PROLOG

Gynecologic Oncology and Critical Care

SEVENTH EDITION

Online Assessment
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The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

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Critique Book

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This PROLOG unit was developed under the direction of the PROLOG Advisory Committee and the Task Force for *Gynecologic Oncology and Critical Care*, Seventh Edition. PROLOG is planned and produced in accordance with the Standards for Enduring Materials of the Accreditation Council for Continuing Medical Education. Any discussion of unapproved use of products is clearly cited in the appropriate critique.

Current guidelines state that continuing medical education (CME) providers must ensure that CME activities are free from the control of any commercial interest. The task force and advisory committee members declare that neither they nor any business associate nor any member of their immediate families has material interest, financial interest, or other relationships with any company manufacturing commercial products relative to the topics included in this publication or with any provider of commercial services discussed in the unit except for **Linda R. Duska, MD**, who is a principal investigator for clinical trials funded by GSK, Millenium, and BMS, and a contractor with Parexel working as an independent reviewer of clinical trials, and a member of a DMSC for Inovio; **Michael McHale, MD**, who is on the speakers bureau for Ethicon Biosurgery; and **Jason D. Wright, MD**, who is a consultant with TheVax Genetics. All potential conflicts have been resolved through the American College of Obstetricians and Gynecologists' mechanism for resolving potential and real conflicts of interest.

Preface

Purpose

PROLOG (Personal Review of Learning in Obstetrics and Gynecology) is a voluntary, strictly confidential, self-evaluation program. PROLOG was developed specifically as a personal study resource for the practicing obstetrician–gynecologist. It is presented as a self-assessment mechanism that, with its accompanying performance information, should assist the physician in designing a personal, self-directed lifelong learning program. It may be used as a valuable study tool, a reference guide, and a means of attaining up-to-date information in the specialty. The content is carefully selected and presented in multiple-choice questions that are clinically oriented. The questions are designed to stimulate and challenge physicians in areas of medical care that they confront in their practices or when they work as consultant obstetrician–gynecologists.

PROLOG also provides the American College of Obstetricians and Gynecologists (the College) with one mechanism to identify the educational needs of the Fellows. Individual scores are reported only to the participant; however, cumulative performance data and evaluation comments obtained for each PROLOG unit help determine the direction for future educational programs offered by the College.

Process

The PROLOG series offers the most current information available in five areas of the specialty: obstetrics, gynecology and surgery, reproductive endocrinology and infertility, gynecologic oncology and critical care, and patient management in the office. A new PROLOG unit is produced annually, addressing one of those subject areas. *Gynecologic Oncology and*

Critical Care, Seventh Edition, is the fourth unit in the seventh 5-year PROLOG series.

Each unit of PROLOG represents the efforts of a special task force of subject experts under the supervision of an advisory committee. PROLOG sets forth current information as viewed by recognized authorities in the field of women's health. This educational resource does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognized methods and techniques of clinical practice for consideration by obstetrician–gynecologists to incorporate in their practices. Variations of practice that take into account the needs of the individual patient, resources, and the limitations that are special to the institution or type of practice may be appropriate.

Each unit of PROLOG is presented as a two-part set, with performance information and cognate credit available to those who choose to submit their answer sheets for confidential scoring. The first part of the PROLOG set is the Assessment Book, which contains educational objectives for the unit and multiple-choice questions, and an answer sheet with a return mailing envelope. Participants can work through the book at their own pace, choosing to use PROLOG as a closedor open-book assessment. Return of the answer sheet for scoring is encouraged but voluntary.

The second part of PROLOG is the Critique Book, which reviews the educational objectives and questions set forth in the Assessment Book and contains a discussion, or critique, of each question. The critique provides the rationale for correct and incorrect options. Current, accessible references are listed for each item.

Continuing Medical Education Credit

ACCME Accreditation

The American College of Obstetricians and Gynecologists is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AMA PRA Category 1 Credit(s)™

The American College of Obstetricians and Gynecologists designates this enduring material for a maximum of **25** *AMA PRA Category 1 Credits*™.

Physicians should claim only the credit commensurate with the extent of their participation in the activity.

College Cognate Credit(s)

The American College of Obstetricians and Gynecologists designates this enduring material for a maximum of 25 Category 1 College Cognate Credits. The College has a reciprocity agreement with the American Medical Association that allows *AMA PRA Category 1 Credits*™ to be equivalent to College Cognate Credits.

Fellows who submit their answer sheets for scoring will be credited with 25 hours. Participants who return their answer sheets for CME credit will receive a Performance Report that provides a comparison of their scores with the scores of a sample group of physicians who have taken the unit as an examination. An individual may request credit only once for each unit. *Please allow 4–6 weeks to process answer sheets*.

Credit for PROLOG *Gynecologic Oncology and Critical Care*, Seventh Edition, is initially available through December 2018. During that year, the unit will be reevaluated. If the content remains current, credit is extended for an additional 3 years, with credit for the unit automatically withdrawn after December 2021.

Conclusion

PROLOG was developed specifically as a personal study resource for the practicing obstetrician–gynecologist. It is presented as a self-assessment mechanism that, with its accompanying performance information, should assist the physician in designing a personal, self-directed learning program. The many quality resources developed by the College, as detailed each year in the College's *Publications and Educational Materials Catalog*, are available to help fulfill the educational interests and needs that have been identified. PROLOG is not intended as a substitute for the certification or recertification programs of the American Board of Obstetrics and Gynecology.

PROLOG CME SCHEDULE

Gynecologic Oncology and Critical Care, Sixth Edition	Credit through 2016
Patient Management in the Office, Sixth Edition	Reevaluated in 2014–Credit through 2017
Obstetrics, Seventh Edition	Reevaluated in 2015–Credit through 2018
Gynecology and Surgery, Seventh Edition	Reevaluated in 2016–Credit through 2019
Reproductive Endocrinology and Infertility, Seventh Edition	Reevaluated in 2017–Credit through 2020
Gynecologic Oncology and Critical Care, Seventh Edition	Reevaluated in 2018–Credit through 2021

PROLOG Objectives

PROLOG is a voluntary, strictly confidential, personal continuing education resource that is designed to be stimulating and enjoyable. By participating in PROLOG, obstetrician–gynecologists will be able to do the following:

- Review and update clinical knowledge.
- Recognize areas of knowledge and practice in which they excel, be stimulated to explore other areas of the specialty, and identify areas requiring further study.
- Plan continuing education activities in light of identified strengths and deficiencies.
- Compare and relate present knowledge and skills with those of other participants.
- Obtain continuing medical education credit, if desired.
- Have complete personal control of the setting and of the pace of the experience.

The obstetrician–gynecologist who completes *Gynecologic Oncology and Critical Care*, Seventh Edition, will be able to

- identify epidemiologic factors that contribute to the risks of various malignancies and determine appropriate screening tests.
- analyze the pathophysiology and evaluate the histopathology of various malignancies.
- associate symptoms with early onset of specific malignancies, determine appropriate diagnostic tests, and select diagnosis.
- identify physical and surgical findings related to specific stages of malignant disease.
- determine appropriate surgical and nonsurgical management for various types of cancer and identify common complications of therapy.

- determine approaches for preoperative assessment, select surgical techniques for gynecologic disorders, and identify common complications of surgery.
- apply knowledge of anatomy, wound management, and appropriate surgical techniques in the surgical therapy of gynecologic disease.
- determine the appropriate management of the critical care patient.

Gynecologic Oncology and Critical Care, Seventh Edition, includes the following topics (item numbers appear in parentheses):

SCREENING AND DIAGNOSIS

Atypical glandular cells test result (23)
Breast cancer (121)
Breast cancer risk factors (36, 55)
Breast surveillance in patients who are *BRCA* positive (13)
Cervical cancer staging (93)
Cervical cytology screening (67, 102)
Colon cancer (53)
Complete mole (144–147)
Endometrial cancer (78)
Endometrial cancer recurrence (85)
Evaluation of palpable breast mass (10)
Follow-up of patient with endometrial cancer (35)
High-risk gestational trophoblastic disease (4)
Human papillomavirus primary screening (86)
Human papillomavirus vaccination (15)
Immunohistochemistry staining for pathologic evaluation (29)
Indications for *BRCA* testing (2)
Lung compliance complications (105)
Lymph node involvement in cervical cancer (101)
Lynch syndrome (1, 91)
Malignant ascites (103)
Ovarian cancer (113)
Ovarian cancer recurrence (65)
Paraneoplastic syndrome (3)
Posttreatment surveillance in cervical cancer (72)

Preoperative cardiac risk assessment (20)
Preoperative diagnosis of pelvic mass (41)
Pseudomyxoma peritonei (27)
Pulmonary embolism (5)
Radiation cystitis (114)
Systemic inflammatory response syndrome and sepsis (151–153)
Tumor markers (143)
Vulvar cancer (118)

MEDICAL MANAGEMENT

Acupuncture for cancer patients (124)
Acute kidney injury (139)
Acute respiratory distress syndrome (77)
Adenocarcinoma in situ of the cervix (89)
Adverse effects of aromatase inhibitors (52)
Antibiotic prophylaxis (154–157)
Basal cell carcinoma of the vulva (100)
Breast cancer (98)
Breast ductal carcinoma in situ (119)
Cancer in older women (129)
Cell salvage (60)
Cervical cancer (135)
Cervical cancer in pregnancy (9)
Cervical dysplasia in younger women (82)
Chemoradiotherapy and cervical cancer (97)
Chemotherapy-associated emesis (34)
Chemotherapy for recurrent ovarian cancer (75)
Chemotherapy for serous endometrial cancer (94)
Chemotherapy-induced anemia (28)
Clostridium difficile infection (69)
Complementary and alternative medicine (45)
Complex adnexal mass in a postmenopausal woman (42)
Complex hyperplasia with atypia (43)
Complications of chemotherapy (26)
Deep vein thrombosis (14)
Early-stage cervical cancer (38)

