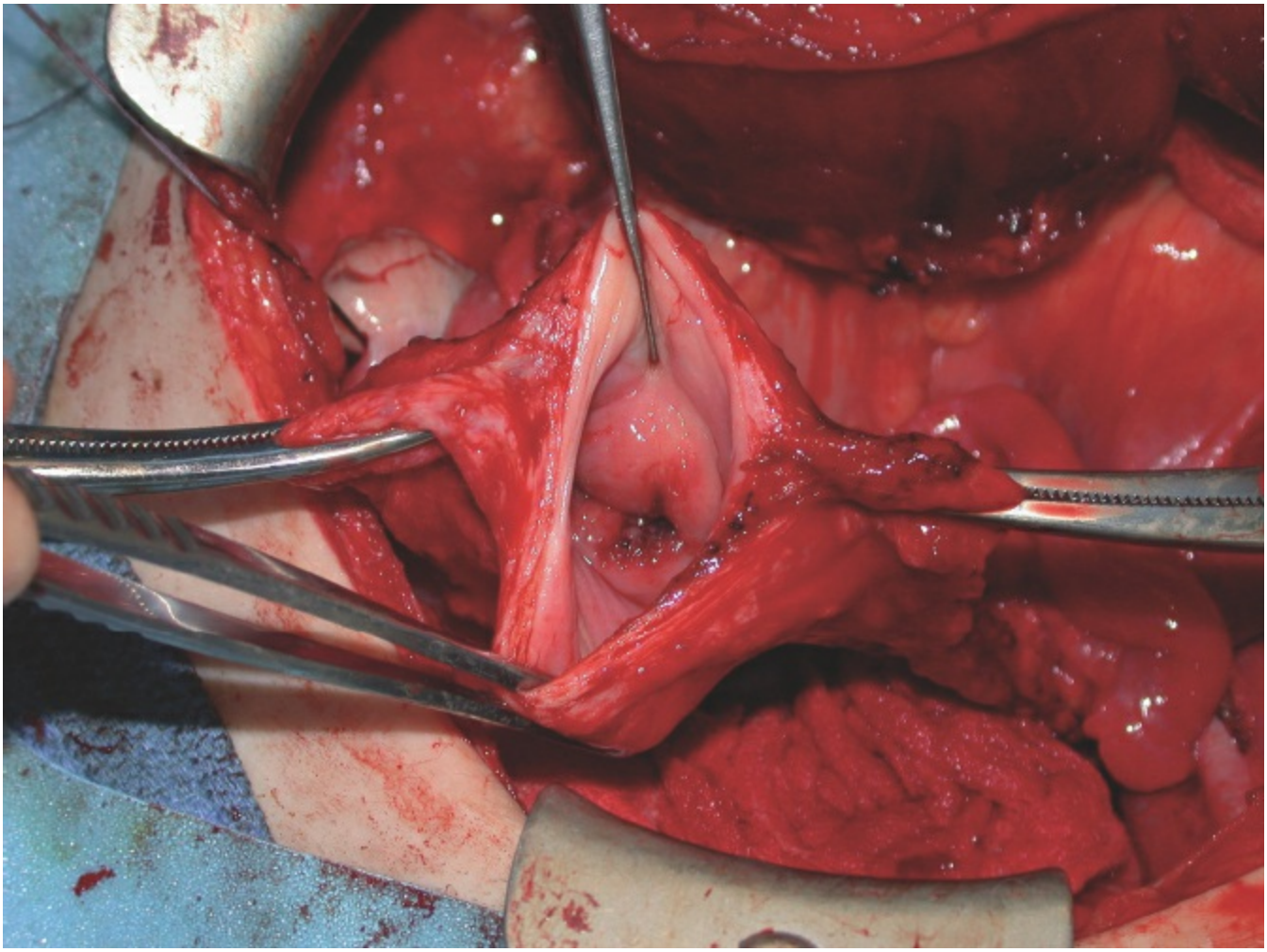
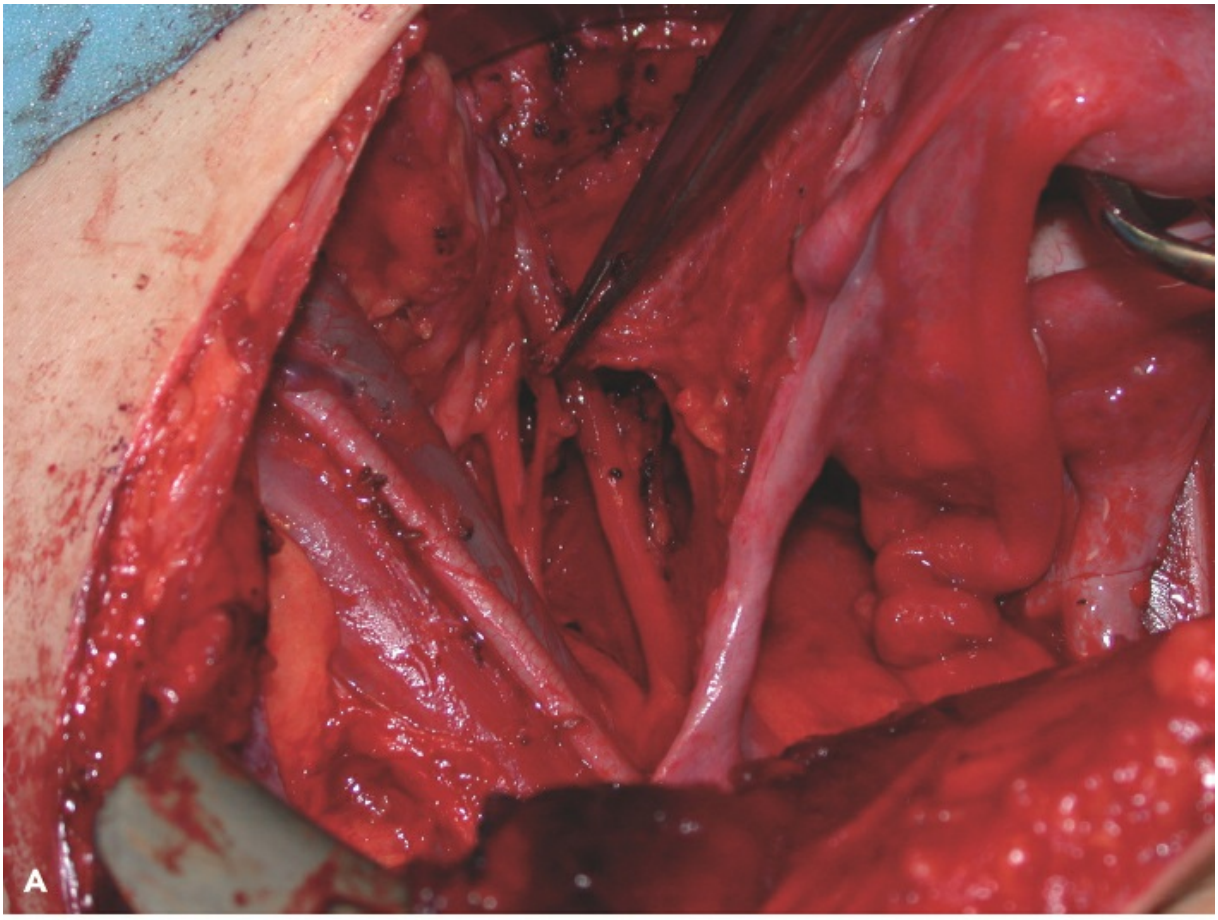


FIGURE 38-6 Abdominal radical trachelectomy.

Radical Trachelectomy

Radical trachelectomy is a procedure that is gaining popularity as a surgical management option for women with stage 1A2 and IB1 disease who desire uterine preservation and fertility. This procedure may be performed vaginally, abdominally, laparoscopically, or robotically (Fig. 38-6), and it usually is accompanied by pelvic lymphadenectomy and cervical cerclage placement. The risk of positive pelvic lymph nodes with stage IA2 cancer may be as high as 8%, indicating the need for lymphadenectomy. Lymphadenectomy may be performed laparoscopically, robotically, or by the open laparotomy technique. Experience with this therapeutic modality is limited, although early results are promising, and it is uncertain whether the long-term outcome is similar to that of traditional therapy. **Patients who are ideal candidates for this procedure have tumors less than 2 cm in diameter and have negative lymph nodes (2018 FIGO Stage IB1).** Lymphadenectomy can be performed at the beginning of the procedure, and depending on those results, the procedure can be continued or abandoned. A retrospective trial comparing patients who had tumors with these

attributes and were treated with either laparoscopic radical hysterectomy or laparoscopic radical trachelectomy showed similar outcomes and recurrence (72). There are limited data on subsequent pregnancy outcomes after radical trachelectomy; however, successful outcomes were reported. A study found that for women attempting to conceive after radical trachelectomy, the 5-year cumulative pregnancy rate was 52.8%, with an increased risk of miscarriage (73). Although radical trachelectomy and lymphadenectomy are performed with curative intent, it should be remembered that if a recurrence develops, definitive therapy with surgery or radiation is necessary.


A


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FIGURE 38-7 A: Radical hysterectomy. An intraoperative photograph showing the lateral dissection during a radical hysterectomy. Note the ureter running beneath the uterine artery (tissue in the clamp). **B:** Radical hysterectomy specimen.

Radical Hysterectomy

The **radical hysterectomy (Fig. 38-7A,B)** performed most often in the United States is that described by Meigs in 1944 (74). **The operation includes pelvic lymphadenectomy along with removal of most of the uterosacral and cardinal ligaments and the upper one-third of the vagina. This operation is referred to as type III radical hysterectomy** (75).

The hysterectomy described by Wertheim is less extensive than a radical hysterectomy and removes the medial half of the cardinal and uterosacral ligaments (65). **This procedure is often referred to as modified radical or type II hysterectomy.** Wertheim's original operation did not include pelvic lymphadenectomy but instead included selective removal of enlarged lymph nodes. **The modified radical hysterectomy (type II) differs from the radical hysterectomy (type III) in the following ways:**

1. **The uterine artery is transected at the level of the ureter, thus preserving the ureteral branch to the ureter.**
2. **The cardinal ligament is not divided near the sidewall but instead is divided close to its midportion near the ureteral dissection.**
3. **The anterior vesicouterine ligament is divided, but the posterior vesicouterine ligament is conserved.**
4. **A smaller margin of vagina is removed.**

Radical hysterectomies can be further classified as extended radical hysterectomy (type IV and type V). In the type IV operation, the periureteral tissue, superior vesicle artery, and as much as three-fourths of the vagina are removed. In the type V operation, portions of the distal ureter and bladder are resected. This procedure is rarely performed because radiotherapy should be used when such extensive disease is encountered (75).

The abdomen is opened through a midline incision or a low transverse incision after the methods of Maylard or Cherney. The low transverse incision requires division of the rectus muscles and provides excellent exposure of the lateral pelvis. It allows adequate pelvic lymphadenectomy and wide resection of the primary tumor. After the abdomen is entered, the peritoneal cavity is explored to exclude metastatic disease. The stomach is palpated to ensure that it has been decompressed to facilitate packing of the intestines. The liver is palpated, and the omentum is inspected for

metastases. Both kidneys are palpated to ensure their proper placement and lack of congenital and other abnormalities. The para-aortic nodes are palpated transperitoneally.

During exploration of the pelvis, the fallopian tubes and ovaries are inspected for any abnormalities. **In premenopausal patients, the ovaries can be conserved.** The peritoneum of the vesicouterine fold and the rectouterine pouch should be inspected for signs of tumor extension or implantation. The cervix is palpated between the thumb anteriorly and the fingers posteriorly to determine its extent, and the cardinal ligaments are palpated for evidence of lateral tumor extension or nodularity.

Lymphadenectomy

After inspection of the abdomen and pelvis, the pelvic and para-aortic lymph nodes should be inspected and palpated. Lymph nodes suspicious for gross disease should be excised and evaluated by frozen section. If metastatic disease is identified, consideration should be given to abandoning radical surgery in favor of primary chemoradiation therapy. If the patient has no gross evidence of metastatic disease, the pelvic lymphadenectomy is begun.

Pelvic Lymphadenectomy

The pelvic lymphadenectomy is begun by opening the round ligaments at the pelvic sidewall and developing the paravesical and pararectal spaces. The ureter is elevated on the medial flap by a Deaver retractor to expose the common iliac artery. The common iliac and external iliac nodes are dissected, with care taken to avoid injuring the genitofemoral nerve, which lies laterally on the psoas muscle. At the bifurcation of the common iliac artery, the external iliac node chain is divided into lateral and medial portions.

The lateral chain is stripped free from the artery to the circumflex iliac vein distally. A hemoclip is placed across the distal portion of the lymph node chain to reduce the incidence of lymphocyst formation. The medial chain is dissected. The obturator lymph nodes are dissected; for this procedure, the lymph nodes are grasped just under the external iliac vein, and traction is applied medially. In most patients, the obturator artery and vein are dorsal to the obturator nerve; however, 10% have an aberrant vein arising from the external iliac vein. The node chain is separated from the nerve and vessels and clipped caudally. Dissection continues cephalad to the hypogastric artery. The cephalad portion of the obturator space should be entered lateral to the external iliac artery and medial to the psoas muscle, where the remainder of the obturator node tissue can be dissected as far cephalad as the common iliac artery. Drainage of the pelvic and para-aortic lymph node beds is not performed because of the increase in complications in patients in whom drains were used (76).

Patients who have bulky cervical tumors or grossly positive pelvic nodes, or for whom frozen section evaluation will be performed, should undergo para-aortic

lymph node evaluation to determine the full extent of disease and to guide adjuvant therapy.

Para-Aortic Lymph Node Evaluation

The bowel is packed to expose the peritoneum overlying the bifurcation of the aorta. The peritoneum is incised medial to the ureter and over the right common iliac artery. A retractor is placed retroperitoneally to expose the aorta and the vena cava. Any enlarged para-aortic lymph nodes are removed, hemoclips are applied for hemostasis, and specimens are sent for analysis by frozen section. If the lymph nodes are positive for metastatic cancer, an option is to discontinue the operation and treat the patient with radiation therapy (74). If the lymph nodes are negative for disease, the left side of the aorta is palpated through the peritoneal incision with a finger passed under the inferior mesenteric artery. The lymph nodes on this side of the aorta are more lateral and nearly behind the aorta and the common iliac artery. If the left para-aortic lymph nodes appear healthy and the cervical tumor is small with no suspicious pelvic lymph nodes, these additional lymph nodes are not submitted for frozen-section analysis. If they are removed, they may be dissected through the incision made for the right para-aortic nodes, or they may be dissected after reflection of the sigmoid colon medially.

Development of Pelvic Spaces

The pelvic spaces are developed by sharp and blunt dissection **(Fig. 38-8)**.

The paravesical space is bordered by the following structures:

1. The obliterated umbilical artery running along the bladder medially
2. The obturator internus muscle along the pelvic sidewall laterally
3. The cardinal ligament posteriorly
4. The pubic symphysis anteriorly

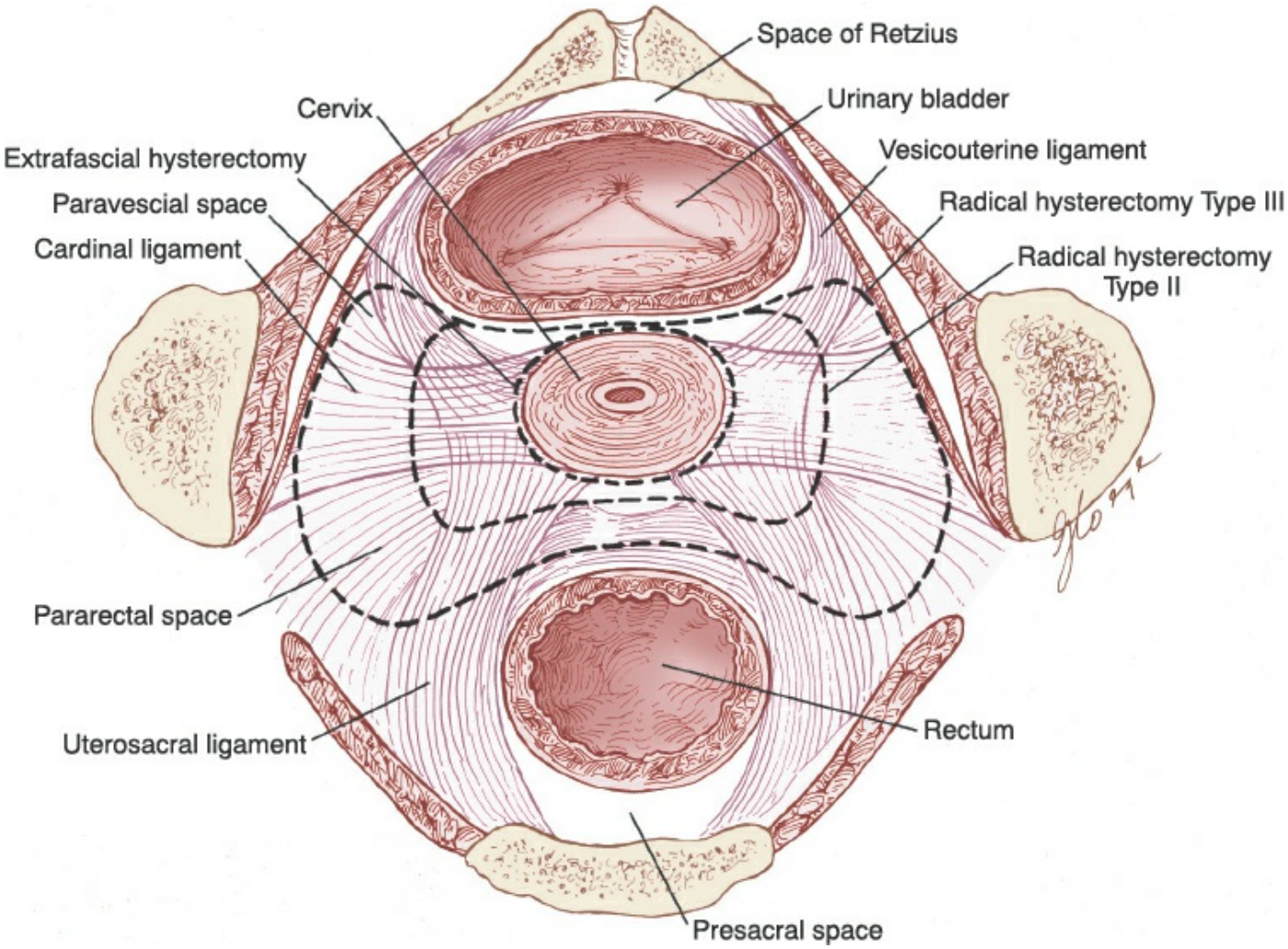


FIGURE 38-8 The pelvic ligaments and spaces. (From **Hacker NF, Vermorken JB.** Cervical cancer. In: Berek JS, Hacker NF. *Berek & Hacker's Gynecologic Oncology*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:345.)

The attachments of the vagina to the tendinous arch form the floor of the paravesical space.

The pararectal space is bordered by the following structures:

1. Rectum medially
2. Cardinal ligament anteriorly
3. Hypogastric artery laterally
4. Sacrum posteriorly

The coccygeus (levator ani) muscle forms the floor of the pararectal space.

The development of these spaces before pelvic lymphadenectomy will aid in identification and dissection of the pelvic lymph nodes and dissection of the ureter as it passes into the vesicouterine ligament tunnel.

Dissection of the Bladder

The dissection of the bladder from the anterior part of the cervix and vagina is a critical step. Occasionally, tumor extension into the base of the bladder (which cannot be detected with cystoscopy) precludes adequate mobilization of the bladder flap, leading to the abandonment of the operation. Therefore, this portion of the operation should be undertaken early in the procedure. The bladder should be mobilized off of the upper third of the vagina to remove the tumor safely and with adequate margins.

Dissection of the Uterine Artery

The superior vesicle artery is dissected away from the cardinal ligament at a point near the uterine artery. **The uterine artery, which usually arises from the superior vesicle artery, is thus isolated and divided, preserving the superior vesicle arteries.** The uterine vessels are brought over the ureter by application of gentle traction. Occasionally, the uterine vein passes under the ureter.

Dissection of the Ureter

The ureter is dissected free from the medial peritoneal flap at the level of the uterosacral ligament. As the ureter passes near the uterine artery, there is a consistent arterial branch from the uterine artery to the ureter. This branch is sacrificed in the standard radical (type III) hysterectomy but preserved in the modified radical (type II) hysterectomy. Dissection of the ureter from the vesicouterine ligament (ureteral tunnel) may now be accomplished. If the patient has a deep pelvis, ligation of the uterosacral and cardinal ligaments may be undertaken first to bring the ureteral tunnel dissection closer to the operator. The roof of the ureteral tunnel is the anterior vesicouterine ligament. It should be ligated and divided to expose the posterior ligament. **The posterior ligament is divided in the radical (type III) hysterectomy but conserved in the modified radical (type II) hysterectomy.**

Posterior Dissection

The peritoneum across the cul-de-sac is incised, exposing the uterosacral ligaments. **The rectum is rolled free from the uterosacral ligaments, which are divided midway to the sacrum in a radical (type III) hysterectomy and near the rectum in the modified radical (type II) operation. This allows the operator to isolate and separate the cardinal ligament from the rectum.** A surgical clamp is placed on the cardinal ligament at the lateral pelvic sidewall in a radical hysterectomy and at the level of the ureteral bed in the modified radical procedure. A clamp is placed on the specimen side to maintain traction and to ensure that the full cardinal ligament is excised with the specimen. A right-angled clamp is placed caudad to this clamp across the paravaginal tissues. A second paravaginal clamp is usually needed to reach the vagina.

The vagina is entered anteriorly, and a suitable margin of proximal vagina is

removed with the specimen. More vaginal epithelium can be excised if necessary, depending on the previous colposcopic findings. The vaginal edge may be sutured in a hemostatic fashion and left open with a drain from the pelvic space or closed with a suction drain placed percutaneously. The ureteral fistula and pelvic lymphocyst rates from these two techniques are similar.

Complications of Radical Hysterectomy

Acute Complications

The acute complications of radical hysterectomy include (77):

- Blood loss (average, 0.8 L)
- Ureterovaginal fistula (1% to 2%)
- Vesicovaginal fistula (1%)
- Pulmonary embolus (1% to 2%)
- Small bowel obstruction (1%)
- Febrile morbidity (25% to 50%)

Febrile morbidity is most often caused by pulmonary infection (10%) and is seen frequently with pelvic cellulitis (7%) and urinary tract infection (6%). Wound infection, pelvic abscess, and phlebitis all occur in fewer than 5% of patients (78).

Subacute Complications

The subacute effects of radical hysterectomy are postoperative bladder dysfunction and lymphocyst formation. For the first few days after radical hysterectomy, bladder volume is decreased, and filling pressure is increased. The sensitivity to filling is diminished, and the patient is unable to initiate voiding. The cause of this dysfunction is unclear. It is important to maintain adequate bladder drainage during this time to prevent overdistention. Bladder drainage is usually accomplished with a suprapubic catheter. It is more comfortable for the patient and allows the physician to perform cystometrography and determine residual urine volume without the need for frequent catheterization. In addition, the patient is able to accomplish voiding trials at home by clamping the catheter, voiding, and releasing to check the residual urine level. Cystometrography may be performed 3 to 4 weeks after surgery. For the catheter to be discontinued, the patient must be able to sense the fullness of the bladder, initiate voiding, and void with a residual urine level of less than 75 to 100 mL. Otherwise, voiding trials should continue at home until these criteria can be fulfilled.

Lymphocyst formation occurs in fewer than 5% of patients, and the cause is uncertain (78). Adequate drainage of the pelvis after radical hysterectomy may be an important step in prevention. However, routine placement of retroperitoneal drains did not reduce this morbidity (75). Ureteral obstruction, partial venous obstruction, and

thrombosis may occur from lymphocyst formation. Simple aspiration of the lymphocyst is generally not curative, but percutaneous catheters with chronic drainage may allow healing. If this treatment is unsuccessful, operative intervention with excision of a portion of the lymphocyst wall and placement of either large bowel or omentum into the lymphocyst should be performed.

Chronic Complications

The most common chronic effect of radical hysterectomy is bladder hypotonia or, in extreme instances, atony. This condition occurs in about 3% of patients, regardless of the method of bladder drainage used (79,80). It may be a result of bladder denervation and not simply a problem associated with bladder overdistention (81). Voiding every 4 to 6 hours, increasing intra-abdominal pressure with Credé's maneuver, and intermittent self-catheterization may be used to manage bladder hypotonia.

Ureteral strictures are uncommon in the absence of postoperative radiation therapy, recurrent cancer, or lymphocyst formation (81). If the stricture is associated with lymphocyst formation, treatment of the lymphocyst usually alleviates the problem. Strictures that occur after radiation therapy should be managed with ureteral stenting. If a ureteral stricture is noted in the absence of radiotherapy or lymphocyst formation, recurrent carcinoma is the most common cause. A CT scan of the area of obstruction should be obtained and cytologic assessment by FNA should be performed if there is a target lesion to exclude carcinoma. If the results of these tests are negative, a ureteral stent may be placed to relieve the stricture. Close observation for recurrent carcinoma is necessary, and the diagnosis of recurrence may ultimately require laparotomy.

Nerve-Sparing Radical Hysterectomy

Nerve-sparing radical hysterectomies were described in an attempt to diminish the bladder dysfunction, sexual dysfunction, and colorectal motility disorders commonly encountered after traditional radical hysterectomy. Multiple techniques were described involving the identification of the pelvic autonomic nerves at the sacral promontory followed by various surgical methods of nerve preservation as the nerves transit the cardinal ligaments. These techniques are promising and in small series did reduce postoperative bladder dysfunction (82,83).

Minimally Invasive Radical Hysterectomy

[7] **Laparoscopic and Robotic Radical Hysterectomies were being performed with large degree of frequency in highly selected patients world wide.** The use of laparoscopy in cervical cancer patients is appealing because it may lead to less blood loss, improved cosmetic results, shorter duration of hospitalization, and faster recovery. In one large series of 200 women with stages IA1 to IIB cervical cancer treated with laparoscopic lymphadenectomy followed by radical vaginal hysterectomy, the authors found a 5-year survival rate comparable to patients treated with a similar abdominal

approach and a comparable rate of intraoperative complications (84).

One study reports comparable body mass index, operative times, parametrial margin, and number of lymph nodes collected when compared with open cases. Robotic cases had significantly shorter hospital stays and blood loss, while having significantly larger incidence of postoperative bladder dysfunction (85–88).

Minimally Invasive Versus Open Radical Hysterectomy

Although there are benefits to minimally invasive procedures, a non-inferiority randomized control trial showed that minimally invasive radical hysterectomies were associated with a lower rate disease-free survival at 86.0% compared to open radical hysterectomy at 96.5% at 4.5 years (89). This study also showed worse overall survival at the 3-year rate of 91.2% versus 97.1% in the minimally invasive versus open radical hysterectomy respectively. This study reported that minimally invasive radical hysterectomy is inferior to open radical hysterectomy in respect to disease-free survival and overall survival (90). While the explanation for this finding is unclear, it was suggested that spread of malignant cells by the uterine manipulator or CO_2 gas insufflation are potential causes.

Another study utilizing the National Cancer data base also showed that patient with IA2 and IB1 undergoing a minimally invasive radical hysterectomy had a higher 4 year mortality rate compared to those who underwent and open radical hysterectomy (91).

Sentinel Lymph Node Evaluation

Sentinel lymph node detection has become an integral part of the management strategy for breast cancer and melanoma and is being investigated as a diagnostic tool in multiple human malignancies, including carcinoma of the cervix. The sentinel node is a specific lymph node (or nodes) that is the first to receive drainage from a malignancy and is a primary site of nodal metastasis. In theory, the presence or absence of metastatic disease in the sentinel node should reflect the status of the nodal basin as a whole. Thus, a negative sentinel lymph node would allow omission of lymphadenectomy of the involved nodal basin. Sentinel lymph nodes are detected through perilesional injection of radiolabeled technetium-99 or blue dye followed by intraoperative identification of the sentinel lymph nodes utilizing handheld gamma probes or visual identification of blue-stained nodes. These techniques are primarily applicable in patients with early-stage disease and clinically negative lymph nodes, in whom lymph node status may influence the extent of the procedure or the use of adjuvant treatment.

National Comprehensive Cancer Network guidelines on the use of sentinel lymph node mapping in cervical cancer recommend the technique be considered in tumors less than 2 cm (90). The procedure is performed by **direct cervical injection with dye or radiocolloid technetium-99 into the cervix, usually at the 3 and 9 o'clock positions**

of the cervix. The sentinel lymph nodes are identified at by direct visualization at time of laparotomy or laparoscopy of colored dye, a fluorescent camera if indocyanine green (ICG) was used, or a gamma probe if ^{99}Tc was used. The nodes are commonly located medial to the external iliac, ventral to the hypogastric, or in the superior aspect of the obturator space (90).

Sentinel nodes can be detected in 80% to 100% of cervical cancer patients, and these rates were confirmed by both laparotomy and laparoscopy. A combination of dye and radiolabeled techniques appears to be superior for the detection of sentinel lymph nodes over either technique used alone. Test sensitivity of 65% to 87% can be expected with a 90% to 97% negative predictive value. The likelihood of detecting sentinel nodes may depend on the tumor volume, the time from injection to retrieval of the sentinel nodes, and the volume of dye or radiolabeled tracer injected. Sentinel node detection rates do not appear to be influenced by prior cold knife cone biopsy. Although increasingly used, **the role of sentinel node detection in early-stage cervix cancer continues to be defined** (92).

Postoperative Management

Prognostic Variables for Early-Stage Cervical Cancer (IA2–IIA)

The survival of patients with early-stage cervical cancer after radical hysterectomy and pelvic lymphadenectomy depends on the presence or absence of several intermediate and high-risk pathologic factors (79,93–107).

Intermediate risk factors for recurrent disease are:

1. Large tumor size
2. Cervical stromal invasion to the middle or deep one-third
3. Lymph–vascular space invasion

High risk factors for recurrent disease are:

1. Positive or close margins
2. Positive lymph nodes
3. Microscopic parametrial involvement

Patients treated with radical hysterectomy who have intermediate or high risk factors have a 30% and 40% risk, respectively, of recurrence within 3 years (108–110).

Lesion Size

Lesion size is an independent predictor of survival. Patients with lesions smaller

than 2 cm have a survival rate of approximately 90%, and patients with lesions larger than 2 cm have a 60% survival rate (97). **When the primary tumor is larger than 4 cm, the survival rate drops to 40%** (95,105). An analysis of a GOG prospective study of 645 patients showed a 94.6% 3-year disease-free survival rate for patients with occult lesions, 85.5% for those with tumors smaller than 3 cm, and 68.4% for patients with tumors larger than 3 cm (106).

Depth of Invasion

Patients in whom depth of invasion is less than 1 cm have a 5-year survival rate of approximately 90%, but the survival rate falls to 63% to 78% if the depth of invasion is more than 1 cm (79,106,110–113).

Parametrial Spread

Patients with spread to the parametrium have a 5-year survival rate of 69%, compared with 95% when the parametrium is negative. When the parametrium is involved and pelvic lymph nodes are positive, the 5-year survival rate falls to 39% to 42% (98,114).

Lymph–Vascular Space Involvement

The significance of finding lymph–vascular space involvement is somewhat controversial. Several reports show a 50% to 70% 5-year survival rate when lymph–vascular space invasion is present and a 90% 5-year survival rate when invasion is absent (79,97,101,115,116). Others found no significant difference in survival if the study is controlled for other risk factors (106,107,117–120). Lymph–vascular space involvement may be a predictor of lymph node metastasis and not an independent predictor of survival.

Lymph Nodes

The variable that is most independently predictive of survival is the status of the lymph nodes. Patients with negative nodes have an 85% to 90% 5-year survival rate, whereas the survival rate for those with positive nodes ranges from 20% to 74%, depending on the number of nodes involved and the location and size of the metastases (102–104,107,110,113,119–121).

Data on lymph node status is summarized as follows:

1. When the common iliac lymph nodes are positive, the 5-year survival rate is about 25%, compared with about 65% when only the pelvic lymph nodes are involved (114,122,123).
2. Bilateral positive pelvic lymph nodes portend a less favorable prognosis (22% to 40% survival rate) than unilateral positive pelvic nodes (59% to 70%) (122,123).
3. The presence of more than three positive pelvic lymph nodes is accompanied by a

68% recurrence rate, compared with 30% to 50% when three or fewer lymph nodes are positive (102,120).

4. Patients in whom tumor emboli are the only findings in the pelvic lymph node have an 82.5% 5-year survival rate, whereas the survival rate is 62.1% and 54% with microscopic invasion and macroscopic disease, respectively (90).

Given the high risk of recurrent disease in surgically treated patients with early-stage cervical cancer who exhibit intermediate- or high-risk pathologic factors, adjuvant radiation or chemoradiation therapy should be considered.

Primary Radiation Therapy

[5] Radiotherapy can be used to treat all stages of cervical cancer, with cure rates of about 70% for stage I, 60% for stage II, 45% for stage III, and 18% for stage IV (4). A comparison of surgery and radiation for treatment of low-stage disease is shown in Table 38-5. Primary radiation treatment plans consist of a combination of external beam radiation therapy to treat the regional lymph nodes and to decrease the tumor volume, and brachytherapy delivered by intracavitary applicators and/or interstitial implants to provide a treatment boost to the central tumor. Intracavitary therapy alone may be used in patients with early disease when the incidence of lymph node metastasis is negligible.

The treatment sequence can depend on tumor volume. Patients commonly receive 5 weeks of pelvic external beam radiation upfront, with brachytherapy introduced at week 4. In some cases, stage IB lesions smaller than 2 cm may be treated first with an intracavitary source to treat the primary lesion, followed by external therapy to treat the pelvic lymph nodes. Larger lesions require external radiotherapy first to shrink the tumor and to reduce the anatomic distortion caused by the cancer. Tumor shrinkage averaging >1 cm per week can be achieved with adequate external beam radiation prior to starting brachytherapy (124,125). Such a treatment strategy enables the radiation oncologist to physically implant brachytherapy applicators and achieve dosimetric radiation coverage of the tumor target volume.

Table 38-5 Comparison of Surgery Versus Radiation for Stage IB/IIA Cancer of the Cervix

	Surgery	Radiation
Survival	85%	85%
Serious complications	Urologic fistulas 1–2%	Intestinal and urinary strictures and fistulas 1.4–5.3%
Vagina	Initially shortened, but may lengthen with regular intercourse	Fibrosis and possible stenosis, particularly in postmenopausal patients

Ovaries	Can be conserved	Destroyed
Chronic effects	Bladder atony in 3%	Radiation fibrosis of bowel and bladder in 6–8%
Applicability	Best candidates are younger than 65 years of age, <200 lb, and in good health	All patients are potential candidates
Surgical mortality	1%	1% (from pulmonary embolism during intracavitary therapy)

Cervix cancer brachytherapy has classically been delivered with low dose rate (LDR) technique involving inpatient admission and x-ray film–based radiation dose prescription to "point A." Over decades, multiple advances in radiation oncology have resulted in improved brachytherapy techniques (e.g., image-guided adaptive brachytherapy [IGABT]) that have translated to superior survival, better tumor control, less side effects, and improved safety. The RetroEMBRACE study included 731 locally advanced cervix cancer patients from 12 centers who received external beam radiation ± chemotherapy plus 3D IGABT from 1998 to 2008. Patients achieved excellent local control (91%), pelvic control (87%), OS (74%), and cancer-specific survival (79%) with limited severe morbidity (126).

One chief modern innovation in cervix cancer brachytherapy is the shift from classically prescribing dose to a generic "point A" localized via 2D x-ray films, to volumetrically prescribing dose shaped to the patient's individual tumor geometry as defined on 3D MRI or CT imaging. The 2D approach delivers similar brachytherapy treatments to all patients regardless of tumor geometry or patient anatomy, which can result in underdosing of larger tumors or overdosing of smaller tumors plus over-irradiation of the adjacent bladder, rectum, and sigmoid. In contrast, the modern 3D approach permits individualization and shaping of the radiation prescription dose to fit patient's tumor and normal organ anatomy. The French multicenter STIC trial compared classical 2D versus modern 3D approaches in 705 cervix cancer patients, prospectively demonstrating that 3D brachytherapy resulted in improved local control and half the toxicity seen with 2D brachytherapy (127).

In classical 2D cervix brachytherapy, usual doses delivered are 7,000 to 8,000 cGy to point A (defined as 2 cm superior to the external cervical os and 2 cm lateral to the internal uterine canal) and 6,000 cGy to point B (defined as 3 cm lateral to point A), limiting the bladder and rectal dosage to less than 6,000 cGy. To achieve this level, it is necessary to adequately pack the bladder and bowel away from the intracavitary source. Localization films and careful calculation of dosimetry are mandatory to optimize the dose of radiation and to reduce the incidence of bowel and bladder complications. Local control depends on delivering an adequate dose to the tumor from the intracavitary source.

In modern 3D IGABT, usual cumulative radiation doses delivered are 8,500 to 9,500

cGy to the high-risk CTV D90 per GEC-ESTRO recommendations and 8,000 to 9,000 cGy per American Brachytherapy Society recommendations (128). This is often achieved with a radiation treatment course of 25 to 28 days once daily external beam fractions, plus 4 to 5 brachytherapy fractions. The cumulative dose to control a cervix tumor is related to the tumor's volume, with higher doses required to control larger tumors (129). Image-guided computerized planning is performed on CT or MRI images acquired of the patient's pelvis with brachytherapy applicators in place. An updated CT or MRI scan is performed with each brachytherapy applicator insertion, so that the radiation plan can be adapted to match shrinking geometry of the tumor and sculpted away from the daily position of the bladder, rectum, and sigmoid. Cumulative dose refers to the combined dose from external beam radiation plus all brachytherapy fractions, converted to a 2 Gy per fraction equivalent. The high-risk CTV (clinical target volume) consists of the entire cervix plus any clinically/radiographically identifiable tumor at time of brachytherapy (130). "D90" refers to 90% of the HR-CTV receiving the highest radiation doses. Typically, dose constraints to organs at risk are specified to the D2cc, or the 2 cc of the organ receiving the highest radiation dose. GEC-ESTRO recommendations include keeping the cumulative D2cc dose to bladder <90 Gy EQD2, rectum <75 Gy EQD2, sigmoid <75 Gy EQD2 (131). The current EMBRACE II protocol (www.embracestudy.dk) for cervix cancer suggests more stringent D2cc constraints with the goal of further reducing toxicity.

Another chief innovation in modern cervix brachytherapy has been the use of newer radiation isotopes and loading techniques. Classic 2D brachytherapy is often performed with LDR isotopes such as cesium-137. LDR isotopes like Cs-137 are placed manually by hand, require inpatient admissions for extended overnight irradiation over 1 to 3 days with prolonged patient immobilization, DVT prophylaxis, and the need for careful radiation shielding/precautions taken by potentially exposed medical personnel. LDR isotopes are only capable of emitting therapeutic radiation at a rate of less than 0.4 Gy per hour, whereas high-dose rate (HDR) isotopes can treat at a speed of greater than 12 Gy per hour. Modern 3D brachytherapy is most often performed with the HDR isotope iridium-192 (Ir-192). Ir-192 is capable of delivering the prescribed brachytherapy radiation dose in just a few minutes, typically delivered in the ambulatory/outpatient setting with a robotic remote afterloader system that minimizes radiation exposure to medical personnel.

Pulsed-dose rate (PDR) brachytherapy is a relatively uncommon technique mostly seen at specialized academic centers. PDR uses an Ir-192 HDR source with a pulsed treatment regimen designed to mimic the radiobiologic effects of LDR treatment. Like LDR, PDR brachytherapy requires patient immobilization and admission (132).

Although brachytherapy was traditionally prescribed using a low-dose rate technique, high-dose rate techniques are becoming more popular. Proponents of high-dose rate techniques argue that the exposure of radiation to medical personnel is

less, ambulatory therapy is possible, and total treatment time is less. Advocates of low-dose rate techniques cite literature suggesting that complication rates are higher with high-dose rate therapy. Several published trials show that there may be slight stage-related differences in survival between patients treated with low- and high-dose rate regimens, but the techniques have comparable survival and complication rates (133–135). A Cochrane review of published studies comparing LDR versus HDR brachytherapy for locally advanced cervix cancer showed no significant differences in OS, disease-specific survival, recurrence-free survival, local control, recurrence, metastases, or treatment-related complications. However, these conclusions were based on a small (4) number of trials that met inclusion criteria (136).

Newer combined intracavitary/interstitial brachytherapy applicators permit successful treatment of bulky and/or irregularly shaped tumor targets, and can often obviate the need to treat with the more morbid techniques of Syed and MUPIT template needle implants. An important innovation in the treatment of cervix cancer is the development of newer brachytherapy applicators that allow interstitial needles to be incorporated into the standard geometry of classical intracavitary tandem and ovoids, or tandem and ring, applicators (137). The incorporation of interstitial needles permits more effective dosing of tumor targets beyond the normal reach of standard intracavitary brachytherapy applicators while keeping adjacent organs at risk within safe radiation limits (138). Patients on the retroEMBRACE study with locally advanced cervix cancer receiving combined intracavitary and interstitial brachytherapy treatment (versus intracavitary only) had an improved therapeutic ratio, with a 10% increase in local control seen in those with larger tumors (cervix + tumor volume > 30 cm^3) (139).

Clinical staging is imprecise and fails to accurately predict disease extension to the para-aortic nodes in 7% of patients with stage IB, 18% with stage IIB, and 28% with stage III disease (140). Such patients will have “geographic” treatment failures if standard pelvic radiotherapy ports are used. As a result, treatment plans for these patients are individualized based on CT scans, PET scans, and biopsies of the para-aortic lymph nodes for consideration of extended-field radiotherapy. The routine use of extended-field radiation for prophylactic para-aortic radiation without documentation of distant metastasis to the para-aortic nodes was evaluated and is not practiced because of the increased enteric morbidity associated with this treatment modality. If available, PET/CT scans are encouraged as they can detect potential pelvic, para-aortic, or supraclavicular nodal involvement, which in turn relates to clinical stage, potential recurrence, and survival outcomes (141).

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) continues to be a significant therapeutic development. IMRT is an external beam radiation technique that improves

upon older 3D conformal radiation therapy (3D-CRT) external beam techniques. While 3D-CRT is capable of projecting block or polygonal-shaped radiation into target tumors, IMRT is capable of projecting curved, even concave, conformal radiation that is more precisely shaped to the target tumor space. IMRT permits more accurate irradiation of tumor targets and significantly enhances sparing of nearby normal organs. In the treatment of cervix cancer, use of IMRT could reduce radiation dose to multiple organs at risk including bone marrow, rectum, bladder, small bowel, and femurs. Technically, IMRT is achieved with volumetric image-based (CT or MRI) radiation treatment planning in which the radiation oncologist manually draws the tumor/target volume(s) on a computerized dosimetry system, followed by a computer algorithm that generates a set of treatment external beam angles and patterns that conform to the physician-delineated target(s) while meeting prescription goals and normal organ radiation constraints. IMRT has been used in postoperative and intact cervix cancer patients, and is an advanced technique under active investigation within radiation oncology.

Prior to the advent of IMRT, women receiving pelvic radiation typically received 3D-CRT "four field box" plans that delivered full external beam prescription dose (45 to 50 Gy) to their rectum, bladder, femurs, small bowel, and bone marrow. IMRT allows the radiation oncologist to essentially sculpt dose away from these organs at risk to reduce radiation side effects. For postoperative cervix (and endometrial) cancer patients, the NRG-RTOG 1203 TIME-C trial demonstrated that 278 women randomized between IMRT and 3D-CRT had, with IMRT, better patient-reported bowel and bladder function (EPIC, FACT-Cx, PRO-CTCAE) and less use of antidiarrheal medications. Longer follow-up is needed to evaluate long-term toxicity (142).

A consensus guideline for IMRT use in intact cervix cancer was published in 2011, with IMRT targeting the gross tumor, entire cervix, uterus, parametria, ovaries, and vaginal tissues (143). The amount of vaginal length covered can vary from half to full depending on the extent of vaginal disease. For involvement of uterosacral ligaments, IMRT coverage of the mesorectum is advised. The INTERTECC-2 study was an international multicenter phase II clinical trial of 83 stages IB to IVA intact cervix cancer patients who received weekly *cisplatin* concurrent with daily IMRT treatments followed by intracavitary brachytherapy. Patients who received IMRT had reduced acute hematologic and GI toxicity compared with 3D-CRT treatment (144). However, the cervix and uterus are known to be quite mobile, capable of up to 3.5 cm shifts (even retroversion/anteversion) between daily radiation fractions as evidenced by daily cone beam CT scans acquired on the treating linear accelerator (145). IMRT plans for intact cervix cancer need to be carefully designed to account for the possibility of significant interfraction cervix movement caused by cervix/uterus mobility and variations in daily bladder and rectal filling. In the case of node-positive cervix cancer patients, IMRT with simultaneous integrated boost (SIB or "dose painting") allows simultaneous

delivery of higher external beam radiation dose (e.g., 55 Gy in 2.2 Gy per fraction) to FDG+ nodes beyond the reach of brachytherapy, while maintaining standard fraction dosing (45 Gy in 1.8 Gy per fraction) to central disease that will receive the remainder of curative radiation via brachytherapy boosts (146,147). Cervix cancer patients requiring irradiation of para-aortic nodes can potentially benefit from IMRT, which is associated with low rates of GI toxicities (6.5% acute and late) and no duodenal-specific toxicities even in the setting of concurrent radiosensitizing chemotherapy (148).

Despite the technical sophistication of IMRT, in the field of radiation oncology, IMRT is considered complementary to brachytherapy and not a replacement for brachytherapy. A SEER propensity score matching analysis of 7,359 patients with stages IB2 to IVA cervix cancer indicated that inclusion of brachytherapy as part of definitive treatment was independently associated with significantly higher cause-specific survival (CSS; 64.3% vs. 51.5%, P <0.001) and OS (58.2% vs. 46.2%, P <0.001) (149). The study identified a significant decrease in American brachytherapy utilization from 83% in 1988 to a nadir of 43% in 2003 (and some recovery to 58% in 2009) quite possibly driven in the early 2000s by attempted substitution of brachytherapy by IMRT. This suggests a strong need to improve modern brachytherapy training in the field of radiation oncology and promote awareness of brachytherapy's importance to collaborating gynecologic oncologists.

Adjuvant Radiation

In an effort to improve survival rates, postoperative radiotherapy was recommended for patients with high and intermediate risk factors such as metastasis to pelvic lymph nodes, invasion of paracervical tissue, deep cervical invasion, or positive surgical margins (79,94,97,98,114,119,120,150). Although most authors agree that postoperative radiotherapy is necessary in the presence of positive surgical margins, the use of radiation in patients with other high-risk factors is controversial. Increasing evidence supports the use of adjuvant radiation. Particularly controversial, and best studied, is the use of radiation in the presence of positive pelvic lymph nodes. The rationale for treatment is the knowledge that pelvic lymphadenectomy does not remove all of the nodal and lymphatic tissue and subsequent radiotherapy can eradicate microscopic disease. The hesitancy to recommend postoperative radiotherapy derives from the significant rate of postradiation bowel and urinary tract complications (151). Most of the available data are retrospective. However, a randomized study by the GOG comparing radiation with no further treatment for patients at high risk for recurrence with negative pelvic nodes revealed a 30% serious complication rate, 16% reoperation rate, and a 2% mortality rate as a result of treatment-related complications (152).

Based on retrospective studies, it appears that postoperative radiation therapy for positive pelvic nodes can decrease pelvic recurrence but does not improve 5-

year actuarial survival rates. One multi-institutional study showed no difference in survival in patients with three or fewer positive pelvic nodes (59% vs. 60%) (120). However, there seemed to be a benefit when radiotherapy was given to those with more than three positive nodes.

In a study of 60 pairs of irradiated and nonirradiated women matched for age, lesion size, number, and location of positive nodes after radical hysterectomy, no significant difference was found in projected 5-year survival rates (72% for surgery alone, 64% for surgery plus radiation) (153). The proportion of recurrences confined to the pelvis was 67% in patients treated with surgery only and 27% in patients treated with postoperative radiation ($P = 0.03$). In a Cox regression analysis of 320 women who underwent radical hysterectomy, for the 72 who received postoperative radiation, there was a significant decrease in pelvic recurrence but no survival benefit (103). A multi-institutional retrospective study was performed on 185 women with positive pelvic nodes after radical hysterectomy, including 103 who received postoperative radiotherapy (105). Multivariate analysis disclosed that radiotherapy was not an independent predictor of survival, whereas age, lesion diameter, and number of positive nodes did influence survival. These authors concluded that additional treatment is needed to improve survival rates. Because survival is limited by distant recurrence, the addition of chemotherapy to postoperative radiotherapy was proposed. A 75% disease-free survival rate was reported at 3 years in 40 high-risk patients given *cisplatin*, *vinblastine*, and *bleomycin* after radical hysterectomy, and a 46% disease-free survival rate was found in 79 comparable patients who refused treatment (154). Only 4 (11.8%) of 34 patients with positive pelvic nodes had recurrences, whereas disease recurred in 8 (33%) of 24 untreated patients with positive nodes. An 82% rate of disease-free survival was reported at 2 years among 32 patients who were treated postoperatively with radiation therapy plus *cisplatin* and *bleomycin* (155).

The location of lymph node metastases apparently is relevant to postirradiation recurrence rates. When common iliac lymph nodes are involved, the survival rate drops to 20%. As the number of positive pelvic nodes increases, the percentage of positive common iliac and low para-aortic nodes increases (i.e., 0.6% when pelvic lymph nodes are negative, 6.3% with one positive pelvic node, 21.4% with two or three positive nodes, and 73.3% with four or more positive nodes). This information was used to recommend extended-field radiotherapy to patients with positive pelvic lymph nodes in an attempt to treat undetected extrapelvic nodal disease (115). A 3-year disease-free survival rate of 85% occurred in patients with positive pelvic nodes, and a survival rate of 51% occurred in patients with positive common iliac nodes; these rates are better than the survival rates of 50% and 23%, respectively, for historical control groups receiving radiotherapy to the pelvis alone.

The GOG reported the results of a randomized controlled trial on patients with cervical cancer treated by radical hysterectomy and found to have at least two of

the following risk factors: capillary lymphatic space invasion, more than one-third stromal invasion, and large tumor burden (109). A total of 277 patients were entered into the study, with 140 patients randomized to no further therapy and 137 patients randomized to adjuvant pelvic radiotherapy. **Patients with these risk factors who were treated postoperatively with radiation therapy had a statistically significant (47%) decrease in recurrent disease.** After extensive follow-up, there is no statistically significant difference in mortality rates (156). The morbidity with combination therapy was acceptable, with a low rate of enteric and urinary complications. A second GOG study of patients with high-risk cervical cancer randomized patients to concurrent chemoradiation therapy or radiation therapy alone (108).

Concurrent Chemoradiation

Radiation therapy fails to achieve tumor control in 20% to 65% of patients with advanced cervical cancer. Chemotherapy, despite its relative lack of success in treating patients with cervical cancer, was evaluated as neoadjuvant treatment in combination with surgery. **Concomitant use of chemotherapy and radiation was studied extensively by the GOG and results of five randomized studies were reported.** The concept of chemoradiation encompasses the benefits of systemic chemotherapy with the benefits of regional radiation therapy. **The use of chemotherapy to sensitize cells to radiation therapy improved local–regional control.** These results changed the way cervical cancer is treated in many medical centers.

An intergroup trial involving the GOG, the Southwestern Oncology Group, and the Radiation Therapy Oncology Group evaluated postoperative chemoradiation therapy in patients with stage IA2, IB, or IIA cervical cancer who had positive pelvic lymph nodes, positive parametrial extension, or positive vaginal margins at the completion of radical hysterectomy (155). A total of 243 patients were assessed in this trial, with 127 receiving chemoradiation (*cisplatin*, *5-fluorouracil* [*5-FU*], radiation therapy) and 116 receiving radiation. **The results of this trial showed a statistically significant improvement in progression-free survival (PFS) and overall survical (OS) at 43 months for the patients receiving concurrent chemoradiation.** The 4-year survival rates for the patients receiving chemoradiation versus radiation alone were 81% and 71%, respectively. The toxicity levels in the two groups were acceptable, with a higher rate of hematologic toxicity in the concurrent chemoradiation arm. **This study showed that in patients with these high-risk factors after radical hysterectomy for stages IA2, IB, and IIA disease, chemoradiation is the postoperative treatment of choice.**

Concurrent chemoradiation was evaluated in patients with advanced cervical carcinoma. GOG protocol 85 was a prospective study that enrolled patients with stages

IIb to IVA cervical cancer and compared concurrent chemoradiation (157). There were 177 patients treated with *cisplatin*, *5-FU*, and radiation. These patients were compared with 191 patients treated with *hydroxyurea* and radiation. The median follow-up of patients who were alive at the time of the analysis was 8.7 years. Patients who received concurrent chemoradiation and were treated with *cisplatin* and *5-FU* had a statistically significant improvement in progression-free interval and OS (157). Hematologic toxicity levels in the two groups were similar. **This study showed that *cisplatin*-based concurrent chemoradiation was a superior treatment when compared with *hydroxyurea* and concurrent radiation.**

GOG Protocol 120 was initiated to evaluate patients with negative para-aortic nodes and cervical carcinoma stages IIB to IVA treated with concurrent chemoradiation. The treatment arms in this study consisted of radiation plus weekly *cisplatin*; or *cisplatin*, *5-FU*, and *hydroxyurea*; or *hydroxyurea*. There were 176 patients in the weekly *cisplatin* arm; 173 patients in the *cisplatin*, *5-FU*, and *hydroxyurea* arm; and 177 patients in the *hydroxyurea* arm (158). The two treatment arms with *cisplatin*-based chemotherapy and radiation showed an improvement in progression-free interval and OS at a median follow-up of 35 months. The relative risks for progression of disease or death were 0.55 and 0.57, respectively, for patients treated with *cisplatin*-based chemotherapy and radiation, compared with the patients treated with *hydroxyurea* and radiation (158). **This study confirmed the findings of GOG Protocol 85 and reaffirmed the finding that *cisplatin*-based concurrent chemoradiation is the treatment of choice for patients with advanced-stage cervical cancer.**

A third GOG trial evaluated patients with stages IB to IVA cervical cancer. Of the patients enrolled in this study, 70% had stage IB or IIA disease (159). A total of 403 patients were enrolled and evaluated. The 5-year survival rates were 73% in patients treated with chemoradiation and 58% in patients treated with radiation therapy alone. The cumulative rates of disease-free survival at 5 years were 67% in patients treated with concurrent chemoradiation and 40% in patients treated with radiation therapy alone. Survival and progression-free intervals for patients receiving concurrent chemoradiation were significantly improved (159). **The results of this study suggested that chemoradiation is the treatment of choice for stages IIB to IVA disease and that those patients with stages IB2 and IIA disease may benefit from chemoradiation.**

A GOG study of chemoradiation comparing concurrent *cisplatin* and radiation with radiation alone in patients with bulky IB cervical cancer included adjuvant hysterectomy after completion of the radiation (160). There were 183 patients assigned to the concurrent chemotherapy and radiation arm and 186 patients treated with radiation alone. The median duration of follow-up was 36 months, with disease recurrence detected in 37% of the patients treated with radiation alone, compared with

21% who were treated with concurrent chemoradiation (160). The 3-year survival rates were 83% in the group who received concurrent chemoradiation and 74% in the group who received radiation alone (160). The study included adjuvant hysterectomy after completion of radiation treatment. Because the results did not show an improvement in survival by using adjuvant hysterectomy, the authors concluded that adjuvant hysterectomy would not be part of their recommendations. **This study supports the results of previous studies and shows that patients with bulky stages IB and IIA cervical cancer treated with concurrent chemoradiation have survival rates superior to those treated with radiation alone. These two studies indicate that patients with bulky stages IB and IIA disease should have primary treatment consisting of chemoradiation, with the chemotherapy agent being weekly *cisplatin*.**

Based on 2,042 patients enrolled on prior GOG trials, modern nomograms have been developed to predict 2-year PFS, 5-year OS, and pelvic recurrence risk for women with locally advanced cervix cancer treated with definitive chemoradiation. Prognostic factors include histology, race/ethnicity, performance status, tumor size, FIGO stage, grade, presence of pelvic and para-aortic nodes, and use of *cisplatin*-based chemotherapy (161).

Surgical Staging Before Radiation

Surgical staging procedures designed to discover positive lymph nodes may be forgone with use of PET/CT imaging studies. The use of transperitoneal exploration was associated with a 16% to 33% mortality rate from radiotherapy-induced bowel complications and a 5-year survival rate of only 9% to 12% (162,163). **To avoid these complications, extraperitoneal dissection of the para-aortic nodes is recommended, and the radiation dose should be reduced to 5,000 cGy or less** (164,165). **When this approach is used, postradiotherapy bowel complications occur in fewer than 5% of patients, and the 5-year survival rate is 15% to 26% in patients with positive para-aortic nodes** (22,166,167). Survival appears to be related to the amount of disease in the para-aortic nodes and to the size of the primary tumor. In patients whose metastases to the para-aortic lymph nodes are microscopic and whose central tumor has not extended to the pelvic sidewall, the 5-year survival rate improves to 20% to 50% (168,169). Surgical staging techniques have improved to include laparoscopic assessment of the para-aortic and pelvic lymph nodes. Studies demonstrated benefit from surgical staging with improved survival and changes in treatment plans in 40% of patients (165,166). When PET/CT is compared with surgicopathologic staging of para-aortic lymph nodes, some patients with histologically positive para-aortic lymph nodes are missed with surgicopathologic staging (170).

Management of Grossly Positive Para-Aortic Lymph Nodes

The management of patients with macroscopic or grossly positive para-aortic

lymph nodes discovered at the time of surgery or by imaging studies is controversial. It is likely that grossly positive nodes may be beyond the ability of radiation therapy alone to sterilize. Therefore, to improve survival, additional therapy is required. In a representative study of the multiple reports in the literature, lymph node metastases were noted in 133 of 266 patients. Pelvic and para-aortic nodes were positive in 44 patients and positive para-aortic nodes were noted in only 2 patients. Five- and 10-year survival rates were similar for patients with macroscopically positive resectable nodes and microscopically positive nodes. Patients with unresectable nodal disease had a worse survival rate than those with resectable disease. All patients underwent extraperitoneal lymph node resections and subsequent radiotherapy. There was a 10% incidence of severe morbidity related to radiation use. Consistent with other reports in the literature, this study showed that **extraperitoneal debulking lymphadenectomy confers a survival advantage similar to that enjoyed by patients with micrometastatic disease without additional morbidity** (30). The topic nevertheless remains in debate because chemoradiation may permit the treatment of larger volume disease without the need for surgical debulking.

Prophylactic Para-Aortic Radiation Therapy

Prophylactic extended-field radiation therapy is an alternative to surgical staging of the para-aortic lymph node chain in women with advanced cervical cancer judged to be at high risk but without radiologic or clinical evidence of para-aortic lymph node involvement. This treatment strategy was evaluated in 441 patients with stages I to III disease (171). High rates of gastrointestinal toxicity were noted in the treatment group. There was no difference in disease-free survival or OS between the control and treated groups, although treated patients had fewer para-aortic failures. A lack of difference in survival rates in this study may be related to high local and regional failure rates, suggesting that ideal patients for prophylactic radiotherapy would be those in whom there is a high likelihood of achieving pelvic control. A survival benefit was noted in a study by the Radiation Therapy Oncology Group, in which 367 patients with stages IB to IIB disease were randomized to pelvic radiotherapy versus pelvic and extended field radiotherapy (172). The extended field treatment arm suffered more grade 4 and 5 toxicity, confirming previous studies. Complicating the issue is another study from the Radiation Therapy Oncology Group revealing that in locally advanced cervical cancer, pelvic radiation therapy with concurrent *cisplatin* chemotherapy was superior to extended-field radiation therapy (159). There are no large prospective trials that compare pelvic chemoradiation with extended-field chemoradiation. Given the potential toxicity, it seems prudent to administer extended-field radiation only to patients with suspected para-aortic node involvement.

Supraclavicular Lymph Node Biopsy

Although not standard practice, the performance of a supraclavicular lymph node biopsy was advocated in patients with positive para-aortic lymph nodes before the initiation of extended-field irradiation and in patients with a central recurrence before exploration for possible exenteration. The incidence of metastatic disease in the supraclavicular lymph nodes in patients with positive para-aortic lymph nodes is 5% to 30% (173). Node enlargement and increased metabolic activity can be assessed with chest PET/CT scanning. Cytologic assessment by FNA can obviate the need for an excisional biopsy and should be performed if any enlarged nodes are present. If the scalene lymph nodes are positive, palliative chemotherapy should be considered.

Complications of Radiation Therapy

Perforation of the uterus may occur (~9%) with the insertion of the uterine tandem. This is particularly a problem for elderly patients and those who had a previous diagnostic conization procedure. When perforation is recognized, an LDR tandem should be removed, and the patient should be observed for bleeding or signs of peritonitis. Survival may be decreased in patients who have uterine perforation, possibly because these patients have more extensive uterine disease (174). Fever may occur after insertion of the uterine tandem and ovoids. Fever most often results from infection of the necrotic tumor and occurs 2 to 6 hours after insertion of the intracavitary system. If uterine perforation was excluded by ultrasonography, intravenous broad-spectrum antibiotic coverage, usually with a *cephalosporin*, should be administered. If the fever does not decrease promptly or if the temperature is higher than 38.5°C, an aminoglycoside and a *bacteroides* species–specific antibiotic should be administered. If fever persists or if the patient shows signs of septic shock or peritonitis, any LDR intracavitary system must be removed. Antibiotics are continued until the patient recovers, and any LDR intracavitary application is delayed for 1 to 2 weeks. In case of HDR brachytherapy, antibiotics can be given and the tandem should be repositioned into proper place so that the HDR radiation treatment (typically only several minutes duration) can be delivered without delay followed by removal of the applicators (175). The use of intraoperative real-time transabdominal ultrasound guidance during placement of the brachytherapy tandem can significantly reduce the chance of perforation and help ensure an accurate brachytherapy implant.

Acute Morbidity

The acute effects of radiotherapy are caused by ionizing radiation on the epithelium of the intestine and bladder and occur after administration of 2,000 to 3,000 cGy. Symptoms include diarrhea, abdominal cramps, nausea, frequent urination, and occasional bleeding from the bladder or bowel mucosa. Bowel symptoms can be treated with a low-gluten, low-lactose, and low-protein diet. Antidiarrheal and antispasmodic agents may help. Bladder symptoms may be treated with antispasmodic

medication. Severe symptoms may require a week of rest from radiotherapy.

Chronic Morbidity

The chronic effects of radiotherapy result from radiation-induced vasculitis and fibrosis and are more serious than the acute effects. These complications occur several months to years after radiotherapy is completed. The bowel and bladder fistula rate after pelvic radiation therapy for cervical cancer is 1.4% to 5.3%, respectively (62,64). Other serious toxicity (e.g., bowel bleeding, stricture, stenosis, or obstruction) occurs in 6.4% to 8.1% of patients (62,64).

Radiation Proctopathy

Rectal bleeding after pelvic radiotherapy (radiation proctopathy) commonly self-resolves over time. Patients with continued bleeding can be offered at least flexible sigmoidoscopy to rule out causes unrelated to radiation therapy. For radiation-induced bleeding, first-line sucralfate enemas can be used. For refractory bleeding, interventions such as argon plasma coagulation, laser therapy and formalin can be considered (176).

Rectovaginal Fistula

Rectovaginal fistulas or rectal strictures occur in fewer than 2% of patients. The successful closure of fistulas with bulbocavernosus flaps or sigmoid colon transposition was reported (177,178). Occasionally, resection with anastomosis is feasible. Diversion resulting in colostomy may be the optimal therapy in patients who have poor vascular supply to the pelvis and a history of an anastomotic leak or breakdown from prior repairs.

Small Bowel Complications

Patients with previous abdominal surgery are more likely to have pelvic adhesions and thus sustain more radiotherapy complications in the small bowel. The terminal ileum may be particularly susceptible to chronic damage because of its relatively fixed position at the cecum. Patients with small bowel complications have a long history of crampy abdominal pain, intestinal rushes, and distention characteristic of partial small bowel obstruction. Often, low-grade fever and anemia accompany the symptoms. **Patients who have no evidence of disease should be treated aggressively with total parenteral nutrition, nasogastric suction, and early surgical intervention after the anemia resolves and good nutritional status is attained.** The type of procedure performed depends on individual circumstances (179). Small bowel fistulas that occur after radiotherapy rarely close spontaneously while total parenteral nutrition is maintained. Recurrent cancer should be excluded; aggressive fluid replacement, nasogastric suction, and wound care should be instituted. Fistulography and a barium enema should be performed to exclude a combined large and small bowel fistula. The fistula-containing loop of bowel may be either resected or isolated and left in situ. In the

latter case, the fistula will act as its own mucous fistula.

Urinary Tract

Chronic urinary tract complications occur in 1% to 5% of patients and depend on the dose of radiation to the base of the bladder. Vesicovaginal fistulas are the most common complication and usually require supravesicular urinary diversion. Occasionally, a small fistula can be repaired with either a bulbocavernosus flap or an omental pedicle. Ureteral strictures are usually a sign of recurrent cancer, and a cytologic sample should be obtained at the site of the obstruction using FNA guided by a CT scan. If the findings are negative, the patient should undergo exploratory surgery to evaluate the presence of recurrent disease. If radiation fibrosis is the cause, ureterolysis may be possible or indwelling ureteral stents may be passed through the open urinary bladder to relieve obstruction.

Chemotherapy

Neoadjuvant Chemotherapy

Randomized trials were initiated by the GOG and other large centers to determine the efficacy of neoadjuvant chemotherapy. **In the era of effective chemoradiation therapy, there is no evidence that neoadjuvant chemotherapy offers superior results or a survival advantage over standard therapy.**

Chemotherapy for Advanced Disease

Chemotherapy was studied in advanced cervical cancer with mixed results (180–183). Doublet therapy compared four *cisplatin*-containing doublets (*gemcitabine*, *paclitaxel*, *topotecan*, *vinorelbine*), and there were no major differences in OS, although the *cisplatin* and *paclitaxel* doublet trended toward the best results (GOG 204) (184). **Studies showed comparable survival and lower toxicity with *carboplatin* and *paclitaxel* compared with *cisplatin* and *paclitaxel* (185). A survival benefit was demonstrated when *bevacizumab*, an anti-VEGF-A monoclonal antibody, was added to the combination of platinum-based chemotherapy in patients with metastatic, persistent, or recurrent cervical carcinoma (GOG 240). However, the addition of bevacizumab to the combination increased the risk of fistula formation** (186).

While multiagent regimens offer an improved response rate and several months longer OS, they are more toxic than single-agent regimens. **For women who cannot tolerate combination chemotherapy, single-agent chemotherapy with *carboplatin* is an appropriate treatment.**

Treatment of Cervical Cancer by Stage

[5] *Stage IA*

Until 1985, no FIGO recommendation existed concerning the size of lesion or the depth

of invasion that should be considered microinvasive (stage IA). This led to considerable confusion and controversy in the literature. Over the years, as many as 18 different definitions were used to describe microinvasion. In 1974, the Society of Gynecologic Oncologists recommended a definition that is accepted by FIGO: **A microinvasive lesion is one in which neoplastic epithelium invades the stroma to a depth of less than 3 mm beneath the basement membrane and in which lymphatic or blood vascular involvement is not demonstrated.** The purpose of defining microinvasion is to identify a group of patients who are not at risk for lymph node metastases or recurrence and who therefore may be treated with less than radical therapy.

Diagnosis must be determined on the basis of a cone biopsy of the cervix. The treatment decision rests with the gynecologist and should be based on a review of the conization specimen with the pathologist. It is important that the pathologic condition be described in terms of (i) depth of invasion, (ii) presence or absence of lymph–vascular space invasion, and (iii) margin status. These variables are used to determine the degree of radicality of the operation and whether the regional nodes should be treated (171).

Stage IA1 <3 mm Invasion

Lesions with invasion less than 3 mm have less than 1% incidence of pelvic node metastases. Within this group, it appears that the patients most at risk for nodal metastases or central pelvic recurrence are those with definitive evidence of tumor emboli in lymph vascular spaces (77,187). Therefore, patients with less than 3 mm invasion and no lymph–vascular space invasion may be treated with extrafascial hysterectomy without lymphadenectomy. Therapeutic conization appears to be adequate therapy for these patients if preservation of childbearing capability is desired. Surgical margins and postconization endocervical curettage must be free of disease. If there is lymph–vascular space invasion, a type I (extrafascial) or II (modified radical) hysterectomy with pelvic lymphadenectomy should be considered.

Treatment of microinvasive cervical adenocarcinoma is complicated by a lack of agreement on approaches. Reports show that patients with stage IA1 cervical adenocarcinoma may be treated in a fashion similar to patients with this stage and a squamous lesion (111–113). Some experts disagree with this interpretation because of the difficulty in establishing a pathologic diagnosis of microinvasion from a frankly invasive adenocarcinoma. **Patients diagnosed with microinvasive cervical adenocarcinoma should have expert pathologic assessment before considering treatment with extrafascial hysterectomy or conization alone.**

Stage IA2 ≥3 mm to <5 mm Invasion

Lesions with invasion of greater than or equal to 3 to 5 mm have a 3% to 8%

incidence of pelvic node metastases; thus, pelvic lymphadenectomy or sentinel lymph node mapping is necessary for these lesions (187,188). The primary tumor may be treated with a modified radical hysterectomy (type II) or a radical trachelectomy if preservation of fertility is desired. If intermediate- or high-risk pathologic factors are identified in the surgical specimen, adjuvant radiation or chemoradiation therapy is recommended.

[5] ***Stages IB1, IB2, and IIA1 Invasive Cancer***

Stage IB lesions are subdivided into stage IB1, which denotes lesions that have 5 mm or more stromal invasion and are smaller than 2 cm in maximum diameter, and stage IB2, for lesions that are 2 cm or larger and less than 4 cm, and IB3, which denotes lesions that are 4 cm or larger. Patient's with lesions 2 cm or less may be managed with either a radical trachelectomy or type III radical hysterectomy with pelvic lymphadenectomy. Radical trachelectomy should be restricted to candidates who desire future fertility with low-risk disease and a tumor size less than 2 cm. The para-aortic lymph node chain should be evaluated if pelvic nodal disease is encountered. Adjuvant radiation therapy is recommended if intermediate risk factors are identified postoperatively. Adjuvant chemoradiation is indicated if high-risk features are found.

Alternatively, primary chemoradiation therapy with curative intent is appropriate. A comparison of radical hysterectomy with radiation resulted in similar survival rates for the two treatment modalities. Several studies comparing patients treated by either radical hysterectomy or radiation therapy showed similar survival rates and outcomes for both groups (93,189). However, patients treated with type III radical hysterectomy who subsequently received postoperative radiation had a higher rate of intestinal and urinary morbidity compared with patients treated with either modality alone. Therefore, some clinicians advocate using radiation and avoiding surgery in these patients because many will require adjuvant postoperative radiation.

[5] ***Bulky Stages IB3 and IIA2 Invasive Cancer***

Patients with bulky IB3 and IIA2 disease may be treated with either primary chemoradiation or radical surgery. Because many of these patients will have intermediate- or high-risk factors postoperatively, strong consideration should be given to primary chemoradiation. If surgical therapy is desired, a type III radical hysterectomy with pelvic and para-aortic lymphadenectomy, followed by adjuvant chemoradiation if intermediate- or high-risk factors are present, is appropriate therapy. This option has the benefits of complete surgical staging and ovarian preservation, if desired. Disadvantages of primary surgery include increased morbidity if multimodality therapy is utilized (189).

Stages IIB to IIIB Invasive Cancer

Therapy for patients with stage IIB or greater cervical cancer traditionally was radiation therapy. Primary pelvic radiotherapy fails to control disease progression in 30% to 82% of patients with advanced cervical carcinoma (4). Two-thirds of these failures occur in the pelvis (190). A variety of agents were used in an attempt to increase the effectiveness of radiation therapy in patients with large primary tumors. **Because chemoradiation was superior to radiation therapy alone, chemoradiation is the preferred treatment strategy for these patients, with *cisplatin* the chemotherapy agent of choice.** Nodal involvement, particularly the para-aortic lymph nodes, is the most important factor related to survival.

Stage IIIC1 and IIIC2

The updated staging system adds this new category to reflect metastatic disease to the pelvic lymph nodes (Stage IIIC1) and/or the para-aortic lymph nodes (Stage IIIC2). If the pelvic lymph nodes only are involved, chemoradiation to the pelvis is the recommended treatment, while if the para-aortic lymph nodes are involved, extended-field radiation with chemosensitization can be used and this can be followed by systemic chemotherapy (191–195).

[5] *Stages IVA and IVB Cancer*

Primary exenteration may be considered for patients with direct extension to the rectum or bladder, but it is rarely performed. For patients with extension to the bladder, the survival rate with radiation therapy is as high as 30%, with a urinary fistula rate of only 3.8% (196). The presence of tumor in the bladder may prohibit cure with radiation therapy alone; thus, consideration must be given to removal of the bladder on completion of external beam radiation treatment. This is particularly true if the disease persists at that time and the geometry is not conducive to brachytherapy. Rectal extension is less commonly observed but may require diversion of the fecal stream before chemoradiation to avoid septic episodes from fecal contamination. In certain clinical situations, such as with patients who have stage IVA disease and present with vesicovaginal or rectovaginal fistula, urinary or rectal diversion may be performed, followed by chemoradiation.

Patients with stage IVB cervical carcinoma are candidates for chemotherapy and palliative pelvic radiation therapy. Control of symptoms with the least morbidity is of primary concern in this patient population.

Patient Evaluation and Follow-Up After Therapy

Patients who receive radiotherapy should be monitored closely to assess treatment response. Tumors may be expected to regress for up to 3 months after radiotherapy. During the pelvic examination, progressive shrinkage of the cervix and possible stenosis of the cervical os and surrounding upper vagina are expected and should be noted. During rectovaginal examination, careful palpation of the uterosacral

and cardinal ligaments for nodularity is important. Cytologic assessment by FNA of suspicious areas should be performed to allow early diagnosis of persistent disease. In addition to the pelvic examination, the supraclavicular and inguinal lymph nodes should be carefully examined, and cervical or vaginal assessment should be performed every 3 to 6 months for 2 years and then every 6 to 12 months for the next 3 to 5 years. Endocervical curettage may be performed in patients with large central tumors (90).

Patients with isolated recurrences may benefit from surgical resection. Metastasis to the lung is reported in 1.5% of cases of patients with advanced disease. Solitary nodules are present in 25% of cases with metastasis. Resection of a solitary nodule in the absence of other persistent disease may yield some long-term survivors (197). After radical hysterectomy, about 80% of recurrences are detected within 2 years (198). The larger the primary lesion, the shorter the median time is to recurrence (199). Although CT, PET, or IVP is not a part of routine postradiotherapy surveillance, it should be performed if a pelvic mass is detected or if other symptoms warrant evaluation. The finding of ureteral obstruction after radiotherapy in the absence of a palpable mass may indicate unresectable pelvic sidewall disease, but this finding should be confirmed, usually by FNA cytologic assessment (200).

Special Considerations

Cervical Cancer During Pregnancy

The incidence of invasive cervical cancer associated with pregnancy is 1.2 in 10,000 (201). A Pap test should be performed on all pregnant patients at the initial prenatal visit, and any grossly suspicious lesions should be biopsied. Diagnosis is often delayed during pregnancy because bleeding is attributed to pregnancy-related complications. **If the result of the Pap test is positive for malignant cells, and invasive cancer cannot be diagnosed using colposcopy and biopsy, a diagnostic conization procedure may be necessary. Conization in the first trimester of pregnancy is associated with hemorrhagic and infectious complications, and an abortion rate as high as 33%** (202,203). **Because conization subjects the mother and fetus to complications, it should not be performed before the second trimester and only in patients with colposcopy findings consistent with cancer, biopsy-proven microinvasive cervical cancer, or strong cytologic evidence of invasive cancer.** Inadequate colposcopic examination may be encountered during pregnancy in patients who had prior ablative therapy. Close follow-up throughout pregnancy may allow the cervix to evert and develop an ectropion, allowing satisfactory colposcopy in the second or third trimester. Patients with obvious cervical carcinoma may undergo cervical biopsy and clinical staging similar to that of nonpregnant patients.

After conization, there appears to be no harm in delaying definitive treatment

until fetal maturity is achieved in patients with stage IA cervical cancer (202,204,205). Patients with less than 3 mm of invasion and no lymphatic or vascular space involvement may be followed to term. Historically, these patients were allowed to deliver vaginally, and a hysterectomy was performed 6 weeks postpartum if further childbearing was not desired. However, in a multivariate analysis of 56 women with cervical cancer diagnosed during pregnancy and 27 women with cervical cancer diagnosed within 6 months of delivery, vaginal delivery was the most significant predictor of recurrence. In addition, most recurrences after vaginal delivery involved distant sites. The ideal delivery method for these patients is not known definitively; however, strong consideration should be given to performing a cesarean birth in women with cervical cancer of any stage (206). If vaginal delivery is chosen, close inspection of the episiotomy site is required during follow-up because of rare reports of metastatic cervical cancer at these locations (207).

Patients with 3 to 5 mm of invasion and those with lymph–vascular space invasion may be followed to term or delivered early after establishment of fetal pulmonary maturity (202,205). They may have cesarean delivery, immediately followed by modified radical hysterectomy and pelvic lymphadenectomy. **Patients with more than 5 mm invasion should be treated as having frankly invasive carcinoma of the cervix.** Treatment depends on the gestational age of the pregnancy and the wishes of the patient. Modern neonatal care affords a 75% survival rate for infants delivered at 28 weeks of gestation and 90% for those delivered at 32 weeks of gestation. Fetal pulmonary maturity can be determined by amniocentesis, and prompt treatment can be instituted when pulmonary maturity is documented. Although timing is controversial, it is probably unwise to delay therapy for longer than 4 weeks (204,205). The recommended treatment is classic cesarean delivery followed by radical hysterectomy with pelvic lymphadenectomy. There should be a thorough discussion of the risks and options with both parents before any treatment is undertaken.

Patients with stages II to IV cervical cancer should be treated with radiotherapy. If the fetus is viable, it is delivered by classic cesarean birth, and therapy is begun postoperatively. If the pregnancy is in the first trimester, external radiation therapy can be started with the expectation that spontaneous abortion will occur before the delivery of 4,000 cGy. In the second trimester, a delay of therapy may be entertained to improve the chances of fetal survival. If the patient wishes to delay therapy, it is important to ensure fetal pulmonary maturity before delivery is undertaken. Neoadjuvant chemotherapy has been administered to women during pregnancy with cervical cancer after 13 weeks gestation, without clear short-term harm to the fetus, although longer clinical follow-up is necessary (208).

The clinical stage is the most important prognostic factor for cervical cancer during pregnancy. OS for these patients is slightly better because an increased

proportion of these patients have stage I disease. For patients with advanced disease, there is evidence that pregnancy impairs the prognosis (202,205). The diagnosis of cancer in the postpartum period is associated with a more advanced clinical stage and a corresponding decrease in survival (206).

Cancer of the Cervical Stump

Cancer of the cervical stump was more common many decades ago when supracervical hysterectomy was popular; because this operation is being performed more frequently, this situation may become increasingly familiar. Early-stage disease is treated surgically, with very little change in technique from that used when the uterus is intact (209). **Radical parametrectomy with upper vaginectomy and pelvic lymphadenectomy is the standard procedure.** Advanced-stage disease may present a therapeutic problem for the radiation oncologist if the length of the cervical canal is less than 2 cm. This length is necessary to allow satisfactory placement of the uterine tandem. If the uterine tandem cannot be placed, radiation therapy can be completed with vaginal ovoids or external beam techniques such as IMRT. Radiation oncology departments skilled in combined interstitial/intracavitary brachytherapy offer the ability to achieve curative brachytherapy coverage of cervical stump carcinomas. Intravaginal ovoids abutting the stump can be loaded with interstitial needles arrayed through the entire diameter and thickness of the stump to achieve comprehensive tumor coverage.

Pelvic Mass

The origin of a pelvic mass must be clarified before treatment is initiated. A CT urogram can exclude a pelvic kidney, and a barium enema helps to identify diverticular disease or carcinoma of the colon. An abdominal x-ray film may show calcifications typically associated with benign ovarian teratomas or uterine leiomyomas. Pelvic ultrasonography differentiates between solid and cystic masses and indicates uterine or adnexal origin. Solid masses of uterine origin are most often leiomyomas and do not need further investigation.

Pyometra and Hematometra

An enlarged fluid-filled uterine cavity may be a pyometra or a hematometra. The hematometra can be drained by dilation of the cervical canal and will not interfere with treatment. The pyometra should be drained, and the patient should be given antibiotics to cover *Bacteroides* species, anaerobic *Staphylococcus* and *Streptococcus* species, and aerobic coliform bacterial infection. Placement of a large mushroom catheter through the cervix was advocated, but the catheter may become obstructed, leading to further occlusion of the drainage. Repeated dilation of the cervix with aspiration of pus every 2 to 3 days is more effective.

If the disease is stage I, a radical hysterectomy and pelvic lymphadenectomy

may be performed. However, a pyometra is usually found in patients with advanced disease, and thus radiotherapy is required. External-beam therapy can begin after the pyometra is healed. Patients often have a significant amount of pus in the uterus or a tubo-ovarian abscess without signs of infection; therefore, a normal temperature and a normal white blood cell count do not necessarily exclude infection. Repeat physical examination or pelvic ultrasonography is necessary to ensure adequate drainage.

Cervical Carcinoma After Extrafascial Hysterectomy

When invasive cervical cancer is found after simple hysterectomy, further treatment is predicated on the extent of disease. Microinvasive disease in patients at low risk for lymph node metastasis does not require further treatment. Invasive disease may be treated with radiotherapy or reoperation involving a pelvic lymphadenectomy and radical excision of parametrial tissue, cardinal ligaments, and the vaginal stump (210).

Reoperation

Reoperation is indicated for a young patient who has a small lesion and in whom preservation of ovarian function is desirable. It is not indicated for patients who have positive margins or obvious residual disease (210). Survival rates after radical reoperation are similar to those after radical hysterectomy for stage I disease.

Concurrent *cisplatin*-based chemoradiation is recommended for gross residual disease, positive imaging, disease in the lymph nodes or parametrium, or a positive surgical margin; individualized brachytherapy is clearly indicated for a positive vaginal margin (211).

Radiation Therapy

Survival after radiotherapy depends on the volume of disease, the status of the surgical margins, and the length of delay from surgery to radiotherapy. Patients with microscopic disease have a 95% to 100% 5-year survival rate; the 5-year survival rate is 82% to 84% in those with macroscopic disease and free margins, 38% to 87% in those with microscopically positive margins, and 20% to 47% in those with obvious residual cancer (212–214). A delay in treatment of more than 6 months is associated with a 20% survival rate (214).

Acute Hemorrhage

Occasionally, a large lesion can produce life-threatening hemorrhage. A biopsy of the lesion should be performed to verify neoplasia, and a vaginal pack soaked in Monsel's solution (*ferric subsulfate*) should be packed tightly against the cervix. After proper evaluation, **external radiation therapy can be started with the expectation that control of bleeding may require 8 to 10 daily treatments at 180 to 200 cGy per day.** Broad-spectrum antibiotics should be used to reduce the incidence of infection. If the

patient becomes febrile, the pack should be removed. Rapid replacement of the pack may be necessary, and a fresh pack should be immediately available. This approach to management of hemorrhage in patients previously untreated is preferable to exploration and vascular ligation. **Vascular embolization under fluoroscopic control may be required in severe cases, and this procedure may obviate a laparotomy.** However, vascular occlusion ultimately may lead to decreased blood flow and oxygenation of the tumor, compromising the effectiveness of subsequent radiotherapy.

Ureteral Obstruction

Treatment of bilateral ureteral obstruction and uremia in previously untreated patients should be determined on an individual basis. Transvesical or percutaneous ureteral catheters should be placed in patients with no evidence of distant disease, and radiotherapy with curative intent should be instituted. Patients with metastatic disease beyond curative treatment fields should be presented with the options of ureteral stenting, palliative radiotherapy, and chemotherapy. With aggressive management, a median survival rate of 17 months may be achieved for these patients (215).