Endometrial cancer (39, 83)
Febrile neutropenia (48)
Fertility-sparing therapy for gynecologic malignancies (108, 138)
Hemodynamic monitoring (148–150)
Heparin-induced thrombocytopenia (73)
Hereditary breast and ovarian cancer (88)
Hormone therapy in *BRCA* patients (133)
Human chorionic gonadotropin (19, 49)
Hyperkalemia (32)
Initial chemotherapy for ovarian cancer (54)
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Low-grade serous ovarian cancer (74)
Low-risk gestational trophoblastic disease (136)
Malignant ovarian germ cell tumor (31)
Malignant pleural effusion (44)
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Microinvasive cervical cancer (70, 142)
Necrotizing fasciitis (16)
Needlestick injury and human immunodeficiency virus infection (109)
Nosocomial aspiration pneumonia (95)
Nutrition in a postsurgical patient (63)
Ovarian cancer (68, 130)
Paget disease of the vulva (92)
Pain medication after surgery (123)
Palliative care (30, 111)
Perioperative venous thromboprophylaxis (7)
Placental-site trophoblastic tumor (64)
Postmolar gestational trophoblastic disease (110)
Postoperative feeding (46)
Postoperative ileus (131)
Radiation enteritis (132)
Sepsis (87)
Sex cord–stromal tumors of the ovary (47)
Small cell cervical cancer (106)
Squamous dysplasia in pregnancy (125)
Tamoxifen citrate therapy (8, 141)

Thromboprophylaxis (127)
Uterine carcinosarcoma (25)
Uterine smooth muscle tumor of uncertain malignant potential (33)
Vulvar intraepithelial neoplasia (62)

PHYSIOLOGY

Sexual function after vulvectomy (99)
Ureteral injury (76, 90)

SURGICAL MANAGEMENT

Bladder injury during abdominal surgery (71)
Blood product selection after massive hemorrhage (18)
Breast cancer (96)
Cervical cancer (59)
Cystoscopy (50)
Cytoreductive surgery (22)
Follow-up of patient with endometrial cancer (35)
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Intraoperative hemorrhage (58)
Intraoperative rupture of a malignant ovarian cyst (122)
Intraperitoneal chemotherapy (115)
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Leiomyosarcoma (21)
Low-malignant-potential tumor of ovary (66)
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Pelvic exenteration (84)
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Preoperative care of an obese patient (120)
Preoperative mechanical bowel preparation (57)
Ureteral injury (76, 90)
Use of sealants in gynecologic cancer surgery (158–160)
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EPIDEMIOLOGY AND BIOSTATISTICS

Breast cancer risk factors (36, 55)
Clear cell ovarian cancer (80)
Colon cancer (79)
Endometriosis-associated ovarian cancer (104)
Fibrocystic changes and risk of breast cancer (17)
In vitro fertilization and ovarian cancer (56)
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Performance characteristics of a test (24)
Risk of infection from blood transfusion (81)
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Sexual function after vulvectomy (99)
Tamoxifen citrate therapy (8, 141)

COUNSELING

Acupuncture for cancer patients (124)
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Human papillomavirus (37)
Sexual function after vulvectomy (99)
Tamoxifen citrate therapy (141)

ETHICAL AND LEGAL ISSUES

Advance directives (6)

A complete subject matter index appears at the end of the Critique Book.

1 ⇦

Lynch syndrome

A 45-year-old woman is diagnosed with grade 2 endometrioid adenocarcinoma of the endometrium, and she undergoes hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. She has a family history that includes cancer of the breast, lung, and colon in first-degree relatives. The test that will best inform her of her risk of future cancer is immunohistochemical staining of tumor tissue for

* (A) *MLH1*, *MSH2* overexpression
(B) *BRCA1* mutation
(C) progesterone receptor
(D) *TP53* mutation
(E) *PTEN* mutation

Lynch II syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, is an autosomal dominant disorder characterized by germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*. Affected individuals have increased risks of cancer of the endometrium, ovary, gastric tract, and small bowel. Lynch syndrome-associated endometrial cancer accounts for up to 6% of all endometrial cancer. Therefore, identification of women who may have Lynch syndrome is important to inform the patient and her family of additional cancer risks. Based on the described patient's family history and her personal history of endometrial cancer, she and her family are more likely to have Lynch syndrome than another inherited familial cancer syndrome, as suggested clinically by the modified Amsterdam and Bethesda criteria (Appendix B). The modified Amsterdam criteria have only 40% sensitivity to identify individuals with an HNPCC mutation. Alternatively, when HNPCC is present, characteristic abnormalities are seen in tumor tissue more than 90% of the time with immunohistochemistry testing for mismatch repair protein overexpression or with microsatellite instability (MSI) testing. Individuals whose tumors

are identified as having markers for HNPCC then can elect to proceed with genetic counseling and possible germline mutation testing.

The Bethesda guidelines for testing colorectal tumors for MSI were established in 1997 and revised in 2002. The guidelines recommend that MSI testing of the tumor should be performed in any patient with colon cancer who is younger than 50 years or in a patient with synchronous or metachronous colon cancer or other HNPCC-candidate cancer, colon cancer with MSI histology, or colon cancer when the Amsterdam criteria are fulfilled. When MSI testing is completed and two or more of the nucleotide markers are unstable, the sensitivity of detecting HNPCC is 94%. For endometrial cancer, results from immunohistochemistry for mismatch repair proteins *MLH1*, *MSH2*, *MSH6*, and *PMS2* can be used for rapid triage of patients at risk of HNPCC by family or personal history or by age at diagnosis. Some institutions recommend universal screening for endometrial cancer with immunohistochemistry profiling of mismatch repair proteins. Women with positive screening test results are referred for genetic counseling. In one series using universal screening, approximately 25% of women referred for genetic testing were found to have Lynch syndrome.

Germline mutations in *BRCA1* and *BRCA2* are associated with breast and ovarian cancer but not with endometrial cancer. Although *TP53* mutations can be seen in high-grade endometrial cancer, germline *TP53* mutations are associated with Li–Fraumeni syndrome, which is associated with a high risk of soft tissue sarcomas; leukemia; and adrenocortical cancer, breast cancer, and brain cancer. In women, the lifetime risk of an associated cancer reaches 100%, often with the first cancer occurring in the fourth decade of life. Presence of progesterone receptors suggests a type I endometrial cancer with good prognosis but does not suggest risk of other types of cancer. Overexpression of *PTEN* is associated with Cowden disease, which is an autosomal dominant disorder characterized by predisposition for breast cancer, thyroid cancer, and endometrial cancer as well as benign mucocutaneous lesions.

Heald B, Plesec T, Liu X, Pai R, Patil D, Moline J, et al. Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing Lynch syndrome in a large academic medical center. J Clin Oncol 2013;31:1336–40.

Lachiewicz MP, Kravochuck SE, O'Malley MM, Heald B, Church JM, Kalady MF, et al. Prevalence of occult gynecologic malignancy at the time of risk reducing and nonprophylactic surgery in patients with Lynch syndrome. Gynecol Oncol 2014;132:434–7.

Leenen CH, van Lier MG, van Doorn HC, van Leerdam ME, Kooi SG, de Waard J, et al. Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer </= 70 years. Gynecol Oncol 2012;125:414–20.

Moline J, Mahdi H, Yang B, Biscotti C, Roma AA, Heald B, et al. Implementation of tumor testing for Lynch syndrome in endometrial cancers at a large academic medical center. Gynecol Oncol 2013;130:121–6.

Resnick KE, Hampel H, Fishel R, Cohn DE. Current and emerging trends in Lynch syndrome identification in women with endometrial cancer. Gynecol Oncol 2009;114:128–34.

* Indicates correct answer.
Note: See Appendix A for a table of normal values for laboratory tests.

2 ⇦

Indications for *BRCA* testing

A 42-year-old woman, gravida 2, para 2, in whom breast cancer was diagnosed at age 38 years, comes to your office for her annual well-woman visit. Her family history is significant for a mother who was diagnosed with ovarian cancer at age 68 years and a maternal aunt who developed a low-malignant-potential tumor of the ovary in her 20s. Her risk of having an inherited predisposition for ovarian cancer or breast cancer is

(A) less than 1% (B) 1–10%
(C) 11–20%
* (D) greater than 20%

The lifetime risk of breast cancer for a woman who carries a *BRCA1* or *BRCA2* mutation is approximately 65–74%. The lifetime risk of ovarian cancer is 39–46% for a woman with a *BRCA1* mutation and 12–20% for a woman with a *BRCA2* mutation. *BRCA* mutations occur in 3–5% of all cases of breast cancer. Approximately 10–15% of cases of ovarian cancer are associated with a genetic predisposition. Ovarian cancer is the most lethal of the gynecologic malignancies. It is important to identify women with a personal or family history suggestive of a genetic component to allow for timely referral for genetic testing, increased accuracy of risk assessment, and implementation of risk-reducing strategies.

Women with *BRCA1* mutations have earlier onset of breast cancer and ovarian cancer and a 40% higher risk of second primary breast cancer

compared with *BRCA2* mutation carriers. This risk of secondary cancer can be reduced with the use of adjuvant tamoxifen citrate, chemotherapy, and salpingo-oophorectomy. Male *BRCA2* mutation carriers have a higher risk of breast cancer and early prostate cancer. Both genders have a higher incidence of pancreatic cancer and melanoma.

To identify women with a genetic predisposition, the family history should include a woman's personal history of cancer, first-degree relatives (parents, siblings, and children) with cancer, second-degree relatives (aunts, uncles, grandparents, nieces, and nephews) with cancer, ages at diagnosis of cancer, and Ashkenazi Jewish ancestry (ie, individuals who are descended from Jews who came from Eastern Europe). Family history can accurately place a patient in a highor low-risk group for an inheritable mutation. Efforts should be made to confirm family history through pathology reports that confirm invasive disease. For the described patient, her personal history of breast cancer at age 38 years and her first-degree relative with ovarian cancer make her risk of a genetic mutation greater than 20% (Box 2-1).

The spectrum of *BRCA* mutation-associated gynecologic cancer includes ovarian cancer of predominantly serous and endometrioid histologies, tumors of the fallopian tube, and primary peritoneal cancer. Tumors of low malignant potential and mucinous histology are associated with other mutations and are not included in the spectrum of *BRCA*-associated cancer. Therefore, the low-malignant-potential ovarian tumor in the patient's maternal aunt does not increase the patient's risk of having an inheritable genetic mutation.

Several risk-reducing strategies have been demonstrated to decrease the incidence of breast cancer and ovarian cancer in patients with *BRCA* mutations. Risk-reducing salpingo-oophorectomy has been shown to decrease the risk of breast cancer by approximately 50% and to decrease the risk of ovarian cancer by 80–95%. Although breast cancer screening has been effective, screening for ovarian cancer has not been proved to be effective in *BRCA* mutation carriers. Oral contraceptives also have been proved to be a successful preventive strategy for patients with *BRCA* mutations. The risk reduction after 5 years of use ranges from 33% to 38%; however, the effect on breast cancer risk remains controversial.

Hereditary breast and ovarian cancer syndrome. ACOG Practice Bulletin No. 103. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009;113:957–66.

Meaney-Delman D, Bellcross CA. Hereditary breast/ovarian cancer syndrome: a primer for obstetricians/gynecologists. Obstet Gynecol Clin North Am 2013;40:475–512.

National Comprehensive Cancer Network. Genetic/familial high-risk assessment: Breast and ovarian. NCCN clinical practice gudelines in oncology, version 1.2015 [after login]. Ft. Washington (PA): NCCN; 2015. Available at: http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Retrieved June 17, 2015.

BOX 2-1

Criteria for Genetic Risk Assessment

Patients with greater than an approximate 20–25% chance of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment is recommended:

- Women with a personal history of breast cancer and ovarian cancer*
- Women with ovarian cancer* and a close relative † with ovarian cancer, premenopausal breast cancer, or both
- Women with ovarian cancer* who are of Ashkenazi Jewish ancestry
- Women with breast cancer at 50 years or younger and a close relative† with ovarian cancer* or male breast cancer at any age
- Women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger
- Women with a close relative† with a known *BRCA1* or BRCA2 mutation

Patients with greater than an approximate 5–10% chance of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment may be helpful:

- Women with breast cancer at age 40 years or younger
- Women with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high grade, serous histology at any age
- Women with bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age 50 years or younger)
- Women with breast cancer at age 50 years or younger and a close relative† with breast cancer at age 50 years or younger
- Women of Ashkenazi Jewish ancestry with breast cancer at age 50 years or younger
- Women with breast cancer at any age and two or more close relatives† with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed at age 50 years or younger)
- Unaffected women with a close relative† that meets one of the previous criteria

*Cancer of the peritoneum and fallopian tubes should be considered a part of the spectrum of the hereditary breast and ovarian cancer syndrome.

† Close relative is defined as a first-degree relative (mother, sister, daughter) or second-degree relative (grandmother, granddaughter, aunt, niece).

Hereditary breast and ovarian cancer syndrome. ACOG Practice Bulletin No. 103. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009; 113:957–66.

3 ⇦

Paraneoplastic syndrome

A 45-year-old woman, para 2, has been hospitalized with symptoms of diplopia, vertigo, and dizziness for the past 10 days. Three days ago, she had a contrast magnetic resonance imaging (MRI) scan of the head, which was negative for mass effect, lesions, and plaques. She has an elevated platelet count of 800,000/mm^3. A body computed tomography scan is negative except for a 6-cm complex lesion in the left ovary. Mammography was negative 1 month ago. On physical examination, you confirm the neurologic deficits. Analysis of serum and cerebrospinal fluid samples show elevated anti-Yo antibody levels. The best explanation for these findings is

(A) hemorrhagic stroke
(B) embolic stroke
* (C) paraneoplastic syndrome
(D) multiple sclerosis

Paraneoplastic syndromes are systemic manifestations of cancer that are not caused by direct (local or metastatic) effects of the tumor. This patient exhibits the signs and symptoms of cerebellar degeneration, a rare paraneoplastic sequelae of ovarian cancer. Patients may complain of diplopia, vertigo, loss of dexterity, dysarthria, oscillopsia, and nystagmus. Subtle motor system or cognitive dysfunction may be present. Without early intervention, symptoms may be irreversible even with appropriate treatment of the underlying cause.

Anti-Yo progressive cerebellar degeneration most commonly is associated with ovarian or breast carcinoma. Frequently, the neurologic disorder predates discovery of the tumor. The Yo antigen is one of three cerebellar degeneration-related antigens identified by expression cloning and causes direct toxicity to Purkinje cells, which may not be restored. Progressive cerebellar degeneration renders patients unable to walk, and dysarthria is frequently severe. Once the disorder reaches this stage, treatment with immunosuppression or effective treatment of the underlying

malignancy rarely produces significant improvement. Effective antitumor treatment is the most important determinant of outcome.

The differential diagnosis includes embolic or hemorrhagic stroke and multiple sclerosis. These are unlikely for this patient primarily because imaging performed several days after the onset of symptoms was negative. Multiple sclerosis is unlikely given that the MRI scan is negative for plaques. An elevated anti-Yo antibody level usually points to a paraneoplastic syndrome, most likely of breast or ovarian origin. Mammography is negative, which suggests that the ovarian mass is malignant.

Plasmapheresis has been used to treat paraneoplastic syndrome but only after the malignancy has been addressed. Its use also has been advocated for thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, which cause low platelet counts. Steroids and immunoglobulin therapy also offer limited success. Elevated platelet count is often another paraneoplastic manifestation of ovarian cancer resulting from increased production of thrombopoietic cytokines in the tumor and host tissue. This is theorized to lead to paraneoplastic thrombocytosis and further tumor growth. In advanced or protracted cases of cerebellar degeneration, MRI scans of the head may demonstrate cerebellar atrophy.

Braik T, Evans AT, Telfer M, McDunn S. Paraneoplastic neurological syndromes: unusual presentations of cancer. A practical review. Am J Med Sci 2010;340:301–8.

Dalmau J, Rosenfeld MR. Paraneoplastic neurologic syndromes. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, editors. Abeloff's clinical oncology. 5th ed. Philadelphia (PA): Elsevier Saunders; 2014. p. 597–607.

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4 ⇦

High-risk gestational trophoblastic disease

A 42-year-old Asian woman with a history of molar pregnancy comes to your office 13 months after initial diagnosis. Her serum β-hCG level is 14,650 international units/L. You diagnose gestational trophoblastic neoplasia (GTN). Her physical examination shows a 1-cm vaginal lesion. Pelvic ultrasonography shows a 4-cm intrauterine tumor. Chest, abdomen, and pelvic computed tomography (CT) scans show a 2-cm lung lesion consistent with metastatic disease. Head magnetic resonance imaging is negative for metastasis. Her age, β-hCG level, 4-cm intrauterine tumor, and total of two metastatic sites give her a modified World Health Organization (WHO) risk score of 5. The factor that increases her WHO score to 9 is

(A) previous molar pregnancy
* (B) interval from molar pregnancy to GTN diagnosis longer than 12 months
(C) vaginal metastasis on physical examination
(D) lung metastasis

The diagnosis of malignant GTN requiring chemotherapy is made based on a plateau or increase of β-hCG levels after evacuation of hydatidiform mole, histologic diagnosis of choriocarcinoma, an invasive mole on endometrial curettage, or the presence of metastatic disease on clinical examination or radiographic imaging. Repeat endometrial curettage is controversial and generally is not recommended except in the case of persistent heavy vaginal bleeding because of the high risk of uterine perforation and the chemosensitive nature of this disease.

Malignant GTN includes invasive moles, choriocarcinoma, placental-site trophoblastic tumors, and epithelioid trophoblastic tumors. After the diagnosis has been made, the following studies should be performed: laboratory studies including complete blood count, renal and liver function studies, coagulation studies, blood type and antibody screening, and pretreatment quantitative β-hCG level; CT scan of the chest, abdomen, and pelvis (chest X-ray can be used, although it misses up to 30–40% of lung metastases); and brain CT or magnetic resonance imaging. Staging of these tumors includes the International Federation of Gynecology and Obstetrics (FIGO) anatomic staging system in combination with a modified WHO risk score (see Appendix C).

Treatment is based on a combination of the FIGO stage and WHO risk score. For stage I disease and low-risk (score less than 7) stage II and III disease, single-agent chemotherapy with either methotrexate or

actinomycin D is recommended. For patients classified with high-risk disease, which is either stage IV disease or high-risk (score 7 or more) stage II and III disease, multiagent chemotherapy is recommended with or without site-directed surgery or radiotherapy. Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine, as well as methotrexate, actinomycin D, and cyclophosphamide, are the most commonly used regimens, with complete response rates of greater than 70% and long-term survival rates of greater than 90%. In contrast with the other forms of GTN, placental-site trophoblastic tumors and epithelioid trophoblastic tumors are relatively chemoresistant, and hysterectomy with lymph node dissection is recommended because of the high risk of lymphatic metastases. A platinum-containing chemotherapy regimen after surgery is recommended for patients with metastatic disease and patients with poor prognostic factors such as interval from antecedent pregnancy of longer than 2 years, deep myometrial invasion, or tumor necrosis, with or without a mitotic rate of greater than 6/10 high-power fields.

The described patient has FIGO stage III cancer, given the lung metastasis. Based on the information provided, her WHO risk score is at least 5 (age greater than 40 years = 1 point; pretreatment β-hCG level greater than 10,000 international units/L = 2 points; two metastatic sites = 1 point; largest tumor size 3–4 cm = 1 point). The addition of the interval from molar pregnancy to diagnosis of GTN longer than 12 months = 4 points, which would increase the total risk score to 9 and, thus, qualify as high-risk stage III disease for which combination chemotherapy is recommended. An antecedent molar pregnancy does not add any points; however, additional points would have been added had the antecedent pregnancy been an abortion (1 point) or a term pregnancy (2 points). The presence of vaginal and lung metastases does not add any points based on sites of metastases, but the number of metastases is part of the scoring system. One to four metastases is given a score of 1 (already included in the aforementioned calculation).