Barrel-Shaped Cervix

The expansion of the upper endocervix and lower uterine segment by tumor is referred to as a **barrel-shaped cervix. Patients with tumors larger than 6 cm in diameter have a 17.5% central failure rate when treated with radiotherapy alone because the tumor at the periphery of the lower uterine segment is too far from the standard intracavitary source to receive an adequate tumoricidal dose** (216). Attempts were made to overcome this problem radiotherapeutically by means of interstitial implants into the tumor with a perineal template, but high central failure rates were reported with this technique (217).

One approach is to use a combination of radiotherapy and surgery for treatment of patients with a barrel-shaped cervix. An extrafascial hysterectomy is performed 2 to 3 months after the completion of radiation therapy in an effort to resect a small, centrally persistent tumor. The dose of external radiotherapy is reduced to 4,000 cGy, and a single intracavitary treatment is given, which is followed by an extrafascial hysterectomy (218,219). This method appears to result in a lower rate of central failure (2%), although it is not clear that the OS rate is improved. **There is disagreement concerning the need for extrafascial hysterectomy**, and the GOG is undertaking a randomized study to compare adjuvant hysterectomy with radiotherapy alone in patients who have no evidence of occult metastases in the para-aortic nodes (see stages IB and IIA discussion).

The narrow upper vagina of older patients may preclude the use of an intracavitary source of radiation. Because of the significant OS advantage experienced by patients who successfully receive brachytherapy boosts, placement of brachytherapy applicators

with smaller geometry (mini-ovoids, or tandem and cylinder, or tandem alone) should be strongly considered prior to switching to an external beam-only regimen. Patients receiving their entire course of therapy from external beam radiation have a higher central failure rate and more significant bowel and bladder morbidity. If stage I disease is present in such a patient, a radical hysterectomy with pelvic lymphadenectomy is preferable, if the patient's medical condition allows this approach. There may be a role for IMRT and/or stereotactic radiation boosts in the management of such tumors.

Recurrent Cervical Cancer

Treatment of recurrent cervical cancer depends on the mode of primary therapy and the site of recurrence. Patients who were treated initially with surgery should be considered for radiation therapy, and those who had radiation therapy should be considered for surgical treatment. Chemotherapy is palliative only and is reserved for patients who are not considered curable by either surgery or radiation therapy.

Radiotherapy for recurrence after surgery consists primarily of external treatment. Vaginal ovoids may be placed in patients with isolated vaginal cuff recurrences. Patients with a regional recurrence may require interstitial implantation with a Syed type of template in addition to external therapy. A 25% survival rate can be expected in patients treated with radiation for a postsurgical recurrence (198).

Radiation Retreatment

Retreatment of recurrent pelvic disease by means of radiotherapy with curative intent is confined to patients who had suboptimal or incomplete primary therapy. This may allow the radiation oncologist to deliver curative doses of radiation to the tumor. The proximity of the bladder and rectum to the cancer and the relative sensitivity of these organs to radiation injury are the major deterrents to retreatment with radiation. The insertion of multiple interstitial radiation sources into locally recurrent cancer through a perineal template or next-generation combined intracavitary/interstitial applicator may help overcome these dosimetric considerations (210,220). The fistula rates can be high, and those consequences must be considered before interstitial therapy is initiated. For patients considered curable with interstitial implant therapy, pelvic exenteration is a better treatment choice. Palliative radiotherapy can be given to patients with localized metastatic lesions that are deemed incurable. Painful bony metastases, central nervous system lesions, and severe urologic or vena caval obstructions are specific indications.

Surgical Therapy

Surgical therapy for postirradiation recurrence is limited to patients with central pelvic disease. A few carefully selected patients with small-volume disease limited to the cervix may be treated with an extrafascial or radical hysterectomy. However, the

difficulty of assessing tumor volume and the 30% to 50% rate of serious urinary complications in these previously irradiated patients have led most gynecologic oncologists to recommend pelvic exenteration as a last chance for cure (221,222).

Exenteration

There are three types of exenterative procedures: (i) an anterior exenteration (removal of the bladder, vagina, cervix, and uterus), (ii) a posterior exenteration (removal of the rectum, vagina, cervix, and uterus), and (iii) a total exenteration (removal of bladder and rectum with the vagina, cervix, and uterus) (Fig. 38-9). A total exenteration that includes a large perineal phase removes the entire rectum and leaves the patient with a permanent colostomy and a urinary conduit (infralevator). In selected patients, a total exenteration may take place above the levator muscle (supralevator), leaving a rectal stump that may be anastomosed to the sigmoid, thus avoiding a permanent colostomy.

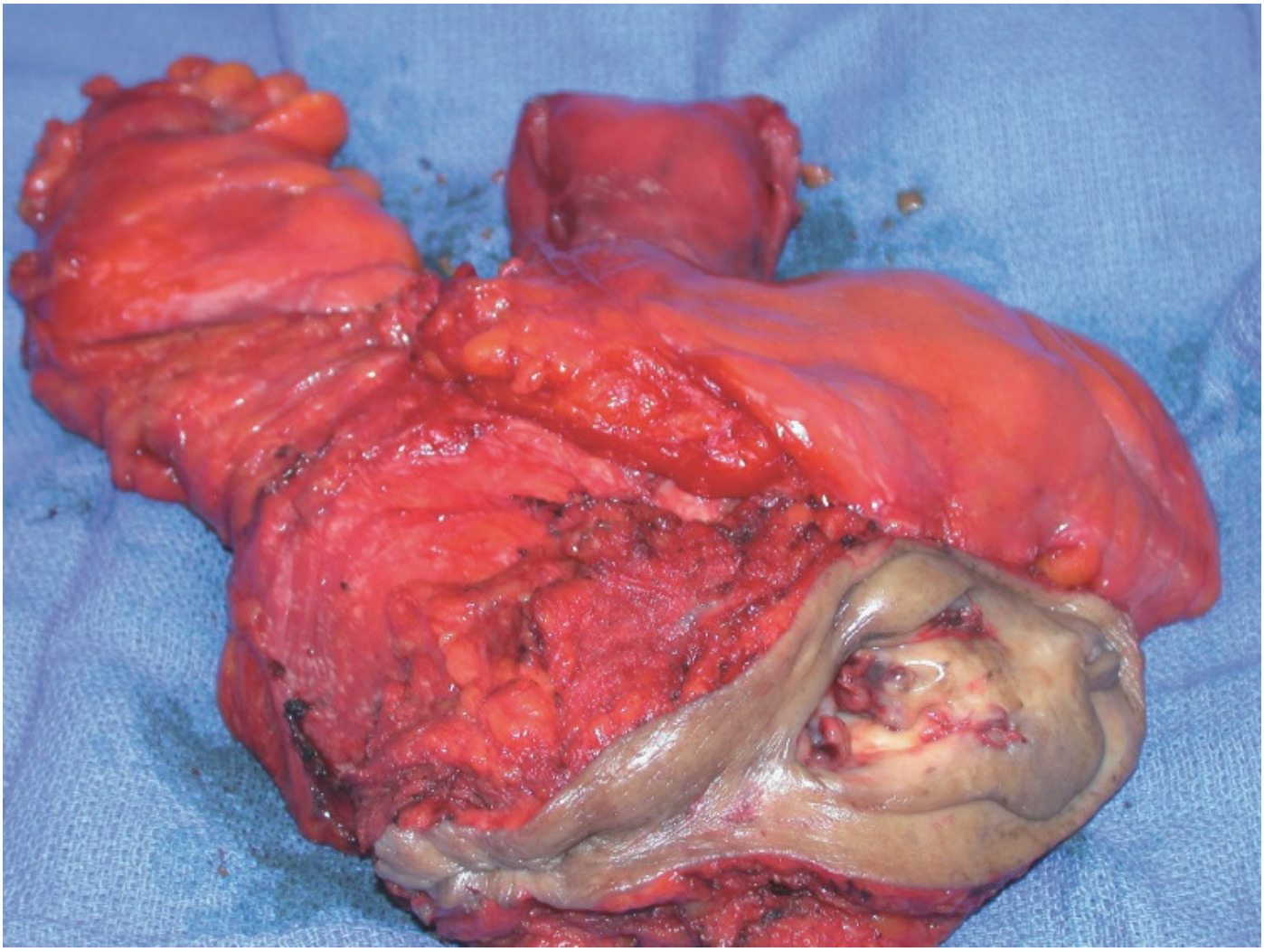


FIGURE 38-9 Pelvic exenteration specimen.

Preoperative Evaluation and Patient Selection

It is imperative to search for metastatic disease before the patient undergoes an exenteration. The presence of metastatic disease in this setting is considered a contraindication to exenterative procedures. Physical examination includes careful palpation of the peripheral lymph nodes with FNA cytologic sampling of any nodes that appear suspicious. A random biopsy of nonsuspicious supraclavicular lymph nodes is advocated by some clinicians but is not routinely practiced (174,223). A PET/CT scan of the chest and abdomen and pelvis CT help in the detection of liver metastases and enlarged nodes. Cytologic study of any abnormality should be undertaken with CT-guided FNA. If a positive cytologic diagnosis is obtained, it will obviate the need for exploratory laparotomy.

Extension of the tumor to the pelvic sidewall is a contraindication to exenteration; however, this may be difficult for even the most experienced examiner to determine because of radiation fibrosis. If any question of resectability arises, exploratory laparotomy and parametrial biopsies should be offered (224–227). **The clinical triad of unilateral leg edema, sciatic pain, and ureteral obstruction is nearly always pathognomonic of unresectable disease on the pelvic sidewall.** Preoperatively, the patient should be prepared for a major operation. Total parenteral nutrition may be necessary to place the patient in an anabolic state for optimal healing. A bowel preparation, preoperative antibiotic administration, and prophylaxis for deep venous thrombosis with low-dose *heparin* or pneumatic calf compression should be undertaken (228). Surgical mortality increases with age, and the operation should rarely be considered in a patient who is older than 70 years. Other medical illnesses should be taken into account. When life expectancy is limited, exenterative surgery is unwise.

Anterior Exenteration

Candidates for anterior exenteration are those in whom the disease is limited to the cervix and anterior portion of the upper vagina. Proctoscopic examination should be performed because a positive finding would mandate a total exenteration. However, a negative proctoscopic examination finding does not exclude disease in the rectal muscularis, and findings at laparotomy still must be considered. The presence of disease in the posterior vaginal mucosa directly over the rectum mandates removal of the underlying rectum.

Posterior Exenteration

A posterior exenteration is rarely performed for recurrent cervical cancer. It is indicated, however, for the patient with an isolated posterior vaginal recurrence in which dissection of the ureters through the cardinal ligaments will not be necessary.

Total Exenteration

Total exenteration with a large perineal phase is indicated when the disease

extends to the lower part of the vagina (Fig. 38-9). Because distal vaginal lymphatics may empty into the nodal basins of the inguinal region, these nodes should be carefully evaluated preoperatively. A supralevator total exenteration with low rectal anastomosis is indicated in the patient whose disease is confined to the upper vagina and cervix (229,230). Samples from margins of the rectal edge should be obtained for frozen-section evaluation because occult metastases to the muscularis may occur.

The development of techniques to establish continent urinary diversion helps improve a woman's physical appearance after exenteration (231–233). When both a rectal anastomosis and a continent diversion are performed, the patient will not have a permanent external appliance. Associated psychological trauma in such cases may be avoided. **Every effort should be made to create a neovagina simultaneously with the exenteration** (234). This procedure helps in the reconstruction of the pelvic floor after extirpation of the pelvic viscera. Regardless of whether a neovagina is constructed, it is desirable to mobilize the omentum on the left gastroepiploic artery to create a new pelvic floor.

Surgical mortality from exenterative procedures has steadily decreased to less than 10%. Common causes of postoperative death are sepsis, pulmonary thromboembolism, and hemorrhage. Fistulas of the gastrointestinal and genitourinary tract are serious surgical complications, with a 30% to 40% mortality rate despite attempts at surgical repair. The risk for fistula formation is decreased if nonirradiated segments of bowel are used for formation of the urinary conduit (228). **The 5-year survival rate is 33% to 60% for patients undergoing anterior exenteration and 20% to 46% for those undergoing total exenteration** (224–234). Survival rates are worse for patients with recurrent disease (larger than 3 cm), invasion into the bladder, positive pelvic lymph nodes, and recurrence diagnosed within 1 year after radiotherapy (227). The 5-year survival rate of patients with positive pelvic lymph nodes is less than 5%; thus, the performance of an extensive lymphadenectomy in the irradiated field is not warranted. Discontinuation of the procedure is advisable if any nodes are positive for metastatic cancer. Patients who have any disease in the peritoneal cavity have no chance of survival.

Laterally Extended Endopelvic Resection

Locally recurrent cervical cancer in a previously irradiated field is associated with a dismal prognosis. Exenterative therapy traditionally was reserved for the highly select patient with centrally recurrent disease, a selection criteria that excludes most patients with recurrence. A technique called the **laterally extended endopelvic resection (LEER)** procedure was described, which offers a surgical treatment option for patients with recurrent disease involving the pelvic sidewall. The LEER procedure involves extending the lateral resection plane of the traditional pelvic exenteration to include resection of the internal iliac vessels; the endopelvic portion of the obturator internus

muscle; and the coccygeus, iliococcygeus, and pubococcygeus muscles. Extension of the surgical plane allows for resection of lateral tumors with a negative margin. Experience with it is limited to one center, which reports as high as a 62% recurrence-free survival, but as high as 70% moderate-to-severe morbidity (235).

Chemotherapy for Recurrent Cervical Cancer

Recurrent cervical cancer is not considered curable with chemotherapy (236–238). Several clinical trials with various drugs (e.g., *carboplatin*, *cisplatin*, and *paclitaxel*) showed response rates of up to 45%. Most responses are partial; complete responses are unusual and limited to patients with chest metastases in whom the dose of drug delivered to the disease is better than that delivered to the fibrotic postirradiated pelvis (237,238). The uptake of chemotherapy to recurrent tumor in a previously irradiated field may be compromised because of altered blood supply caused by that radiation.

***Carboplatin* and *paclitaxel* combination chemotherapy is as effective and less toxic than the *cisplatin* and *paclitaxel* combination** (185). **Combination chemotherapy with *carboplatin– paclitaxel–bevacizumab* may produce better survival, but it is more toxic than doublet chemotherapy** (186). **Single-agent *carboplatin* is an acceptable alternative in these patients whose disease cannot be cured.**

Palliative Therapy

Palliative therapy for patients with incurable disease consists of radiation or chemotherapy or both. **Palliative radiation therapy is intended to relieve symptoms of pain or bleeding associated with advanced disease and may be administered as either external beam therapy (teletherapy) or brachytherapy.** Special care should be given to previously irradiated sites because additional radiation therapy may be associated with unacceptable morbidity. Single or multiagent palliative chemotherapy may be used with variable response rates. Symptomatic recurrent disease within previously irradiated fields may not respond well to palliative chemotherapy.

VAGINAL CARCINOMA

[6] Primary vaginal cancer is a relatively uncommon tumor, representing only 2% to 3% of malignant neoplasms of the female genital tract. In the United States, it is estimated that there were 1,312 new cases in 2014, and 430 deaths from the disease (1). Squamous histology accounts for 80% (239). **Primary vaginal cancer should be differentiated from cancers metastatic to the vagina, which constitute the majority of cancers found in the vagina (84%)** (240).

Table 38-6 FIGO Staging of Vaginal Cancer

Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to stage IV
IVA	Tumor invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

FIGO, International Federation of Gynecology and Obstetrics.

From **Beller U, Benedet JL, Creasman WT, et al.** Carcinoma of the vagina. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynecol Obstet* 2006;95:S29–S42 and FIGO Committee on Gynecologic Oncology. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynecol Obstet* 2009;105:3–4.

Staging

The FIGO staging of vaginal cancer dictates that a tumor extending to the vagina from the cervix be regarded as a cancer of the cervix, whereas a tumor involving both the vulva and the vagina should be classified as a cancer of the vulva.

The FIGO staging for vaginal carcinoma is shown in Table 38-6. **Staging is performed by clinical examination** and, if indicated, cystoscopy, proctoscopy, and chest and skeletal radiography. Information derived from lymphangiography, CT, MRI, or PET cannot be used to change the FIGO stage; however, it can be used for planning treatment. Less than 30% of vaginal cancers present at stage I (241–243).

Surgical staging and resection of enlarged lymph nodes may be indicated in selected patients. FIGO staging does not include a category for microinvasive disease. Because vaginal cancer is rare and treatment is by radiotherapy, there is very little information concerning the spread of disease in relation to depth of invasion, lymph–vascular space invasion, and size of the lesion.

Etiology

The association of cervical cancer with HPV suggests that vaginal cancer has a similar association (244). A study of 341 cases revealed that in younger patients, the disease seemed to be related to HPV infection, while in older patients, there was no association (243). **As many as 30% of women with vaginal cancer have a history of cervical cancer treated within the previous 5 years** (186,235–247). As with cervical cancer, there appears to be a premalignant phase called **vaginal intraepithelial neoplasia**

(VAIN) (see Chapter 16). **The exact incidence of progression to invasive vaginal cancer from VAIN is not known;** however, there are documented cases of invasive disease occurring despite adequate treatment of VAIN (248,249).

By convention, any new vaginal carcinoma developing at least 5 years after cervical cancer is considered a new primary lesion. There are three possible mechanisms for the occurrence of vaginal cancer after cervical neoplasia:

1. Residual disease in the vaginal epithelium after treatment of the cervical neoplasia
2. New primary disease arising in a patient with increased susceptibility to lower genital tract carcinogenesis (the role of HPV in this setting is suspected)
3. Increased susceptibility to carcinogenesis caused by radiation therapy

Screening

Routine screening of all patients for vaginal cancer is inappropriate. For women who had a cervical or vulvar neoplasm, the Pap test is an important part of routine follow-up with each physician visit, because these patients are at an increased lifetime risk for developing vaginal cancer. It is recommended that Pap test surveillance for vaginal cancer be performed yearly after the patient has completed surveillance for cancer of the cervix or vulva. **For women who had a hysterectomy for benign disease and have no antecedent history of CIN 2–3, performance of Pap testing is unnecessary. If the patient has a history of cervical dysplasia or cervical cancer, yearly screening is recommended.** When adjusted for age and prior cervical disease, the incidence of vaginal cancer is not increased in women who had hysterectomy for benign disease (250). Because primary vaginal tumors tend to be multicentric, the entire vaginal mucosa should be considered at-risk. Therefore, in addition to screening cytology, careful bimanual examination of the entire vagina and vulva is recommended for women at high risk.

Symptoms

Painless vaginal bleeding and discharge are the most common symptoms of vaginal cancer. With more advanced tumors, urinary retention, bladder spasm, hematuria, and frequency of urination may occur. In a large series, 14% were asymptomatic and diagnosis was made by routine examination or abnormal cytology (243). Tumors developing on the posterior vaginal wall may produce rectal symptoms, such as tenesmus, constipation, or blood in the stool.

Diagnosis

The diagnostic workup includes a complete history and physical examination, careful

speculum examination and palpation of the vagina, and bimanual pelvic and rectal examinations. **It is important to rotate the speculum to obtain a careful view of the entire vagina because posterior wall lesions frequently occur and may be overlooked.**

In early squamous cell lesions, the diagnosis is often suggested by an abnormal HPV or Pap test result; however, this is not true for clear-cell adenocarcinomas, which are characterized by submucosal growth. In these cases, the diagnosis is suggested by cytologic findings in only 33% of cases. Visually suspicious areas in the vagina should be evaluated with a targeted biopsy using the same instruments as those used for cervical biopsies. Careful palpation of the vagina may be helpful in detecting submucosal irregularities. **The most common site of vaginal cancer is in the upper one-third of the vagina on the posterior wall.** The developing tumor may be missed during initial inspection because of obscured visualization caused by the blades of the speculum (251). Colposcopy is valuable in evaluating patients with abnormal HPV or Pap test results, unexplained vaginal bleeding, or ulcerated erythematous patches in the upper vagina. A colposcopically targeted biopsy may not allow a definitive diagnosis, and a partial vaginectomy may be necessary to determine invasion. Occult invasive carcinoma may be detected by such an excision, particularly in patients who have a history of prior hysterectomy in whom the vaginal vault closure may bury some of the vaginal epithelium at risk for cancer (252).

Pathology

Cancer of the vagina spreads most often by direct extension into the pelvic soft tissues and adjacent organs. Metastases to the pelvic and para-aortic lymph nodes may occur in advanced disease. Lesions in the lower one-third of the vagina may spread directly to the inguinal femoral lymph nodes and the pelvic nodes (253). Hematogenous dissemination to the lungs, liver, or bone may occur as a late phenomenon.

Squamous cell carcinomas are the most common form of vaginal cancer, occurring in 80% to 90% of cases. These tumors most commonly occur in the upper one-third, posterior wall of the vagina. The mean age of patients with squamous cell cancer is 60 years (254,255).

Malignant melanoma is the second most common cancer of the vagina, accounting for 2.8% to 5% of all vaginal neoplasms (256–258). Other histologic subtypes include adenocarcinoma and sarcoma.

Primary adenocarcinoma of the vagina is rare, constituting 9% of primary tumors of the vagina. The most common adenocarcinoma of the vagina is metastatic, originating from the colon, endometrium, ovary, or, rarely, pancreas and stomach. In general, adenocarcinomas affect a younger population of women, regardless of whether they were exposed to *diethylstilbestrol* (*DES*) *in utero* (259).

Adenocarcinomas may arise in wolffian rest elements, periurethral glands, and foci of endometriosis (260). In women exposed to *DES in utero*, adenocarcinoma may develop in vaginal adenosis.

DES was used in the United States from 1940 until 1971 to maintain high-risk pregnancies in women with a history of spontaneous abortions. In 1970, seven young women were reported with clear-cell adenocarcinoma of the vagina **(Fig. 38-10)**; later, an association between this cancer and maternal ingestion of *DES* during pregnancy was identified (261). Subsequently, more than 500 cases of clear-cell cancer of the vagina and cervix were reported to the Registry for Research on Hormonal Transplacental Carcinogenesis.

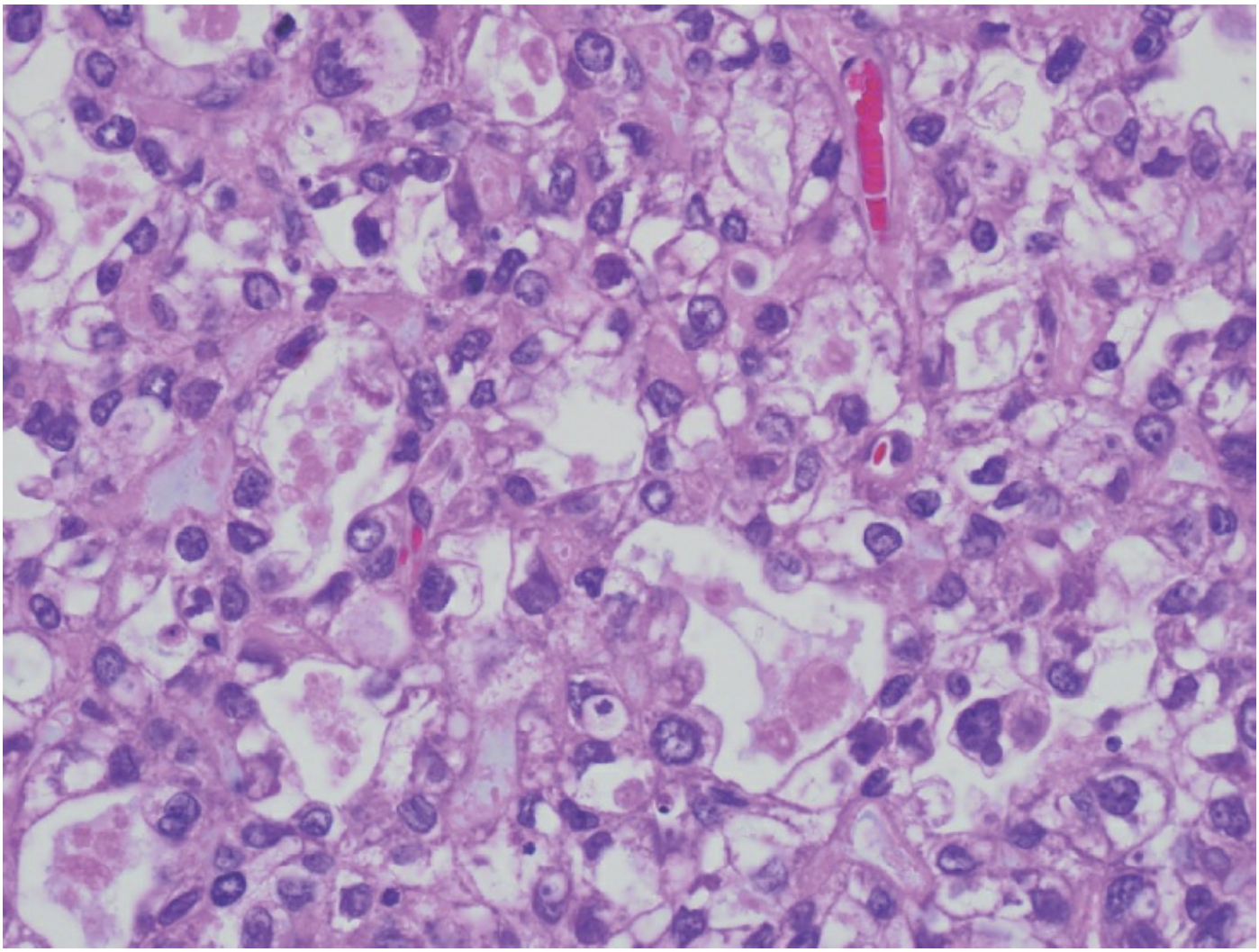


FIGURE 38-10 Vaginal clear-cell carcinoma. Note the formation of tubules with hobnail cells lining the lumen. These cells are characterized by nuclear protrusion into the apical cytoplasm.

The estimated risk for developing clear-cell adenocarcinoma for an exposed offspring is 1 in 1,000 or less. The mean age of diagnosis is 19 years (262). Because the use of *DES* in pregnant women was discontinued in 1971, most of these tumors

probably have been discovered. Clear-cell adenocarcinoma in women with a history of in utero exposure to *DES* typically presented in the exocervix or anterior, upper one-third of the vagina. These tumors varied greatly in size and were most frequently exophytic and superficially invasive. Stage is the most important prognostic factor. Other statistically significant factors included a tubulocystic growth pattern, size less than 3 cm^2, and less than 3 mm of stromal invasion. It is uncertain, however, what will happen to this cohort of women as they move into their fifth, sixth, and seventh decades of life. Continued surveillance of these women is indicated.

Ninety-seven percent of cases of vaginal clear-cell adenocarcinoma are associated with adenosis. Adenosis is characterized by the presence of persistent müllerian-type glandular epithelium. Although adenosis is the most common histologic abnormality in women exposed to *DES in utero*, adenosis can be found in women without a history of exposure. Adenosis typically appears as red, grapelike clusters in the vagina.

Malignant melanoma of the vagina is rare and lethal, occurring most often in white women. The average age of these patients is 58 years (263). Most lesions are deeply invasive, corresponding to a Clark level IV when compared with the staging for vulvar melanomas. The most common location of these tumors is in the lower one-third of the vagina (264). Melanomas have a wide variety of size, color, and growth patterns (262,265). Radical excision (vaginectomy, hysterectomy, and pelvic lymphadenectomy) is the mainstay of treatment. The goal of treatment is to avoid local (vaginal) recurrence, which is the most common site of recurrence (263,264). The need to dissect regional lymph nodes is uncertain. Because the disease is deeply invasive, hematogenous spread is the most common lethal recurrence. There is no difference in OS of patients with local as opposed to radical excision (263). The survival rate is approximately 10% at 5 years.

The most common benign and malignant mesenchymal tumors of the vagina in adult women are smooth muscle tumors (266). Vaginal sarcomas are usually fibrosarcomas or leiomyosarcomas and are extremely rare. Radical local excision, followed by adjuvant chemotherapy or radiation therapy, is the indicated treatment.

The most common malignant mesenchymal tumor of the vagina in children and infants is botryoid rhabdomyosarcoma (Fig. 38-11). Botryoid sarcoma is usually found in the vagina during infancy and early childhood, in the cervix during the reproductive years, and in the corpus uteri during postmenopausal years. Preoperative chemotherapy with *vincristine*, *actinomycin D*, and *cyclophosphamide*, followed by conservative surgery or radiation, has improved survival.

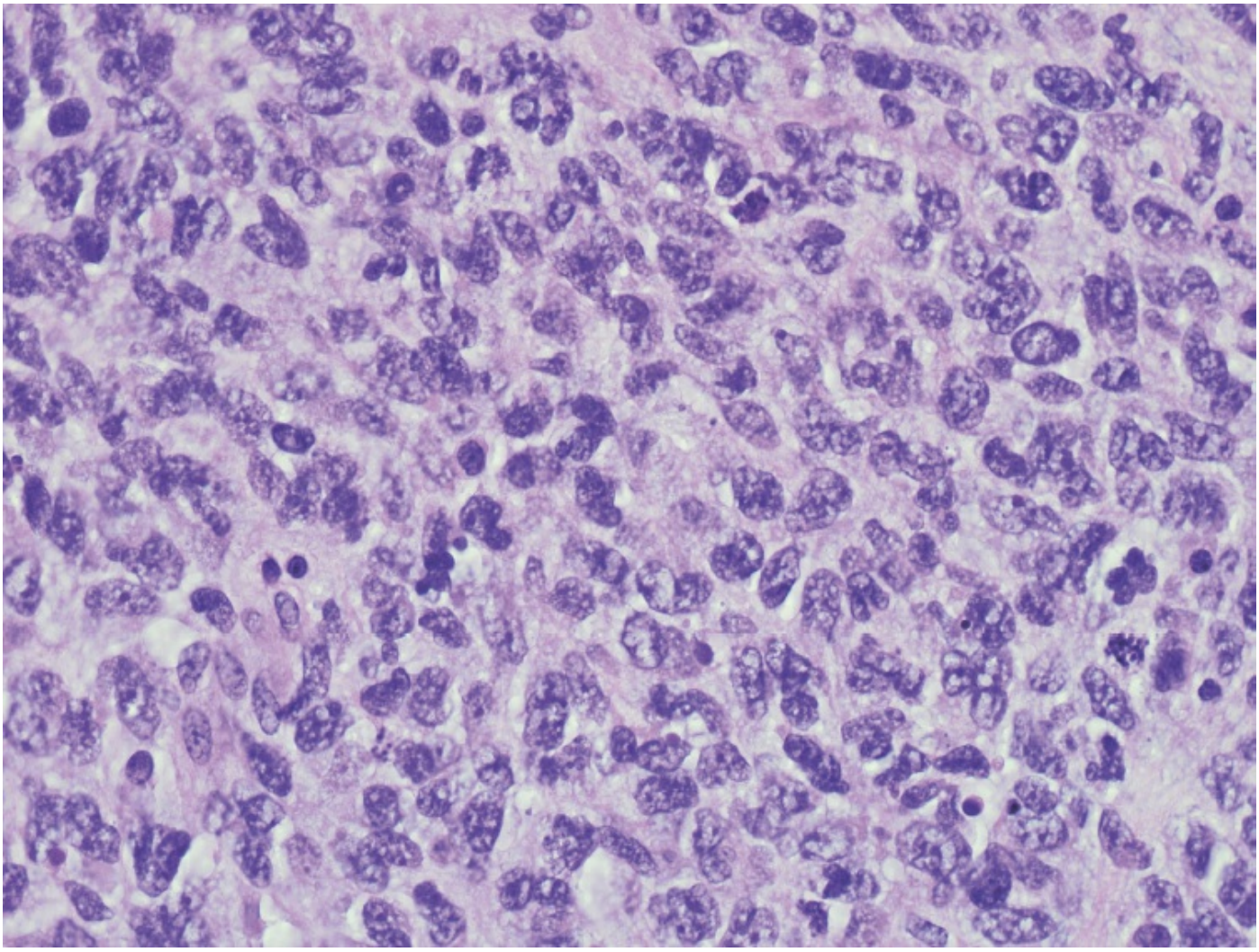


FIGURE 38-11 Embryonal rhabdomyosarcoma of the vagina (botryoid sarcoma). This lesion consists of primitive mesenchymal cells and rhabdomyoblasts, which have abundant eosinophilic cytoplasm. With further differentiation, cross-striations may become evident.

[6] Treatment

Treatment selection is based on the clinical examination, CT scan results, chest radiography results, age, and condition of the patient. PET scans may give more accurate information about disease spread than MRI or CT scan alone (267). Most tumors are treated by radiation therapy. Surgery is limited to selected cases. These are as follows:

1. **Women with stage I disease involving the upper posterior vagina may be treated by radical vaginectomy and pelvic lymphadenectomy.** If the uterus is in situ, it is removed as a radical hysterectomy specimen. When margins are clear and lymph nodes are negative, no additional therapy is necessary.
2. **Patients with stage IV disease with either rectovaginal or vesicovaginal fistula** may be candidates for primary pelvic exenteration with pelvic and para-aortic

lymphadenectomy (262). Low rectal anastomosis, continent urinary diversion, and vaginal reconstruction are indicated and are more successful in these nonirradiated patients than in patients who received prior radiation therapy.

3. **Women with central pelvic recurrence after radiation therapy are candidates for pelvic exenteration similar to that used for cervical cancer.**
4. **Surgical staging with resection of enlarged lymph nodes followed by radiation therapy may improve the control of pelvic disease.**

Radiation therapy is the treatment of choice for all patients except those described previously. Small superficial lesions may be treated with intracavitary radiation alone (262). **Larger, thicker lesions should be treated first with external teletherapy to decrease tumor volume and to treat the regional pelvic nodes, followed by intracavitary and interstitial therapy to deliver a high dose to the primary tumor** (255,263). If the uterus is intact and the lesion involves the upper vagina, an intrauterine tandem and ovoids can be used. If the uterus was previously removed, a vaginal cylinder may be used for superficial irradiation. When brachytherapy is used, high- and low-dose rate techniques were described. If the lesion is more than 0.5-cm thick, interstitial radiation techniques can improve the dose distribution to the primary tumor. Surgical exploration or laparoscopy at the time of insertion of Syed interstitial implants defines more precisely the placement of the needles and ensures that needles do not pass into adherent loops of bowel. Extended-field radiation may be used for vaginal cancer in a manner similar to its use for cervical carcinoma, although there is no experience reported with the use of this technique in the treatment of vaginal cancer. Likewise, there is little reported experience with combination chemoradiation treatment (268). Although there will never be enough patients for a proper randomized control trial, concurrent use of *5-FU* and *cisplatin* was highly successful in anal and cervical cancer and thus should be considered for treatment of vaginal cancer.

Sequelae

The proximity of the rectum, bladder, and urethra leads to a major complication rate of 10% to 15% for surgery and radiation treatment. For large tumors, the risk of bladder or bowel fistula is significant. Radiation cystitis and proctitis are common, as are rectal strictures or ulcerations. Radiation necrosis of the vagina occasionally occurs, requiring debridement, and often leads to fistula formation. Vaginal fibrosis, stenosis, and stricture are common after radiation therapy. **Use of vaginal dilators and resumption of regular sexual relations should be encouraged, along with the use of topical *estrogen* to maintain adequate vaginal function.**

Survival

The overall 5-year survival rate for patients with vaginal cancer is 52% (Table 38-7). This reflects the difficulties of treatment and the fact the disease presents at late stage. **For patients with stage I disease, the 5-year survival rate is 74%.** Most recurrences are in the pelvis, either from enlarged regional nodes or from large central tumors. Radiation techniques, including interstitial implants with Syed template and combination chemoradiation, are the mainstay of therapy. Careful evaluation of patients who receive radiation therapy to detect central recurrence may allow some patients to be saved by pelvic exenteration. Because of the rarity of vaginal cancer, these patients should be treated in a center that is familiar with the complexity of treatment and modalities of therapy.

Table 38-7 Primary Vaginal Carcinoma: 5-Year Survival

Stage	No. of Patients	No. Surviving 5 Years	Percentage
I	509	378	74.3
II	622	333	53.5
III	377	128	34.0
IV	163	24	15.3
Total	**1,671**	**864**	**51.7**

Data compiled from Pride et al. (269); Houghton and Iversen (266); Benedet et al. (242); Rubin et al. (244); Kucera et al. (265); Eddy et al. (270); Kirkbride et al. (271); Perez et al. (272); Tewari et al. (273); Otton et al. (274); Frank et al. (275); Hellman et al. (241); Tran et al. (276).

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CHAPTER 39

Ovarian, Fallopian Tube, and Peritoneal Cancer



Jonathan S. Berek, Diana P. English, Teri A. Longacre, Michael Friedlander

Epithelial Ovarian Cancer
- Pathology
  - *Invasive Cancer*
  - *Borderline Tumors*
  - *Classification of Epithelial Ovarian Tumors*
  - *Peritoneal Carcinomas*
  - *Mesotheliomas*
- Clinical Features
- Etiology
- Prevention
- Screening
- Genetic Risk for Epithelial Ovarian Cancer
  - *Hereditary Ovarian Cancer*
  - *Management of Women at High Risk for Ovarian Cancer*
- Symptoms
- Signs
- Diagnosis
  - *Differential Diagnosis*
- Patterns of Spread
  - *Transcoelomic*
  - *Lymphatic*
  - *Hematogenous*
- Prognostic Factors
  - *Pathologic Factors*
  - *Clinical Factors*
- Initial Surgery for Ovarian Cancer
  - *Staging*
  - *Borderline Tumors*

Stage I
Advanced-Stage Ovarian Cancer
Chemotherapy
Stage I Epithelial Ovarian Cancer
Advanced-Stage Epithelial Ovarian Cancer
Treatment Assessment
Second-Line Therapy
Chemotherapy for Recurrent Ovarian Cancer
Hormonal Therapy
Bevacizumab
Radiation Therapy
Intestinal Obstruction
Survival
Nonepithelial Ovarian Cancers
Germ Cell Malignancies
Classification
Epidemiology
Clinical Features
Dysgerminoma
Immature Teratomas
Endodermal Sinus Tumors
Rare Germ Cell Tumors of the Ovary
Mixed Germ Cell Tumors
Late Effects of Treatment of Malignant Germ Cell Tumors of the Ovary
Sex Cord–Stromal Tumors
Granulosa–Stromal Cell Tumors
Sertoli–Leydig Tumors
Uncommon Ovarian Cancers
Steroid Cell Tumors
Sarcomas
Small Cell Carcinoma, Hypercalcemic Type
Metastatic Tumors
Gynecologic
Nongynecologic
Krukenberg Tumor
Other Gastrointestinal Tumors
Melanoma
Carcinoid Tumors
Lymphoma and Leukemia

KEY POINTS

1 The peak age incidence of invasive epithelial ovarian cancer is approximately 60 years. About 30% of ovarian neoplasms in postmenopausal women are malignant, whereas only about 7% of ovarian epithelial tumors in premenopausal patients are malignant. The average age at diagnosis of patients with borderline tumors is approximately 46 years.

2 Ovarian cancer is associated with low parity and infertility. Because parity is inversely related to the risk of ovarian cancer, having at least one child is protective, with a risk reduction of 0.3 to 0.4.

3 Oral contraceptive use reduces the risk of epithelial ovarian cancer—women who use oral contraceptives for 5 or more years reduce their relative risk by 0.5 (i.e., there is a 50% reduction in the likelihood of development of ovarian cancer).

4 Given the false-positive results for CA-125 and transvaginal ultrasonography, particularly in premenopausal women and the absence of evidence from randomized trials that screening with CA-125 and TVUS reduces the mortality of ovarian cancer, these tests should not be used routinely to screen women for ovarian cancer.

5 Most epithelial ovarian cancers are sporadic, but up to one-quarter of cases may be associated with germline mutations in predisposing genes and may be hereditary. Hereditary ovarian cancers, particularly those caused by *BRCA1* mutations, occur at a younger age, typically about 10 years earlier than sporadic ovarian cancers.

6 Most hereditary ovarian cancers result from germline mutations in the *BRCA1* and *BRCA2* genes. The mutations are inherited in an autosomal dominant fashion, and therefore a full pedigree analysis (i.e., maternal and paternal sides of the family history for breast and ovarian cancer) must be carefully evaluated in all patients with epithelial ovarian cancer, fallopian tube cancer, and peritoneal cancer. It is important to note that almost 40% of women with BRCA-associated ovarian cancer do not have a family history and hence genetic testing should be offered to all women with ovarian cancer.

7 In unaffected women with a known *BRCA1* mutation, the value of prophylactic salpingo-oophorectomy is well established and is the most effective way to reduce the risk of these cancers and reduce mortality.

8 The importance of thorough surgical staging cannot be overemphasized, because subsequent treatment and prognosis will be determined by the stage of the disease. All patients with suspected ovarian cancer should be evaluated by a gynecologic oncologist. Patients with advanced-stage ovarian cancer (stage IIIC or IV) should have clinical evaluation including chest, abdomen and pelvis imaging. Patients determined to have a poor performance status, a high perioperative risk, or a low probability of attaining optimal cytoreduction to no visible, or palpable, residual disease, or at least cytoreduction to less than 1 cm of residual disease, should be considered for neoadjuvant chemotherapy prior to attempt at interval cytoreductive surgery after two to three cycles of chemotherapy. Patients with advanced ovarian cancer who are medically fit for major surgery and who potentially have resectable disease should be offered primary cytoreductive surgery followed by adjuvant chemotherapy. In the United States, primary cytoreductive surgery is preferred, if there is a high likelihood of achieving optimal cytoreduction with acceptable morbidity from surgery. Prior to initiating neoadjuvant chemotherapy, the pathologic diagnosis of ovarian, fallopian tube, or peritoneal cancer must be made on biopsy.

9 Combination chemotherapy with *carboplatin* and *paclitaxel* (CP) is recommended for patients with high-risk, low-stage disease. For advanced-stage epithelial ovarian cancer, the choice of intravenous (IV) versus intraperitoneal (IP) *platinum* and *taxane* chemotherapy with the addition of bevacizumab should be individualized.

10 The ICON8 trial did not confirm the JGOG study that showed that a dose-dense regimen of weekly paclitaxel and 3-weekly carboplatin was significantly superior to the standard every 3-week chemotherapy regimen of both drugs. Therefore 3-weekly regimens remain the standard of care in non-Japanese women.

11 BRCA-associated ovarian cancers have increased sensitivity to platinum chemotherapy and to poly (ADP-ribose) polymerase (PARP) inhibitors. PARP inhibitors are approved to treat selected patients with recurrent ovarian cancer and for maintenance therapy following response to platinum-based chemotherapy in the recurrent setting. There is good evidence from a number of randomized trials that maintenance therapy with PARP inhibitors results in a significant increase in the progression-free survival (PFS), particularly in BRCA mutation carriers (including tumors with somatic BRCA mutations). PARP inhibitors *niraparib* and *olaparib* are U.S. Food and Drug Administration (FDA) approved for maintenance therapy in patients with platinum-sensitive disease with a partial or complete response to platinum-based chemotherapy. PFS is improved with these agents regardless of BRCA status, although the PFS is significantly longer in patients with BRCA mutations. Maintenance therapy with *rucaparib* was reported to be associated with significant improvement in PFS in patients with platinum-sensitive recurrent ovarian cancer after response to chemotherapy, with the benefits being greater in women with somatic or germline BRCA (gBRCA) mutations.

12 In the first two decades of life, almost 70% of ovarian tumors are of germ cell origin, and one-third of these are malignant. In contrast to the relatively slow-growing epithelial ovarian tumors, germ cell malignancies grow rapidly.

13 The most common types of malignant germ cell tumors are dysgerminomas, immature teratomas, and endodermal sinus tumors (EST). Preservation of fertility should be standard in most patients. The most effective chemotherapy is *bleomycin*, *etoposide*, and *cisplatin* (BEP).

14 Stromal tumors include adult granulosa cell tumors, which are low-grade malignancies. They account for 70% of ovarian sex cord–stromal tumors. Granulosa cell tumors are the most common type of malignant ovarian sex cord–stromal tumors. In premenopausal women, they can be treated conservatively. Adjuvant chemotherapy is of unproven value.

15 Metastatic tumors to the ovaries are most frequently from the breast and gastrointestinal tract.

16 Epithelial serous fallopian tube carcinomas and peritoneal cancers are the same as ovarian cancer and are treated in the same way, with staging and cytoreductive surgery followed by *platinum* and *taxane* chemotherapy. The distinction between high-grade serous ovarian, fallopian tube, and peritoneum cancers is an anachronism because as most high-grade serous cancers arise from the fimbriae of the fallopian tube.

Ovarian cancer is the second most common gynecologic cancer in the United States but it accounts for the majority of deaths from these cancers. Epithelial cancers are the most common ovarian/fallopian malignancy, and at initial diagnosis, over two-thirds of patients have advanced disease. Ovarian cancer represents a major surgical challenge as the aim is to resect all visible disease. Optimal therapy includes maximal attempt at surgical cytoreduction to no gross disease, or at least optimal debulking (to <1 cm of residual disease), followed by *platinum*-based combination chemotherapy. It has the highest fatality-to-case ratio of all the gynecologic malignancies. There are nearly 22,280 new cases annually in the United States, and 14,240 women can be expected to succumb to their illness (1). Ovarian cancer is the seventh most common cancer in women in the United States, accounting for 3% of all malignancies, 6% of deaths from cancer in women, and almost one-third of invasive malignancies of the female genital organs. Ovarian cancer is the fifth most common cause of death from malignancy in women. **The lifetime risk of being diagnosed with ovarian cancer is 1% to 1.5% and of dying from ovarian cancer is almost 0.5%** (2).

EPITHELIAL OVARIAN CANCER

Developments, based in part on meticulous pathologic assessment of risk-reducing salpingo-oophorectomy specimens from BRCA patients, have completely changed our perception and understanding of "ovarian" cancer. While previously thought to be derived from the coelomic epithelium on the surface of the ovary or from ovarian inclusion cysts, it is now apparent that most serous carcinomas originate from the fallopian tube (3)**, while other subtypes (clear cell, endometrioid) are derived from endometriosis.** A detailed classification of the histologic types of epithelial tumors of the ovary is presented in Table 39-1. Neoplastic transformation can

occur when the cells are genetically predisposed to oncogenesis, exposed to an oncogenic agent, or both (4).

Table 39-1 Epithelial Ovarian Tumors

Histologic Type	Cellular Type
I. Serous	Endosalpingeal
A. Benign	
B. Borderline	
C. Malignant	
II. Mucinous	Intestinal, endocervical
A. Benign	
B. Borderline	
C. Malignant	
III. Endometrioid	Endometrial
A. Benign	
B. Borderline	
C. Malignant	
IV. Clear-cell	Müllerian
A. Benign	
B. Borderline	
C. Malignant	
V. Brenner	Transitional
A. Benign	
B. Borderline (proliferating)	
C. Malignant	
VI. Mixed epithelial	Mixed
A. Benign	
B. Borderline	
C. Malignant	
VII. Undifferentiated	May be anaplastic

VIII. Unclassified	

From **Seroy SF, Scully RE, Sobin LH.** *International Histological Classification of Tumours No. 9. Histological Typing of Ovarian Tumors*. Geneva, Switzerland: World Health Organization; 1973, with permission.

Pathology

Invasive Cancer

Seventy-five percent to 80% of epithelial cancers are of the serous histologic type. Less common types are endometrioid (10%), clear cell (5%), mucinous (5%), transitional, and undifferentiated carcinomas, with the last two types representing less than 1% of epithelial lesions (2). Each of the major tumor types is named on the basis of a histologic pattern that resembles the epithelium in the lower genital tract (4). For example, serous tumors have an appearance similar to that of the glandular epithelial lining of the fallopian tube, endometrioid tumors resemble proliferative endometrium, and clear cell tumors resemble secretory or gestational endometrium. Mucinous tumors may contain cells that resemble endocervical glands, but more commonly these cells resemble the gastrointestinal epithelium. Transitional tumors are so named because of a resemblance to the epithelium in Walthard rests and bladder urothelium.

There is growing evidence that many, if not most, high-grade serous carcinomas of the ovary arise from the fimbrial end of the fallopian tube rather than from the ovary (5,6). **Serous epithelial ovarian cancers can be separated into two distinct groups—type I and type II serous tumors—as they differ considerably in the cell of origin, molecular pathogenesis, and their biologic behavior** (7). **Type I tumors include serous borderline tumors and low-grade serous carcinoma; they are genetically stable, do not have p53 mutations, and may have mutations in *KRAS* or *BRAF*. In contrast, type II serous tumors are rapidly growing, highly aggressive neoplasms that may have precursor lesions in the fimbriae of the fallopian tube; most are advanced stage at diagnosis** (8). **The type II tumors are genetically unstable and almost universally have p53 mutations.**

Borderline Tumors

An important group of tumors to distinguish are *tumors of low malignant potential*, also called the *borderline tumors*. Borderline tumors tend to remain confined to the ovary for long periods, they occur predominantly in premenopausal women, and are associated with a very good prognosis (2,4,8–13). They are diagnosed most frequently in women between the ages of 30 and 50 years, whereas invasive carcinomas occur more often in women between the ages of 50 and 70 years (2).

Although uncommon, extraovarian implants may occur with serous borderline tumors. These implants are characterized as either *noninvasive* or *invasive (analogous to low-grade serous carcinoma)*. The latter has a higher likelihood of progression, in the peritoneal cavity, which can ultimately lead to intestinal obstruction caused by associated fibrosis and death (2,7).

Classification of Epithelial Ovarian Tumors

Serous Tumors

Serous tumors are so classified because they resemble tubal secretory cells. *Psammoma bodies* are frequently found in these neoplasms, and they are made up of concentric rings of calcification. Several hypotheses pertaining to the origin and development of psammoma bodies are proposed, including apoptosis of tumor cells and osteoinductive cytokines produced by macrophages, which result in calcification that can be extensive (7). In the wall of the mesothelial invaginations, papillary ingrowths are common, representing the early stages of development of a papillary serous cystadenoma. There are many variations in the proliferation of these mesothelial inclusions. Several foci may be lined with flattened inactive epithelium; in adjacent cavities, papillary excrescences are present, often resulting from local irritants (2).

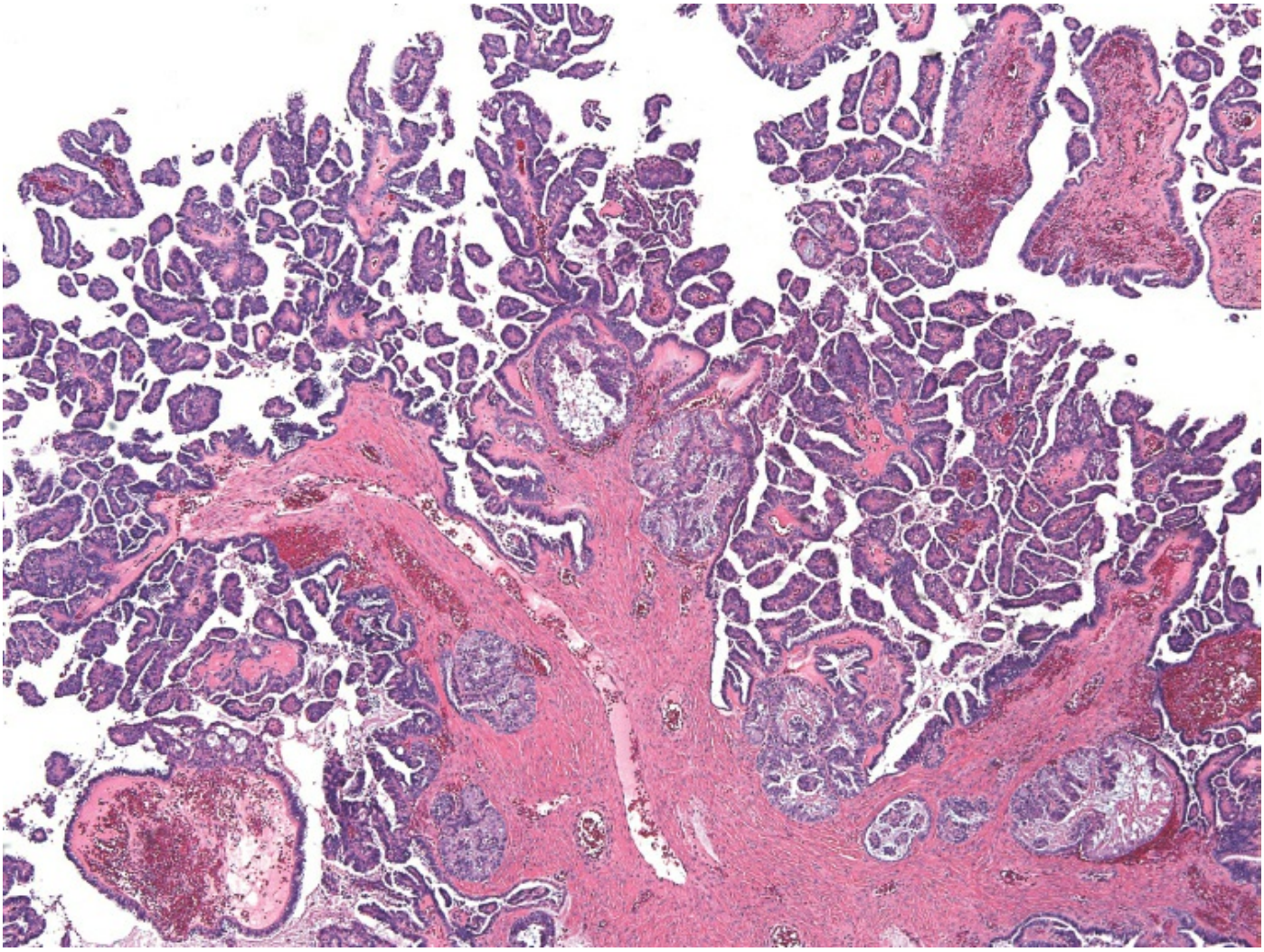


FIGURE 39-1 Serous borderline tumor of the ovary. Complex papillary fronds with hierarchical branching are lined with pseudostratified columnar cells. The epithelium and the stroma are clearly separated by a basement membrane, indicating no stromal invasion.

Borderline Serous Tumors

Approximately 10% of all ovarian serous tumors fall into the category of a tumor of low malignant potential or borderline tumor (Fig. 39-1), and 50% occur before the age of 40 years. The criteria for the diagnosis of serous borderline tumors are as follows (12):

1. Epithelial hyperplasia in the form of pseudostratification, tufting, cribriform, and micropapillary architecture
2. Mild nuclear atypia and mild increased mitotic activity
3. Detached cell clusters
4. Absence of destructive stromal invasion (i.e., without tissue destruction)

Serous borderline tumors that are composed of an exuberant micropapillary architecture are designated as serous borderline tumors with micropapillary features

(Fig. 39-2); these tumors are more frequently bilateral, exophytic, and high stage than the usual serous borderline tumor.

It should be emphasized that up to 40% of serous borderline tumors are associated with spread beyond the ovary, but high-stage disease does not necessarily warrant a diagnosis of an invasive carcinoma. The diagnosis of a serous borderline tumor versus serous carcinoma is based on the histologic features of the primary tumor (12). Up to 10% of women with ovarian serous borderline tumors and extraovarian implants may have invasive implants (i.e., low-grade serous carcinoma), and these can behave more aggressively (14). The 5-year overall survival for women with invasive implants (low-grade serous carcinoma) is about 50% if stringent criteria are applied (11,14–16). Most implants are noninvasive (11,17). In the noninvasive implants, papillary proliferations of atypical cells involve the peritoneal surface and form smooth invaginations (11). In contrast, the invasive implants resemble well-differentiated serous carcinoma and are characterized by atypical cells forming irregular glands with sharp borders. Implants are usually confined to the abdominal cavity and may be seen in the pelvis, omentum, and adjacent tissues, including lymph nodes, but spread outside the abdominal cavity is rare. Death can occur as the result of intestinal obstruction (17–20).

Borderline serous tumors may harbor foci of stromal microinvasion (19). Most patients are young and their tumors are International Federation of Obstetrics and Gynecology (FIGO) stage I. Stromal microinvasion is increased about ninefold in pregnant women with serous borderline tumors.

The presence of stromal microinvasion is associated with lymphovascular space invasion in the primary ovarian tumor (and likely represents a form of true stromal invasion), but it is not associated with an aggressive clinical course, and patients with this finding should be managed in the same way as patients without stromal microinvasion.

Serous Carcinomas

In malignant serous tumors, stromal invasion is present (2). The grade of tumor is important and needs to be documented. In low-grade serous adenocarcinomas, papillary and glandular structures predominate **(Fig. 39-3)**; high-grade neoplasms are characterized by solid sheets of cells, nuclear pleomorphism, and high mitotic activity **(Fig. 39-4)**. Laminated, calcified psammoma bodies are found in 80% of serous carcinomas. ***Serous psammocarcinoma*** **is a rare variant of serous carcinoma characterized by massive psammoma body formation and low-grade cytologic features.** At least 75% of the epithelial nests are associated with psammoma body formation. Patients with serous psammocarcinoma have a protracted clinical course and a relatively favorable prognosis; their clinical course more closely resembles that of high-stage, progressive serous borderline tumor than serous carcinoma.

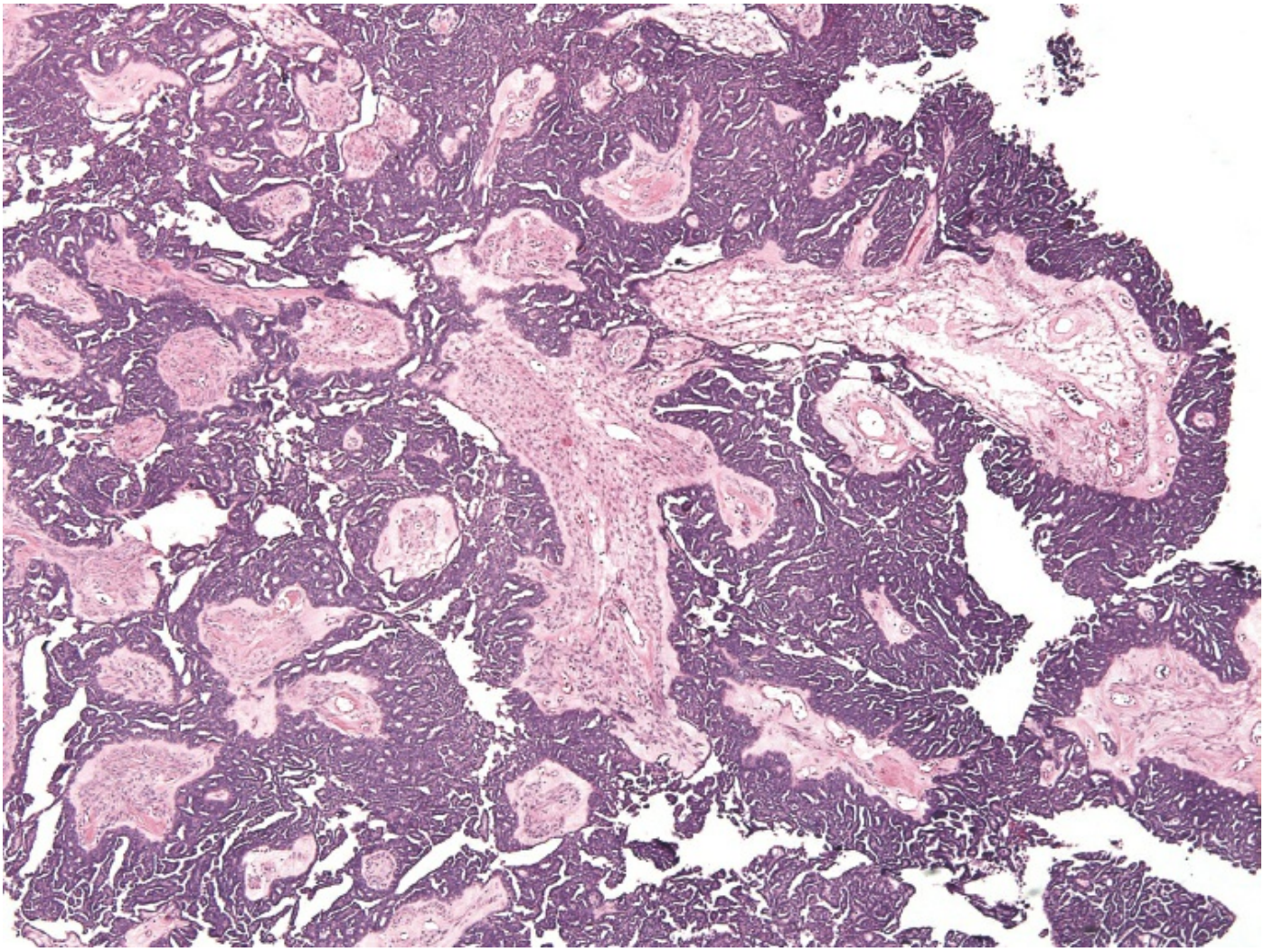


FIGURE 39-2 Serous borderline tumor with micropapillary features. The papillae have a nonhierarchical branching pattern and are lined by a monomorphous population of cells.

Mucinous Tumors

These cystic ovarian tumors have loculi lined with mucin-secreting epithelium. The lining epithelial cells contain intracytoplasmic mucin and resemble those of endocervix, gastric pylorus, or intestine. **They represent about 8% to 10% of epithelial ovarian tumors.** They may reach enormous size, filling the entire abdominal cavity (2).

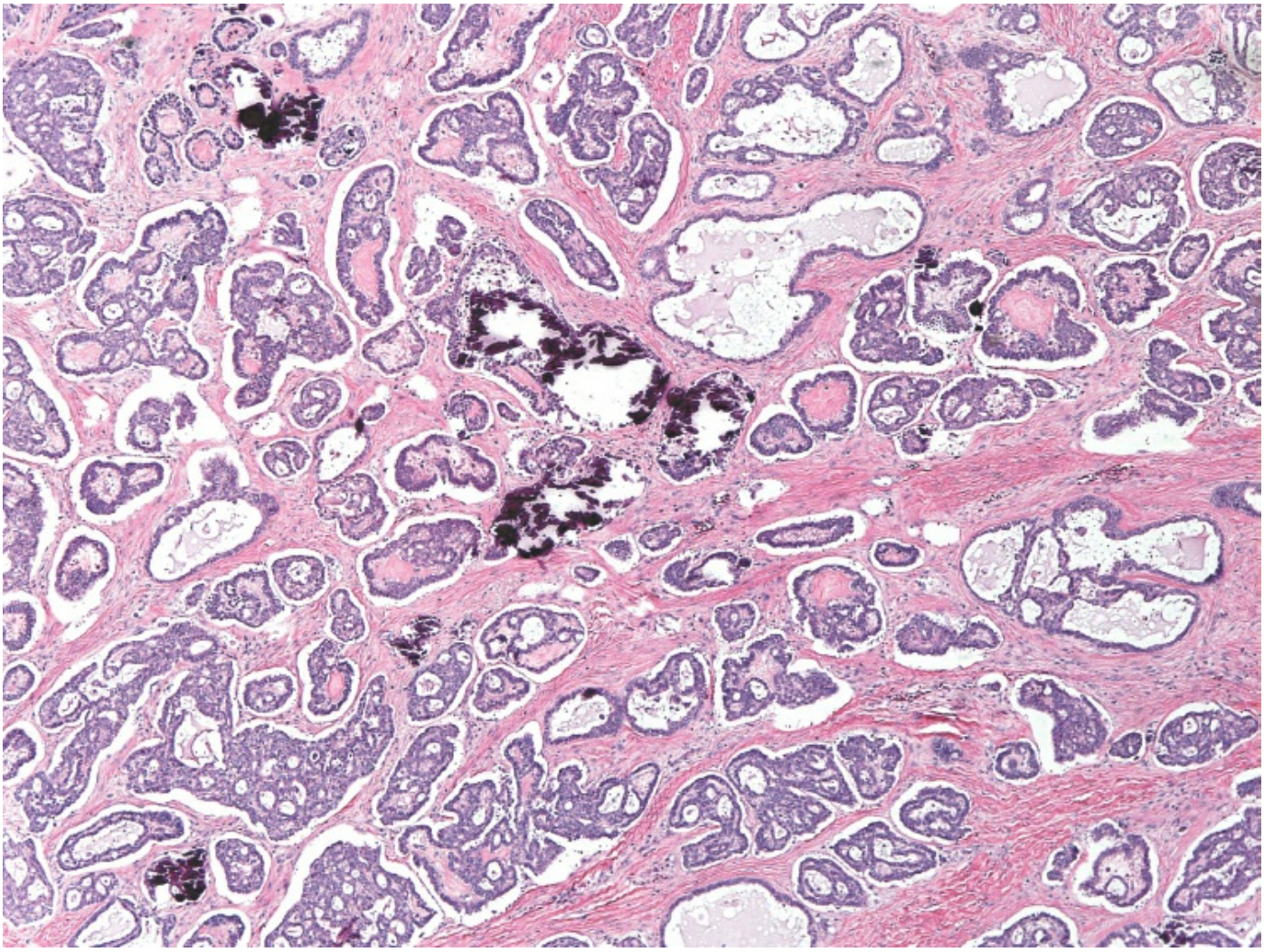


FIGURE 39-3 Low-grade serous adenocarcinoma of the ovary. Clusters and papillae of malignant cells are in direct contact with fibrous stroma indicative of stromal invasion.

Borderline Mucinous Tumors

The mucinous tumor of low malignant potential is often difficult to diagnose. Although it is common to find a rather uniform pattern from section to section in the serous borderline tumor, this is not true in the mucinous tumors. **Well-differentiated mucinous epithelium may be seen immediately adjacent to a poorly differentiated focus. It is important to take multiple sections from many areas in the mucinous tumor to identify the most malignant alteration** (2).

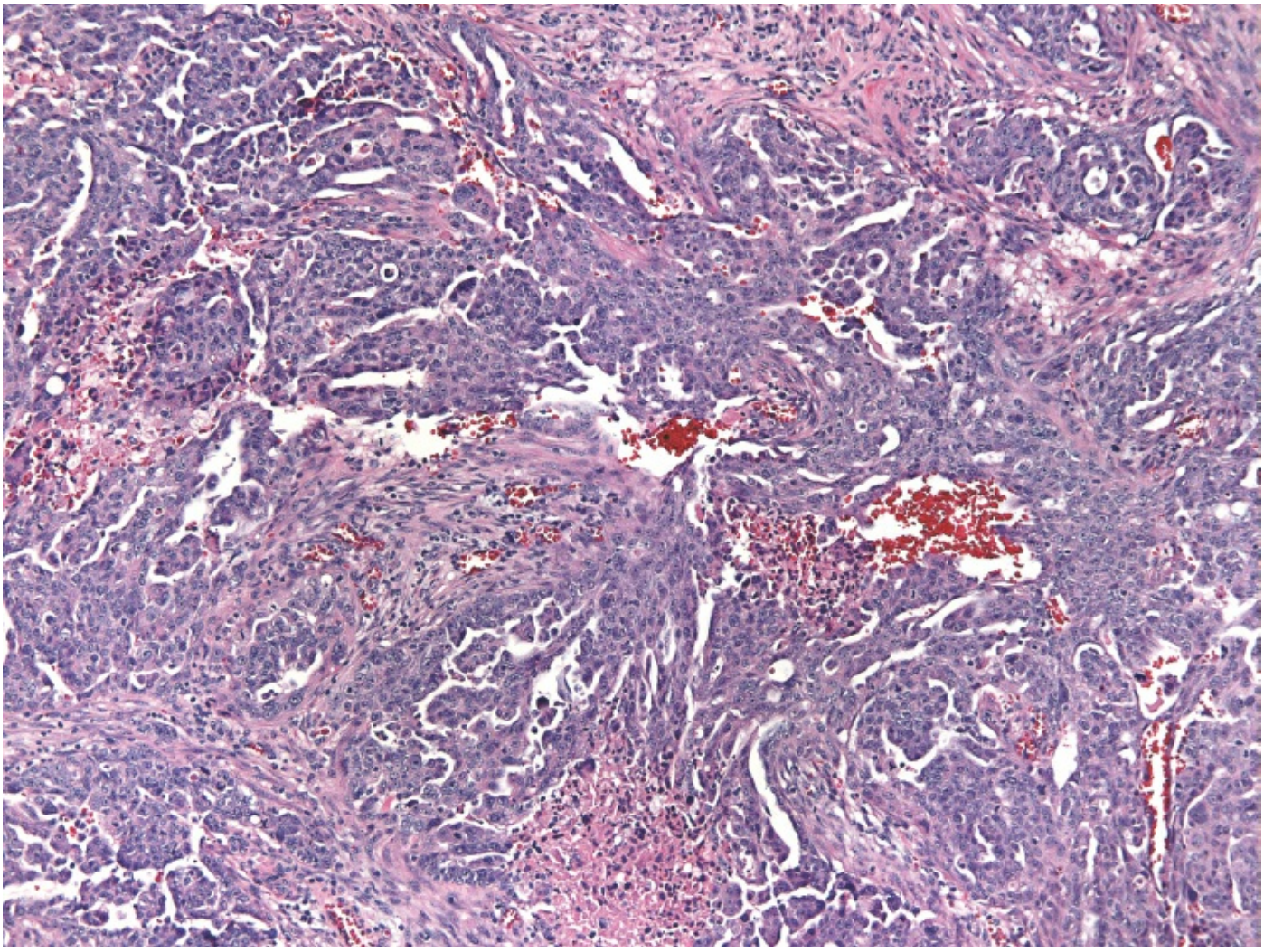


FIGURE 39-4 High-grade serous adenocarcinoma. Papillae lined by sheets of cytologically malignant cells invade stroma, often with associated necrosis.

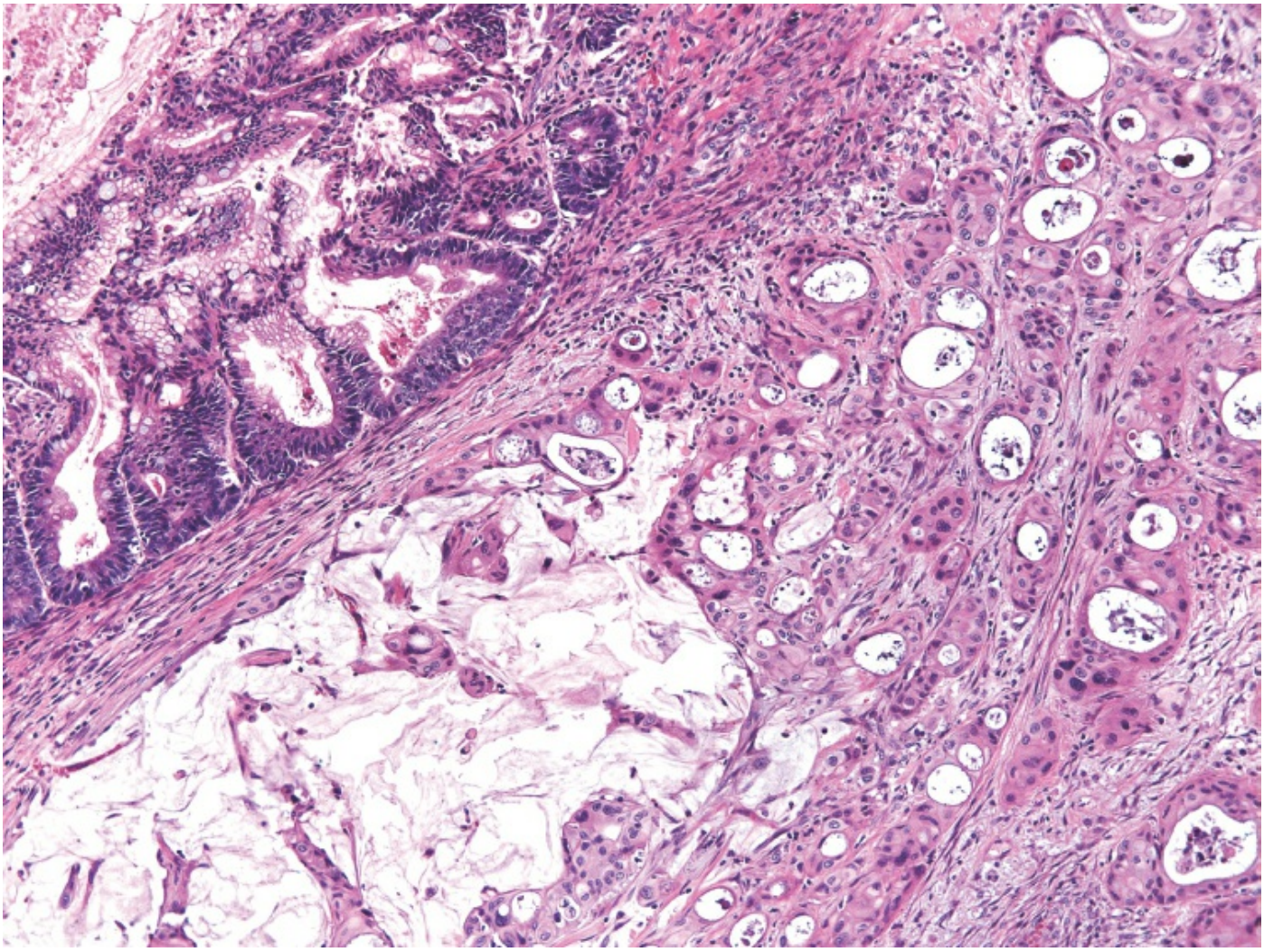


FIGURE 39-5 Mucinous adenocarcinoma of the ovary. Irregular glandular spaces are lined with a layer of tall columnar cells with abundant mucinous cytoplasm, resembling intestinal epithelium at the left. At the right, there is destructive invasion into the ovarian stroma.

Mucinous Carcinomas

Bilateral tumors occur in 8% to 10% of cases. The mucinous lesions are confined to the ovary in 95% to 98% of cases **(Fig. 39-5)**. Because most ovarian mucinous carcinomas contain enteric-type cells, they cannot be distinguished from metastatic carcinoma of the gastrointestinal tract on the basis of histology alone. Primary ovarian neoplasms rarely metastasize to the mucosa of the bowel, although they commonly involve the serosa, whereas gastrointestinal lesions frequently involve the ovary by direct extension or lymphatic spread (2).

Pseudomyxoma Peritonei

Pseudomyxoma peritonei is a clinical term used to describe the finding of abundant mucoid or gelatinous material in the pelvis and abdominal cavity surrounded by fibrous tissue. It is **most commonly secondary to a well-differentiated appendiceal mucinous neoplasm** or other gastrointestinal primary; rarely, mucinous tumors arising in an

ovarian mature teratoma are associated with pseudomyxoma peritonei.

Endometrioid Tumors

Endometrioid lesions constitute 6% to 8% of epithelial tumors. Endometrioid neoplasia includes all the benign demonstrations of endometriosis. In 1925, Sampson suggested that certain cases of adenocarcinoma of the ovary probably arose in areas of endometriosis (20). The adenocarcinomas are similar to those seen in the uterine corpus. The malignant potential of endometriosis is very low, although a transition from benign to malignant epithelium may be demonstrated.

Borderline Endometrioid Tumors

The endometrioid tumor of low malignant potential has a wide morphologic spectrum. Tumors may resemble an endometrial polyp or complex endometrial hyperplasia with glandular crowding. When there are back-to-back, architecturally complex glands with no intervening stroma, the tumor is classified as a well-differentiated endometrioid carcinoma. Some borderline endometrioid tumors have a prominent fibromatous component. In such cases, the term *adenofibroma* is used to describe them (2).

Endometrioid Carcinomas

Endometrioid tumors are characterized by a markedly complex glandular pattern with all the potential variations of epithelia found in the uterus **(Fig. 39-6)**.

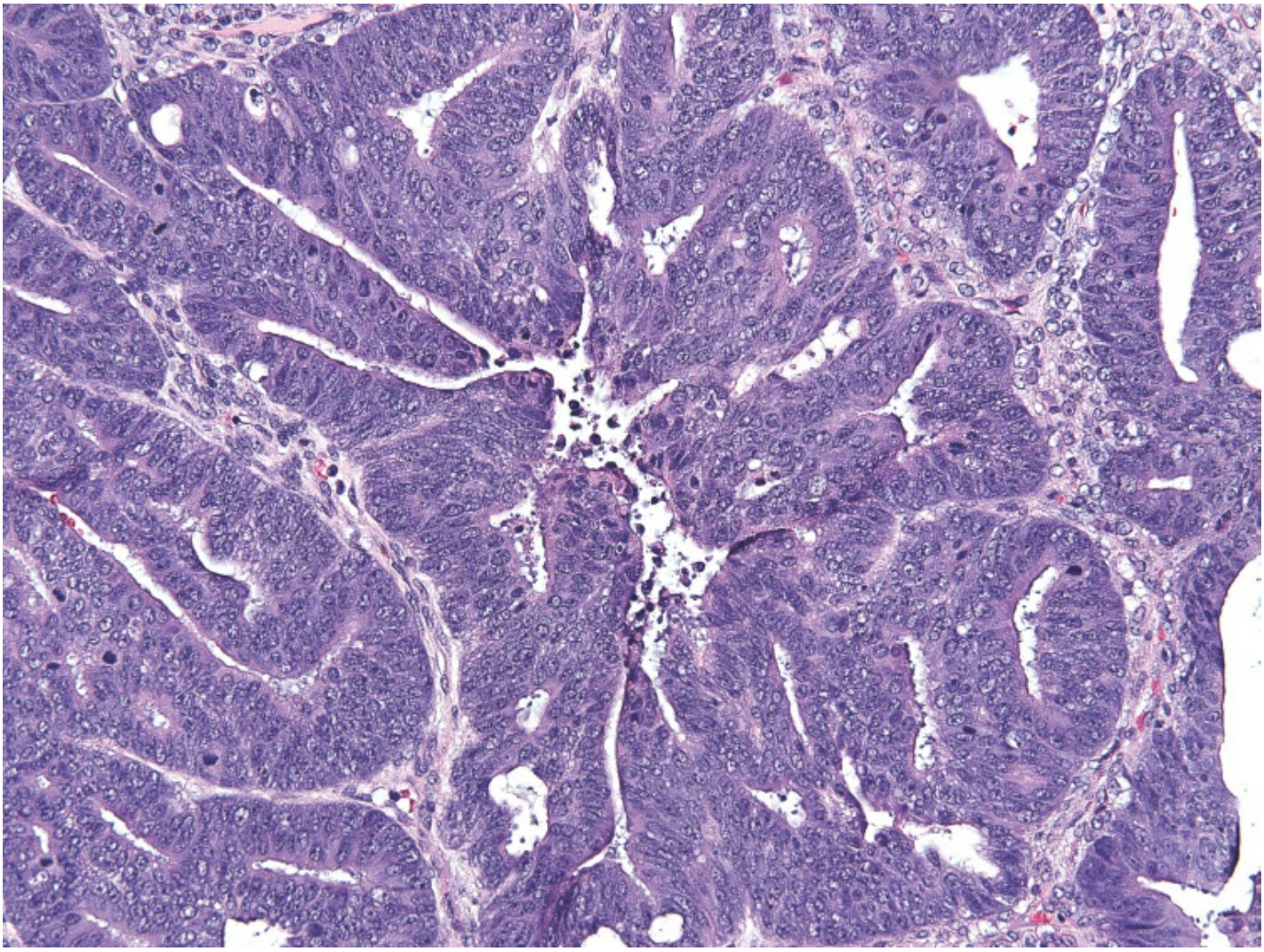


FIGURE 39-6 Endometrioid cancer. Round to tubular glands lined by stratified columnar cells with a confluent growth pattern.

Multifocal Disease

The endometrioid tumors afford the greatest opportunity to evaluate multifocal disease. **Endometrioid carcinoma of the ovary is associated in 15% to 20% of the cases with carcinoma of the endometrium. Identification of multifocal disease is important because patients with disease metastatic from the uterus to the ovaries have a 30% to 40% 5-year survival, whereas those with synchronous multifocal disease have a 75% to 80% 5-year survival** (21). When the histologic appearance of endometrial and ovarian tumors is different, the two tumors most likely represent two separate primary lesions. When they appear similar, the endometrial tumor can be considered a separate primary tumor if it is well differentiated and only superficially invasive.

Clear Cell Carcinomas

Several basic histologic patterns are present in the clear cell adenocarcinoma (i.e.,

tubulocystic, papillary, reticular, and solid). The tumors are made up of clear and hobnail cells that project their nuclei into the apical cytoplasm. The clear cells have abundant clear or vacuolated cytoplasm, hyperchromatic irregular nuclei, and nucleoli of various sizes **(Fig. 39-7)**. **Focal areas of endometriosis are common and mixed clear cell and endometrioid carcinoma may occur** (21). The clear cell carcinoma seen in the ovary is histologically identical to that seen in the uterus or vagina of the young patient who has been exposed to *diethylstilbestrol* (DES) *in utero.* **Almost invariably high-grade nuclei are identified. Hence, clear cell carcinomas are not graded.**

Transitional (Brenner) Tumors

Borderline Brenner Tumors

Proliferative Brenner tumors were previously subclassified as proliferating tumors (those tumors that resemble low-grade papillary urothelial carcinoma of the urinary bladder) and borderline tumors (those tumors that resemble high-grade papillary urothelial carcinoma), these groups of tumors are now classified as borderline Brenner tumors (22). Complete surgical removal usually results in cure.

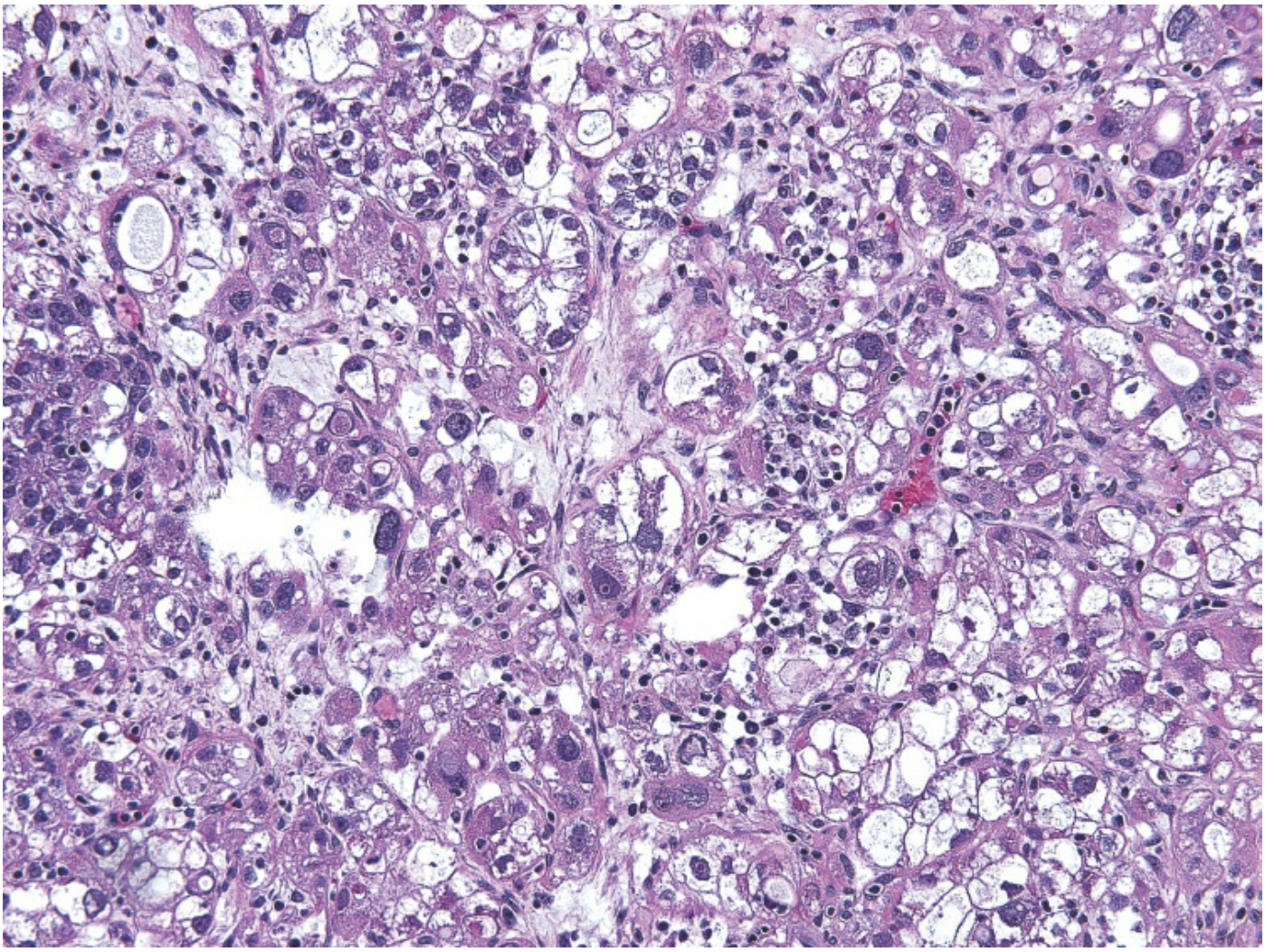


FIGURE 39-7 Clear cell carcinoma of the ovary. Note the solid variant of clear cell carcinoma with sheets of cells that have clear cytoplasm ("hobnail" cells).