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5 ⇦

Pulmonary embolism

On postoperative day 2, a 65-year-old woman develops shortness of breath and tachycardia after a radical vulvectomy and bilateral inguinal lymphadenectomy. An arterial blood gas study shows a significant alveolar–arterial oxygen gradient, Sao_2 of 84%, and Pao_2 of 50 mm Hg. On physical examination, her lungs are clear bilaterally. The best next step in management is

(A) D-dimer assay
(B) ventilation–perfusion (V/Q) scan
(C) pulmonary angiography
* (D) computed tomography (CT)–pulmonary angiography
(E) lower extremity venous ultrasonography

Pulmonary embolism (PE) is a common and often fatal medical condition that requires early diagnosis and therapy to reduce the risk of mortality. Despite the prevalence of PE, its diagnosis remains challenging because the clinical presentation is nonspecific. Tachycardia, tachypnea, dyspnea, and hypoxemia are among a broad spectrum of clinical features described in patients with suspected PE, but no features are specific to the disease. A meta-analysis of 25,343 patients demonstrated relatively poor sensitivity (85%) and specificity (51%) for clinical impression. Multiple diagnostic tools were used to reach the diagnoses. Several diagnostic algorithms using a variety of tools have been evaluated for management of suspected PE.

In recent decades, the V/Q scan has been the diagnostic test used to evaluate patients with suspected PE. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study evaluated the diagnostic accuracy of the V/Q scan compared with the criterion standard, pulmonary angiography. When clinical probability was combined with the V/Q scan, the diagnostic accuracy was improved significantly. A high-probability

scan, especially in patients with a high clinical suspicion, had a positive predictive value of 96%. In contrast, in patients with low clinical probability and a low probability on V/Q scan, the risk of PE was 4%. Most scans in the PIOPED study were interpreted as either intermediate or low probability. The likelihood of a PE in these patients ranged from 10% to 40%. Consequently, most patients had clinical features and V/Q scan results that could not confirm or exclude diagnosis of PE. Given high clinical suspicion and an intermediate V/Q scan, further diagnostic testing with pulmonary angiography was indicated. The sensitivity and specificity of pulmonary angiography have been reported to be as high as 95%. However, this test is invasive and is associated with serious complications in 2–5% of patients.

Since the early 1990s, CT–pulmonary angiography and helical CT have been investigated as minimally invasive tests for the diagnosis of PE. An early study reported a sensitivity of 100% and a specificity of 96% for the detection of PE by helical CT. Since then, multiple studies have demonstrated sensitivities and specificities of 53–100% and 81–100%, respectively, for the detection of PE with CT–pulmonary angiography. Some investigators have suggested that a CT–pulmonary angiography should be used as the initial study in any diagnostic algorithm for PE because it also can detect alternative pulmonary abnormalities that could explain the clinical presentation.

One of the largest studies to assess the diagnostic accuracy of CT–pulmonary angiography was the PIOPED II study. In this investigation, 824 patients were evaluated, and the diagnostic accuracy of CT–pulmonary angiography was compared with a composite standard reference. A validated clinical probability assessment (modified Wells criteria score) was used before administering CT–pulmonary angiography to assess the clinical probability of PE (Table 5-1). The sensitivity and specificity of CT–pulmonary angiography were 83% and 96%, respectively. For patients with a high, intermediate, or low clinical probability and a positive CT, the likelihood of PE was 96%, 92%, and 58%, respectively.

Computed tomography–pulmonary angiography was compared with V/Q scan in a randomized, noninferiority trial in 1,471 patients with suspected PE, defined by a modified Wells score of greater than 4.5 or a positive D-dimer assay. Eligible patients were then randomized to receive V/Q scan or CT–pulmonary angiography. At baseline, PE was identified in 19.2% of patients in the CT–pulmonary angiography group and in 14.2% of patients in the V/Q scan group. More importantly, over the 3-month

follow-up, there was a similar incidence of PE in the V/Q scan and CT–pulmonary angiography groups, 1.0% and 0.6%, respectively. This study clearly illustrated that CT–pulmonary angiography was not inferior to the V/Q scan as a noninvasive diagnostic tool. The relative widespread availability of CT–pulmonary angiography coupled with its diagnostic accuracy and ability to detect alternative pulmonary abnormalities make this diagnostic tool an attractive option for patients with suspected PE. Patients with renal failure or a contrast allergy are not candidates for a CT–pulmonary angiography. They are more appropriately assessed with a V/Q scan.

D dimer is a degradation product of fibrin that can be detected in serum by several assays. The role of D dimer in the diagnosis of PE or deep vein thrombosis is unclear. Part of the difficulty in assessing its role may be related to the variety of assays available that have been evaluated in multiple studies. A systematic review of these studies has demonstrated that the quantitative rapid enzyme-linked immunosorbent assay is the most clinically reliable assay. A D-dimer assay less than 500 ng/mL by a quantitative enzyme-linked immunosorbent assay is sufficient to exclude PE in patients with a low clinical probability. However, multiple factors can falsely elevate D-dimer levels, including pregnancy, malignancy, or recent surgery, thus limiting its utility in the case of values greater than 500 ng/mL. Many investigators include D dimer in a diagnostic algorithm for PE. The purpose of these algorithms is to efficiently diagnose a PE and limit unnecessary testing or missed disease. The certainty of a negative diagnosis is best supported when used in a diagnostic pathway. Using the D dimer in this way ultimately may limit cost and radiation exposure from unnecessary imaging, such as with CT–pulmonary angiography.

Over the past decade, several diagnostic algorithms have been assessed. Although there is consensus regarding the need for a diagnostic algorithm, to date no algorithm has been accepted universally. Most of the algorithms combine clinical assessment with D-dimer testing and imaging, often CT–pulmonary angiography. The Christopher Study was a multicenter cohort study to evaluate an algorithm consisting of serial application of a clinical assessment or clinical decision rule, D-dimer testing, and CT scan. The clinical decision rule used the modified Wells criteria. For patients with a clinical decision score of 4 or less (unlikely PE), D-dimer testing was performed. In this group, patients with a value less than 500 ng/mL had no further testing, such as imaging, performed. In contrast, if the D-dimer assay was greater than 500 ng/mL, a CT–

pulmonary angiography was performed. For patients with an initial clinical decision score greater than 4 (likely PE), CT–pulmonary angiography was performed but not D-dimer testing. Patients then began anticoagulation if CT–pulmonary angiography was positive. This strategy proved to be effective, facilitated a management decision in 98% of the patients, and was associated with a low risk of subsequent fatal or nonfatal PE. More importantly, it demonstrated that this simplified algorithm was applicable for a wide spectrum of patients with suspected PE.

TABLE 5-1. Clinical Decision Rule According to the Modified Wells Score*

Clinical Feature(s)	**S**
Clinical signs/symptoms of DVT	3.
PE likely or more likely than alternative diagnosis	3.
Heart rate greater than 100 beats/minute	1.
Immobilization greater than 3 days or surgery in previous 4 weeks	1.
Previously objectively diagnosed PE or DVT	1.
Hemoptysis	1.
Cancer	1.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

*Clinical probability of PE if score 4 or less, PE unlikely; clinical probability of PE if score than 4, PE likely.

van Belle A, Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, Effectiveness of managing suspected pulmonary embolism using an algorithm combining probability, D-dimer testing, and computed tomography. Christopher Study Investigators. 2006;295:172–9. Copyright . 2006 American Medical Association. All rights reserved.

The described patient has a high clinical probability of PE based on the Wells criteria. Therefore, CT–pulmonary angiography is indicated. If she had evidence of renal compromise or a contrast allergy, a V/Q scan could be used. The use of a D-dimer assay postoperatively in a cancer patient coupled with a high clinical suspicion excludes independent use of this diagnostic tool. Although PA continues to be the diagnostic criterion standard, there are substantial risks with this invasive tool. As such, it should be reserved for cases with a high clinical suspicion and an inconclusive V/Q scan or CT–pulmonary angiography. The utility of lower extremity venous ultrasonography is limited. It is likely to miss many patients with PE. Lower extremity venous ultrasonography could be considered in patients with a high clinical suspicion and an inconclusive CT–pulmonary angiography before initiation of anticoagulation.

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6 ⇦

Advance directives

A 76-year-old woman undergoes an abdominal hysterectomy, a bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection for endometrial cancer. On postoperative day 2, she suffers a stroke with neurologic deficit. Her 78-year-old husband is by her side. She is clinically deteriorating and after a complete discussion, she states that she does not wish to pursue additional treatment. The most appropriate action is to

(A) perform life-sustaining measures
(B) allow the treating physician to decide
(C) sign do-not-resuscitate orders
(D) allow her husband to make the decision
* (E) assess her decision-making competence

Advance care planning and advance directives are part of a dynamic process that addresses the patient's goals for current and future medical care and decision making that maintain patient autonomy. This process consists of a legal document with do-not-resuscitate orders, anatomic gifts, health care power of attorney (also referred to as durable power of attorney for health care or health care proxy), living will, and written wishes regarding life-sustaining treatment. Although advance directives can be completed at any time, they are most applicable at the time of a serious life-threatening diagnosis, such as cancer, or at the time of a change in medical status. Completion of advance directives has been shown to be associated with adherence to the patient's wishes, higher patient and family satisfaction, and decreased hospital costs. However, research indicates that most patients who are terminally or seriously ill will not have had advance directives completed.

Advance directives may include the patient's wishes in the event of incapacitation and assignment of the health care power of attorney. This document assigns legal rights to another person to make decisions for the patient in the event that the patient is incapacitated. If there is no health care power of attorney assigned, state laws typically determine the next of kin or other surrogate who is responsible for decision making. A living will, if completed, is a document that includes preferences for resuscitation and use of life-sustaining measures. It is difficult for living wills to cover all topics and, therefore, the importance of the health care power of attorney and the living will is apparent.

Advance directives only apply when the patient has lost the ability to make decisions for herself. This requires the physician to assess the ability or capacity of the patient to make a decision, or the patient's competence. Although physicians attempt to respect autonomy, they often do not assess the patient's competency to make decisions, which may result in inappropriate decisions. The assessment for decision-making capacity may be permanently compromised or temporarily affected, in which case all efforts should be made to reverse the source of impairment. Any condition that affects mental status may be associated with incapacity, as are certain medical conditions such as dementia, psychiatric disorders (eg, depression, schizophrenia), and neurologic disorders. Stroke also may affect capacity for decision making; however, this is dependent on the residual effect (size and location) of the stroke.

In order to assess decision-making capacity, a number of general criteria have been recommended. These recommended criteria include that

the patient should be able to

- communicate a choice between treatment options
- understand treatment options
- understand the information leading to the decision
- understand the consequences of treatment

If the patient does not have capacity or is not likely to regain it, a health care power of attorney or health care proxy would make the decision. When a health care power of attorney has not been assigned, a health care surrogate must make the decision for the patient. Although the typical order of assignment by default is the spouse, adult children, parents, and siblings, followed by other relatives, the legal assignment may vary from state to state.

If the patient declines life-sustaining interventions, and she has been deemed to have decision-making capacity, physician orders should be placed regarding code status to ensure that the patient's wishes are followed. In the described scenario, although the patient expresses the desire for no further intervention, her decision-making capacity should be assessed first. If she meets the outlined criteria, she should be considered competent and her decision should be respected.

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Silveira MJ, Kim SY, Langa KM. Advance directives and outcomes of surrogate decision making before death. N Engl J Med 2010;362: 1211–8.

7 ⇦

Perioperative venous thromboprophylaxis

A 70-year-old woman is taken to the operating room with bilateral adnexal masses, omental caking, ascites, and an elevated CA 125 level. Her medical history is notable for a body mass index of 40 (calculated as weight in kilograms divided by height in meters squared), hypertension, and diabetes mellitus. Intraoperative frozen section demonstrates a poorly differentiated papillary serous ovarian adenocarcinoma. Extensive cytoreduction is performed. The most appropriate option for venous thromboprophylaxis for this patient is

(A) intermittent pneumatic compression
(B) graduated compression stockings
(C) low-molecular-weight heparin (LMWH)
* (D) intermittent pneumatic compression plus LMWH
(E) unfractionated heparin

Although there has been significant progress in the treatment and prevention of thromboembolic events, pulmonary embolism (PE) continues to be a common cause of preventable hospital-related death. It has been estimated that one third of the 150,000–200,000 annual deaths caused by PE occur after surgery. The risk of venous thromboembolism in women who undergo major gynecologic surgery ranges from approximately 17% to 40% without prophylaxis. The Agency for Healthcare Research and Quality identified venous thromboembolism prevention as high priority with the potential to improve patient safety in hospitals. Over the past decade, this initiative has been the impetus for multiple prevention strategies. Despite these guidelines and available prophylactic mechanisms, multiple studies have demonstrated poor adherence to thromboprophylaxis in surgical patients. Recently, the Premier Perspective database, which includes data from 500 hospitals, was studied to assess the use of venous thromboembolism prophylaxis in 738,150 women who underwent gynecologic surgery. Billing data show that 46.6% of patients received mechanical prophylaxis, 5.5% received pharmacologic prophylaxis, 8.4% received dual prophylaxis, and 39.6% received no venous thromboembolism prophylaxis. Prophylaxis was used more commonly in patients at teaching or rural hospitals and by high-volume surgeons and hospitals. Similar findings were noted in the ENDORSE survey. This study included 358 hospitals in 32 countries and demonstrated that approximately 40% of at-risk patients did not receive venous thromboembolism prophylaxis. The investigators found that use of

prophylaxis was dependent on surgery type; among gynecologic surgery patients, venous thromboembolism prophylaxis was given to approximately 53.8% of patients.

Two prophylaxis strategies have been studied extensively: mechanical and pharmacologic. Mechanical prophylaxis, which reduces venous stasis, includes graduated compression stockings and intermittent pneumatic compression. Pharmacologic therapy, which prevents thrombus formation by interacting with the clotting cascade at different points, includes unfractionated heparin, LMWH, fondaparinux sodium, warfarin, and direct factor Xa and IIa inhibitors.

Data from multiple clinical trials have shown comparable efficacy for LMWH, unfractionated heparin, and intermittent pneumatic compression. Compared with no prophylaxis, intermittent compression significantly reduces risk of venous thromboembolism. In a retrospective study of 1,862 gynecologic surgery patients treated with pneumatic compression, a high-risk cohort of patients who were more likely to fail was identified. Low-dose unfractionated heparin has been the most extensively studied medication for thromboprophylaxis. Two large meta-analyses of randomized trials in general surgery demonstrated a two-thirds reduction in fatal PE with low-dose unfractionated heparin compared with no prophylaxis. In high-risk gynecologic oncology patients, a large cohort demonstrated that a preoperative dose followed by a dose every 8 hours provided more effective venous thromboembolism prophylaxis compared with a dose every 12 hours.

Multiple trials have demonstrated the efficacy of LMWH for thromboprophylaxis compared with lowdose unfractionated heparin. A Cochrane review of gynecologic patients demonstrated equivalent efficacy for LMWH and low-dose unfractionated heparin with no difference in bleeding complications. A randomized trial of 211 gynecologic surgery patients older than 40 years found LMWH and pneumatic compression to be equally effective. In regard to choice of heparin, LMWH possesses numerous advantages: ease of use once a day, predictable pharmacodynamics, greater anti-factor Xa activity, less thrombin activity, and reduced risk of thrombocytopenia.

Patients should be assessed preoperatively for risk of thromboembolism to determine the appropriate thromboprophylaxis strategy. Risk of venous thromboembolism typically is dependent on procedure-specific (type and duration) and patient-specific risk factors. The American College of Chest Physicians has defined multiple risk

factors for thromboembolism, including age, surgery, prior venous thromboembolism, cancer, obesity, venous compression (from tumor), pregnancy, and one or more medical comorbidities such as heart disease and inherited thrombophilia. In 2012, the American College of Chest Physicians published revised clinical practice guidelines for the prevention of venous thromboembolism in nonorthopedic surgical patients. Patients were divided into four risk categories: 1) very low, 2) low, 3) moderate, and 4) high risk. Categories were defined by using a modification of the Caprini Risk Assessment Model score. Points were assigned based on particular risks (eg, major open surgery or laparoscopic surgery lasting longer than 45 minutes was assigned a score of 2 points) (Box 7-1). Using this model, a risk category is assigned a score and an associated risk (0.5–6.0%) for venous thromboembolism in the absence of prophylaxis (Table 7-1). When the risk of venous thromboembolism is considered very low (less than 0.5%), no specific prophylaxis is recommended. This typically pertains to laparoscopic surgery of less than 45 minutes.

For patients at low risk of venous thromboembolism (1.5%), mechanical prophylaxis is recommended over no prophylaxis (eg, patients with benign disease and no additional risk factors who undergo laparoscopy that lasts longer than 45 minutes). For patients at moderate risk of venous thromboembolism (3%), LMWH, unfractionated low-dose heparin, or mechanical prophylaxis is recommended (eg, patients with additional risk factors who undergo major open surgery for benign disease, extensive laparoscopies, or minor procedures). For patients at high risk of venous thromboembolism (6%), mechanical and pharmacologic prophylaxis with either LMWH or low-dose unfractionated heparin are recommended (eg, patients older than 60 years or with multiple risk factors, including cancer). In cancer patients, extended duration prophylaxis with LMWH is preferred.

BOX 7-1

Caprini Risk Assessment Model for Venous Thromboembolism

Each risk factor represents 1 point.

- Age 41–60 years
- Swollen legs (current)
- Varicose veins
- Obesity (BMI greater than 25)
- Minor surgery planned
- Sepsis (less than 1 month)

- Acute myocardial infarction
- Congestive heart failure (less than 1 month)
- Medical patient currently at bed rest
- History of prior major surgery (less than 1 month)
- History of inflammatory bowel disease
- Abnormal pulmonary function (COPD)
- Serious lung disease including pneumonia (less than 1 month)
- Oral contraceptives or hormone replacement therapy
- Pregnancy or postpartum (less than 1 month)
- History of unexplained stillborn infant, recurrent spontaneous abortion (greater than 3), premature birth with toxemia or growth-restricted infant

Each risk factor represents 2 points.

- Age 61–74 years
- Arthroscopic surgery
- Malignancy (present or previous)
- Laparoscopic surgery (greater than 45 minutes)
- Patient confined to bed (greater than 72 hours)
- Immobilizing plaster cast (less than 1 month)
- Central venous access
- Major surgery (greater than 45 minutes)

Each risk factor represents 3 points.

- Age 75 years or older
- History of DVT/PE
- Positive factor V Leiden
- Elevated serum homocysteine
- Heparin-induced thrombocytopenia
- Elevated anticardiolipin antibodies
- Positive prothrombin 20210A
- Positive lupus anticoagulant
- Other congenital or acquired thrombophilia

Each risk factor represents 5 points.

- Stroke (less than 1 month)
- Multiple trauma (less than 1 month)
- Elective major lower extremity arthroplasty
- Hip, pelvis, or leg fracture (less than 1 month)
- Acute spinal cord injury (paralysis) (less than 1 month)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism.

In the model, each independent risk factor is associated with specific points (ranging from 1 to 5) based on the risk of venous thromboembolism for each factor. A total risk factor score is calculated and corresponds to risk of developing venous thromboembolism. The scores stratify patients into risk levels based on reported incidence of venous thromboembolism. Risk levels are reported as follows:

low risk (0–1 point) with venous thromboembolism incidence of 2%; moderate risk (2 points) with venous thromboembolism incidence of 10–20%; higher risk (3–4

points) with venous thromboembolism incidence of 20–40%; highest risk (5 or more points) with venous thromboembolism incidence of 40–80%.

Reprinted from Stroud W, Whitworth JM, Miklic M, Schneider KE, Finan MA, Scalici J, et al. Validation of a venous thromboembolism risk assessment model in gynecologic oncology. Gynecol Oncol 2014;134:160–3. Copyright 2014, with permission from Elsevier.

TABLE 7-1. American College of Chest Physicians Evidence-Based Clinical Practice Guide 9th Edition: 2012 Update ⇦

Risk category	Risk for VTE	Recommendations
Very low	0.5%	No prophylaxis
Low	1.5%	Mechanical prophylaxis
Moderate	3.0%	LMWH or low-dose unfractionated or mechanical
High	6.0%	Pharmacologic plus mechanical
High with cancer		Same as above PLUS extended duration LMWH

Abbreviations: LMWH, low-molecular weight heparin; VTE, venous thromboembolism.

Reproduced with permission from the American College of Chest Physicians. Gould MK, DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in Nonorth Surgical Patients, 9th edition: American College of Chest Physicians Evidence-Based Practice Guidelines. Chest 2012;141:227–77.

The described patient has multiple procedureand patient-specific risk factors for venous thromboembolism, including type and extent of surgery, age, obesity, and newly diagnosed cancer. As such, she is considered “high risk with cancer” and is a candidate for intermittent pneumatic compression plus LMWH.