Malignant Brenner Tumors

These rare tumors are defined as benign or borderline Brenner tumors coexisting with invasive transitional cell carcinoma.

Transitional Cell Carcinoma

The designation *transitional cell carcinoma* has been attributed to primary ovarian carcinoma resembling transitional cell carcinoma of the urinary bladder without a recognizable Brenner tumor. It is now thought that these are a variant of high-grade serous carcinoma and do not represent a distinct epithelial subtype of carcinoma (23,24). Unlike malignant Brenner tumors these tumors are more frequently diagnosed in an advanced stage and are associated with a survival rate similar to that of high-grade serous carcinoma (25).

Peritoneal Carcinomas

Peritoneal tumors are histologically indistinguishable from ovarian and fallopian tube serous tumors. In the case of ***borderline serous peritoneal tumors*** and ***serous peritoneal carcinomas*****,** the ovaries are normal or minimally involved, and the tumors affect predominantly the uterosacral ligaments, pelvic peritoneum, or omentum. The overall prognosis for borderline serous peritoneal tumors is excellent and comparable to that of ovarian borderline serous tumors (26–28). In the review of 38 cases of peritoneal borderline serous tumors from the literature, 32 women had no persistent disease, 4 were well after resection of recurrence, 1 developed an invasive serous carcinoma, and 1 died from the effects of the tumor (26).

Carcinomas that appear to be predominantly peritoneal without appreciable ovarian or fallopian tube enlargement have traditionally been called *peritoneal carcinoma,* when tumors spread from the breast, gastrointestinal tract, and other organs of non-müllerian origin are excluded. Most are *peritoneal serous carcinomas*, and have the appearance of a moderately to poorly differentiated serous ovarian carcinoma. Peritoneal endometrioid carcinoma also occurs, but is less common; peritoneal clear cell carcinoma is rare.

[15] Peritoneal serous carcinoma should be considered clinically the same as ovarian and fallopian tube cancers, as all these cancers share a similar pathogenesis and clinical behavior and treatment. Patients in whom exploratory surgery is performed, there may be microscopic or small macroscopic cancer on the surface of the ovary and extensive disease in the upper abdomen, particularly in the omentum (29).

Mesotheliomas

Peritoneal malignant mesotheliomas may be epithelial, sarcomatous, or biphasic (2,30). Deciduoid peritoneal mesothelioma is an unusual variant that resembles exuberant, ectopic decidual reaction of the peritoneum. Asbestos exposure is not correlated with peritoneal mesotheliomas in women. These lesions typically appear as multiple intraperitoneal (IP) masses, often coating the entire peritoneum and can develop after hysterectomy and bilateral salpingo-oophorectomy for benign disease. Malignant mesotheliomas should be distinguished from benign multicystic peritoneal mesothelioma (multilocular peritoneal inclusion cyst), and ovarian tumor implants and primary peritoneal müllerian neoplasms.

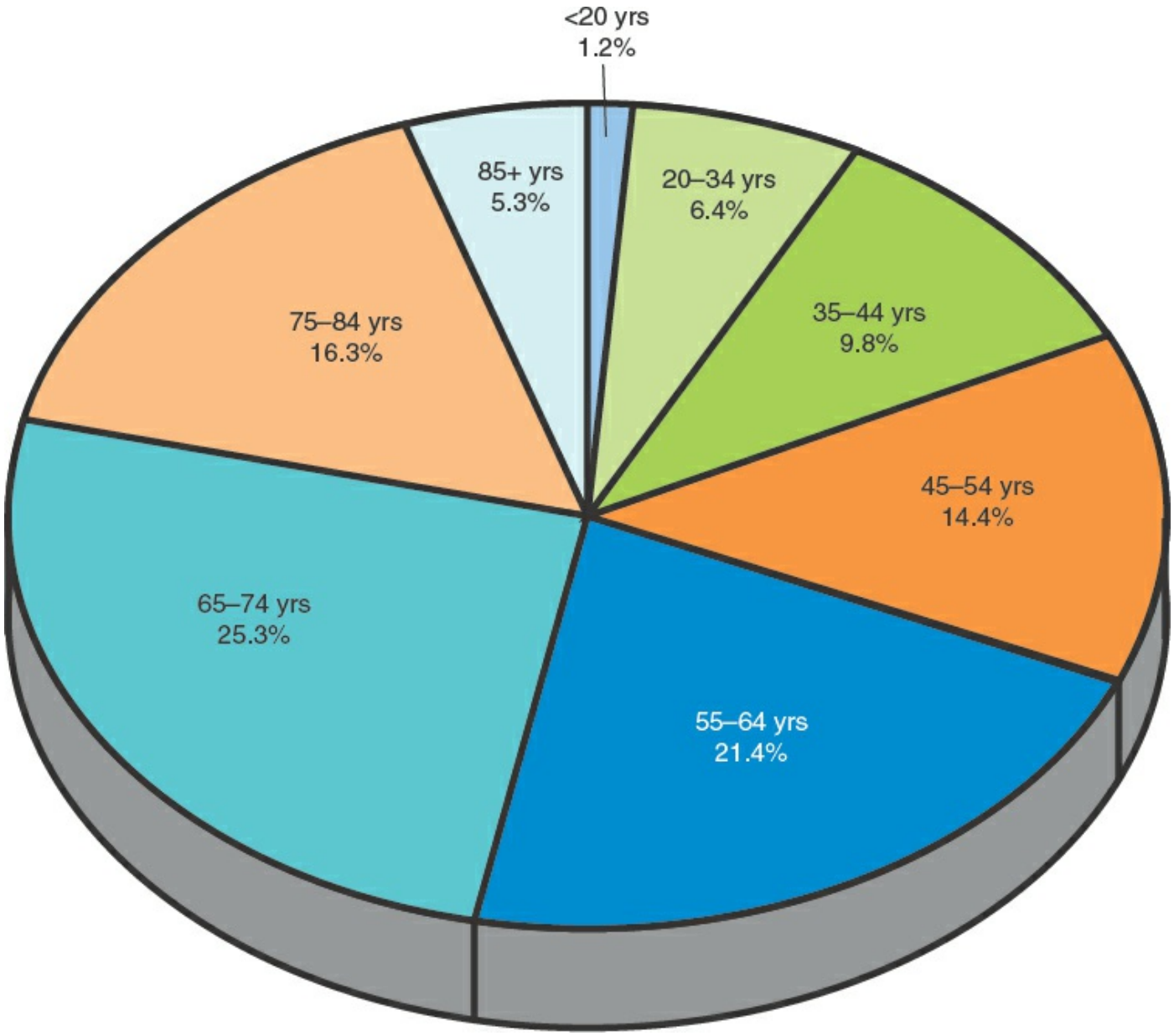


FIGURE 39-8 Ovarian cancer incidence: distribution by age. (From **Nagy K.** The side effects of managed care on the drug industry. J Natl Cancer Inst 1995;87:1280, with permission.)

Clinical Features

More than 80% of epithelial ovarian cancers are found in postmenopausal women **(Fig. 39-8)**. **The peak incidence of invasive epithelial ovarian cancer is at 56 to 60 years of age** (2,3). The age-specific incidence of ovarian epithelial cancer rises precipitously from 20 to 80 years of age and subsequently declines. These cancers are relatively uncommon in women younger than age 45. Fewer than 1% of epithelial ovarian cancers occur before the age of 21 years, two-thirds of ovarian malignancies in such patients being germ cell tumors (2,31). **[1] About 30% of ovarian neoplasms in women are malignant, whereas only about 7% of ovarian epithelial tumors in premenopausal patients are malignant** (2,3).

The average age of patients with borderline tumors is approximately 46 years (2,3,9). Eighty percent to 90% of ovarian cancers, including borderline forms, occur after the age of 40 years, whereas 30% to 40% of malignancies occur after the age of 65 years. The chance that a primary epithelial tumor will be of borderline or invasive malignancy in a patient younger than 40 years is approximately 1 in 10, but after that age it rises to 1 in 3 (2,3). Less than 1% of epithelial ovarian cancers occur before the age of 20 years, with two-thirds of ovarian malignancies in such patients being germ cell tumors (31).

Etiology

[2] Ovarian cancer is associated with low parity and infertility (32). Although there are a variety of epidemiologic variables correlated with ovarian cancer, such as talc use, galactose consumption, and tubal ligation, none is as strongly correlated as prior reproductive history and duration of the reproductive career (32,33). Early menarche and late menopause increase the risk of ovarian cancer (33). These factors and the relationship of parity and infertility to the risk of ovarian cancer led to the hypothesis that suppression of ovulation may be an important factor.

Prevention

[2] Because parity is inversely related to the risk of ovarian cancer, having at least one child is protective for the disease, with a risk reduction of 0.3 to 0.4. Oral contraceptive use reduces the risk of epithelial ovarian cancer [3] (32). **Women who use oral contraceptives for 5 or more years reduce their relative risk to 0.5 (i.e., there is a 50% reduction in the likelihood of development of ovarian cancer).** Women who had two children and used oral contraceptives for 5 or more years have a relative risk of ovarian cancer as low as 0.3, or a 70% reduction (34). **The oral contraceptive pill is the only documented method of chemoprevention for ovarian cancer, and it should be recommended to women for this purpose. When counseling**

patients regarding birth control options, this important benefit of oral contraceptive use should be emphasized. This is important for women with a strong family history of ovarian cancer.

The performance of a prophylactic salpingo-oophorectomy significantly reduces, but does not totally eliminate, the risk of nonuterine pelvic cancers; because the entire peritoneum is at risk, peritoneal carcinomas can occur in 2% to 3% of women even after prophylactic bilateral salpingo-oophorectomy (26,29).

A thorough discussion of the risks and benefits of oophorectomy should be undertaken in premenopausal women who are undergoing a hysterectomy for benign disease, do not carry germline mutations, and do not have a family history that suggests that they are at higher than average risk for ovarian cancer (35). **The ovaries may provide protection from cardiovascular disease and osteoporosis, and long-term mortality may not be decreased by the performance of prophylactic oophorectomy in women at population risk of ovarian cancer** (36).

Screening

CA-125 is useful for monitoring epithelial ovarian cancer patients during their chemotherapy; and is elevated in 50% of patients with stage I disease and in 80% to 90% of patients with advanced serous cancers **(**37–46). Transvaginal ultrasonography is useful to characterize the morphology of ovarian tumors (47,48). However, **the value of tumor markers and ultrasonography to screen for epithelial ovarian cancer is not established by prospective studies** (49). **[4] The use of transvaginal ultrasound alone or in combination with CA-125 for early ovarian cancer detection has not proven effective in average-risk women to decrease mortality from ovarian cancer, instead there are harms to this strategy, including false-positive results and more invasive procedures being performed such as surgery** (50). The inability to use these modalities for screening is discussed in the American College of Obstetricians and Gynecologists (ACOG) committee opinion (51).

The U.S. Preventative Services Task Force (USPSTF) recommends against screening asymptomatic women for ovarian cancer with pelvic examination, pelvic ultrasound, or serum tumor marker measurements (52). **The USPSTF concluded that there is adequate evidence that there is no mortality benefit to routine screening for ovarian cancer with transvaginal ultrasonography or single-threshold serum CA-125 testing and that the harms of such screening are at least moderate. There is no effective strategy for early detection of ovarian cancer that translates to a reduction in ovarian cancer mortality** (52). **Ultrasonography, despite being able to detect changes in size and morphology of the ovaries, has not been shown be effective for ovarian cancer screening** (2,5).

Final results from United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which is fully accrued and follow-up is pending, should provide more information about the relative benefits and harms of an algorithm-based approach to screening for ovarian cancer. In the **UKCTOCS study**, 202,638 healthy average-risk postmenopausal patients in the age range 50 to 74 years were randomized to receive no screening, annual pelvic ultrasound or multimodal screening using a combination of CA-125 testing (interpreted using risk of ovarian cancer algorithm [ROCA]) and ultrasound triggered by a ROCA score signifying increased risk. Multimodal screening with the ROCA was superior to using fixed CA-125 cut-off values in combination with ultrasound screening (positive predictive value = 35.1%). Ten women had surgical intervention because of a false-positive screening result, demonstrating that the harm related to unnecessary surgical procedures as a consequence of a false-positive test can occur (50,53). Thus far, follow-up data has not shown a significant reduction of ovarian cancer mortality with multimodal screening when compared with no screening (50,54).

The **ROCA** uses serially measured CA-125 and mathematical modeling to determine whether an increase in levels should prompt referral for ultrasound and has a better predictive performance for detecting ovarian cancer than using a fixed CA-125 value cut-off (55,56–59). The U.S. Food and Drug Administration (FDA) has warned that early detection tests, including the ROCA test, are unreliable (60).

Other large prospective randomized trials in the United States and the United Kingdom sought to address the utility of a multimodality assessment for early detection of ovarian cancer. In the US-based **Prostate, Lung, Colorectal, and Ovarian (PLOC) Cancer Screening Trial,** 78,216 healthy average-risk women between age 55 and 74 years were randomized to have either annual CA-125 testing for 6 years and transvaginal ultrasound examination for 4 years (tested group) versus the "usual care" who were patients not offered this testing, many of these patients did have annual pelvic examinations. There was an ovarian cancer mortality rate of 3.1 deaths per 10,000 person-years versus 2.6 deaths per 10,000 person-years in the tested group versus usual care group respectively, after a median follow-up period of 12.4 years. **This study also showed that using a baseline and annual measurement of CA-125 with a cut-off (35 U/mL) in combination with pelvic ultrasound as a way for early assessment does not result in decreased ovarian cancer mortality** (45,61). **Thus far, this large trial showed that screening women at average risk with annual transvaginal ultrasound provided no mortality benefit when compared with no screening.**

In the future, new markers or technologies may improve the specificity of ovarian cancer screening, but proof of this will require a large, prospective study (41,42).

Screening in women who have a familial risk may provide a better yield, but **there is no evidence to demonstrate a benefit of screening high-risk women,** even with

active investigation (62,63). The findings of two prospective studies of annual transvaginal ultrasound and CA-125 screening in 888 *BRCA1* and *BRCA2* mutation carriers in the Netherlands and 279 mutation carriers in the United Kingdom are not encouraging and suggest a very limited benefit of screening in high-risk women (62,64). Despite annual gynecologic screening, Hermsen et al. reported that a high proportion of ovarian cancers in *BRCA1* and *BRCA2* carriers were interval cancers and the large majority of all cancers diagnosed were at advanced stages; similar results were reported by Woodward et al. (62,64).

Women with particular genetic syndromes are at increased risk of ovarian cancer, for example patients with a BRCA gene mutation or Lynch syndrome (hereditary nonpolyposis colorectal cancer). These patients should be referred to genetic counseling to have an evaluation in order to properly quantify their level of risk and have a discussion about the available risk reduction strategies.

Genetic Risk for Epithelial Ovarian Cancer

The lifetime risk of ovarian carcinoma for women in the United States is about 1.4% (2,4,65). The risk of ovarian cancer is higher than that in the general population in women with certain family histories (55,62–64,66–71). **[5] Most epithelial ovarian cancer is sporadic, with causes accounting for up to 24% of invasive epithelial ovarian cancer** (14).

Hereditary Ovarian Cancer

BRCA1 and BRCA2

Most hereditary ovarian cancers result from pathogenic mutations in either the *BRCA1* or *BRCA2* genes. Many studies have found that at least 15% of women with high-grade nonmucinous ovarian cancers have germline mutations in *BRCA1*/*BRCA2* and almost 40% of these women do not have a family history of breast/ovarian cancer (71). There are other low-to-moderate–penetrance genes that predispose to ovarian cancer, and this is an area of intense research interest (65,72,73). Norquist et al. used next-generation sequencing of constitutional DNA samples from over 1,900 women with ovarian cancer to identify germline mutations in a panel of 20 genes, including *BRCA1* and *BRCA2*, DNA mismatch repair genes, double-stranded DNA break repair genes such as CHEK2 and ATM, and the *BRCA1*-associated complex or the *BRCA2*/Fanconi Anemia pathway genes (including *BRIP1, BARD1, PALB2, RAD50, RAD51C, RAD51D* among others). About 80% of mutations were in *BRCA1* or *BRCA2*. Approximately 3% of patients carried mutations in the Fanconi Anemia pathway genes, while only 0.4% had mutations in mismatch repair genes (74).

[6] The mutations are inherited in an autosomal dominant fashion, and therefore a full pedigree analysis (i.e., maternal and paternal sides of the family) is essential

when taking a family history. All women with high-grade invasive ovarian cancers should be offered genetic testing, even if they do not have a family history of breast/ovarian cancer (75). A very large study that followed women enrolled in familial cancer registries primarily in the United Kingdom, Holland, and France provides the most comprehensive data on the risk of ovarian cancer and breast cancer in BRCA mutation carriers. Women were recruited into this cohort from 1997 to 2011 and had not undergone risk-reducing breast or gynecologic surgery; follow-up continued until 2013 (median, 5 years). A total of 6,036 *BRCA1* and 3,820 *BRCA2* mutation carriers were followed (median age at study entry, 38). The cumulative risk for breast cancer by age 80 was 72% in *BRCA1* carriers and 69% in *BRCA2* carriers. For ovarian cancer, the cumulative risk was 44% and 17%, respectively. The peak breast cancer incidence occurred at age 41 to 50 for *BRCA1* carriers and age 51 to 60 for *BRCA2* carriers. The incidence of ovarian cancer was 3.6 times higher among *BRCA1* than *BRCA2* carriers.

[5] Hereditary ovarian cancers occur in women who are approximately 10 years younger than those with nonhereditary tumors (i.e., closer to age 50 compared to age 60 for those with sporadic cancer) (70). A woman with a first- or second-degree relative who had premenopausal ovarian cancer may have a higher probability of being a BRCA carrier. Women with BRCA germline mutations tend to be diagnosed at a younger age than women with sporadic ovarian cancers. In women with *BRCA1* mutations, less than 2% to 3% of carriers develop ovarian cancer by the age of 40 which increases to 10% to 21% by the age of 50. In women with *BRCA2* mutations, less than 3% of carriers develop ovarian cancer by the age of 50 and most develop after age 50. Most BRCA ovarian cancers are high-grade serous carcinomas **(Fig. 39-9)**.

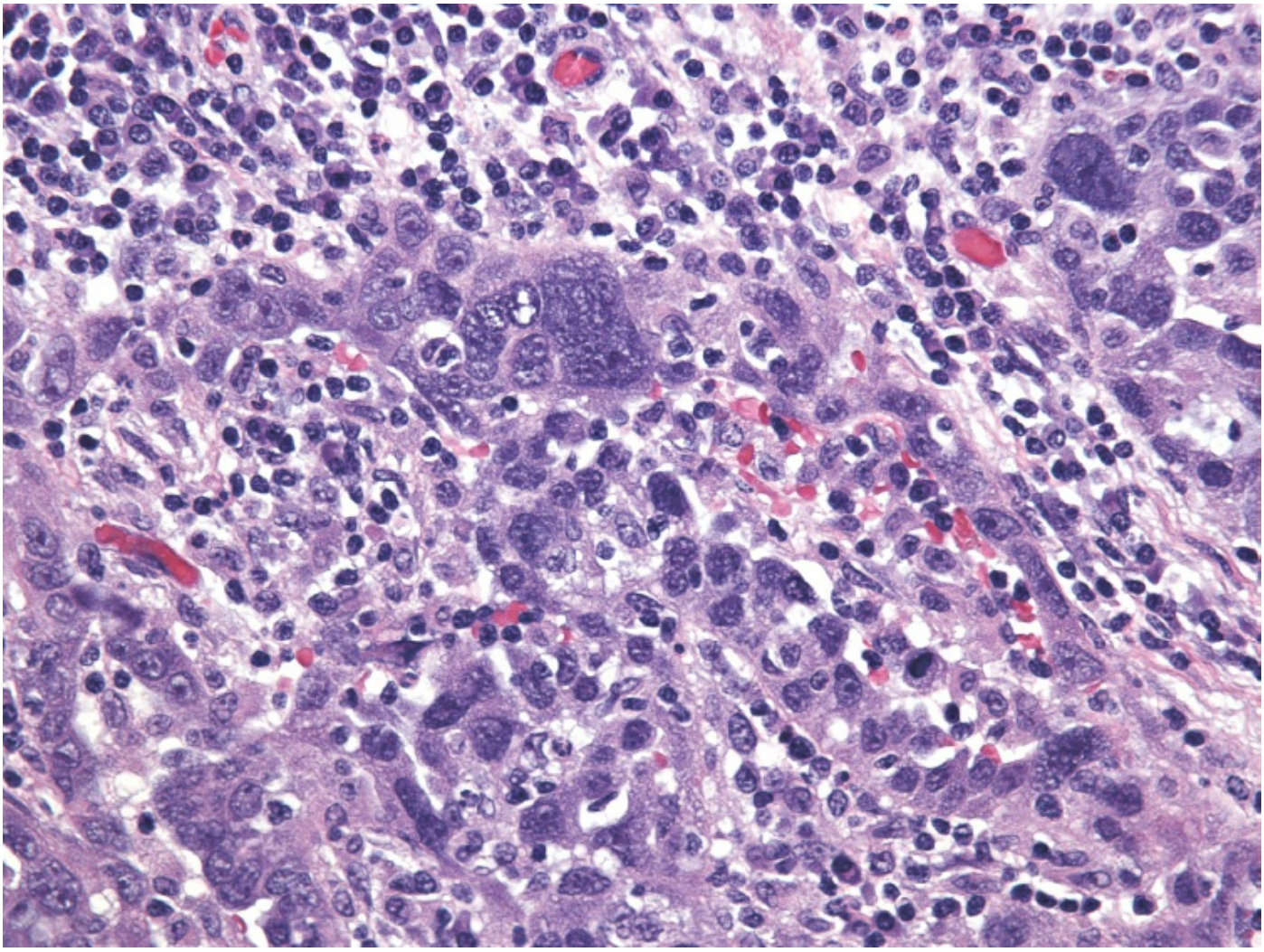


FIGURE 39-9 *BRCA1*-associated ovarian carcinoma is typically a high-grade serous adenocarcinoma with numerous mitotic figures and marked nuclear pleomorphism. A brisk lymphocytic infiltrate with tumor-infiltrating lymphocytes is not uncommon in these tumors.

Founder Effect

There is a higher carrier rate of *BRCA1* and *BRCA2* mutations in women of Ashkenazi Jewish descent, Icelandic women, and many other ethnic groups (76–81). There are three specific founder mutations carried by the Ashkenazi population, 185delAG and 5382insC on *BRCA1*, and 6174delT on *BRCA2*. **Individuals of Ashkenazi Jewish descent have a 1 in 40, or 2.5%,** chance of having a mutation in *BRCA1* or *BRCA2*, in contrast to a 1 in 500 risk in the Caucasian population (82). The increased risk is a result of the *founder effect*, in which a higher rate of specific mutations occurs in an ethnic group from a defined geographic area. These founder mutations generated considerable interest, because they facilitate studies of prevalence and penetrance and can be used to quantify the degree of homogeneity within a population.

Pedigree Analysis

[6] The risk of carrying a germline mutation that predisposes to ovarian cancer depends on the number of first- or second-degree relatives (or both) with a history of epithelial ovarian carcinoma or breast cancer (or both) and on the number of malignancies that occur at an earlier age. The degree of risk is difficult to determine precisely without performing a full pedigree analysis. It is important to be aware that 40% of women with BRCA-related ovarian cancer do not have a family history.

Lynch Syndrome or Hereditary Nonpolyposis Colon Cancer

Lynch syndrome (HNPCC), which includes multiple adenocarcinomas, involves a combination of colon cancer and endometrial or ovarian cancer and other malignancies of the gastrointestinal and genitourinary systems (83). **The chief gene mutations that are associated with this syndrome include *MSH2*, *MLH1*, *MSH6*, and *PMS2* or the *EPCAM* gene.** The risk that a woman who is a member of one of these families will develop epithelial ovarian cancer depends on the frequency of this disease in first- and second-degree relatives, although these women appear to have at least three times the relative risk of the general population. A full pedigree analysis of such families should be performed by a geneticist to more accurately determine the risk.

Management of Women at High Risk for Ovarian Cancer

The management of an unaffected woman with a germline BRCA (gBRCA) mutation or a strong family history of epithelial ovarian cancer where a mutation has not been found must be individualized and depends on her age, reproductive plans, and the estimated risk. All these women should be seen by a geneticist in a high-risk clinic. Decisions about management are best made after careful study and, whenever possible, verification of the histologic diagnosis of the family members' ovarian cancer.

The value of testing for *BRCA1* and *BRCA2* is well **established, and there are guidelines for testing** (75,82,84,85). Essentially all women with epithelial ovarian cancer, excluding mucinous cancers, should be offered testing irrespective of whether she has a family history of breast/ovarian cancer. The American Society of Clinical Oncology offered guidelines that emphasize careful evaluation by geneticists, careful maintenance of medical records, and a genetic screening clinic with an understanding of how to effectively counsel and manage these patients. Concerns remain over the use of the information, impact on insurability, interpretation of the results, and how the information will be used within a specific family (e.g., to counsel children).

Although there are some conflicting data, the behavior of breast cancers arising in women with germline mutations in *BRCA1* or *BRCA2* is comparable to the behavior of sporadic tumors (86,87). **Women with breast cancer who carry these mutations are at a greatly increased risk of ovarian cancer and a second breast cancer: the**

lifetime risk of ovarian cancer is 54% for women who have a *BRCA1* mutation and 23% for those with a *BRCA2* mutation, and for the two groups together, there is an 82% lifetime risk of breast cancer (87).

[4] Despite recommendation by the National Institutes of Health Consensus Conference on Ovarian Cancer, the value of screening with transvaginal ultrasonography, CA-125 levels, or other procedures is not established in women at high risk (88). Bourne and coworkers showed that, using this approach, tumors can be detected approximately 10 times more often than in the general population, and they recommend screening in high-risk women, but other groups have not confirmed these findings, and bilateral salpingo-oophorectomy remains the most effective way to reduce the risk (89).

Data derived from a multicenter consortium of genetic screening centers indicate that the use of the oral contraceptive pill is associated with a lower risk for development of ovarian cancer in women who have a mutation in either *BRCA1* or *BRCA2* (90,91). The risk reduction is significant: in women who take oral contraceptives for 5 or more years, the relative risk of ovarian cancer is 0.4, or a 60% reduction in the incidence of the disease (92).

Prophylactic Salpingo-oophorectomy in High-Risk Women

[6] The value of prophylactic salpingo-oophorectomy in these patients is well established (93–99). Women at high risk for ovarian cancer who undergo prophylactic salpingo-oophorectomy have a risk of harboring occult neoplasia: in one series of 98 such operations, 3 (3.1%) patients were found to have an ovarian cancer or early invasive cancer in a fallopian tube (96). **[6] The protection against ovarian cancer is high: the performance of a prophylactic salpingo-oophorectomy reduced the risk of BRCA-related gynecologic cancer by 96%** (96). In a series of 42 such operations, 4 patients (9.5%) had a malignancy, 1 of which was noted at surgery and 3 that were microscopic; all were smaller than 5 mm (94). Although the risk of ovarian cancer is significantly diminished, there remains the small risk of peritoneal carcinoma. In these series, the subsequent development of peritoneal carcinoma was reported to be 0.8% and 1%, respectively (78,79). **The risk of developing subsequent breast cancer may be reduced by 50% to 80% in BRCA carriers. However, this has been challenged by a prospective study.** In an analysis stratified by BRCA mutation status and age at diagnosis, they found that oophorectomy was associated with a significantly reduced risk of breast cancer in *BRCA2* carriers diagnosed at age <50 years (age-adjusted hazard ratio [HR], 0.18; $p = 0.007$) but not among *BRCA1* carriers diagnosed at <50 years (age-adjusted HR, 0.79; $p = 0.51$). These findings warrant further evaluation (100).

The role of hysterectomy is more controversial. Most studies show no increase in

the rate of uterine and cervical tumors, but there are rare reports of an increase of serous tumors of the endometrium. A large multicenter prospective cohort study concluded that the overall risk of uterine cancer after a risk-reducing bilateral salpingo-oophorectomy was not increased; however, the risk of serous and serous-like uterine cancer was increased in *BRCA1*-positive women, although still very low, and the benefit of a hysterectomy remains uncertain (101). Women on *tamoxifen* are at higher risk for benign endometrial lesions (e.g., polyps) and endometrial cancer. **It is reasonable to consider the performance of a prophylactic hysterectomy in conjunction with salpingo-oophorectomy in women with BRCA mutations who are potentially at increased risk of an endometrial cancer,** but this decision should be individualized. The progression-free survival (PFS) of women who have a *BRCA1* or *BRCA2* mutation and develop ovarian cancer is longer than that for those who do not have a mutation. In one study, the median PFS for mutation carriers was 60 months compared with 22 months for controls. There was no difference in the overall survival between BRCA mutation carriers and controls (102). **BRCA patients have increased sensitivity to platinum drugs and to the newer agents, poly(ADP-ribose) polymerase (PARP) inhibitors. [10] The advent of PARP inhibitors and their increased use for recurrent disease and maintenance therapy, particularly in BRCA mutation carriers may translate to an improvement in the PFS and overall survival for BRCA patients.**

Recommendations

Recommendations for the management of women at high risk for ovarian cancer are based on the ACOG practice bulletin no. 182 and summarized as follows:

1. **Genetic counseling is recommended for all women with ovarian/fallopian tube/peritoneal epithelial cancer and for individuals who have a personal or family history of breast cancer or ovarian cancer.** Genetic testing is recommended when the results of a detailed risks assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome and when the results of testing are likely to influence medical management.
2. **Women who wish to preserve their reproductive capacity can undergo screening by transvaginal ultrasonography every 6 months or CA-125 measurement and this may be a reasonable short-term surveillance strategy for women at high risk of ovarian cancer starting at age 30 to 35 years until they decide to pursue definitive risk-reducing bilateral salpingo-oophorectomy.**
3. **Oral contraceptives should be recommended** to young women before they embark on an attempt to have a family.
4. **Women who do not wish to maintain their fertility or who have completed their families should be recommended to undergo prophylactic bilateral salpingo-**

oophorectomy after the age of 35, but by age 40 years. The risk of ovarian cancers under the age of 40 is very low but the decision regarding the age of surgery should be based on the age of onset of ovarian cancers in the family. Most *BRCA2*-related ovarian cancers tend to occur after the age of 50, whereas *BRCA1*-related cancers occur at an earlier age. **Typically, risk-reducing salpingo-oophorectomy is recommended at age 35 to 40 years for *BRCA1* carriers with the highest lifetime risk of ovarian cancer, whereas women with *BRCA2* may consider delaying until age 40 to 45 years because of later onset of ovarian cancer.** These women should be counseled that this operation does not offer absolute protection, because peritoneal carcinomas can occur after bilateral salpingo-oophorectomy (26,29,87).

5. **Women with BRCA mutations or who carry another actionable deleterious mutation that is predisposing to breast cancer should be offered risk-reducing bilateral mastectomy.** Women with BRCA mutations or who carry another actionable deleterious mutation that is predisposing to ovarian cancer should be offered risk-reducing bilateral salpingo-oophorectomy.
6. **For a risk-reducing bilateral salpingo-oophorectomy, all tissue from the ovaries and fallopian tubes should be removed.** Thorough visualization of the peritoneal surfaces should be done and pelvic washings taken. Complete serial sectioning of the ovaries and fallopian tubes is necessary with microscopic examination for occult cancer.
7. **For women aged 25 to 29 years with known BRCA mutations, recommended breast cancer surveillance includes clinical breast examination every 6 to 12 months and annual radiographic evaluation (preferably magnetic resonance imaging [MRI], with contrast). For women aged 30 years and older with known BRCA mutations or other actionable breast cancer mutations, recommended breast cancer surveillance includes annual mammography and annual breast MRI with contrast, often alternating every 6 months.**
8. **Women with a personal or family history of breast or ovarian cancer but who do not have a documented mutation in *BRCA1* or *BRCA2* or other hereditary breast- or ovarian-cancer–associated genes should be managed based on their family history.**
9. **Women with a documented Lynch syndrome (HNPCC) should undergo periodic colonoscopy every 1 to 2 years, starting at age 20 to 25 years or 2 to 5 years before the earliest colon cancer diagnosis in the family, depending on which is earlier. Endometrial biopsy every 1 to 2 years starting at age 30 to 35 years, is recommended for women with Lynch syndrome, prophylactic hysterectomy, and bilateral salpingo-oophorectomy is a risk-reducing option after the completion of childbearing. In general, risk-reducing hysterectomy and salpingo-**

oophorectomy should be discussed with patients by their early to mid-40s (103,104).

Symptoms

The majority of women with epithelial ovarian cancer have vague and nonspecific symptoms (4,105). In the early-stage disease, if the patient is premenopausal, she may experience irregular menses. If a pelvic mass is compressing the bladder or rectum, she may report urinary frequency or constipation (105–107). Occasionally, she may perceive lower abdominal distention, pressure, or pain, such as dyspareunia. Acute symptoms, such as pain secondary to rupture or torsion, shortness of breath from a malignant pleural effusion, or symptoms of a bowel obstruction are possible reasons for presentation.

In advanced-stage disease, patients have symptoms related to the presence of ascites, omental metastases, or bowel metastases. The symptoms include abdominal distention, bloating, constipation, nausea, anorexia, or early satiety. Premenopausal women may report irregular or heavy menses, whereas vaginal bleeding may occur in postmenopausal women but this is not a typical presentation of ovarian cancer unless the ovarian tumors are estrogen producing (107).

Traditionally, ovarian cancer was considered a "silent killer" that did not produce symptoms until far advanced. Some patients with ovarian cancers confined to the ovary are asymptomatic, but the majority will have nonspecific symptoms that do not necessarily suggest an origin in the ovary (107,108–110). In one survey of 1,725 women with ovarian cancer, 95% recalled symptoms before diagnosis, including 89% with stages I and II disease and 97% with stages III and IV disease (107). Some 70% had abdominal or gastrointestinal symptoms, 58% pain, 34% urinary symptoms, and 26% pelvic discomfort. At least some of these symptoms could have reflected pressure on the pelvic viscera from the enlarging ovary. Goff et al. developed an ovarian cancer symptom index and reported that symptoms associated with ovarian cancer, when present for less than 1 year and occurring longer than 12 days a month, were pelvic/abdominal pain, urinary frequency/urgency, increased abdominal size or bloating, and difficulty eating or feeling full (108). The index had a sensitivity of 56.7% for early ovarian cancer and 79.5% for advanced-stage disease. This study and others suggest that women and their obstetrician–gynecologist should maintain an appropriate level of suspicion for further investigation when potential symptoms and signs of ovarian, fallopian tube, or peritoneal cancer may be present.

A population-based study from Australia found that there did not appear to be a significant difference in the duration of symptoms or the nature of symptoms in patients with early as opposed to advanced-stage ovarian cancer, reinforcing the concept that they are biologically different entities and arguing against the widely held

misconception that early-stage ovarian cancers are at an early stage because they were diagnosed earlier than patients with more advanced-stage cancers (109). For fallopian tube carcinoma, the classic triad of symptoms that have been reported include clear or blood-tinged vaginal discharge, pelvic pain, and a finding of a pelvic mass. The vaginal discharge termed *hydrops tubae profluens* historically has been considered pathognomonic of fallopian tube cancer; however, in retrospect, these signs are uncommon.

Signs

The most important sign of epithelial ovarian cancer is the presence of a pelvic mass on physical examination. A solid, irregular, fixed pelvic mass is highly suggestive of an ovarian malignancy. If an upper abdominal mass or ascites is present, the diagnosis of ovarian cancer is almost certain. Because the patient usually reports abdominal symptoms, she may not have a pelvic examination, and a tumor may be missed.

In patients who are at least 1 year past menopause, the ovaries should be atrophic and not palpable. It was proposed that any palpable pelvic mass in these patients should be considered potentially malignant, a situation that was referred to as the postmenopausal palpable ovary syndrome (111). This concept was challenged, because subsequent authors reported that only about 3% of palpable masses measuring less than 5 cm in postmenopausal women are malignant (63). Atypical glandular cells on cervical pathology may signal an upper genital tract malignancy. This finding on a Papanicolaou (Pap) test should prompt further evaluation for cervical or endometrial carcinoma. If there are no findings to suggest these cancers, evaluation should continue for other malignancies of the female genital tract. In a systematic review of approximately 7,000 women with atypical glandular cells on a Pap test only 5.2% of patients had a malignancy. Among patients with a malignancy, there were 5.4% ovarian cancers and 1.0% fallopian tube cancers (112).

Women with ovarian cancer can rarely present with signs of a paraneoplastic syndrome, which may include disseminated intravascular coagulation, polyneuritis, dermatomyositis, hemolytic anemia, and cerebellar degeneration (113).

Diagnosis

Ovarian epithelial cancers must be differentiated from benign neoplasms and functional cysts of the ovaries. A variety of benign conditions of the reproductive tract, such as pelvic inflammatory disease, endometriosis, and pedunculated uterine leiomyomas, can simulate ovarian cancer. Nongynecologic causes of a pelvic tumor, such as an inflammatory (e.g., diverticular) disease or neoplastic colonic mass, must be excluded (4). A pelvic kidney can simulate ovarian cancer.

Serum CA-125 levels are useful in distinguishing malignant from benign pelvic masses (114). **For a postmenopausal patient with an adnexal mass and a very high serum CA-125 level (>200 U/mL), there is a 96% positive predictive value for malignancy. For premenopausal patients, the specificity of the test is low because the CA-125 level tends to be elevated in common benign conditions.**

For the premenopausal patient, a period of observation is reasonable, provided the adnexal mass does not have characteristics that suggest malignancy (i.e., it is mobile, mostly cystic, unilateral, and of regular contour). An interval of no more than 2 months is allowed, during which hormonal suppression with an oral contraceptive may be used. If the lesion is not neoplastic, it should regress, as measured by pelvic examination and pelvic ultrasonography. If the mass does not regress or if it increases in size, it must be presumed to be neoplastic and must be removed surgically.

The size of the lesion is important. If a cystic mass is greater than 8 cm in diameter, the probability is high that the lesion is neoplastic, unless the patient is taking *clomiphene citrate* or other agents to induce ovulation (115–118). **Premenopausal patients whose lesions are clinically suspicious (i.e., large, predominantly solid, relatively fixed, or irregularly shaped) should undergo laparoscopy or laparotomy with keen attention to avoid intraoperative rupture or spillage, as should postmenopausal patients with complex adnexal masses of any size. Image-guided biopsy is not performed for fear of rupture and seeding a potential malignancy.**

Ultrasonographic signs of malignancy include an adnexal pelvic mass with areas of complexity, such as irregular borders, multiple echogenic patterns within the mass, and dense multiple irregular septae. Bilateral tumors are more likely to be malignant, although the individual characteristics of the lesions are of greater significance. Transvaginal ultrasonography may have a somewhat better resolution than transabdominal ultrasonography for adnexal neoplasms (119–122). Doppler color flow imaging may enhance the specificity of ultrasonography for demonstrating findings consistent with malignancy (123–125).

In postmenopausal women with unilocular cysts measuring 8 to 10 cm or less and normal serial CA-125 levels, expectant management is acceptable, and this approach may decrease the number of surgical interventions (126–128).

The suspicion of ovarian cancer or the diagnosis of an ovarian cancer requires surgical exploration by a gynecologic oncologist, which may be by an exploratory laparotomy or a minimally invasive technique such as laparoscopy or a robotic platform. The preoperative evaluation of the patient with an adnexal mass is outlined in Figure 10.2 (see Chapter 10, page 201).

Before the planned exploration, the patient should undergo routine hematologic and biochemical assessments. A preoperative evaluation in a patient undergoing laparotomy should include a radiograph of the chest. Abdominal and pelvic computed tomography

(CT) or magnetic resonance imaging (MRI) are of limited value for a patient with a definite pelvic mass (129–131). A CT or MRI should be performed for patients with ascites and no pelvic mass to look for liver or pancreatic tumors. The findings only rarely preclude laparotomy (129). The value of PET scanning is still being evaluated (131–133). If the hepatic enzyme values are normal, the likelihood of liver disease is low. Liver–spleen scans, bone scans, and brain scans are unnecessary unless symptoms or signs suggest metastases to these sites.

The preoperative evaluation should exclude other primary cancers metastatic to the ovary. A barium enema or colonoscopy is indicated in selected patients with symptoms and signs suspicious for colon cancer. This study should be performed for any patient who has evidence of occult blood in the stool or has signs of lower intestinal obstruction. An upper gastrointestinal radiographic series or gastroscopy is indicated if there are upper gastrointestinal symptoms such as nausea, vomiting, or hematemesis (4,134). Bilateral diagnostic mammography is indicated if there is any breast mass, because breast cancer metastatic to the ovaries can simulate primary ovarian cancer.

A Pap test can be performed, although its value for the detection of ovarian cancer is very limited. Patients who have irregular menses or postmenopausal vaginal bleeding should have endometrial biopsy and endocervical curettage to exclude the presence of uterine or endocervical cancer metastatic to the ovary.

Differential Diagnosis

Ovarian epithelial cancers must be differentiated from benign neoplasms and functional cysts of the ovaries (126–128). **A variety of benign conditions of the reproductive tract, such as pelvic inflammatory disease, endometriosis, and pedunculated uterine leiomyomata, can simulate ovarian cancer.** Nongynecologic causes of a pelvic tumor, such as an inflammatory or neoplastic colonic mass, must be excluded. Gastrointestinal and breast cancers are the most common nongenital malignancies that metastasize to the ovary (135,136).

Patterns of Spread

Ovarian epithelial cancers spread primarily by exfoliation of cells into the peritoneal cavity, lymphatic dissemination, and hematogenous spread.

Transcoelomic

The most common and earliest mode of dissemination of ovarian epithelial cancer is by exfoliation of cells that implant along the surfaces of the peritoneal cavity. The cells tend to follow the circulatory path of the peritoneal fluid. The fluid moves with the forces of respiration from the pelvis, up the paracolic gutters, especially on the right, along the intestinal mesenteries, to the right hemidiaphragm. Metastases are typically seen on the posterior cul-de-sac, paracolic gutters, right hemidiaphragm, liver capsule,

the peritoneal surfaces of the intestines and their mesenteries, and the omentum. The disease seldom invades the intestinal lumen but progressively agglutinates loops of bowel, leading to a functional intestinal obstruction. This condition is known as carcinomatous ileus (4).

Lymphatic

Lymphatic dissemination to the pelvic and para-aortic lymph nodes is common, particularly in advanced-stage disease (137–139). Spread through the lymphatic channels of the diaphragm and through the retroperitoneal lymph nodes can lead to dissemination above the diaphragm, especially to the supraclavicular lymph nodes (137). Burghardt et al. reported that 78% of patients with stage III disease have metastases to the pelvic lymph nodes (139). In another series, the rate of para-aortic lymph nodes positive for metastasis was 18% in stage I, 20% in stage II, 42% in stage III, and 67% in stage IV (137).

Hematogenous

Hematogenous dissemination at the time of diagnosis is uncommon. Spread to vital organ parenchyma, such as the lungs and liver, occurs in only about 2% to 3% of patients. Most patients with disease above the diaphragm when diagnosed have a right pleural effusion (4). Systemic metastases appear more frequently in patients who survived for some years. Dauplat et al. reported that distant metastasis consistent with stage IV disease ultimately occurred in 38% of the patients whose disease was originally IP (140).

Prognostic Factors

The outcome of treatment can be evaluated in the context of prognostic factors, which can be grouped into pathologic, biologic, and clinical factors (141).

Pathologic Factors

The morphology and histologic pattern, including the architecture and grade of the lesion, are important prognostic variables (4). The histologic type was not believed to have prognostic significance, but several papers contained suggestions that clear cell carcinomas are associated with a prognosis worse than that of other histologic types (141,142).

Histologic grade, as determined either by the pattern of differentiation or by the extent of cellular anaplasia and the proportion of undifferentiated cells, seems to be of prognostic significance (143–146). Studies of the reproducibility of grading ovarian cancers show a high degree of intraobserver and interobserver variation (147,148). Baak et al. have presented a standard grading system based on the morphometric analysis, and the system seems to correlate with prognosis, especially in its ability to

distinguish low-grade or borderline patterns from other tumors (149).

Clinical Factors

In addition to the stage, the extent of residual disease after primary surgery, the volume of ascites, patient age, and performance status are all independent prognostic variables (150–159). Among patients with stage I disease, Dembo et al. showed, in a multivariate analysis, that tumor grade and dense adherence to the pelvic peritoneum had a significant adverse impact on prognosis, whereas intraoperative tumor spillage or rupture did not (156). Sjövall et al. confirmed that **ovarian cancers that undergo intraoperative rupture or spillage do not worsen prognosis, whereas tumors that are ruptured preoperatively do have a poorer prognosis** (157). A multivariate analysis of these and several other studies was performed by Vergote et al., who found that for **early-stage disease, poor prognostic variables were tumor grade, capsular penetration, surface excrescences, and malignant ascites, but not iatrogenic rupture** (159).

Table 39-2 2013 FIGO Staging for Primary Carcinoma of the Ovary, Fallopian Tube, or Primary Peritoneal Cancer

Stage I	**Growth Limited to the Ovaries or Fallopian Tubes**
IA	Growth limited to one ovary or fallopian; no ascites containing malignant cells
	No tumor on the external surface; capsule intact
IB	Growth limited to both ovaries or fallopian tubes; no ascites containing malignant cells
	No tumor on the external surfaces; capsules intact
IC	Tumor limited to one or both ovaries or fallopian tubes with any of the following:
IC1	Surgical spill
IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
IC3	Malignant cells in the ascites or peritoneal washings
Stage II	**Growth involving one or both ovaries or fallopian tubes with pelvic extension (below the pelvic brim)**
IIA	Extension and/or metastases to the uterus and/or fallopian tubes and/or ovaries
IIB	Extension to other pelvic tissues
Stage III	**Tumor involving one or both ovaries or fallopian tubes or peritoneal cancer with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes**
IIIA	Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond pelvis

IIIA1(i)	Positive retroperitoneal lymph nodes with metastasis up to 10 mm in greatest dimension
IIIA1(ii)	Positive retroperitoneal lymph nodes with metastasis more than 10 mm in greatest dimension
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement, with or without positive retroperitoneal lymph nodes
IIIB	Macroscopic peritoneal metastasis beyond pelvis up to 2 cm in greatest dimension, with or without positive retroperitoneal nodes
IIIC	Macroscopic peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ), with or without positive retroperitoneal nodes
IV	**Distant metastasis (excludes peritoneal metastasis)**
IVA	**Pleural effusion is present, there must be positive cytologic test results**
IVB	**Parenchymal metastases and metastases to extra-abdominal organs (including lymph nodes and lymph nodes outside the abdominal cavity)**

The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

FIGO, International Federation of Obstetrics and Gynecology.

[a]Dense adhesions with histologically proven tumor cells justify upgrading to stage II.

Transmural bowel infiltration or umbilical deposit are stage IVB.

Initial Surgery for Ovarian Cancer

Staging

Ovarian epithelial malignancies are staged according to the FIGO system listed in Table 39-2 (160). **The FIGO staging is based on findings at surgical exploration. A preoperative evaluation should exclude the presence of extraperitoneal metastases.**

[7] Thorough surgical staging and search for microscopic metastasis should be performed when there is no visible or palpable disease in the intra-abdominal space outside the ovaries and fallopian tubes. Subsequent treatment may be determined by the stage of the disease. In earlier series in which patients did not undergo careful surgical staging, the overall 5-year survival for patients with apparent stage I epithelial ovarian cancer was only about 60% (161). Survival rates of 90% to 100% are reported for patients who were properly staged and were found to have stage IA or IB disease.

Technique for Surgical Staging

In patients whose preoperative evaluation suggests a probable malignancy, a

vertical abdominal incision is recommended to allow adequate access to the upper abdomen (4,161). When a malignancy is unexpectedly discovered in a patient who has a lower transverse incision, the rectus muscles can be either divided or detached from the symphysis pubis to allow better access to the upper abdomen. If this is not sufficient, the incision can be extended on one side to create a "J" incision (4).

The ovarian tumor should be removed intact, if possible, and a frozen histologic section should be obtained. A thorough surgical staging should be performed. Staging involves the following steps (4,161):

1. **Any free fluid, especially in the pelvic cul-de-sac, should be submitted for cytologic evaluation.**
2. **If no free fluid is present, peritoneal washings should be performed by instilling and recovering 50 to 100 mL of saline from the pelvic cul-de-sac, each paracolic gutter, and beneath each hemidiaphragm.** Obtaining the specimens from under the diaphragms can be facilitated with the use of a rubber catheter attached to the end of a bulb syringe.
3. **A systematic exploration of all the intra-abdominal surfaces and viscera is performed,** proceeding in a clockwise fashion from the cecum cephalad along the paracolic gutter and the ascending colon to the right kidney, the liver and gallbladder, the right hemidiaphragm, the entrance to the lesser sac at the para-aortic area, across the transverse colon to the left hemidiaphragm, down the left gutter and the descending colon to the rectosigmoid colon. The small intestine and its mesentery from the Treitz ligament to the cecum should be inspected.
4. **Any suspicious areas or adhesions on the peritoneal surfaces should be biopsied.** If there is no evidence of disease, multiple IP biopsies should be performed. Tissue from the peritoneum of the pelvic cul-de-sac, both paracolic gutters, the peritoneum over the bladder, and the intestinal mesenteries should be taken for biopsy.
5. **The diaphragm should be sampled, either by biopsy or by scraping with a tongue depressor, and a sample obtained for cytologic assessment.** Biopsies of any irregularities on the surface of the diaphragm can be facilitated by the use of the laparoscope and the associated biopsy instrument.
6. **The omentum should be resected from the transverse colon, including from the hepatic and splenic flexure of the colon and separated from its attachment to the greater curvature of the stomach, including ligation of the left and right gastroepiploic and short gastric arteries, a procedure called *supracolic omentectomy*.** The procedure is initiated on the underside of the greater omentum, where the peritoneum is incised a few millimeters away from the transverse colon. The branches of the gastroepiploic vessels are clamped, ligated, and divided, along with all the small branching vessels that feed the infracolic omentum.

7. **The retroperitoneal spaces should be explored to evaluate the pelvic and para-aortic lymph nodes.** The retroperitoneal dissection is performed by incision of the peritoneum over the psoas muscles. Any enlarged lymph nodes should be resected and submitted for frozen section. If no metastases are present, a formal pelvic lymphadenectomy should be performed. The para-aortic area should be palpated and lymph nodes sampled if enlarged or suspicious.

Results

Metastases in apparent stages I and II epithelial ovarian cancer occur in as many as 3 in 10 patients whose tumors appear to be confined to the pelvis but who have occult metastatic disease in the upper abdomen or the retroperitoneal lymph nodes (138,162–169). In a literature review, occult metastases in such patients were found in biopsies of the diaphragm in 7.3%, biopsies of the omentum in 8.6%, the pelvic lymph nodes in 5.9%, the aortic lymph nodes in 18.1%, and in 26.4% of peritoneal washings (161).

The importance of careful initial surgical staging is emphasized by the findings of a cooperative national study in which 100 patients with apparent stages I and II disease were referred for subsequent therapy and underwent additional surgical staging (162). In this series, 28% of the patients initially believed to have stage I disease were upstaged and 43% of those believed to have stage II disease had more advanced lesions. **A total of 31% of the patients were upstaged as a result of additional surgery, and 77% were reclassified as having actual stage III disease. Histologic grade was a significant predictor of occult metastasis.** Sixteen percent of the patients with grade 1 lesions were upstaged, compared with 34% with grade 2 disease and 46% with grade 3 disease.

Borderline Tumors

The principal treatment of borderline (low malignant potential) ovarian tumors is surgical resection of the primary tumor. There is no evidence that either subsequent chemotherapy or radiation therapy improves survival. When a **frozen section determines that the histology is borderline, premenopausal patients who desire preservation of the ovarian function may undergo a conservative operation, a unilateral oophorectomy** (4,170). In a study of patients who underwent unilateral ovarian cystectomy for apparent stage I borderline serous tumors, Lim-Tan et al. found that this conservative operation was safe, with only 8% of the patients developing recurrences 2 to 18 years later, all with curable disease confined to the ovaries (170). Recurrence was associated with positive margins of the removed ovarian cyst. Thus, hormonal function and fertility can be maintained (4,170). For patients who had an oophorectomy or cystectomy and a borderline tumor is documented later in the permanent pathology, no additional immediate surgery is necessary.

Stage I

After a comprehensive staging laparotomy, only a minority of women will have local disease (FIGO stage I). There are over 20,000 women diagnosed yearly with epithelial ovarian cancer in the United States, and nearly 4,000 of these have disease confined to the ovaries (65,171). The prognosis for these patients depends on the clinical–pathologic features. Because of this emphasis on the importance of surgical staging, the rate of lymph node sampling increased in the United States, with a study showing that for women with stages I and II disease, the percentage having lymph nodes sampled increased from 38% to 59% from 1991 to 1996 (172).

The primary surgical treatment for stage I epithelial ovarian cancer is surgical, and patients should undergo total abdominal hysterectomy, bilateral salpingo-oophorectomy, and surgical staging (161,162). **In certain circumstances, a unilateral salpingo-oophorectomy may be performed as a part of fertility-sparing surgery.** Based on the findings at surgery and the pathologic evaluation, patients with stage I ovarian cancer can be grouped into low-risk and high-risk categories (Table 39-3).

Table 39-3 Prognostic Variables in Early-Stage Epithelial Ovarian Cancer

Low Risk	High Risk
Low grade	High grade
Intact capsule	Tumor growth through capsule
No surface excrescences	Surface excrescences
No ascites	Ascites
Negative peritoneal cytologic findings	Malignant cells in fluid
Unruptured or intraoperative rupture	Preoperative rupture
No dense adherence	Dense adherence
Diploid tumor	Aneuploid tumor

From **Berek JS, Friedlander ML, Hacker NF.** Epithelial ovarian, fallopian tube, and peritoneal cancer. In: Berek JS, Hacker NF. *Berek & Hacker's Gynecologic Oncology*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:483.

Stage I Low Risk

Fertility Preservation in Early-Stage Ovarian Cancer

For patients who underwent a thorough staging laparotomy and who have no evidence of spread beyond the ovary, abdominal hysterectomy and bilateral salpingo-oophorectomy are appropriate therapy. The uterus and the contralateral ovary can be preserved in women with stage IA, grade 1 to 2 disease who desire to

preserve fertility. The women undergoing disease surveillance should be monitored carefully with routine periodic pelvic examinations and determinations of serum CA-125 levels. The other ovary and the uterus are removed at the completion of childbearing.

Guthrie et al. studied the outcome of 656 patients with early-stage epithelial ovarian cancer (169). No untreated patients who had stage IA, grade 1 cancer died of their disease; thus, adjuvant radiation and chemotherapy are unnecessary. The Gynecologic Oncology Group (GOG) carried out a prospective, randomized trial of observation versus *melphalan* for patients with stages IA and IB, grade 1 or 2 disease (142). Five-year survival for each group was 94% and 96%, respectively, confirming that no further treatment is needed for such patients.

Stage I High Risk

Patients who have more poorly differentiated disease or who have malignant cells either in ascites fluid or in peritoneal washings, must undergo complete surgical staging (4). Most patients require chemotherapy.

Advanced-Stage Ovarian Cancer

The management of all patients with advanced-stage disease is approached in a similar manner, with modifications made in response to the overall status and general health of the patient and the extent of residual disease present at the time treatment is initiated. A treatment scheme is outlined in Figure 39-10. Most patients subsequently receive combination chemotherapy for an empiric number of cycles.

Cytoreductive Surgery for Advanced-Stage Disease

If the patient is medically stable, she should undergo cytoreductive surgery to remove as much of the tumor and its metastases as possible (173–200). **The operation to remove the primary tumor and the associated metastatic disease is referred to as *debulking*** or cytoreductive surgery. The operation typically includes the performance of a total abdominal hysterectomy and bilateral salpingo-oophorectomy, along with a complete omentectomy and resection of any metastatic lesions from the peritoneal surfaces or from the intestines. The pelvic tumor often directly involves the rectosigmoid colon, the terminal ileum, and the cecum **(Fig. 39-11)**. In a minority of patients, most or all of the disease is confined to the pelvic viscera and the omentum, so that removal of these organs will result in extirpation of all gross tumor, a situation that is associated with a reasonable chance of prolonged PFS.

The paradigm of routine lymphadenectomy in patients with advanced ovarian cancer and clinically and radiographically negative nodes has been challenged with the reporting of the Lymphadenectomy in Ovarian Neoplasms (LION) study. This was a

prospective randomized trial of 647 patients with stage IIB to IV ovarian cancer with macroscopic complete resection and preoperative and intraoperative clinically negative lymph nodes randomized intraoperatively to systematic pelvic and para-aortic lymphadenectomy versus no lymphadenectomy. This trial showed that systematic pelvic and para-aortic lymphadenectomy in patients with advanced ovarian cancer with intra-abdominal complete resection and clinically negative lymph nodes does not provide a PFS or overall survival benefit, despite the detection and removal of subclinical lymph nodal metastases in approximately 56% of patients. The authors suggest that routine lymphadenectomy should be omitted in these patients to reduce postoperative morbidity and mortality (201).

The removal of bulky tumor masses may reduce the volume of ascites present. Often, ascites will disappear after removal of the primary tumor and a large omental "cake." Removal of the omental cake may alleviate the nausea and early satiety that many patients experience. Removal of intestinal metastases may restore adequate intestinal function and improve the overall nutritional status of the patient, thereby facilitating the patient's ability to tolerate subsequent chemotherapy.

A large, bulky tumor may contain areas that are poorly vascularized, and these areas will be exposed to suboptimal concentrations of chemotherapeutic agents. Similarly, these areas are poorly oxygenated, so that radiation therapy, which requires adequate oxygenation to achieve maximal cell kill, will be less effective. Surgical removal of these bulky tumors may eliminate areas that could be relatively resistant to radiation and chemotherapeutic treatment.

Larger tumor masses tend to be composed of a higher proportion of cells that are either nondividing or in the "resting" phase (i.e., G_0 cells, which are essentially resistant to the therapy). A low growth fraction is characteristic of bulky tumor masses, and cytoreductive surgery can result in smaller residual masses with a relatively higher growth fraction.

Goals of Cytoreductive Surgery

The principal goal of cytoreductive surgery is removal of all of the primary cancer and, if possible, all metastatic disease. If resection of all metastases is not feasible, the goal is to reduce the tumor burden by resection of all individual tumors to an optimal status (<1 cm of any single implant of residual disease). **Patients whose disease is completely resected to no macroscopic (microscopic only) residual disease have the best overall survival (Fig. 39-12)** (178). **Approximately 30% to 40% of patients in this category will be free of disease at 5 years.**

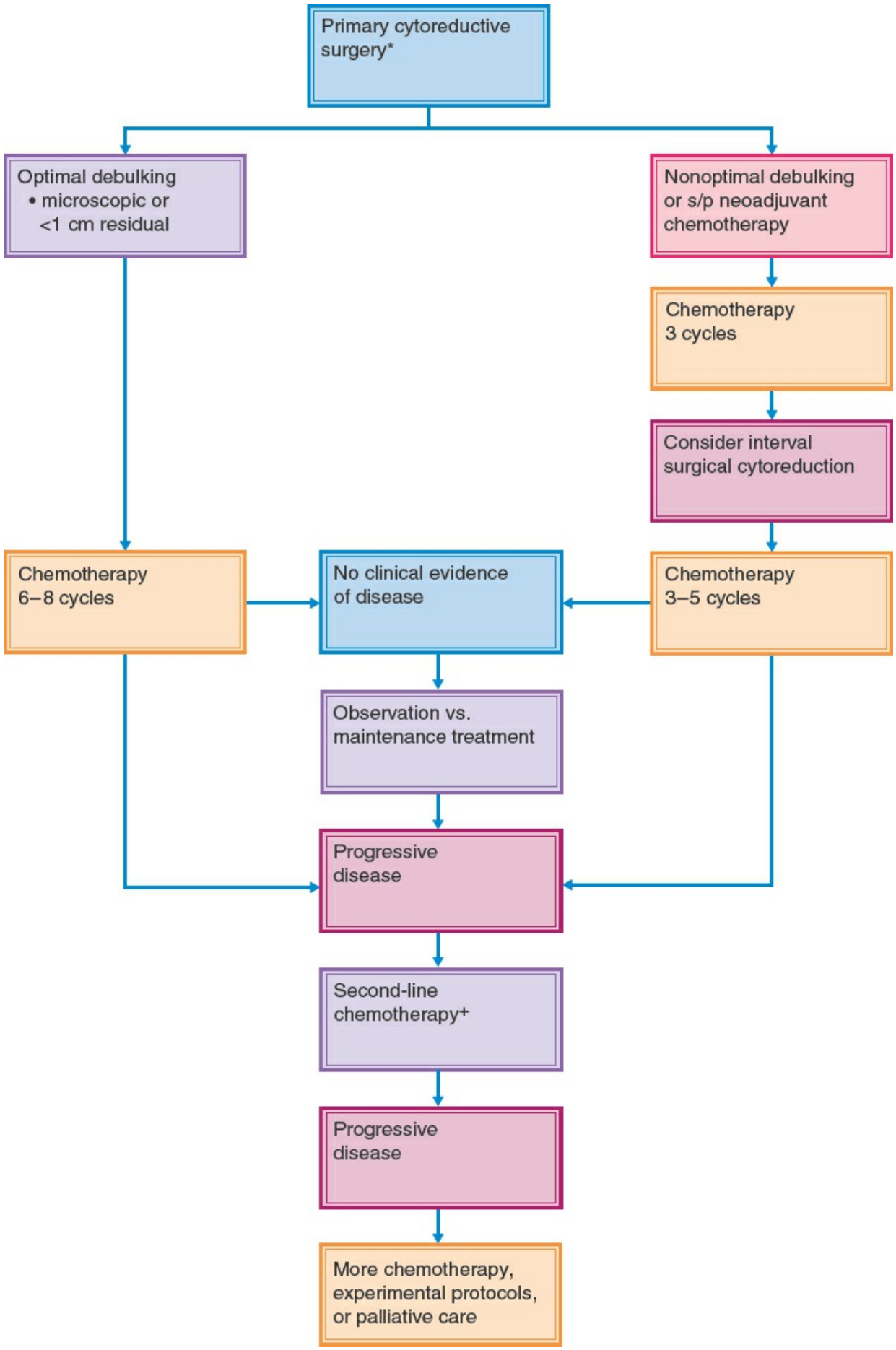

Primary cytoreductive surgery*
Optimal debulking
• microscopic or
<1 cm residual
Nonoptimal debulking or s/p neoadjuvant chemotherapy
Chemotherapy
3 cycles
Consider interval surgical cytoreduction
Chemotherapy
6–8 cycles
No clinical evidence of disease
Chemotherapy
3–5 cycles
Observation vs. maintenance treatment
Progressive disease
Second-line chemotherapy+
Progressive disease
More chemotherapy, experimental protocols, or palliative care

FIGURE 39-10 Treatment scheme for patients with advanced-stage ovarian cancer. *In selected cases of stage IIIC/IV disease, neoadjuvant chemotherapy may be given, and then an interval cytoreductive surgery is performed after three cycles. +Chemotherapy depends on whether platinum-sensitive or platinum-resistant. (Modified from **Berek JS, Friedlander ML, Hacker NF.** Epithelial ovarian, fallopian tube, and peritoneal cancer. In: Berek JS, Hacker NF. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:485.)

The resectability of the metastatic tumor is usually determined by the location of the disease. Optimal cytoreduction is difficult to achieve in the presence of extensive disease on the diaphragm, in the parenchyma of the liver, along the base of the small bowel mesentery, in the lesser omentum, or in the porta hepatis. **[7] Neoadjuvant chemotherapy is an option for patients with advanced ovarian/fallopian tube or peritoneal cancer who are determined to have a low likelihood of optimal cytoreduction or in women determined to have a high perioperative risk** (202).

In two published large randomized control trials, neoadjuvant chemotherapy was noninferior to upfront cytoreduction (203,204). There was no significant difference between the PFS or overall survival between the two groups. In one trial, the EORTC 55971, outcomes were found to vary by the stage of disease and tumor size. In particular, patients with stage IV disease and more extensive tumors greater than 45 mm had a better survival with neoadjuvant chemotherapy; however, patients with stage IIIC cancer and metastatic lesions less than 45 mm had a better survival with primary cytoreductive surgery (205). All randomized clinical trials have shown lower perioperative morbidity with neoadjuvant chemotherapy compared to primary cytoreductive surgery (202).

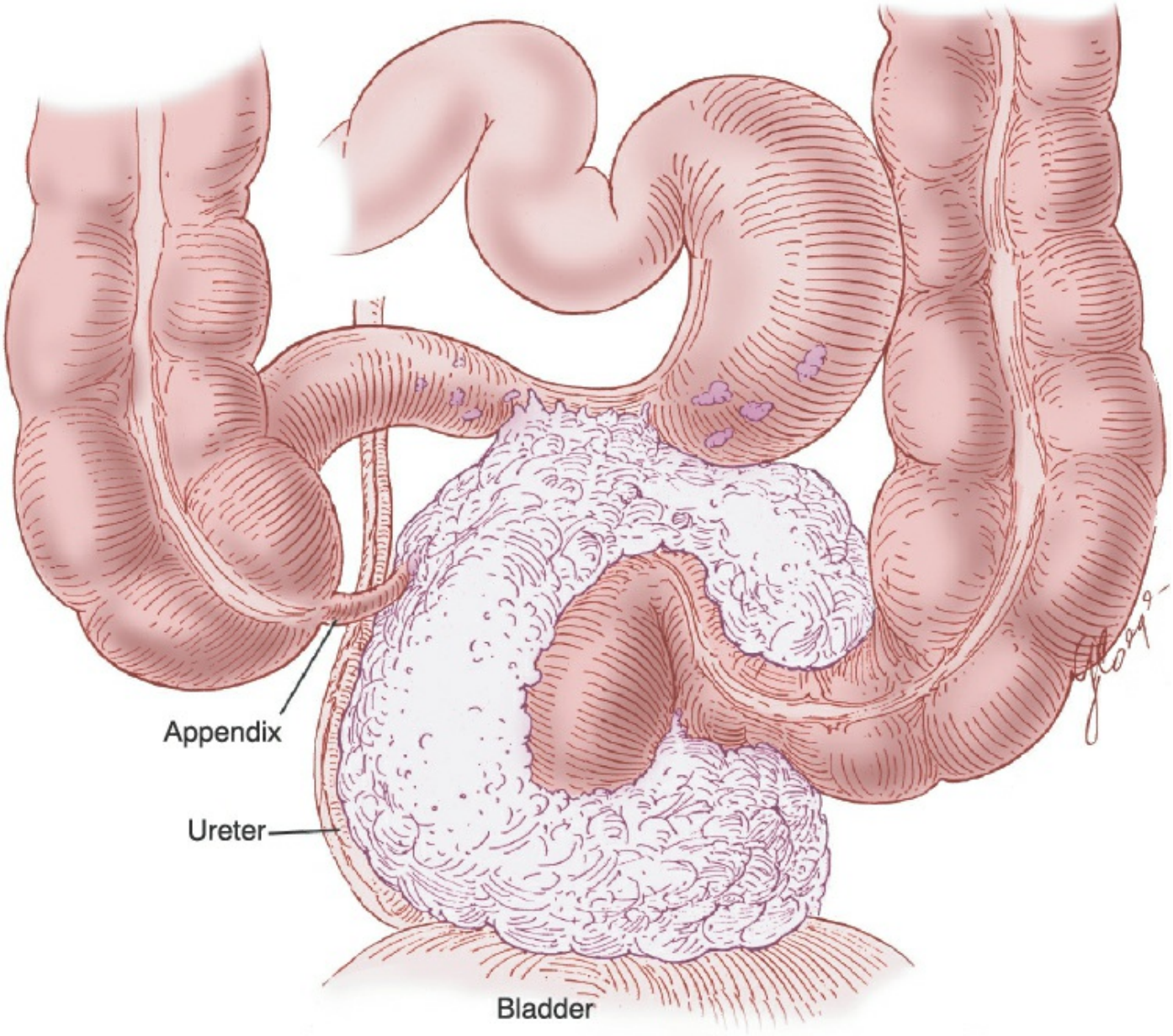


FIGURE 39-11 Extensive ovarian carcinoma involving the bladder, rectosigmoid, and ileocecal area. (Redrawn from **Heintz APM, Berek JS.** Cytoreductive surgery for ovarian carcinoma. In: Piver MS, ed. Ovarian Malignancies. Edinburgh, UK: Churchill Livingstone; 1987:134, with permission.)

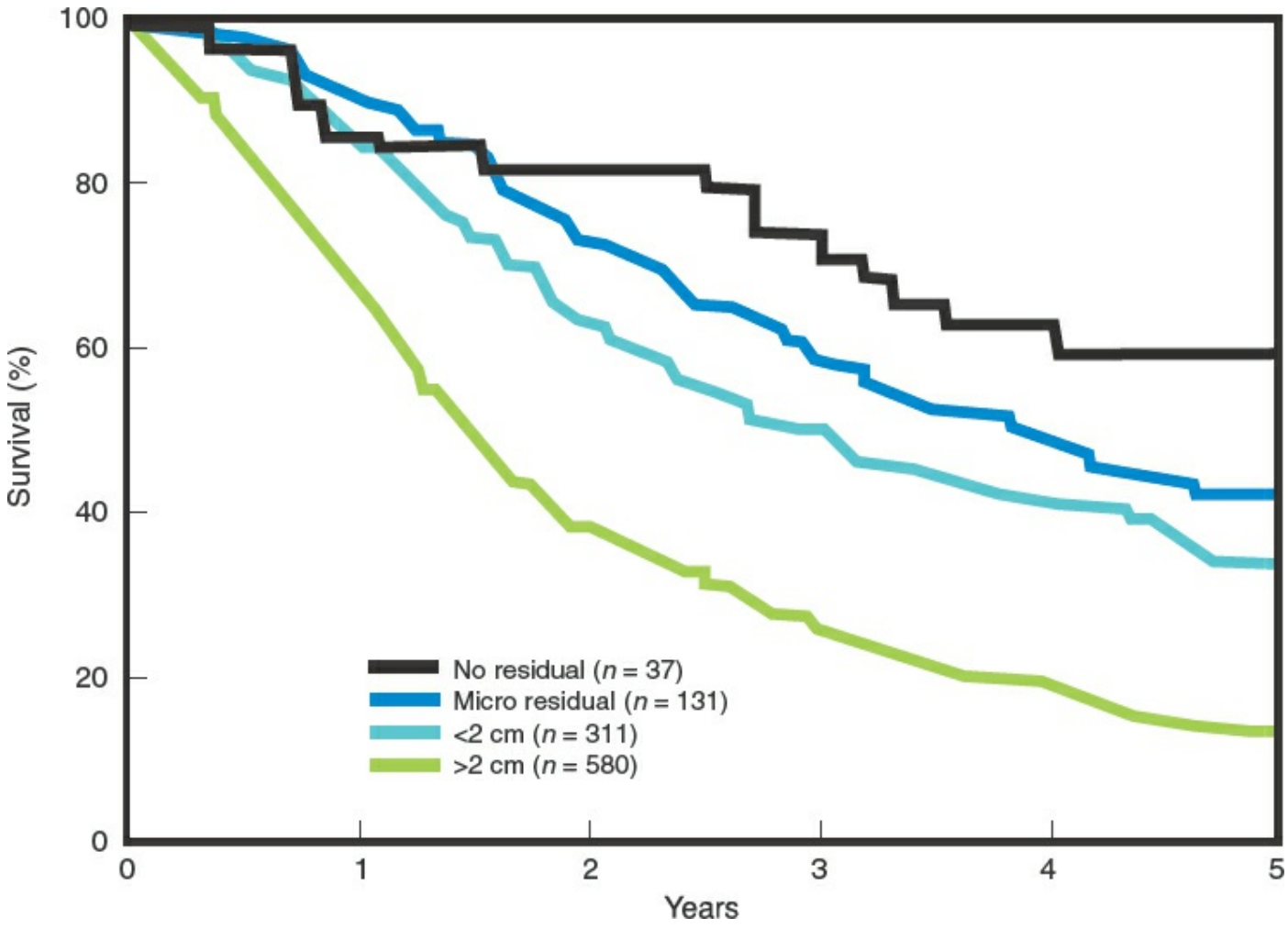


FIGURE 39-12 Survival of patients with stage IIIC epithelial ovarian cancer based on the maximal size of residual tumor after exploratory laparotomy and tumor resection. (From **Heintz APM, Odicino F, Maisonneuve P, et al.** Carcinoma of the ovary. Twenty-sixth annual report of the results of treatment of gynaecological cancer. Int J Gynecol Oncol 2006;95(suppl 1): S161–S192, with permission.)

Exploration

The supine position on the operating table may be sufficient for surgical exploration of most patients. For patients with extensive pelvic disease and for whom a low resection of the colon may be necessary, the low lithotomy position should be used. Debulking operations should be performed through a vertical incision to gain adequate access to the upper abdomen and to the pelvis.

After the peritoneal cavity is opened, ascites fluid, if present, should be evacuated. In some centers, fluid is submitted for *in vitro* research studies, such as molecular analyses. In cases of massive ascites, careful attention must be given to hemodynamic monitoring, especially for patients with borderline cardiovascular function.

The peritoneal cavity and retroperitoneum are thoroughly inspected and palpated to assess the extent of the primary tumor and the metastatic disease. All abdominal viscera must be palpated to exclude the possibility that the ovarian disease is

metastatic, particularly from the stomach, colon, or pancreas. If optimal cytoreduction is not considered achievable, extensive bowel and urologic resections are not indicated, except to overcome a bowel obstruction. Removal of the primary tumor and omental cake is usually feasible and desirable.

Pelvic Tumor Resection

The essential principle of pelvic tumor removal is the retroperitoneal approach. To accomplish this, the retroperitoneum is entered laterally, along the surface of the psoas muscles, which avoids the iliac vessels and the ureters. If the uterus is present, the procedure is initiated by bilateral division of the round ligaments. The peritoneal incision is extended cephalad, lateral to the ovarian vessels within the infundibulopelvic ligament, and caudally toward the bladder. With careful dissection, the retroperitoneal space is explored, and the ureter and pelvic vessels are identified. The pararectal and paravesical spaces are identified and developed, as described in Chapter 38.

The peritoneum overlying the bladder is dissected to connect the peritoneal incisions anteriorly. The vesicouterine plane is identified, and with careful sharp dissection the bladder is mobilized from the anterior surface of the cervix. The ovarian vessels are isolated, doubly ligated, and divided.

Hysterectomy is performed. The ureters must be carefully displayed to avoid injury. During this procedure, the uterine vessels can be identified. Ligation of the uterine vessels and the remainder of the tissues within the cardinal ligaments completes the hysterectomy and resection of the contiguous tumor.

Because epithelial ovarian cancers tend not to invade the lumina of the colon or bladder, it is usually feasible to resect pelvic tumors without having to resect portions of the lower colon or the urinary tract (183,184). Resection of a small portion of the bladder may be required and, if so, a cystotomy should be performed to assist in resection of the disease (184).

Intestinal Resection

Resection of focal areas of disease involving the small or large intestine should be performed if that would permit the removal of all or most of the abdominal metastases and leave the patient with optimal cytoreduction at the end of surgery. Apart from the rectosigmoid colon, the most frequent sites of intestinal metastasis are the terminal ileum, the cecum, and the transverse colon. Resection of one or more of these segments of bowel may be necessary (183,185).

If the disease surrounds the rectosigmoid colon and its mesentery, that portion of the colon may have to be removed in order to clear the pelvic disease **(Fig. 39-13)** (183). After the pararectal space is identified, the proximal site of colonic involvement is identified, the colon and its mesentery are divided, and the rectosigmoid is removed

along with the uterus *en bloc.* A reanastomosis of the colon is performed.

Omentectomy

Advanced epithelial ovarian cancer often completely replaces the omentum, forming an "omental cake." This disease may be adherent to the parietal peritoneum of the anterior abdominal wall, making entry into the abdominal cavity difficult. After freeing the omentum from any adhesions to the parietal peritoneum, adherent loops of the small intestine are freed by sharp dissection. The omentum is lifted and pulled gently in the cranial direction, exposing the attachment of the infracolic omentum to the transverse colon. The peritoneum is incised to open the appropriate plane, which is developed by sharp dissection along the serosa of the transverse colon. Small vessels are ligated with hemoclips, suture, or a vessel-sealing device. The omentum is separated from the greater curvature of the stomach by ligation of the right and left gastroepiploic arteries and ligation of the short gastric arteries **(Fig. 39-14)**.

The disease in the gastrocolic ligament can extend to the hilus of the spleen and splenic flexure of the colon on the left and to the capsule of the liver and the hepatic flexure of the colon on the right. Usually, the disease does not invade the parenchyma of the liver or spleen, and a plane can be found between the tumor and these organs. It will occasionally be necessary to perform splenectomy to remove all the omental disease (186).

Resection of Other Metastases

Other large masses of tumor located on the parietal peritoneum should be removed, particularly if they are isolated masses and their removal will permit optimal cytoreduction. Resection of extensive disease from the surfaces of the diaphragm is neither practical nor feasible, although solitary metastases may be resected, the diaphragm sutured, and a chest tube placed for a few days if needed (186,187). The use of the Cavitron Ultrasonic Surgical Aspirator (CUSA) and the argon beam coagulator may facilitate resection of small tumor nodules, especially those on flat surfaces (188,189).

Feasibility and Outcome

There was no randomized prospective study performed to define the value of primary cytoreductive surgery, but all retrospective studies indicate that the diameter of the largest residual tumor nodule before the initiation of chemotherapy is significantly related to the PFS in patients with advanced ovarian cancer (190). The quality of life may be significantly enhanced by the removal of bulky tumor masses from the pelvis and upper abdomen (191).

An analysis of the retrospective data indicates that, when performed by gynecologic oncologists, successful operations are feasible in 70% to 90% of patients (181,182). Major morbidity is approximately 5% and operative mortality is

1% (185,192,193). Intestinal resection in these patients does not appear to increase the overall morbidity caused by the operation (185).

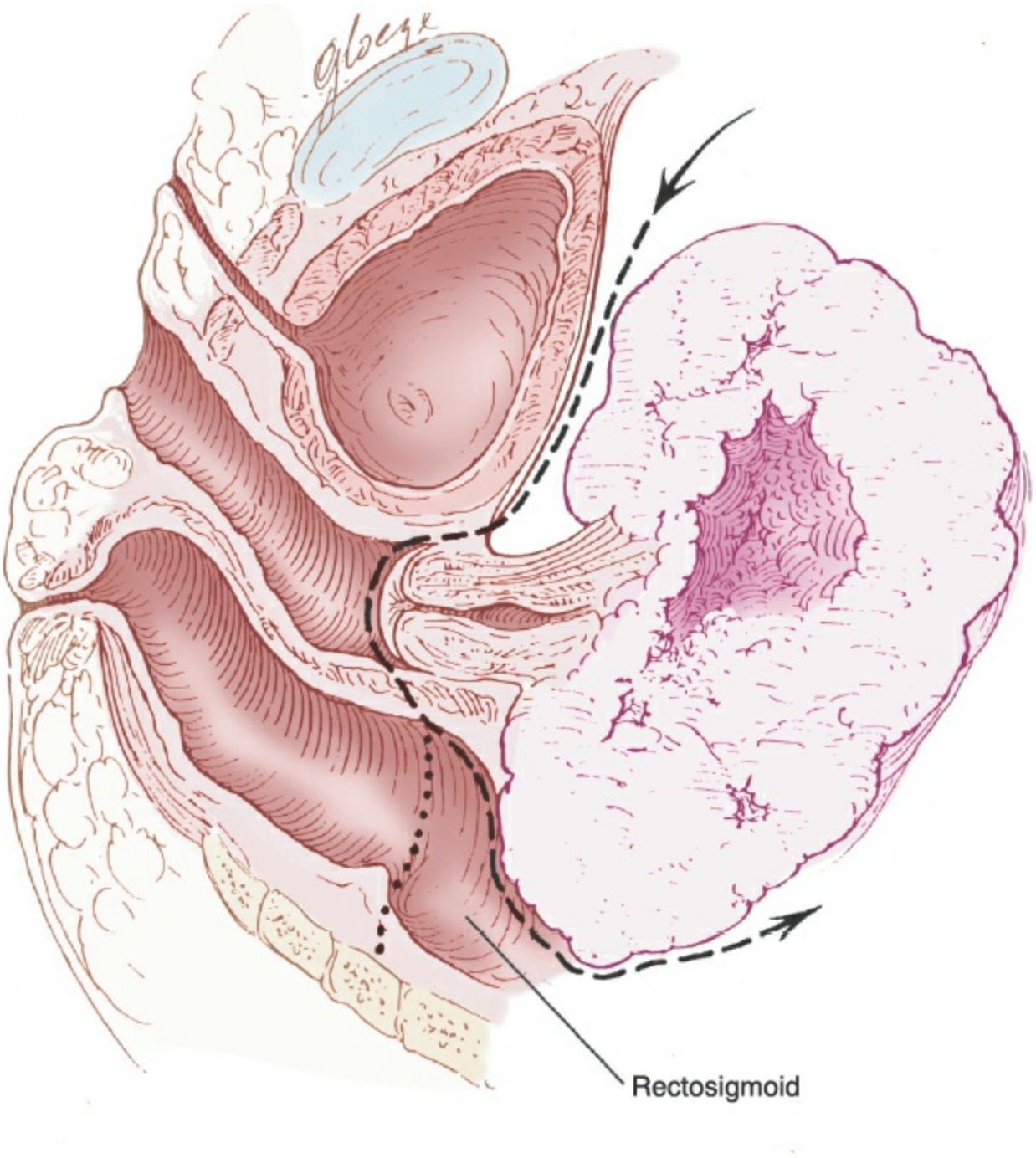


FIGURE 39-13 The resection of the pelvic tumor may include removal of the uterus, tubes, and ovaries, as well as portions of the lower intestinal tract. The *arrows* represent the plane of resection. (Modified from **Berek JS, Friedlander ML, Hacker NF.** Epithelial ovarian, fallopian tube, and peritoneal cancer. In: Berek JS, Hacker NF. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:490.)

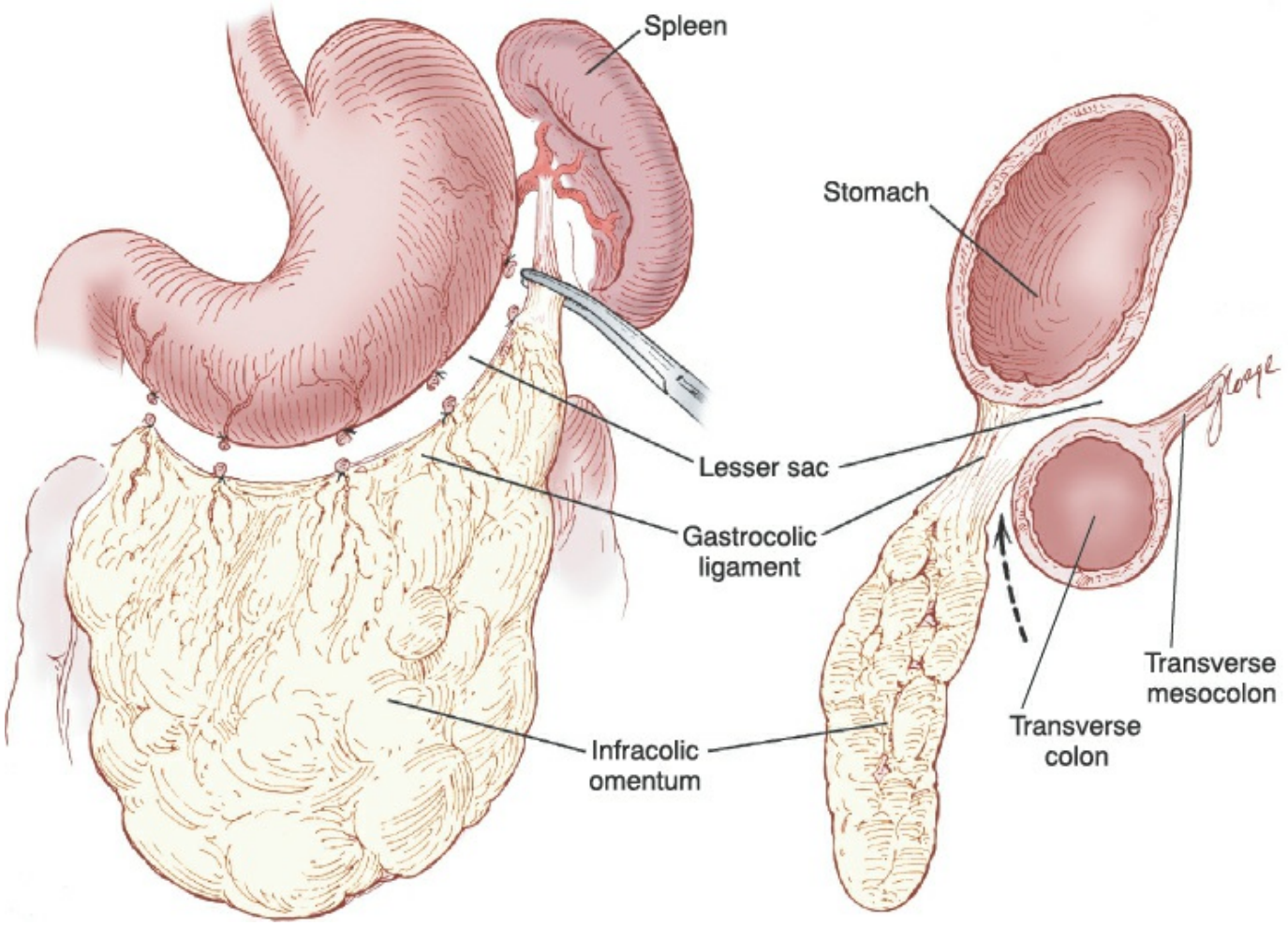


FIGURE 39-14 Separation of the omentum from stomach and transverse colon. *Arrow*, the direction of the initial surgical approach. (From **Heintz APM, Berek JS.** Cytoreductive surgery for ovarian carcinoma. In: Piver MS, ed. Ovarian Malignancies. Edinburgh, UK: Churchill Livingstone; 1987:134, with permission.)

In a meta-analysis of 81 studies of women who underwent cytoreductive surgery for advanced ovarian cancer, Bristow et al. documented that the extent of debulking correlated with incremental benefits in survival (i.e., the greater the percentage of tumor reduction, the longer the survival). Each 10% increase in cytoreduction equaled a 5.5% increase in median survival (190). **Women whose cytoreduction was greater than 75% of their tumor burden had a median survival of 33.9 months compared with 22.7 months for women whose tumors were cytoreduced less than 75%** (p <0.001). The performance of a pelvic and para-aortic lymphadenectomy in patients with stage III disease does not prolong survival, based on the results of a large prospective, randomized trial (194).

A prospective randomized study of "interval" cytoreductive surgery was carried out by the European Organization for the Research and Treatment of Cancer (EORTC). Interval surgery was performed after three cycles of *platinum*-combination chemotherapy in patients whose primary attempt at cytoreduction was suboptimal. The

initial surgery for most of these patients was not an aggressive attempt to debulk their tumors. Patients in the surgical arm of the study demonstrated a survival benefit when compared with those who did not undergo interval debulking (195). The risk of mortality was reduced by more than 40% in the group that was randomized to the debulking arm of the study. Based on these data, the performance of a debulking operation as early as possible in the course of the patient's treatment should be considered the standard of care (191).

A prospective phase III study of interval cytoreductive surgery was conducted by the GOG; the patients entered on the trial had a maximal attempt at tumor resection at their initial surgery (196). The randomized findings showed no difference between the patients who had an additional attempt at debulking after three cycles of chemotherapy compared with those who did not. The median survival of the 216 women who underwent interval cytoreduction was 32 months compared with 33 months for the 209 women who did not undergo surgical cytoreduction.

There is evidence that the survival of women with advanced ovarian cancer is improved when the surgeon is specifically trained to perform cytoreductive surgery and when there is centralization of care (197–200). **Whenever feasible, patients with advanced ovarian malignancy should be referred to a subspecialty unit for primary surgery, and every effort should be made to attain as complete a cytoreduction as possible.**

Chemotherapy

Stage I Epithelial Ovarian Cancer

Early Stage, Low Risk

Guthrie et al. studied the outcome of 656 patients with early-stage epithelial ovarian cancer (169). Patients who had stage IA, grade 1 cancer and did not receive radiation or chemotherapy did not die of their disease; indicating that adjuvant therapy is unnecessary. The GOG carried out a prospective, randomized trial of observation versus *melphalan* for patients with stages IA and IB, grades 1 and 2 disease (142). **Five-year survival for each group was 94% and 96%, respectively, confirming that adjuvant treatment did not improve survival. Therefore, no adjuvant chemotherapy is recommended for these patients.**

Early Stage, High Risk

In patients whose disease is high risk (e.g., high-grade serous or in whom there are malignant cells either in ascites fluid or in peritoneal washings), additional therapy is indicated. Chemotherapy is recommended for these patients to reduce recurrence risk (206–219).

Two large parallel randomized phase III clinical trials were conducted on women with early-stage disease more than 20 years ago and reported in 2003: the **International Collaborative Ovarian Neoplasm Trial 1 (ICON1)** and the **Adjuvant Chemotherapy Trial in Ovarian Neoplasia (ACTION)** (220,221).

In the ICON1 trial, 477 patients from 84 centers in Europe were entered. Patients of all stages were eligible for the trial if, in the opinion of the investigator, it was unclear whether adjuvant therapy would be of benefit. Most patients were considered to have stages I and IIA disease, but optimal **surgical staging was not required,** and it is likely that a significant number of these women had stage III disease. Adjuvant *platinum*-based chemotherapy was given to 241 patients, and no adjuvant chemotherapy was given to 236 patients. **The 5-year survival was 73% in the group who received adjuvant chemotherapy compared with 62% in the control group** (HR, 0.65; p = 0.01) (221).

In the ACTION trial, 440 patients from 40 European centers were randomized; 224 patients received adjuvant *platinum*-based chemotherapy, and 224 patients did not (220). **Patients with stages I and II, grades 2 and 3 were eligible.** Only about one-third of the total group was optimally staged (151 patients). **In the observation arm, optimal staging was associated with a better survival** (HR, 2.31; p = 0.03), **and in the suboptimally staged patients, adjuvant chemotherapy was associated with an improvement in survival** (HR, 1.78; p = 0.009). **In the ACTION trial, the initial trial results suggested that the benefit from adjuvant chemotherapy was limited to the patients with suboptimal staging. However, a long-term follow-up of the randomized trial after a median of 10.1 years showed that the overall survival after optimal staging was improved even among those who received adjuvant chemotherapy** (HR of death, 1.89; p = 0.05) (222).

When the data from the two trials were combined and analyzed, a total of 465 patients were randomized to receive *platinum*-based adjuvant chemotherapy and 460 to observation until disease progression (223). After a median follow-up of more than 4 years, the overall survival was 82% in the chemotherapy arm and 74% in the observation arm (HR, 0.67; p = 0.001). Recurrence-free survival was better in the chemotherapy arm: 76% versus 65% (HR, 0.64; p = 0.001). The results of this analysis must be interpreted with caution, because most of the patients did not undergo thorough surgical staging, but the **findings suggest that *platinum*-based chemotherapy should be given to patients who were not optimally staged.** It is generally accepted that high-risk early-stage ovarian cancer patients, including stage I, grade 3 endometrioid, stage IC, serous and carcinosarcoma, benefit from adjuvant chemotherapy just as advanced-stage ovarian cancer patients do. There remains uncertainty about the impact of chemotherapy in women with stage I clear cancers as these cancers are less chemosensitive than high-grade serous cancers.

A randomized phase III trial of three versus six cycles of adjuvant *carboplatin* and *paclitaxel (CP)* in 457 patients with early-stage epithelial ovarian carcinoma was conducted by the GOG (224). An unexpectedly large number of patients (126 patients, 29%) had incomplete or inadequately documented surgical staging in this study. The recurrence rate for six cycles was 24% lower (HR, 0.76; confidence interval [CI], 0.5–1.13; $p = 0.18$) versus three cycles, but this was not statistically significant. The estimates of probability of recurrence at 5 years were 20.1% for six cycles and 25.4% for three cycles (225). An exploratory analysis of high-risk early-stage epithelial ovarian cancer patients from this trial reported by Chan et al., suggested that six cycles rather than three cycles may decrease risk of recurrence, particularly in patients with serous ovarian tumors (226).

The recommendations for therapy follow:

- **Patients with high-grade, high-risk stage I epithelial ovarian cancer should be offered adjuvant chemotherapy depending on the patient's overall health and medical comorbidities.**
- **Treatment with *CP* chemotherapy for three to six cycles is used in these patients, whereas single-agent *carboplatin* may be preferable for older women and patients with other medical comorbidities.**

Advanced-Stage Epithelial Ovarian Cancer

Systemic multiagent chemotherapy is the standard treatment for metastatic epithelial ovarian cancer (227–251). After the introduction of *cisplatin* in the latter half of the 1970s, *platinum*-based combination chemotherapy became the most frequently used treatment regimen in the United States. **The second-generation *platinum* analogue, *carboplatin*, was developed to have less toxicity than its parent compound, *cisplatin*** (238). Fewer gastrointestinal side effects, especially nausea and vomiting, were observed than with *cisplatin*, and there was less nephrotoxicity, neurotoxicity, and ototoxicity. *Carboplatin* is associated with a higher degree of myelosuppression (240). **The dose of *carboplatin* is calculated by using the area under the curve (AUC) and the glomerular filtration rate (GFR) according to the *Calvert formula*** (241). **The target AUC is 5 to 6 for previously untreated patients with ovarian cancer.**

A **major advance in the treatment of advanced-stage disease was the incorporation of *paclitaxel* into the chemotherapeutic regimens in the late 1990s** (224,227–230). **Based on two studies** (228,229), ***paclitaxel* is included in the primary treatment of all women with advanced-stage epithelial ovarian cancer, unless there are contraindications to *paclitaxel*, such as preexisting peripheral neuropathy.**

Carboplatin and Paclitaxel

A series of randomized, prospective clinical trials with *paclitaxel*-containing arms defined *CP* as the standard treatment protocol in advanced epithelial ovarian cancer, although there are data to support IP chemotherapy in selected patients (228,229,235,236). **[8]** Two randomized, prospective clinical studies compared the combination of *paclitaxel* and *carboplatin* to *paclitaxel* and *cisplatin* (235,236). In both studies, the efficacy and survivals were similar, but the toxicity was more acceptable with the carboplatin-containing regimen **(Fig. 39-15)** (237).

Carboplatin and Docetaxel

Docetaxel* has a different toxicity profile from *paclitaxel. The SCOT-ROC (Scottish Gynaecological Cancer Trials Group) study randomly assigned 1,077 women with stages IC to IV epithelial ovarian cancer to *carboplatin* with either *paclitaxel* or *docetaxel* (244). **The efficacy of *docetaxel* appeared to be similar to *paclitaxel:*** The median PFS was 15.1 months versus 15.4 months, and the ***docetaxel* group had fewer neurologic effects, arthralgias, myalgias, and extremity weakness than the *paclitaxel* group.** The *docetaxel* plus *carboplatin* regimen was associated with significantly more myelosuppression and its consequences (i.e., serious infections and prolonged grade 3 to 4 neutropenia). *Docetaxel* is not widely used, but is an option in patients who have had a significant allergic reaction to *paclitaxel* or who develop early sensory neuropathy.

Five-Arm Trial

An Intergroup, international trial—GOG 182/Southwest Oncology Group (SWOG) 182/ICON5—compared the standard combination of *CP* with these drugs in combination with *gemcitabine*, *topotecan*, or *liposomal doxorubicin* in sequential doublets or triplets (245). The study showed that the addition of any these three drugs to the standard chemotherapy with *CP* did not improve the PFS or overall survival.

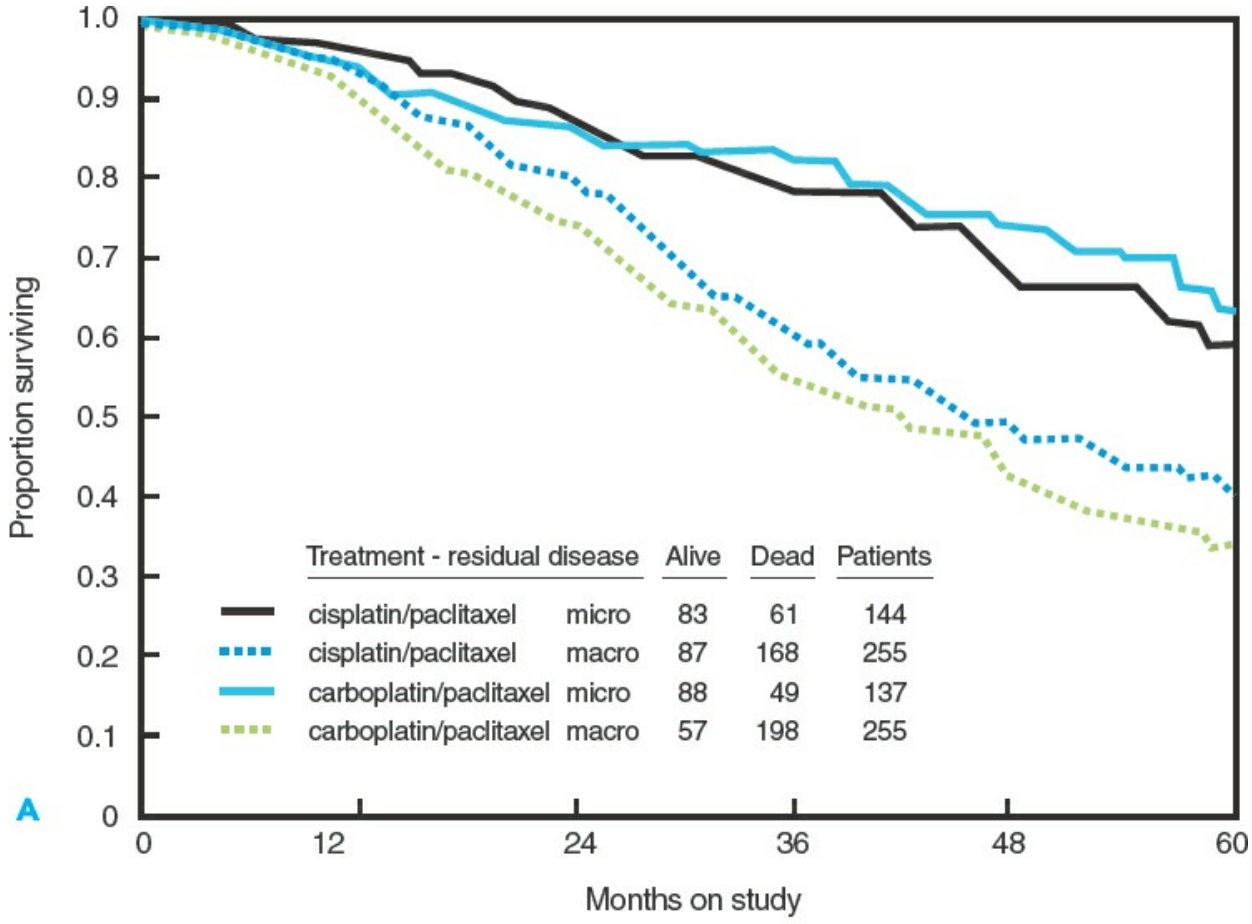
Intraperitoneal Chemotherapy

A randomized, prospective GOG study (Protocol 104) of IP *cisplatin* versus intravenous (IV) *cisplatin* (100 mg/m^2), each given with 750 mg/m^2 *cyclophosphamide*, was performed jointly by the SWOG and the GOG in patients with minimal residual disease (246). **[8]** **The IP *cisplatin* arm had a somewhat longer overall median survival than the IV arm, 49 months versus 41 months** (p = 0.03). In the patients with minimal residual disease (<0.5 cm maximal residual), paradoxically, there was no difference between the two treatments, 51 **months** versus 46 months (p = 0.08).

In a follow-up GOG study (Protocol 114), the dose-intense arm was initiated by giving a moderately high dose of *carboplatin* (dose AUC = 9) for two induction cycles, followed by IP *cisplatin* 100 mg/m^2 and IV *paclitaxel* 135 mg/m^2 over 24 hours, versus IV *cisplatin* 75 mg/m^2 and IV *paclitaxel* 135 mg/m^2 (247). The dose-intense arm results

were slightly better—the disease progression-free median survival was 27.6 months compared with 22.5 months for the control arm ($p = 0.02$). There was no difference in overall survival (52.9 months vs. 47.6 months, $p = 0.056$). Based on this study, it was unclear whether dose intensification with IP *cisplatin* has a sustained long-term impact on the survival of these patients.

A third randomized prospective GOG study (Protocol 172) compared IP *cisplatin* and *paclitaxel* versus IV *cisplatin* and *paclitaxel* (248). The combination of *cisplatin* 75 mg/m^2 and *paclitaxel* 135 mg/m^2 given IV every 3 weeks was compared with *paclitaxel* 135 mg/m^2 IV day 1, followed by *cisplatin* 100 mg/m^2 IP day 2, and *paclitaxel* 60 mg/m^2 IP day 8 every 3 weeks, each given for six cycles. **Although 83% of the patients randomized to IV chemotherapy completed all six cycles of therapy, only 42% of those treated with IP chemotherapy completed the six cycles, principally because of catheter-related complications. For patients in either group who could not complete the therapy because of *cisplatin*-related toxicity, the chemotherapy was switched to IV *carboplatin*.** Comparing the IV and IP arms, the median duration of the PFS was 18.3 and 23.8 months, respectively ($p = 0.05$). **[8] The median duration of the overall survival in the IV-therapy and IP-therapy groups was 49.7 and 65.6 months, respectively** ($p = 0.03$) (248). The **quality of life was significantly worse in the IP-therapy group before cycle four and 3 to 6 weeks after treatment but not 1 year after treatment.** A summary of the IP-catheter–related issues in this trial was presented (249).


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Proportion surviving
Treatment - residual disease Alive Dead Patients
cisplatin/paclitaxel micro 83 61 144
cisplatin/paclitaxel macro 87 168 255
carboplatin/paclitaxel micro 88 49 137
carboplatin/paclitaxel macro 57 198 255
A
0
12
24
36
48
60
Months on study

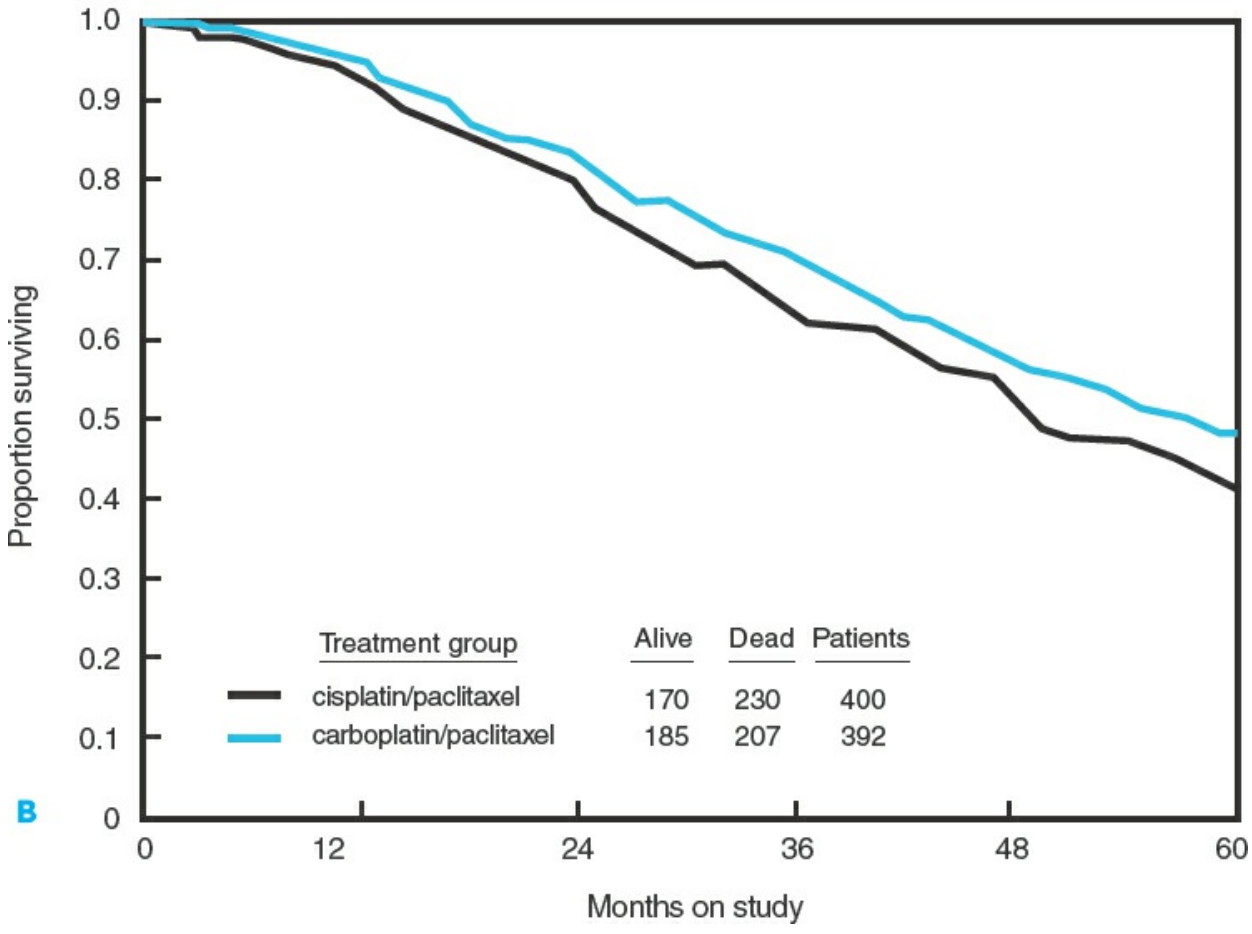

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Proportion surviving
Treatment group Alive Dead Patients
cisplatin/paclitaxel 170 230 400
carboplatin/paclitaxel 185 207 392
B
0
12
24
36
48
60
Months on study

FIGURE 39-15 Survival of patients with stage III epithelial ovarian cancer treated with *carboplatin* and *paclitaxel* versus *cisplatin* and *paclitaxel:* a Gynecologic Oncology Group study. **A:** Survival by treatment. **B:** Survival by treatment group (micro vs. macro). (From **Ozols RF, Bundy BN, Greer BE, et al.** Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2003;21:3194–3200, with permission.)

In GOG 252, 1,560 patients with stage II to IV epithelial ovarian, fallopian tube, or peritoneal carcinoma were randomized to receive six cycles of chemotherapy. There were three treatment arms: Arm 1, IV *carboplatin* AUC 6/IV weekly *paclitaxel* at 80 mg/m^2; Arm 2, IP *carboplatin* AUC 6/IV weekly *paclitaxel* at 80 mg/m^2; Arm 3, IV *paclitaxel* at 135 mg/m^2 on day 1/IP *cisplatin* at 75 mg/m^2 on day 2/IP *paclitaxel* 60 mg/m^2 on day 8. Each arm received IV *bevacizumab* at 15 mg/kg with cycles 2 through 6 of chemotherapy and then single-agent *bevacizumab* for cycles 7 through 22. The trial results showed a median PFS of 27 to 29 months in patients with optimal stage II to III disease treated with regimens consisting of different combinations of IV and IP *cisplatin*, *carboplatin*, and *paclitaxel*, in combination with *bevacizumab.* An analysis limited to patients with optimal stage III tumors and no gross residual disease found a median PFS of 31 to 34 months. By comparison, the GOG 172 trial comparing IP and IV chemotherapy regimens in ovarian cancer had a median PFS of 23.8 months with IP *cisplatin* (vs. 18.3 months with IV) with an improvement in OS in favor of IP (252). Differences in the *cisplatin* arm from the GOG 172 study include a dose reduction from 100 to 75 mg and a shorter infusion time from 24 to 3 hours. If IP is used, it would be appropriate to follow the GOG 172 protocol rather than the modified protocol with a lower dose of *cisplatin*. Investigators at the Mayo Clinic reported in 2009 at the SGO that only 20% of the 105 patients they treated in the clinic could complete 3 or more cycles of the 172 protocol because of toxicity. However, the GOG 172 study did find a significant survival advantage for IP therapy and there is still support for IP chemotherapy in some centers.

[8] Based on these randomized trials, the IP route of administration for *carboplatin* or *cisplatin* and *paclitaxel* chemotherapy in the primary treatment of optimally resected stage III ovarian cancer is an acceptable therapeutic alternative to IV chemotherapy with *CP* (250). IP chemotherapy is best suited to patients who have optimally resected tumors, a good performance status, and are in overall good health. Because IP chemotherapy is more cumbersome and has a higher morbidity than IV therapy, this technique of drug delivery should be individualized after thorough discussion with the patient.

Dose-Dense Intravenous Chemotherapy

The Japanese GOG randomized 637 patients with ovarian cancer to receive

carboplatin AUC 6 and *paclitaxel* 180 mg/m^2 every 3 weeks, or the same dose of *carboplatin* and 80 mg/m^2 *paclitaxel* every week for at least six cycles (251). The median PFS was 28 months in the dose-dense arm and 17 months in the control group, and the median overall survival was 100.5 months for those patients receiving dose-dense therapy, versus 62 months for the every-3-weeks arm. They reported relatively little difference in toxicity between the two arms and that grade 3 to 4 neurotoxicity in particular was very low. In the 417 patients who had stage III disease, about half had less than 1 cm maximum residual disease, similar to the patients in GOG 172. Women with at least 1 cm of residual disease following cytoreductive surgery appeared to benefit the most from dose-dense therapy compared to every 3 weeks therapy. In this analysis, the median PFS was 17.6 months versus 12 months and the median overall survival was 51 months versus 33 months, respectively. **There is good evidence that weekly *paclitaxel* is more effective than *paclitaxel* every 3 weeks in breast cancer and the Japanese GOG study suggests that the same may apply to ovarian cancer.** Other studies have led to questioning this treatment approach in the United States. In GOG 262, patients with stage II to IV epithelial ovarian cancer were randomly assigned to *CP* every 3 weeks versus dose-dense chemotherapy (*carboplatin* every 3 weeks and weekly *paclitaxel*). *Bevacizumab* administration was optional in both arms and 84% of the patients were treated with *bevacizumab*. Sixty-three percent had gross residual disease, 24% had microscopic residual disease, and in 13% the amount of residual disease was not noted.

At a median follow-up of 28 months, no difference in PFS was found between the two groups. The subset analysis suggested a difference based on whether or not *bevacizumab* was received. **In patients who did not receive *bevacizumab*, dose-dense treatment prolonged PFS versus the every 3-week chemotherapy** (median of 14 months vs. 10 months). Among patients treated with chemotherapy and *bevacizumab,* there was no significant difference among the every 3-week chemotherapy versus dose-dense patients (median of 15 months in both arms) (253).

The Multicenter Italian Trial in Ovarian Cancer (MITO-7), compared every 3-week *CP* to a modified dose-dense regimen where *CP* were delivered on a weekly schedule (*carboplatin* AUC 2 and *paclitaxel* 60 mg/m^2 on days 1, 8, 15 every 3 weeks) in stage 1C to IV epithelial ovarian cancer.

In this study, there was a similar PFS between the two regimens with the weekly regimen having better quality-of-life scores. Severe myelosuppression and neuropathy were less common in the weekly regimen (254).

[9] More convincing evidence that the dose-dense therapy may be not superior to every 3-week chemotherapy of the JCOG study can be found in the results from the ICON8 trial. In this trial, 1,566 predominantly European patients were randomized to receive one of three regimens: Arm 1, *carboplatin* AUC 5/6 and *paclitaxel* 175

mg/m^2 every 3 weeks; Arm 2, *carboplatin* AUC 5/6 every 3 weeks and *paclitaxel* 80 mg/m^2 weekly; Arm 3, *carboplatin* AUC 2 and *paclitaxel* 80 mg/m^2 weekly. All patients had received neoadjuvant chemotherapy with planned interval debulking or received chemotherapy after initial primary cytoreductive surgery. **There was no benefit found for the dose-dense regimens. The PFS was 24.4 months with every 3-week dosing, compared to 24.9 and 25.3 months in arms 2 and 3, respectively** (255).

Neoadjuvant Chemotherapy

[7] Neoadjuvant chemotherapy may be considered for patients with advanced ovarian/fallopian tube/peritoneal carcinoma who are thought to have a low likelihood of upfront optimal cytoreduction or in women determined to have a high perioperative risk based on a poor performance status. A series performed by Schwartz et al. suggested that these patients treated with neoadjuvant or cytoreductive chemotherapy had survival that was comparable to those patients treated in the same institution with debulking surgery followed by conventional chemotherapy (256). It is accepted that two or three cycles of chemotherapy before cytoreductive surgery may be helpful in patients with massive ascites and large pleural effusions. The chemotherapy may decrease the effusions, improve the patient's performance status, and decrease postoperative morbidity, particularly chest morbidity (257,258).

The EORTC completed a large randomized trial in 718 patients with advanced ovarian cancer comparing initial surgery followed by six cycles of *CP* with three cycles of neoadjuvant chemotherapy followed by surgical debulking and another three cycles of chemotherapy. The study found that the PFS was identical in both arms (12 months) and the overall survival (30 months) was the same in both arms (203). The morbidity of surgery was significantly less in patients receiving neoadjuvant chemotherapy, suggesting that **in selected patients with very advanced (stages IIIC and IV) ovarian cancer and on average had a poor performance status, two to three cycles of neoadjuvant chemotherapy prior to surgical debulking is a reasonable option.** There have been other studies in support of neoadjuvant chemotherapy as an option for advanced ovarian/ fallopian tube/peritoneal carcinoma including the CHORUS trial. This phase III randomized, noninferiority, controlled trial was done across 87 hospitals in New Zealand and the United Kingdom and enrolled patients with suspected stage III or IV cancer. Patients were randomly assigned to either primary surgery followed by six cycles of chemotherapy versus three cycles of primary chemotherapy followed by surgery, then three additional cycles of completion chemotherapy. Patients could receive *CP* or another *carboplatin* combination regimen or single-agent carboplatin. There was no difference in the median overall survival comparing primary surgery to the primary chemotherapy group. **The CHORUS trial also concluded that in women with very advanced stage III or IV ovarian cancer**

and a poor performance status, survival with primary chemotherapy is noninferior to primary surgery (204).

Chemotherapy and Bevacizumab

Inhibition of angiogenesis with drugs such as *bevacizumab* demonstrated activity and benefit in women with recurrent ovarian cancer. There is evidence in other tumor types such as breast cancer and colon cancer that the addition of *bevacizumab* to chemotherapy increases response rates, PFS, and survival in some studies (259–261). Two large randomized trials (GOG 218 and ICON7) investigating the impact of the addition of *bevacizumab* to standard *CP* in patients with advanced ovarian cancer were carried out to address this question (262,263). GOG 218 was a phase III three-arm randomized double-blind placebo-controlled trial. Patients in arm one received six cycles of *CP* and placebo starting with the second cycle and continuing for 16 additional cycles after the completion of chemotherapy. Patients in arm two received six cycles of chemotherapy with *bevacizumab* starting with cycle two and administered with chemotherapy followed by 16 cycles of placebo, and in arm three patients received *bevacizumab* starting with cycle two of chemotherapy and then received 16 additional cycles after the completion of chemotherapy. This study was designed to investigate the benefit of *bevacizumab* in combination with chemotherapy and as a maintenance therapy. The *bevacizumab* was administered at a dose of 15 mg/kg, starting with the second cycle of chemotherapy, to decrease the risk of gastrointestinal perforation, which is a rare complication of this agent. The GOG 218 reported a modest improvement of 3.8 months in the PFS in patients randomized to receive *bevacizumab* in combination with *CP* every 3 weeks and then as a maintenance therapy every 3 weeks for an additional 16 cycles for a total of 15 months' treatment (262). The toxicity of *bevacizumab* was acceptable and the risk of bowel perforation low (below 2%). The study did not find any improvement in the overall survival with *bevacizumab* in either arm receiving the drug. An unplanned subgroup analysis demonstrated that treatment with *bevacizumab* improved the PFS and overall survival particularly in patients with ascites but not in other patients. The ICON7 study is similar to the GOG study, although it was a two-arm study of *CP* plus or minus *bevacizumab* 7.5 mg/kg administered every 3 weeks with chemotherapy for six cycles and then as maintenance therapy for 12 additional cycles. The ICON7 results reported a longer median PFS at 42 months of follow-up for the arm including *bevacizumab* compared to the standard therapy arm (24 months vs. 22 months). There was no difference in the overall survival noted (263). In an exploratory analysis of a predefined subgroup of patients with poor prognosis/ high-risk disease, a significant difference in the overall survival was noted between women who received *bevacizumab* plus chemotherapy and those who received chemotherapy alone (restricted mean survival time, 34.5 months [95% CI, 32.0–37.0] with standard chemotherapy vs. 39.3 months [37.0–41.7] with *bevacizumab*; log-rank $p = 0.03$). In

non–high-risk patients, the restricted mean survival time did not differ significantly between the two treatment groups (49.7 months [95% CI, 48.3–51.1] in the standard chemotherapy group vs. 48.4 months [47.0–49.9] in the *bevacizumab* group; $p = 0.20$) (264). **The results of these studies support a potential role of *bevacizumab* in combination with chemotherapy in selected patients with advanced ovarian cancer. However, the cost of *bevacizumab* is very high and the improvement in PFS is short and no survival improvement was seen.**

Chemotherapeutic Recommendation in Advanced Epithelial Ovarian Cancer

For the treatment of advanced-stage epithelial ovarian cancer, the following treatment regimens should be considered (Table 39-4):

- **Combination chemotherapy or IV *CP every 3 weeks* or IP *carboplatin* or *cisplatin* and *paclitaxel* are the treatments of choice for patients with advanced disease. The advantages and disadvantages of the IV versus IP routes of administration of these drugs should be discussed with the patient.**
- **The recommended doses and schedule for IV chemotherapy are *carboplatin* (starting dose AUC = 5 to 6), and *paclitaxel* (175 mg/m^2), every 3 weeks for six cycles. Alternatively, the dose-dense regimen of *carboplatin* AUC 6 every 3 weeks for six cycles and weekly *paclitaxel* 80 mg/m^2 could be used, but is not superior to the 3-weekly regimen in non-Japanese women (251). There are no good data to show any benefit for treatment beyond six cycles but the number of cycles may need to be individualized based on time to response and toxicity. Ideally the CA-125 should have normalized by the end of chemotherapy.**
- **The recommended doses and schedule for IP chemotherapy are *paclitaxel* 135 mg/m^2 IV on day 1, followed by *carboplatin* AUC 5 or *cisplatin* 75 to 100 mg/m^2 IP on day 2, followed by *paclitaxel* 60 mg/m^2 IP on day 8, every 3 weeks for six cycles, as tolerated.**
- ***Bevacizumab* 7.5 to 15 mg/kg can be added to any of these IV or IP chemotherapy regimens.**
- **In patients who cannot tolerate combination chemotherapy, single-agent, IV-administered *carboplatin* (AUC 5 to 6) can be given.**
- **In patients who have a hypersensitivity to *paclitaxel* or *carboplatin*, an alternative active drug can be substituted (e.g., *docetaxel*, nanoparticle *paclitaxel*, *cisplatin*). In the case of *carboplatin* hypersensitivity, desensitization could be attempted.**

Table 39-4 Combination Chemotherapy for Advanced Epithelial Ovarian Cancer: Recommended Regimens

Drugs[a]	Dose (mg/m²)[b]	Route	Interval (weeks)	Treatments (cycles)
Standard Regimens				
Intraperitoneal chemotherapy				
Paclitaxel	135	IV	3, day 1	6
Cisplatin	50–100	IP	day 2	
Paclitaxel	60	IP	day 8	
Intravenous chemotherapy				
Paclitaxel	175	IV	3	6–8
Carboplatin	AUC = 5–6[a]	IV		
Paclitaxel	135	IV	3	6–8
Cisplatin	75	IV		
Alternative Drugs[c]				
Docetaxel	75	IV	3	
Doxorubicin, liposomal	35–50	IV	3–4	
Topotecan	1.0–1.25	IV	1	
	4.0	IV	3 (daily × 3–5 days)	
Etoposide	50	PO	3, days 14–21	

[a] *Bevacizumab* 7.5–15 mg/kg can be added to any of these regimens.

[b] Except for carboplatin dosing, where AUC—area under the curve—dose calculated by using the Calvert formula (**Calvert AH, Newell DR, Gumbrell LA, et al.** Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;7:1748–1756).

[c] Drugs that can be substituted for paclitaxel if hypersensitivity to that drug occurs; the number of treatments administered as tolerated.

The treatment of all patients with advanced-stage disease is approached in a similar manner, with modifications based on the overall status and general health of the patient and the extent of residual disease present at the time treatment is initiated.

Maintenance Therapy Following Response to First-Line Chemotherapy

Almost 80% of women with advanced-stage disease who respond to first-line chemotherapy will relapse. There have been several trials conducted to determine if there is a benefit of maintenance therapy in these patients immediately following their primary treatment in an effort to decrease the relapse rate.

Paclitaxel

In a study conducted by the GOG and SWOG, 277 women with advanced ovarian cancer who had a complete clinical remission to first-line chemotherapy were

randomized to receive 3 or 12 cycles of additional single-agent *paclitaxel* (175 or 135 mg/m^2 every 28 days) (265). Patients were excluded if they developed grade 2 or 3 neurotoxicity during their initial chemotherapy. Because of cumulative toxicity, the mean number of actual cycles of *paclitaxel* received by the group assigned to receive 12 cycles was 9. The treatment-related grade 2 to 3 neuropathy was more common with longer treatment, 24% versus 14% of patients, respectively. The study closed after a median follow-up of only 8.5 months, and an interim analysis showed a significant 7-month prolongation in the median PFS (28 months vs. 21 months) with 9 months versus 3 months of consolidation *paclitaxel*. There was no difference in the median overall survival and this study has not changed practice. It is improbable that a survival benefit will appear with longer follow-up, because patients assigned to three cycles were given the option of receiving an additional nine courses of *paclitaxel* after the study was discontinued (266). Another placebo-controlled, randomized trial using two formulations of *paclitaxel* was conducted by the GOG. A total of 1,157 patients with stage III to IV ovarian/fallopian tube/peritoneal cancer who achieved a clinical complete response after first-line treatment were randomized to surveillance, *paclitaxel* infusion every 28 days for 12 cycles, or CT-2103 (paclitaxel poliglumex) on the same schedule. After a median follow-up of 71 months, the median overall survival was not different between the groups. There was a small extension in the PFS with maintenance therapy compared to surveillance (267).

Topotecan

Four additional treatment courses of *topotecan* were administered to patients following six cycles of *CP* in two randomized trials, one conducted in Italy and the other in Germany (268,269). In the larger trial conducted in Germany, 1,059 evaluable patients were randomly assigned to six cycles of *paclitaxel* (175 mg/m^2 over 3 hours) and *carboplatin* (AUC 5) with (537 patients) or without (522 patients) four additional cycles of *topotecan* (1.25 mg/m^2 IV days 1 to 5 every 3 weeks) (269). In the Italian trial, 273 women were randomly assigned to receive four additional cycles (137 patients) of *topotecan* at a dose of 1 mg/m^2 on days 1 to 5 every 3 weeks or no further chemotherapy (136 patients) (268). No significant differences in either the PFS or overall survival in patients who received four to six cycles of consolidation *topotecan*.

Cisplatin

In a randomized clinical trial of IP *cisplatin* for consolidation versus observation, there was no difference in survival between the treatment arms (270). A meta-analysis concluded that maintenance chemotherapy was associated with increased toxicity but no significant improvement in the PFS or overall survival (271).

Biologic Therapies

Adding the monoclonal antibody (MonAb) *bevacizumab* to first-line *CP*

chemotherapy followed by maintenance *bevacizumab* for a year was associated with a modest improvement in the PFS (262,263).

There are a number of trials that addressed the role of oral angiogenesis inhibitors as maintenance therapy after completion of first-line therapy in women with advanced ovarian cancer. *Pazopanib* is an oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and c-KIT. In the randomized double-blinded placebo-controlled phase III AGO-OVAR16/VEG110655 trial, maintenance *pazopanib* for up to 2 years after completion of first-line chemotherapy in women with advanced epithelial ovarian cancer improved the PFS over placebo (HR, 0.77; 95% CI, 0.64–0.91; $P = 0.0021$; median PFS 17.9 with PZ vs. 12.3 months with placebo) (272). However, there was a higher incidence of grade 3 and 4 adverse events in the *pazopanib* arm, which led to dose reductions in 58% of patients and early discontinuation caused by adverse events (AE) in 33% of patients. In view of the toxicity, the pharmaceutical company who sponsored the trial decided not to submit for regulatory approval. *Nintedanib* is a triple angiokinase inhibitor of VEGF, fibroblast growth factor, and platelet-derived growth factor. AGO-OVAR 12 randomized 1,366 patients 2:1 to maintenance *nintedanib* or placebo as maintenance therapy following first-line chemotherapy. The median PFS in *nintedanib* was 17.2 months vs. 16.6 months in placebo arm and this is not a reasonable therapeutic option (273).

Studies investigating MonAbs directed toward CA-125 (OvaRex) and toward the HMFG (human milk fat globulin) tumor–associated antigens were conducted (274–276). In a randomized, placebo-controlled trial of IV *oregovomab* (anti-CA-125 MonAb) as maintenance therapy, Berek et al. reported that *oregovomab* did not demonstrate a survival advantage as a maintenance therapy (275). A randomized trial of an IP-administered yttrium-labeled anti-mucin (HMFG) MonAb versus placebo was not associated with an improved overall survival after a negative second-look laparoscopy (276).

Treatment Assessment

Many patients who undergo optimal cytoreductive surgery and subsequent chemotherapy for epithelial ovarian cancer have no evidence of disease at the completion of treatment. Tumor markers and radiologic assessments are too insensitive to exclude the presence of subclinical disease. **Historically, a second-look surgery was performed to evaluate these patients, but that was abandoned, as there was no evidence of a meaningful benefit to patients** (161,277–286).

Tumor Markers

CA-125 is a surface glycoprotein associated with müllerian epithelial tissues, and is elevated in about 80% of patients with epithelial ovarian cancers, particularly those

with nonmucinous tumors (287–289). The CA-125 level frequently falls below the normal range after the initial surgical resection and one or two cycles of chemotherapy. Carcinoembryonic antigen (CEA) levels may be elevated in patients with ovarian cancer, but the test is too nonspecific and insensitive to be used in the management of these patients, apart from patients with a mucinous cancer of the ovary who may have an elevated CEA and CA19-9 (42).

Levels of CA-125 were correlated with findings at second-look operations. Elevated levels predicted the presence of residual disease, but levels within the normal range are an insensitive determinant of the absence of disease. In a prospective study, the predictive value of a positive test was 100%; if the level of CA-125 was elevated (>35 U/mL), the disease was always detectable in patients at the second-look procedure (287). The predictive value of a negative test was only 56%; if the level was less than 35 U/mL, disease was present in 44% of the patients at the time of the second-look surgery. **A literature review suggests that an elevated CA-125 level predicts persistent disease at second-look surgery in 97% of the cases, but the CA-125 level is not sensitive enough to exclude subclinical disease in many patients** (288).

Serum CA-125 levels can be used during chemotherapy to follow those patients whose levels were elevated at initial diagnosis and at the initiation of therapy (287). **The fall in the CA-125 correlates with response.** Those patients with persistently elevated levels after three cycles of treatment almost certainly will still have persistent disease. The majority of patients will have a CA-125 in the normal range following surgery and first-line chemotherapy and are typically followed with CA-125 levels every 3 to 4 months. There are well-accepted Gynecologic Oncology Intergroup (GCIG) criteria for CA-125 progression. Patients with an elevated CA-125 pretreatment and in the normal range following the completion of treatment must have a CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least 1 week apart to be classified as having CA-125 progression (289).

Radiologic Assessment

CT can be used to assess the response in patients with measurable lesions at the start of therapy. In patients who have no or minimal residual disease following cytoreductive surgery, the value of these tests is limited, but they may be useful in follow-up, especially to document the site of recurrence in patients with CA-125 progression. Ascites can be readily detected, but other diseases can be missed on a CT scan in patients with recurrent disease (290). A CT scan and fine-needle aspiration (FNA) cytology, if appropriate, can diagnose persistent or recurrent disease, but the false-negative rate of a CT scan is about 45% (291). MRI can be used as an alternative to CT in patients with allergies to the contrast medium (131,133). PET/CT has high diagnostic accuracy in patients with recurrent ovarian cancer. The reported sensitivity, specificity, and accuracy range from 86% to 96%, 93% to 100%, and 85% to 100%,

respectively (292).

Second-Line Therapy

Secondary Cytoreductive Surgery

Secondary cytoreduction is defined as an attempt at cytoreductive surgery in patients with recurrent ovarian cancer. This is usually considered in patients with platinum-sensitive recurrent ovarian cancer with localized recurrence or limited number of sites of recurrence when it is considered possible to resect all disease (293–296). Patients with progressive disease on chemotherapy (platinum refractory) or with platinum-resistant ovarian cancer are not suitable candidates for secondary cytoreduction. Although there are no hard and fast rules, secondary debulking should be restricted to patients who have a disease-free interval of at least 12, but preferably 24 months or those in whom it is expected that all macroscopic disease can be resected, regardless of the disease-free interval (293–301). **The role of secondary debulking surgery has been addressed in the DESKTOP III trial.** This study included patients with a PFS OF >6 months after first-line chemotherapy and who were considered to be good candidates for surgery based on a positive AGO Study Group score, defined as an ECOG performance status score of 0, ascites of 500 mL or less, and complete resection at initial surgery. The PFS results have been presented at ASCO 2017 and DuBois reported that the median PFS **in 204 women who met these criteria and were randomized to undergo surgery followed by chemotherapy was 19.6 months, compared with 14 months in 203 women who were randomized to receive only second-line chemotherapy.** The primary endpoint of the study is overall survival which will be available in a few years (302).

Chemotherapy for Recurrent Ovarian Cancer

The majority of women who relapse will be offered more chemotherapy with the likelihood of benefit related to the initial response and the duration of response. **The goals of treatment include improving control of disease-related symptoms, maintaining or improving the quality of life, delaying the time to progression, and possibly prolonging survival, particularly in women with *platinum*-sensitive recurrences.** Many active chemotherapy agents (*platinum*, *paclitaxel, topotecan, liposomal doxorubicin, docetaxel, gemcitabine*, and *etoposide*) and targeted agents (*bevacizumab*) and PARP inhibitors are available, and the choice of treatment is based on many factors including the likelihood of benefit, potential toxicity, and patient convenience.

Women who relapse later than 6 months after primary chemotherapy are classified as *platinum*-sensitive and usually receive further *platinum*-based chemotherapy with response rates ranging from 27% to 65% and a median survival

of 12 to 24 months (303–307). **Patients who relapse within 6 months of completing first-line chemotherapy are classified as *platinum*-resistant and have a median survival of 6 to 9 months and a 10% to 30% likelihood of responding to chemotherapy. Patients who progress while on treatment are classified as having *platinum*-refractory disease.** Objective response rates to chemotherapy in patients with *platinum*-refractory ovarian cancer are low—less than 20% (308).

The potential adverse effects associated with chemotherapy in trials in women with recurrent ovarian cancer are well documented and should not be underestimated. The three most commonly used drugs are *paclitaxel, topotecan*, and *liposomal doxorubicin* (309–335). The reported adverse effects associated with *paclitaxel* include alopecia in 62% to 100%, neurotoxicity (any grade) in 5% to 42% of patients, and grade 3 to 4 leukopenia in 4% to 24% of patients. *Topotecan* is associated with significantly greater myelosuppression than *liposomal doxorubicin* or *paclitaxel* and is observed in 49% to 76% of patients. *Liposomal doxorubicin* is associated with palmar-plantar erythrodysesthesia (PPE) of any grade in over 50% of patients and is severe in 23% particularly in patients treated at higher doses such 50 mg/m^2. Severe stomatitis is reported in up to 10% of patients (309–312).

Platinum-Sensitive Disease

The use of combination *platinum* plus *paclitaxel* chemotherapy versus a single-agent *platinum* was tested in two multinational randomized phase III trials and a randomized phase II study (336,337). In a report of the ICON4 and AGO-OVAR-2.2 (AGO Studiengruppe Ovarialkarzinom) trials, 802 women with *platinum*-sensitive ovarian cancer, who relapsed after being treatment free for at least 6 to 12 months were randomized to *platinum*-based chemotherapy (72% *carboplatin* or *cisplatin* alone; 17% *CAP;* 4% *carboplatin* plus *cisplatin;* and 3% *cisplatin* plus *doxorubicin*) or *paclitaxel* plus *platinum*-based chemotherapy (80% *paclitaxel* plus *carboplatin;* 10% *paclitaxel* plus *cisplatin;* 5% *paclitaxel* plus both *carboplatin* and *cisplatin;* and 4% *paclitaxel* alone) (336). The AGO-OVAR-2.2 trial did not accrue its planned number of patients. **In both trials, a significant proportion of the patients did not receive *paclitaxel*** as **part of their initial chemotherapeutic regimen. Combining the trials for analysis, there was a significant survival advantage for the *paclitaxel*-containing therapy** (HR, 0.82) with a median follow-up of 42 months. **The absolute 2-year survival advantage was 7% (57% vs. 50%), and there was a 5-month improvement in median survival (29 months vs. 24 months).** The PFS was better with the *paclitaxel* regimen (HR, 0.76); there was a 10% difference in 1-year PFS (50% vs. 40%) and a 3-month prolongation in the median PFS (13 months vs. 10 months). The toxicities were comparable, except for a significantly higher incidence of neurologic toxicity and alopecia in the *paclitaxel* group, while myelosuppression was significantly

greater with the *non-paclitaxel*–containing regimens. **These data support the slight advantage of a second-line regimen containing both *paclitaxel* and a *platinum* agent compared with *platinum*-based therapy alone. There were two randomized trials comparing *carboplatin alone to carboplatin and gemcitabine or liposomal doxorubicin*** (338,339). There was a higher response rate with the combination therapy and a longer PFS, but the studies were not powered to look at the overall survival. In the GCIG study comparing *carboplatin* and *gemcitabine* with *carboplatin* alone, the response rate was 47.2% for the combination and 30.9% for *carboplatin*, with the PFS being 8.6 months and 5.8 months, respectively (338). **A large GCIG study (CALYPSO) compared *carboplatin and liposomal doxorubicin* (CD) with *CP* in 976 patients** (340). **The PFS for the CD arm was statistically superior to the *CP* arm with a median PFS of 11.3 months versus 9.4 months, respectively.** There was no statistically significant difference in the overall survival between the treatment groups. Median survival was 33 months versus 30.7 months for CP versus CD. **The CD arm was better tolerated with less severe toxicities, and this combination is now widely used** (340).

***Carboplatin, gemcitabine,* and *bevacizumab* have been shown in a phase III randomized control trial to be superior to *carboplatin* and *gemcitabine* alone for platinum-sensitive recurrent epithelial ovarian cancer.** In the OCEANS study, 484 with platinum-sensitive disease were randomly assigned to *carboplatin* (AUC 4 on day 1) and *gemcitabine* 1,000 mg/m^2 on days 1 and 8 with or without *bevacizumab* (15 mg/kg on day 1) with every 21-day cycles. *Bevacizumab* could be given concurrently with chemotherapy for a maximum of 10 cycles followed by *bevacizumab* alone until progression of disease or toxicity.

The addition of *bevacizumab* to *carboplatin* and *gemcitabine* resulted in an improvement in the PFS (12 months vs. 8 months; HR, 0.48; 95% CI, 0.39–0.61); however, there was no overall survival difference between the two arms. Treatment with *bevacizumab* was associated with higher rates of serious hypertension (17% vs. <1%), proteinuria grade 3 or higher (9% vs. 1%) and noncentral nervous system bleeding (6% vs. 1%) (341,342).

In GOG 213, patients with platinum-sensitive recurrent epithelial ovarian cancer were assigned randomly to secondary cytoreduction versus no secondary cytoreduction and separately to chemotherapy (*CP*) with or without *bevacizumab*. Patients treated with *bevacizumab* received the drug with chemotherapy and afterward it was continued as a single agent until disease progression.

Compared with chemotherapy alone, the addition of *bevacizumab* resulted in an improvement in the PFS (13.8 months vs. 10.4 months, respectively; HR, 0.61; 95% CI, 0.51–0.72). There was an improvement of the overall survival of 5 months with chemotherapy and *bevacizumab* versus chemotherapy alone; median overall survival

(42.6 months vs. 37.3 months, respectively; HR, 0.84; 95% CI, 0.69–1.01) (343). **These studies show that maintenance with *bevacizumab* can improve the PFS and may improve the overall survival in a subset of patients.**

PARP Inhibitors

PARP inhibitors, including *niraparib* and *olaparib,* have been approved by FDA for maintenance therapy in patients with platinum-sensitive disease following a partial or complete response to platinum-based chemotherapy. The PFS is improved with these agents regardless of the BRCA status, although the patients with BRCA germline/somatic mutations have a greater benefit than patients without mutations.

Niraparib

***Niraparib* has been approved by the U.S. FDA for maintenance therapy in patients with platinum-sensitive disease following a partial or complete response to platinum-based chemotherapy for both germline *BRCA1* and *BRCA2* carriers and nongermline carriers.**

In the NOVA study, a phase III trial, 553 patients with platinum-sensitive recurrent ovarian cancer were assigned randomly after completion of platinum-based chemotherapy in a 2:1 ratio to *niraparib* maintenance or placebo. Patients were stratified based on the presence or absence of a gBRCA mutation. The patients in the non-gBRCA mutation cohort were further classified by whether or not homologous recombination deficiency (HRD) was observed. *Niraparib* compared to placebo increased the PFS in all groups of patients. **In the gBRCA group, the PFS was 21 months versus 5.5 months** (HR, 0.27; 95% CI, 0.17–0.41) in contrast to the **non-gBRCA group, where the PFS was 9.3 months versus 3.9 months** (HR, 0.45; 95% CI, 0.34–0.61). This study also attempted to identify the subset of patients with tumors with HRD and reported that in the HRD-positive group of non-gBRCA patients, the PFS was 12.9 months versus 3.8 months (HR, 0.38; 95% CI, 0.24–0.59). An exploratory analysis of HRD-negative patients demonstrated an improvement in the median PFS in favor of *niraparib* (6.9 months vs. 3.8 months; HR, 0.58; 95% CI, 0.08–0.90) (344).

Olaparib

***Olaparib* is FDA approved for the treatment of patients with gBRCA-mutated recurrent ovarian cancer who have received three or more prior lines of chemotherapy.**

There are data in support of maintenance *olaparib* in women with platinum-sensitive recurrent high-grade serous ovarian cancer from Study 19. This was a randomized phase II controlled trial of approximately 300 women with platinum-sensitive recurrent high-grade ovarian cancer who had achieved a response to their most recent treatment regardless of their BRCA status. The patients were randomly

assigned to *olaparib* 400 mg twice daily or placebo. Compared with placebo, *olaparib* was shown to improve the PFS (8 months vs. 5 months; HR for progression or death, 0.35; 95% CI, 0.25–0.49) (345). A separate analysis of Study 19 evaluated outcomes for gBRCA patients and showed that the clinical benefit was greatest for these patients. The PFS was (11 months vs. 4 months; HR, 0.18; 95% CI, 0.10–0.31) for *olaparib* versus placebo, respectively (346,347).

A randomized, double-blind, placebo-controlled, phase 3 trial was of maintenance *olaparib* after first-line combination chemotherapy known as the SOLO1 study was conducted in 15 countries (348). Of the 391 patients who underwent randomization, 260 were assigned to receive *olaparib* and 131 to receive placebo. A total of 388 patients had a germline *BRCA1* or *BRCA2* mutation, and 2 patients had a somatic *BRCA1* or *BRCA2* mutation. After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with *olaparib* than with placebo (at 3 years, 60% vs. 27%, HR = 0.30; 95% CI, 0.23 to 0.41; p <0.0001). Adverse events were consistent with the known toxic effects of *olaparib*. **The use of maintenance therapy with olaparib provided a substantial benefit in progression-free survival among women with newly diagnosed advanced ovarian cancer and a *BRCA1* or *BRCA2* mutations, and they had a 70% lower risk of disease progression or death with *olaparib* than with placebo**.

These results were confirmed in the much larger SOLO2 trial, which included 295 patients with gBRCA mutations and platinum-sensitive recurrent ovarian cancer who had responded to platinum-based chemotherapy. They were randomly assigned to receive *olaparib* (n = 196) or placebo (n = 99). The median PFS was significantly longer with *olaparib* (19.1 months [95% CI, 16.3–25.7]) than with placebo (5.5 months [5.2–5.8]; HR, 0.30; 95% CI, 0.22–0.41]; p <0.0001).

Rucaparib

***Rucaparib* is approved for treatment of BRCA-mutation–associated advanced ovarian cancer after completion of treatment with two or more chemotherapy regimens regardless of whether patients are platinum-sensitive or resistant.**

Ariel 3 included patients with platinum-sensitive, high-grade serous or endometrioid ovarian, fallopian tube, or peritoneal carcinoma, who had received at least two prior platinum-based chemotherapy regimens, complete or partial response to their last platinum-based regimen, and a CA-125 concentration of less than the upper limit of normal. They were randomized 2:1 to receive oral *rucaparib* 600 mg twice daily or placebo. The median PFS in patients with a BRCA-mutant carcinoma was 16.6 months (95% CI, 13.4–22.9; 130 [35%] patients) in the *rucaparib* group versus 5.4 months (3.4–6.7; 66 [35%] patients) in the placebo group (HR, 0.23 [95% CI, 0.16–0.34]; p <0.0001). Similar to the NOVA trial, the investigators analyzed all tumors for HRD using a different method. In patients with an HRD carcinoma (236 [63%] vs. 118

[62%]), the PFS was 13.6 months (10.9–16.2) versus 5.4 months (5.1–5.6; 0.32 [0.24–0.42]; p <0.0001).

In a phase II trial of 204 patients with recurrent platinum-sensitive, high-grade ovarian cancer treated with *rucaparib*, patients with BRCA mutations and high loss of heterozygosity (LOH) had a longer PFS compared to patients with low LOH. Patients were divided into three groups for the study; those with germline or somatic BRCA mutations, those who were BRCA-wild type but LOH high, and those who were BRCA-wild type and LOH low. The PFS was longer for patients with BRCA mutations (12.8 months; HR, 0.27; 95% CI, 0.16–0.44) and/or LOH high (5.7 months; HR, 0.62; 95% CI, 0.42–0.90) subgroups compared to those with LOH low (5.2 months) (349).

Other PARP Inhibitors

There are a number of other PARP inhibitors under investigation. *Veliparib* is another PARP inhibitor with encouraging results in a phase II trial of 50 women with BRCA mutations who were treated with *veliparib* monotherapy at a dose of 400 mg twice daily. There was a 26% overall response rate for platinum-sensitive and resistant patients and a 35% response rate among those with platinum-sensitive disease (350). *Veliparib* is being investigated in GOG-3005 in combination with chemotherapy in the frontline and maintenance setting.

Platinum-Resistant and Refractory Disease

Patients with *platinum*-refractory and resistant ovarian cancer are often treated with chemotherapy and may have a number of lines of therapy depending on the response and performance status. In *platinum*-refractory patients (i.e., those progressing on treatment), response rates to second-line chemotherapy are less than 10% and the median survival is short, around 3 to 5 months (304–308). **The management of women who are *platinum*-resistant (i.e., progressing within 6 months of completion of chemotherapy) is difficult and "non–cross-resistant agents" are selected, but there does not appear to be one best treatment.** Single-agent therapy is typically used because combination regimens are associated with more toxicity without any apparent additional benefit. High response rates of 48% to 64% were reported with dose-dense weekly *carboplatin* (AUC 2) plus *paclitaxel* (80 mg/m^2), and this deserves more study (351). There are a variety of potentially active drugs: *paclitaxel*, *docetaxel*, *topotecan*, *liposomal doxorubicin*, *gemcitabine*, *oral etoposide*, *tamoxifen*, and *bevacizumab* are the most frequently used. **Other agents include *vinorelbine* and newer drugs such as *trabectedin.***

Chemotherapy plus *bevacizumab* leads to improved responses in platinum-resistant disease. In the Aurelia study, 361 patients with platinum-resistant, *bevacizumab* naïve ovarian cancer (progression less than or equal to 6 months after 4 or more platinum-based cycles) were randomly assigned to treatment with chemotherapy with or without

bevacizumab at 15 mg/kg every 3 weeks. No more than two prior lines were allowed.

Chemotherapy options included the investigator's choice of *paclitaxel* 80 mg/m^2 on days 1, 8, 15, and 22 every 4 weeks, *or topotecan* 4 mg/m^2 on days 1, 8, 15 every 4 weeks or 1.25 mg/m^2 on days 1 through 5 every 3 weeks, or *Doxil* 40 mg/m^2 on day 1 every 4 weeks. Patients who received chemotherapy alone were allowed to crossover at time of disease progression to single-agent *bevacizumab*. The median follow-up was 13.5 months and compared to chemotherapy alone, the addition of chemotherapy to *bevacizumab* resulted in a reduction in the risk of disease progression. Median duration of response was 6.7 months versus 3.4 months (HR, 0.48; 95% CI, 0.38–0.60) in favor of *bevacizumab* and chemotherapy. There was no statistical improvement in overall survival. A planned subset analysis was performed and showed among those patients who received *paclitaxel*, the median PFS with or without *bevacizumab* was longer, 10 months versus 4 months, respectively; HR, 0.46; 95% CI, 0.30–0.71 (352).

The results of a study comparing *topotecan* with *liposomal doxorubicin* demonstrate the low response rates and poor prognosis among women with *platinum*-resistant ovarian cancer (309). There were two randomized trials comparing *liposomal doxorubicin* with either *topotecan* or *paclitaxel.* In a study of 237 women who relapsed after receiving one *platinum*-containing regimen, 117 of whom (49.4%) had *platinum*-refractory disease, *liposomal doxorubicin* 50 mg/m^2 over 1 hour every 4 weeks was compared with *topotecan* 1.5 mg/m^2/day for 5 days every 3 weeks (309). **The two treatments had a similar overall response rate** (20% vs. 17%), **time to progression** (22 weeks vs. 20 weeks), **and median overall survival** (66 weeks vs. 56 weeks). The myelotoxicity was significantly lower in the *liposomal doxorubicin*–treated patients than with those receiving *topotecan.* In a second study comparing *liposomal doxorubicin* with single-agent *paclitaxel* in 214 *platinum*-treated patients who had not received prior *taxanes*, the overall response rates for *liposomal doxorubicin* and *paclitaxel* were 18% versus 22%, respectively, and median survival durations were 46 and 56 weeks, respectively, and these were not significantly different (310). In practice, most patients are treated with a starting dose of 40 mg/m^2 of *liposomal doxorubicin* every 4 weeks, because of the toxicity associated with the higher dose and the need to dose reduce when 50 mg/m^2 is used. In a subset analysis of *platinum*-resistant patients, the median time to progression ranged from 9.1 to 13.6 weeks for *topotecan* and *liposomal doxorubicin*, respectively. The median survival (p = 0.455) was 35.6 weeks for pegylated *liposomal doxorubicin* and 41.3 weeks for *topotecan.* Objective response rates were recorded in 6.5% of patients who received *topotecan* and in 12.3% of those who received pegylated *liposomal doxorubicin* (p = 0.118). It is not known whether the treatment-improved symptom control or quality of life because this was not specifically addressed.

In another randomized trial of 195 patients with *platinum*-resistant ovarian cancer,

patients were randomized to receive either liposomal doxorubicin (PLD) or *gemcitabine* (353). In the *gemcitabine* and PLD groups, the median PFS was 3.6 months versus 3.1 months; the median overall survival was 12.7 months versus 13.5 months; the overall response rate was 6.1% versus 8.3%; and in the subset of patients with measurable disease, the overall response rate was 9.2% versus 11.7%, respectively. None of the efficacy end points showed a statistically significant difference between treatment groups. The PLD group experienced significantly more hand–foot syndrome and mucositis; the *gemcitabine* group experienced significantly more constipation, nausea or vomiting, fatigue, and neutropenia.

Taxanes

Single-agent *paclitaxel* shows objective responses in 20% to 30% in phase II trials of women with *platinum*-resistant ovarian cancer (313–318). The main toxicities are fatigue and peripheral neuropathy. **Weekly *paclitaxel* appears to be more active than 3-weekly administration in patients with platinum-resistant ovarian cancer.** In a study of 53 women with *platinum*-resistant ovarian cancer, weekly *paclitaxel* (80 mg/m^2 over 1 hour) had an objective response of 25% in patients with measurable disease, and 27% of patients without measurable disease had a 75% decline in serum CA-125 levels (313).

Docetaxel has some activity in these patients (354–356). The GOG studied 60 women with *platinum*-resistant ovarian or primary peritoneal cancer (356). Although there was a 22% objective response rate, the median response duration was only 2.5 months, and therapy was complicated by severe neutropenia in three-quarters of the patients.

Topotecan

Topotecan is a relatively active second-line treatment for patients with *platinum*-sensitive and *platinum*-resistant disease (321–335). In a study of 139 women receiving *topotecan* 1.5 mg/m^2 daily for 5 days, response rates were 19% and 13% in patients with *platinum*-sensitive and *platinum*-resistant disease, respectively (331). **The predominant toxicity of *topotecan* is hematologic, especially neutropenia.** With the 5-day dosing schedule, approximately 70% to 80% of patients have severe neutropenia, and 25% have febrile neutropenia with or without infection. In some studies, regimens of 5 days produce better response rates than regimens of shorter duration, but in others, reducing the dose to 1.0 mg/m^2 per day for 3 days is associated with similar response rates but lower toxicity (324,334). In a study of 31 patients, one-half of whom were *platinum* refractory, *topotecan* 2 mg/m^2 per day for 3 days every 21 days had a 32% response rate (329). Continuous infusion *topotecan* (0.4 mg/m^2 per day for 14 to 21 days) had a 27% to 35% objective response rate in *platinum*-refractory patients (328).

Weekly *topotecan* administered at a dose of 4 mg/m^2 per week for 3 weeks with a week off every month produced a response rate similar to the 5-day regimen with considerably less toxicity, and this dose schedule is commonly used in the recurrent setting (334).

Oral *topotecan*, not available in the United States, **results in similar response rates with less hematologic toxicity** (330). The IV and oral formulations of *topotecan* were compared in a randomized trial of 266 women as a third-line regimen after an initial *platinum*-based regimen (335). Compared with IV *topotecan* (1.5 mg/m^2 daily for 5 days every 3 weeks), oral *topotecan* (2.3 mg/m^2 per day for 5 days every 3 weeks) produced a similar response rate (13% vs. 20%), less severe myelosuppression, and only a slightly shorter median survival (51 weeks vs. 58 weeks).

Liposomal Doxorubicin

Liposomal doxorubicin (*Doxil* in the United States and *Caelyx* in Europe) has activity in *platinum*- and *taxane*-refractory disease (309–312,339). One of the **most important side effects of *liposomal doxorubicin* is the hand–foot syndrome, also known as palmar-plantar erythrodysesthesia or acral erythema, which occurs in 20% of patients who receive 50 mg/m^2 every 4 weeks** (310). Most oncologists administer 40 mg/m^2 and escalate only if there are no side effects. *Liposomal doxorubicin* has a low rate of alopecia. In a study of 89 patients with *platinum*-refractory disease, including 82 *paclitaxel*-resistant patients, *liposomal doxorubicin* (50 mg/m^2 every 3 weeks) produced a response in 17% (1 complete and 14 partial responses) (312). In another study, an objective response of 26% was reported, although there were no responses in women who progressed during first-line therapy (309).

Gemcitabine

Gemcitabine is associated with response rates of 20% to 50%, with 15% to 30% in patients who are *platinum*-resistant (357–361). **The principal toxicity is myelosuppression.**

Oral Etoposide

The most common toxicities with oral *etoposide* are myelosuppression and gastrointestinal issues: grade 4 neutropenia is observed in about one-fourth of patients, and 10% to 15% have severe nausea and vomiting (362,363). A study of oral *etoposide* given for a prolonged treatment (50 mg/m^2 daily for 21 days every 4 weeks) had a 27% response rate in 41 women with *platinum*-resistant disease, 3 of whom had durable complete responses (363). In 25 patients with *platinum* and *taxane*-resistant disease, 8 objective responses (32%) were reported.

Hormonal Therapy

***Tamoxifen* is associated with CA-125 response rates of 15% to 20% in small studies of patients with recurrent ovarian cancer** (364–370). The efficacy of tamoxifen was analyzed in a Cochrane review which included 623 women with recurrent epithelial ovarian cancer across several studies. Overall, 10% achieved an objective response, although the range within individual studies was 0% to 56%. The duration of response is short-lived for patients with high-grade ovarian cancer (366). Aromatase inhibitors (e.g., *letrozole*, *anastrozole*, and *exemestane*), which have activity in metastatic breast cancer, are being studied in relapsed ovarian cancer (371). One of the principal advantages of this class of agents is its very low toxicity (372).

Bevacizumab

***Bevacizumab* was the first targeted drug to show significant single-agent activity in ovarian cancer.** It is a humanized MonAb that targets angiogenesis by binding to VEGF-A, thereby blocking the interaction of VEGF with its receptor. There are a number of phase II studies reported using *bevacizumab* in patients with *platinum*-sensitive and *platinum*-resistant ovarian cancer with response rates ranging from 16% to 22% in *platinum*-sensitive and refractory patients (373). Up to 40% of patients had stabilization of disease for at least 6 months. A study of low-dose metronomic chemotherapy with 50 mg of *cyclophosphamide* daily and *bevacizumab* 10 mg/kg IV every 2 weeks showed significant activity in a study of 70 patients with recurrent ovarian cancer (374). The primary end point was PFS at 6 months. The probability of being alive and progression free at 6 months was 56%. A partial response was achieved in 17 patients (24%). The median time to progression and survival were 7.2 and 16.9 months, respectively. The use of *bevacizumab* brings potential toxicity. The side effects of *bevacizumab* are well recognized and include hypertension, fatigue, proteinuria, gastrointestinal perforation or fistula, and uncommonly, vascular thrombosis and central nervous system ischemia, pulmonary hypertension, and bleeding and wound-healing complications. The most common side effects are hypertension that is grade 3 in 7% of patients but is manageable in most patients. The most concerning side effect is bowel perforation and the study by Cannistra et al. was stopped after recruiting 44 patients because of an 11% incidence of perforation of the bowel (375). The bowel perforation complication could be minimized by carefully screening patients. Simpkins et al. limited *bevacizumab* treatment to patients without clinical symptoms of bowel obstruction or evidence of rectosigmoid involvement on pelvic examination or bowel involvement on CT scan (376). Their study included 25 patients with *platinum*-resistant ovarian cancer who were heavily pretreated, and they observed a response rate of 28% without any bowel perforations or other grade 3 or 4 toxicities. This highlights the importance of patient selection.

Radiation Therapy

Whole-abdominal radiation therapy was given as a treatment for recurrent or persistent disease but is associated with high morbidity and is not used. The principal problem with this approach is the development of acute and chronic intestinal morbidity. As many as 30% of patients receiving this treatment develop intestinal obstruction, which necessitated exploratory surgery with potential morbidity (377).

Intestinal Obstruction

Patients with epithelial ovarian cancer often develop intestinal obstruction, either at the time of initial diagnosis or in association with recurrent disease (378–393). Obstruction may be related to a mechanical blockage or to carcinomatous ileus.

The intestinal blockage can be corrected in most patients with obstruction at initial diagnosis. The decision to perform an exploratory procedure to ease intestinal obstruction in patients with recurrent disease is more difficult. For patients whose life expectancy is very short (e.g., less than 2 months), surgical relief of the obstruction is not indicated (378–383). **In those patients with a longer projected lifespan, features predicting a reasonable likelihood of correcting the obstruction include young age, good nutritional status, and the absence of rapidly accumulating ascites** (379).

For most patients with recurrent ovarian cancer and intestinal obstruction, particularly small bowel obstruction, initial management should include proper radiographic documentation of the obstruction, hydration, correction of any electrolyte disturbances, parenteral alimentation, and intestinal intubation. For some patients, the obstruction may be alleviated by this conservative approach. A preoperative upper gastrointestinal radiographic series and a barium enema will define possible sites of obstruction.

If exploratory surgery is deemed appropriate, the type of operation to be performed will depend on the site and the number of obstructions. **Multiple sites of obstruction are not uncommon in patients with recurrent epithelial ovarian cancer.** More than one-half of the patients have small bowel obstruction, one-third have colonic obstruction, and one-sixth have both (380–384). If the obstruction is principally contained in one area of the bowel (e.g., the terminal ileum), this area can be either resected or bypassed, depending on what is easier to accomplish safely. Intestinal bypass is less morbid than resection, and in patients with progressive cancer, the survival time after these two operations is the same (385–390).

If multiple obstructions are present, resection of several segments of intestine is usually not indicated, and intestinal bypass and/or colostomy should be performed. A gastrostomy may be useful in this circumstance, and this can usually be placed percutaneously (389,392).

Surgery for bowel obstruction in patients with ovarian cancer carries an operative mortality of about 10% and a major complication rate of about 30% (378–390). The need for multiple reanastomoses and poor nutrition increases the

morbidity, which consists primarily of sepsis and enterocutaneous fistulae. The median survival ranges from 3 to 12 months, although about 20% of these patients survive longer than 12 months (390–393).

Survival

The prognosis for patients with epithelial ovarian cancer is related to several clinical variables. Survival analyses based on prognostic variables are presented (4,65,151–155,160). Including patients at all stages, patients younger than 50 years of age have a 5-year survival rate of about 40%, compared with about 15% for patients older than 50 years.

The 5-year survival rate for carefully and properly staged patients with stage I disease is as high as 94%, for stage II is 73%, for stage III or IV 28% (65). **The 5-year survival rate for stage IIIA is 41%, for stage IIIB about 25%, for stage IIIC 23%, and for stage IV disease 11% (Fig. 39-16). An analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database reveals a trend toward improved survival for ovarian cancer in the United States. In this cohort, the survival for stage I was 93%, for stage II 70%, for stage III 37%, and for stage IV 25%** (394).

Survival of patients with borderline tumors is excellent, with stage I lesions having a 98% 15-year survival (160). When all stages of borderline tumors are included, the 5-year survival rate is about 86% to 90%.

Patients with stage III disease with microscopic residual disease at the start of treatment have a 5-year survival rate of about 40% to 75%, compared with about 30% to 40% for those with optimal disease, and only 5% for those with suboptimal disease (154,155,178). Patients whose Karnofsky index (KI) is low (<70) have a significantly shorter survival than those with a KI greater than 70 (160).

NONEPITHELIAL OVARIAN CANCERS

Compared with epithelial ovarian cancers, other malignant tumors of the ovary are uncommon. **Nonepithelial malignancies of the ovary account for about 10% of all ovarian cancers** (2,3,395). Nonepithelial ovarian cancers include malignancies of germ cell origin, sex cord–stromal cell origin, metastatic carcinomas to the ovary, and a variety of extremely rare ovarian cancers (e.g., sarcomas). Although there are similarities in the presentation, evaluation, and management of these patients, the tumors have unique qualities that require a special approach (2,395–398).

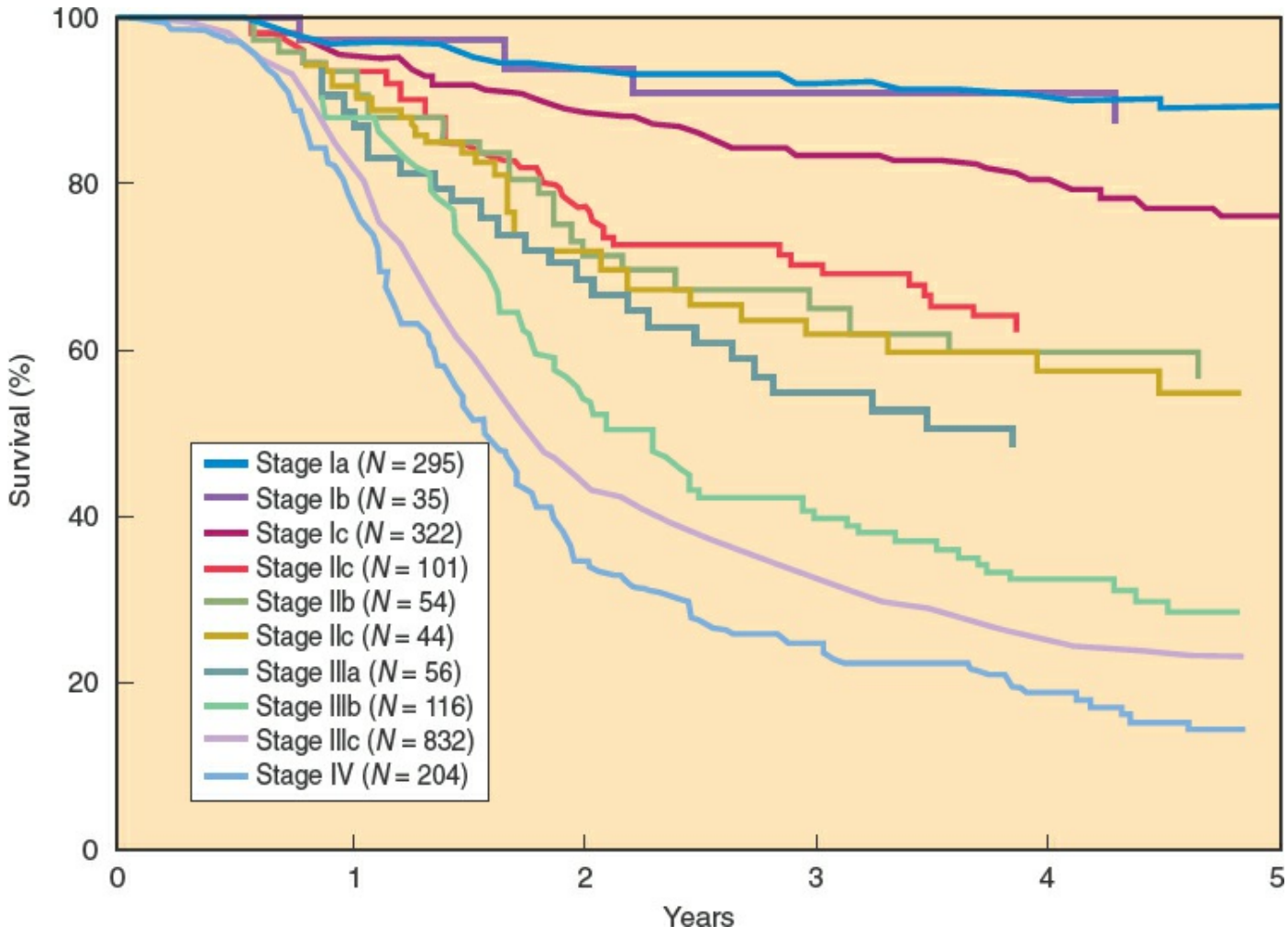


FIGURE 39-16 Survival of patients with epithelial ovarian cancer by substage. (Adapted from **Heintz APM, Odicino F, Maisonneuve P, et al.** Carcinoma of the ovary. In Twenty-sixth annual report of the results of treatment of gynaecological cancer. Int J Gynecol Oncol. 2006;95(suppl 1): S161–S192.)

Germ Cell Malignancies

Germ cell tumors are derived from the primordial germ cells of the ovary. Their incidence is about one-tenth the incidence of malignant germ cell tumors of the testis, so

most of the advances in the management of these tumors are extrapolations from experience with the corresponding testicular tumors. Although malignant germ cell tumors can arise in extragonadal sites such as the mediastinum and the retroperitoneum, most germ cell tumors arise in the gonad from undifferentiated germ cells. The variation in the site of these cancers is explained by the embryonic migration of the germ cells from the caudal part of the yolk sac to the dorsal mesentery before their incorporation into the sex cords of the developing gonads (2,4,395).

Table 39-5 Histologic Typing of Ovarian Germ Cell Tumors

1. Primitive germ cell tumors
- A. Dysgerminoma
- B. Yolk sac tumor
- C. Embryonal carcinoma
- D. Polyembryoma
- E. Nongestational choriocarcinoma
- F. Mixed germ cell tumor

2. Biphasic or triphasic teratoma
- A. Immature teratoma
- B. Mature teratoma
  1. Solid
  2. Cystic
     a. Dermoid cyst
     b. Fetiform teratoma (homunculus)

3. Monodermal teratoma and somatic-type tumors associated with dermoid cysts
- A. Thyroid tumor
  1. Struma ovarii
     a. Benign
     b. Malignant
- B. Carcinoid
- C. Neuroectodermal tumor
- D. arcinoma
- E. Melanocytic
- F. Sarcoma
- G. Sebaceous tumor
- H. Pituitary-type tumor
- I. Others

Adapted from **Kurman RJ, Carcangui ML, Herrington CS, et al.,** eds. *World Health Organization Classification of Tumours of Female Reproductive Organs*. Lyon: IARC Press; 2014.

Classification

A histologic classification of ovarian germ cell tumors is presented in Table 39-5 (4,395). **Both α-fetoprotein (AFP) and human chorionic gonadotropin (hCG) are secreted by some germ cell malignancies and can be clinically useful in the diagnosis of a pelvic mass and monitoring patients after surgery. Placental alkaline phosphatase (PLAP) and lactate dehydrogenase (LDH) are elevated to 95% of dysgerminomas, and serial measurements of LDH may be useful for monitoring the disease.** A classification of germ cell tumors is based on the histologic and immunocytochemical feature which include AFP and β-hCG **(Fig. 39-17)** (399).

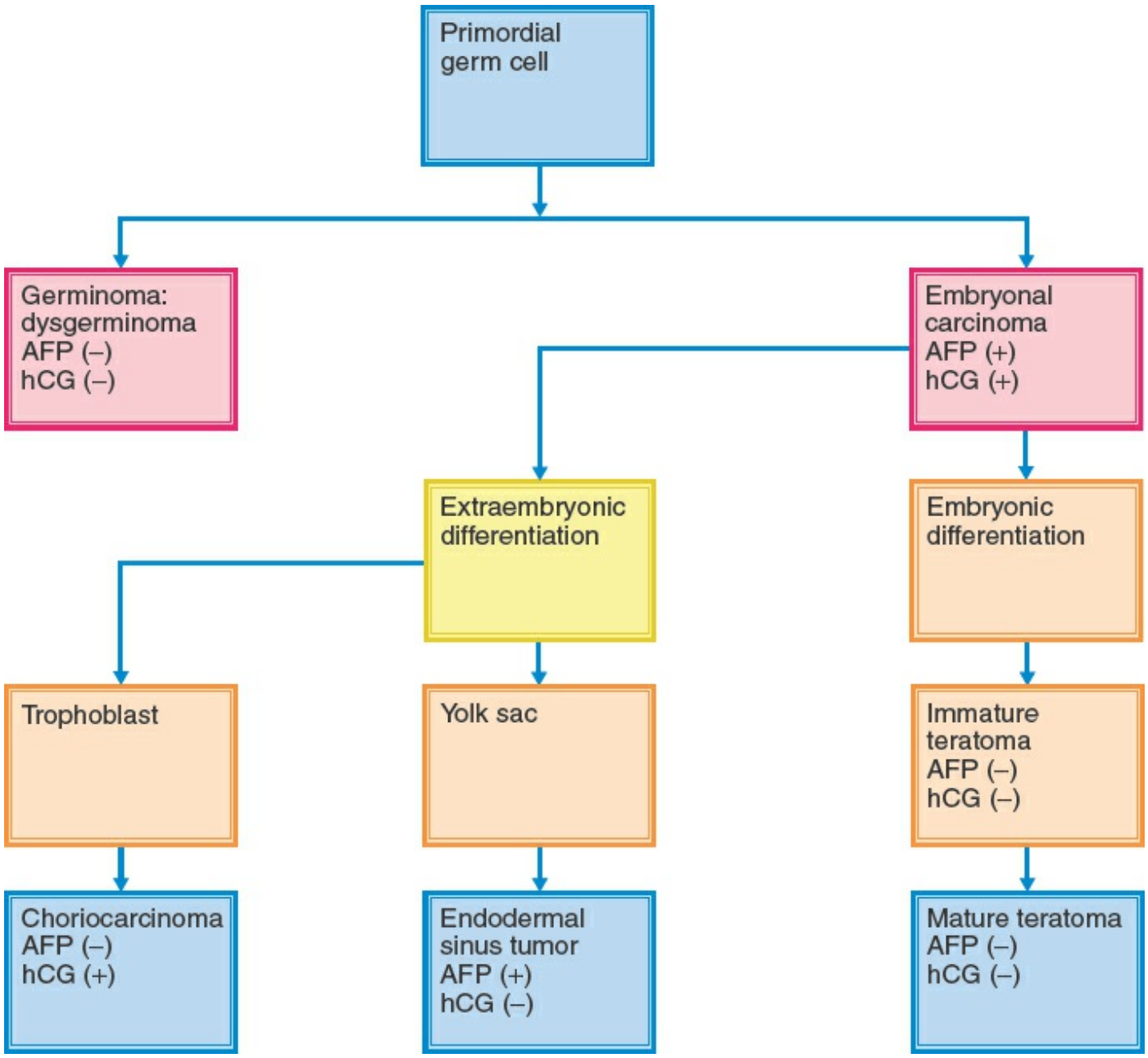


FIGURE 39-17 Relationship between types of pure malignant tumors. Germ cell tumors and their secreted marker substances. (From **Berek JS, Friedlander ML, Hacker NF.** Germ cell and nonepithelial ovarian cancer. In: Berek JS, Hacker NF. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:532.)