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Kakkar AK, Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Deslandes B, et al. Venous thromboembolism risk and prophylaxis in the acute care hospital setting (ENDORSE survey): findings in surgical patients. ENDORSE Investigators. Ann Surg 2010;251:330–8.

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8 ⇦xi ⇦xii

Tamoxifen citrate therapy

A 52-year-old woman with a history of breast cancer comes to your office with postmenopausal bleeding. She has taken tamoxifen citrate for 8 months. Transvaginal ultrasonography shows an endometrial stripe of 4 mm. The next step is management is

* (A) endometrial biopsy
(B) follow-up ultrasonography in 6 months
(C) hysterosalpingography
(D) hysteroscopy with dilation and curettage
(E) observation

Tamoxifen, a selective estrogen receptor modulator, has agonist as well as antagonist properties that affect target organs, likely because of variable effects on gene expression in different cell types. Tamoxifen can be prescribed as adjuvant therapy for patients with breast cancer or as a chemopreventive agent for patients at increased risk of developing breast cancer. Common adverse effects associated with tamoxifen use include menstrual irregularities, hot flushes, vaginal discharge, sexual dysfunction, and thromboembolic events.

The relative risks of pulmonary embolism and deep vein thrombosis are increased twofold to threefold in patients who take tamoxifen. Tamoxifen's estrogen-like effect on the endometrium has been associated with endometrial hyperplasia, leiomyomas, polyps, and uterine cancer. Women who take tamoxifen have more than a than twofold increased risk of developing endometrial cancer. This risk increases with higher doses and longer duration of therapy. The rate of endometrial cancer in women who take tamoxifen is 1.6 per 1,000 patient-years, compared with 0.2 per 1,000 patient-years in women who do not take tamoxifen. The risk

decreases with treatment discontinuation. Long-term follow-up data have documented a small increased incidence of uterine sarcoma associated with tamoxifen use, which has resulted in a black box warning issued by the U.S. Food and Drug Administration.

Routine annual pelvic ultrasonography or sampling of the endometrium in asymptomatic patients taking tamoxifen has been associated with no improvement in endometrial cancer detection and with increased operative interventions on the uterus for benign pathologic findings. The American College of Obstetricians and Gynecologists recommends annual gynecologic examination for all asymptomatic women who take tamoxifen. For patients who have uterine bleeding while they are taking tamoxifen, such as the described patient, endometrial sampling by biopsy is indicated, irrespective of endometrial thickness. Hysteroscopy with dilation and curettage is a more invasive procedure that may require anesthesia. Because tissue needs to be procured in order to rule out an occult malignancy or hyperplasia, it would not be appropriate to schedule this patient for follow-up ultrasonography in 6 months, to perform hysterosalpingography, or to just observe her.

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9 ⇦

Cervical cancer in pregnancy

A 38-year-old multiparous woman comes to your office with vaginal bleeding at 16 weeks of gestation. She is found to have a 3-cm friable mass confined to the cervix. She undergoes a cervical biopsy, which reveals an invasive squamous cell carcinoma of the cervix. Clinical staging and metastatic workup confirm tumor confined to the cervix. After extensive

discussion of management options, the patient states that she has no desire to continue the pregnancy and requests definitive oncologic management. The most appropriate management strategy for this patient is

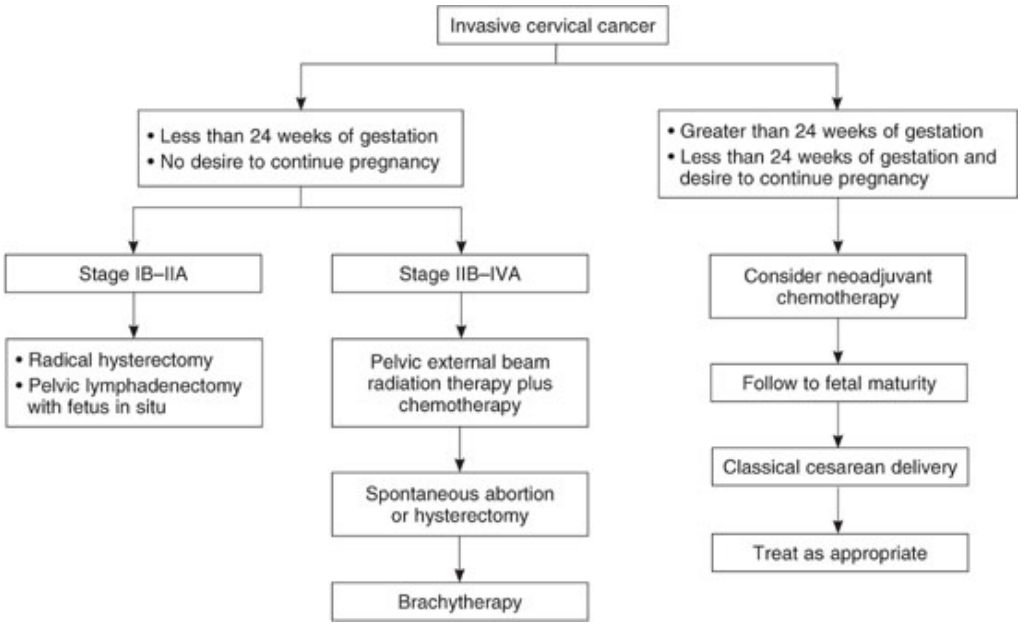
(A) cesarean delivery, radical hysterectomy, and pelvic lymphadenectomy after documenting fetal lung maturity
(B) pelvic irradiation with fetus in situ
(C) neoadjuvant chemotherapy, then radical hysterectomy and pelvic lymphadenectomy
* (D) radical hysterectomy with pelvic lymphadenectomy and fetus in situ

Any malignancy diagnosed during pregnancy poses a complex management problem. In terms of medical ethics, the patient's autonomy is of paramount importance. Survival of the patient is of great concern and must be weighed against fetal status and fetal well-being. Although cervical cancer is encountered infrequently in pregnancy, cancer of the cervix remains the most commonly diagnosed gynecologic cancer in pregnancy. Because of the rarity of the disease in pregnancy, evidence-based, standardized management guidelines are lacking. Treatment options for cervical cancer in pregnancy are similar to those for the nonpregnant patient with variations to try to optimize fetal outcomes, when desired, without compromising maternal survival. Of utmost importance are extensive counseling and discussion with the patient and her family, as appropriate, and involvement of a multidisciplinary team that should include specialists in maternal–fetal medicine, neonatology, gynecologic oncology, psychology, and other fields.

Cesarean delivery after documentation of fetal lung maturity with concomitant radical hysterectomy and pelvic lymphadenectomy is a viable option in patients who desire continuation of the pregnancy, particularly if they are close to fetal maturity. Serial magnetic resonance imaging and clinical examination can be used to evaluate for stability of disease as the pregnancy progresses. When there is no appreciable progression of disease, such patients may be treated with cesarean delivery and radical hysterectomy in the third trimester. If the patient is remote from delivery but desires to continue the pregnancy, consideration can be given to prescribing neoadjuvant chemotherapy until fetal maturity is achieved, followed by cesarean delivery and treatment as appropriate. Favorable

obstetric and oncologic outcomes have been documented in patients with stage IB cervical cancer.

Radiation therapy typically is employed in locally advanced, later-stage cervical cancer (bulky stage IB tumors and stage II–IVA cervical cancer) or patients who are not suitable surgical candidates. Stage II, stage III, and stage IV cervical cancer are encountered far less commonly in pregnancy. Although survival rates are similar for radiation therapy compared with surgery, this patient is a better candidate for surgical management, which would enable her to avoid the adverse effects of radiation treatment, particularly premature ovarian failure. The described patient has no desire to continue the pregnancy, and so the most appropriate management option is to perform a radical hysterectomy and pelvic lymphadenectomy with fetus in situ. Figure 9-1 shows an algorithm for the management of cervical cancer in pregnancy.



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10 ⇦

Evaluation of a palpable breast mass

A 52-year-old postmenopausal woman comes to your clinic for an annual well-woman examination. She had normal mammography and colonoscopy 2 years ago. She has a body mass index of 30 (calculated as weight in kilograms divided by height in meters squared) but is otherwise healthy and takes no medications. On examination of the right breast, you note a firm, nontender, fixed 1-cm mass in the right upper outer quadrant. There is no palpable axillary lymphadenopathy. The best next step to enable you to reach a diagnosis is

(A) screening mammography of both breasts
(B) ultrasonography of the right breast
(C) magnetic resonance imaging (MRI) of both breasts
* (D) diagnostic mammography of the right breast

Cancer of the breast is diagnosed in more than 230,000 U.S. women each year. In most of these cases, the cancer is a palpable breast mass, often discovered by the patient herself. Although most cases of breast cancer will occur in postmenopausal women, 31% of women in whom breast cancer was diagnosed between 1996 and 2000 were younger than 50 years. The most common benign breast mass is a fibroadenoma, and the most common malignant breast mass is invasive ductal carcinoma.

By definition, masses are three dimensional, distinct from surrounding breast tissue, and usually asymmetric with respect to the other breast. The accuracy of palpation in making a diagnosis of a mass is limited. In general, benign masses do not cause skin changes and are smooth, soft to firm, and mobile, with well-defined margins. Diffuse, symmetric thickening, which is common in the upper outer quadrants, may indicate

fibrocystic changes. Cysts cannot be distinguished reliably from solid masses by palpation alone. Malignant masses are hard, immobile, and fixed to surrounding skin and soft tissue, with irregular margins. Dimpling of the skin, retraction of the nipple, or bloody nipple discharge all are suggestive of malignancy. Lack of tenderness is characteristic but not definitive for a malignant lesion. In evaluating a palpable breast mass, the woman's age is important: a mass in a woman younger than 25 years is most likely benign, whereas a mass in a woman 70 years or older is more likely to be malignant. In addition, there are certain women who are at higher risk of malignancy by virtue of gene status, history of prior breast cancer, and history of chest irradiation; in these women, a higher index of suspicion for malignancy is warranted.

Mammography and ultrasonography are the primary imaging studies used to evaluate palpable breast masses. For women younger than 30 years, ultrasonography may be the only indicated radiologic test, whereas in women older than 30 years, diagnostic mammography should be ordered. Screening mammography consists of two standard views of each breast and is appropriate for asymptomatic women. Thus, in this symptomatic woman, screening mammography would not be appropriate.