In this scheme, **embryonal carcinoma (a cancer composed of undifferentiated cells) synthesizes both hCG and AFP,** and this lesion is the progenitor of several other germ cell tumors (399–401). More differentiated germ cell tumors, such as the endodermal sinus tumor, which secretes AFP, and the choriocarcinoma, which secretes hCG, are derived from the extraembryonic tissues; the immature teratomas derived from the embryonic cells have lost the ability to secrete these substances. Pure germinomas do not secrete these markers.

Epidemiology

Although 20% to 25% of all benign and malignant ovarian neoplasms are of germ cell origin, only about 3% of these tumors are malignant (2,4). Germ cell malignancies account for fewer than 5% of all ovarian cancers in Western countries. Germ cell malignancies represent up to 15% of ovarian cancers in Asian and African American societies, where epithelial ovarian cancers are much less common.

[11] In the first two decades of life, almost 70% of ovarian tumors are of germ cell origin, and one-third of these are malignant (2,4,395). Germ cell cancers are seen in the third decade, but thereafter they become quite rare.

Clinical Features

Symptoms

[11] In contrast to the slower-growing epithelial ovarian tumors, germ cell malignancies grow rapidly and commonly present with acute/subacute pelvic pain related to capsular distention, hemorrhage, or necrosis. The rapidly enlarging pelvic mass may produce pressure symptoms on the bladder or rectum, and menstrual irregularities may occur in menarcheal patients. Some young patients misinterpret the early symptoms of a neoplasm as those of pregnancy, which can lead to a delay in the diagnosis. Acute symptoms associated with torsion or rupture of the adnexa can develop. These symptoms may be confused with acute appendicitis. In more advanced cases, ascites may develop, and the patient can have abdominal distention (389).

Signs

For a patient with a palpable adnexal mass, the evaluation can proceed as outlined. Some patients with germ cell tumors will be premenarcheal and may require examination under anesthesia. **If the lesions are principally solid or a combination of solid and cystic, as might be noted on an ultrasonographic evaluation, a neoplasm is probable and a malignancy is possible** (see Fig. 9.8 and Chapter 9). During the remainder of the physical examination, effort should be directed to searching for signs of ascites, pleural effusion, and organomegaly.

Diagnosis

Adnexal masses measuring 2 cm or larger in premenarcheal girls or 8 cm or larger in other premenopausal patients will usually require surgical exploration. For young patients, blood tests should include serum hCG and AFP and LDH. A CT scan of the chest is important because germ cell tumors can metastasize to the lungs or mediastinum. **A karyotype should be obtained preoperatively for all premenarcheal girls, particularly those with dysgerminomas, because they may arise in dysgenetic gonads** (396,402). A preoperative CT scan or MRI may document the presence and extent of retroperitoneal lymphadenopathy or liver metastases; however, because these

patients require surgical exploration, preoperative imaging may not impact initial surgical management. If postmenarcheal patients have predominantly cystic lesions up to 8 cm in diameter, they may be observed or given oral contraceptives for two menstrual cycles, which may reduce new ovarian cyst formation (403).

Dysgerminoma

[12] Dysgerminoma is the most common malignant germ cell tumor, accounting for about 30% to 40% of all ovarian cancers of germ cell origin (2,4,399). The tumors represent only 1% to 3% of all ovarian cancers, but they represent as many as 5% to 10% of ovarian cancers in patients younger than 20 years. Seventy-five percent of dysgerminomas occur between the ages of 10 and 30 years, 5% occur before the age of 10 years, but they rarely occur after 50 years of age (2,4,389). Because these malignancies occur in young women, 20% to 30% of ovarian malignancies associated with pregnancy are dysgerminomas.

Germinomas are found in both sexes and may arise in gonadal or extragonadal sites. The latter includes the midline structures from the pineal gland to the mediastinum and the retroperitoneum. Histologically, they represent abnormal proliferations of the basic germ cell. In the ovary, the germ cells are encapsulated at birth (the primordial follicle), and the unencapsulated or free cells die. If either of the latter processes fails, it is possible that the germ cell could free itself of its normal control and multiply indiscriminately.

The size of dysgerminomas varies widely, but they are usually 5 to 15 cm in diameter (2,4). The capsule is slightly bosselated, and the consistency of the cut surface is fleshy and pale tan to gray-brown in color **(Fig. 39-18)**.

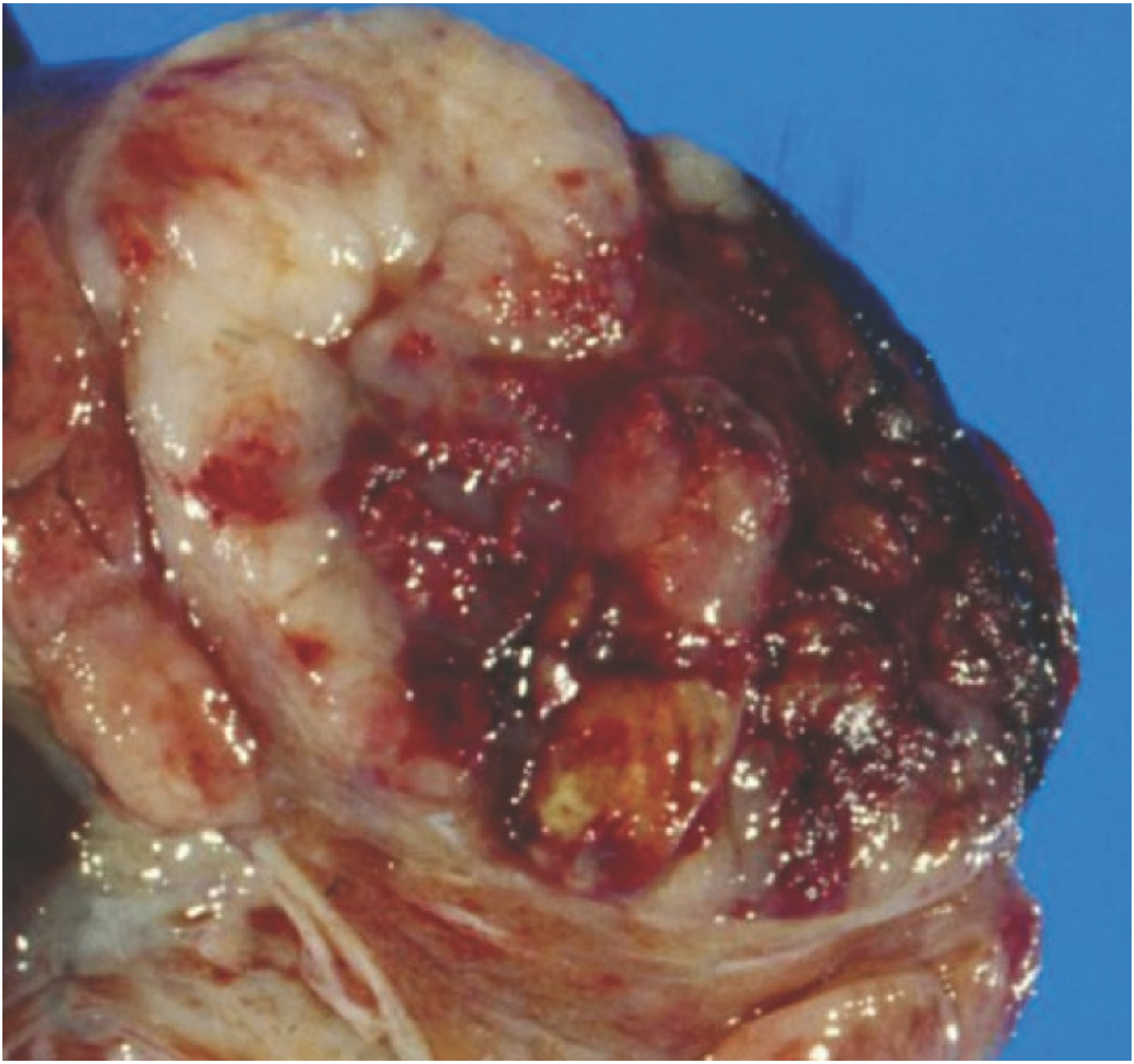


FIGURE 39-18 Dysgerminoma of the ovary. Note that the lesion is principally solid with some cystic areas and necrosis.

The histologic characteristics of the dysgerminoma are very distinctive. The large round, ovoid, or polygonal cells have abundant, clear, very-pale–staining cytoplasm, large and irregular nuclei, and prominent nucleoli (Fig. 39-19). Mitotic figures are seen in varying numbers, although they are usually numerous. Another characteristic feature is the arrangement of the elements in lobules and nests separated by fibrous septa, which are often extensively infiltrated with lymphocytes, plasma cells, and granulomas with epithelioid cells and multinucleated giant cells. When necrosis is extensive, the lesion may be confused with tuberculosis. Dysgerminomas may contain

syncytiotrophoblastic giant cells and may be associated with precocious puberty or virilization. The presence of these cells does not seem to alter prognosis (2,4). The presence of calcifications should prompt a search for a possible underlying gonadoblastoma.

Because the dysgerminoma is a germ cell tumor and parthenogenesis (stimulation of the basic germ cell to atypical division) is the accepted genesis for the more immature teratomas, it is logical that these two tumors may coexist. Choriocarcinoma, endodermal sinus tumor, and other extraembryonal lesions may be associated with the dysgerminoma.

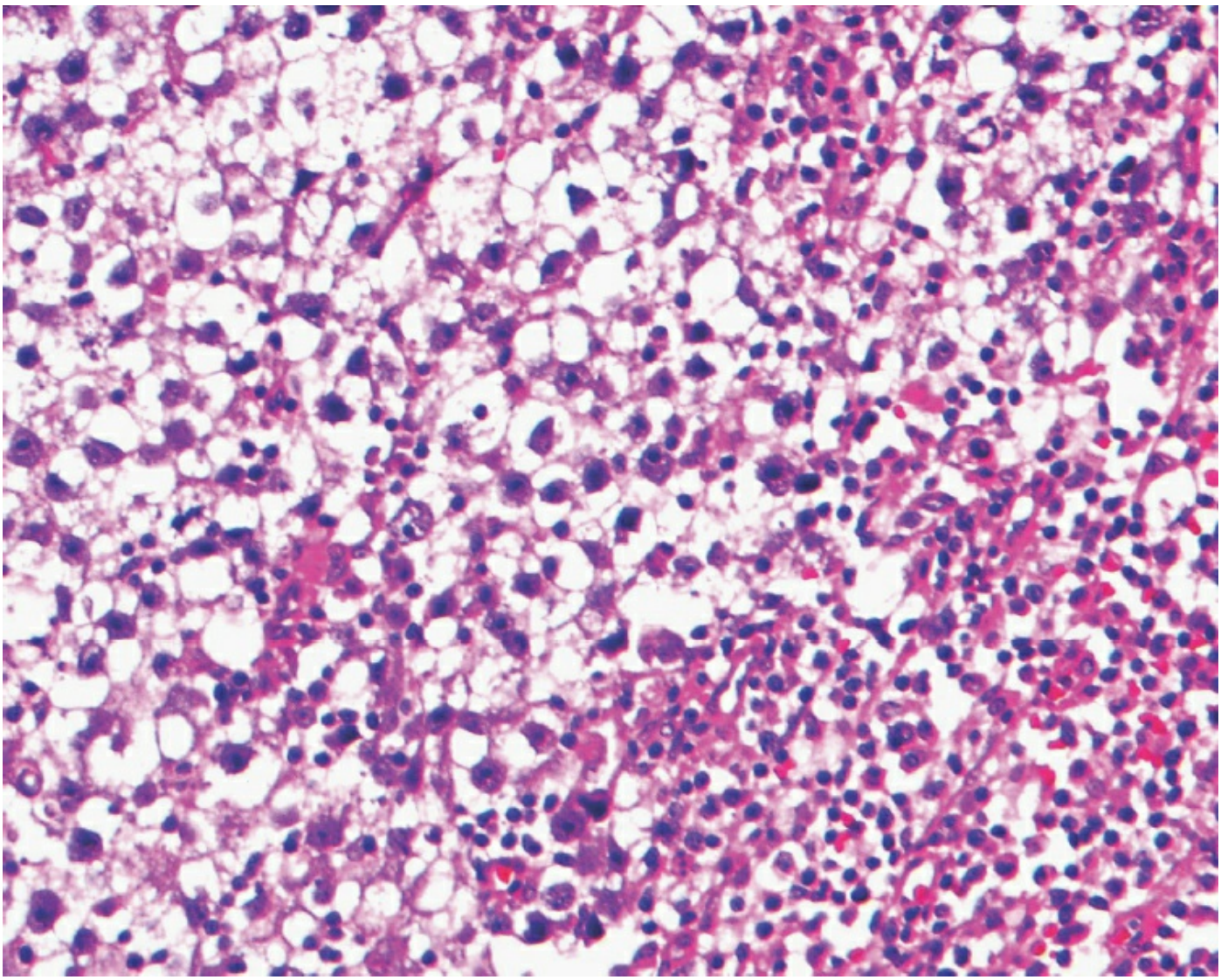


FIGURE 39-19 Dysgerminoma of the ovary. Primitive germ cells are divided into clusters and lobules by fibrous septa rich in lymphocytes.

Approximately 5% of dysgerminomas are discovered in phenotypic women with abnormal gonads (2,402,404). This malignancy can be associated with patients who have pure gonadal dysgenesis (46,XY, bilateral streak gonads), mixed gonadal

dysgenesis (45,X/46,XY, unilateral streak gonad, contralateral testis), and the androgen insensitivity syndrome (46,XY, testicular feminization). For premenarcheal patients with a pelvic mass, the karyotype should be determined (see Chapter 34).

For most patients with gonadal dysgenesis, dysgerminomas arise in gonadoblastomas, which are benign ovarian tumors that are composed of germ cells and sex cord stroma. If gonadoblastomas are left *in situ* in patients with gonadal dysgenesis, more than 50% will develop into ovarian malignancies (404).

About 65% of dysgerminomas are stage I (i.e., confined to one or both ovaries) at diagnosis (2,4,405–409). **About 85% to 90% of stage I tumors are confined to one ovary; 10% to 15% are bilateral. Dysgerminoma is the only germ cell malignancy that has this significant rate of bilaterality. Other germ cell tumors are rarely bilateral.**

For patients whose contralateral ovary is preserved, disease can develop in 5% to 10% of the retained gonads over the next 2 years (2). This figure includes those not given additional therapy and patients with gonadal dysgenesis.

In the 25% of patients who are diagnosed initially with metastatic disease, the tumor commonly spreads via the lymphatic system. It can spread hematogenously or by direct extension through the capsule of the ovary with exfoliation and dissemination of cells throughout the peritoneal surfaces. Metastases to the contralateral ovary may be present when there is no other evidence of spread. An uncommon site of metastatic disease is bone; when metastasis to this site occurs, the lesions are principally in the lower vertebrae. Metastases to the lungs, liver, and brain are often in patients with longstanding or recurrent disease. Metastasis to the mediastinum and supraclavicular lymph nodes is usually a late manifestation of disease (405,406).

Treatment

The treatment of patients with early dysgerminoma is primarily surgical, including resection of the primary lesion and proper surgical staging. Chemotherapy is administered to patients with metastatic disease. [12] Because the disease principally affects girls and young women, special consideration must be given to the preservation of fertility whenever possible. An algorithm for the management of ovarian dysgerminoma is presented in **Figure 39-20**.

Surgery

The minimal surgical operation for ovarian dysgerminoma is a unilateral oophorectomy (407). **If there is a desire to preserve fertility, as there almost always is, the contralateral ovary, fallopian tube, and uterus should be left *in situ*, even in the presence of metastatic disease, because of the sensitivity of the tumor to chemotherapy.** If fertility need not be preserved, it may be appropriate to perform a total abdominal hysterectomy and bilateral salpingo-oophorectomy for patients with

advanced disease (409). For patients whose karyotype analysis reveals a Y chromosome, both ovaries should be removed, although the uterus may be left *in situ* for possible future embryo transfer (404). Whereas cytoreductive surgery is of unproved value, bulky disease that can be readily resected (e.g., an omental cake) should be removed during the initial operation.

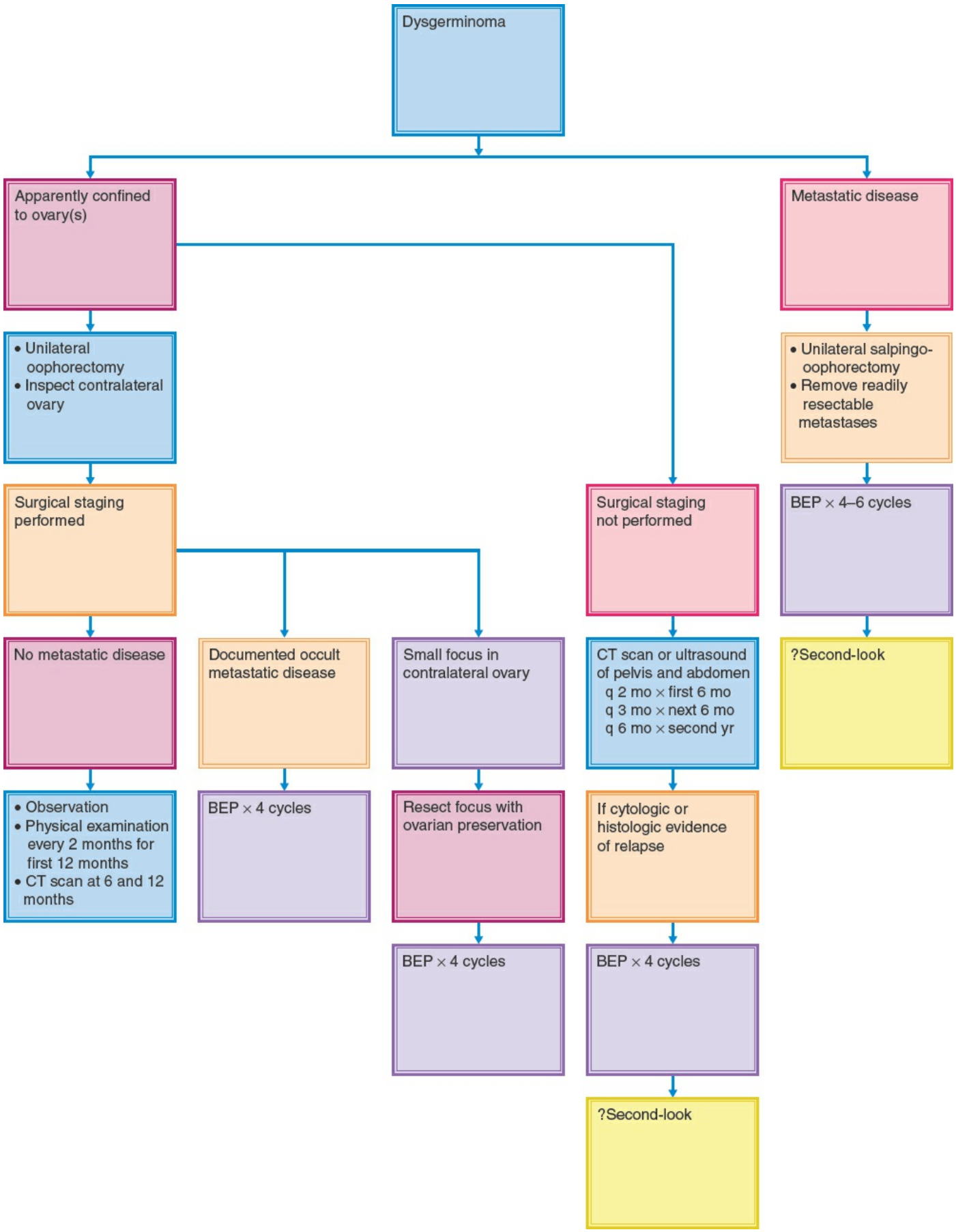

Dysgerminoma
Apparently confined to ovary(s)
Metastatic disease
• Unilateral oophorectomy
• Inspect contralateral ovary
• Unilateral salpingo-oophorectomy
• Remove readily resectable metastases
Surgical staging performed
Surgical staging not performed
BEP × 4–6 cycles
No metastatic disease
Documented occult metastatic disease
Small focus in contralateral ovary
CT scan or ultrasound of pelvis and abdomen
q 2 mo × first 6 mo
q 3 mo × next 6 mo
q 6 mo × second yr
?Second-look
• Observation
• Physical examination every 2 months for first 12 months
• CT scan at 6 and 12 months
BEP × 4 cycles
Resect focus with ovarian preservation
If cytologic or histologic evidence of relapse
BEP × 4 cycles
BEP × 4 cycles
?Second-look

FIGURE 39-20 Management of dysgerminoma of the ovary. BEP, *bleomycin, etoposide*, and *cisplatin;* CT, computed tomogram. (From **Berek JS, Friedlander ML, Hacker NF.** Germ cell and nonepithelial ovarian cancer. In: Berek JS, Hacker NF. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:536.)

In patients in whom the neoplasm appears on inspection to be confined to the ovary, a careful staging operation should be undertaken to determine the presence of any occult metastatic disease. All peritoneal surfaces should be inspected and palpated, and any suspicious lesions should be sampled for biopsy. Unilateral pelvic lymphadenectomy and careful palpation and biopsy of enlarged para-aortic nodes are particularly important parts of the staging. These tumors may metastasize to the para-aortic nodes around the renal vessels. Dysgerminoma is the only germ cell tumor that tends to be bilateral, excisional biopsy of any suspicious masses is desirable (407–409). If a small contralateral tumor is found, it may be possible to resect it and preserve some normal ovary.

Many patients with a dysgerminoma will have a tumor that is apparently confined to one ovary and will be referred after unilateral salpingo-oophorectomy without surgical staging. Recommended options depend on the pathologic findings, the results of imaging and tumor markers (BHCG and LDH), the age of the patient and whether she desires fertility preservation.

The options include (i) completion of surgical staging as stage 1 dysgerminomas do not require adjuvant chemotherapy, (ii) close surveillance with pelvic and abdominal CT scans and tumor markers, or (iii) adjuvant chemotherapy if capsular rupture or more advanced stage. Tumor markers (LDH, AFP, and β-hCG) should be monitored in case occult mixed germ cell elements are present.

Radiation Therapy

Dysgerminomas are very sensitive to radiation therapy, and doses of 2,500 to 3,500 cGy may be curative, even for gross metastatic disease. Loss of fertility is a problem with radiation therapy, and radiation is rarely used as first-line treatment.

Chemotherapy

There is very good evidence to demonstrate the effectiveness of *platinum*-based chemotherapy, which is regarded as the treatment of choice (409–420). **The obvious advantage is the preservation of fertility** (421).

[12] The most frequently used chemotherapeutic regimen for germ cell tumors is *BEP* (*bleomycin*, *etoposide*, and *cisplatin*), EP (*etoposide* and *cisplatin*), or EC (*etoposide* and *carboplatin*) (**Table 39-6**) (409–426).

Table 39-6 Combination Chemotherapy for Germ Cell Tumors of the Ovary

Regimen and Drugs	Dose and Schedule[a]

BEP	
Bleomycin	30,000 IU on days 1, 8, and 15 every 3 wks
Etoposide	100 mg/m^2/day × 5 days every 3 wks
Cisplatin	20 mg/m^2/day × 5 days, or 100 mg/m^2/day × 1 day every 3 wks
VBP	
Vinblastine	0.15 mg/kg days 1 and 2 every 3 wks
Bleomycin	15 units/m^2/wk × 5; then on day 1 of course 4
Cisplatin	100 mg/m^2 on day 1 every 3 wks
VAC	
Vincristine	1–1.5 mg/m^2 on day 1 every 4 wks
Actinomycin D	0.5 mg/day × 5 days every 4 wks
Cyclophosphamide	150 mg/m^2/day × 5 days every 4 wks

[a]All doses given intravenously.

The GOG studied three cycles of the EC regimen, consisting of *etoposide* (120 mg/m^2 IV on days 1, 2, and 3 every 4 weeks) and *carboplatin* (400 mg/m^2 IV on day 1 every 4 weeks) for patients with completely resected ovarian dysgerminoma, stage IB, IC, II, or III (417). The results showed a sustained disease-free remission rate of 100%. This study was carried out many years ago when *carboplatin* dose was based on surface area, but it is now based on AUC.

For patients with advanced, incompletely resected germ cell tumors, the GOG studied *cisplatin*-based chemotherapy in two consecutive protocols (410,411). In the first study, patients received four cycles of *vinblastine* (12 mg/m^2 every 3 weeks), *bleomycin* (20 units/m^2 IV every week for 12 weeks), and *cisplatin* (20 mg/m^2 per day IV for 5 days every 3 weeks). Patients with persistent or progressive disease at second-look laparotomy were treated with six cycles of *VAC* (*vincristine*, *actinomycin D*, and *cyclophosphamide*). In the second trial, patients received three cycles of *BEP* initially, followed by consolidation with *VAC*, which was later discontinued in patients with dysgerminomas (411). The *VAC* consolidation after *BEP* is no longer used. A total of 20 evaluable patients with stages III and IV dysgerminoma were treated in these two protocols, and 19 were alive and free of disease after 6 to 68 months (median = 26 months). Fourteen of these patients had a second-look laparotomy, and all findings were negative. Another study at MD Anderson Cancer Center used *BEP* in 14 patients with

residual disease, and all patients were free of disease during long-term follow-up (414). **These results demonstrate that patients with advanced-stage, incompletely resected dysgerminoma have an excellent prognosis when treated with *EP*-based combination chemotherapy. [12] The standard regimen is three to four cycles of *BEP*, depending on assigned risk based on the data from testicular cancers, including advanced-stage seminomas which are the male equivalent of dysgerminoma** (425,429).

Recurrent Disease

About 75% of recurrences occur within the first year after initial treatment, the most common sites being the peritoneal cavity and the retroperitoneal lymph nodes (2,388,389). These patients should be treated with chemotherapy. Patients with recurrent disease who had no therapy other than surgery should be treated with chemotherapy as described above. If prior chemotherapy with *BEP* was given, there are a number of second-line options including *TIP* (*paclitaxel*, *ifosfamide*, *cisplatin*) or *VIP* (*vinblastine*, *ifosfamide*, *cisplatin*) (Table 35-7), and consideration should be given to the use of high-dose chemotherapy in selected patients. Patients with recurrent dysgerminomas following *BEP* should be managed in specialized centers. Radiation therapy may be an option in very selected subsets, with the major disadvantage being loss of fertility if pelvic and abdominal irradiation is required.

Table 39-7 POMB-ACE Chemotherapy for Germ Cell Tumors of the Ovary

POMB	
Day 1	*Vincristine* 1 mg/m^2 IV; *methotrexate* 300 mg/m^2 as a 12-hr infusion
Day 2	*Bleomycin* 15 mg as a 24-hr infusion: *folinic acid* rescue started at 24 hr after the start of *methotrexate* in a dose of 15 mg every 12 hrs for 4 doses
Day 3	*Bleomycin* infusion 15 mg as a 24-hr infusion
Day 4	*Cisplatin* 120 mg/m^2 as a 12-hr infusion, given with hydration and 3-g magnesium sulfate supplementation
ACE	
Days 1–5	*Etoposide* (VP16–213) 100 mg/m^2 IV, days 1–5
Days 3–5	*Actinomycin D* 0.5-mg IV, days 3, 4, and 5
Day 5	*Cyclophosphamide* 500 mg/m^2 IV, day 5

OMB	
Day 1	*Vincristine* 1 mg/m^2 IV; *methotrexate* 300 mg/m^2 as a 12-hr infusion
Day 2	*Bleomycin* 15 mg as a 24-hr infusion; *folinic acid* rescue started at 24 hrs after the start of *methotrexate* in a dose of 15 mg every 12 hrs for 4 doses
Day 3	*Bleomycin* 15 mg as a 24-hr infusion

IV, intravenous.

The sequence of treatment schedules is two courses of POMB followed by ACE. POMB is then alternated with ACE until patients are in biochemical remission as measured by human chorionic gonadotropin (hCG) and α-fetoprotein (AFP), placental alkaline phosphatase (PLAP), and lactate dehydrogenase (LDH). The usual number of courses of POMB is three to five. Following biochemical remission, patients alternate ACE with OMB until remission has been maintained for approximately 12 weeks. The interval between courses of treatment is kept to the minimum (usually 9 to 11 days). If delays are caused by myelosuppression after courses of ACE, the first 2 days of etoposide are omitted from subsequent courses of ACE.

From **Newlands ES, Southall PJ, Paradinas FJ, et al.** Management of ovarian germ cell tumours. In: Williams CJ, Kaikorian JG, Green MR, et al., eds. *Textbook of Uncommon Cancer*. New York: John Wiley & Sons; 1988:47, with permission.

Pregnancy

Because dysgerminomas tend to occur in young patients, they may coexist with pregnancy. When a stage IA cancer is found, the tumor can be removed intact and the pregnancy continued. For patients with more advanced disease, continuation of the pregnancy depends on the gestational age of the fetus. Chemotherapy can be given safely in the second and third trimesters in the same dosages as given for the nonpregnant patient without apparent detriment to the fetus (421).

Prognosis

For patients whose initial disease is stage IA (i.e., a unilateral encapsulated dysgerminoma), unilateral oophorectomy alone results in a 5-year disease-free survival rate of greater than 95% (408). The features associated with a higher tendency to recur, include lesions larger than 10 to 15 cm in diameter, age younger than 20 years, and a microscopic pattern that includes numerous mitoses, anaplasia, and a medullary pattern (2,399,409–426,430–432).

Immature Teratomas

Immature teratomas contain elements that resemble tissues derived from the embryo. Immature teratomatous elements may occur in combination with other germ cell tumors as mixed germ cell tumors. [12] The pure immature teratoma accounts for fewer than 1% of all ovarian cancers, but it is the second most common germ cell malignancy and accounts for 10% to 20% of all ovarian

malignancies seen in women younger than 20 years (2). About 50% of pure immature teratomas of the ovary occur in women between the ages of 10 and 20 years, and they rarely occur in postmenopausal women.

Pathology and Grading

Of fundamental importance in the understanding of the teratoma is recognition of the maturation of the various elements. If maturation continues along normal lines, it results in a mature teratoma, and the prognosis is excellent as these are benign tumors with the rare exception of other tumors arising from mature elements, such as squamous cell carcinomas. Conversely, abnormal maturation of these elements can result in an immature teratoma that has metastatic potential. Teratomas containing immature elements, although relatively rare, are recognized more often as pathologists are aware of the importance of differentiating them from mature teratomas **(Fig. 39-21)**. Among the tumors with embryonal elements, those containing neural tissues demonstrate the ability to mature.

Semiquantification of immature neuroepithelium correlates with survival in ovarian immature teratoma and is the basis for grading of these tumors (433–435). **Those with less than one low-power field (X 4) of immature neuroepithelium on the slide with the greatest amount of such tissue (grade 1) have a survival of at least 95%, whereas greater amounts of immature neuroepithelium (grades 2 and 3) appear to have a higher risk of recurrence and a lower overall survival (approximately 85%)** (435). This may not apply to immature teratomas of the ovary in children because they have a good outcome with surgery alone, regardless of the degree of immaturity (436,437). The significant inter- and intraobserver difficulty with a three-tier system led some authorities to recommend the two-tier grading system in use, with immature teratomas categorized as either low grade or high grade (433). Immature ovarian teratomas may be associated with gliomatosis peritonei, a favorable prognostic finding if composed of completely mature tissues; molecular analyses suggest that these glial implants are not tumor derived but rather represent teratoma-induced metaplasia of pluripotent müllerian stem cells in the peritoneum (438,439).

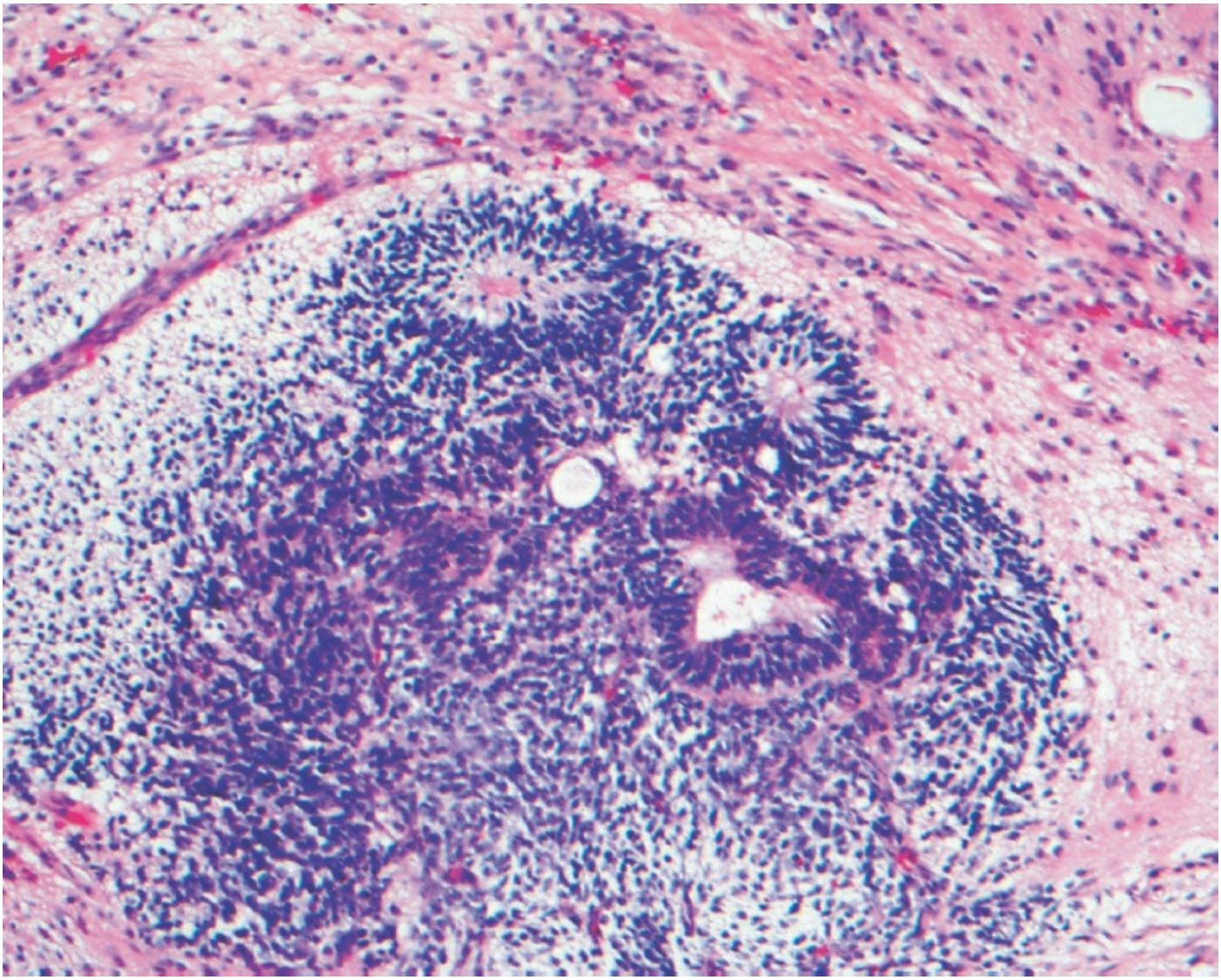


FIGURE 39-21 Ovarian teratoma. This tumor contains both mature and immature neural elements with a neural tube-like structure near its center.

Somatic malignant change in benign cystic teratomas was recorded as occurring in 0.5% to 2% of cases, usually in patients older than 40 years of age (433). **The most common malignancy that develops in the initially benign teratoma is squamous cell carcinoma.** Other neoplasms were reported (e.g., adenocarcinomas, melanomas, which may arise from the skin or retinal anlage, and sarcomas, including leiomyosarcomas and mixed mesodermal tumors) (2). Carcinomas may arise from any of the epithelial elements.

Diagnosis

The preoperative evaluation and differential diagnosis of immature teratomas are the same as for other germ cell tumors. Some of these tumors will contain calcifications similar to those of mature teratomas, which can be detected by a radiograph of the abdomen or by ultrasonography. Rarely they are associated with the production of

steroid hormones and can be accompanied by sexual pseudoprecocity (395). Tumor markers are negative unless a mixed germ cell tumor is present. Immature teratoma may contain embryonal hepatic or intestinal differentiation, and the presence of these elements in a tumor with high AFP levels. It is possible to have a slightly elevated AFP in a pure IT if they have evidence of hepatic or intestinal differentiation, but high levels would be associated with a mixed germ cell tumor.

Treatment

Surgery

In a premenopausal patient, immature teratomas are typically confined to a single ovary, and therefore unilateral oophorectomy and fertility-sparing surgical staging should be performed. For a postmenopausal patient, a total abdominal hysterectomy and bilateral salpingo-oophorectomy may be performed along with complete staging. Contralateral involvement is rare, and routine resection or wedge biopsy of the contralateral ovary is unnecessary (4,434,435). Any lesions on the peritoneal surfaces should be sampled and submitted for histologic evaluation. The most frequent site of dissemination is the peritoneum and, much less commonly, the retroperitoneal lymph nodes. Blood-borne metastases to organ parenchyma, such as the lungs, liver, or brain, are uncommon. When present, they are usually seen in patients with late or recurrent disease and most often in tumors that are poorly differentiated (i.e., grade 3).

It is unclear whether extensive debulking enhances the response to combination chemotherapy (440–442). These are chemosensitive tumors and the cure depends on the prompt delivery of chemotherapy. Therefore, any surgical resection that is potentially morbid and could delay chemotherapy should be resisted.

Chemotherapy

Patients with IA, grade 1 tumors have an excellent prognosis, and no adjuvant therapy is required. For patients whose tumors are stage IA, high-grade, adjuvant chemotherapy has been generally recommended, although there is evidence to support close surveillance (412–414,430–434). Chemotherapy is indicated for patients who have ascites, regardless of tumor grade. The standard approach is *BEP* (412,413,443–449). The GOG investigated three cycles of *BEP* for patients with completely resected stages I, II, and III ovarian germ cell tumors (412,413,449). Overall, the toxicity was acceptable, and 91 of 93 patients treated were clinically free of disease. **The *BEP* regimen, which is the standard of care for testicular cancer, is the most appropriate chemotherapy regimen for nondysgerminomatous germ cells tumors of the ovary.** As these tumors can progress rapidly, treatment should be initiated as soon as possible after surgery, preferably within 7 to 10 days (450). The combined *BEP* regimen is the international standard of care, usually administered for

three cycles in completely resected disease or in the adjuvant setting and four cycles for macroscopic residual disease.

The switch from *VBP* to *BEP* was prompted by the experience in patients with testicular cancer, in which the replacement of *vinblastine* with *etoposide* was associated with a better therapeutic index (i.e., equivalent efficacy and lower morbidity), especially less neurologic and gastrointestinal toxicity. The inclusion of *bleomycin* is particularly important those patients with nondysgerminomatous germ cell tumors. In a randomized study of three cycles of *EP* with or without *bleomycin* (*EP* vs. *BEP*) in 166 patients with germ cell tumors of the testes, the *BEP* regimen had a relapse-free survival rate of 84% compared with 69% for the *EP* regimen ($p = 0.03$) (425). *Cisplatin* appears to be superior to *carboplatin* in the setting of metastatic germ cell tumors. One hundred ninety-two patients with germ cell tumors of the testes were entered into a study of four cycles of *EP* versus four cycles of EC. There were three relapses with the *EP* regimen versus seven with the EC regimen, although the overall survival of the two groups is identical (426). In view of these results, ***BEP* is the preferred treatment regimen for patients with ovarian germ cell tumors.**

It is unclear whether adjuvant chemotherapy is indicated or required for all patients with resected immature teratomas. Several reports support the successful management of these patients with surgery alone and close surveillance (442,451). In the largest series, an Intergroup study from the Pediatric Oncology Group and the Children's Cancer Group, 73 children with immature teratoma (44 of ovarian origin) underwent surgery followed by surveillance. With a median follow-up of 35 months, the overall 3-year event-free survival rates for all patients and those with ovarian teratomas were 93% and 100%, respectively. Thirteen of the 44 girls with an immature ovarian teratoma had microscopic foci of yolk sac tumor in the teratoma; one developed recurrent disease and was successfully treated with *cisplatin*-based chemotherapy. Eighty-two percent of the tumors were grade 1 or 2; however, 92% of those with foci of yolk sac tumor were grade 2 or 3.

Second-Look Laparotomy or Laparoscopy

Second-look operation is not justified in patients who received adjuvant chemotherapy, because chemotherapy in these patients is effective (431,432). In the absence of any residual disease, there is no indication for second-look laparotomy or laparoscopy. In patients with radiographic evidence of residual tumor after surgery and chemotherapy, this may represent residual germ cell tumor, benign teratoma or more commonly, necrotic tissue in a patient whose tumor markers have normalized.

Second-look laparotomy or laparoscopy in patients with macroscopic residual disease at the start of chemotherapy should be considered, as patients with residual mature teratoma and are at risk of growing teratoma syndrome, an uncommon complication of immature teratomas (452,453). Cancers can arise at a later date in

residual mature teratoma. It is important to resect or biopsy any residual mass and exclude persistent disease because further chemotherapy may be indicated. The principles of surgery are based on the much larger experience of surgery in males with residual masses following chemotherapy for germ cell tumors with a component of immature teratoma (454). Mathew et al. reported their experience of laparotomy in assessing the nature of postchemotherapy residue in ovarian germ cell tumors. Sixty-eight patients completed combination chemotherapy with *cisplatin* regimes, and 35 had radiologic residual masses. Twenty-nine of these 35 patients underwent laparotomy and 3 patients had viable tumor, 7 immature teratomas, 3 mature teratoma, and 16 necrosis or fibrosis. None of the patients with dysgerminoma, embryonal carcinoma, absence of teratoma element in the primary tumor, and radiologic residual mass of less than 5 cm had viable tumor, whereas all patients with tumors containing the teratoma component initially had residual tumor, strengthening the case for surgery in patients with immature teratoma and any residual mass (455,456).

Prognosis

The most important prognostic feature of the immature teratoma is the grade (2,423). The stage of disease and the extent of tumor at the initiation of treatment have an impact on the curability of the lesion. Overall, the 5-year survival rate for patients with all stages of pure immature teratomas is 70% to 80%, and it is 90% to 95% for patients with surgically staged, stage I lesions (430,433,457).

Endodermal Sinus Tumors

[12] Endodermal sinus tumors (EST) are also referred to as *yolk sac carcinomas* because they are derived from the primitive yolk sac (2,4). **They are the third most frequent malignant germ cell tumors of the ovary.** ESTs occur in patients with a median age of 16 to 18 years (2,4,458). About one-third of the patients are premenarcheal at the time of diagnosis. Abdominal or pelvic pain is the most frequent initial symptom, occurring in about 75% of patients, whereas an asymptomatic pelvic mass is documented in 10% of patients (396).

Pathology

The gross appearance of an EST is soft grayish-brown. Cystic areas caused by degeneration or necrosis are present in these rapidly growing lesions. The capsule is intact in most cases.

The EST is unilateral in 100% of cases; thus, biopsy of the opposite ovary is contraindicated. The association of such lesions with gonadal dysgenesis must be appreciated, and chromosomal analysis should be performed preoperatively in premenarcheal patients (4).

Microscopically, the characteristic feature is the endodermal sinus, or the *Schiller–Duval body* (Fig. 39-22). The cystic space is lined with a layer of flattened or

irregular endothelium into which projects a glomerulus-like tuft with a central vascular core. These structures vary throughout the tumor, and the reticular, myxoid elements simulate undifferentiated mesoblast. The lining of the papillary infolding and the cavity is irregular, with an occasional cell containing clear, glassy cytoplasm, simulating the hobnail appearance of the epithelium in clear cell tumors. There is a possible association of EST with dysgerminoma in mixed germ cell tumors (2,4).

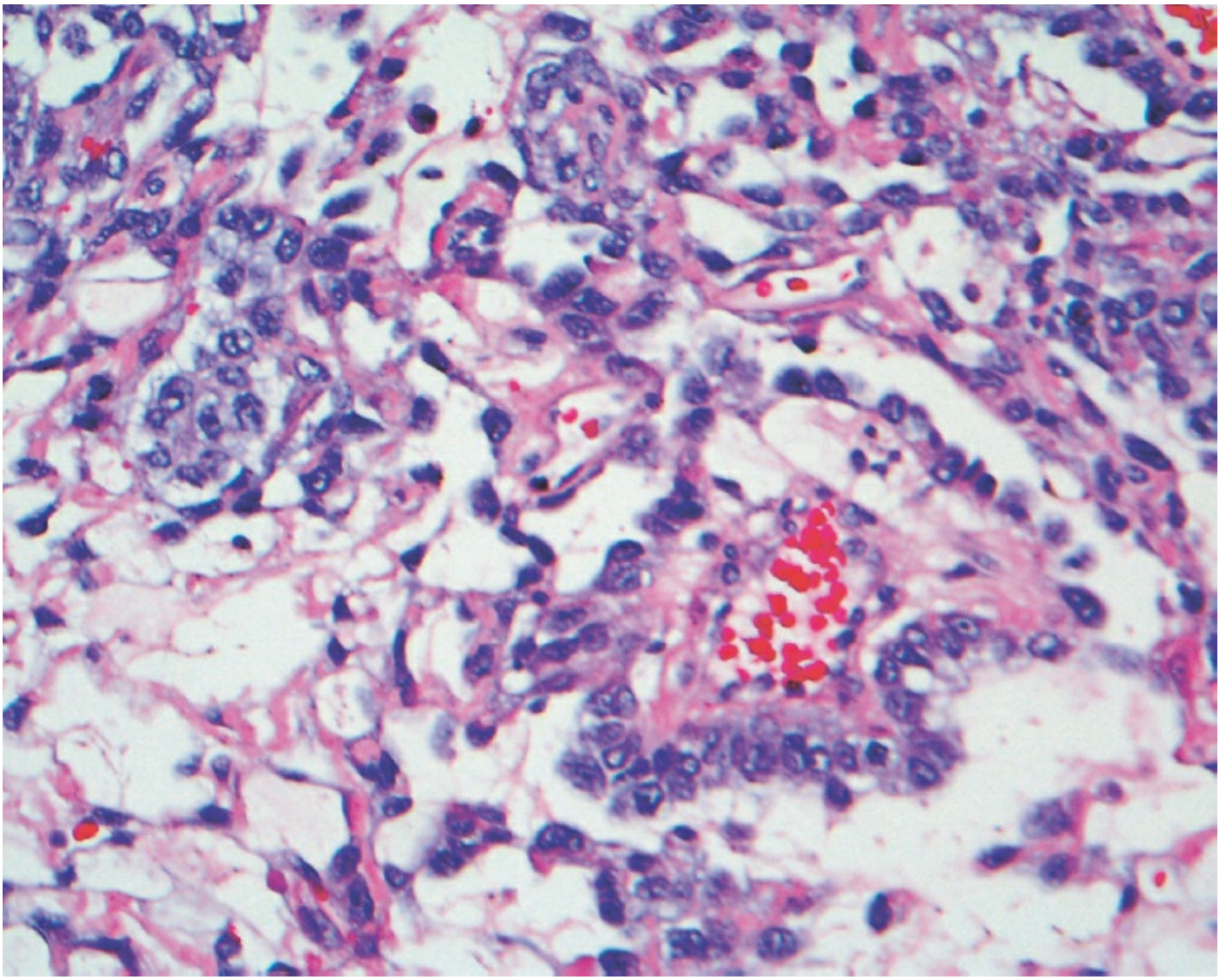


FIGURE 39-22 Yolk sac tumor of the ovary. Note the classic Schiller–Duval body with its central vessel and mantle of endoderm.

Most EST secrete AFP and, rarely, alpha-1 antitrypsin (AAT). AFP can be demonstrated in the tumor by immunohistochemistry. There is a good correlation between the extent of disease and the level of AFP, although discordance can occur. The serum level of these markers, particularly AFP, is useful in monitoring the patient's response to treatment (458–462).

Treatment

Surgery

The treatment of the EST consists of surgical exploration, unilateral salpingo-oophorectomy, and a frozen section for diagnosis. The addition of a hysterectomy and contralateral salpingo-oophorectomy does not alter the outcome and is not indicated (460). Any gross metastases should be removed, if possible, but thorough surgical staging may be omitted because all patients need chemotherapy. At surgery, the tumors tend to be solid and large, ranging in size from 7 to 28 cm (median, 15 cm) in the GOG series (449). Bilaterality does not occur, and the other ovary is involved with metastatic disease only when there are other metastases in the peritoneal cavity. Most patients have early-stage disease: 71%, stage I; 6%, stage II; and 23%, stage III (462).

Chemotherapy

All patients with ESTs are treated with either adjuvant or therapeutic chemotherapy. Before the routine use of combination chemotherapy for this disease, the 2-year survival rate was only about 25%. The introduction of the *VAC* regimen, improved survival rates to 60% to 70%, indicating the chemosensitivity of most of these tumors (444,445). With conservative surgery and adjuvant chemotherapy, fertility can be preserved as with other germ cell tumors.

***Cisplatin*-containing combination chemotherapy with three to four cycles of *BEP* should be used as primary chemotherapy for EST.** The GOG protocols used three to four treatment cycles given every 3 weeks (449,463). The number of cycles is dependent on prognostic factors including whether there is bulky residual disease after surgery and the site of metastases.

Rare Germ Cell Tumors of the Ovary

Embryonal Carcinoma

[12] Embryonal carcinoma of the ovary is an extremely rare tumor that is distinguished from a choriocarcinoma of the ovary by the absence of syncytiotrophoblastic and cytotrophoblastic cells. The patients are very young; ages ranged between 4 and 28 years (median, 14 years) in two series (464). Older patients were reported (465). Embryonal carcinomas may secrete estrogen, with the patient exhibiting symptoms and signs of precocious pseudopuberty or irregular bleeding (2). The clinical picture is otherwise similar to that of the EST. The primary lesions tend to be large, and about two-thirds are confined to one ovary at the time of diagnosis. These lesions frequently secrete AFP and hCG, which are useful for following the response to subsequent therapy (461). **The treatment of embryonal carcinomas is the same as for the EST (i.e., a unilateral oophorectomy followed by combination chemotherapy with *BEP*)** (413,449).

Choriocarcinoma of the Ovary

Pure nongestational choriocarcinoma of the ovary is an extremely rare tumor. Histologically, it has the same appearance as gestational choriocarcinoma metastatic to the ovaries (466). Most patients with this cancer are younger than 20 years. The presence of hCG can be useful in monitoring the patient's response to treatment. **In the presence of high hCG levels, isosexual precocity occurs in about 50% of patients whose lesions appear before menarche** (466,467).

There are only limited reports on the use of chemotherapy for nongestational choriocarcinomas, but complete responses were reported with the *MAC* (*methotrexate*, *actinomycin D*, and *cyclophosphamide*) regimen used in a manner described for gestational trophoblastic disease (see Chapter 41) (435). Alternatively, the *BEP* regimen can be used. The prognosis of ovarian choriocarcinomas is poor, with most patients having metastases to organ parenchyma at the time of diagnosis.

Polyembryoma

Polyembryoma of the ovary is another extremely rare tumor, which is composed of embryoid bodies. This tumor replicates the structures of early embryonic differentiation (i.e., the three somatic layers: endoderm, mesoderm, and ectoderm) (2,399). They tend to occur in very young, premenarcheal girls with signs of pseudopuberty and elevated AFP and hCG levels. The same principles of management apply (399,468).

Mixed Germ Cell Tumors

Mixed germ cell malignancies of the ovary contain two or more elements of the lesions described above. In one series, the most common component of a mixed malignancy was dysgerminoma, which occurred in 80%, followed by EST in 70%, immature teratoma in 53%, choriocarcinoma in 20%, and embryonal carcinoma in 16% (468). **The most frequent combination is a dysgerminoma and an EST. The mixed germ cell tumors may secrete either AFP, hCG, both, or neither of these markers, depending on the components.**

These tumors should be managed with *BEP* combination chemotherapy. The serum marker, if positive initially, may become negative during chemotherapy, but this finding may reflect regression of only a particular component of the mixed lesion.

The most important prognostic features are the size of the primary tumor and the relative size of its most malignant component (469). For stage IA tumors smaller than 10 cm, survival is 100%. Tumors composed of less than one-third EST, choriocarcinoma, or grade 3, immature teratoma have an excellent prognosis, but it is less favorable when these components constitute most of the mixed lesions.

Late Effects of Treatment of Malignant Germ Cell Tumors of the Ovary

Although there are substantial data regarding late effects of *cisplatin*-based therapy in men with testicular cancer, there is much less information available for women with

ovarian germ cell tumors. However, it is likely that the late effects will be similar to men treated with BEP and include renal and gonadal dysfunction, neurotoxicity, cardiovascular toxicity, and secondary malignancies.

Gonadal Function

An important cause of infertility in patients with ovarian germ cell tumors is unnecessary bilateral salpingo-oophorectomy and hysterectomy. **Although temporary ovarian dysfunction or failure is common with *platinum*-based chemotherapy, most women will resume normal ovarian function, and childbearing is usually preserved** (402,408). In one representative series of 47 patients treated with combination chemotherapy for germ cell malignancies, 91.5% resumed normal menstrual function, and there were 14 healthy live births and no birth defects (423). Factors such as older age at the initiation of chemotherapy, greater cumulative drug dose, and longer duration of therapy all have an adverse effect on future gonadal function.

Secondary Malignancies

An important cause of late morbidity and mortality in patients receiving chemotherapy for germ cell tumors is the development of secondary tumors. ***Etoposide* in particular was implicated in the development of treatment-related leukemias** (470,471).

The chance of developing treatment-related leukemia following *etoposide* is dose related. **The incidence of leukemia is approximately 0.4% to 0.5%** (representing a 30-fold increased likelihood) in patients receiving a cumulative *etoposide* dose of less than 2,000 mg/m^2, compared with as much as 5% (representing a 336-fold increased likelihood) in those receiving more than 2,000 mg/m^2 (470). In a typical three- or four-cycle course of *BEP*, patients receive a cumulative *etoposide* dose of 1,500 or 2,000 mg/m^2, respectively.

Despite the risk of secondary leukemia, risk–benefit analyses concluded that *etoposide*-containing chemotherapy regimens are beneficial in advanced germ cell tumors; one case of treatment-induced leukemia would be expected for every 20 additionally cured patients who receive *BEP* as compared with *platinum, vincristine, bleomycin* (*PVB*). The risk–benefit balance for low-risk disease, or for high-dose *etoposide* in the recurrence setting, is less clear (471–473).

Surveillance Versus Immediate Adjuvant Chemotherapy in Stage I Germ Cell Tumors

Close surveillance is a well-accepted and standard approach to the management of young men with apparent stage I testicular germ cell tumors. There is a large body of evidence to support this approach, and guidelines on surveillance protocols (474). **Although as many as 20% to 30% of patients will relapse, almost all will be cured using second-line chemotherapy with *BEP*,** and the potential adverse effects of chemotherapy can therefore be avoided in most patients. Although this is a very common

approach to management of young men with stage I testicular germ cell tumors, it has not been widely adopted in females with ovarian germ cell tumors in the United States. In the United Kingdom, all women with stage IA malignant ovarian germ cell tumors are offered surveillance regardless of histologic subtype. However, prior to making this recommendation there is close scrutiny of operative findings, central pathologic review, measurement of tumor markers, and whole-body imaging to ensure that the staging is correct. Surveillance includes regular clinical review, physical examination, interval imaging, and tumor marker assessments (hCG, AFP, and LDH). The frequency of surveillance with tumor marker monitoring is highest early on, as most relapses occur within 2 years.

The Charing Cross Group initially reported a prospective study of 24 patients with stage IA ovarian germ cell tumors who were also enrolled in a surveillance program. The group consisted of nine patients (37.5%) with dysgerminoma, nine (37.5%) with pure immature teratoma, and six (25%) with EST (with or without immature teratoma). Treatment consisted of surgical resection without adjuvant chemotherapy, followed by a surveillance program of clinical, serologic, and radiologic review. A second-look operation was performed, and **all patients, but one, were alive and in remission after a median follow-up of 6.8 years.** The 5-year overall survival was 95%, and the 5-year disease-free survival was 68%. Eight patients required chemotherapy for recurrent disease or second primary ovarian germ cell tumor. This included three patients with grade II immature teratoma, three patients with dysgerminoma, and two patients with dysgerminoma who developed a contralateral dysgerminoma 4.5 and 5.2 years after their first tumor. All but one, who died of a pulmonary embolus, were successfully salvaged with chemotherapy. The same group updated its experience and reported on the safety of the ongoing surveillance program of all stage IA female germ cell tumors (474). Thirty-seven patients (median age 26, range 14 to 48 years) with stage I disease were referred to Mount Vernon and Charing Cross Hospitals between 1981 and 2003. Patients underwent surgery and staging followed by intense surveillance, which included regular tumor markers and imaging. The median period of follow-up was 6 years. **Relapse rates for stage IA nondysgerminomatous tumors and dysgerminomas were 8 of 22 (36%) and 2 of 9 (22%), respectively.** In addition, one patient with mature teratoma and glial implants relapsed. Ten of these 11 patients (91%) were successfully cured with platinum-based chemotherapy. Only one patient died from chemoresistant disease. **All relapses occurred within 13 months of initial surgery.** The overall disease-specific survival of malignant ovarian germ cell tumors was 94%. If this approach is considered, then the Charing Cross surveillance protocol should be followed.

Sex Cord–Stromal Tumors

Sex cord–stromal tumors of the ovary account for about 5% to 8% of all ovarian malignancies (2,4,395,396,475–481). This group of ovarian neoplasms is derived from the sex cords and the ovarian stroma or mesenchyme. The tumors usually are composed of various combinations of elements, including the "female" cells (i.e., granulosa and theca cells) and "male" cells (i.e., Sertoli and Leydig cells), and morphologically indifferent cells. A classification of this group of tumors is presented in Table 39-8.

Granulosa–Stromal Cell Tumors

[13] Granulosa cell tumors are the most common type of malignant ovarian sex cord–stromal tumor and make up 2% to 5% of all ovarian malignancies Granulosa–stromal cell tumors include granulosa cell tumors, thecomas, and fibromas. They account for 70% of ovarian sex cord–stromal tumors. Granulosa cell tumors are considered to be a low-grade malignancy.

The majority of granulosa cell tumors are adult (95%) with juvenile granulosa cell tumors being much less common (5%). Adult granulosa cell tumors almost always occur in postmenopausal women while juvenile granulosa cell tumors are diagnosed in women under 30 years of age and may be seen in prepubertal girls in 5% of cases (478). **[13]** Granulosa cell tumors are bilateral in only 2% of patients (482).

Table 39-8 Sex Cord–Stromal and Steroid Cell Tumors

1. Granulosa-stromal cell tumors
A. Granulosa cell tumor
B. Tumors in thecoma–fibroma group
a. Thecoma
b. Fibroma
b. Unclassified
2. Androblastomas; Sertoli–Leydig cell tumors
A. Well differentiated
a. Sertoli cell tumor
b. Sertoli–Leydig cell tumor
c. Leydig cell tumor; hilus cell tumor
B. Moderately differentiated
C. Poorly differentiated (sarcomatoid)
D. With heterologous elements

3. Gynandroblastoma
4. Sex cord tumor with annular tubules
5. Sex cord–stromal tumors, unclassified
6. Steroid cell tumors
A. Stromal luteoma
B. Leydig cell tumor
C. Steroid cell tumor, not otherwise classified

Pathology

Granulosa cell tumors range from a few millimeters to 20 cm or more in diameter. **The tumors are rarely bilateral** and have a smooth, lobulated surface. The solid portions of the tumor are granular, frequently trabeculated, and yellow or gray-yellow in color. After clear cell carcinoma, the granulosa-theca cell tumor is probably the most inaccurately diagnosed tumor of the female gonad. Of 477 ovarian tumors from the Emil Novak Ovarian Tumor Registry diagnosed initially as granulosa-theca cell tumors, almost 15% were reclassified after histologic review. The FOXL2 gene is mutated in almost all adult granulosa cell tumors. It plays a role in the development of normal granulosa cells and mutations in this gene have been found in up to 97% of adult granulomas cell tumors. Molecular testing for mutations in the FOXL2 gene may help to improve the diagnostic accuracy among patients with sex cord–stromal tumors (483,484). Tumors misdiagnosed as granulosa cell tumors included primary or metastatic carcinomas, teratoid tumors, and poorly differentiated mesothelial tumors (475). A Norwegian study found that almost 30% of adult granulosa cell tumors had been misdiagnosed after reviewing the pathology and testing for FOXL2 mutations, which raises questions about the reliability of historical series.

Juvenile granulosa cell tumors, so named because of their tendency to occur in younger patients, feature rounder, more hyperchromatic nuclei, and may contain numerous mitotic figures. The presence of large, irregular follicle spaces is an additional distinguishing feature of the juvenile granulosa cell tumor.

The classic adult granulosa cell is round or ovoid with scant cytoplasm. The nucleus contains compact, finely granular chromatin and is either euchromatic or hypochromatic (4). Better-differentiated granulosa cell tumors may have a variety of patterns including macrofollicular, microfollicular, trabecular, solid-trabecular, and insular while less-differentiated tumors have a more diffuse pattern described as sarcomatoid. “Coffee bean” grooved nuclei are characteristic; mitotic figures may be present, but numerous mitotic figures should prompt consideration for poorly differentiated or undifferentiated carcinoma. **In the most common variety, the adult granulosa cells show a tendency to arrange themselves in small clusters or rosettes around a central cavity, so there**

is a resemblance to primordial follicles (i.e., *Call–Exner bodies*) (Fig. 39-23). The stroma is similar to the theca and may be luteinized. In children and adolescents, the granulosa cell tumors are often cystic, contain luteinized cells, and can be associated with precocious puberty. The adult granulosa cell tumor tends to occur in older women and the juvenile tumor in children and young women, with the diagnosis not being based on age of presentation, but on histology. Adult granulosa cell tumors, but not juvenile granulose cell tumors, harbor a somatic mutation in the *FOXL2* gene (483).

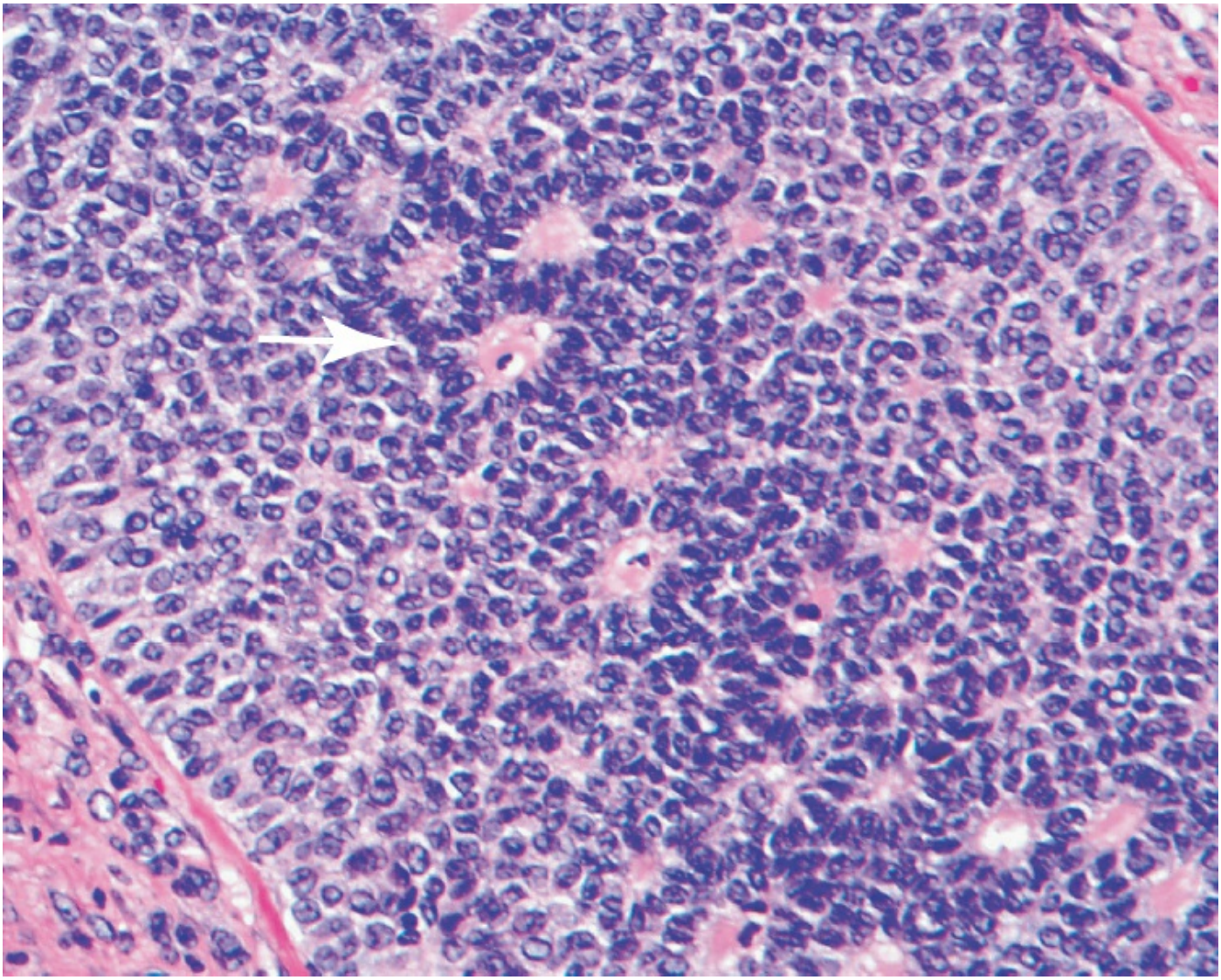


FIGURE 39-23 Granulosa cell tumor of the ovary. Note the classic Call–Exner bodies with a minimal stromal component in this tumor of folliculoid pattern (*arrow* points to an example).

Diagnosis

About 70% of granulosa cell tumors secrete estrogen or androgens.

Inhibin is secreted by some adult granulosa cell tumors and is a useful marker for the disease (485–489). Inhibin is a peptide hormone that is produced by granulosa cells

and plays a role in regulation of FSH secretion. **Inhibin exists in two different isoforms: inhibin A and inhibin B. Although some laboratories only perform testing for inhibin A, serum levels of inhibin B are more frequently elevated** (490).

Inhibin levels can be used to monitor patients during follow-up or to assess response to treatment. The lead-time between inhibin levels rising and documented recurrence is about 12 months.

An elevated serum inhibin level in a premenopausal woman presenting with amenorrhea and infertility is suggestive of a granulosa cell tumor (491). Seventy-five percent of women with AGCT's also have an elevated anti-müllerian hormone preoperatively and AMH has a >90% sensitivity in detecting recurrence.

Juvenile Granulosa Cell Tumors

Juvenile granulosa cell tumors of the ovary are rare and constitute less than 5% of ovarian tumors in childhood and adolescence (492). Most juvenile granulosa cell tumors are clinically benign; only about 10% recur and when they do, it is generally within 5 years of the initial diagnosis. **Of the rare prepubertal juvenile GCTs, 75% are associated with sexual pseudoprecocity because of the estrogen secretion** (477).

About 90% are diagnosed in stage I, and they have a favorable prognosis. The juvenile subtype behaves less aggressively than the adult type. Only about 10% of juvenile granulosa cell tumors are malignant and late relapse is unusual. Advanced-stage tumors can be treated with *platinum*-based combination chemotherapy (e.g., *BEP*) (493,494).

Adult Granulosa Cell Tumors

Low-grade endometrial cancer occurs in association with adult granulosa cell tumors in at least 5% of cases, and 25% to 50% are associated with endometrial hyperplasia (2,466,475–478,483). Most reproductive-age patients have menstrual irregularities or secondary amenorrhea, and, frequently, cystic hyperplasia of the endometrium. Abnormal uterine bleeding is often the initial symptom for postmenopausal women. The estrogen secretion in these patients can be sufficient to stimulate the development of endometrial cancer.

The other symptoms and signs of granulosa cell tumors are nonspecific and the same as most ovarian malignancies. Ascites is present in about 10% of cases, and, rarely, a pleural effusion is present (475–478). Granulosa tumors tend to be hemorrhagic; occasionally, they rupture and produce a hemoperitoneum.

Adult granulosa cell tumors are stage I at diagnosis in 90% of patients and are associated with a very good prognosis, but may recur 5 to 30 years after initial diagnosis (477). The tumors may spread hematogenously, and metastases can develop in the lungs, liver, and brain years after initial diagnosis. Malignant thecomas are

extremely rare, and their signs and symptoms, management, and outcome are similar to those of the granulosa cell tumors (475).

Treatment

The treatment of granulosa cell tumors depends on the age of the patient and the extent of disease. For most patients, surgery alone is sufficient primary therapy; radiation and chemotherapy are reserved for the treatment of recurrent or metastatic disease (478–481,483,485–487,492,495–497).

Surgery

Because granulosa cell tumors are bilateral in only about 2% of patients, a unilateral salpingo-oophorectomy is appropriate therapy for stage IA tumors in children or in women of reproductive age (476). At the time of laparotomy or laparoscopy, if a granulosa cell tumor is identified by frozen section, a staging operation is performed, including an assessment of the contralateral ovary. If the opposite ovary appears enlarged, it should be sampled for biopsy. For perimenopausal and postmenopausal women for whom ovarian preservation is not important, a hysterectomy and bilateral salpingo-oophorectomy should be performed. **For premenopausal patients in whom the uterus is left *in situ*, an endometrial biopsy should be performed because of the possibility of a coexistent adenocarcinoma of the endometrium** (478).

Radiation Therapy

There is no evidence to support the use of adjuvant radiation therapy for granulosa cell tumors, although pelvic irradiation may help to palliate isolated pelvic recurrences (478,495).

Chemotherapy

[13] There is no evidence that adjuvant chemotherapy will prevent recurrence of disease and improve prognosis (497–500). Patients with metastatic disease at initial presentation or with recurrent disease may benefit from chemotherapy. Although the data are inconclusive, *BEP* or *CP* are the most commonly used regimens in selected patients with stage III or IV tumors or recurrent disease (493). In a GOG study, 37% (14 of 30) patients treated with *BEP* had a negative second-look laparotomy, and these patients had a median time to progression of 24.4 months (494). The GOG is performing a randomized phase II trial comparing *BEP* with the combination of paclitaxel and carboplatin for patients with newly diagnosed and chemo-naïve recurrent/metastatic sex cord–stromal tumors of the ovary. Taxanes and *bevacizumab* are active in AGCT's. The Alienor trial has recently completed recruitment and randomized patients with recurrent/metastatic sex cord–stromal tumors to either *paclitaxel* alone or in combination with *bevacizumab* and the results are eagerly awaited. Granulosa cell tumors are potentially hormonally responsive, with about 30% of granulosa tumors

expressing estrogen receptors and almost 100% expressing progesterone receptors. Hormonal agents such as progestins or luteinizing hormone–releasing hormone agonists or aromatase inhibitors have been used to treat these patients (501–505). There are case reports of durable response to aromatase inhibitors in patients with metastatic granulosa cell tumors who received multiple prior treatment (503). Small clinical series and case reports indicated that luteinizing hormone– releasing hormone agonists had a 50% response rate in 13 patients, while 4 of 5 patients in the literature responded to a progestational agent. Two case series reported durable responses in a total of 6 patients receiving aromatase inhibitors among those who progressed on or were intolerant of chemotherapy (502–505). There are fewer than 100 patients reported in the literature who have received hormonal therapies and typically these have been individual case reports or small retrospective series that are subject to bias. The role of hormonal therapy remains uncertain.

Adult granulosa cell tumors have a prolonged natural history and a tendency toward late relapse, reflecting their low-grade biology. Ten-year survival rates of about 90% are reported, with 20-year survival rates dropping to 75% (476–478,491,493). Most histologic types have the same prognosis, but patients with the more poorly differentiated diffuse or sarcomatoid type tend to do worse (475).

The DNA ploidy of the tumors is correlated with survival. Holland et al. reported DNA aneuploidy in 13 of 37 patients (35%) with primary adult granulosa cell tumors (498). The presence of residual disease is the most important predictor of PFS, but DNA ploidy is an independent prognostic factor. **Patients with residual-negative DNA diploid tumors had a 10-year PFS of 96%.**

Sertoli–Leydig Tumors

Sertoli–Leydig tumors occur most frequently in the third and fourth decades of life; 75% of these tumors are seen in women younger than 40 years. These neoplasms are extremely rare and account for less than 0.2% of ovarian cancers (2,506,507). Sertoli–Leydig cell tumors are most frequently low-grade malignancies; a poorly differentiated variety may behave more aggressively **(Fig. 39-24)** (506–508).

The tumors typically produce androgens, and clinical virilization is noted in 70% to 85% of patients (508). Signs of virilization include oligomenorrhea followed by amenorrhea, breast atrophy, acne, hirsutism, clitoromegaly, deepening of the voice, and a receding hairline. Measurement of plasma androgens may reveal elevated testosterone and androstenedione, with normal or slightly elevated dehydroepiandrosterone sulfate (2,509). Rarely, the Sertoli–Leydig tumor is associated with manifestations of estrogenization (i.e., isosexual precocity, irregular or postmenopausal bleeding). Sertoli–Leydig tumors are associated with somatic mutations in the *DICER1* gene (510).

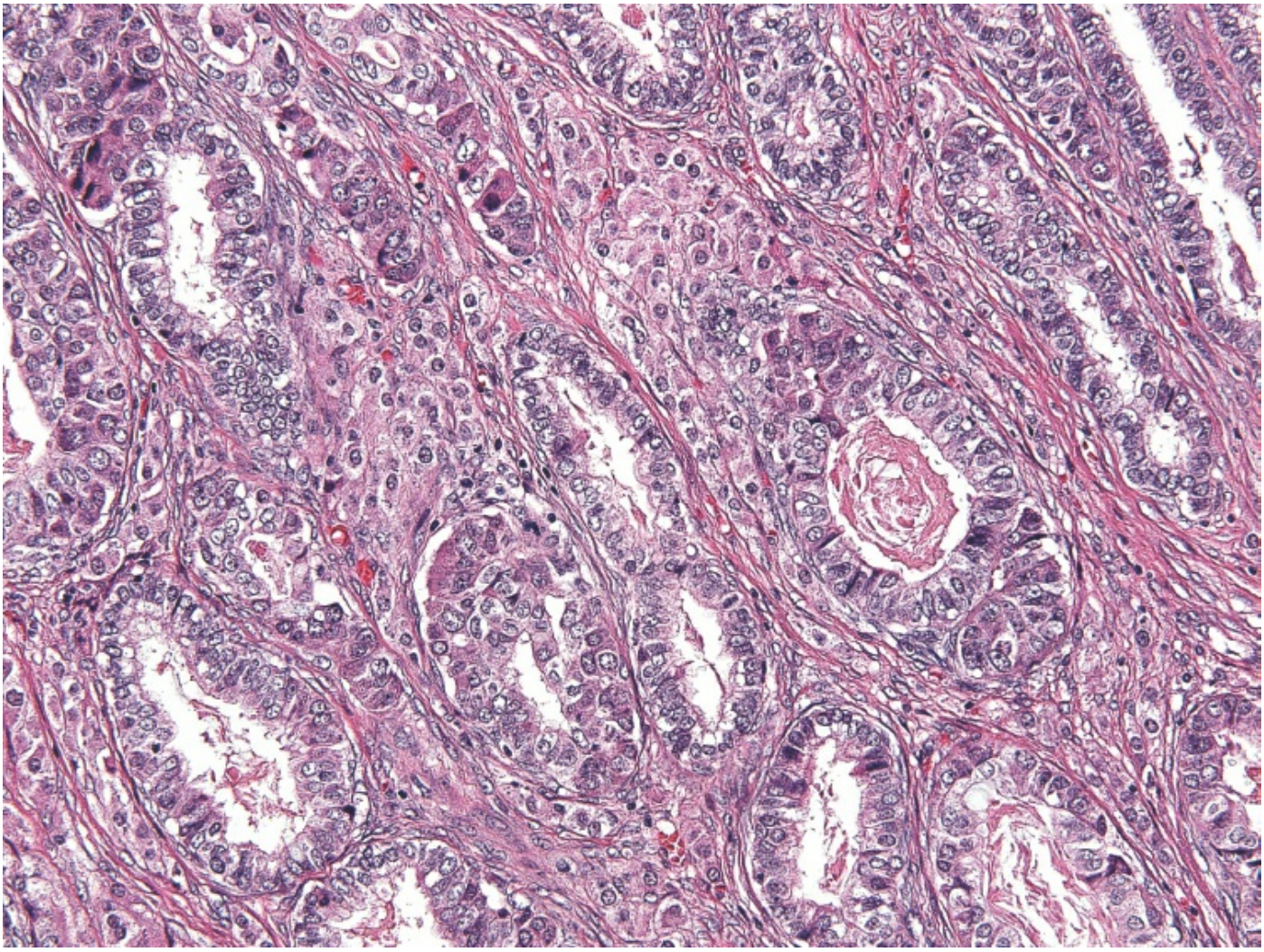


FIGURE 39-24 Sertoli–Leydig cell tumor of the ovary. Note the aggregates of eosinophilic Leydig cells in the stroma adjacent to Sertoli cell tubules.

Treatment

Because these low-grade lesions are rarely bilateral (<1%), the usual treatment is unilateral salpingo-oophorectomy and evaluation of the contralateral ovary for patients who are in their reproductive years (4,478). For older patients, hysterectomy and bilateral salpingo-oophorectomy are appropriate (506,507).

There are insufficient data to document the utility of radiation or chemotherapy for patients with persistent disease, but some responses in patients with measurable disease were reported with pelvic irradiation and the VAC chemotherapy regimen (4,511–515).

Prognosis

The 5-year survival rate is 70% to 90%, and recurrences thereafter are uncommon (4,509,511–515). **Most fatalities occur in the presence of poorly differentiated tumors.**

Uncommon Ovarian Cancers

There are several varieties of malignant ovarian tumors that together constitute only 0.1% of ovarian malignancies (2). Two of these lesions are the lipoid (or lipid) cell tumors and the primary ovarian sarcomas.

Steroid Cell Tumors

Steroid cell tumors account for less than 1% of ovarian neoplasms (2). Most are associated with virilization and, occasionally, with obesity, hypertension, and glucose intolerance, reflecting corticosteroid secretion. Rare cases of estrogen secretion and isosexual precocity have been reported.

Most of these tumors have benign or low-grade behavior, but about 20%, most of which are initially larger than 8 cm in diameter, may metastasize. Metastases are usually in the peritoneal cavity but can occur at distant sites, including the liver. The primary treatment is surgical removal of the ovary. There are no data regarding the effectiveness of radiation or chemotherapy for this disease.

Sarcomas

Carcinosarcomas (malignant mixed mesodermal tumors) of the ovary are uncommon. Clinical, morphologic, and molecular data suggest that they are monoclonal and that both epithelial and mesenchymal components are derived from a single uncommitted, totipotent cell which, after transformation, has proliferated toward separate differentiation lineages. Carcinosarcomas are thought to result from epithelial–mesenchymal transition (EMT) characterized by epithelial plasticity with transdifferentiation toward a mesenchymal cell type. Most tumors are heterologous, and 80% occur in postmenopausal women. The signs and symptoms are similar to those of most ovarian malignancies. These tumors are biologically aggressive, and most patients have evidence of metastases at presentation. They are treated either with *CP* or *ifosfamide* and *cisplatin*, or anthracycline-based combination regimens, but in general have a poor prognosis.

Small Cell Carcinoma, Hypercalcemic Type

This rare tumor occurs at an average age of 24 years (range 2 to 46 years) (516). **The tumors are typically unilateral. Approximately two-thirds of the tumors are accompanied by paraendocrine hypercalcemia.** This tumor accounts for one-half of all of the cases of hypercalcemia associated with ovarian tumors. About 50% of the tumors have spread beyond the ovaries when they are diagnosed (516). Small cell carcinoma, hypercalcemic type is characterized by germline or somatic mutations in *SMARCA4*. Germline and somatic **SMARCA4** mutations characterize **small cell carcinoma** of the ovary, **hypercalcemic** type. Similar mutations have been described in rhabdoid tumors and it has been proposed that small cell ovarian cancers should be

considered to be ovarian rhabdoid tumors and treated as such (517,518).

Immunohistochemical stains are helpful to differentiate this tumor from a lymphoma, leukemia, or sarcoma.

The management of these malignancies consists of surgery followed by *platinum*-based chemotherapy, radiation therapy, or both. It has been suggested that these patients may benefit from aggressive combination chemotherapy regimens that have been used in rhabdoid tumors at other sites. In addition to the primary treatment of the disease, control of the hypercalcemia may require aggressive hydration, loop diuretics, and the use of bisphosphonates or *calcitonin.* The prognosis tends to be poor, with most patients dying within 2 years of diagnosis, in spite of treatment.

METASTATIC TUMORS

[14] About 5% to 6% of ovarian tumors are metastatic from other organs, most frequently from the female genital tract, the breast, or the gastrointestinal tract (519–533). The metastases may occur from direct extension of another pelvic neoplasm, by hematogenous or lymphatic spread, or by transcoelomic dissemination, with surface implantation of tumors that spread in the peritoneal cavity.

Gynecologic

Nonovarian cancers of the genital tract can spread by direct extension or metastasize to the ovaries. Tubal carcinoma involves the ovaries secondarily in 13% of cases, usually by direct extension (2,4). Under some circumstances, it is difficult to know whether the tumor originated in the tube or the ovary, when both are involved. Cervical cancer spreads to the ovary only in rare cases (<1%), and most of these are of an advanced clinical stage or are adenocarcinomas. Adenocarcinoma of the endometrium can spread and implant directly onto the surface of the ovaries in about 5% of cases, but two synchronous primary tumors probably occur with greater frequency (532). In these cases, an endometrioid carcinoma of the ovary is usually associated with the adenocarcinoma of the endometrium.

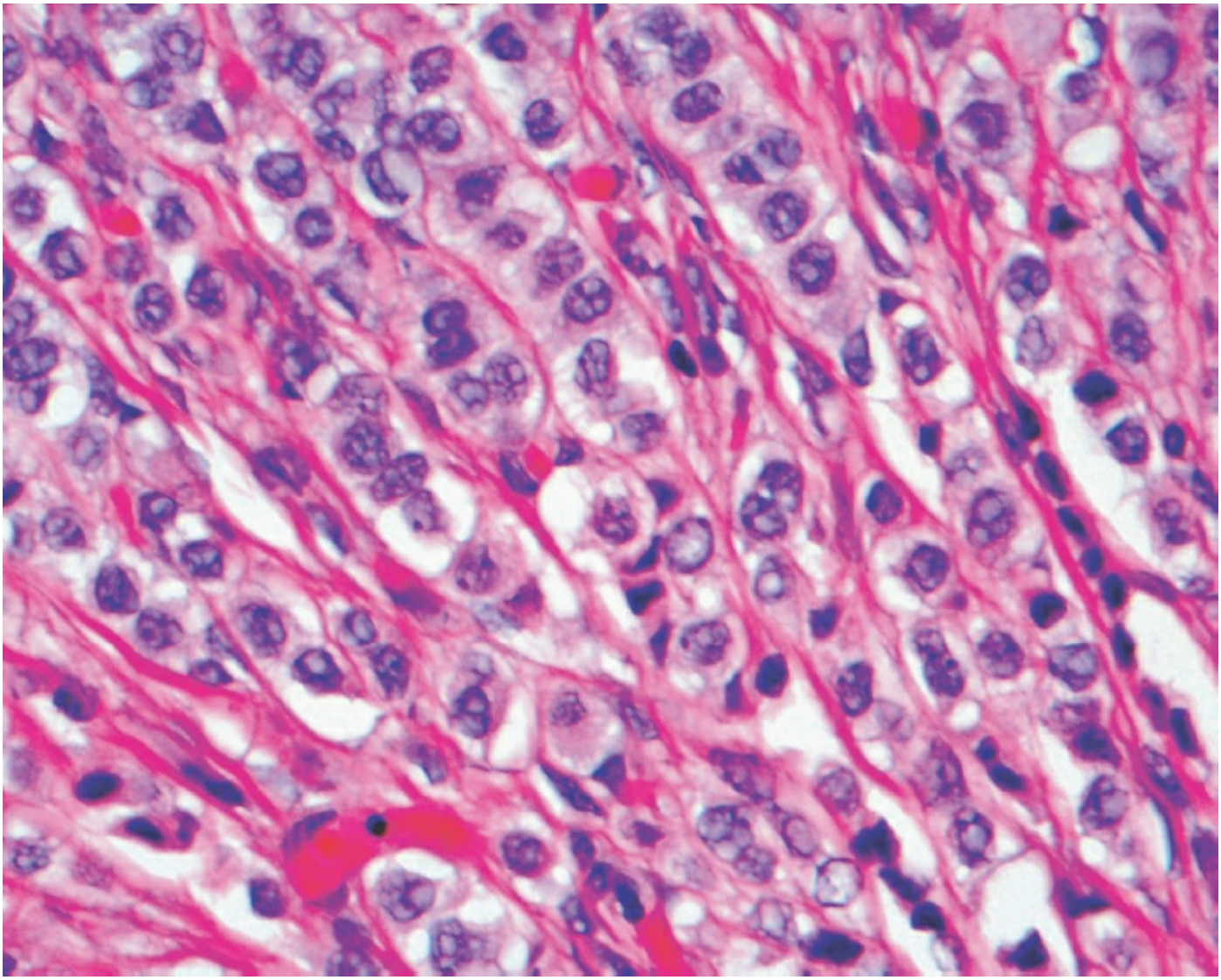


FIGURE 39-25 Metastatic carcinoma in the ovary. Note the linear, single-cell pattern found in this metastatic breast carcinoma.

Nongynecologic

The frequency of metastatic breast carcinoma to the ovaries varies according to the method of determination, but the phenomenon is common (Fig. 39-25). In the autopsy data of women who died of metastatic breast cancer, the ovaries were involved in 24% of cases, and 80% of the involvement was bilateral (519–524). Similarly, when ovaries are removed to palliate advanced breast cancer, about 20% to 30% of the cases reveal ovarian involvement, 60% of those bilaterally. The involvement of ovaries in early-stage breast cancer seems to be considerably lower, but precise figures are not available. In almost all cases, ovarian involvement is occult or a pelvic mass is discovered after other metastatic disease becomes apparent.

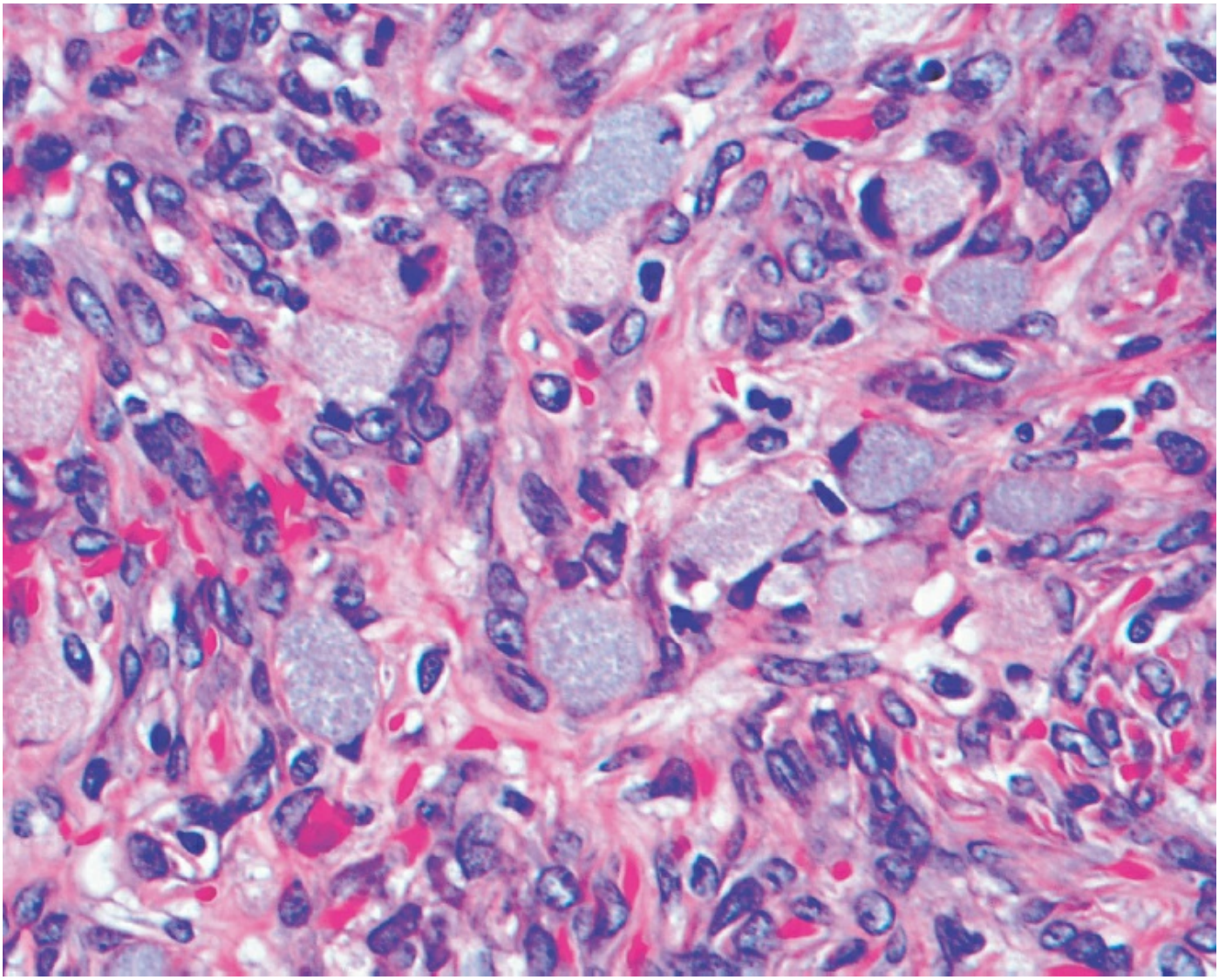


FIGURE 39-26 Krukenberg tumor of the ovary metastatic from a gastric carcinoma. Malignant cells have discrete vacuoles that push nuclei eccentrically, giving a signet-ring appearance. Mucicarmine stain demonstrates the cytoplasmic vacuoles to be mucin.

Krukenberg Tumor

Krukenberg tumors are characterized by mucin-filled signet ring cells and make up 30% to 40% of metastatic cancers to the ovaries (Fig. 39-26) (525,526,534). The primary tumor is frequently located in the stomach and less commonly in the colon, appendix (the so-called goblet cell carcinoid), breast, or biliary tract. Rarely, the cervix or the bladder may be the primary site. Krukenberg tumors can account for about 2% of ovarian cancers, and they are usually bilateral. They are associated with a very poor prognosis and most patients die of their disease within 1 year. In some cases, a primary tumor is never found.

Other Gastrointestinal Tumors

In other cases of metastasis from the gastrointestinal tract to the ovary, the tumor

does not have the classic histologic appearance of a Krukenberg tumor; most of these are from the colon and, less commonly, the pancreatobiliary tract, appendix, and small intestine (Fig. 39-27). As many as 1% to 2% of women with intestinal carcinomas will develop metastases to the ovaries during the course of their disease (521). Before exploration for an adnexal tumor in a woman older than 40 years, a barium enema or colonoscopy is recommended to exclude a primary gastrointestinal carcinoma with metastases to the ovaries, if there are any gastrointestinal symptoms. Metastatic colon cancer can mimic a mucinous cystadenocarcinoma of the ovary histologically, and the histologic distinction between the two can be difficult (520,521,526–530). Tumors that arise in the appendix may be associated with ovarian metastasis and can be confused with primary ovarian mucinous cancer. Pseudomyxoma peritonei almost always is associated with an appendiceal primary and the appendix should always be resected at surgery and carefully examined pathologically (526,530).

Melanoma

Rare cases of malignant melanoma metastatic to the ovaries have been reported (533). In these circumstances, the melanomas are usually widely disseminated. Removal would be warranted for palliation of abdominal or pelvic pain, bleeding, or torsion. Malignant melanoma can arise, rarely, in a mature cystic teratoma (535).

Carcinoid Tumors

Metastatic carcinoid tumors represent fewer than 2% of metastatic lesions to the ovaries (536). Only about 2% of patients with primary carcinoids have evidence of ovarian metastasis, and only 40% of them have the carcinoid syndrome at the discovery of the metastatic carcinoid. In perimenopausal and postmenopausal women explored for an intestinal carcinoid, it is reasonable to remove the ovaries to prevent subsequent ovarian metastasis. The discovery of an ovarian carcinoid should prompt a careful search for a primary intestinal lesion (537).

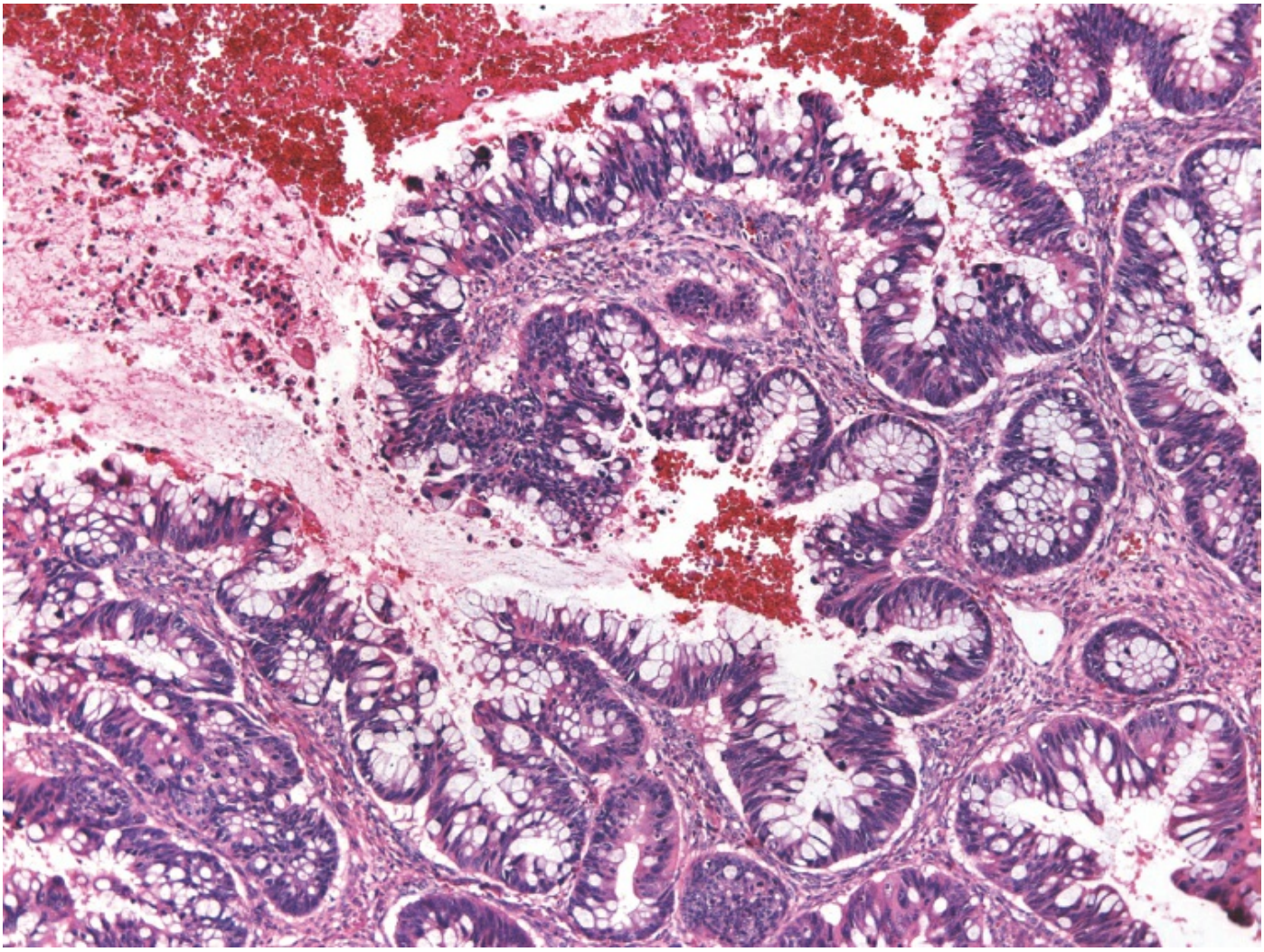


FIGURE 39-27 Metastatic colorectal carcinoma in the ovary often has areas of necrotic debris (so-called dirty necrosis) adjacent to partial gland structures showing a cribriform pattern.

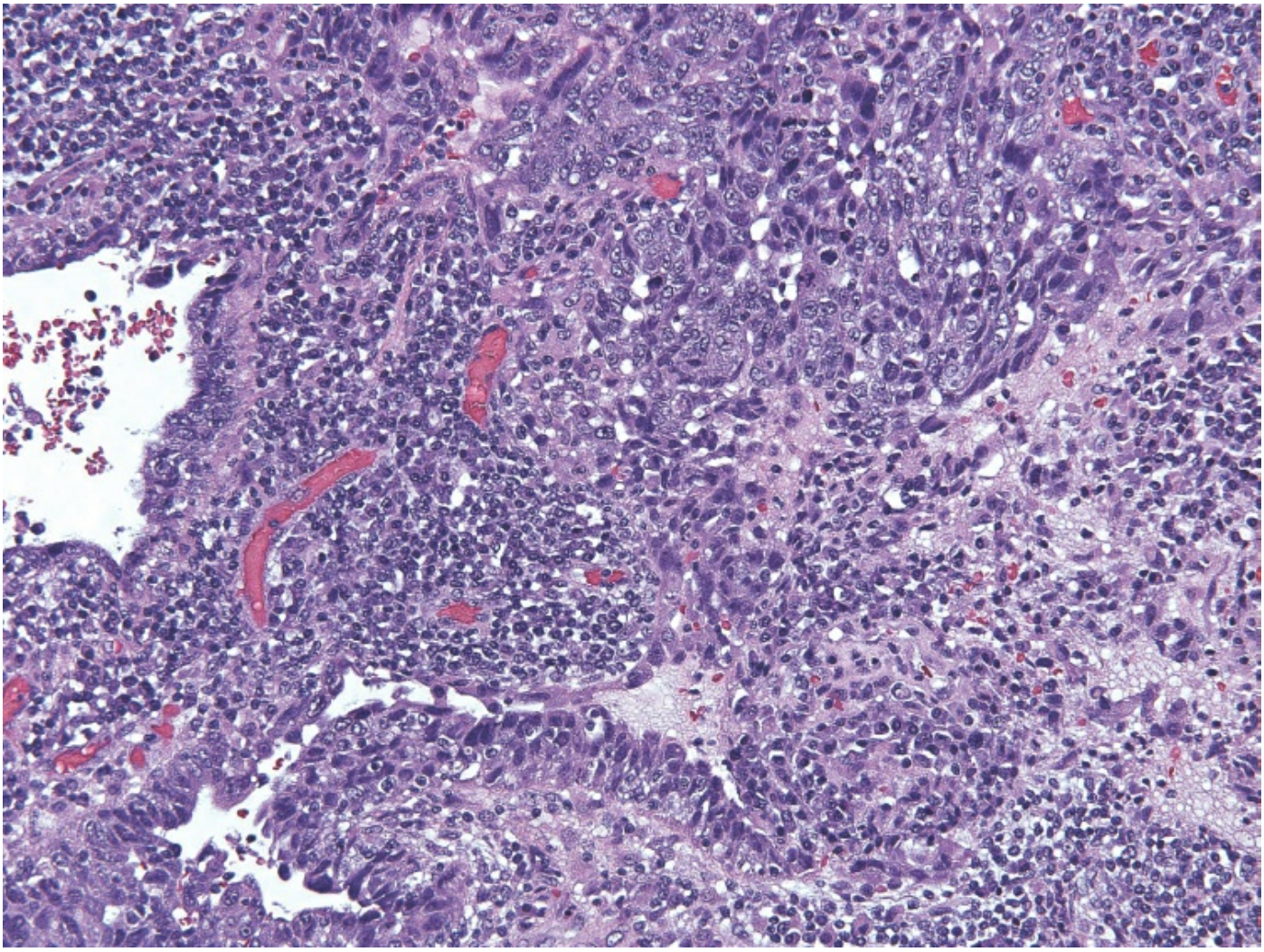


FIGURE 37-28 Carcinoma of the fallopian tube. This is a high-grade serous carcinoma that has invaded the lamina propria of the tubal mucosa. Most primary fallopian tube carcinomas arise in the distal (fimbria) portion of the fallopian tube.

Lymphoma and Leukemia

Lymphomas and leukemia can involve the ovary. When they do, the involvement is usually bilateral (538–540). About 5% of patients with Hodgkin lymphoma will have lymphomatous involvement of the ovaries, but this involvement typically occurs with advanced-stage disease. **With Burkitt lymphoma, ovarian involvement is very common. Other types of lymphoma involve the ovaries less frequently, and leukemic infiltration of the ovaries is uncommon** (540). Sometimes the ovaries can be the only apparent sites of involvement of the abdominal or pelvic viscera with a lymphoma; if this circumstance is found, a careful surgical exploration may be necessary. Intraoperatively, a hematologist–oncologist should be consulted to determine the need for these procedures if frozen section of a solid ovarian mass reveals a lymphoma. Most lymphomas no longer require extensive surgical staging; biopsy of enlarged lymph nodes should be performed. In some cases of Hodgkin lymphoma, a

more extensive evaluation may be necessary. Treatment involves that of the lymphoma or leukemia. Removal of a large ovarian mass may improve patient comfort and facilitate a response to subsequent radiation or chemotherapy.

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CHAPTER 40

Vulvar Cancer

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Etiology
Types of Invasive Vulvar Cancer
- Squamous Cell Carcinoma
  - *Clinical Features*
  - *Diagnosis*
  - *Routes of Spread*
  - *Staging*
  - *Prognosis and Survival*
  - *Treatment*
  - *Advanced Disease: Large T_2 and T_3 Primary Tumors*
  - *Recurrent Vulvar Cancer*

Melanoma
- Histopathology
- Staging
- Treatment
  - *Management of Patients With Nodal Metastases*
- Prognosis

Bartholin Gland Carcinoma
- Epidemiology
- Histopathology
- Signs and Symptoms
- Treatment
- Prognosis

Adenoid Cystic Carcinoma of the Bartholin Gland
Other Adenocarcinomas
- Adenosquamous Carcinoma
- Basal Cell Carcinoma
- Verrucous Carcinoma

Vulvar Sarcoma
Rare Vulvar Malignancies
- Lymphomas
- Endodermal Sinus Tumor
- Merkel Cell Carcinoma
- Dermatofibrosarcoma Protuberans

Metastatic Tumors of the Vulva

KEY POINTS

1 Vulvar lesions require biopsy to avoid delay in diagnosis.
2 The modern approach to patients with vulvar cancer is multidisciplinary and individualized.
3 Management of the primary lesion and groin nodes is determined separately.
4 Most T_1 and early T_2 lesions can be managed with radical local excision.
5 Large T_2 and T_3 primary tumors are best treated with chemoradiation followed by limited surgical resection.
6 Unifocal tumors less than 4 cm in diameter with clinically negative nodes are suitable for sentinel lymph node dissection in experienced hands.
7 When groin dissection is indicated, it should be a thorough inguinofemoral lymphadenectomy.
8 The single most important prognostic factor is lymph node status: 5-year survival without groin node metastases is greater than 90%; with groin node metastases, 5-year survival is 50%.
9 Postoperative (chemo-) radiation decreases the risk of groin recurrence in patients with multiple positive inguinofemoral lymph nodes.
10 Recurrence in the groin is almost universally fatal.

With 6,020 new cases and 1,150 deaths annually in the United States, vulvar cancer is uncommon, resulting in age-adjusted incidence rates of 2.8 and 1.7 per 100,000 in white and black women, respectively. Vulvar cancer represents about 4% to 6% of malignancies of the female genital tract and 0.6% of all cancers in women (1,2). Vulvar cancer predominantly affects postmenopausal women, and it is the most common anogenital cancer in women more than 70 years of age (3). HPV infection is associated with a significant number of vulvar cancers. **[1]** **The incidence of in situ vulvar cancer has been increasing worldwide, primarily because of the increasing occurrence in young women, who account for 75% of the cases. The incidence of lichen sclerosus, which is associated with an increased risk of vulvar cancer, has doubled over the past two decades, predominantly in postmenopausal women** (4). **The overall rate of invasive vulvar carcinoma is increasing, but at a much lower rate** (5,6). Squamous cell carcinomas account for over 80% of all primary vulvar malignancies, whereas melanomas, adenocarcinomas, basal cell carcinomas, Paget disease, and sarcomas are less common. Most vulvar cancers are diagnosed at an early stage. In the United States, 5-year survival rates for vulvar cancer are 72%.

Following the initial reports of Taussig in the United States and Way in Great Britain, radical vulvectomy and en bloc groin dissection, with or without pelvic lymphadenectomy, was standard treatment for all patients with operable disease (7,8). Postoperative morbidity was high and prolonged hospitalization common. **Over the past 4 decades, significant advances in the management of vulvar cancer have been made, reflecting a paradigm shift toward a more conservative surgical approach without compromised survival and with markedly decreased physical and psychological morbidity:**

1. **[2] Individualization of treatment for all patients with invasive disease.**

2. **Vulvar conservation for patients with unifocal tumors and an otherwise normal vulva.**
3. **Omission of the groin dissection for patients with microinvasive tumors (T1a, Ä2 cm diameter and Ä1 mm of stromal invasion).**
4. **Elimination of routine pelvic lymphadenectomy.**
5. **Incorporation of the sentinel lymph node procedure to eliminate complete inguinofemoral lymphadenectomy in node-negative patients who may not derive benefits from the procedure.**
6. **The use of separate incisions for the groin dissection to improve wound healing.**
7. **Omission of the contralateral groin dissection in patients with lateral T_1 lesions and negative ipsilateral nodes.**
8. **The use of preoperative radiation therapy to obviate the need for exenteration in patients with advanced disease.**
9. **The use of postoperative (chemo-) radiation therapy to decrease the incidence of groin recurrence in patients with multiple positive groin nodes.**

ETIOLOGY

The etiology of vulvar cancer is multifactorial. Reported risk factors for vulvar cancer include human papillomavirus (HPV) infection, vulvar intraepithelial neoplasia (VIN), cervical intraepithelial neoplasia (CIN), lichen sclerosus, cigarette smoking, alcohol consumption, obesity, immunosuppression, a prior history of cervical cancer, and northern European ancestry (9,10). **Growing evidence has established two distinct etiologic entities of squamous cell carcinoma of the vulva:**

1. ***Basaloid or warty types*, which comprise about 40% of vulvar squamous cell carcinomas, tend to be multifocal, occur generally in younger patients, and are related to HPV infection, usual type VIN (uVIN), immunosuppression, and cigarette smoking.**
2. ***Keratinizing, differentiated, or simplex types*, which account for about 60% of cases, tend to be unifocal, occur predominantly in older patients, are not related to HPV, and often are found in areas adjacent to lichen sclerosus, chronic inflammatory dermatoses, and differentiated type VIN (dVIN).**

High-grade VIN was closely studied as a potential precancerous lesion. The direct progression of VIN to cancer is difficult to document, but a review of 3,322 published patients with high-grade VIN reports a 9% progression rate to cancer for untreated and 3.8% for treated cases (11). VIN is found adjacent to basaloid or warty vulvar squamous cell carcinomas in more than 80% of cases and 10% to 20% of vulvar

carcinoma in situ lesions harbor an occult invasive component (12,13). A meta-analysis comprising 5,015 vulvar cancers demonstrated a 40% prevalence of HPV in vulvar cancer with nearly 80% of warty or basaloid cancers testing positive for HPV, compared with only 13% of keratinizing carcinomas. The predominant high-risk HPV type was HPV16, followed by HPV33 and HPV18 (14). **Epidemiologic risk factors for the basaloid or warty-type squamous cell carcinoma of the vulva are similar to those for cervical cancer and include a history of multiple lower genital tract neoplasias, immunosuppression, and smoking**. Based on immunogenicity and efficacy studies, it is expected that HPV vaccination, particularly with the nine-valent HPV vaccine, has the potential to prevent up to 90% of HPV-associated vulvar cancers (15).

Frequently implied as an etiologic variable for the keratinizing carcinoma is the itch–scratch cycle associated with lichen sclerosus and chronic inflammatory dermatoses, with atypical changes occurring in the repaired epithelium. Differentiated VIN is a precursor to keratinizing squamous cell carcinoma and is strongly associated with lichen sclerosus. In keratinizing carcinoma, adjacent lichen sclerosus or dVIN is found in more than 80% of patients (4). **Women with vulvar lichen sclerosus are at increased risk of developing invasive squamous cell cancer of the vulva**. A population-based study found a 36-fold increased risk of vulvar cancer for women with lichen sclerosus (16). During the past 20 years, the incidence of lichen sclerosus has nearly doubled from 7.4 to 14.6 per 100,000 woman-years. In a cohort of more than 3,000 women with lichen sclerosus, the observed cumulative incidence of squamous cell carcinoma of the vulva was 6.7% with concurrent VIN and age ≥70 years being independent risk factors (4). Supportive evidence that some of these lesions are precancerous comes from molecular studies that demonstrate aneuploid DNA content, *p53* overexpression, high Ki67 expression, indicating high proliferation indices and monoclonal expansion of keratinocytes in lichen sclerosus and dVIN (17–19), though the exact molecular mechanism of non–HPV-associated vulvar cancer remains to be elucidated. An area of active research explores whether treatment of lichen sclerosus with superpotent topical steroids can impact the malignancy risk (20). A prospective longitudinal cohort study of 507 women with biopsy-proven vulvar lichen sclerosus demonstrated that patients who were compliant with active treatment, typically with superpotent topical steroids, had improved symptom control and a reduced incidence of vulvar carcinoma (21).

TYPES OF INVASIVE VULVAR CANCER

The histologic subtypes of invasive vulvar cancer are shown in Table 40-1.

Squamous Cell Carcinoma

Approximately 90% to 92% of all invasive vulvar cancers are of the squamous cell type. Squamous carcinomas of the vulva can be divided into distinct histologic subtypes designated as *basaloid carcinoma*, *warty carcinoma*, and *keratinizing squamous carcinoma*. Mitoses are noted in these malignancies, but atypical keratinization is the histologic hallmark of invasive vulvar cancer (23). Most vulvar squamous carcinomas reveal keratinization **(Fig. 40-1)**. Histologic features that correlate with the occurrence of inguinal lymph node metastasis are lymph–vascular space invasion, tumor thickness, depth of stromal invasion, grade of differentiation, histologic pattern of invasion (spray and stellate versus confluent, compact, broad, and pushing), and increased amount of keratin (24–27).

Table 40-1 Malignant Tumors of the Vulva Based on IARC/WHO Classification (22)

Type	Percent
Malignant Epithelial Tumors	
Squamous cell carcinoma (keratinizing, non-keratinizing, basaloid, warty, verrucous)	90–92%
Basal cell carcinoma	2–3%
Paget disease	<1%
Bartholin gland (adenocarcinoma, squamous cell, adenosquamous, adenoid cystic, transitional cell)	1%
Tumors arising from other specialized anogenital glands (adenocarcinoma of mammary gland type, adenocarcinoma of Skene gland or minor vestibular gland origin, malignant Phylloides tumor)	<1%
Adenocarcinomas of other types (sweat gland type, intestinal type)	<1%
Malignant Neuroectodermal Tumors	<1%
Ewing sarcoma	
Malignant Soft Tissue Tumors	<1%
Rhabdomyosarcoma	
Leiomyosarcoma	
Epithelioid sarcoma	
Alveolar soft part sarcoma	
Other sarcomas	
Malignant Melanocytic Tumors	

Malignant melanoma	2–5%
Malignant Germ Cell Tumors	<1%
Neuroendocrine tumors (small cell or large cell high-grade neuroendocrine carcinoma)	
Merkel cell tumor	
Yolk sac tumor	
Lymphoid and Myeloid Tumors	<1%
Lymphomas	
Myeloid neoplasms	
Secondary (metastatic) Tumors	1%

IARC, International Agency for Research on Cancer; WHO, World Health Organization.

[3] Microinvasive carcinoma of the vulva (T_{1a}) is defined as a lesion 2 cm or less in diameter with 1 mm or less stromal invasion (28). Depth of stromal invasion is measured vertically from the epithelial–stromal junction (basement membrane) of the adjacent most superficial dermal papilla to the deepest point of tumor invasion (Fig. 40-2). **When the tumor invades 1 mm or less, metastasis to the inguinal lymph nodes is extremely rare among reported series. When invasion is greater than 1 mm, there is a significant risk of inguinal lymph node metastasis.**

Clinical Features

[4] Squamous cell carcinoma of the vulva is predominantly a disease of postmenopausal women. The mean age at diagnosis is about 65 years and 15% of patients who develop vulvar cancer do so before age 40. There may be a longstanding history of an associated vulvar intraepithelial disorder, such as lichen sclerosus or VIN. As many as 27% of patients with vulvar cancer have a second primary malignancy (29–31). Based on data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, patients with invasive vulvar cancer have an increased risk of 1.3% for developing a subsequent cancer. **Most of the excess second cancers were smoking related** (e.g., cancers of the lung, buccal cavity and pharynx, esophagus, nasal cavity, and larynx) **or related to infection with HPV** (e.g., cervix, vulva, vagina, and anus) (32).

Most patients are asymptomatic at the time of diagnosis. If symptoms exist, vulvar pruritus, a lump, or a mass are the most common findings. Less frequent symptoms include a bleeding or ulcerative lesion, discharge, pain, or dysuria. Occasionally, a large metastatic mass in the groin is the initial symptom.

A careful inspection of the vulva should be part of every gynecologic

examination. On physical examination, vulvar carcinoma is usually raised and may be fleshy, ulcerated, plaquelike, or warty in appearance. It may be pigmented, red or white, and tender or painless. The lesion may be clinically indistinct, especially in the presence of VIN, lichen sclerosus, or other vulvar dermatoses (13). Any lesion of the vulva warrants a biopsy.

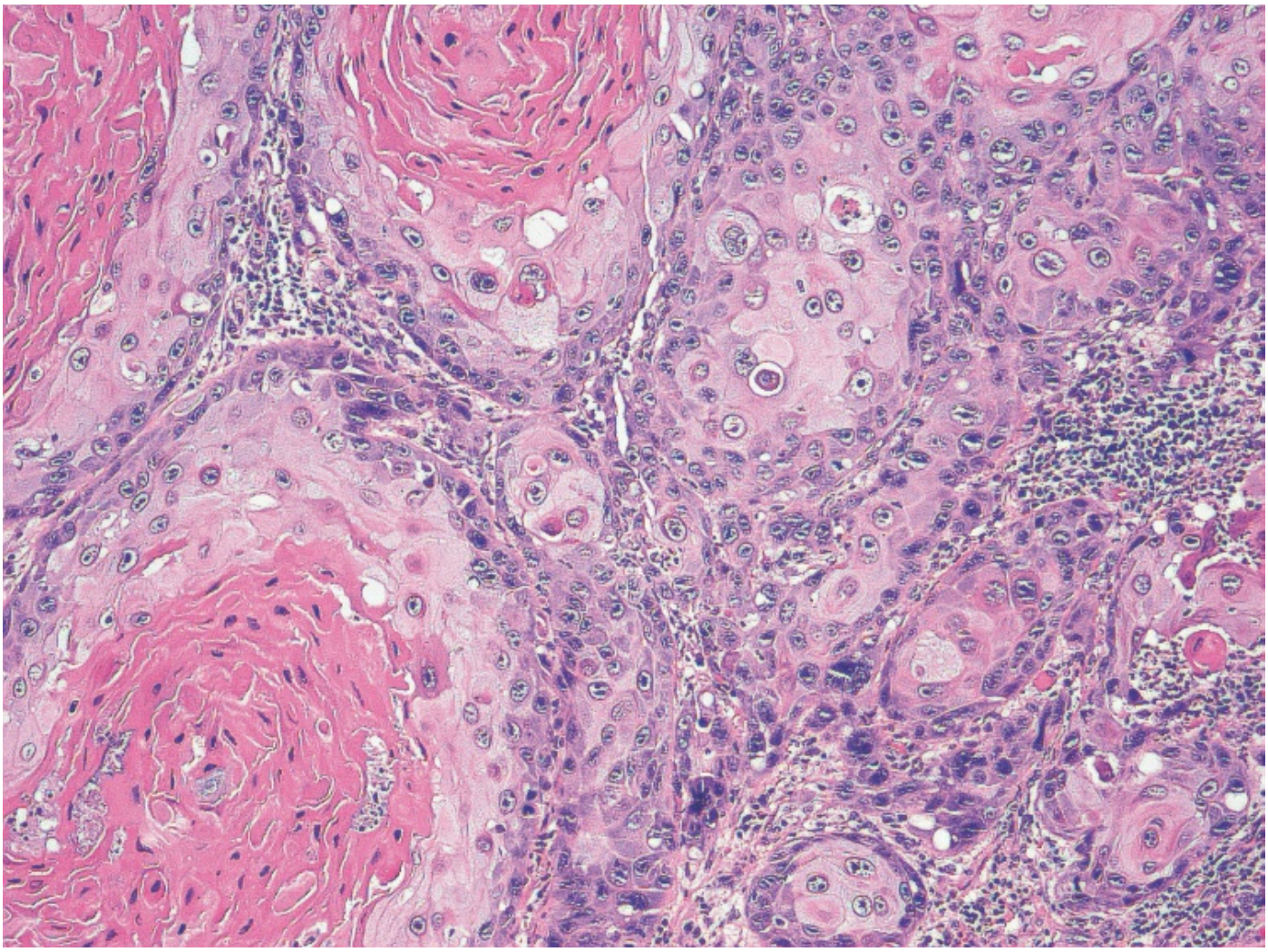


FIGURE 40-1 Squamous cell carcinoma of the vulva, keratinizing type. The multiple pearl formations consist of laminated keratin.

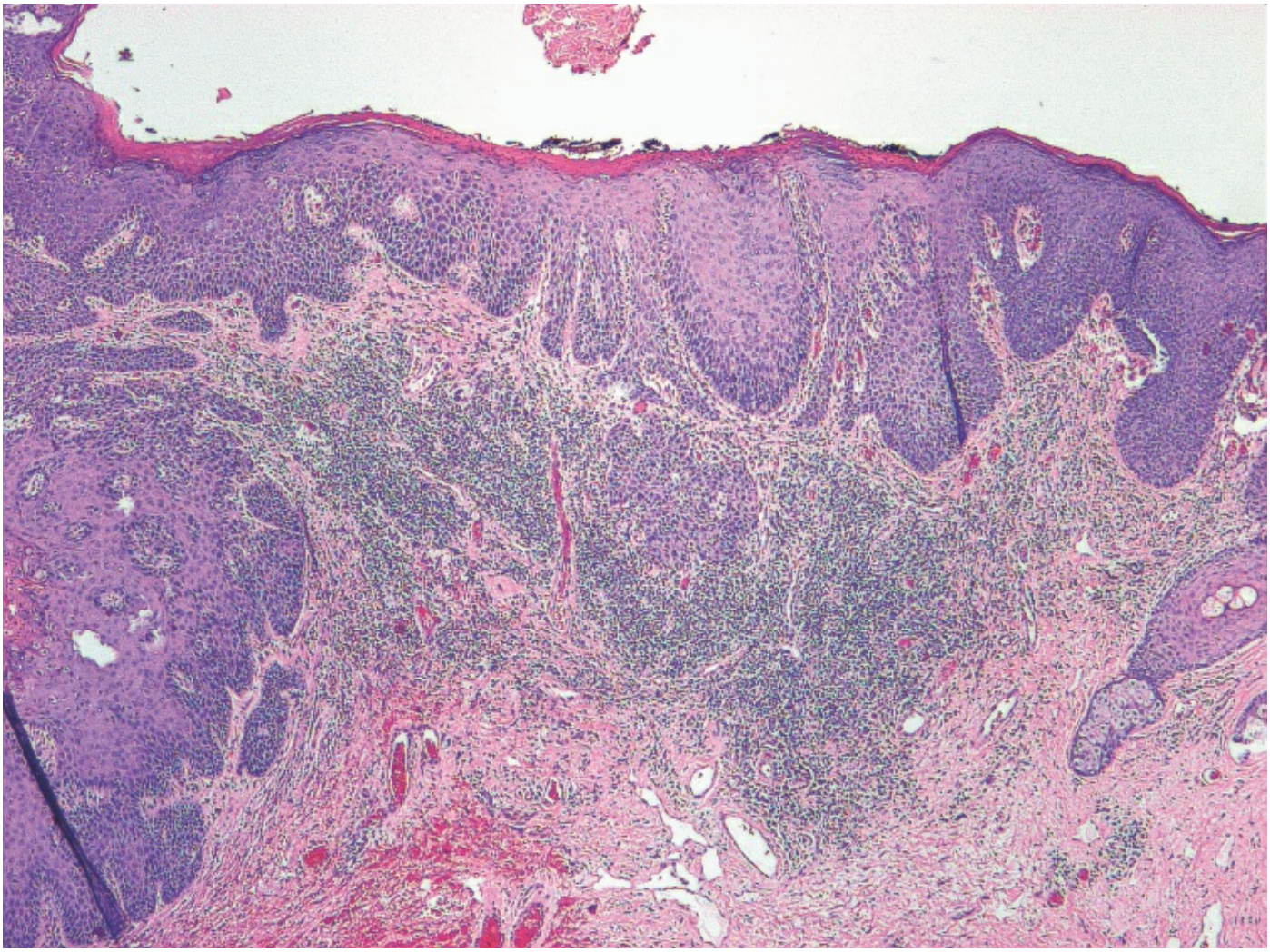


FIGURE 40-2 Early invasive carcinoma of vulva originating from vulvar intraepithelial neoplasia. An irregular nest of malignant cells extend from the base of rete pegs. Desmoplastic stromal reaction and chronic inflammation are useful diagnostic signs of stromal invasion. The depth of stromal invasion is measured from the base of the most superficial dermal papilla vertically to the deepest tumor cells.

Most squamous carcinomas of the vulva occur on the labia majora and minora (60%), but the clitoris (15%) and perineum (10%) may be primary sites. Approximately 10% of the cases are too extensive to determine a site of origin, and about 5% of the cases are multifocal.

As part of the clinical evaluation, a careful assessment of the extent of the lesion, including whether it is unifocal or multifocal, should be performed. The lesion diameter should be measured and its proximity to the midline and/or involvement of midline structures including urethra, vagina, clitoris, and anus should be assessed. The groin lymph nodes should be evaluated carefully, and a complete pelvic examination should be performed. A cytologic sample should be taken from the cervix, and **colposcopy of the vulva, cervix, and vagina should be performed because of the common association with other squamous intraepithelial or invasive neoplasms of the lower genital tract.**

Diagnosis

Diagnosis requires a Keys punch biopsy or wedge biopsy, which can be obtained in the office using local anesthesia. The biopsy must include sufficient underlying dermis to assess for microinvasion.

Physician delay is a common problem in the diagnosis of vulvar cancer, particularly if the lesion has a warty appearance. Any large or confluent warty lesion requires biopsy before medical or ablative therapy is initiated.

Routes of Spread

Vulvar cancer spreads by the following routes:

1. **Direct extension**, to involve adjacent structures such as the vagina, urethra, clitoris, and anus.
2. **Lymphatic embolization** to the regional inguinal and femoral lymph nodes.
3. **Hematogenous spread** to distant sites, including the lungs, liver, and bone.

[5] Lymphatic metastases may occur early in the disease. Twelve percent of tumors 2 cm in diameter or smaller have regional metastases (29,33). Initially, spread is usually to the inguinal lymph nodes, which are located between Camper's fascia and the fascia lata (34). From these superficial groin nodes, the disease spreads to the deep femoral nodes, which are located medial to the femoral vessels (Fig. 40-3). *Cloquet's* or *Rosenmüller's node*, situated beneath the inguinal ligament, is the most cephalad of the femoral node group. **Metastases to the femoral nodes without involvement of the inguinal nodes are reported** (35–38). A study from the M. D. Anderson Cancer Center reported a 9% groin recurrence rate in 104 patients with vulvar cancer who had negative nodes on superficial inguinal lymphadenectomy at initial surgery, and intraoperative lymphatic mapping studies found the sentinel node deep to the cribriform fascia in 5% to 16% of these cases (39–41). This pattern of lymphatic spread needs to be taken into consideration when determining the extent of inguinofemoral lymphadenectomy and the radiotherapeutic techniques and target volumes.

From the inguinal–femoral nodes, the cancer spreads to the pelvic nodes, particularly the external iliac group. Although direct lymphatic pathways from the clitoris and Bartholin gland to the pelvic nodes were described, these channels seem to be of minimal clinical significance (42–44). The lymphatics from either side of the vulva form a rich network of anastomoses along the midline. Lymphatic drainage from the clitoris, anterior labia minora, and perineum is bilateral. Metastases to contralateral lymph nodes in the absence of ipsilateral nodal involvement is very rare (0% to 0.4%) for lateral vulvar tumors that are either 2 cm or less in diameter or with 5 mm or less invasion (33,45).

The overall incidence of inguinal–femoral lymph node metastases is reported to

be about 32% (38,40,43–53) (Table 40-2). **Metastases to pelvic nodes occur in about 12% of cases.** Pelvic nodal metastases are rare (0.6%) in the absence of groin node involvement, but they occur in about 16% of cases with positive groin nodes (Table 40-2). The risk increases to 33% in the presence of clinically suspicious groin nodes and to 40% to 50% if there are three or more pathologically positive inguinal–femoral nodes (30,45,54–57). The incidence of lymph node metastases correlates positively with depth of invasion, as shown in Table 40-3. Hematogenous spread usually occurs late in the course of vulvar cancer and is rare in the absence of lymph node metastases.

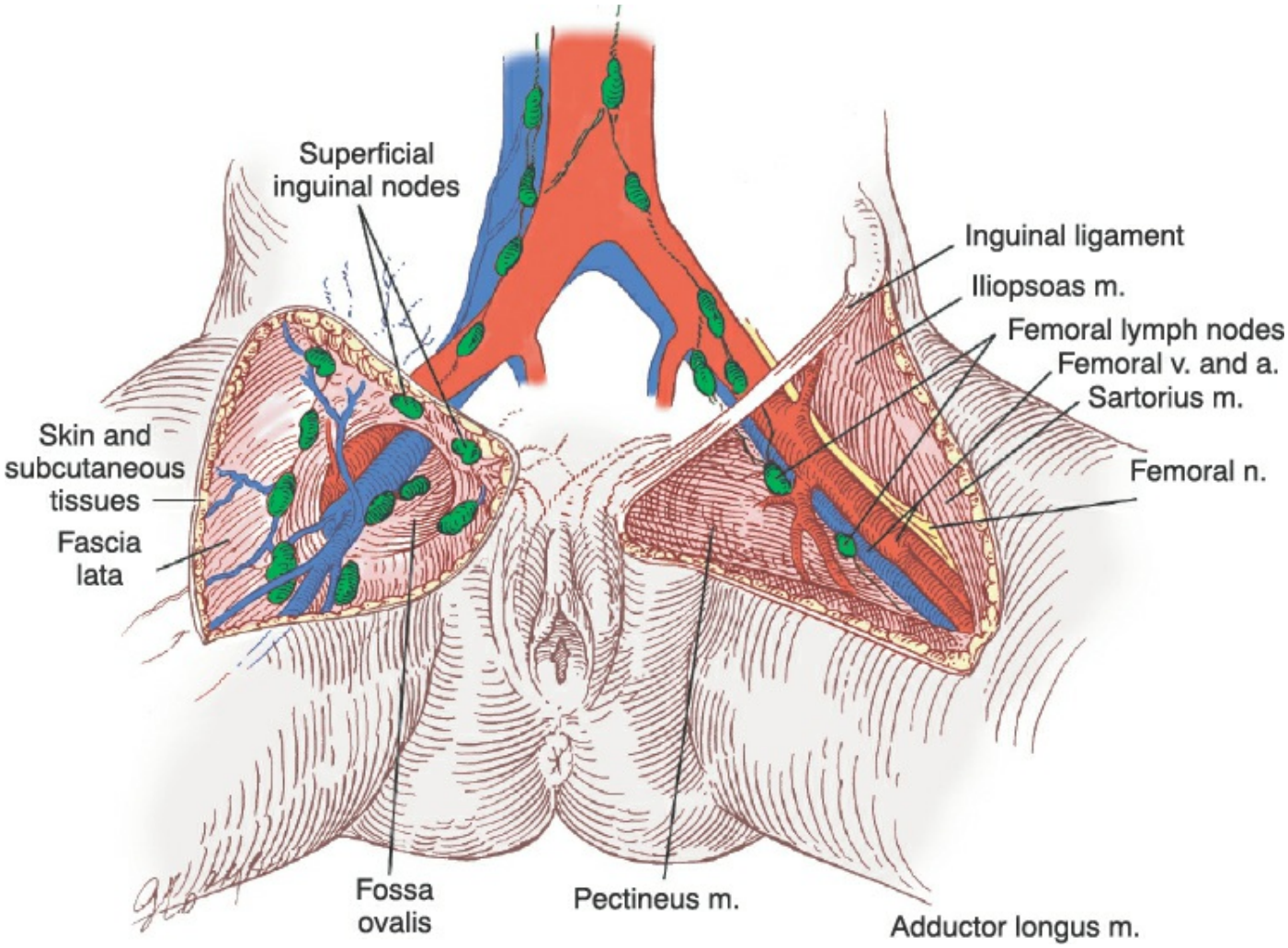


FIGURE 40-3 Inguinal–femoral lymph nodes. (From **Hacker NF.** Vulvar and Vaginal Cancer. In: Hacker NF, Gambone J, Hobel C. *Hacker & Moore's Essentials of Obstetrics and Gynecology*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2015:452, with permission.)

Table 40-2 Incidence of Lymph Node Metastases in Squamous Cell Carcinoma of the Vulva

Author	Positive Inguinal–Femoral Nodes	Positive Pelvic Nodes/Patients s/p Lymphadenectomy	Positive Pelvic Nodes/Patients With Negative Inguinal–Femoral Nodes	Positive Pelvic Nodes/Patients With Positive Inguinal–Femoral Nodes
Rutledge et al. (29)	33/86 (38%)	12/72 (17%)	0/53 (0%)	12/33 (36%)
Collins et al. (48)	27/98 (28%)	11/98 (11%)	4/71 (6%)	7/27 (26%)
Morley (49)	67/180 (37%)	6/23 (26%)	0/113 (0%)	6/67 (9%)
Krupp and Bohm (50)	40/195 (21%)	10/195 (5%)	1/155 (0.6%)	9/40 (23%)
Benedet et al. (52)	34/120 (28%)	4/51 (8%)	N/A	N/A
Curry et al. (42)	57/191 (30%)	9/52 (17%)	0/134 (0%)	9/57 (16%)
Iversen et al. (53)	90/262 (34%)	7/100 (7%)	1/172 (0.6%)	6/90 (7%)
Hacker et al. (54)	31/113 (27%)	6/18 (33%)	0/82 (0%)	6/31 (19%)
Podratz et al. (30)	59/175 (34%)	7/114 (6%)	0/116 (0%)	7/59 (12%)
Monaghan and Hammond (55)	37/134 (28%)	3/80 (4%)	N/A	N/A
Hopkins et al. (56)	61/145 (42%)	13/38 (34%)	0/84 (0%)	13/61 (21%)
Keys (51)	203/588 (35%)	15/53 (28%)	N/A	N/A
Gonzales Bosquet (45)	108/320 (34%)	NA	NA	14/108 (13%)
Total	847/2,607 (32%)	103/894 (12%)	6/980 (0.6%)	89/573 (16%)

N/A, data not available; s/p, status post.

Staging

Initially, vulvar carcinoma was staged clinically based on tumor size and location, palpable regional lymph node status, and a limited search for distant metastases. The prognostic importance of the lymph node status is significant, but clinical assessment of the lymph nodes has limited accuracy. This led the Cancer Committee of FIGO to introduce a surgical staging system for vulvar cancer in 1988, which underwent several revisions, most recently in 2009, to provide better prognostic discrimination between stages and less heterogeneity within stages (28,58,59) (Table 40-4), by separating patients whose tumors involve adjacent perineal structures from those with positive lymph nodes and taking into account the number and morphology of the involved nodes.

The new FIGO staging system was validated in 269 patients, 42% of whom were restaged (61). The number of positive nodes negatively correlated with survival, as did the presence of extracapsular growth. This study confirmed Gynecologic Oncology Group (GOG) and SEER data indicating that in patients with negative nodes, tumor size was not predictive of survival (59). This study confirmed reports demonstrating that, when corrected for the number of positive nodes, bilaterality of nodal metastases was not predictive of survival (61–65).

Paralleling the changes to the FIGO staging, the American Joint Committee on Cancer (AJCC) significantly modified the vulvar cancer tumor-node-metastasis (TNM) classification with the release of the 2009 edition of the AJCC Cancer Staging Manual (Table 40-4) (60).

Table 40-3 Nodal Status in T_1 Squamous Cell Carcinoma of the Vulva Versus Depth of Stromal

Invasion

Depth of Invasion	No. of Patients	Positive Nodes	Nodes
1 mm	163	0	0
1.1–2 mm	145	11	7.7
2.1–3 mm	131	11	8.3
3.1–5 mm	101	27	26.7
>5	38	13	34.2
Total	578	62	10.7

From **Hacker NF, Eifel PJ.** Vulvar cancer. In: Berek JS, Hacker NF. *Berek & Hacker's Gynecologic Oncology*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:569.

Table 40-4 The 2009 FIGO Staging and TNM Classification for Vulvar Cancer (28,61)

FIGO Stage	TNM Classification	Clinical/Pathologic Findings
Stage IA	$T_{1a}N_0M_0$	Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1 mm,[a] no nodal metastasis
Stage IB	$T_{1b}N_0M_0$	Lesions >2 cm in size or with stromal invasion >1 mm, confined to the vulva or perineum, with negative nodes
Stage II	$T_2N_0M_0$	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
Stage III		Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguinofemoral lymph nodes
IIIA	$T_{1or2}\ N_{1b}\ M_0\ T_{1or2}\ N_{1a}\ M_0$	(i) with 1 lymph node metastasis (≥5 mm) or (ii) 1–2 lymph node metastasis(es) (<5 mm)
IIIB	$T_{1or2}\ N_{2b}\ M_0\ T_{1or2}\ N_{2a}\ M_0$	(i) with 2 or more lymph node metastasis (≥5 mm) or (ii) 3 or more lymph node metastases (<5 mm)
IIIC	$T_{1or2}\ N_{2c}\ M_0$	with positive nodes with extracapsular spread
Stage IV		Tumor invades other regional (2/3 upper

		urethra, 2/3 upper vagina), or distant structures
IVA	$T_3N_{any}M_0$ $T_{any}N_3$	Tumor invades any of the following:
(i) Upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone		
(ii) Fixed or ulcerated inguino-femoral lymph nodes		
IVB	$T_{any}N_{any}M_1$	Any distant metastasis including pelvic lymph nodes
TNM Classification	T: Primary tumor	N: Regional lymph nodes (femoral and inguinal nodes)
	T_x: Primary tumor cannot be assessed	N_x: Regional lymph nodes cannot be assessed
	T_0: No evidence of primary tumor	N_0: No regional lymph node metastases
	T_{is}: Carcinoma in situ (preinvasive carcinoma)	N_1: One or two regional lymph node metastases with the following features:
	T_{1a}: Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1 mm	N_{1a}: One or two lymph node metastases each <5 mm
	T_{1b}: Lesions >2 cm in size or any size with stromal invasion >1 mm, confined to the vulva or perineum	N_{1b}: One lymph node metastasis ≥5 mm
	T_2: Tumor of any size with extension to adjacent perineal structures (lower 1/3 of urethra, lower of 1/3 vagina, anal involvement)	N_2: Regional lymph node metastases with the following features:
	T_3: Tumor of any size with extension to any of the following:	N_{2a}: ≥3 lymph node metastases, each <5 mm in diameter
	upper 2/3 of urethra, upper 2/3 of vagina, bladder mucosa, rectal mucosa, or fixed to pelvic	N_{2b}: ≥2 lymph node metastases ≥5 mm

	bone	
	M_1: Distant metastasis (including pelvic lymph node metastasis)	N_{2c}: Lymph node metastases with extracapsular spread
		N_3: Fixed or ulcerated regional lymph node metastasis
		M: Distant metastasis
		M_0: No distant metastasis

[a]The depth of stromal invasion is measured from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumor node metastasis.

FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obstet* 2009;105:103–104 (31); **American Joint Committee on Cancer.** *AJCC Cancer Staging Manual*. 7th ed. Chicago, IL: Springer New York, Inc.; 2010.

Table 40-5 Five-Year Survival for Patients With Vulvar Carcinoma (28)

FIGO Stage	No. of Patients	5-Year Survival (%)
I	286 (34%)	79
II	266 (32%)	59
III	216 (26%)	43
IV	71 (8%)	13

FIGO, International Federation of Gynecology and Obstetrics.

Prognosis and Survival

Survival of patients with vulvar cancer correlates with FIGO stage (66). The prognosis for patients with early-stage disease is generally good (Table 40-5). **The single most important prognostic factor is lymph node status** (51–53,56,67,68). A report from the Mayo Clinic on 330 patients with primary squamous cell carcinoma of the vulva demonstrated a significant correlation between lymph node status and risk of treatment failure, especially in the first 2 years following initial therapy: 44.2% overall recurrence rate with positive versus 17.5% with negative lymph nodes. **[6]** **More than one-third of relapses presented 5 years or more after initial therapy** (69). There is a strong negative correlation between the number of positive lymph nodes and survival (Table 40-6). **Patients with negative lymph nodes have a 5-year survival rate of over 80%; for patients with positive nodes, 5-year survival falls below 50%.** The number of positive nodes is of critical importance: **Patients with one microscopically positive lymph node have a prognosis similar to those with all negative lymph nodes, whereas patients with three or more positive nodes have a poor prognosis and a 2-**

year survival rate of 20% (70). The survival rate for patients with positive pelvic nodes is about 11% (71). In addition to the number of nodes involved, the morphology of the positive groin nodes is of prognostic significance. As demonstrated in several studies, significant negative predictors of survival are the size of the nodal metastasis, the proportion of the node replaced by tumor cells, and the presence of any extracapsular spread (59,67,72,73). Histologic grade, tumor thickness, depth of stromal invasion, and lymph–vascular space involvement contribute to the risk of lymph node involvement but are not independent predictors of survival (70).

Post-treatment surveillance as recommended by the Society of Gynecologic Oncology entails serial reviews of systems and careful physical examination with annual cervical/vaginal cytology and imaging reserved for patients where findings are concerning for recurrent disease (74). The frequency of surveillance visits depends on the stage and recurrence risk:

- Stage I, II disease every 6 months in years 1 and 2, and annually thereafter.
- Stage III/IV disease every 3 months for the first two years, every 6 months in years 3 to 5, and annually thereafter.

Table 40-6 Five-Year Survival for Patients With Vulvar Squamous Cell Carcinoma by Number of Lymph Node Metastases (28)

No. of Lymph Node Metastases	No. of Patients	5-Year Survival (%)
0	302 (61%)	81
1	66 (13%)	63
2	43 (9%)	30
3	24 (5%)	19
4 or more	62 (12%)	13

Treatment

[7] To individualize the patient's care and determine the appropriate therapy, it is necessary to independently manage the primary lesion and groin lymph nodes using a separate incision technique for resection of the vulvar lesion and for the node dissection. This is associated with lower morbidity and metastases rarely occur in the skin bridge between vulva and groin in patients without clinically suspicious inguinofemoral nodes (75,76). Before initiation of therapy, all patients should undergo a careful clinical examination, and colposcopy of the cervix, vagina, and vulva. Preinvasive (and rarely invasive) lesions may be present at other sites along the lower genital tract, and vulvar cancer is frequently multifocal. If disease is locally advanced, an examination under anesthesia may be required to determine its full extent. Imaging

with PET/CT or MRI is performed for all but T1a lesions to aid in assessment of the local disease and evaluate for metastases.

Management of the Primary Lesion

Microinvasive Vulvar Cancer (T_{1a})

[8] Tumors 2 cm or less in diameter with 1 mm or less invasion are appropriately treated with a wide local excision, which is as effective as radical surgery for the prevention of vulvar recurrences for these tumors (77). The excision should go sufficiently deep into the dermis that depth of invasion is fully assessed.

Early Vulvar Cancer (T_{1b})

[9] The modern approach to the management of patients with T_{1b} carcinoma of the vulva should be individualized. There is no standard approach applicable to every patient, and emphasis is on performing the most conservative operation that is consistent with cure of the disease through radical local excision and surgical lymph node assessment while minimizing anatomic alterations and disfigurement. An analysis of the literature indicates that the incidence of local invasive recurrence after radical local excision or radical hemivulvectomy is not higher than that after the historically performed radical vulvectomy (33,46,71,78–80). In the presence of an otherwise normal-appearing vulva, **radical local excision is a safe surgical option, regardless of the size of the tumor or the depth of invasion.** Based on cumulative data of 413 patients reported in four studies, an 8 mm or greater histopathologic resection margin results in a high rate of local disease control (78,81–83). Of the 252 patients whose tumors were resected with margins of 8 mm or greater, 2.4% experienced a local recurrence, compared with 30.3% of the 161 patients whose margins were less than 8 mm. Neither clinical tumor size nor the presence of coexisting benign vulvar pathology correlated with local recurrence. It is important to bear in mind that paraffin-embedded tissue shrinks by 20% to 25%. **At the time of radical local excision, at least a 1-cm grossly negative margin, without putting the skin under tension, should be obtained and extended down to the level of the inferior fascia of the urogenital diaphragm.**

When vulvar cancer arises in the presence of VIN, lichen sclerosus, or some nonneoplastic epithelial disorder, treatment is influenced by the patient's age, treatment history, and symptomatology. Elderly patients who often had many years of chronic itching may not be disturbed by the prospect of a vulvectomy. In younger women, it is desirable to conserve as much of the vulva as possible. Radical local excision should be performed for the invasive disease, and the associated intraepithelial disease should be treated in the manner most appropriate to the patient. For example, topical steroids may be required for lichen sclerosus, whereas VIN may require superficial local excision with primary closure, ablation, topical therapy, or a combination thereof.



FIGURE 40-4 Small (T1) vulvar carcinoma at the posterior fourchette. (From **Hacker NF, Eifel PJ.** Vulvar cancer. In: Berek JS, Hacker NF. *Berek & Hacker's Gynecologic Oncology*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:574.)

Radical local excision is most appropriate for lesions on the lateral or posterior aspects of the vulva (Fig. 40-4). Midline lesions pose special challenges because of their proximity to clitoris, urethra, or anus. For anterior lesions, conservative clitoris-

sparing surgery allows for excellent local control as long as pathologic margins are at least 8 mm (84). For tumors that involve the clitoris or that are in close proximity to it, any type of surgical excision will have psychosexual consequences. In addition, marked edema of the posterior vulva may occur. For young patients with periclitoral lesions, the primary lesion can be treated with a small field of radiation therapy with concomitant sensitizing chemotherapy. Small vulvar lesions should respond very well to about 5,000 cGy external radiation, and biopsy can be performed after therapy to confirm the absence of any residual disease (58).

Early T_2 Vulvar Cancer

[10] The indications for vulvar conservation can be extended to selected patients with early T_2 tumors. The tumor-free margin should be the same, whether or not a radical vulvectomy or a radical local excision is performed. It seems feasible and desirable to extend the indications for vulvar conservation, particularly for younger patients. Tumors that are suitable for a conservative resection are those involving the posterior vulva and lower vagina, where preservation of the anus, clitoris, and urethra is feasible.

For patients with more advanced T_2 lesions, management consists of radical vulvectomy and/or chemoradiation therapy. When the disease involves the distal urethra or anus, partial resection of these organs would be required. Thus, it is often preferable to give preoperative radiation therapy with chemosensitization to allow for a less radical resection depending on location and response.

Closure of Large Defects

After radical local excision, primary closure without tension can be accomplished for smaller defects. If an extensive dissection is required to treat a large primary lesion, a number of options are available to repair the defect based on the defect location, dimension, patient age, and comorbidities:

1. An area may be left open to granulate, which it will usually do over a period of 6 to 8 weeks (85); this may be hastened by the application of vacuum-assisted wound closure and negative pressure dressings (86).
2. Full-thickness rotational or advancement fasciocutaneous flaps may be devised, such as the rhomboid flap, the mons pubis pedicle flap, the pudendal thigh flap, or the V-Y-advancement flap (87–91). Fasciocutaneous flaps are reliable and can be transferred as pedicle or island flaps (92). For the lower and mid vulva, a V-Y gluteal fold flap may be preferred because of the good esthetic outcome and well-concealed donor scar (91,93).
3. A broad range of myocutaneous flaps have been used for vulvar reconstruction to cover large defects. These include unilateral or bilateral gracilis myocutaneous

grafts or a vertically oriented rectus abdominis muscle flap. Because the graft brings a new blood supply to the area, it is particularly applicable if the vulva is poorly vascularized from prior surgical resection or radiation (91,93,94). Disadvantages include complexity and duration of the procedure, the bulkiness of the flap, and donor-site sequelae.

Advanced Disease: Large T_2 and T_3 Primary Tumors

Treatment of locally advanced vulvar cancer remains challenging. To achieve primary surgical clearance for tumors involving the upper urethra, anus, rectum, or rectovaginal septum, pelvic exenteration is needed in addition to radical vulvectomy and inguinal–femoral lymphadenectomy, which carries an extremely high physical and psychological morbidity (95,96). Reported 5-year survival rates with this approach are about 50% (97–99), with survival being significantly determined by lymph node status. A series including 57 patients undergoing primary anovulvectomy reported a median survival of 69 months with 59% of patients experiencing one or more postoperative complications and 33% requiring adjuvant therapy (100). For many of these patients, a combined approach of chemoradiation therapy with or without subsequent surgery offers equal or improved survival with reduced morbidity and may be the preferred treatment approach. Numerous small prospective and retrospective series report on the use of external beam radiation with concomitant chemotherapy to shrink the primary tumor. Reported initial response rates to chemoradiation are 80% to 90%, and operability is achieved in 63% to 92% of cases (101–109). This chemoradiation is followed by a limited resection of the tumor bed on an individualized basis. Case series suggest that approximately one-half of the specimens will contain residual tumor, and local relapse rates are as high as 50% with external chemoradiation alone (110). The GOG phase II study using a combination of weekly cisplatin with radiation followed by surgical resection of gross residual disease, or biopsy if clinically no residual cancer, resulted in a complete clinical response in 64% of patients, with biopsy showing complete pathologic response in 50% of patients without the need for posttreatment surgery in this subset of patients (111).

As experience with this combination therapy evolved, it appeared that **external beam therapy is appropriate for most cases, with more selective use of brachytherapy. The extensiveness of the surgery is significantly modified. A limited vulvar resection is advocated, and bulky N2 and N3 nodes are resected without full groin lymphadenectomy to avoid the leg edema associated with groin lymphadenectomy and radiation. With this combined radiation–surgical approach, 5-year survival rates as high as 76% are reported**. With the experience accrued, preoperative radiation with concurrent chemotherapy is regarded as the first treatment of choice for patients with advanced vulvar cancer who would otherwise require some

type of pelvic exenteration or stoma. Neoadjuvant therapy is not justified in patients with tumors that can be adequately treated with primary radical vulvectomy and bilateral groin node dissection.

Management of the Lymph Nodes

Appropriate assessment for nodal involvement and groin dissection is the single most important factor in decreasing the mortality from early vulvar cancer. A careful examination of the groin is carried out as the presence of clinically palpable inguinofemoral lymph nodes is an important determinant of management.

When assessing a patient for groin dissection, the following facts should to be kept in mind:

1. The only patients with virtually no risk of lymph node metastases are those whose tumor is small (≤2 cm) and invades the stroma to 1 mm or less (T_{1a}).
2. Patients who develop recurrent disease in an undissected groin have a greater than 90% mortality (111).
3. Based on the laterality of the vulvar lesions and the status of the ipsilateral groin, an ipsilateral or bilateral lymphadenectomy becomes necessary.

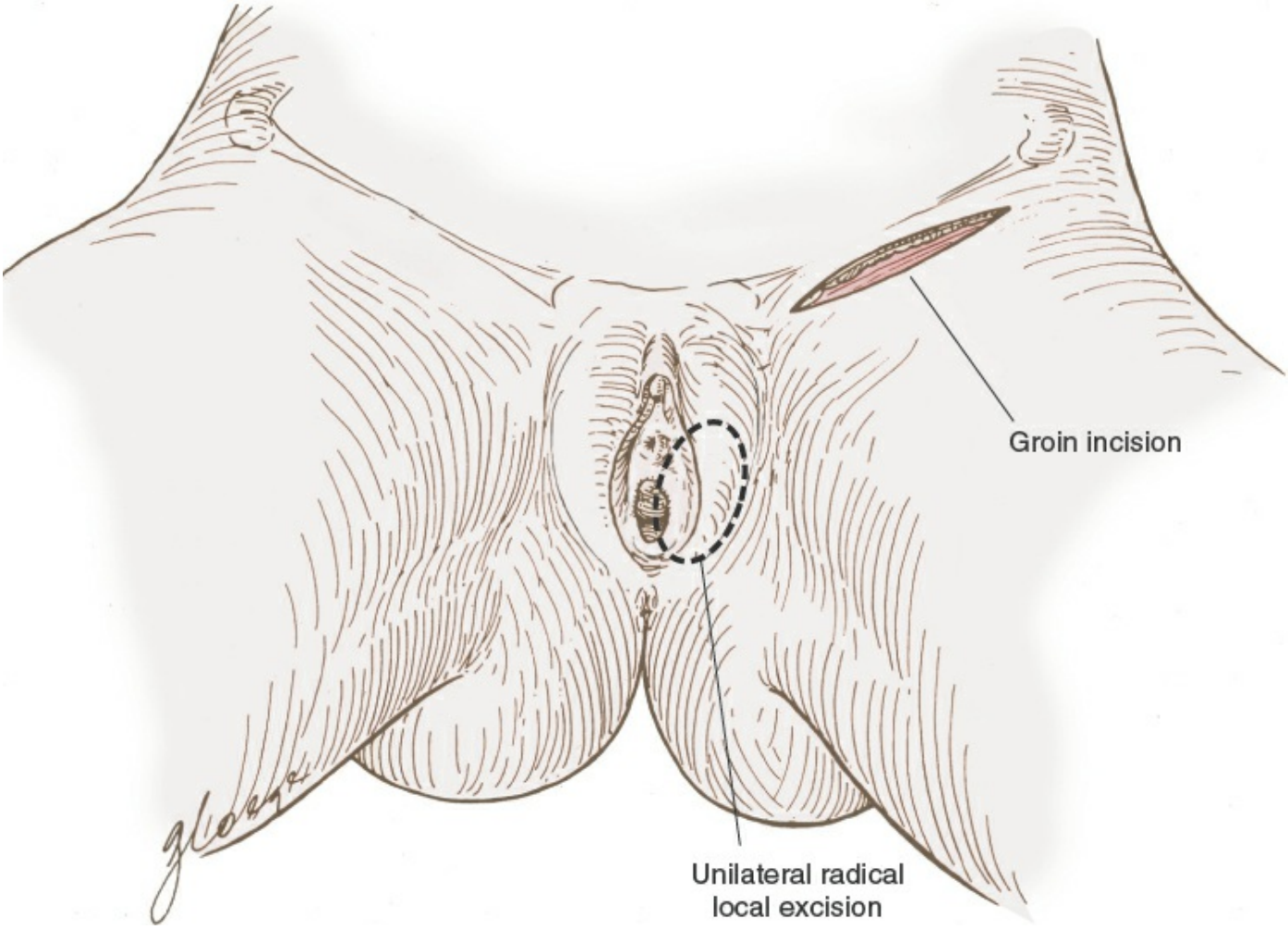


FIGURE 40-5 Skin incision for groin dissection through a separate incision. A line is drawn 1 cm above and parallel to the groin crease, and a narrow ellipse of skin is removed. (Revised with permission from **Berek JS, Hacker NF.** *Practical Gynecologic Oncology*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1994:418.)

Groin dissection is associated with postoperative wound infection and breakdown. Although the incidence of wound breakdown is reduced significantly when separate incisions are used for the groin dissection and drains are left in situ until daily output is below 25 to 30 cc, lymphocyst formation and chronic leg edema remain a major problem **(Fig. 40-5)** (77).

All patients whose tumors demonstrate more than 1 mm of stromal invasion or whose tumors are larger than 2 cm (T_{1b} and above) require inguinal–femoral lymphadenectomy. If there is any question regarding the need for inguinofemoral lymphadenectomy, a Keys biopsy or wedge biopsy of the primary tumor should be obtained, and the depth of invasion should be determined. If it is smaller than 1 mm on the wedge biopsy specimen, the entire lesion should be locally excised and analyzed histologically to determine the depth of invasion. If the lesion is 2 cm in diameter or smaller and there is no invasive focus larger than 1 mm, groin dissection may be omitted, provided there is no lymph–vascular space invasion and there are no clinically

suspicious groin lymph nodes. An occasional patient with less than 1 mm of stromal invasion has documented groin node metastases, but the incidence is so low that it is of no practical significance (112,113).

Inguinal–Femoral Lymphadenectomy

If groin dissection is indicated in patients with vulvar cancer, it should be a thorough inguinal–femoral lymphadenectomy. The GOG reported six groin recurrences among 121 patients with tumors 2 cm or less after a superficial (inguinal) dissection, although the removed inguinal nodes were negative, and a study from the M. D. Anderson Cancer Center reported a 9% groin recurrence rate in 104 patients with vulvar cancer and negative nodes on superficial inguinal lymphadenectomy (38,39). Although it is unclear whether all of these recurrences were in the femoral nodes, both studies indicate that an incomplete groin dissection will increase the number of groin recurrences and mortality. GOG data indicate that radiation therapy cannot substitute for groin dissection followed by selective radiation as indicated, even in patients with clinically nonsuspicious lymph nodes (114). This GOG study was closed early because a significantly higher incidence of recurrences occurred in women who were receiving groin radiation therapy only (19% vs. 0%). The dose of radiation was 5,000 cGy given in daily 200-cGy fractions to a depth of 3 cm below the anterior skin surface. Although the radiation regimen prescribed was criticized extensively, other uncontrolled studies give no evidence for better groin control with radiotherapy (115,116). Surgery remains the treatment of choice for the groin for women with vulvar cancer. Vulvar cancer patients with T_2 or T_3 lesions scheduled for primary or neoadjuvant chemoradiation should undergo an inguinofemoral lymphadenectomy prior to initiation of chemoradiation, given the lower survival with primary groin radiation compared with groin dissection followed by radiation (115). Some patients with T_{1b} and T_2 tumors and no palpable groin lymph nodes on examination are candidates for sentinel lymph node assessment.

Unilateral Versus Bilateral Groin Dissection

It is not necessary to perform a bilateral groin dissection if the primary lesion is unilateral and the ipsilateral lymph nodes are negative. In a patient with a unilateral lesion and negative ipsilateral groin nodes, the risk of contralateral lymph node metastasis is very low (33,45). In a study from the Mayo Clinic, 8 of 163 patients with unilateral vulvar cancers (4.8%) had bilateral lymph node metastases and only 3 (1.8%) had isolated contralateral lymph node metastases. None of the patients with unilateral vulvar lesions that were either 2 cm or less or had 5 mm or less depth of invasion had bilateral groin node involvement at diagnosis (45). There is an increase in the risk of contralateral nodal involvement proportional to the number of positive ipsilateral inguinal nodes (45,57). **It is recommended that patients with any bulky or multiple**

microscopically positive ipsilateral groin lymph nodes undergo contralateral inguinal–femoral lymphadenectomy. Bilateral inguinal–femoral lymphadenectomy should be performed for midline lesions (clitoris, anterior labia minora, posterior fourchette) or those within 2 cm of the midline because of the more frequent contralateral lymph flow from these regions (117).

Management of Bulky Groin Nodes

All clinically or radiologically suspicious groin nodes should be resected if deemed resectable and the patient is a surgical candidate. If nodal metastasis is confirmed by preoperative biopsy or intraoperative frozen section, a full inguinofemoral lymphadenectomy may be omitted to decrease morbidity with subsequent radiation without compromising survival (118,119). If groin lymph nodes are palpably enlarged, but frozen section does not demonstrate metastatic disease, a complete inguinofemoral lymphadenectomy should be performed. Patients with fixed, unresectable groin nodes should be treated with primary chemoradiation. If there is no other evidence of metastatic disease following chemoradiation, GOG data suggest that it may be appropriate to resect the residual nodes (120).

Management of Pelvic Lymph Nodes

In the past, pelvic lymphadenectomy was part of the routine surgery for invasive vulvar cancer. The incidence of pelvic lymph node metastasis is rare in the absence of groin node involvement, and a more selective approach is preferred **(Table 40-2)**. Patients most prone to pelvic lymph node metastasis are those with three or more pathologically positive groin nodes (30,42,54,121). In addition to the number of nodes involved, the morphology of the positive groin nodes is of prognostic significance. As demonstrated in several studies, significant negative predictors of survival are the number of positive nodes, the size of the nodal metastasis, the proportion of the node replaced by tumor cells, and the presence of any extracapsular spread (63,67,72,73). In these patients, the pelvis requires treatment by radiation. **If a preoperative pelvic imaging study reveals bulky pelvic lymph nodes, resection of these nodes should be performed via an extraperitoneal approach prior to radiation because of the limited ability of external beam radiation therapy to sterilize bulky positive pelvic nodes.**

Sentinel Lymph Node Studies

Increasing evidence supports the use of intraoperative lymphatic mapping using lymphoscintigraphy with technetium-99m-labeled nanocolloid and isosulfan blue dye to identify a sentinel node that would predict the presence or absence of regional nodal metastases. The strong interest in the sentinel node concept lies in the desire to reduce the significant lifelong morbidity of lymphedema associated with a thorough inguinofemoral lymphadenectomy, as only 25% to 35% of patients with early-stage vulvar cancer will have lymph node metastases and thus benefit from the procedure.

Reliable identification of the sentinel node and forgoing full lymphadenectomy in patients with clinically nonsuspicious groin lymph nodes and a negative sentinel node significantly reduces the number of patients who undergo unnecessary, extensive lymphadenectomy in the absence of disease. This is contingent upon a negative sentinel lymph node reliably predicting the absence of any other nodal metastases given the greater than 90% mortality associated with a groin recurrence.

The sentinel lymph node procedure has led to a major decrease in morbidity compared with a complete inguinofemoral lymphadenectomy without negatively impacting prognosis in select patients (122–126). **In experienced hands, this procedure is reliable and suitable in early-stage disease with unifocal tumor lesions less than 4 cm in size and clinically negative lymph nodes on groin examination and imaging.** A Cochrane Database review of 34 studies evaluating 2,396 groins in 1,614 women reported for blue dye plus technetium combined a sentinel node detection rate of 98% with a pooled sensitivity estimate of 0.95 (95% CI 0.89 to 0.97), and a negative predictive value of greater than 95% (127). The combination of blue dye and radiocolloid is superior over blue dye alone for sentinel node identification. Ultrastaging techniques such as serial micro-sectioning and immunohistochemistry staining are used to detect micrometastases in the sentinel node if initial hematoxylin and eosin section is negative. This increases the detection rate of lymph node metastasis (123).

Recurrence in the groin is fatal in over 90% of patients. Thus, groin recurrence is ultimately a critical outcome measure for surgical groin assessment techniques. A meta-analysis of recurrence rate included 23 studies and demonstrated a significantly higher groin recurrence rate with superficial inguinal lymphadenectomy (6.6%; 95% CI 4.4–9.0) than with complete inguinofemoral lymphadenectomy (1.4%; 95% CI 0.4–2.9) with the recurrence rate for patients undergoing the sentinel node procedure being 3.4% (95% CI 1.8–5.4) (128). Long-term follow-up of the GROINSS-V study, one of the largest studies on the safety of the sentinel node procedure in vulvar cancer, reported for 377 patients with unifocal <4 cm T1 vulvar cancer a local recurrence rate of 27.2% at 5 years and 39.5% at 10 years. Isolated groin recurrences occurred in 2.5% of patients with negative sentinel nodes and 8% of patients with positive sentinel nodes. All groin recurrences occurred within 25 months of primary treatment (129). Some small series of sentinel nodes in vulvar cancer with inclusion criteria similar to those in GROINSS-V showed unexpectedly high false-negative rates of 8% to 27%, some of which may be attributable to patient selection and insufficient experience of low-volume providers. This highlights the prerequisites for high-quality sentinel node procedures, which include careful patient selection, trained personnel, and appropriate infrastructure. The technique might otherwise carry with it an unjustifiable rise in the frequency of groin recurrences.

Postoperative Management

Despite the age and general medical condition of many elderly patients with vulvar cancer, surgery is usually remarkably well tolerated. Patients should be able to commence eating a low-residue diet on the first postoperative day. In the past, bed rest was advised for 3 to 5 days postoperatively to allow for immobilization of the wounds and to foster healing. **Because radical local excisions are being performed with increasing frequency and groin lymphadenectomy is done through separate incisions, patients begin ambulation on postoperative day 1 or 2.** Pneumatic calf compression and subcutaneous *low molecular weight heparin* should be given to help prevent deep venous thrombosis, and active leg movements are to be encouraged. Frequent dressing changes are performed to keep the vulvar wound dry. Meticulous perineal hygiene is maintained. Suction drainage of each side of the groin is continued until output is minimal to help decrease the incidence of groin seromas. It is not uncommon for suction drainage to continue for 10 or more days. The Foley catheter is removed when the patient is ambulatory. If there is significant periurethral swelling, prolonged bladder drainage may be advisable. If there is breakdown of the vulvar wound, sitz bath or whirlpool therapy is helpful, followed by drying of the perineum with a hair dryer.

Early Postoperative Complications

The major immediate morbidity is related to groin wound infection, necrosis, and breakdown. This complication used to be reported in as many as 53% to 85% of patients having an en bloc operation (29,30). **With the separate-incision approach,** the incidence of wound breakdown has been reduced to approximately 44%; **major breakdown occurs in about 14% of patients** (31,75,130,131). With appropriate antibiotics, debridement, and wound dressings, the area will granulate and re-epithelialize over several weeks and may be managed with home nursing. Whirlpool therapy is effective for areas of extensive breakdown. The most common complication with the separate incision approach continues to be wound infection requiring antibiotic therapy and lymphocyst formation, reported in up to 40% of cases (131). The GROINSS-V study reported wound break down of the groin in 34% of patients undergoing complete inguinofemoral lymphadenectomy and 12% of patients undergoing the sentinel lymph node procedure with respective cellulitis rates of 21% and 5% (122). Symptomatic lymphocysts should be managed by periodic sterile aspiration.

Other early postoperative complications include urinary tract infection, seromas in the femoral triangle, deep venous thrombosis, pulmonary embolism, myocardial infarction, hemorrhage, and, rarely, osteitis pubis. Anesthesia of the anterior thigh resulting from femoral nerve injury is common and usually resolves slowly.

Late Complications

One major late complication is chronic lymphedema, which occurs in about 30% of patients (29–31,130–132). Recurrent lymphangitis or cellulitis of the leg develops in about 10% of patients and usually responds to oral antibiotics. The GROINSS-V study, prospectively following 403 patients and 623 groin evaluations, reports lymphedema in 25% of patients undergoing complete inguinofemoral lymphedema and 2% of patients undergoing the sentinel lymph node procedure with respective recurrent erysipela rates of 16% and 0.4% (122). Urinary stress incontinence, with or without genital prolapse, occurs in about 10% of patients after radical vulvectomy and may require corrective surgery. Introital stenosis can lead to dyspareunia and may require a vertical relaxing incision, which is sutured transversely. An uncommon late complication is femoral hernia, which can be prevented intraoperatively by closure of the femoral canal with a suture from the inguinal ligament to Cooper's ligament. Pubic osteomyelitis and rectovaginal or rectoperineal fistulas are rare late complications.

Other major long-term treatment complications associated with the extent of vulvar surgery include depression, altered body image, and sexual dysfunction (95,96). Modifications in the radical extent of the surgical approach and appropriate preoperative and postoperative counseling may help lessen some of the psychological trauma.

Role of Radiation Therapy

Radiation therapy traditionally had a limited role in the management of patients with vulvar cancer. In the orthovoltage era, local tissue tolerance was poor and vulvar necrosis was common, but with megavoltage therapy, tolerance improved significantly. Radiation therapy, frequently with concurrent chemotherapy, has an increasingly important role in the management of patients with vulvar cancer. It is important to remember that, with a rare exception, radiation therapy alone has little place in the primary management of vulvar cancer. It is primarily indicated in conjunction with surgery.

The indications for radiation therapy for patients with primary vulvar cancer are evolving. **Radiation is indicated in the following situations:**

1. Preoperative chemoradiation in patients with advanced disease who would otherwise require pelvic exenteration or suffer loss of anal or urethral sphincteric function.
2. Preoperative chemoradiation in patients with fixed, unresectable groin nodes.
3. Postoperatively, to treat the pelvic lymph nodes and groins of patients with multiple microscopically positive groin nodes, one or more macrometastasis (10 mm or larger), or any evidence of extracapsular spread.

Possible indications for radiation therapy to the vulva include the following:

1. Postoperatively, to help prevent local recurrences in patients with involved (or close) surgical margins. Radiation to the primary tumor bed following resection with involved margins may improve 5-year overall survival to 67%, which is comparable to that of patients with negative margins (133,134).
2. As primary therapy for patients with small primary tumors, particularly clitoral or periclitoral lesions in young and middle-aged women, for whom surgical resection would have significant psychological consequences (135).

The benefit to adjuvant radiation therapy in patients with a single groin micrometastasis is unclear. While the prognosis appears somewhat worse for this group of patients compared with node negative patients (126,136), there is little evidence of benefit to adjuvant radiation therapy (54,136,137). Thus, no additional treatment and careful observation is an option if one microscopically positive groin node (5 mm or less tumor deposit) is found in a fully dissected groin. For patients with a single groin node metastasis, a retrospective SEER database review suggests that adjuvant radiation may provide a therapeutic benefit, especially if the groin dissection was limited (138). However, size and characteristics of the nodal metastasis were not known. If unilateral groin dissection was performed for a lateral lesion, there seems to be no indication for dissection of the other side, because contralateral lymph node involvement is likely only if there are multiple microscopic or any gross ipsilateral inguinal node metastases (54,57). **If clinically evident groin metastases, any extracapsular spread, or two or more microscopically positive groin nodes are found, the patient is at increased risk of groin and pelvic recurrence and should receive postoperative groin and pelvic irradiation.** In 1977, the GOG initiated a prospective trial in which patients with positive groin nodes were randomized to either ipsilateral pelvic node dissection or bilateral pelvic plus groin irradiation (57). The survival rate for the radiation group (68% at 2 years) was significantly better than the survival rate for the pelvic lymphadenectomy group (54% at 2 years) ($p = 0.03$). The survival advantage was limited to patients with clinically evident groin nodes or more than one microscopically positive groin node. Groin recurrence occurred in 3 of 59 patients (5%) treated with radiation, compared with 13 of 55 (23.6%) patients treated with lymphadenectomy ($p = 0.02$). Four patients who received radiation had a pelvic recurrence, compared with one who had lymphadenectomy. These data highlight the value of groin irradiation in preventing groin recurrence in patients with multiple positive groin nodes. This concept of adjuvant radiation therapy including bilateral groins and pelvis for patients with two or more positive nodes is further supported by the contemporary AGO-CaRE-1 study demonstrating better outcomes with this adjuvant treatment approach (136).