For women older than 30 years with a palpable mass, diagnostic mammography is the appropriate test to order. In diagnostic mammography, additional views are obtained, such as tangential or spot-compression views, to better define the clinically concerning area. In a tangential view, a metallic skin marker is placed on the skin overlying the site of the palpable abnormality. Diagnostic mammography has a sensitivity in detecting cancer of up to 87%, a specificity of 88%, and a positive predictive value of 22%. Although MRI is a very sensitive test for breast imaging, it lacks specificity and, therefore, is not the first imaging choice for a patient with a palpable mass. In addition, MRI is inferior to mammography in detecting in situ cancer and cancer smaller than 3 mm, and provides no cost benefit over excisional biopsy for verifying malignancy. However, MRI may be useful in the diagnosis of a breast mass in patients with silicone breast implants and in patients for whom mammography is less sensitive, such as women who have

- breast-conserving surgery
- known carcinoma for whom disease must be ruled out
- an axillary mass and no identifiable primary tumor
- extensive postoperative scarring

- extremely dense breasts

Ultrasonography complements diagnostic mammography and can be used as a first imaging study to evaluate a palpable breast mass in a woman younger than 30 years with dense breast tissue, for whom mammography is less sensitive. Ultrasonography also is helpful in distinguishing cystic lesions from solid masses. It also may be recommended when a palpable mass is mammographically occult. When a mass appears suspicious on either ultrasonography or mammography, ultrasonography can be used to guide core biopsy or fine-needle aspiration.

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11 ⇦

Laparoscopic complications

You are dissecting the left sidewall for obturator lymph nodes during a robotic staging procedure in a morbidly obese patient who is otherwise healthy. During the dissection, significant venous oozing occurs. The operation has been going well after intubation 1.5 hours ago until the anesthesiologist urgently reports that the patient's end-tidal carbon dioxide, Sao_2, and blood pressure have dropped. Approximately 1,800 mL of saline have been infused intravenously. On heart auscultation, a millwheel murmur is noted. Breath sounds are clear and equal. The most likely diagnosis is

(A) migration of endotracheal tube
(B) myocardial infarction

(C) pulmonary edema
(D) pneumothorax
* (E) gas embolism

Gas embolism is a dangerous complication of laparoscopy. Intravascular injection of gas may follow direct needle or trocar placement into a vessel, or it may occur as a consequence of gas insufflation into an abdominal organ. This complication develops principally during the induction of pneumoperitoneum, particularly in patients with previous abdominal surgery. This also may occur later during surgery (eg, when dissecting tissue causes venous bleeding with open sinuses, allowing for venous accumulation of carbon dioxide [CO_2]). In laparoscopy, CO_2 is used because it is more soluble in blood than air, oxygen, or nitrous oxide (N_2O). Rapid elimination also increases the margin of safety in cases of intravenous injection of CO_2. All of these characteristics explain the rapid reversal of the clinical signs of CO_2 embolism with treatment. Consequently, the lethal dose of embolized CO_2 is approximately five times greater than that of air.

The pathophysiology of gas embolism also is determined by the size of the bubbles and the rate of intravenous entry of the gas. During laparoscopy, the rapid insufflation of gas under high pressure causes a “gas lock” in the vena cava and right atrium; obstruction to venous return can result in a decrease in cardiac output or circulatory collapse. Acute right ventricular hypertension may open the foramen ovale, allowing paradoxical gas embolization. Paradoxical embolism may occur without a patent foramen ovale. Volume preload diminishes the risk of gas embolism and of paradoxical embolism. Ventilation–perfusion mismatching develops with increases in physiologic dead space and hypoxemia.

The diagnosis depends on detection of gas emboli in the right side of the heart or on recognition of the physiologic changes from embolization. Signs of an enlarging gas embolus include tachycardia, cardiac arrhythmias, hypotension, increased central venous pressure, alteration in heart tones (mill-wheel murmur), cyanosis, and electrocardiographic changes of right heart strain. Capnography or capnometry are more valuable than oximetry in detection of gas embolus because the end-tidal CO_2 decreases because of a decrease in cardiac output and increase in dead

space. Aspiration of gas bubbles by a central line into the right atrium is diagnostic but rarely needed.

Release of the pneumoperitoneum should be the first treatment maneuver. The patient should then be placed in a steeper Trendelenburg position and turned to the left side (Durant position) to further prevent flow of the gas into the pulmonary circulation. She should be placed on 100% fraction of inspired oxygen. Hyperventilation will accelerate elimination of CO_2. Pulmonary edema can occur occasionally with CO_2 embolus. The patient's mill-wheel murmur is highly suggestive of gas embolism. Intraoperative myocardial infarction is unlikely given her insignificant prior history. Patients with pulmonary edema will have abnormal breath sounds such as rales or rhonchi, and patients with endotracheal tube migration or pneumothorax will have decreased breath sounds on at least one side.

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12 ⇦

Large-bowel abnormalities

A 76-year-old woman underwent primary cytoreductive surgery for ovarian cancer. She developed recurrent disease 3 months after she completed chemotherapy. She is considered to be platinum resistant. She subsequently received two additional chemotherapy regimens without response. Currently, she is near the end of her third cycle of a new regimen. She tells you she has had abdominal pain, bloating, and no bowel movement for the past 6 days. Computed tomography scan reveals

worsening pelvic disease, narrowing of the distal sigmoid colon, normal small bowel, and an enlarged colon with a cecum diameter of 10 cm (Fig. 12-1). The most appropriate treatment is

(A) nasogastric tube
(B) percutaneous endoscopic gastrostomy tube
* (C) endoscopic colorectal stent
(D) ileostomy
(E) cecostomy tube

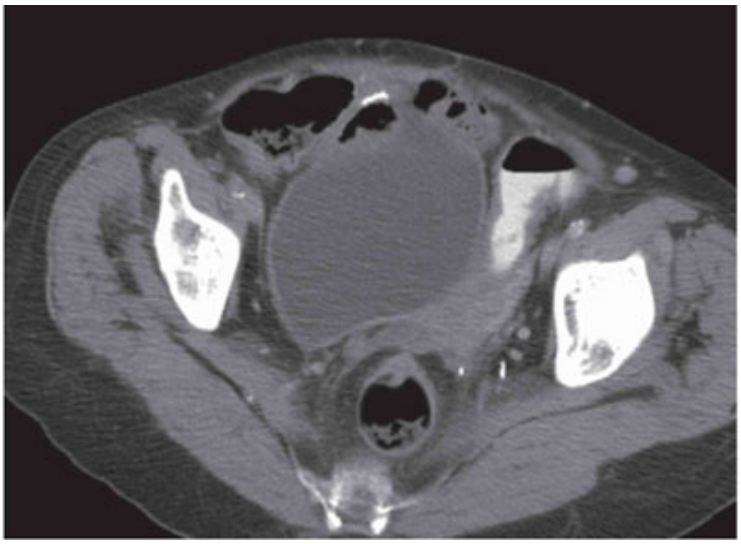

FIG. 12-1. ⇦

Intestinal obstruction is a common complication in patients with a gynecologic cancer. Such obstructions can occur in up to 50% of patients with ovarian cancer. Obstruction may occur at any level of the gastrointestinal tract, and it is important to distinguish the site of obstruction as soon as possible. Small-bowel obstruction occurs more often in patients with abdominal disease or carcinomatosis; it generally is accompanied by nausea and vomiting and is often multifocal. Nasogastric suctioning is critical, and management usually includes a combination of gastrointestinal rest, surgical repair or bypass, ostomy creation, or gastrostomy tube placement. The management of small-bowel obstruction in the palliative setting is complex.

Large-bowel obstruction, although less common, often presents in a dramatic fashion. Patients with large-bowel obstruction are severely ill and urgent decision making is required. The majority of patients who

experience largebowel obstruction are those with colorectal cancer and, therefore, most of the literature is derived from patients with this disease. The major difference between largebowel obstruction and small-bowel obstruction is related to the concept of a “closed loop.” In most patients, the ileocecal valve does not allow reflux of air or gastrointestinal contents from the large bowel into the ileum. Any process, such as a tumor, scarring, or radiation therapy, that closes off access of gastrointestinal contents to the anus will lead to a closed loop and ultimately result in large-bowel perforation if not treated.

Treatment for large-bowel obstruction includes direct decompression of the potential closed loop. Therefore, gastric decompression with either a nasogastric tube or a percutaneous endoscopic gastrostomy tube would not alleviate the problem. Although an ileostomy would decrease the inflow of gastrointestinal contents to the large bowel, it would not relieve the obstruction or decrease the risk of perforation.

In patients with gynecologic malignancies, most cases of large-bowel obstruction occur in the pelvis. Figure 12-2 shows the computer tomography scan from Figure 12-1 with labeling that shows the tumor compressing the sigmoid colon against the pelvic sidewall. Classically, treatment for this condition includes emergency surgery with colostomy by means of either a transverse loop or an end colostomy with a mucous fistula. It is important that the proximal and distal large-bowel loops be allowed to drain to avoid creation of a new closed loop. A cecostomy tube can be used in a patient for whom surgical ostomy creation is not feasible. A cecostomy tube can be a temporizing solution, but such tubes work poorly in the long term because formed stool does not pass easily through the tube.

Colonic stenting has been evaluated extensively in the management of acute malignant large-bowel obstruction in an effort to avoid surgery while relieving the obstruction. These stents are placed endoscopically. They require that a small endoscope be passed transrectally beyond the area of obstruction. As soon as the stent is deployed, it begins to embed permanently in the wall of the colon. Such large-bowel stents have been evaluated primarily among patients who are under palliative care, such as the described patient. This patient has platinum-resistant disease without response to chemotherapy. She has a limited life span, and avoiding recovery from surgery, if possible, is important. In one study that involved 35 gynecologic cancer patients, 25 patients had recurrent ovarian cancer, and 77% underwent successful stent placement and immediate

decompression. In these patients, the median survival was 7.7 months. One third of the patients subsequently required additional surgery to relieve their obstruction.