Recurrent Vulvar Cancer

Recurrence of vulvar cancer correlates closely with the number of positive groin nodes (54). Patients with fewer than three positive nodes, particularly if the nodes are only microscopically involved, have a lower incidence of recurrence at any site, whereas patients with three or more positive nodes have a high incidence of local, regional, and systemic recurrences (54,57).

Most recurrences of vulvar cancer occur within the first 2 years from initial therapy, with groin recurrences occurring sooner (median time to recurrence 6 to 7 months) than vulvar recurrences (median time to recurrence 3 years) (69,139–141). **About one-third of vulvar cancer relapses present 5 or more years after initial therapy** (69). In a long-term follow-up study at the Mayo Clinic, nearly 1 in 10 patients with vulvar cancer had a late (longer than 5 years) reoccurrence of disease (69). More than 95% of those late relapses had local reoccurrences (same site recurrence or second primary vulvar site). Because of this propensity for late local reoccurrence, regular and long-term careful examinations of the vulva and groin constitute the cornerstone of posttreatment surveillance for these patients.

The published literature on the management and outcome of recurrent disease is limited. The timing and primary site of recurrence is critical to the prognosis postrecurrence. Although groin recurrences tend to occur early and are nearly always fatal, 5-year overall survival rates of 50% to 70% are reported for patients with surgically treated isolated vulvar recurrences and more than 60% of patients with local recurrence or reoccurrence were alive at 20 years in the Mayo Clinic long-term follow-up study (69,141,142). In contrast, a series of 502 patients demonstrate the poor prognosis for patients with groin, pelvic, or distant recurrences: 5-year survival rates of 27% with inguinal or pelvic recurrence, 15% with distant recurrence, and 14% with multiple sites of recurrence (143). Management of recurrent vulvar cancer depends on site of recurrence, prior treatments, and patient performance status.

Local Vulvar Recurrence

Margin status at the time of radical resection of the vulvar cancer is the most powerful predictor of local vulvar recurrence, with an almost 50% recurrence risk with margins closer than 0.8 cm (81). Margin status does not predict survival (68). Local vulvar recurrences are more likely in patients with primary lesions larger than 4 cm in diameter, especially if lymph–vascular space invasion is present, and in patients with deeply invasive tumors (133,144,145). When detected early, isolated local failure is usually treatable by additional surgical therapy, often with a myocutaneous graft to cover the defect (31,38,46,75,146). Radiation therapy, particularly a combination of external beam therapy plus interstitial needles, frequently combined with chemotherapy, is used to treat vulvar recurrences (147).

Three distinct patterns of local recurrence are described: remote vulvar recurrence (greater than 2 cm from the primary tumor site), primary tumor site recurrence (within 2

cm of the primary tumor site), and skin bridge recurrence (78,145). Although reported treatment outcomes are excellent for remote site recurrences with 3-year survival rates of 67% to 100%, the literature is controversial as to the prognostic significance of primary tumor site recurrences, with one study reporting a 3-year survival rate of only 15% and the other a 5-year survival of 93% (78,145). Patients with skin bridge recurrence have a very poor prognosis, similar to those with groin recurrence.

Regional Inguinal and Distant Recurrence

Regional and distant recurrences are difficult to manage and are associated with a poor prognosis (133,139,140). Radiation therapy may be used in conjunction with surgery for groin recurrence, and chemotherapeutic agents that have activity against squamous carcinomas may be offered for distant metastases. The literature on the use of chemotherapy for recurrent vulvar cancer consists mainly of small series. The most extensively studied regimens contain *bleomycin*, *methotrexate*, and *lomustine* (a nitrosourea); *bleomycin* and *mitomycin C;* or *cisplatin*, *vinorelbine*, and *paclitaxel*, but response rates are low and the duration of response is usually disappointing (148–152). Extrapolating from data for the management of recurrent cervical cancer, many experts recommend the administration of platinum/taxane-based chemotherapy with or without *bevacizumab*. There is a role for palliative radiation of select symptomatic recurrences. Long-term survival is very uncommon with regional or distant recurrence. Symptom control and quality of life are important treatment goals, and early involvement of a multidisciplinary palliative care team is generally indicated.

MELANOMA

Vulvar melanomas are rare, with an incidence of 0.1 to 0.19 per 100,000 women (153,154). **They account for approximately 10% of all cases and are the second most common form of vulvar malignancy.** Most melanomas arise de novo, but they may arise from a preexisting junctional nevus. Vulvar melanomas occur most frequently in postmenopausal white women, but are commonly seen in individuals with darker pigmented skin. Contrary to cutaneous melanoma, based on SEER data, there are low racial differences in vulvar melanomas, the development of which appears to be determined by factors other than ultraviolet radiation exposure and the photoprotective effects of melanin seen in cutaneous melanoma (155). The incidence of cutaneous melanomas worldwide is increasing significantly, but not that of vulvar melanoma (155). Vulvar melanomas appear to behave in a manner similar to that of other truncal cutaneous melanomas. From a molecular genetic perspective, vulvar melanoma more closely resembles acral lentiginous melanoma rather than cutaneous melanoma. KIT is the most commonly mutated gene detected in up to 35% of vulvar melanomas. More rarely NRAS and BRAF mutations have been described (156).



FIGURE 40-6 Melanoma of the vulva involving the right labium minus. (From **Hacker NF, Eifel PJ.** Vulvar cancer. In: Berek JS, Hacker NF. *Berek & Hacker's Gynecologic Oncology*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015:595.)

Most patients with vulvar melanoma have no symptoms other than a pigmented lesion that may be enlarging. The lesion may present as macules, papules, or nodules of irregular configuration and coloration, typically greater than 7 mm in diameter. Some patients have pruritus or bleeding, a few have a groin mass, and some lesions are amelanotic. Vulvar melanomas occur most frequently on the labia majora, followed by the labia minora and the clitoris (157) **(Fig. 40-6)**; extension into the urethra or vagina at discovery is not uncommon. Any pigmented lesion on the vulva should be excised or, if the lesion is large, sampled for biopsy unless it is known to have been present and unchanged for some years. Most vulvar nevi are junctional and may be precursor lesions to melanoma; any nevus of the vulva should be removed. **Excisional biopsy, rather than a shave, wedge, or punch biopsy, is recommended to ensure evaluation of the entire lesion and facilitate microstaging and measurement of tumor thickness.**

Histopathology

There are three basic histologic types of vulvar melanoma (158; Fig. 40-7):

1. The *mucosal lentiginous melanoma* (25% to 57%) is a flat freckle that may become quite extensive but tends to remain superficial.
2. The *nodular melanoma* (22% to 28%), which is the most aggressive, is characterized by a raised lesion that penetrates deeply and may metastasize widely.
3. The *superficial spreading melanoma* (4% to 56%) tends to remain relatively superficial early in its development.

In one of the larger reported series, more than one-fourth of the cases of melanomas were macroscopically amelanotic (153). Vulvar melanoma tends to spread early, lymphatically and hematogenously.

Staging

The FIGO staging used for squamous lesions is not applicable to melanomas because the lesions are usually much smaller and the prognosis is related to tumor thickness rather than to the diameter of the lesion. The vulvar skin lacks a well-defined papillary dermis. Breslow measured the thickest portion of the melanoma from the surface of intact epithelium to the deepest point of invasion (159). It is important to recognize that tumor thickness and lymph node status are the primary determinants of survival. **The AJCC staging guidelines for cutaneous melanoma** (160) **should be used for vulvar melanoma.** Validation studies of staging systems for vulvar melanoma have confirmed that survival is best predicted by the AJCC staging system (161,162). The AJCC staging system for cutaneous melanoma is shown in Table 40-7.

The revised 2017 eighth edition of the AJCC staging for cutaneous melanoma reflects that tumor thickness remains the primary determinant of the T staging in addition to the presence of ulcerations (160). The mitotic rate is no longer a staging criterion for T1 tumors, but it remains an important prognostic factor and should be recorded for all patients with a T1 to T4 primary melanoma lesion. Specific immunohistochemistry criteria for the detection of micrometastases are included. Regional lymph node involvement is classified as either clinically occult (found microscopically, usually based upon a sentinel lymph node biopsy) or clinically detected (on physical examination or by imaging) without associated specific size criteria. Microsatellites, satellites, and in-transit cutaneous and/or subcutaneous metastases are included to stratify the lymph node staging. The site(s) of distant metastatic disease as stratified by serum lactate dehydrogenase levels remain part of the staging.

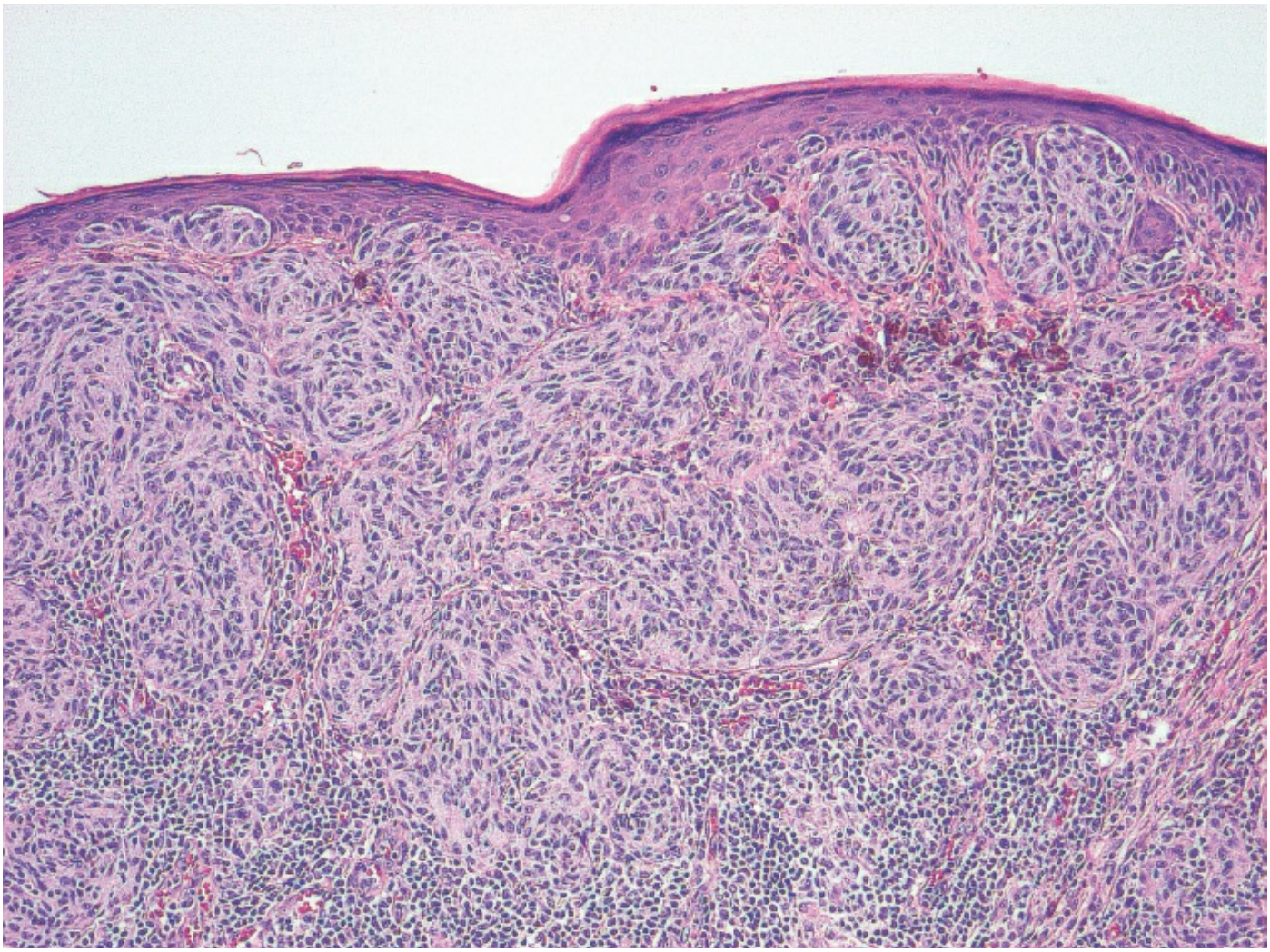


FIGURE 40-7 Vulvar melanoma. Spindle-shaped melanoma cells form interlacing bundles, and some contain melanin pigment (right upper corner). Epidermal invasion is evident in the form of Pagetoid migration (left upper corner).

Treatment

Vulvar melanomas are rare and there is minimal data specific to the treatment of vulvar melanoma. With better understanding of the prognostic significance of the microstage, some individualization of treatment developed. When feasible, the primary treatment modality for vulvar melanoma is excision. **It is accepted that lesions with less than 1 mm of invasion may be treated with radical local excision alone**. With more invasive lesions, radical vulvectomy with bilateral inguinofemoral lymphadenectomy has historically been the recommended treatment (163). Extrapolating from cutaneous melanoma and supported by smaller case series of the vulva, it has become apparent that most failures are distant and radical vulvectomy does not appear to enhance survival. Based on this recognition, the contemporary more conservative surgical approach evolved, where **surgery for vulvar melanoma entails a radical local excision with sentinel lymph node biopsy in clinically node negative patients,**

followed by complete inguinofemoral lymphadenectomy for those with involved sentinel lymph nodes. Skin margins for melanomas <1 mm thick should be 1 cm; if anatomically feasible, margins should be extended to 2 cm for melanomas with ≥1 mm thickness. At least a 1-cm tumor-free deep surgical margin down to the fascia is recommended, irrespective of tumor thickness. This conservative surgical approach is further supported by a SEER data analysis of 644 patients with vulvar melanoma which did not find a survival difference in patients with localized disease treated with more conservative versus radical surgery. Five-year disease-specific survival rates for patients undergoing conservative surgery for localized disease were 75% versus 79% for those undergoing radical surgery (164). Because melanomas commonly involve the clitoris and labia minora, the vaginourethral margin of resection is a common site of failure, and care should be taken to obtain an adequate "inner" resection margin (165). A 10-year survival rate of 61% was shown for lateral lesions, compared with 37% for medial lesions (p = 0.027) (144). In locally advanced cases, primary exenteration should not be routinely offered because of the high risk of distant failure. In these cases, radiation therapy with or without immunotherapy may be a preferred consideration.

Controversy exists as to which patients may benefit from inguinal–femoral lymphadenectomy. A prospective study by the GOG demonstrated that the risk of inguinal–femoral lymph node metastasis correlated with the Breslow microstage (166). As with cutaneous melanoma, it appears that for superficial lesions (tumor thickness <1 mm), the risk for nodal spread is so low that routine lymphadenectomy is not indicated as long as the nodes appear clinically free of disease. For intermediate-thickness (1 to 4 mm) cutaneous melanoma, a randomized controlled trial of elective lymph node dissection versus observation showed a 5-year survival advantage for patients who underwent elective lymph node dissection, who were younger than 60 years, and whose tumors were characterized by 1- to 2-mm thickness and no ulcerations (167). Patients with deeply invasive cutaneous melanomas (≥4 mm tumor thickness) have a high risk of regional and systemic metastases and were noted to be unlikely to benefit from regional lymphadenectomy (168). A randomized controlled trial evaluated 2,001 patients with intermediate thickness cutaneous melanoma and clinically negative nodes who underwent either nodal observation with lymphadenectomy for local relapse or sentinel node biopsy with immediate complete lymphadenectomy for those with positive sentinel nodes. Significantly improved melanoma-specific 10-year survival rates were observed in the sentinel node assessment group (169). Specific to patients with vulvar melanoma, there is a small body of literature to suggest that there may be a clinical benefit in elective groin lymphadenectomy and the resection of clinically positive nodes (170,171). Studies on the sentinel lymph node procedure specific to vulvar melanoma are limited. Although the sentinel node procedure appears appropriate for select patients with vulvar melanoma, the importance of an expert team familiar with the procedure and consisting of a gynecologic oncologist, a nuclear medicine specialist,

and a pathologist with expertise in microstaging cannot be overemphasized. The prognosis for patients with positive pelvic nodes is so poor that there seems to be no value in performing pelvic lymphadenectomy for this disease.

Table 40-7 Eighth (2017) Edition AJCC Melanoma TNM Definitions and Staging (161)

Primary Tumor	
Tx	Primary tumor thickness cannot be assessed
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	≤1 mm thickness
T1a	a: <0.8 mm and without ulceration
T1b	b: 0.8–1 mm or with ulceration
T2	>1 to 2 mm thickness
T2a	a: without ulceration
T2b	b: with ulceration
T3	>2 to 4 mm thickness
T3a	a: without ulceration
T3b	b: with ulceration
T4	>4 mm thickness
T4a	a: without ulceration
T4b	b: with ulceration
Regional Lymph Nodes	
NX	Regional nodes not assessed
N0	No regional metastases detected
N1	One tumor-involved node *or* in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
N1a	a: one clinically occult (i.e., detected by SLN biopsy)
N1b	b: one clinically detected (on examination or imaging)
N1c	c: in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
N2	Two or three tumor-involved nodes *or* in-transit, satellite, and/or microsatellite metastases with one tumor-involved node

N2a	a: two or three clinically occult (i.e., detected by SLN biopsy)
N2b	b: two or three positive, at least one clinically detected
N2c	c: in-transit, satellite, and/or microsatellite metastases with one tumor-involved node (occult or clinically detected)
N3	Four or more tumor-involved nodes *or* in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, *or* any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases
N3a	a: four or more clinically occult (i.e., detected by SLN biopsy)
N3b	b: four or more, at least one clinically detected, or any number of matted nodes
N3c	c: in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes (occult or clinically detected) or any matted nodes
Distant Metastases	
M0	No evidence of distant metastasis
M1	Evidence of distant metastasis
M1a	a: Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node
M1a(0)	a(0): LDH not elevated
M1a(1)	a(1): LDH elevated
M1b	b: Distant metastasis to lung with or without M1a sites of disease
M1b(0)	b(0): LDH not elevated
M1b(1)	b(1): LDH elevated
M1c	c: Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease
M1c(0)	c(0): LDH not elevated
M1c(1)	c(1): LDH elevated
M1d	d: Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease
M1d(0)	d(0): LDH not elevated
M1d(1)	d(1): LDH elevated
Stage	
0	Tis, N0, M0
IA	T1a, N0, M0
IB	T1b or T2a, N0, M0

IIA	T2b or T3a, N0, M0
IIB	T3b or T4a, N0, M0
IIC	T4b, N0, M0
III	Any T, ≥N1, Mo
IV	Any T, Any N, M1

SLN, sentinel lymph node.

Management of Patients With Nodal Metastases

The decision whether to recommend adjuvant therapy depends upon the stage at diagnosis, in the context of patient age, comorbidity, and patient preferences. The presence of lymph node involvement is associated with a significant increase in risk of recurrence. Adjuvant immunotherapy with *nivolumab*, a programmed cell death protein 1 (PD-1) inhibitor, is frequently recommended for patients with lymph node involvement. *Nivolumab* is more effective and less toxic than *ipilimumab*, which targets cytotoxic T-lymphocyte– associated protein 4 (CTLA-4) (172). In BRAF wild-type patients, *ipilimumab* is associated with improved disease-free and overall survival compared with *interferon alfa*, which had been the most promising adjuvant therapy prior to the development of checkpoint inhibitor immunotherapy. Among previously untreated patients with metastatic melanoma, *nivolumab* alone or combined with *ipilimumab* results in significantly longer progression-free survival than *ipilimumab* alone. In patients with PD-L1–negative tumors, the combination of PD-1 and CTLA-4 blockade appears more effective than either agent alone (173). The combined inhibition of T-cell checkpoint pathways by *nivolumab* and *ipilimumab* in previously untreated BRAF wild-type melanoma was associated with a 55% objective response rate compared with 11% with *nivolumab* monotherapy (174). For patients whose tumor contains a BRAF V600 mutation, adjuvant therapy targeting the mitogen-activated protein (MAP) kinase pathway with a combination of a BRAF inhibitor, such as *dabrafenib*, and a MEK inhibitor, such as *trametinib*, is an important treatment option (175).

Traditionally, melanomas were thought to be radiation resistant. However, radiation therapy can provide effective palliation in the setting of unresectable, locally recurrent, or symptomatic metastatic disease. Stereotactic radiosurgery and stereotactic body radiation therapy can be particularly useful in ablating oligometastatic disease.

Prognosis

The behavior of melanomas can be unpredictable, but the prognosis is poor. The reported 5-year overall survival rate for vulvar melanoma is in the range of 50% to 60% (153,154,164). A SEER database analysis showed disease-specific survival rates

for patients with localized, regional, and distant disease of 76%, 39%, and 22%, respectively (164). Localized disease, negative lymph nodes, and younger age were significant independent prognostic factors for improved survival. Because vulvar melanoma has a propensity for late recurrences, 5-year survival may not reflect cure. Prognosis is best predicted by microstaging. Patients with lesions invading to 1 mm or less have a good prognosis, but as depth of invasion increases, the prognosis worsens. For the primary tumor (T), increasing tumor thickness, an increased mitotic rate, and the presence of ulceration (i.e., the loss of the epidermal layer overlying the primary tumor) are associated with an increased risk of relapse. The AJCC stage correlates well with prognosis and takes into consideration tumor thickness, ulceration, lymph node status, in-transit, satellite, and/or microsatellite metastases, distant metastases, and serum Lactate dehydrogenase (LDH) level. Additional prognostic factors are the patient's age, central tumor location, histologic growth pattern, lymph–vascular space involvement, aneuploidy, and elevated serum S-100B protein (153,163,170,171,176–181).

BARTHOLIN GLAND CARCINOMA

Epidemiology

Primary carcinoma of the Bartholin gland is a rare form of vulvar cancer, which accounts for about 2% to 7% of vulvar malignancies (182). Because of its rarity, individual experience with the tumor is limited, and recommendations for management must be based on the review of small published series (43,182–184). Bartholin gland carcinoma is five times more common in postmenopausal than in premenopausal women (185).

Histopathology

The bilateral Bartholin glands are greater vestibular glands situated posterolaterally in the vulva. Their main duct is lined with stratified squamous epithelium, which changes to transitional epithelium as the terminal ducts are reached. Because tumors may arise from the gland or the duct, a variety of histologic types occur, including adenocarcinomas, squamous carcinomas, and, rarely, transitional cell, adenosquamous, and adenoid cystic carcinomas. A series from the MD Anderson Cancer Center reported squamous histology in 88% of the cases (184).

Classification of a vulvar tumor as a Bartholin gland carcinoma typically required that it fulfill Honan's criteria, which are as follows:

1. The tumor is in the correct anatomic position.
2. The tumor is located deep in the labium majus.
3. The overlying skin is intact.

4. There is some recognizable normal gland present.

Strict adherence to these criteria results in underdiagnosis of some cases. Large tumors may ulcerate through the overlying skin and obliterate the residual normal gland. Although transition between normal and malignant tissue is the best criterion, some cases will be diagnosed on the basis of their histologic characteristics and anatomic location.

Signs and Symptoms

The most common initial symptom of Bartholin gland carcinoma is a vulvar mass or perineal pain. About 10% of patients have a history of inflammation of the Bartholin gland, and malignancies may be mistaken for benign cysts or abscesses. Delay of diagnosis is common, particularly for premenopausal patients. A biopsy with histologic evaluation is indicated for all cases with a palpable or visible solid mass within a Bartholin cyst or abscess, and in all instances where a presumed Bartholin cyst or abscess does not respond to treatment.

Treatment

Traditionally, treatment was radical vulvectomy with bilateral groin and pelvic node dissection (186). There seems to be no indication for dissection of the pelvic nodes in the absence of positive groin nodes, and good results are reported with hemivulvectomy or radical local excision for the primary tumor (183,184). Because these lesions are deep in the vulva, extensive dissection is required in the ischiorectal fossa; surgical margins are often close. Patients with Bartholin gland carcinoma are more likely to require postoperative radiation therapy (184). Postoperative radiation to the vulva decreased the likelihood of local recurrence from 27% (6 of 22 patients) to 7% (1 of 14 patients) (183). If the ipsilateral groin nodes are positive, bilateral groin and pelvic irradiation may decrease regional recurrence. If the tumor is fixed to the inferior pubic ramus or involves adjacent structures, such as the anal sphincter or rectum, preoperative radiation and chemotherapy is preferable to avoid ultra-radical surgery. A report of 10 consecutive patients with primary Bartholin gland carcinoma suggests that treatment with radiation or chemoradiation using teletherapy combined with a boost to the primary site or regional nodes and/or interstitial brachytherapy may offer an effective alternative to surgery with 3- and 5-year survival rates of 72% and 66%, respectively (187).

Prognosis

Because of the deep location of the gland, disease tends to be more advanced than

squamous carcinomas at the time of diagnosis but, stage for stage, the prognosis is similar. A recent single-institution series from the MD Anderson Cancer Center reported on 429 patients with invasive vulvar carcinoma (184) and compared 33 patients with Bartholin gland carcinoma with 396 patients with non-Bartholin carcinoma. Patients with Bartholin gland carcinoma had a younger median age (57 vs. 63 years), higher rate of stage III/IV disease (61% vs. 36%), and were more likely to receive radiation therapy (79% vs. 44%). However, there was no significant difference in recurrence-free and overall survival. Five-year disease-free survival rates by stage are summarized in Table 40-8.

ADENOID CYSTIC CARCINOMA OF THE BARTHOLIN GLAND

The adenoid cystic variety accounts for 15% of Bartholin gland carcinomas. A review of 62 cases reported in the literature demonstrates that adenoid cystic carcinoma of the Bartholin gland is a slow-growing tumor characterized by perineural infiltration and a marked propensity for local relapse preceding distant recurrences by years. It is less likely to metastasize to lymph nodes and carries a somewhat better prognosis (Fig. 40-8) (188–190). The slowly progressive nature of these tumors and the tendency for late recurrences are reflected in the disparity between progression-free interval and overall survival (190).

OTHER ADENOCARCINOMAS

Adenocarcinomas of the vulva usually arise in a Bartholin gland or occur in association with Paget disease. They may arise rarely from the skin appendages, paraurethral glands, minor vestibular glands, aberrant breast tissue, endometriosis, or a misplaced cloacal remnant (191).

Adenosquamous Carcinoma

A particularly aggressive type of carcinoma is the adenosquamous carcinoma. This tumor has a number of synonyms, including cylindroma, pseudoglandular squamous cell carcinoma, adenoid squamous cell carcinoma, and adenoacanthoma of the sweat gland of Lever. The tumor has a propensity for perineural invasion, early lymph node metastasis, and local recurrence. One study noted a crude 5-year survival rate of 5.5% (1 of 18) for adenosquamous carcinoma of the vulva, compared with 62.3% (48 of 77) for patients with squamous cell carcinoma (192). Treatment should be radical surgical resection and groin dissection. Postoperative radiation therapy may be appropriate.

Table 40-8 Survival of Patients With Bartholin Gland Carcinoma

FIGO Stage	No. of Patients	No. of Patients With Recurrent Disease	No. of Patients NED at Last F/U[a]
I	15 (21%)	3 (20%)	14 (93%)
II	16 (23%)	2 (13%)	15 (94%)
III	30 (42%)	11 (37%)	22 (73%)
IV	10 (14%)	5 (50%)	5 (50%)
Total	71 (100%)	21 (30%)[b]	56 (79%)[b]

From references (43,185,186,188).

[a]Median follow-up in each study was at least 5 years.

[b]Total >100% because some patients with recurrence remained NED.

FIGO, International Federation of Gynecology and Obstetrics; NED, no evidence of disease; F/U, follow-up.

Basal Cell Carcinoma

Basal cell carcinomas represent about 2% of vulvar cancers. As with other basal cell carcinomas, vulvar lesions commonly appear as a "rodent ulcer" with rolled edges, although nodules and macules are other morphologic varieties that occur. Most lesions are smaller than 2 cm in diameter and are usually situated on the anterior labia majora. Giant lesions occasionally occur (193). Basal cell carcinoma usually affects postmenopausal white women and is locally aggressive. Symptoms are frequently present for a prolonged period and most often include pruritus, soreness, and irritation (194). It is diagnosed by biopsy, and **radical local excision is adequate treatment** (195). **Metastasis to regional lymph nodes is reported but is rare** (196–198). The local recurrence rate is about 10% to 20% (194,199). Basal cell carcinoma of the vulva is associated with a high incidence of antecedent or concomitant malignancies elsewhere (194). In a series of 28 women with vulvar basal cell carcinoma, 10 patients had other basal cell carcinomas, and 10 patients suffered from other primary malignancies (194).

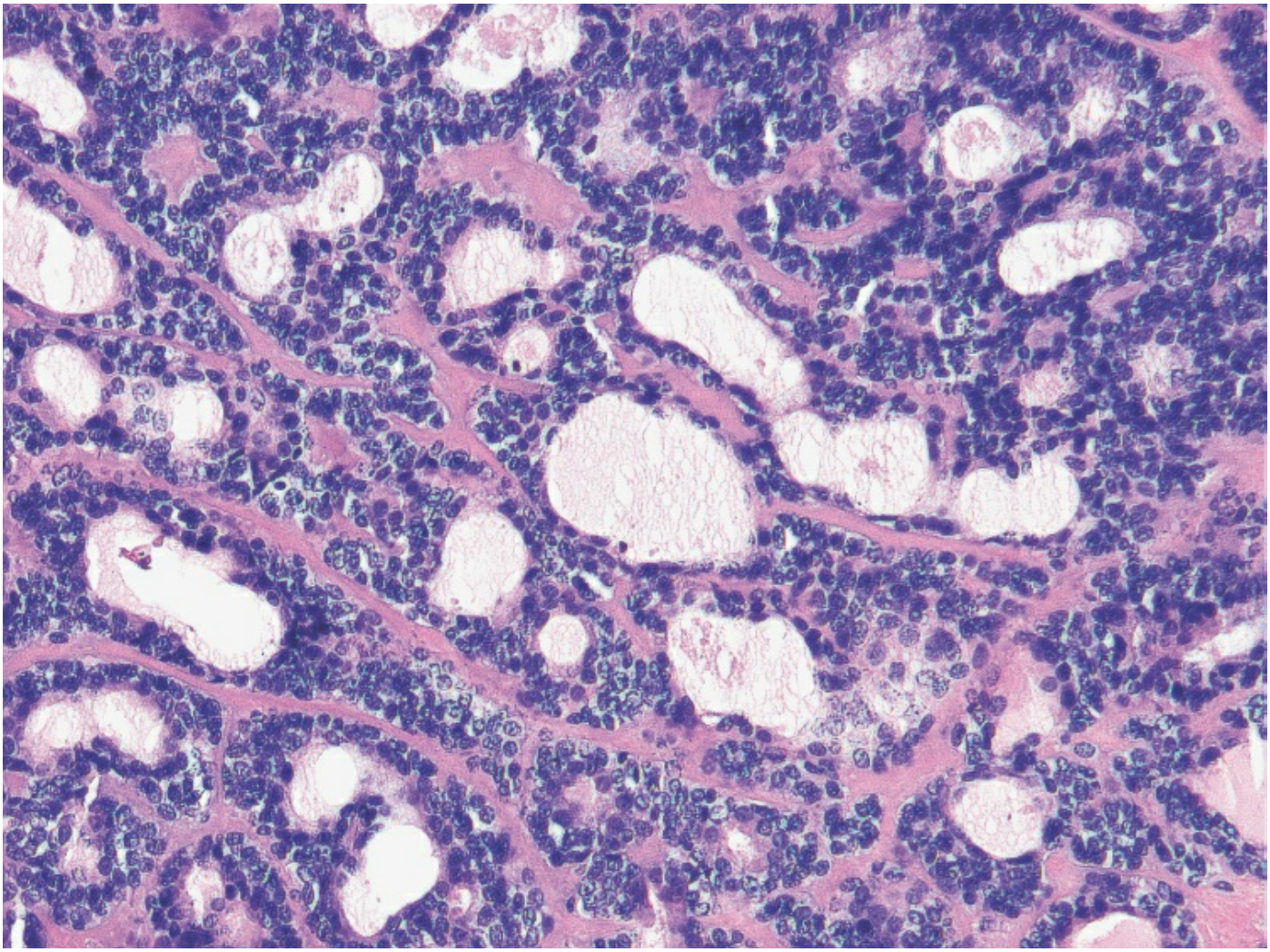


FIGURE 40-8 Adenoid cystic tumor of the Bartholin gland. Basaloid cells form cribriform, sieve-like spaces containing mucinous material. The hyaline stroma is another distinct feature of this tumor.

About 3% to 5% of basal cell carcinomas contain a malignant squamous component, the so-called *basosquamous carcinoma*. These lesions are more aggressive and should be treated as squamous carcinomas (198). Another subtype of basal cell carcinoma is the adenoid basal cell carcinoma, which must be differentiated from the more aggressive adenoid cystic carcinoma arising in a Bartholin gland or the skin (198).

Verrucous Carcinoma

Verrucous carcinoma is a variant of squamous cell carcinoma and has distinctive clinical and pathologic characteristics (200). Although most commonly found in the oral cavity, verrucous lesions may be found on any moist membrane composed of squamous epithelium (201). In the female genital tract, these lesions may develop on the cervix, vulva, and vagina. The cause of the lesion in the female genital tract is not fully understood, but associations with HPV-6 and HPV-11 were found in some studies,

whereas others found no association with HPV infection (202,203). Some studies found as many as one-third of the cases to have coexisting squamous carcinoma of the vulva, underscoring the importance of careful histopathologic assessment of these tumors (204).

Grossly, the tumors have a cauliflower-like appearance; microscopically, they contain multiple papillary fronds that lack the central connective tissue core that characterizes condylomata acuminata **(Fig. 40-9)**. The gross and microscopic features of a verrucous carcinoma are very similar to those of the **giant condyloma of Buschke-Loewenstein**, and they probably represent the same disease entity (191). Adequate biopsy from the base of the lesion is required to differentiate a verrucous carcinoma from a benign condyloma acuminatum or a squamous cell carcinoma with a verrucous growth pattern.

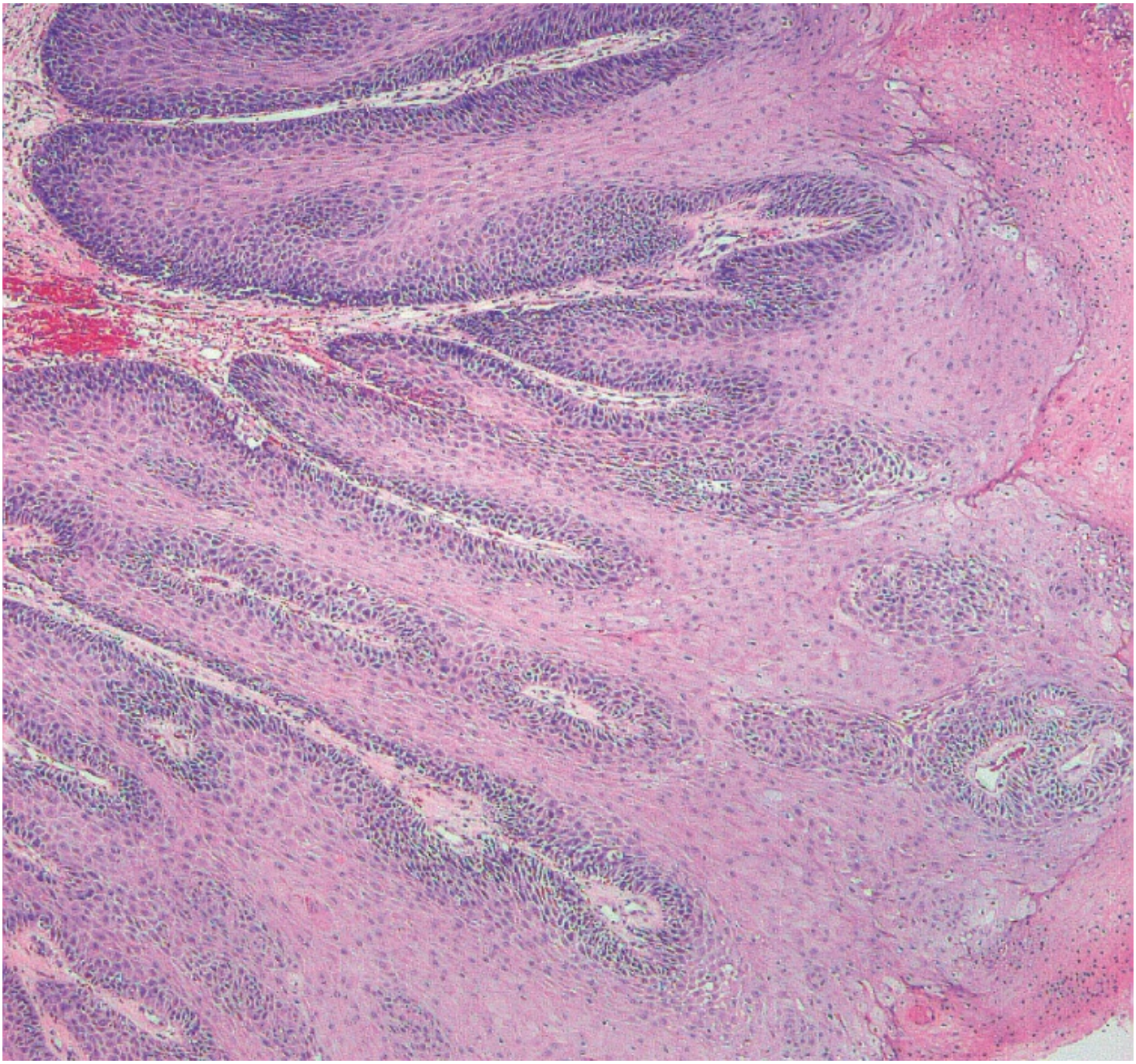


FIGURE 40-9 Verrucous carcinoma of the vulva. Note the exophytic hyperkeratotic papillary fronds and endophytic bulky rete pegs with smooth borders.

Verrucous carcinomas usually occur in postmenopausal women, and they are slow-growing but locally destructive lesions. Even bone may be invaded. Metastasis to regional lymph nodes is rare but was reported (205). Radical local excision is the basic treatment, although any palpably suspicious groin nodes should be evaluated with fine-needle aspiration cytology or excisional biopsy. Usually, enlarged nodes will be caused by inflammatory hypertrophy (206). If the nodes contain metastases, radical vulvectomy and bilateral inguinal–femoral lymphadenectomy are indicated.

Several small studies failed to document any therapeutic advantage with radiation therapy (206). There is concern that radiation may induce anaplastic transformation with

subsequent regional and distant metastasis (207). One study reported a corrected 5-year survival rate of 94% for 17 patients treated with surgery alone, compared with 42% for 7 patients treated with surgery and radiation (206). The latter patients had more advanced disease. If there is a recurrence, further surgical excision is the treatment of choice, which occasionally may necessitate some type of exenteration.

VULVAR SARCOMA

Sarcomas represent 1.5% of vulvar malignancies and constitute a heterogeneous group of tumors (208). Leiomyosarcomas are the most common, and other histologic types include fibrosarcomas, neurofibrosarcomas, liposarcomas, rhabdomyosarcomas, angiosarcomas, epithelioid sarcomas, and malignant schwannomas.

***Leiomyosarcomas* usually appear as enlarging, often painful masses, in the labium majus.** Smooth muscle tumors of the vulva that show at least three of the following four criteria should be regarded as sarcomas: (i) diameter greater than 5 cm, (ii) infiltrating margins, (iii) 5 or more mitotic figures per 10 high-power fields, (iv) moderate-to-severe cytologic atypia (209). The absence of one, or even all, of these features does not guarantee against recurrence (210). Lymphatic metastases are uncommon, and radical local excision is the usual treatment.

***Epithelioid sarcomas* characteristically develop in the soft tissues of the extremities of young adults but rarely may occur on the vulva.** A description of two cases and review of three other reports concluded that these tumors might mimic a Bartholin cyst, leading to inadequate initial treatment (211). The study indicated that vulvar epithelioid sarcomas behave more aggressively than their extragenital counterparts, with four of the five patients dying of metastatic disease, and suggested that early recognition and wide excision should improve the prognosis.

***Rhabdomyosarcomas* are the most common soft tissue sarcomas in childhood, and 20% involve the pelvis or genitourinary tract** (212). Dramatic gains were made in the treatment of these tumors during the past 20 years. Previously, radical pelvic surgery was the standard approach, but results were poor. A multimodal approach evolved, and survival rates improved significantly, with a corresponding decrease in morbidity. In a report of the experience of the Intergroup Rhabdomyosarcoma Study I and II (1972 to 1984) with primary tumors of the female genital tract, nine patients aged 1 to 19 years had primary vulvar tumors, and these tumors were often regarded as a form of Bartholin gland infection before biopsy (213). They were all managed with chemotherapy (*vincristine*, or *actinomycin D* and *cyclophosphamide* and *doxorubicin*), with or without radiotherapy. Wide local excision of the tumor, with or without inguinal–femoral lymphadenectomy, was carried out before or after the chemotherapy. Seven of the nine patients were free of disease 4 or more years from diagnosis, one patient was free of disease when lost to follow-up at 5 years, and one patient was alive

with disease.

RARE VULVAR MALIGNANCIES

In addition to the previously mentioned tumors, a number of malignancies more commonly seen in other areas of the body may rarely occur as isolated vulvar tumors.

Lymphomas

The genital tract may be involved primarily by malignant lymphomas but, more commonly, involvement is a manifestation of systemic disease. In the lower genital tract, the cervix is most often involved, followed by the vulva and the vagina (214). Most patients are in their third to sixth decades of life, and about three-fourths of the cases involve diffuse large cell or histiocytic non-Hodgkin lymphomas. The remainder are nodular or Burkitt lymphomas. Treatment is by surgical excision followed by chemotherapy and radiation or both, and the overall 5-year survival rate is approximately 70% (214).

Endodermal Sinus Tumor

There were four case reports of endodermal sinus tumor of the vulva, and three of the four patients died of distant metastases (215). All patients were in their third decade of life, but none was treated with modern chemotherapy.

Merkel Cell Carcinoma

Merkel cell carcinomas are primary small cell carcinomas of the skin that resemble oat cell carcinomas of the lung. They metastasize widely and have a very poor prognosis (216–218). They should be locally excised and treated with *cisplatin*-based chemotherapy.

Dermatofibrosarcoma Protuberans

This rare, low-grade cutaneous malignancy occasionally involves the vulva. It has a marked tendency for local recurrence but a low risk of systemic spread (219). Radical local excision should be sufficient treatment.

METASTATIC TUMORS OF THE VULVA

Metastatic tumors to the vulvas are rare. The most common primary site is the cervix, followed by the endometrium, kidney, and urethra. Most patients in whom vulvar metastases develop have advanced primary tumors when diagnosed, and in

approximately one-fourth of the patients, the primary lesion and the vulvar metastasis are diagnosed simultaneously (220).

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CHAPTER 41

Gestational Trophoblastic Disease



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Pregnancies After GTN

KEY POINTS

1 Gestational trophoblastic disease (GTD) is a group of interrelated tumors which include complete and partial moles, invasive moles, choriocarcinoma, placental-site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).

2 Complete and partial moles differ in terms of chromosomal origin, histopathology, clinical presentation, and risk of gestational trophoblastic neoplasia (gestational trophoblastic neoplasia [GTN]-persistent tumor).

3 Human chorionic gonadotropin (hCG) is a critical marker for GTD to diagnose the development of GTN, monitor response to chemotherapy, and occurrence of relapse.

4 Metastases can occur after any type of GTD but is more common after nonmolar pregnancies and most commonly occur in the lung and the vagina.

5 Single-agent chemotherapy achieves a high remission rate in nonmetastatic and low-risk metastatic GTN.

6 High-risk GTN requires primary combination chemotherapy, surgery to control complications of disease and drug-resistant sites and infrequently radiation therapy.

7 After achieving remission with chemotherapy, patients can anticipate normal future reproduction.

Gestational trophoblastic disease (GTD) is the term used to describe the heterogeneous group of interrelated lesions that arise from abnormal proliferation of placental trophoblasts. GTD lesions are histologically distinct and can be benign or malignant. Benign lesions consist of hydatidiform moles, complete and partial, whereas malignant lesions consist of invasive moles, placental-site trophoblastic tumors (PSTT), epithelioid trophoblastic tumors (ETT), and choriocarcinoma. [1] This subset of malignant lesions that have varying propensities for local invasion

and metastasis is referred to as gestational trophoblastic neoplasia (GTN). GTNs are among the rare human tumors that can be cured even in the presence of widespread dissemination (1,2). Although GTNs commonly follow a molar pregnancy, they can occur after any gestational event, including induced or spontaneous abortion, ectopic pregnancy, or term pregnancy.

HYDATIDIFORM MOLES

Epidemiology

[1] The incidence of molar pregnancy in Japan (2:1,000 pregnancies) is reported to be about threefold higher than the incidence in Europe or North America (about 0.6 to 1.1 per 1,000 pregnancies) (3). In Taiwan, 1 in 125 pregnancies are molar, while in the United States the incidence is 1 in 1,500 live births. The incidences of complete and partial hydatidiform moles in Ireland were investigated by reviewing all products of conception from first- and second-trimester abortions (4). **[1] Based on a thorough pathologic review, the incidence of complete and partial hydatidiform moles was 1:1,945 and 1:695 pregnancies, respectively.**

Table 41-1 Features of Complete and Partial Hydatidiform Moles

Features	Complete Mole	Partial Mole
Fetal or embryonic tissue	Absent	Present
Hydatidiform swelling of chorionic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Karyotype	46,XX (90%); 46,XY	Triploid

While variations in the worldwide incidence of molar pregnancy may result in part from reporting population-based versus hospital-based data, a number of studies suggest that the high incidence in some populations can be attributed to socioeconomic and nutritional factors. The decreasing incidence of molar pregnancy in South Korea is attributed to a more Western diet and improved standard of living (5). Case-control studies from Italy and the United States show that the rate of complete mole increases with decreasing consumption of dietary carotene (vitamin A precursor) and animal fat (6,7). **Maternal age and reproductive history influence the rate of molar pregnancy. Women older than 40 years have a 2- to 10-fold greater risk of having a complete mole,** while one in three pregnancies in women older than 50 years results in a molar

gestation (8,9). Similarly, **adolescents have a sevenfold increased risk of developing a complete mole** (8). **[1] These findings suggest that ova from adolescent and older women may be more susceptible to abnormal fertilization, resulting in a complete hydatidiform mole.**

Limited information is available concerning risk factors for partial molar pregnancy. The epidemiologic characteristics of complete and partial moles appear to differ significantly (8–11). The risk for partial moles is associated with the use of oral contraceptives and a history of irregular menstruation, but not with dietary factors (10). Nor does there appear to be a strong association between maternal age and the risk for partial moles (8,9).

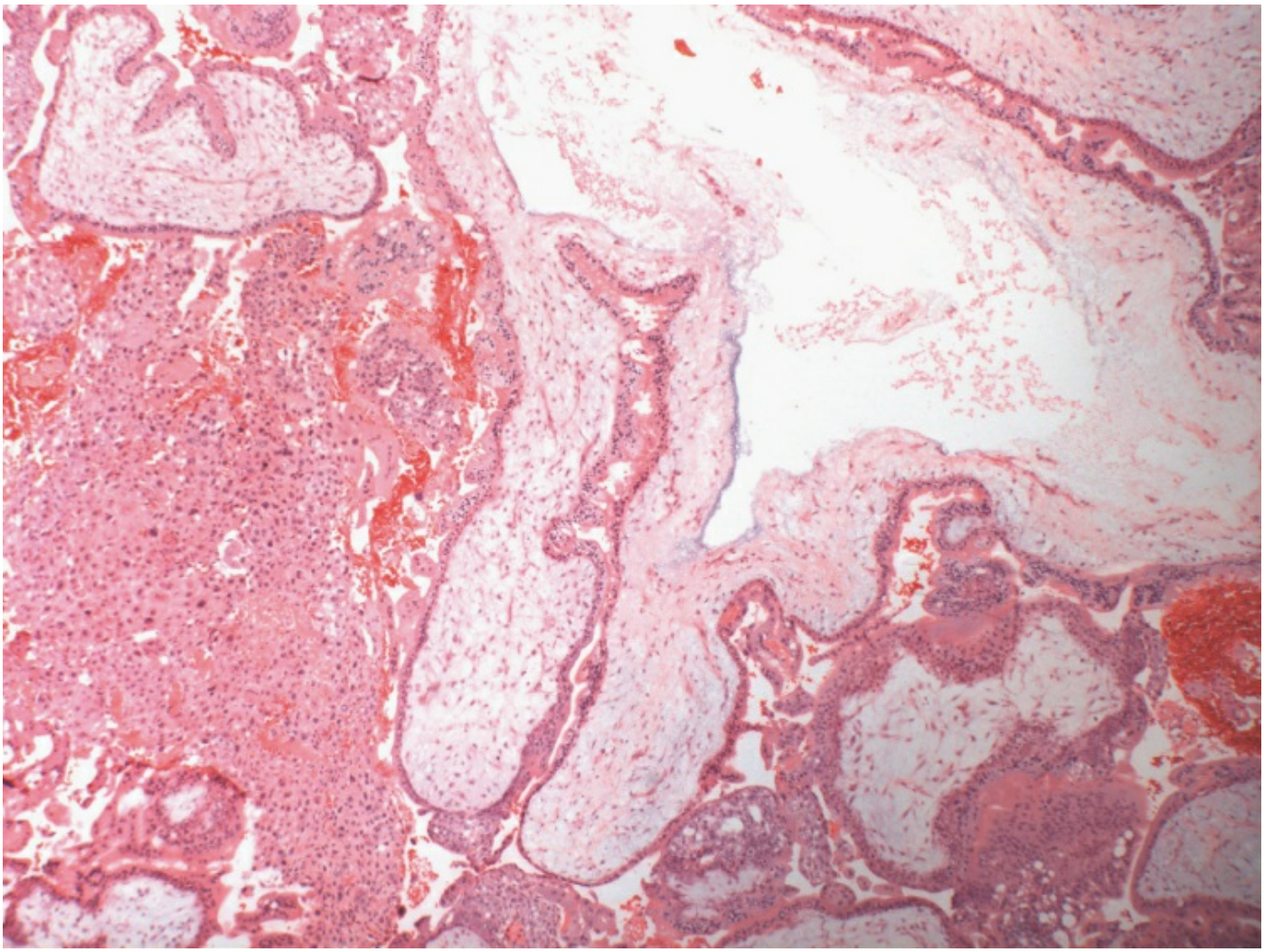


FIGURE 41-1 Photomicrograph of a complete mole demonstrating enlarged villous with central cavitation and surrounding trophoblastic hyperplasia.

Pathology and Cytogenetics

Hydatidiform moles may be categorized as either complete or partial moles on the

basis of gross morphology, histopathology, and karyotype (Table 41-1).

Complete Hydatidiform Mole

Complete hydatidiform moles exhibit characteristic swelling and trophoblastic hyperplasia (Fig. 41-1). They usually have a 46,XX karyotype, but about 10% have a 46,XY karyotype (12,13). **[2] The molar chromosomes are entirely of paternal origin,** with mitochondrial DNA of maternal origin **(Fig. 41-2)** (14). Complete moles usually arise from an ovum fertilized by a haploid sperm, which duplicates its own chromosomes. The ovum nucleus may be absent or inactivated (15).

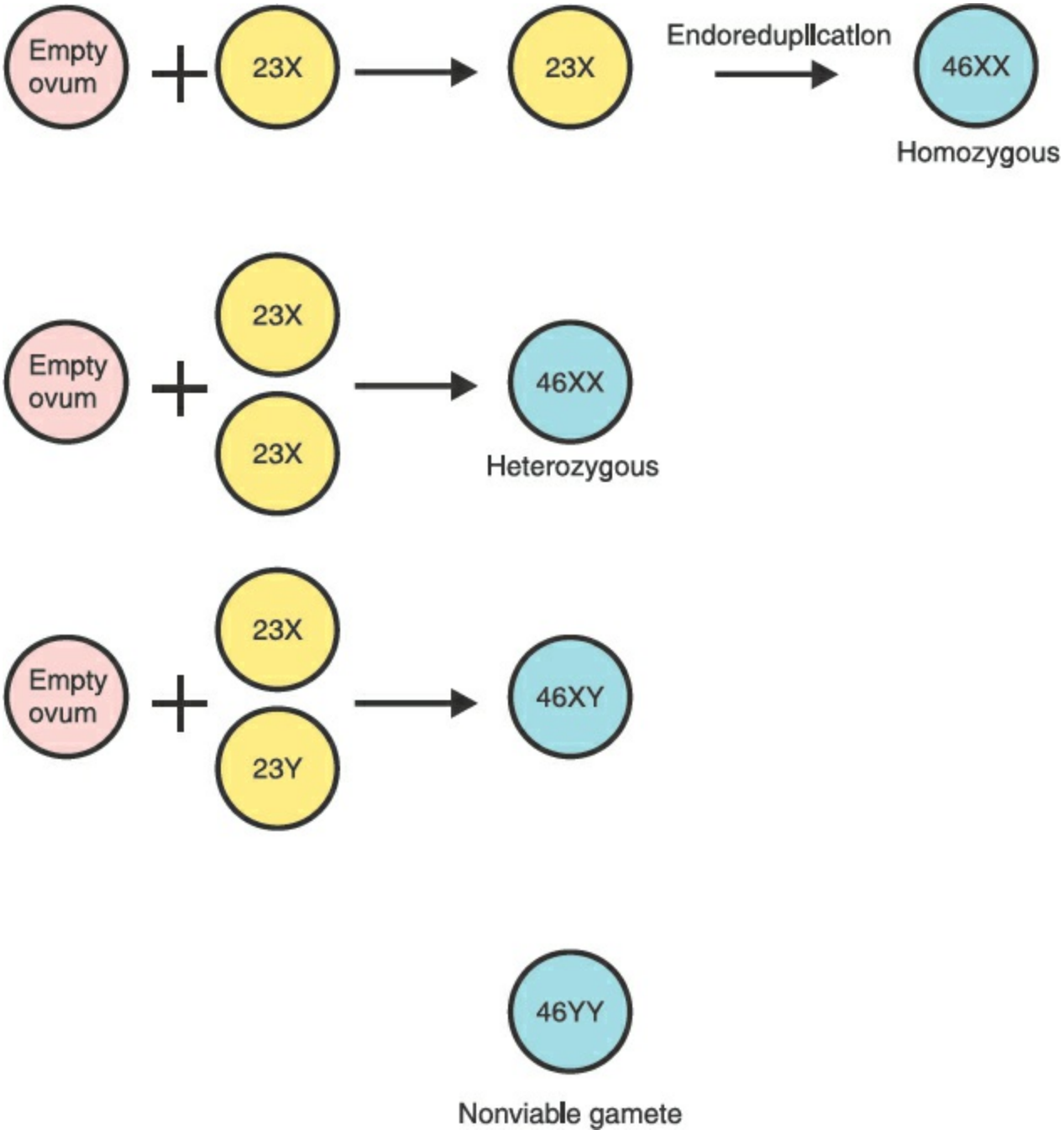


FIGURE 41-2 The karyotype of complete hydatidiform mole.

Partial Hydatidiform Mole

Partial hydatidiform moles are characterized by the following pathologic features (Fig. 41-3) (16):

1. Chorionic villi of varying size with focal hydatidiform swelling, cavitation, and trophoblastic hyperplasia
2. Marked villous scalloping
3. Prominent stromal trophoblastic inclusions
4. Identifiable embryonic or fetal tissues

[2] Partial moles have a triploid karyotype (69 chromosomes); the extra haploid set of chromosomes is derived from the father (Fig. 41-4) (17). It is possible that nontriploid partial moles do not exist (18). When a fetus is present in conjunction with a partial mole, it generally exhibits the stigmata of triploidy, including growth retardation and multiple congenital malformations such as syndactyly and hydrocephaly **(Fig. 41-5)**.

Advances in Pathologic Diagnosis

When molar pregnancy is diagnosed early in the first trimester, the pathologist can have difficulty distinguishing complete hydatidiform moles from partial hydatidiform moles or hydropic abortions because of smaller villi, less trophoblastic hyperplasia, more primitive villous stroma, and less global necrosis (19,20). Accurate diagnosis can be facilitated using flow cytometry to determine ploidy (i.e., diploid versus triploid moles) (21) and through assessment of biomarkers of paternally imprinted and maternally expressed gene products (22). Biomarkers that take advantage of imprinted genes to distinguish between complete moles and hydropic abortions from other gestations are identified. Because complete moles generally have no maternal chromosomes, paternally imprinted gene products, normally expressed only by maternal chromosomes, should be absent. In complete moles, the nuclei of the villous stroma and cytotrophoblastic cells do not express p57, whereas all other gestations, including partial moles, are characterized by nuclear immunostaining in these cells. Thus, a complete mole is diploid and negative for p57, a hydropic abortion is diploid (sometimes triploid) and positive for p57, and a partial mole is triploid and positive for p57.

Familial Recurrent Molar Pregnancy

Evaluation of families with recurrent molar pregnancy suggests that dysregulation of normal parental imprinting of genes, with loss of maternally transcribed genes, is likely

to contribute to the pathogenesis of molar pregnancy. Familial recurrent hydatidiform moles, is a rare occurrence, characterized by recurrent complete hydatidiform mole of biparental origin, rather than the more usual androgenetic origin (23). Genetic mapping shows that in most families the gene responsible, NLRP7, is located in a 1.1 Mb region on chromosome 19q13.4. Mutations in the gene result in dysregulation of imprinting in the female germline with abnormal development of embryonic and extraembryonic tissue.

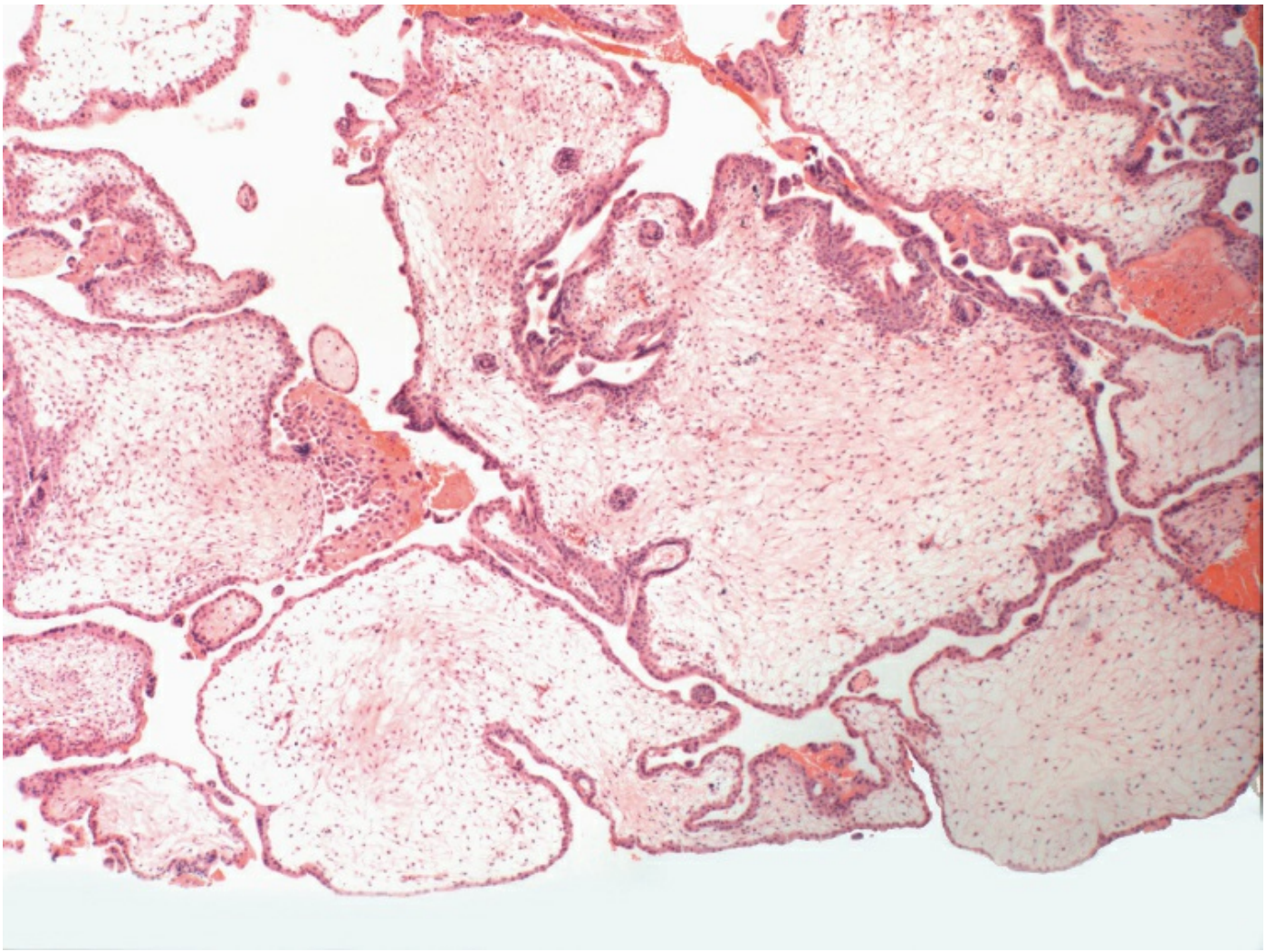


FIGURE 41-3 Photomicrograph of a partial mole showing marked disparity in the villous size, trophoblastic inclusions (*center*), and mild trophoblastic hyperplasia. (From **Berkowitz RS, Goldstein OP.** Gestational trophoblastic diseases. In: Ryan KJ, Berkowitz R, Barbieri R, eds. Kistner's Gynecology Principles and Practice. 5th ed. Chicago, IL: Year Book Medical Publishers; 1990:433, with permission.)

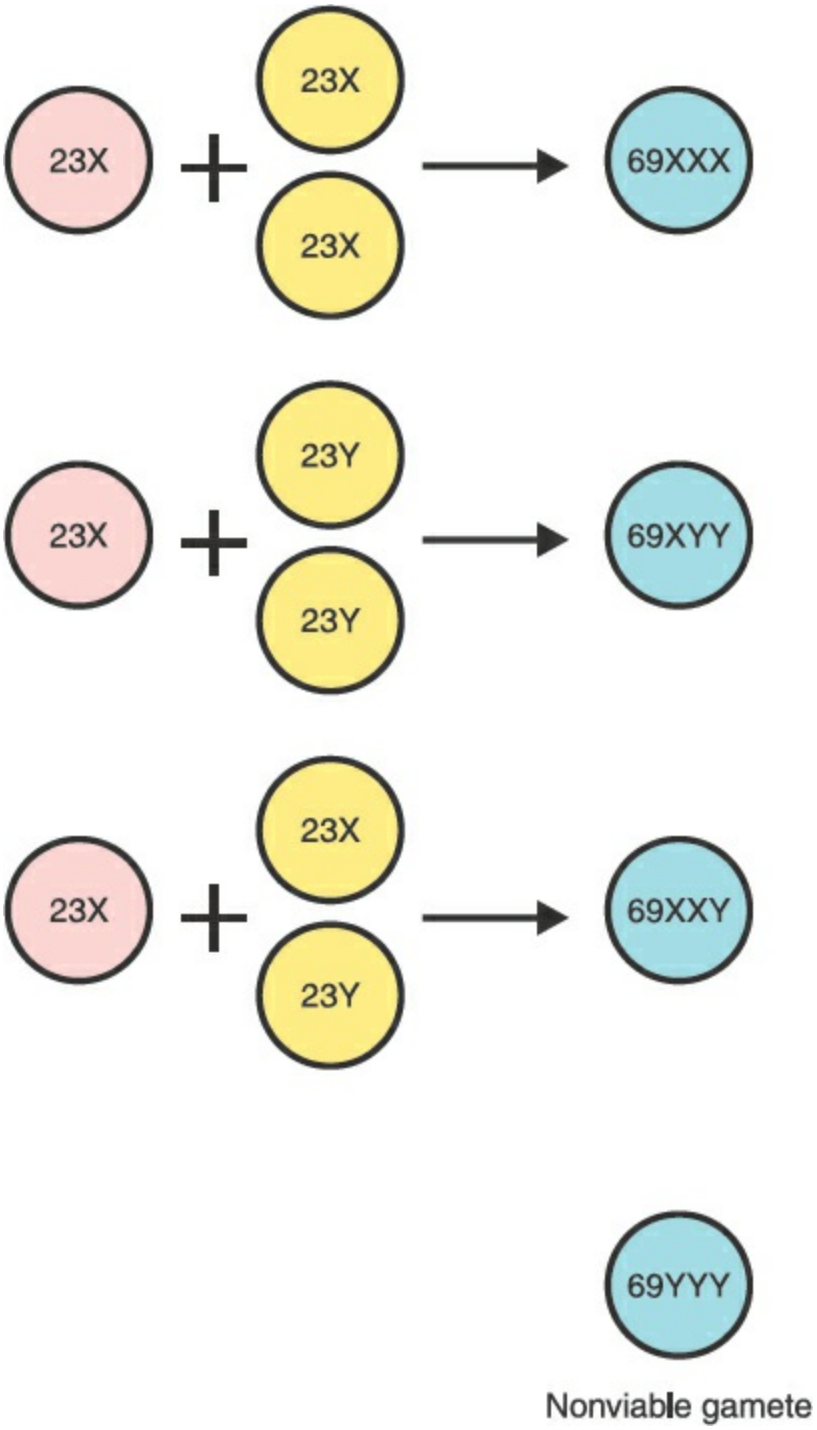


FIGURE 41-4 The karyotype of a partial hydatidiform mole.

Clinical Features

Patients with complete molar pregnancy are diagnosed increasingly earlier in pregnancy and treated before they develop the classic clinical signs and symptoms. **[2]** This is the result of many changes in clinical practice, such as the frequent use of human chorionic gonadotropin (hCG) measurement and transvaginal ultrasonography in early pregnancy for women with vaginal staining and for determining the gestational dates in

asymptomatic women. The following is a description of the classic and current clinical features of complete molar pregnancy (24,25).

Complete Hydatidiform Mole

Vaginal Bleeding

[2] Vaginal bleeding is the most common symptom causing patients to seek treatment for complete molar pregnancy. It is reported to occur in 46% of patients, rather than the previous reports of 97% of cases. Molar tissues may separate from the decidua and disrupt maternal vessels, and large volumes of retained blood may distend the endometrial cavity. Because vaginal bleeding may be considerable and prolonged, in the past one-half of these patients had anemia (hemoglobin <10 g/100 mL). Anemia is typically present in only 5% of patients.

Excessive Uterine Size

[2] Excessive uterine enlargement relative to the gestational age is one of the classic signs of a complete mole, although it was present in only about half of patients. Excessive uterine size occurs in only 28% of patients. The endometrial cavity may be expanded by chorionic tissue and retained blood. Excessive uterine size is generally associated with markedly elevated levels of hCG, because uterine enlargement results in part from trophoblastic overgrowth.



FIGURE 41-5 Photomicrograph of a fetal hand demonstrating syndactyly. The fetus had a triploid karyotype, and the chorionic tissues were a partial mole.

Preeclampsia

[2] Preeclampsia was observed in 27% of patients with a complete hydatidiform mole. Preeclampsia is reported in only 1 of 74 patients with complete mole at the initial visit. Although preeclampsia is associated with hypertension, proteinuria, and hyperreflexia, eclamptic convulsions rarely occur. Preeclampsia develops almost exclusively in patients with excessive uterine size and markedly elevated hCG levels. Hydatidiform moles should be considered whenever preeclampsia develops early in pregnancy.

Hyperemesis Gravidarum

[2] Hyperemesis requiring antiemetic or intravenous (IV) replacement therapy historically occurred in one-fourth of women with a complete mole, particularly those with excessive uterine size and markedly elevated hCG levels. Severe electrolyte disturbances may develop and require treatment with parenteral fluids. Typically 8% of patients have hyperemesis.

Hyperthyroidism

[2] Clinically evident hyperthyroidism was observed in 7% of patients with a complete molar gestation. These women may have tachycardia, warm skin, and tremor, and the diagnosis can be confirmed by detection of elevated serum levels of free thyroxine (T_4) and triiodothyronine (T_3). Clinical evidence of hyperthyroidism with complete mole is rare.

Anesthesia or surgery may precipitate thyroid storm. Thus, if hyperthyroidism is suspected before the induction of anesthesia for molar evacuation, a-adrenergic blocking agents should be administered. Thyroid storm may be manifested by hyperthermia, delirium, convulsions, tachycardia, high-output heart failure, or cardiovascular collapse. Administration of β-adrenergic blocking agents prevents or rapidly reverses many of the metabolic and cardiovascular complications of thyroid storm. After molar evacuation, thyroid function test results rapidly return to normal.

[2] Hyperthyroidism develops almost exclusively in patients with very high hCG levels. Some investigators suggest that hCG is the thyroid stimulator in women with molar pregnancy because positive correlations between serum hCG levels and total T_4 or T_3 concentrations were observed. However, in one study in which thyroid function was measured in 47 patients with a complete mole, no significant correlation was found between serum hCG levels and serum values of free T_4 index or free T_3 index (26). Although some investigators speculated about a separate chorionic thyrotropin, this substance is not yet isolated.

Trophoblastic Embolization

Respiratory distress rarely occurs in patients with a complete mole. It is usually diagnosed in patients with excessive uterine size and markedly elevated hCG levels.

These patients may have chest pain, dyspnea, tachypnea, and tachycardia and may experience severe respiratory distress during and after molar evacuation. Auscultation of the chest usually reveals diffuse rales, and chest radiographic evaluation may show bilateral pulmonary infiltrates. Respiratory distress usually resolves within 72 hours with cardiopulmonary support. In some circumstances, patients may require mechanical ventilation. Respiratory insufficiency may result from trophoblastic embolization and the cardiopulmonary complications of thyroid storm, preeclampsia, and massive fluid replacement.

Theca Lutein Ovarian Cysts

[2] **Prominent theca lutein ovarian cysts (6 cm in diameter) develop in about one-half of patients with a complete mole** (27). Theca lutein ovarian cysts result from high serum hCG levels, which cause ovarian hyperstimulation (28). Because the uterus may be excessively enlarged, theca lutein cysts can be difficult to palpate during physical examination; however, ultrasonography can accurately document their presence and size. **After molar evacuation, theca lutein cysts normally regress spontaneously within 2 to 4 months.**

Prominent theca lutein cysts may cause symptoms of marked pelvic pressure, and they can be decompressed by laparoscopically or ultrasonographically directed aspiration. If acute pelvic pain develops, laparoscopy should be performed to assess possible cystic torsion or rupture.

Partial Hydatidiform Mole

[2] Patients with partial hydatidiform mole usually do not have the dramatic clinical features characteristic of complete molar pregnancy. **These patients have the signs and symptoms of incomplete or missed abortion, and a partial mole is diagnosed after histologic review of the tissue obtained by curettage** (29).

In a survey of 81 patients with a partial mole, the main initial sign was vaginal bleeding, which occurred in 59 patients (72.8%) (30). Excessive uterine enlargement and preeclampsia were present in 3 patients (3.7%) and 2 patients (2.5%), respectively. No patient had theca lutein ovarian cysts, hyperemesis, or hyperthyroidism. The initial clinical diagnosis was an incomplete or missed abortion in 74 patients (91.3%) and hydatidiform mole in 5 patients (6.2%). Pre-evacuation hCG levels were measured in 30 patients and were higher than 100,000 mIU/mL in 2 patients (6.6%).

Natural History

Complete Hydatidiform Mole

[2] Complete moles have a potential for local invasion and dissemination. **After molar evacuation, local uterine invasion occurs in 15% of patients, and metastasis occurs**

in 4% (27).

A review of 858 patients with complete hydatidiform mole at the New England Trophoblastic Disease Center (NETDC) revealed that two-fifths of the patients had the following signs of marked trophoblastic proliferation at the time they sought treatment:

1. **[2] hCG level greater than 100,000 mIU/mL**
2. **Excessive uterine enlargement**
3. **Theca lutein cysts 6 cm in diameter or larger**

In this review, patients with any one of these signs were considered at high risk for developing postmolar tumor. [2] After molar evacuation, local uterine invasion occurred in 31%, and metastases developed in 8.8% of the 352 high-risk patients. For the 506 low-risk patients, local invasion was found in only 3.4%, and metastases developed in 0.6%.

Older patients are at increased risk of developing postmolar GTN. One study reported that persistent tumor developed after a complete molar pregnancy in 37% of women older than 40 years (27), whereas in another study this finding occurred in 60% of women older than 50 years (31).

Partial Hydatidiform Mole

[2] Persistent tumor, usually nonmetastatic, develops in approximately 1% to 4% of patients with a partial mole, and chemotherapy is required to achieve remission (32). **Patients who develop persistent disease have no distinguishing clinical or pathologic characteristics** (33).

Diagnosis

[2] Ultrasonography is a reliable and sensitive technique for the diagnosis of complete molar pregnancy. Because the chorionic villi exhibit diffuse hydropic swelling, complete moles produce a characteristic vesicular ultrasonographic pattern as early as the first trimester (Fig. 41-6).

[2] Ultrasonography may contribute to the diagnosis of partial molar pregnancy by demonstrating focal cystic spaces in the placental tissues and an increase in the transverse diameter of the gestational sac (34). **When these criteria are present, the positive predictive value for a partial mole is 90%.**

Treatment

When molar pregnancy is diagnosed, the patient should be evaluated for the presence of associated medical complications, including preeclampsia, hyperthyroidism, electrolyte imbalance, and anemia. After the patient's condition is stabilized, a decision must be

made concerning the most appropriate method of evacuation.

Suction Curettage

[2] Suction curettage is the preferred method of evacuation, regardless of uterine size, for patients who desire to preserve fertility (32). It involves the following steps:

1. **Oxytocin infusion**—This procedure is begun before the induction of anesthesia.
2. **Cervical dilation**—As the cervix is being dilated, uterine bleeding often increases. Retained blood in the endometrial cavity may be expelled during cervical dilation. Active uterine bleeding should not deter the prompt completion of cervical dilation.
3. **Suction curettage**—Within a few minutes of commencing suction curettage, the uterine size may decrease dramatically, and the bleeding will be well controlled. The use of a 12-mm cannula is strongly advised to facilitate evacuation. If the uterus is larger than 14 weeks of gestation, one hand should be placed on top of the fundus, and the uterus should be massaged to stimulate uterine contraction and reduce the risk of perforation.
4. **Sharp curettage**—When suction evacuation is believed to be complete, gentle sharp curettage is performed to remove any residual molar tissue.



FIGURE 41-6 Ultrasonogram of a uterus showing a typical pattern of a complete hydatidiform mole. Note the characteristic vesicular ultrasonographic pattern.

Because trophoblast cells express the RhD factor, patients who are Rh negative should receive Rh immune globulin at the time of evacuation.

Hysterectomy

[2] If the patient desires surgical sterilization, a hysterectomy may be performed with the mole in situ. The ovaries may be preserved at the time of surgery, even in the presence of prominent theca lutein cysts. Large ovarian cysts may be decompressed by aspiration. Hysterectomy does not prevent metastasis; patients

still require follow-up with assessment of hCG levels.

Prophylactic Chemotherapy

The use of prophylactic chemotherapy at the time of molar evacuation is controversial. The debate concerns the wisdom of exposing all patients to potentially toxic treatment when only about 20% are at risk of developing persistent tumor.

In a study of 247 patients with complete molar pregnancy who prophylactically received a single course of *actinomycin D* (*ActD*) at the time of evacuation, local uterine invasion developed in 10 patients (4%), and no patients experienced metastasis (35). All 10 patients with local invasion achieved remission after one additional course of chemotherapy. **Prophylactic chemotherapy, prevented metastasis and reduced the incidence and morbidity of local uterine invasion.**

In two prospective randomized studies of prophylactic chemotherapy in patients with a complete mole, a significant decrease in persistent tumor was detected in patients with high-risk moles who received prophylactic chemotherapy (47% and 50% vs. 14%) (36,37). **[2] Prophylaxis may be particularly useful in the management of high-risk complete molar pregnancy, especially when hCG assessments for follow-up are unavailable or unreliable (38).**

Follow-Up

Human Chorionic Gonadotropin

[2] After molar evacuation, patients should be monitored with weekly determinations of a-subunit hCG levels until these levels are normal for 3 consecutive weeks, followed by monthly determinations until the levels are normal for 6 consecutive months (39). **The average time to achieve the first normal hCG level after evacuation is about 9 weeks** (40). **After achieving nondetectable serum hCG levels, the risk of developing GTN approaches zero** (41–43). If these findings are confirmed, it is possible that postmolar hCG surveillance could be safely abbreviated.

Contraception

Patients are encouraged to use effective contraception during the entire interval of hCG follow-up. Because of the potential risk of uterine perforation, bleeding, and infection, intrauterine devices should not be inserted until the patient achieves a normal hCG level. If the patient does not desire surgical sterilization, either oral contraceptives or barrier methods should be used.

Increased incidence of postmolar persistent tumor was reported among patients who used oral contraceptives before gonadotropin remission (44). However, data from a prospective trial and other centers indicate that oral contraceptive use does not increase

the risk of postmolar trophoblastic disease (45–47). **It appears that oral contraceptives may be used safely after molar evacuation during the entire interval of hormonal follow-up.**

GESTATIONAL TROPHOBLASTIC NEOPLASIA

Nonmetastatic Disease

[2] Locally invasive GTN develops in about 15% of patients after evacuation of a complete mole and infrequently after other gestations (1). These patients usually present with the following symptoms:

1. Irregular vaginal bleeding
2. Theca lutein cysts
3. Uterine subinvolution or asymmetric enlargement
4. Persistently elevated serum hCG levels.

The trophoblastic tumor may perforate the myometrium, causing intraperitoneal bleeding, or erode into uterine vessels, causing vaginal hemorrhage. Bulky, necrotic tumor may involve the uterine wall and serve as a nidus for infection. Patients with uterine sepsis may have a purulent vaginal discharge and acute pelvic pain.

[1] After molar evacuation, persistent GTN may exhibit the histologic features of either hydatidiform moles or choriocarcinoma. After a nonmolar pregnancy, persistent GTN always has the histologic pattern of choriocarcinoma. Histologic characterization of choriocarcinoma depends on sheets of anaplastic syncytiotrophoblast and cytotrophoblast without chorionic villi.

Placental-Site Trophoblastic Tumor and Epithelioid Trophoblastic Tumor

PSTT and ETT are uncommon but important variants of GTN that consist predominantly of intermediate trophoblast (48). Relative to their mass, these tumors produce small amounts of hCG and human placental lactogen (hPL), and they tend to remain confined to the uterus, metastasizing late in their course. **[1] In contrast to other trophoblastic tumors, they are relatively insensitive to chemotherapy.**

Metastatic Disease

[4] Metastatic GTN occurs in about 4% of patients after evacuation of a complete mole, but it is seen more often when GTN develops after nonmolar pregnancies (1). GTN usually metastasizes as choriocarcinoma because of its tendency for early vascular invasion with widespread dissemination. Trophoblastic tumors often are perfused by fragile vessels and are frequently hemorrhagic. Symptoms of metastases may result from

spontaneous bleeding at metastatic foci. [3] The most common sites of metastases are the lungs (80%), vagina (30%), pelvis (20%), liver (10%), and brain (10%).

Pulmonary

At the time of diagnosis, lung involvement is visible by chest radiography in 80% of patients with metastatic GTN. [4] Patients with pulmonary metastasis may have chest pain, cough, hemoptysis, dyspnea, or an asymptomatic lesion visible by chest radiography. Respiratory symptoms may be acute or chronic, persisting over many months.

GTN may produce four principal pulmonary patterns:

1. An alveolar or "snowstorm" pattern
2. Discrete rounded densities
3. Pleural effusion
4. An embolic pattern caused by pulmonary arterial occlusion.

Because respiratory symptoms and radiographic findings may be dramatic, the patient may be thought to have a primary pulmonary disease. Some patients with extensive pulmonary involvement have minimal, if any, gynecologic symptoms because the reproductive organs may be free of trophoblastic tumor. The diagnosis of GTN may be confirmed only after thoracotomy is performed, particularly in patients with a nonmolar antecedent pregnancy.

Pulmonary hypertension may develop in patients with GTN secondary to pulmonary arterial occlusion by trophoblastic emboli. The development of early respiratory failure requiring intubation is associated with a poor clinical outcome (49).

Vaginal

[4] **Vaginal metastases occur in 30% of the patients with metastatic tumor. These lesions are highly vascular and may bleed vigorously when biopsied.** Metastases to the vagina may occur in the fornices or suburethrally and may produce irregular bleeding or a purulent discharge.

Hepatic

Liver metastases occur in 10% of patients with disseminated trophoblastic tumor. Hepatic involvement is encountered when there is a protracted delay in diagnosis and the patient has an extensive tumor burden. Epigastric or right upper quadrant pain may develop if metastases stretch the hepatic capsule. Hepatic lesions may be hemorrhagic, causing hepatic rupture and exsanguinating intraperitoneal bleeding.

Central Nervous System

[4] **Metastatic trophoblastic disease involves the brain in 10% of patients.** Cerebral

involvement is seen in patients with advanced disease; virtually all patients with brain metastasis have concurrent pulmonary or vaginal involvement or both. Because cerebral lesions frequently hemorrhage spontaneously, most patients develop acute focal neurologic deficits (50,51).

Staging and Prognostic Score

Staging

[5] **An anatomic staging system for GTN was adopted by the International** [6] **Federation of Gynecology and Obstetrics (FIGO)** (Table 41-2). It is hoped that this staging system will encourage the objective comparison of data from various centers (52).

Stage I: Patients have persistently elevated hCG levels and tumor confined to the uterine corpus.

Stage II: Patients have metastases to the genital tract (i.e., adnexa, broad ligament, vagina).

Stage III: Patients have pulmonary metastases with or without uterine, vaginal, or pelvic involvement. The diagnosis is based on a rising hCG level in the presence of pulmonary lesions viewed by plain chest radiography and not chest computed tomography scans (CT scan).

Stage IV: Patients have advanced disease and involvement of the brain, liver, kidneys, or gastrointestinal tract. These patients are in the highest risk category because they are most likely to be resistant to chemotherapy. Choriocarcinoma is usually present, and the disease commonly follows a nonmolar pregnancy.

Table 41-2 Staging of Gestational Trophoblastic Tumors

Stage I	Disease confined to uterus
Stage II	GTN extending outside uterus but limited to genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extending to lungs with or without known genital tract involvement
Stage IV	All other metastatic sites

Prognostic Scoring System

In addition to anatomic staging, it is important to consider other variables to predict the likelihood of drug resistance and to assist in selecting the appropriate chemotherapy (53). [5] **A prognostic scoring system proposed by the World Health** [6] **Organization reliably predicts the potential for resistance to chemotherapy** (Table

41-3).

When the prognostic score is higher than 6, the patient is categorized as high risk and requires multimodal therapy, which includes intensive combination chemotherapy, and may include surgery and radiation to achieve remission. Patients with stage-I disease usually have a low-risk score, and those with stage-IV disease have a high-risk score. The distinction between low and high risk applies mainly to patients with stage-II or III disease.

Table 41-3 Scoring System Based on Prognostic Factors[a]

	0	1	2	4
Age (years)	≤39	>39		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	
Interval between end of antecedent pregnancy and start of chemotherapy (months)	<4	4–6	7–12	>12
Human chorionic gonadotropin (IU/L) at the time of GTN diagnosis	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
ABO groups		O or A	B or AB	
Largest tumor, including uterine (cm)	<3	3–5	>5	
Site of metastases		Spleen, kidney	GI tract	Brain, liver
Number of metastases		1–3	4–8	>8
Prior chemotherapy			1 drug	≥2 drugs

[a]The total score for a patient is obtained by adding the individual scores for each prognostic factor. Total score: <7, low risk; ≥7, high risk.

Diagnostic Evaluation

[4] Optimal management of persistent GTN requires a thorough assessment [5] of the extent of the disease before the initiation of treatment. [6] **All patients with persistent GTN should undergo a careful pretreatment evaluation, including the following:**

1. Complete history and physical examination
2. Measurement of the serum hCG level
3. Hepatic, thyroid, and renal function tests
4. Determination of baseline peripheral white blood cell and platelet counts

The metastatic workup should include the following:

1. Chest radiograph or CT scan (see below regarding micrometastases)
2. Ultrasonography or CT scan of the abdomen and pelvis

3. CT or magnetic resonance imaging (MRI) scan of the head as indicated

When the pelvic examination and chest radiographic findings are negative, metastatic involvement of other sites is uncommon.

Liver ultrasonography and CT or MRI scanning will disclose most hepatic metastases in patients with abnormal liver function tests. CT or MRI scan of the head facilitates the early diagnosis of asymptomatic cerebral lesions. Chest CT scans may detect micrometastases not visible on chest radiography. Chest CT will demonstrate pulmonary micrometastases in about 40% of patients with presumed nonmetastatic disease (54). The presence of pulmonary micrometastases has not been shown to substantially change the clinical outcome.

In patients with choriocarcinoma or metastatic disease, hCG levels may be measured in the cerebrospinal fluid (CSF) to exclude cerebral involvement if the results of CT or MRI scanning of the brain are normal. The ratio of plasma-to-CSF hCG tends to be lower than 60 in the presence of cerebral metastases (55). A single plasma-to-CSF hCG ratio may be misleading, because rapid changes in plasma hCG levels may not be reflected promptly in the CSF (56).

Pelvic ultrasonography appears to be useful in detecting extensive trophoblastic uterine involvement and may aid in identifying sites of resistant uterine tumor (57). Because ultrasonography can accurately and noninvasively detect extensive uterine tumor, it may help identify patients who would benefit from hysterectomy.

Management of GTN

A protocol for the management of GTN is presented in Table 41-4.

Low-Risk Disease

Low-risk GTN includes patients with both nonmetastatic (stage I) and metastatic GTN whose prognostic score is less than 7. In patients with stage-I disease, the selection of treatment is based primarily on whether the patient desires to retain fertility.

Hysterectomy Plus Chemotherapy

[5] If the patient does not wish to preserve fertility, hysterectomy with adjuvant single-agent chemotherapy may be performed as primary treatment. Adjuvant chemotherapy is administered for three reasons:

1. To reduce the likelihood of disseminating viable tumor cells at surgery.
2. To maintain a cytotoxic level of chemotherapy in the bloodstream and tissues in case viable tumor cells are disseminated at surgery.
3. To treat any occult metastases that may be present at the time of surgery.

Chemotherapy can be administered safely at the time of hysterectomy without increasing the risk of bleeding or sepsis. In a series of 31 patients treated with primary hysterectomy and a single course of adjuvant chemotherapy, all achieved complete remission with no additional therapy (58).

Hysterectomy is performed in all patients with stage-I PSTT and ETT. Because PSTT and ETT are relatively resistant to chemotherapy, hysterectomy for presumed nonmetastatic disease is the most certain curative treatment. Patients with metastatic PSTT may still achieve remission, but their tumors are less responsive to chemotherapy (59).

Table 41-4 Protocol for Treatment of GTN

Stage I	
Initial	Single-agent chemotherapy or hysterectomy with adjunctive chemotherapy
Resistant	Combination chemotherapy
	Hysterectomy with adjunctive chemotherapy
	Local resection
	Pelvic infusion
Stages II and III	
Low risk[a]	
Initial	Single-agent chemotherapy
Resistant	Combination chemotherapy
High risk[a]	
Initial	Combination chemotherapy
Resistant	Second-line combination chemotherapy
Stage IV	
Initial	Combination chemotherapy
Brain	Whole-head radiation (3,000 cGy)
	Craniotomy to manage complications
Liver	Resection or embolization to manage complications
Resistant[a]	Second-line combination chemotherapy
	Hepatic arterial infusion

[a]Local resection optional.

Chemotherapy Alone

[5] Single-agent chemotherapy is the preferred treatment in patients with stage-I disease who desire to retain fertility (60). At the NETDC from July 1965 through December 2016, primary single-agent chemotherapy was administered to 592 patients with stage-I GTN and 487 patients (82.3%) attained complete remission. The remaining 105 patients with resistant disease subsequently achieved remission after combination chemotherapy or surgical intervention.

[6] When a patient's disease is resistant to single-agent chemotherapy and she desires to preserve fertility, combination chemotherapy should be administered. If the patient's disease is resistant to single-agent and combination chemotherapy and she wants to retain fertility, local uterine resection may be considered. When local resection is planned, a preoperative ultrasonography, MRI, positron emission tomography (PET) scan, or arteriography may help to define the site of the resistant tumor.

Low-Risk Metastatic GTN (Stages II and III)

Vaginal and Pelvic Metastasis

[5] Low-risk disease treated with primary single-agent chemotherapy has a high (approximately 80%) rate of remission in contrast to high-risk disease that usually does not achieve remission with single-agent treatment and requires treatment with primary intensive combination chemotherapy.

Vaginal metastases may bleed profusely because they are highly vascular and friable. When bleeding is substantial, it may be controlled by packing the vagina or by wide local excision. Infrequently, arteriographic embolization of the hypogastric arteries may be required to control hemorrhage from vaginal metastases (61).

Pulmonary Metastasis

At the NETDC from July 1965 through December 2016, of the 168 patients with low-risk stages II or III disease, 130 (77.3%%) attained complete remission with single-agent chemotherapy. The remaining 38 (22.6%) patients who had disease resistant to single-agent treatment subsequently achieved remission with combination chemotherapy.

Thoracotomy

[6] Thoracotomy has a limited but important role in the management of pulmonary metastases. **If a patient has a persistent viable pulmonary metastasis following intensive chemotherapy, thoracotomy may be indicated to excise the resistant focus.** A thorough metastatic workup should be performed before surgery is undertaken to exclude other sites of persistent disease. It is important to realize that fibrotic pulmonary nodules may persist indefinitely on chest radiography, even after complete gonadotropin remission is attained. In patients undergoing thoracotomy for resistant

disease, chemotherapy should be administered postoperatively to treat potential occult sites of micrometastases.

Hysterectomy

[6] Hysterectomy may be required in patients with metastatic disease to control uterine hemorrhage or sepsis. **[6]** In patients with extensive uterine tumor, hysterectomy may substantially reduce the trophoblastic tumor burden and limit the need for multiple courses of chemotherapy (62).

Follow-Up

[3] All patients with GTN should undergo follow-up with:

1. **Weekly measurement of hCG levels until they are normal for three consecutive weeks.**
2. **Monthly measurement of hCG values until levels are normal for twelve consecutive months.**
3. **Effective contraception during the entire interval of hormonal follow-up.**

High-Risk Metastatic GTN (Stages II to IV)

[6] All patients with high-risk GTN (stages II to IV) should be treated with primary intensive combination chemotherapy and the selective use of radiation therapy and surgery. Between July 1965 and December 2016, of the 144 patients with high-risk GTN stages II to IV treated at the NETDC, 121 (84%) achieved complete remission. Before 1975, when single-agent therapy was used primarily to treat patients with stage-IV GTN, only 6 of 20 patients (30%) attained complete remission. Since 1975, 25 of 33 patients (75.7%) achieved remission. This improvement in survival resulted from the use of multimodal therapy, including primary combination chemotherapy in conjunction with radiation and surgical treatment. Patients with stage-IV disease are at the greatest risk of developing rapidly progressive and unresponsive tumors despite intensive multimodal therapy. They should be referred to centers with special expertise in the management of trophoblastic disease.

Hepatic Metastasis

The management of resistant hepatic metastasis is particularly difficult (63). If a patient becomes resistant to systemic chemotherapy, hepatic arterial infusion of chemotherapy may induce complete remission in selected cases. Hepatic resection may be required to control acute bleeding or to excise a focus of resistant tumor. New techniques of arterial embolization may reduce the need for surgical intervention.

Cerebral Metastasis

At the NETDC, cerebral metastases are treated with either whole-brain radiation (3,000

cGy in 10 fractions) or stereotactic radiosurgery in conjunction with combination chemotherapy. **[6] Because irradiation may be hemostatic and tumoricidal, the risk of spontaneous cerebral hemorrhage may be lessened by the concurrent use of combination chemotherapy and brain irradiation.** Excellent remission rates (86%) were reported in patients with cranial metastases treated with intensive IV combination chemotherapy and intrathecal *methotrexate* (*MTX*) (64).

Craniotomy

[6] Craniotomy may be required to provide acute decompression or to control bleeding. It should be performed to manage life-threatening complications so that the patient ultimately will be cured with chemotherapy. In a study of six patients (65), the use of craniotomy to control bleeding resulted in complete remission in three patients. Infrequently, cerebral metastases that are resistant to chemotherapy may be amenable to local resection (66). Patients with cerebral metastases who achieve sustained remission generally have no residual neurologic deficits.

Follow-Up

An algorithm for the management of persistent GTN is presented in **Figure 41-7**.

CHEMOTHERAPY

Single-Agent Treatment

[5] Single-agent chemotherapy with either *ActD* or *MTX* achieved comparable and excellent remission rates in both nonmetastatic and low-risk metastatic GTN (67). Several protocols using these agents are available. *ActD* can be given every other week as a 5-day regimen or in a pulsatile fashion; similarly, *MTX* can be given either in a 5-day or 8-day regimen or pulsatile weekly (68,69). No study to date has compared these various protocols with regard to success. An optimal regimen should maximize the response rate while minimizing morbidity and cost.

An important phase III randomized trial examining *MTX* and *ActD* in the treatment of low-risk GTN was published by the Gynecologic Oncology Group (GOG) (70). Two hundred sixteen patients were randomized to receive either biweekly *ActD* 1.25 mg/m^2 IV bolus or weekly *MTX* 30 mg/m^2 intramuscular (IM). The remission rate was 58% in the *MTX* arm and 73% in the *ActD* arm. These results suggest that *ActD* is superior to the weekly *MTX* regimen in treating low-risk GTN. Before recommending pulse *ActD* as the primary modality in the treatment of patients with low-risk GTN, it is important to be aware of the potential for significant toxicity of this regimen compared to those receiving *MTX*. All patients with low-risk disease in this study ultimately achieved remission, regardless of their initial response. Regarding the true comparative effectiveness of these agents, it would be prudent to compare the biweekly *ActD*

regimen to the more commonly used 5-day or 8-day *MTX* regimens, which offer a high initial remission rate with minimal toxicity. The GOG attempted to repeat a randomized trial using these regimens but the trial was closed early as a result of lack of accrual. A 2016 meta-analysis of seven randomized controlled trials indicated that substantial heterogeneity made it difficult to be confident which was the preferred single agent (67).

The administration of *methotrexate* with folinic acid (*MTX*-FA) in GTN to limit systemic toxicity was first reported in 1964 (71). It has been confirmed that *MTX*-FA is effective and safe in the management of GTN.

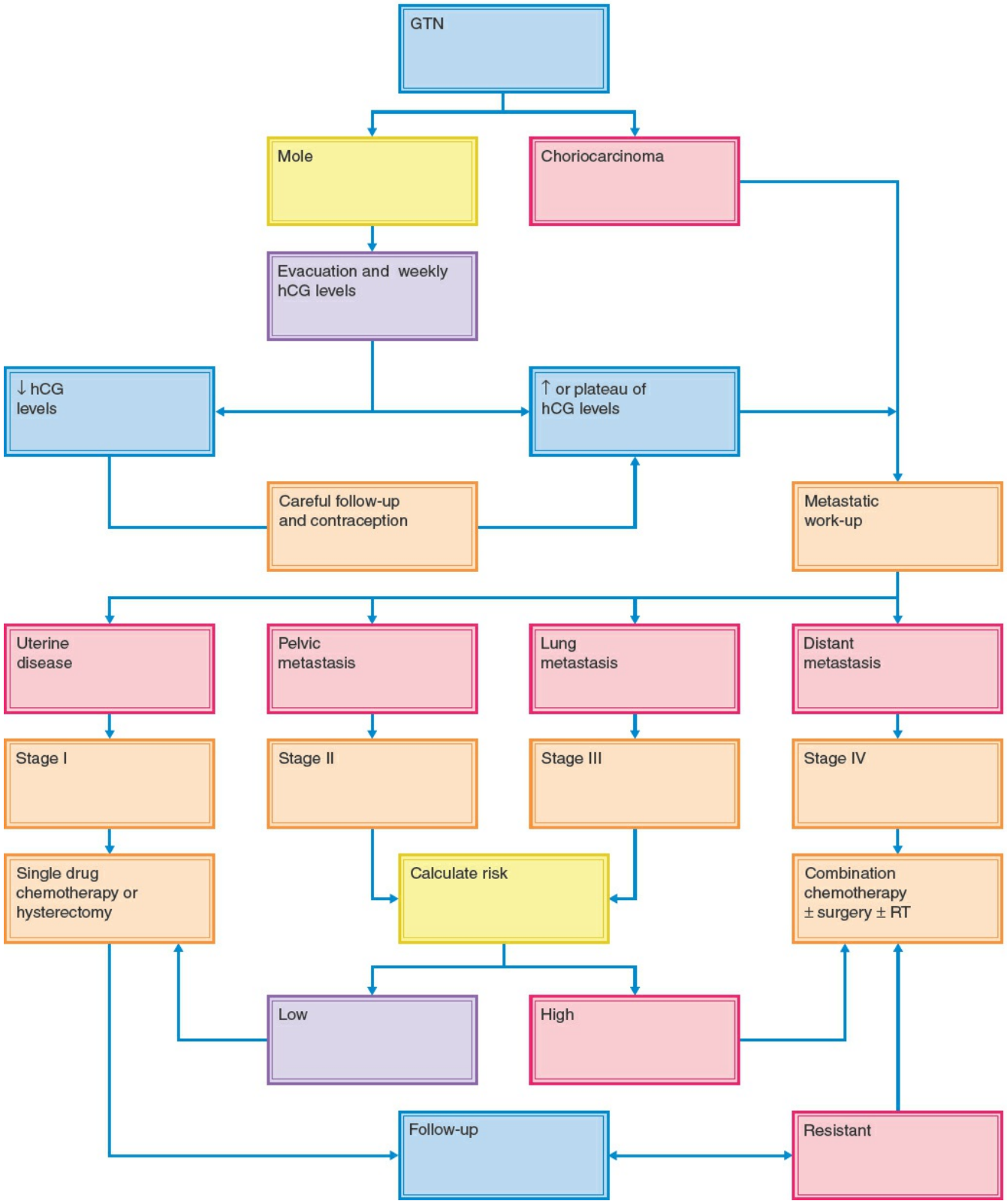


FIGURE 41-7 Management of gestational trophoblastic tumor. GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; RT, radiotherapy. (From **Berkowitz RS, Goldstein DP.** Gestational trophoblastic disease. In: Berek JS, Hacker NF. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer; 2015;642.)

An evaluation of 185 patients treated with 8-day *MTX*-FA revealed that complete remission was achieved in 162 patients (87.6%); of these patients, 132 (81.5%) required only one course of *MTX*-FA to attain remission (72). *MTX*-FA induced remission in 147 of 163 patients (90.2%) with stage-I GTN and in 15 of 22 patients (68.2%) with low-risk stages II and III GTN. **[5] Resistance to therapy was more common in patients with choriocarcinoma, metastasis, and pretreatment serum hCG levels higher than 50,000 mIU/mL.** After treatment with MTX-FA, thrombocytopenia, granulocytopenia, and hepatotoxicity developed in 3 (1.6%), 11 (5.9%), and 26 (14.1%) patients, respectively. **[5] Thus, MTX-FA achieved an excellent therapeutic outcome with minimal toxicity and attained this goal with limited exposure to chemotherapy.**

Technique of Single-Agent Treatment

[5] Administration of single-agent chemotherapy (generally 8-day [6] MTX-FA) every 2 weeks until hCG is undetected and then three consolidation courses to reduce the risk of relapse is recommended (73,74). **Resistance to chemotherapy is diagnosed if the hCG level plateaus +/- 10% over the course of 2 weeks or re-elevates in at least one measurement of hCG level. If the patient is diagnosed as having resistance to the primary chemotherapy, treatment is promptly changed to the alternative single-agent regimen (generally ActD).**

Combination Chemotherapy

Triple Therapy

Prior to the introduction of *etoposide* in combination with *MTX, ActD, cyclophosphamide,* and *vincristine* (*EMA-CO*), triple therapy with *MTX, ActD,* and *cyclophosphamide* was the treatment of choice as initial therapy for patients with low-risk disease resistant to single-agent therapy and as primary therapy for high-risk patients. **Triple therapy is no longer indicated in patients with high-risk disease. It may be useful in selected patients with low-risk scores resistant to single agents.**

EMA-CO

Etoposide induces complete remission in 56 (95%) of 60 patients with nonmetastatic and low-risk metastatic GTN (75). **The use of *EMA-CO* induced an 83% remission rate in patients with metastasis and a high-risk score** (76). Another study confirmed that primary *EMA-CO* induced complete remission in 76% of the patients with metastatic GTN and a high-risk score (77). Another study reported that *EMA-CO* induced complete sustained remission in 87 (90.6%) of 96 patients with high-risk (score >6) GTN (78). Remission occurred with *EMA-CO* in 30 (86%) of 35 patients with brain metastasis (64).

[6] The *EMA-CO* regimen is well tolerated, and treatment seldom is suspended because of toxicity. The *EMA-CO* regimen is the preferred primary treatment in patients with metastasis and a high-risk prognostic score >6.

EMA-EP

[6] Patients resistant to *EMA-CO* can be treated successfully by substituting *etoposide* and *cisplatin* on day 8 (*EMA-EP*). *EMA-EP* induced remission alone or with surgery in 16 (76%) of 21 patients who were resistant to *EMA-CO* (79). The optimal combination drug protocol will most likely include *etoposide, MTX,* and *ActD* and perhaps other agents administered in the most dose-intensive manner.

Management of Refractory GTN

Efforts continue to identify new agents and regimens effective in treating patients who prove resistant to all standard chemotherapy regimens. A combination of *cisplatin, vinblastine,* and *bleomycin* (*PVB*) was used effectively in patients with drug-resistant tumor (80). Although *ifosfamide* and *paclitaxel* were used successfully, further studies are needed to define their potential role in either primary or second-line therapy (81,82). Wang et al. reported that a novel three-drug doublet regimen consisting of paclitaxel, etoposide, and cisplatin (TE/TP) induced response in seven patients (three complete, four partial) who were resistant to EMA-CO (83). Wan et al. demonstrated that *floxuridine* (*FUDR*)-containing regimens induced complete remission in all of 21 patients with drug-resistant GTN (84). Matsui et al. found that 5-*fluorouracil* (5-*FU*) in combination with *ActD* induced remission in 9 of 11 (82%) patients with drug resistance (85). **[6]** The potential role for autologous bone marrow transplantation or stem cell rescue in conjunction with ultra–high-dose chemotherapy has yet to be defined, although complete remissions were reported in patients with refractory GTN (86,87).

Duration of Therapy

[6] Patients who require combination chemotherapy must be treated intensively to attain remission. Combination chemotherapy should be given as often as toxicity permits until the patient achieves three consecutive normal hCG levels. After normal hCG levels are attained, at least three additional courses of chemotherapy are administered to reduce the risk of relapse.

False-Positive hCG Tests

The concept of false-positive hCG tests caused by heterophile antibodies is critical to remember when following patients with molar gestation or GTN. Some assay systems

used by commercial laboratories are particularly vulnerable to false-positive tests resulting from the presence of heterophilic antibodies in the test kits they were using (88). For the most part this problem was corrected by adding blocking antibodies to the test systems. Since the hCG molecules in GTN are significantly more degraded or heterogeneous than in normal pregnancy, with higher proportions of free β-hCG, nicked hCG, and β-core fragments, it is important to use an assay that detects intact hCG and its metabolites and fragments in order to accurately assess the tumor burden (89–91). Cross-reactivity with luteinizing hormone (LH) can cause confusion when dealing with women in the perimenopausal age group whose hCG level may plateau above assay, even when there is no longer active tumor. The pituitary normally produces low hCG levels which may increase into the measurable range when chemotherapy induces ovarian failure. The use of hormone suppression will suppress LH and pituitary hCG and prevent unnecessary treatment. False-positive hCG tests caused by heterophile agglutinins or LH release may cause confusion in the diagnosis of early pregnancy, ectopic pregnancy, and the so-called phantom choriocarcinoma. When there is concern about the possibility of a false-positive serum hCG test, a urine sample should be tested, because patients with phantom hCG generally have no measurable hCG in a parallel urine sample.

Persistent Low-Level "Real" hCG

Some patients with molar pregnancy and GTN have persistent (weeks to months) very low levels of real hCG (usually <500 mIU/mL). In these women, extensive radiologic and clinical evaluations fail to reveal any lesions, and chemotherapy is usually not effective. This condition of "real" low-level hCG, where hCG is not hyperglycosylated, is called "quiescent GTN." These patients should be managed with careful follow-up, because 6% to 10% ultimately will relapse into active disease and rising hCG levels. The risk of relapse to active disease is correlated with the amount of hyperglycosylated hCG. If relapse does occur, chemotherapy usually proves effective (92).

Subsequent Pregnancies

Pregnancies After Uncomplicated Hydatidiform Mole

[7] Patients with hydatidiform moles can anticipate normal reproduction in the future (93). At the NETDC from 1965 until 2014, patients with uncomplicated complete mole had 1,388 subsequent pregnancies that resulted in 949 term live births (68.4%), 103 premature deliveries (7.4%), 11 ectopic pregnancies (0.8%), 7 stillbirths (0.5%), and 20 repeat molar pregnancies (1.4%). First- and second-trimester spontaneous abortions occurred in 256 (18.4%) pregnancies. Major and minor congenital malformations were detected in 40 infants (3.8%).

Although data regarding pregnancies after a partial mole are limited (357 subsequent pregnancies), the information is reassuring (93). [7] **Patients with complete or partial moles should be reassured that they are generally at no increased risk of complications in later gestations.**

[7] **When a patient has had a molar pregnancy, either partial or complete, she should be informed of the increased risk of having a molar gestation in subsequent conceptions. After one molar pregnancy, the risk of having molar disease in a future gestation is about 1% to 1.5%.** Of 37 patients with at least two documented molar pregnancies, every possible combination of repeat molar pregnancy was observed. After two molar gestations, these 37 patients had 40 later conceptions resulting in 25 (62.5%) term deliveries, 7 (17.5%) moles (6 complete, 1 partial), 3 spontaneous abortions, 3 therapeutic abortions, 1 intrauterine fetal death, and 1 ectopic pregnancy. In 6 patients, the medical records indicated that the patient had a different partner at the time of different molar pregnancies (93).

[7] **For any subsequent pregnancy, it seems prudent to undertake the following approach:**

1. **Perform pelvic ultrasonographic examination during the first trimester to confirm normal gestational development.**
2. **Obtain an hCG measurement 6 weeks after completion of the pregnancy to exclude occult trophoblastic neoplasia.**

Pregnancies After GTN

[7] **Patients with GTN who are treated successfully with chemotherapy can expect normal reproduction in the future.** Patients who were treated with chemotherapy at the NETDC from 1965 to 2014 had 667 subsequent pregnancies that resulted in 446 term live births (66.9%), 44 preterm deliveries (6.6%), 7 ectopic pregnancies (1.0%), 10 stillbirths (1.5%), and 9 repeat molar pregnancies (1.3%) (93). First- and second-trimester spontaneous abortions occurred in 123 (18.4%) pregnancies. Major and minor congenital malformations were detected in 12 infants (2.4%). The frequency of congenital anomalies is not increased, although chemotherapeutic agents have teratogenic and mutagenic potential.

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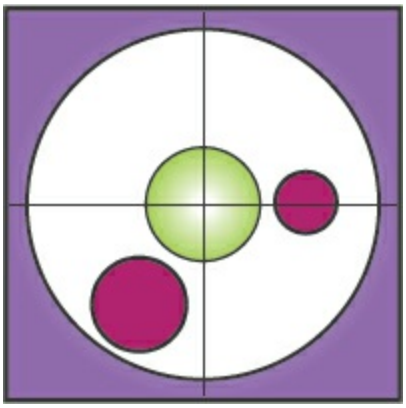
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CHAPTER 42

Breast Cancer



Carlie K. Thompson, JoAnna L. Hunter-Squires, Armando E. Giuliano

Carcinogenesis
Breast Cancer Risk Factors
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- Family History
- Reproductive and Hormonal Factors
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- Breast Cancer Screening
- Physical Examination

Pathology
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- Staging Workup
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- Skin-Sparing Mastectomy
- Nipple-Sparing Mastectomy
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- Breast Conservation Therapy With or Without Radiation Therapy
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- Adjuvant Systemic Therapy

Choice of Regimen
Neoadjuvant Systemic Therapy
Hormonal Therapy
HER2-Targeted Therapy
Systemic Therapy for Metastatic Breast Cancer
Special Breast Cancers
Paget Disease
Inflammatory Breast Cancer
Breast Cancer in Pregnancy

KEY POINTS

1 Breast cancer accounts for 30% of cancers in women. The risk of breast cancer increases with age, a personal or family history of breast cancer, hormone exposure, and breast density.

2 Breast cancer screening modalities include clinical breast examination and imaging.

3 Breast cancer may be either *in situ* or invasive. *In situ* and invasive cancers should be assessed for estrogen and progesterone receptor expression, and invasive cancers should be assessed for the overexpression of human epidermal growth factor 2 receptors (HER2).

4 The combination of segmental mastectomy, axillary staging, and postoperative radiation therapy has the same overall survival compared to mastectomy with axillary staging for stage I and II breast cancer.

5 Sentinel lymph node dissection alone can replace axillary lymph node dissection if the patient is having breast-conserving therapy with adjuvant radiation and the sentinel lymph node is found to be tumor free or there are only one or two lymph nodes positive for malignancy without extracapsular extension.

6 Axillary lymph node status, tumor markers, and tumor genomic analysis are the most important prognostic factors for breast cancer.

7 Cytotoxic chemotherapy, hormone therapy, and targeted agents are used for the adjuvant and neoadjuvant treatment of breast cancer. These treatments decrease locoregional recurrence and improve survival.

[1] Breast cancer accounts for approximately 30% of all new cancers in women and is second only to lung cancer as the leading cause of cancer deaths among women. Breast cancer has the highest incidence of all cancers. According to statistics from the American Cancer Society, over 252,000 new cases of breast cancer will be diagnosed in women in 2017, with more than 40,000 women succumbing to the disease during the same period (1). During the past 50 years, the incidence of breast cancer in the United States increased significantly and then leveled off in the last decade. Some, but not all, of this increase is felt to be related to the diagnosis of indolent cancers that may have remained asymptomatic and undetected for the duration of a woman's life in the pre-screening era. The minor increase in breast cancer incidence during the last 10 years can be attributed almost entirely to cancers diagnosed in non-white women. The breast cancer mortality rate has declined since 1990.

CARCINOGENESIS

The doubling time of breast cancer ranges from several weeks for rapidly growing tumors to months or years for slowly growing lesions. If the doubling time of a breast tumor was constant and a tumor originated from one cell, a doubling time of 100 days would result in a 1-cm tumor in about 8 years **(Fig. 42-1)** (2). During the preclinical phase, tumor cells may be circulating throughout the body. **Because of the long preclinical tumor growth phase and the tendency of infiltrating lesions to metastasize early, many clinicians view breast cancer as a systemic disease at the time of diagnosis.** Although cancer cells may be released from the tumor before diagnosis, variations in the tumor's ability to colonize distant tissues and the host's immune response may inhibit dissemination of the disease. A tumor's ability to metastasize to the regional lymph nodes may not be indicative of the tumor's ability to metastasize to distant sites, and patients may be curable even in the presence of palpable axillary disease. A pessimistic attitude that a breast cancer that has spread to the regional lymph nodes is incurable is unwarranted.

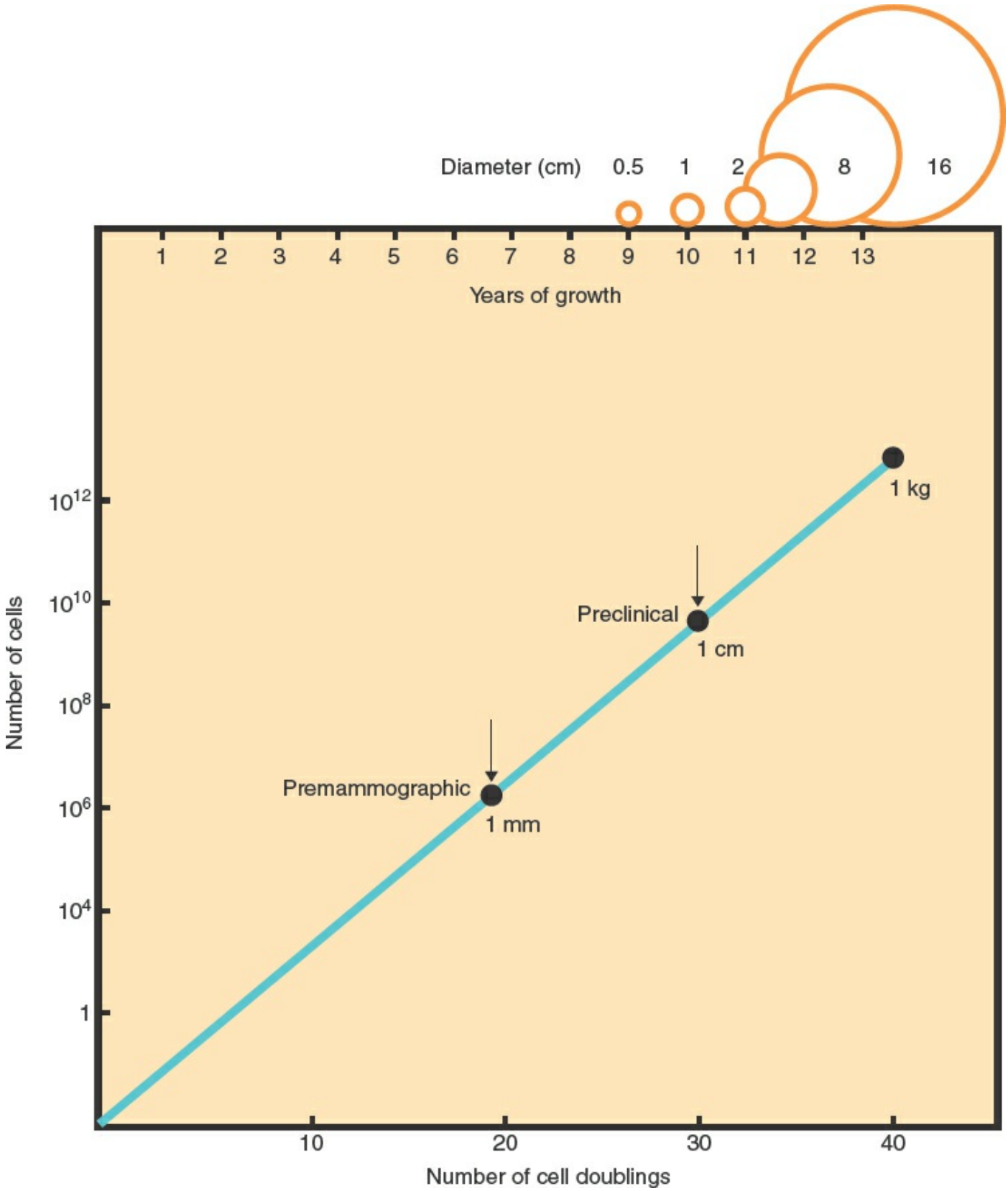


FIGURE 42-1 Growth rate of breast cancer indicating long preclinical phase. (From **Gullino PM**. Natural history of breast cancer: progression from hyperplasia to neoplasia as predicted by angiogenesis. Cancer 1977;39:2699.)

BREAST CANCER RISK FACTORS

Age

[1] The risk of developing breast cancer increases as a woman's age increases. The risk of developing breast cancer is less than 2% in women younger than 50 and increases steadily to almost 7% in women older than 70. The lifetime risk of developing breast cancer for women in the United States is 12.4%, or one in eight women (1).

Family History

[1] A family history of breast cancer is a well-established risk factor for the development of the disease. Although any family history of breast cancer increases a woman's overall relative risk, women with a first-degree relative who has been affected by the disease are at approximately a twofold increased risk of developing breast cancer compared to the general population (3). An individual's risk is not significantly increased if the affected relative was diagnosed postmenopausally (4). **[1] Other familial risk factors include multiple affected family members, early onset of disease in those family members, bilateral breast cancer, and male breast cancer.**

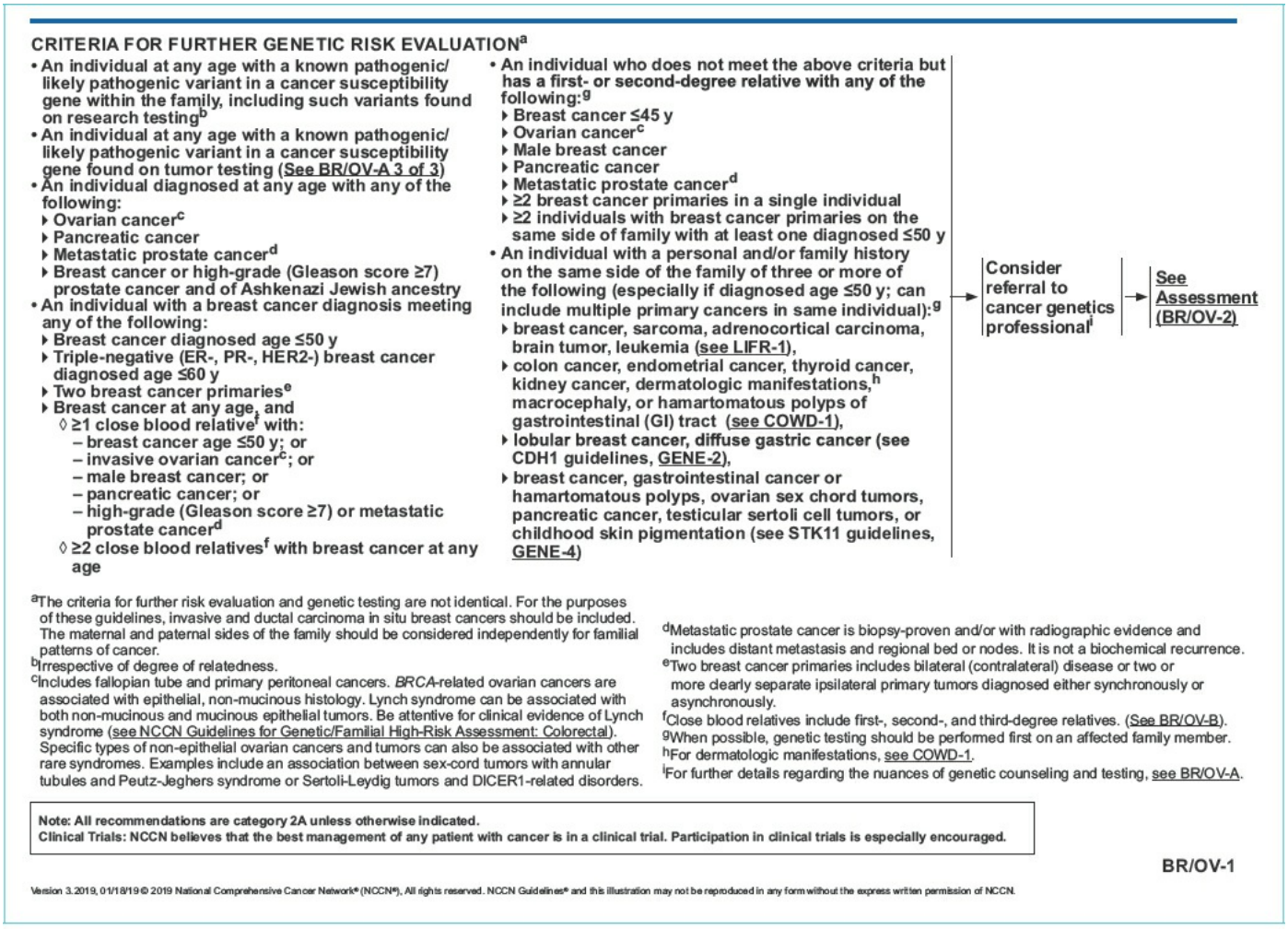
[1] Approximately 5% to 10% of breast cancers have a known inherited basis associated with mutations in high- and low-penetrance genes. The most well-studied mutations are the *BRCA1* (chromosome 17q21) and *BRCA2* (chromosome 13q12-13) gene deletions. Carriers of these germline mutations have a cumulative risk of breast cancer by age 70 of 57% and 49% for *BRCA1* and *BRCA2*, respectively. The *BRCA1* mutation is associated with an increased risk of ovarian and prostate cancer, whereas the *BRCA2* mutation is associated with an increased risk of ovarian, male breast, prostate, pancreatic, gastric and colon cancers, and melanoma. Both mutations are rare in the general population (0.1%) and are more commonly identified in those of Ashkenazi Jewish descent (1% to 2.3%) (5).

Genetic testing is available and should be considered if there is a high likelihood that the results will be positive and used to influence decisions regarding the clinical management of the care of the patient and her family. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines In Oncology (NCCN Guidelines®) regarding who should be referred for a breast and/or ovarian genetic assessment are listed in Table 42-1. If a patient meets the criteria for genetic testing, she should be referred to a cancer genetics specialist for consultation.

Genetic testing has become increasingly important given the evidence that prophylactic mastectomy and oophorectomy prevent new cancers from occurring and may prolong survival. A prospective multicenter cohort study of 2,482 women with *BRCA1* and *BRCA2* mutations between 1974 and 2008 showed prophylactic mastectomy was associated with a decreased risk of breast cancer. Risk-reducing salpingo-

oophorectomy was associated with decreased risk of ovarian cancer, first diagnosis of breast cancer, all-cause mortality, breast cancer–specific mortality, and ovarian cancer–specific mortality (6).

Table 42-1 NCCN Guidelines® for Breast and Ovarian Genetic/Familial Risk Assessment V.3.2019



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Reproductive and Hormonal Factors

[1] The risk of breast cancer increases with the length of a woman's reproductive phase (7). Although early menarche was reported among breast cancer patients, early menopause appears to protect against the development of the disease, with artificial menopause from oophorectomy lowering the risk more than early natural menopause (8). There is no clear association between the risk of breast cancer and menstrual irregularity or the duration of menses. Lactation seems to only affect the incidence of breast cancer in a subset of patients (those lactating for greater than 12 cumulative months) and a subset of cancers (premenopausal). Women who were never pregnant

have a higher risk of breast cancer than those who are multiparous. Women who give birth to their first child later in life have a higher incidence of breast cancer than do younger primigravida women (9).

[1] **Hormonal contraceptive use is associated with a small but statistically significant increased risk of developing breast cancer.** Historic data, from a well-controlled study by the Centers for Disease Control and Prevention, suggested that oral contraceptive use did not increase the risk of breast cancer, regardless of duration of use, family history, or coexistence of benign breast disease (10). Yet a contemporary prospective cohort study that included almost 1.8 million women concludes that women using hormonal contraception for longer than a year are at a 20% increased risk of developing breast cancer (11).

The relationship between the use of postmenopausal hormone replacement therapy and the development of breast cancer has been studied extensively. [1] **Randomized controlled trials have confirmed the finding that the use of combination estrogen plus progesterone hormone replacement increases a woman's risk of breast cancer, but the use of unopposed estrogen does not appear to carry the same risk** (12,13). Longer durations of use (>15 years plus current use) of estrogen alone have been shown to be associated with increased risk (14).

Personal History of Cancer

[1] **In women with a history of breast cancer, the absolute risk of developing a contralateral breast cancer exceeds that of the general population and was approximately 0.6% per year in historical series** (15). In the era of modern systemic adjuvant therapies, this risk is lower (16). Invasive lobular carcinoma (ILC) has a higher incidence of bilaterality than does ductal carcinoma. A history of endometrial, ovarian, or colon cancer is associated with an increased risk of subsequent breast cancer, as is a history of radiation therapy for Hodgkin lymphoma, even if the patient is *BRCA1* and *BRCA2* negative.

DIAGNOSIS

Breast Cancer Screening

[2] **The breast cancer screening modalities of clinical breast examination and breast imaging are complementary. Approximately 10% to 50% of cancers detected mammographically are not palpable, whereas physical examination detects 10% to 20% of cancers not seen radiographically** (17). The purpose of screening is to detect tumors early in an attempt to avoid breast cancer–related morbidity and mortality. Although many randomized controlled trials and systemic reviews comparing mammography screening to no screening have shown a protective

effect among women aged 40 to 69, a long-term follow-up study has raised questions regarding overdiagnosis and the possibility of mammography having less beneficial impact as systemic therapies improve (18). The benefit of breast cancer screening in women aged 40 to 49 is controversial, which has resulted in differing recommendations from medical societies for this age group. However, **[2] most expert groups recommend shared decision making regarding screening in the 40 to 49 age group, annual or biannual screening of women aged 50 to 74, and annual or biannual screening of women over 75 if their life expectancy is at least 10 years.**

Monthly breast self-examination (BSE) is no longer recommended because there is little evidence to show that BSE is superior to heightened breast awareness such that any new symptoms related to the breast in daily activities would be reported promptly when noticed. BSE has not been shown to improve survival. Women should be informed about the benefits and limitations of monthly BSE, including the risk of a false-positive result. Multiple other screening modalities have been suggested, including ultrasonography, computed tomography, sestamibi scan, positron emission tomography (PET), and serum tumor markers, but these have ultimately been found to be ineffective.

[2] The ACS recommends annual screening mammography and annual breast magnetic resonance imaging (MRI) starting at age 30 for women with known *BRCA* or other high-risk genetic mutations, women who are untested with a first-degree relative with the *BRCA* mutation, women with an approximately 20% to 25% or greater lifetime risk of breast cancer, and women who have been treated with radiation for Hodgkin lymphoma (18). Although breast MRI may prove to be advantageous for other women with an elevated risk of breast cancer, there is insufficient evidence to recommend MRI screening for women with less than 20% lifetime risk (19). Some studies have reported the presence of residual gadolinium in the brains of adult and pediatric patients who have undergone multiple gadolinium-based contrast-enhanced MRIs. The clinical significance of this finding is unclear and is under active investigation (20).

Physical Examination

[2] Masses are easier to palpate in older women with fatty breasts than in younger women with dense, nodular breasts. An area of thickening amid normal nodularity may be the only clue to an underlying malignancy. Skin dimpling, nipple retraction or skin erosion, while obvious, are later-stage disease signs. Breast cancer commonly arises in the upper outer quadrant, where there is proportionally more breast tissue. Metastatic breast cancer is found as an axillary mass without an obvious breast primary in less than 1% of cases.

[2] When a breast mass or abnormality is identified, the presence of a carcinoma must be considered, and biopsy should be performed to establish a tissue diagnosis.

About 30% to 40% of lesions clinically believed to be malignant will be benign on histologic examination (21). Conversely, 25% of clinically benign-appearing lesions will be malignant when biopsied (22). Algorithms for the evaluation of breast masses in pre- and postmenopausal women are presented in Chapter 19.

PATHOLOGY

Breast cancer may arise in the intermediate-size ducts, terminal ducts, or lobules. The diagnosis of ductal or lobular carcinoma is based on histologic appearance rather than the site of origin. The cancer may be either *in situ* or invasive.

Ductal Carcinoma *In Situ*

[3] By definition, *in situ* disease does not invade beyond the basement membrane and, therefore, lacks the ability to spread.

[3] The incidence of diagnosis of ductal carcinoma *in situ* (DCIS) has increased dramatically since the introduction of screening mammography. **The entity accounts for approximately 20% of breast cancers diagnosed in the United States** (1). The risk of DCIS increases with age, and although it may rarely manifest as a palpable mass, it is usually detected mammographically as a cluster of suspicious calcifications.

The goal of the treatment of DCIS is to prevent the development of invasive cancer. Thirty percent to 50% of patients with DCIS will develop an IDC within the same breast if treated by biopsy alone (23). **The standard treatment of DCIS includes resection to negative margins via segmental mastectomy followed by radiation or mastectomy. Endocrine therapy should be considered.**

It is being increasingly recognized that DCIS encompasses a spectrum of diseases that spans from indolent lesions, which will never progress to invasive cancer, to aggressive lesions that will progress quickly, and many experts believe that treating low-risk DCIS with surgery and radiation constitutes overtreatment. This notion is supported by evidence that while adjuvant radiation therapy decreases the risk of a patient experiencing an ipsilateral invasive recurrence, it is not associated with improved breast cancer–specific mortality (24). This notion is the basis of the COMET (Comparison of Operative to Monitoring and Endocrine Therapy for low-risk DCIS) study, which is a randomized clinical trial that will compare standard treatment to active surveillance for low-risk DCIS.

[3] Axillary metastases occur in fewer than 5% of patients diagnosed with DCIS on core needle biopsy, making routine axillary staging unnecessary. American Society of Clinical Oncology (ASCO) guidelines regarding the use of sentinel lymph node biopsy (SLNB) for DCIS recommend consideration of SLNB in patients undergoing a mastectomy, in patients undergoing breast-conserving surgery (BCS) for a

tumor in a location that may preclude future node sampling, in cases of DCIS diagnosed as a mass on imaging or clinical exam, or in cases of large-volume DCIS where the risk of finding invasive cancer at pathologic analysis is higher (25).

Invasive Carcinoma

[3] **Invasive ductal carcinoma (IDC) accounts for roughly 80% of all invasive tumors, with the final 20% split between ILC and special variants of infiltrating ductal carcinoma** (26). Mammographically, invasive ductal cancers (IDCs) are characterized by a stellate density or microcalcifications. Macroscopically, invasion of the surrounding stroma and fat with a fibrotic, desmoplastic reaction surrounding the invasive carcinoma generally is present. Microscopically, IDC is characterized by cords and nests of cells with varying amounts of gland formation.

ILC accounts for 5% to 10% of invasive carcinomas. [3] **ILCs more frequently arise in older women, are bilateral or multicentric, and have more favorable clinical features (lower grade, ER-positivity)** (27). Some ILCs have a macroscopic appearance similar to that of IDC, but more commonly no mass is present. Microscopically, ILC is characterized by small cells that insidiously infiltrate the breast and adipose tissue in a single-file pattern. This pattern of infiltration often results in a microscopic size that is greater than anticipated. It has been proposed that ILCs have a more favorable prognosis than IDCs and tend to metastasize later than IDC (28). If ILCs do metastasize, they often spread to unusual locations, such as the peritoneum, meninges, and gastrointestinal tract (29).

[3] **Special types of infiltrating ductal carcinoma are uncommon and typically account for approximately 10% of all invasive cancers. Medullary carcinoma,** which accounts for 5% to 8% of breast carcinomas, arises from larger ducts within the breast and has a dense lymphocytic infiltrate. The tumor **appears to be slower growing and less aggressive than other forms of carcinoma.** Even when axillary disease is present, the prognosis for patients with medullary carcinoma is better than that of other variants of invasive ductal carcinoma. Mucinous (colloid) carcinoma accounts for 5% of all breast cancers. Grossly, areas of the tumor may appear mucinous or gelatinous, whereas microscopically they are relatively acellular. Infiltrating comedocarcinoma accounts for less than 1% of all breast malignancies and is an invasive cancer characterized by foci of necrosis that exude a comedonecrosis-like substance when biopsied. Usually, comedocarcinomas are *in situ* malignancies. Papillary carcinoma is predominantly a noninvasive ductal carcinoma; when invasive components are present, it should be specified as invasive papillary carcinoma. [3] **Tubular carcinoma, a well-differentiated breast cancer that accounts for 1% to 2% of all malignant breast neoplasms, rarely metastasizes to axillary lymph nodes and tends to have a better prognosis than infiltrating ductal carcinoma.** Adenoid cystic carcinomas are

extremely rare breast tumors that histologically are similar to those seen in the salivary glands. They are well-differentiated cancers that are slow to metastasize.

Receptor Testing

[3] All breast cancer tumors should be evaluated for the expression of estrogen and progesterone receptors and for the overexpression of human epidermal growth factor 2 receptors (HER2) as this information guides clinical decision making and facilitates prognostication. Hormone receptor positivity is determined via immunohistochemical testing and is defined by the presence of estrogen or progesterone receptors on at least 1% of tumor cells. HER2 positivity is characterized by immunohistochemical staining of 3+ of the tumor cells or by a HER2/chromosome enumeration probe 17 (CEP17) fluorescent in situ hybridization (FISH) amplification ratio of ≥2.

[3] Breast cancer can be clinically divided into subtypes based on these receptors. Approximately 80% of tumors are hormone receptor positive, 23% overexpress HER2, and 13% are triple negative (estrogen receptor, progesterone receptor, and HER2 negative) (30).

Staging

The eighth edition of the *American Joint Committee on Cancer (AJCC) Staging Manual* was published in 2017 and effective since January of 2018. **[3] In addition to the primary tumor, lymph node, and metastasis (TNM) classification, the eighth edition of the staging manual incorporates biologic factors, such as tumor grade, hormone receptor status, HER2 status, and gene expression profiles into the staging system for breast cancer** (31).

Tumor stage and nodal status continue to be important predictors of outcomes. In a SEER analysis that included over 302,000 patients, survival was 100% in patients with tumors 0.1 to 0.9 cm; 91.8% for tumors 1.0 to 1.9 cm; 75.7% for tumors 2.0 to 2.9 cm; 61.3% for tumors 3.0 to 3.9 cm; 54.2% for tumors 4.0 to 4.9 cm; and 45.7% for tumors 5.0 to 9.9 cm (32). Even small tumors have a significantly worse prognosis if they are associated with positive lymph nodes. In a large series, 5-year survival worsened as number of positive lymph nodes increased (33). The number of positive lymph nodes involved and the presence of extracapsular invasion are important indicators of poor prognosis.

Histologic grade appears to predict overall survival. Patients with well-differentiated tumors tend to have more favorable outcomes than those with poorly differentiated ones. In a British study of 1,168 women, histologic grade, along with tumor size and lymph node status, was an independent predictor of overall survival at

10 years (34).

Hormone receptor status is an important predictor of long-term prognosis and response to endocrine therapy. Several studies have demonstrated that patients with positive estrogen and progesterone receptor (ER and PR) status have improved overall survival (35,36). Receptor status should be known when determining the need for and choice of adjuvant therapy. Additionally, **[3] an assay for HER2 overexpression and/or amplification should be routinely performed. The presence of HER2 amplification predicts sensitivity to several classes of chemotherapy and survival benefit from targeted agents, such as *trastuzumab* and *pertuzumab*** (37–39).

Several multigene assays have been developed and validated and are becoming increasingly important tools for prognosticating and predicting response to therapy. The 21-gene assay (Oncotype DX) and 70-gene signature (MammaPrint) are two of the more commonly used gene expression assays.

Oncotype DX (Genomic Health) evaluates the expression of 21 genes and is primarily validated in hormone receptor– positive, HER2-negative, node-negative breast cancers. Test results are reported as a Recurrence Score (RS). The test categorizes a patient's risk of breast cancer recurrence into low (RS 0 to 18), intermediate (RS 19 to 31), or high (RS 32 to 100) and also predicts benefit from chemotherapy. In the Trial Assigning IndividuaLized Options for Treatment (Rx) (TAILORx), the Oncotype DX test was used in an attempt to better define which patients with early-stage, ER+ breast cancer benefit from chemotherapy and which patients could be spared chemotherapy. The study included over 10,200 women. In TAILORx, women with Recurrence Scores of 0 to 10 were assigned to treatment with endocrine therapy alone and women with scores greater than 25 were assigned to treatment with endocrine therapy plus chemotherapy. Women with midrange scores of 11 to 25 were randomly assigned to receive either endocrine therapy plus chemotherapy or endocrine therapy alone. In 2015, preliminary prospective evidence from TAILORx demonstrated that women with a low risk of recurrence (RS 0 to 10) did well with endocrine therapy alone and could be spared chemotherapy (40). Then in 2018, final results from the TAILORx study revealed that endocrine therapy was not inferior to endocrine therapy plus chemotherapy for women with midrange scores of 11 to 25, although a degree of benefit of chemotherapy was found in some women 50 years of age or younger. Together, these results suggest that chemotherapy can be safely avoided in about 70% of the women with hormone receptor–positive, HER2-negative, node-negative breast cancers who would have received chemotherapy based on traditional criteria (41).

MammaPrint (Agendia) is a 70-gene signature assay that classifies patients into good and poor prognostic groups. This test may be used for patients with hormone receptor–negative or hormone receptor–positive breast cancer and patients with 0 to 3 positive lymph nodes (42). The Breast Cancer Index is another commonly used prognostic assay

that has been validated as an accurate predictor of endocrine therapy responsiveness in patients with estrogen receptor–positive breast cancer.

MANAGEMENT OF BREAST CANCER

Breast cancer should be viewed as a two-component disease involving the breast and the body as a whole. Although the primary breast tumor and issues of local control must be managed, the possibility of systemic metastases with life-threatening consequences should not be overlooked.

Staging Workup

Further preoperative workup for systemic disease should be obtained for patients with signs or symptoms concerning for metastatic disease or patients with locally advanced breast cancer. For patients with symptoms concerning for systemic spread of disease, the appropriate imaging should be obtained (i.e., a bone scan for a patient complaining of localized bone pain concerning for a skeletal metastasis). Only patients who are stage IIIA or higher should undergo a whole-body PET-CT or a bone scan and a CT scan of the chest, abdomen, and pelvis. These recommendations follow the NCCN guidelines (43), and are based on studies that have shown that in the majority of patients with newly diagnosed breast cancer, an extensive preoperative workup is unnecessary (44).

Radical Mastectomy

[4] **Traditionally, the treatment of breast cancer has been surgical and the type of procedure was a controversial and psychologically complex issue.** The selection of surgical treatment remains an emotionally charged, and highly politicized, issue for many patients. During the 19th century, surgical treatment of breast cancer was haphazard, varying from local excision alone to total mastectomy. The radical mastectomy was based on the principle that breast carcinoma was a locally infiltrative process that spread in a radial fashion, spiraling out from breast, to nodes, to distant sites (45). **Radical mastectomy removes the entire breast, the underlying pectoral muscles, and the contiguous axillary lymph nodes in continuity (Fig. 42-2A)** (46). A report of 51 years of experience with radical mastectomy, which included 1,036 patients with a follow-up of 47 years, is unequaled in evaluating any other single method of treating breast cancer (47).

During the 20th century, extensions and modifications of the radical mastectomy were devised that involved removal of more local and regional tissue. At one time, supraclavicular, mediastinal, and internal mammary lymph node dissections were routinely performed (48).


A


B

FIGURE 42-2 Appearance of breast after radical mastectomy (**A**) versus modified mastectomy (**B**). (From **Giuliano AE, Dang CM**. Breast disease. In: Berek JS, Hacker NF, eds. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2014:674.)

An en bloc internal mammary lymph node dissection was added to the standard radical mastectomy in the 1960s. This technique became popular and is the operation commonly referred to as the *extended radical mastectomy* (49). Extended radical mastectomy did not enhance overall survival rates, because only 3% to 5% of patients with negative axillary nodes will have involvement of internal mammary nodes (50). Locally destructive surgery is not justified, based on an understanding of the biologic behavior of breast cancer, and a radical mastectomy is no longer an indicated procedure, except in the most unusual circumstances with extensive pectoralis involvement by the breast tumor.

Modified Radical Mastectomy

[4] In contrast to radical mastectomy, modified radical mastectomy preserves the pectoralis major muscle (Fig. 42-2B) (51,52). The breast is removed in a manner similar to that of radical mastectomy, but neither the axillary lymph node dissection nor the skin excision is as extensive. Consequently, there is no need for skin grafting. There are no differences in survival rates between radical and modified radical mastectomy, but the latter procedure has a better functional outcome and a superior cosmetic result (53). Modified radical mastectomy has replaced radical mastectomy in the United States and is an alternative to BCS for some patients.

Total Mastectomy

The movement away from radical surgery for every patient with breast cancer began after dissemination of the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial, which randomized women to radical mastectomy, total mastectomy with node field irradiation, or total mastectomy with no axillary surgery and delayed axillary dissection if clinically indicated. **After 25 years of follow-up, there are no survival differences between the three arms** (54).

[4] Total mastectomy involves removal of the entire breast, nipple, and areolar complex without resection of the underlying muscles or intentional excision of axillary lymph nodes. Low-lying lymph nodes in the upper outer portion of the breast and low axilla often are excised. Previously, regional recurrence would occur in at least 15% to 20% of patients treated with total mastectomy alone. With the addition of SLNB, which selects patients who are lymph node negative, local recurrence rates should be low in patients who undergo total mastectomy and have node-negative disease compared to those patients with unknown axillary status.

Skin-Sparing Mastectomy

[4] Patients who wish to have immediate reconstruction may wish to undergo a mastectomy that preserves the skin envelope of the breast. A skin-sparing mastectomy (SSM) removes the breast tissue and the nipple–areolar complex and is followed by immediate breast reconstruction. Initially, there were concerns that immediate reconstruction might complicate surveillance for local recurrence, but this has not been shown to be the case (55).

Nipple-Sparing Mastectomy

[4] Removal of all breast parenchyma with preservation of the entire skin envelope, including the nipple–areolar complex, has become increasingly popular because of the improved cosmetic results. However, patient selection is key as involvement of the nipple–areolar complex is seen in 11.5% of cases (56). Despite this finding, many studies have now shown that nipple-sparing mastectomy (NSM) is an oncologically safe procedure in carefully selected patients. In a meta-analysis that included 5,594 women, there were no significant differences in overall survival, disease-free survival, or locoregional recurrence between NSM and SSM groups (57). Patients who have undergone NSM have been reported to have a better postreconstruction quality of life, specifically in the Satisfaction with Breasts and Satisfaction with Outcome domains of the BREAST-Q when compared to non–nipple-sparing mastectomies (58). For these reasons, NSM with immediate implant–based or autologous reconstruction is becoming a common procedure for women who need or desire a mastectomy.

Contralateral Prophylactic Mastectomy

Women may wish to undergo a contralateral prophylactic mastectomy (CPM) in order to reduce their risk of getting a contralateral breast cancer, to eliminate the need for breast cancer screening, or to achieve symmetry of reconstruction. **[4]** Although CPM significantly reduces the risk of cancer developing in the contralateral breast, there has been no demonstrated survival benefit associated with CPM in women who are not at particularly high risk of developing a second breast cancer (59,60).

Postmastectomy Radiation Therapy

Some patients treated with mastectomy benefit from adjuvant radiation therapy. McWhirter developed the concept of total mastectomy followed by radiation (61). Historical trials, both prospective randomized and historical control studies, have shown that **[7]** adjuvant radiation therapy improves local control but not overall survival (62–64). In a prospective randomized trial performed by NSABP, the roles of

postoperative radiation therapy and axillary treatment were examined further. Patients were randomly assigned to either total mastectomy, radical mastectomy, or total mastectomy with radiation therapy. Findings from this trial supported the notion that radiation therapy and axillary treatment improve local and regional control but have no effect on survival, and the 25-year follow-up confirmed these findings (65).

During the 1990s, randomized controlled studies showed that postmastectomy radiation therapy (PMRT) reduced the risk of local–regional failure by 20% and produced an absolute survival benefit of 10% at 10 years among women with stage II to III breast cancer, regardless of menopausal status (66,67). Subsequently, additional trials challenged the need for PMRT among women with only one to three involved axillary nodes and T_1 or T_2 primary tumors. These studies showed adequate local–regional control rates with mastectomy and chemotherapy alone (68–70). In a large meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) that included 1,300 women with one to three involved lymph nodes, PMRT was shown to reduce recurrence and breast cancer mortality in women with one to three positive nodes (71).

Breast Conservation Therapy With or Without Radiation Therapy

[4] Throughout the last quarter of the 20th century, a paradigm shift occurred in the surgical management of breast cancer. NSABP B-04 trial established the equivalency of radical versus total mastectomy with regard to overall survival. **Shortly after initiation of the B-04 trial, a number of studies were designed to evaluate the efficacy of breast conservation among women with early-stage breast cancers.** The Milan trial, a major prospective randomized trial that began accruing patients in 1973, compared treatment with either radical mastectomy or a combination of quadrantectomy, axillary lymph node dissection, and postoperative radiation therapy. In total, 701 clinically node-negative patients with non-centrally located, small tumors (<2 cm) ($T_1N_0M_0$) were enrolled. After 20 years of follow-up, there continues to be no statistically significant difference between the two groups in either local control or overall survival rates (72).



FIGURE 42-3 Appearance of breast after lumpectomy, axillary dissection, and radiation therapy. (From **Giuliano AE, Dang CM**. Breast disease. In: Berek JS, Hacker NF, eds. Berek & Hacker's Gynecologic Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2014:675.)

At nearly the same time, in the NSABP B-06 trial, patients with early breast cancer (stage I or stage II, T_1 or T_2, and N_0 or N_1) were randomized to modified radical mastectomy, segmental mastectomy (lumpectomy) and axillary lymph node dissection, or segmental mastectomy, axillary lymph node dissection, and postoperative radiation therapy. Unlike the quadrantectomy performed in the Milan study, segmental mastectomy consists of removing only the tumor and a small rim of normal surrounding tissue, yielding cosmetically superior results **(Fig. 42-3)**. A total of 1,843 women were enrolled, with the lowest local recurrence rate seen among patients treated with segmental mastectomy and postoperative radiation therapy. The addition of radiation improved the local control rate, but no significant differences in overall survival or disease-free survival rates were detected among the three treatment arms; there was a trend, however, in favor of patients who had received radiation. **This NSABP study, now [4] with a 20-year follow-up, established that the combination of segmental mastectomy (with negative surgical margins), axillary lymph node dissection, and**

postoperative radiation therapy is as effective as modified radical mastectomy for the management of patients with stage I and II breast cancer (73).

There has been considerable debate regarding the definition of a negative margin for BCS. [3] A multidisciplinary panel convened by the Society of Surgical Oncology and the American Society for Radiation Oncology recommended using "no ink on tumor" as the standard margin for patients with stage I and II invasive breast cancer treated with BCS followed by whole-breast irradiation (74). The recommendation was based on a meta-analysis of 33 studies, including 28,162 patients, that reported that a positive margin, defined as ink on tumor, was associated with a greater than twofold increase in ipsilateral breast tumor recurrence and that margins wider than "no ink on tumor" were not associated with a lower incidence of ipsilateral breast tumor recurrence (75). **A similar panel was convened and a meta-analysis was performed that resulted in the recommendation that the standard margin for DCIS should be 2 mm** (76,77).

[4] Many randomized studies have shown that the addition of whole-breast irradiation to BCS for early-stage breast cancer reduces the rate of local recurrence (78–80). **More important than local recurrence, it appears that the use of radiation therapy after BCS reduces the risk of death from breast cancer.** A meta-analysis from the EBCTCG of all of the randomized prospective trials comparing BCS or mastectomy with or without radiation reported a 4:1 ratio between avoiding local recurrence at 5 years and improving overall survival at 15 years. In 2011, an update to this meta-analysis was performed that included only women who had undergone BCS. The updated meta-analysis included 17 randomized trials and 10,801 women, and demonstrated that **[7] radiation therapy reduced the annual rate of failure (local or systemic) by about half and the annual rate of breast cancer death by one-sixth** (81).

Axillary Staging

[6] Although markers of tumor biology are becoming increasingly important in determining the optimal treatment and prognosis of breast cancer, the status of the axillary lymph nodes remains one of the most important prognostic indicators. Axillary lymphadenectomy traditionally was used to detect and quantify the extent of nodal metastasis. Before the introduction of sentinel lymph node dissection in the 1990s, axillary lymph node dissection was performed routinely on all patients with early breast cancer. **[5] Although axillary dissection is associated with a very low risk of regional recurrence (1% to 3%), the rate of acute complications is as high as 30%** (82). **Similarly, the risk of chronic lymphedema ranges from 6% to as high 30%** (83). Because only one-third of patients with a clinically negative axilla will have nodal

metastasis, one can infer that two-thirds of patients will be exposed to the morbidity of axillary lymph node dissection without proven benefit when performed routinely in the presence of invasive breast cancer (84).

In 1991, intraoperative lymphatic mapping and sentinel lymph node dissection were introduced to address these problems (85). [5] **The sentinel node is the lymph node that has the greatest potential to harbor metastasis if axillary disease is present. Numerous investigations have demonstrated that examination of the sentinel lymph nodes can accurately predict the status of the entire nodal basin with identification rates ranging from 90% to 99% and false-negative rates of less than 5% in most large studies.** In one study of 107 patients with T_1 and T_2 breast cancer who underwent sentinel lymph node dissection followed by axillary lymph node dissection, the sentinel node was successfully identified in 100 patients (93.5%). There were no false-negative results, and the sentinel node accurately predicted axillary status in all 100 patients (86).

[5] **Sentinel lymph node dissection is accurate at staging the axilla and has comparable long-term outcomes and less morbidity when compared to axillary lymph node dissection, as supported by numerous randomized controlled trials, including NSABP B-32, ALMANAC, and SNAC** (87–90). **In light of these findings, SLNB has become the preferred procedure for staging the axilla in clinically node-negative early breast cancer.** The standard of care for patients found to have a positive sentinel lymph node was complete axillary lymph node dissection until the Z0011 trial demonstrated that in patients with one or two positive sentinel lymph nodes, without extranodal extension of the metastasis, there was no statistically significant difference in overall survival between those randomized to complete axillary lymph node dissection and those randomized to SLNB alone (91). The 10-year results of the trial confirm this finding (92).

[5] **The use of SLNB after neoadjuvant chemotherapy (NAC) is controversial.** In women with a clinically negative axilla prior to NAC, SLNB performed at the time of breast tumor excision is believed to be safe. A meta-analysis that included 72 prospective and retrospective studies reported a sentinel node identification rate of almost 90% and a false-negative rate of 14.2% in this population (93). In women with a clinically positive axilla prior to NAC who convert to a clinically negative axilla during NAC, the ACOSOG Z1071 and SENTINA trials conclude that SLNB after NAC is not an adequate staging method for patients with positive lymph nodes prior to NAC (94,95). However, the studies suggest that the use of SLNB at the time of breast tumor excision under certain conditions (the use of blue dye and radioactive colloid tracer, obtaining ≥3 sentinel nodes) may yield acceptable false-negative rates.

SYSTEMIC THERAPY

Adjuvant Systemic Therapy

For many patients, local and regional control of breast cancer is achieved with a combination of surgery and radiation therapy. About 90% of patients will never experience an in-breast recurrence, but these [7] patients may develop metastatic disease. **The goal of adjuvant systemic therapy is to eliminate occult metastases and thus reduce the risk of local and distant recurrence.**

Adjuvant systemic therapy prolongs survival in selected breast cancer patients. In patients with favorable biology and a low risk of recurrence and subsequent death, such as those with small, node-negative cancers that have a favorable biomarker and genomic profiles, the benefit of chemotherapy is small and may not justify the risks (43). Cytotoxic chemotherapy and hormonal therapy have inherent risks that must be considered when treatment decisions are made. There are many known acute side effects with standard regimens, and there is growing evidence that patients who undergo chemotherapy report more frequent chronic neurocognitive deficits than do untreated controls (96). The impact of these deficits remains undefined. Systemic therapy with *tamoxifen* is associated with an increased incidence of uterine cancer, vaginal dryness, and hot flashes, whereas aromatase inhibitors (AIs) are linked to osteoporosis and musculoskeletal symptoms. Choosing those patients who should receive adjuvant therapy can be a difficult decision that often entails analyzing a variety of prognostic and predictive factors, identifying patients at risk for recurrence, and quantifying that risk. [7] **Comorbidities, stage, biomarker profile, and results of genomic analysis, such as Oncotype DX and MammaPrint, are often taken into consideration when deciding whether or not a patient needs systemic therapy. Genomic assays examine gene expression in the primary tumor and can indicate a higher or lower than expected risk of recurrence. Patients with low risk of recurrence have been shown not to benefit from the use of adjuvant systemic chemotherapy** (40,41,97,98).

Choice of Regimen

Based on the results of more than 100 prospective, randomized trials examining the role of adjuvant chemotherapy in breast cancer, [7] a variety of systemic regimens emerged. **Systemic therapy includes cytotoxic agents, targeted agents, and hormonal agents, used alone or in combination.**

Initially, trials involved a single perioperative course of chemotherapy aimed at eradicating circulating tumor cells. The Nissen-Meyer study from Norway showed that a single course of *cyclophosphamide* improved overall survival rates (99). Subsequently, numerous trials demonstrated the benefit of adjuvant chemotherapy for certain subgroups of patients (100). In the initial NSABP adjuvant trial, a 2-year course of *melphalan* was superior to no treatment, and further trials demonstrated enhanced beneficial effect with the use of multiple drugs and the combination of hormonal

manipulation with chemotherapy (101,102).

[7] Historically, the most frequently used adjuvant combination chemotherapy was *CMF: cyclophosphamide* (*C*), *methotrexate* (*M*), and *5-fluorouracil* (*5-FU*). In the original study by Bonadonna et al., patients with positive axillary lymph nodes were randomized to receive either 12 monthly cycles of *CMF* or no therapy after radical mastectomy (103). A statistically significant benefit was found with *CMF* treatment for premenopausal patients, especially those with one to three positive nodes. A subsequent study showed six cycles of *CMF* to be as effective as 12 cycles (104). After 20 years of follow-up, this trial demonstrated a persistent survival advantage for premenopausal women receiving *CMF* adjuvant therapy (105). In a later study involving node-negative, estrogen receptor– negative breast cancer patients, after 12 years of follow-up, 71% of patients treated with adjuvant *CMF* remained disease free compared with 48% in the control group, regardless of menopausal status (106).

***Anthracyclines* (*A*) were more commonly used in the adjuvant and metastatic treatment of breast cancer than any other agents.** A large randomized NSABP study compared *CMF* with *AC* regimens in node-positive patients and found similar treatment outcomes among both groups. The *AC* regimen was preferred because of its shorter duration (four cycles for 3 months versus six cycles for 6 months) (107).

[7] Several landmark trials showed that taxanes such as *paclitaxel* and *docetaxel* in combination with *anthracyclines* have significant efficacy and are commonly used as adjuvant therapy for breast cancer. The Cancer and Leukemia Group B was the first to show a 17% improvement in the rate of recurrence and 18% reduction in the rate of death with the addition of *paclitaxel* to *cyclophosphamide* (108). Given concerns over the cardiotoxicity of anthracyclines and the 0.21% risk of leukemia after the *AC* regimen at 5 years, a US oncology trial randomized stage I, II, and III patients to *AC* or *docetaxel* and *cyclophosphamide* (TC) every 3 weeks for four cycles and found that after 7 years' follow-up disease-free survival and overall survival statistically favored the *TC* group (109). This was the first trial to compare a *taxane*-based regimen to an *anthracycline*-based regimen. Concerns remain because multiple trials demonstrate that the duration of therapy is significant and the *TC* regimen used was a short-duration treatment of four cycles (110). In 2017, the Joint Analysis of the Anthracyclines in Early Breast Cancer (ABC) trials compared *TC* chemotherapy to an *anthracyclines-, cyclophosphamide-,* and *taxane*-based regimen in over 4,000 women with HER2-negative disease and found that **[7] *anthracycline*-based chemotherapy does not significantly improve outcomes in low-risk, hormone receptor–positive breast cancer. However, in higher-risk hormone receptor–positive and triple-negative disease, there appears to be a benefit to administering an *anthracycline*-based regimen** (111).

Neoadjuvant Systemic Therapy

Neoadjuvant therapy refers to the use of systemic treatments prior to definitive surgical treatment. NAC regimens are often the same as those that are used for adjuvant treatment.

[7] **Traditionally, the goal of preoperative systemic therapy was to convert inoperable patients into operable patients and to convert mastectomy candidates into candidates for breast conservation on the basis of pathologic and clinical responses** (112). Reports indicate that breast conservation therapy is possible and that low rates of in-breast or local–regional recurrences occur when NAC results in clinical and pathologic tumor downstaging (113). [7] **NAC permits the observation of an in vivo response of the tumor to chemotherapy, and a pathologic complete response is a strong prognostic indicator, especially in triple negative and HER2 positive breast cancer** (114). Randomized trials demonstrate similar long-term outcomes when patients are given the same treatment preoperatively compared with postoperatively (115). **Giving the systemic treatment before surgery permits tailoring the adjuvant regimen, which may affect outcomes.** In the CREATE-X trial, women with residual HER2-negative disease after NAC were randomly assigned to adjuvant treatment with capecitabine versus no further chemotherapy. The women who received adjuvant capecitabine experienced longer disease-free and overall survival (116). This was most significant for patients with triple-negative breast cancer.

Hormonal Therapy

[7] **Hormonal manipulation with *tamoxifen* or an AI, used alone or in combination with a cytotoxic regimen, is beneficial for women with hormone receptor–positive breast cancer. *Tamoxifen*, a selective estrogen receptor modulator, offers substantial benefits in pre- and postmenopausal women.** Taken at a dose of 20 mg per day for 5 or 10 years, ***tamoxifen*** **results in a significant and sustained reduction in the risk of breast cancer recurrence and mortality at 15 years** (117).

AIs suppress plasma estrogen levels by inhibiting or inactivating the enzyme responsible for the peripheral conversion of androgens to estrogens. These drugs should be used only in postmenopausal patients or premenopausal women who have undergone chemical ovarian suppression or oophorectomy. [7] **AIs have consistently been shown to improve outcomes for postmenopausal women with hormone receptor–positive breast cancer compared with *tamoxifen*** (118). The AIs, such as anastrozole, letrozole, and exemestane, have similar efficacy. Although AIs cause fewer episodes of thrombotic events, hot flashes, and endometrial cancers, musculoskeletal symptoms and osteoporosis are more commonly encountered among AI users than those taking *tamoxifen*.

Endocrine therapy is recommended for a minimum of 5 years. The risk of hormone receptor–positive disease recurrence persists for 20 years and extended hormone therapy has been studied. [7] Data supports the use of 10 years of hormone therapy, especially for women at high risk of recurrence (119). Data from the MA.17, ATLAS and aTTom trials suggest that extended endocrine therapy improves disease-free survival and possibly overall survival (120,121).

Ovarian ablation plays a role in the treatment of premenopausal, hormone receptor–positive breast cancer. Ovarian ablation can be achieved surgically via oophorectomy or medically with the administration of gonadotropin-releasing hormone (GnRH) agonists, such as Lupron. According to the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), the addition of ovarian suppression to tamoxifen or aromatase inhibition does not provide a significant benefit for the average-risk patient, but the addition of ovarian suppression to exemestane rather than tamoxifen improves outcomes for high-risk patients (122,123).

[7] Bisphosphonates can be used to prevent or treat cancer therapy–induced bone loss in pre- and postmenopausal women. In addition to improving bone density, bisphosphonates may impact long-term outcomes. A meta-analysis investigating the impact of zoledronic acid on outcomes reported improved overall survival and lower fracture rates with the use of adjuvant zoledronic acid, but there were no improvements in the risks of locoregional recurrence, bone metastases, or disease-free survival (124). *Denosumab*, another bone-stabilizing drug, is being investigated for its impact on breast cancer–related outcomes. Side effects of bisphosphonate therapy include bone pain, fever, and rarely osteonecrosis of the jaw, esophagitis, ulcers or renal failure.

HER2-Targeted Therapy

[6] It is essential that all breast cancers be assessed for HER2 overexpression because HER2-directed therapies, such as *trastuzumab* and *pertuzumab*, are a cornerstone of the treatment of HER2-positive breast cancer (38,125). HER2-amplified breast cancer had been associated with worse prognosis prior to the use of targeted agents. **[7] *Trastuzumab* should be given with chemotherapy and should be given alone or with hormonal therapy to complete 1-year duration. *Pertuzumab* can be added to the neoadjuvant regimen for women with ≥T2 or ≥N1 HER2-positive tumors** (126). *Pertuzumab* was granted accelerated approval by the FDA in 2013 as a result of its beneficial effects on progression-free survival for patients with metastatic disease and on pathologic complete response rates when given neoadjuvantly. The addition of *pertuzumab* to *trastuzumab* and chemotherapy resulted in less remarkable effects as an adjuvant therapy (39). This has led to some controversy regarding the use of pathologic response after neoadjuvant therapy as an indicator of efficacy and basis for accelerated drug approval.

Trastuzumab has been associated with an increased risk for cardiac toxicity, and for that reason, patients receiving *trastuzumab* therapy should have their cardiac function monitored during and after treatment (127).

[7] Summary of recommendations regarding systemic therapy for early breast cancer:

1. Factors to consider when deciding if a patient should receive systemic chemotherapy include age, stage, biomarker profile, and results of genomic assays, such as Oncotype DX or MammaPrint.
2. Combination *anthracycline* and *taxane*-based regimens are the most commonly used in the United States and can be administered before (neoadjuvant) or after (adjuvant) surgery. Neoadjuvant administration may allow for less extensive surgical and radiation treatments and for the tailoring of adjuvant chemotherapy regimens.
3. Hormone receptor–positive breast cancer should be treated with adjuvant AI in postmenopausal patients. In premenopausal patients, *tamoxifen* should be administered or ovarian suppression should be given in conjunction with AI for high-risk patients.
4. HER2-positive breast cancer should be treated with HER2-targeted therapies, such as *trastuzumab* and *pertuzumab*. *Pertuzumab* is approved for use only as neoadjuvant treatment for tumors >2 cm or node-positive patients.

Systemic Therapy for Metastatic Breast Cancer

Up to 5% of women with breast cancer have metastatic disease at the time of presentation and up to 30% will develop metastatic disease over the course of their illness. Breast cancer can metastasize to any organ, and involvement of bone, lungs, or liver occurs in up to 85% of women who develop distant disease (128,129). In addition to these sites, ILC is known to disseminate to the abdominal viscera, uterus, ovaries, and peritoneal surfaces. Patients with visceral metastases and/or a short disease-free interval generally have an aggressive phenotype, while patients with bone metastases have a more indolent phenotype. **The goals of the treatment of metastatic breast cancer are to prolong survival and maintain or improve quality of life.** Treatment strategies are inherently different than those used with curative intent in patients without signs of metastasis.

Systemic disease may be controlled by hormonal, targeted, or cytotoxic therapy. For metastatic hormone receptor–positive disease it is preferable to attempt endocrine manipulation first because the quality of life during an endocrine-induced remission is usually superior to one during treatment with cytotoxic chemotherapy. **First-line treatment for postmenopausal women with metastatic hormone receptor–positive breast cancer includes a combination of an AI and a cyclin-dependent kinase (CDK) 4/6 inhibitor, such as *palbociclib* or *ribociclib*.** *Fulvestrant* appears superior

to *anastrozole* as first-line therapy. *Palbociclib* and *ribociclib* are well tolerated except for nonfebrile neutropenia (130). In phase III studies, the addition of CDK4/6 inhibitors results in improved progression-free survival, but may not substantially improve overall survival (131,132). **For premenopausal patients, ovarian suppression should be administered in addition to endocrine therapy with or without a CDK4/6 inhibitor.**

If organ involvement is potentially life threatening (brain, lung, or liver), hormonal treatment is unsuccessful, or the disease has progressed after an initial response to endocrine manipulation, cytotoxic chemotherapy should be considered. The most useful single chemotherapeutic agent is an *anthracycline* such as *doxorubicin,* which has an estimated response rate of 40% to 50%. Combination therapy using multiple agents has response rates as high as 60% to 80% (133). Metastatic HER2-positive breast cancers should receive HER2-targeted therapy as first-line treatment of their disease. Poly adenosine diphosphate ribose polymerase (PARP) inhibitors are effective agents to treat metastatic breast cancer in patients with *BRCA* mutations (134).

SPECIAL BREAST CANCERS

Paget Disease

In the 1870s, Sir James Paget described a nipple lesion similar to eczema and recognized that this nipple change was associated with an underlying breast malignancy (135). The erosion results from invasion of the nipple and surrounding areola by characteristic large cells with irregular nuclei, now called Paget cells. Although the origin of these cells is debated, they are probably extensions of an underlying carcinoma into the major ducts of the nipple–areolar complex. There may be no visible changes associated with the initial invasion of the nipple. Often, the patient's presenting symptom will be nipple discharge, which is actually a combination of serum and blood from the involved ducts. The patient may have a delay in the diagnosis because the presenting symptoms are often overlooked. The diagnosis is established by incisional or punch biopsy of the area of the nipple changes.

The overall prognosis for patients with this rare form of breast cancer depends on the stage of the underlying malignancy. When an intraductal carcinoma alone is identified, the prognosis remains favorable, whereas patients with infiltrating ductal carcinoma metastatic to the regional lymph nodes have worse outcomes. Traditional treatment was total mastectomy and lymph node dissection, although breast conservation therapy with resection of the tumor and nipple– areolar complex, followed by whole-breast radiation, is being performed in appropriately identified patients (136). In patients without a palpable mass or imaging abnormality, radiation treatment alone has been reported with local recurrence rates ranging from 0% to 17% (137,138).

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is characterized by diffuse erythema and edema involving the skin of the breast. The diagnosis of IBC can be made when the erythema and edema have been present for no more than 6 months, occupy at least one-third of the breast, and when a biopsy confirms invasive carcinoma. Mammographically, the breast shows skin thickening with an infiltrative process and may or may not show a mass or calcifications.

IBC is an aggressive form of locally advanced breast cancer. A metastatic workup should be performed. In women without evidence of metastatic disease, standard treatment begins with chemotherapy. Women who experience a good clinical response to chemotherapy may go on to modified radical mastectomy and postmastectomy radiation. Limited data suggest that BCS with an SLNB is not appropriate for these patients (139,140).

Breast Cancer in Pregnancy

Gestational breast cancer is defined as breast cancer that is diagnosed during pregnancy, in the first postpartum year or any time during lactation. Breast cancer complicates 1 in 3,000 pregnancies (141). It is the second most common malignancy seen in association with pregnancy, surpassed only by cervical cancer. **When pregnant patients are matched stage for stage with nonpregnant patients, outcomes are equivalent** (142).

Patients typically present with a painless mass. Up to 60% will have concurrent lymph node involvement. The evaluation includes imaging with ultrasonography and mammography, which exposes the fetus to less than 0.02 cGy of radiation when used with proper abdominal shielding (143). If biopsy is warranted, the procedure can be performed safely and should not be delayed until after delivery.

The treatment of breast cancer in pregnant women must be highly individualized. Considerations include the patient's age, desire to continue the pregnancy, and overall prognosis. It is believed that the duration of pregnancy does not alter the prognosis for patients with potentially curable breast cancer. Following are generalized recommendations for treatment of pregnant women with breast cancer:

1. **Breast conservation and mastectomy are feasible options for the surgical management of the pregnant patient. The choice between them is guided by clinicopathologic characteristics, patient preferences, and the gestational age of the fetus. SLNB can be performed during pregnancy.** The use of blue dye is contraindicated as it is classified as a pregnancy category C drug. The risk to the fetus is felt to be minimal with the use of radiocolloid, although there is no clear randomized data to confirm this (144).

2. **Adjuvant radiation therapy should be administered after delivery in patients for whom it is indicated.** In a patient diagnosed before the third trimester, waiting until after delivery to administer radiation may result in an unacceptable delay in the initiation of therapy and should not be encouraged.
3. **Adjuvant chemotherapy can be given after the first trimester.** The data suggest that it is safe for the mother and the baby to administer many of the chemotherapeutic agents used for the treatment of breast cancer during pregnancy when initiated after the first trimester (145,146).
4. ***Trastuzumab* during pregnancy is associated with oligo- and anhydramnios, pulmonary hypoplasia, fetal developmental abnormalities, and fetal death and should not be used.**
5. ***Tamoxifen* is a class D drug and should not be given to pregnant or lactating patients with breast cancer.**
6. **If breast cancer is diagnosed during lactation, lactation should be suppressed and the cancer should be treated definitively.**
7. **Advanced, incurable cancer should be treated with palliative therapy.** Decisions regarding continuation of the pregnancy should be based on the therapy necessary and the desires of the patient.

Counseling regarding future childbearing is important for women who have had carcinoma of the breast. It was assumed that subsequent pregnancies would be detrimental because of the high levels of circulating estrogens, but **there is no clear difference in survival for women who become pregnant after the diagnosis of breast cancer.** A meta-analysis that included 1,244 women who became pregnant after being treated for breast cancer found that pregnancy did not impact survival and may even have a protective effect (147).

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