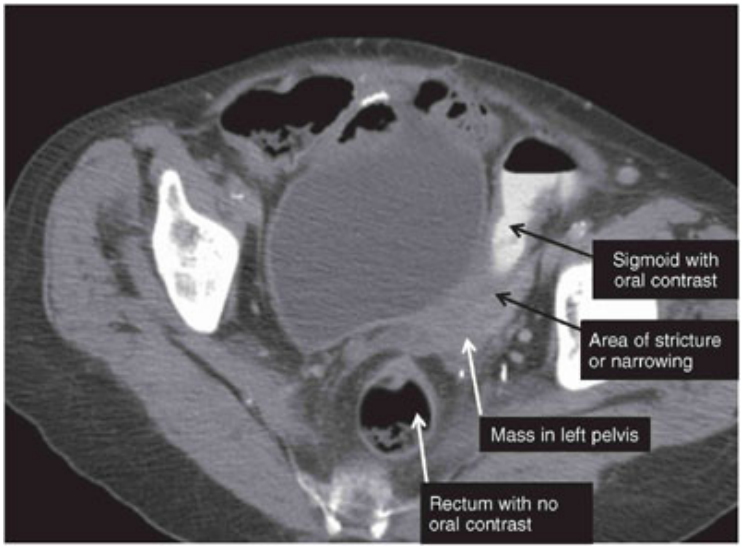

FIG. 12-2. Computerized tomography scan in Figure 12-1 with labeling that shows the tumor compressing the sigmoid colon against the pelvic sidewall.

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13 ⇦

Breast surveillance in patients who are *BRCA* positive

A 35-year-old woman comes to your clinic for her annual well-woman examination. She is healthy and takes no medications. She reports that her mother had ovarian cancer at age 50 years. The patient and her mother

have the *BRCA2* gene mutation. She requests information regarding breast cancer screening. The most appropriate recommendation is

(A) a monthly breast self-examination
(B) mammography at age 40 years
(C) annual breast magnetic resonance imaging (MRI)
* (D) annual breast MRI alternating with semiannual mammography
(E) mammography and breast ultrasonography

Women who carry a *BRCA1* or *BRCA2* gene mutation have a lifetime risk of breast cancer estimated to be 60–90%. Women who are *BRCA* mutation carriers also are at increased risk of developing breast cancer at a young age and of developing a second breast cancer. In the 10 years after diagnosis of breast cancer in a *BRCA1* or *BRCA2* mutation carrier, the risk of contralateral breast cancer is approximately 35%. Options for reducing breast cancer risk in *BRCA* mutation carriers include prophylactic surgery (bilateral mastectomy or bilateral salpingo-oophorectomy), tamoxifen citrate (chemoprophylaxis), and surveillance with imaging and breast examinations.

Annual mammography is the primary screening modality for breast cancer in the general population. It has been demonstrated that yearly screening mammography decreases breast cancer mortality in the general population, but annual mammography is not as effective in *BRCA* mutation carriers for two major reasons. First, younger women are more likely to have dense breast tissue, which decreases the sensitivity of mammography. Second, *BRCA* mutation carriers have a higher rate of so-called interval cancer (ie, cancer that is diagnosed between screening studies) and, as a result, annual screening is insufficient.

Unlike mammography, MRI is unaffected by breast density and does not use ionizing radiation. Screening MRI identifies cancer at smaller sizes and earlier stages in women with an increased risk of breast cancer. The combination of alternating MRI and digital mammography starting at age 25–30 years achieves the greatest reduction in breast cancer mortality in *BRCA1* and *BRCA2* mutation carriers. The *BRCA2* cohort receives the greatest benefit with this alternating strategy, which reduces breast cancer mortality by 16.7% in the *BRCA1* cohort and 31.1% in the *BRCA2* cohort. In one retrospective review from a large cancer center, 73 patients with confirmed genetic mutations (*BRCA1* or *BRCA2*) underwent imaging

screening with alternating MRI and mammography every 6 months, resulting in an overall cancer yield of 15%.

Compared with MRI, ultrasonography has a lower sensitivity (77–91% and 33–44%, respectively) for the detection of breast cancer. The addition of ultrasonography to screening provides no additional benefit over screening with MRI and mammography. However, ultrasonography can be useful to further evaluate suspicious breast lesions identified on MRI.

Potential disadvantages of more intensive breast cancer screening include an increased number of false-positive screens, which lead to additional imaging, biopsies, and patient anxiety. Additional potential harms of more frequent screening include the possibility of mammography-induced breast cancer and overdiagnosis or overtreatment of breast cancer that ultimately may not cause death.

The alternative to breast screening for women at very high risk of breast cancer is bilateral prophylactic mastectomy, which reduces mortality by more than 90%. Most *BRCA* mutation carriers in the United States do not elect to undergo prophylactic mastectomy. Women who are at very high risk of breast cancer and who choose screening over risk-reducing mastectomy should be counseled that no screening test has a sensitivity of 100%. In addition, some very small tumors may be incurable at the time of detection. Women who elect screening should consider other risk-reducing measures such as chemoprophylaxis with tamoxifen or other selective estrogen receptor modulators or else surgery by means of bilateral salpingo-oophorectomy. Bilateral salpingo-oophorectomy has been demonstrated to decrease the risk of breast cancer, particularly in *BRCA1* mutation carriers if performed before age 40 years. The risk of contralateral breast cancer is reduced by 50% in *BRCA1* and *BRCA2* mutation carriers when tamoxifen is used for the treatment of the initial breast cancer.

Other women at high risk of breast cancer include first-degree relatives of known *BRCA* mutation carriers, women who have multiple relatives with early-onset breast or epithelial ovarian cancer, women who were treated with chest irradiation before age 30 years, women with a history of lobular carcinoma in situ or atypical ductal or lobular hyperplasia, and women with very dense breasts for whom mammography is less sensitive. More frequent screening and the addition of MRI may be considered as an option for such women; however, the benefit of MRI in these high-risk populations is unknown. The recent American Cancer Society guidelines recommend MRI of the breast to screen women who had chest irradiation

before age 30 years. This recommendation should not be applied universally.

Breast self-examination alone is not sufficient in high-risk women for the detection of breast cancer. Therefore, the recommendation for this patient, based on the American Cancer Society guidelines, is annual MRI alternating with semiannual mammography.

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14 ⇦

Deep vein thrombosis

A 62-year-old woman comes to your clinic for postoperative evaluation 2 weeks after undergoing an exploratory laparotomy and debulking surgery for a stage IIIC serous ovarian cancer. The patient reports no symptoms and appears to be recovering well. Physical examination reveals a temperature of 37.0°C (98.6°F), pulse of 120 beats per minute, blood pressure of 130/65 mm Hg, respiratory rate of 12 breaths per minute, and pulse oxygen of 96% on room air. She appears well, her lungs are clear to auscultation bilaterally with normal respiratory effort, and heart examination reveals tachycardia with normal rhythm. Electrocardiography shows sinus tachycardia. Computed tomography–pulmonary angiography reveals a right lower lobe pulmonary embolism (PE). The patient's complete blood count and comprehensive metabolic panel are normal. The best next step in management is

(A) warfarin

* (B) low-molecular-weight heparin (LMWH)
(C) argatroban
(D) unfractionated heparin
(E) thrombolysis

Untreated venous thromboembolic events are associated with a mortality rate of 30%. Even patients who have a PE and receive treatment have a risk of death of 11% during the first 3 months of their therapy. Acute morbidity from deep vein thrombosis (DVT) includes pain and swelling that may prohibit ambulation and, in severe cases, can cause arterial compromise. Severe complications of PE include chest pain, dyspnea, and hypoxia, along with more severe complications such as hypotension and shock. Long-term complications of DVT include postphlebitic syndrome in up to 40% of patients. Long-term complications of PE include chronic thromboembolic pulmonary hypertension in 1–4% of patients.

The initial goal of treatment is prevention of DVT/PE extension and relief of acute symptoms and aversion of hemodynamic compromise and death. Options for initial treatment include LMWH, unfractionated heparin, rivaroxaban, or fondaparinux. A Cochrane review comparing LMWH with unfractionated heparin showed that LMWH was associated with decreased risk of recurrent venous thromboembolic events (3.6% versus 5.2%) (odds ratio [OR], 0.70; 95% confidence interval [CI], 0.57–0.85), decreased mortality (4.4% versus 5.8% [OR, 0.77; 95% CI, 0.63–0.93]), and decreased risk of hemorrhage (OR, 0.58; 95% CI, 0.40–0.83). The reduction in mortality was magnified in patients with malignant disease (OR, 0.16; 95% CI, 0.03–0.72). These findings, in combination with the ease of administration of LMWH compared with unfractionated heparin, make LMWH the preferred initial management for venous thromboembolic events except in the case of renal insufficiency, in which unfractionated heparin is the preferred regimen. Rivaroxaban, which is an oral factor Xa inhibitor, has been shown not to be inferior to LMWH with a similar hemorrhagic complication rate; however, the current cost of rivaroxaban in the United States limits its widespread use.

Argatroban is a direct thrombin inhibitor with a short half-life. Its effect can be monitored by partial thromboplastin time. It has been demonstrated to reduce thrombotic events with low risk of bleeding complications. It has been approved for prophylaxis and treatment of thrombosis in the setting of heparin-induced thrombocytopenia.

Because of the initial inhibition of the anticoagulants protein C and protein S before inhibition of the vitamin K-associated coagulation factors (coagulation factors II, VII, IX, X), initial treatment with warfarin without concomitant LMWH is contraindicated. The recommendation is to continue LMWH for at least 5 days and until the international normalized ratio is 2.0. A systematic review of LMWH compared with vitamin K antagonist in cancer patients showed a decreased risk of recurrent venous thromboembolic events in cancer patients with long-term use of LMWH (7.2% versus 13.4% [relative risk, 0.53; 95% CI, 0.36–0.76, *P*=.001]). For patients with malignancy-associated venous thromboembolic events (DVT or PE), the American College of Chest Physicians recommends long-term anticoagulation with LMWH over vitamin K antagonist for the first 3–6 months, with anticoagulant therapy recommended indefinitely or until the cancer is resolved.

Thrombolytic therapy is of limited use for treatment of DVT because of the effectiveness of anticoagulant therapy and an increased risk of hemorrhagic complications. Possible indications for thrombolytic therapy are massive iliofemoral DVT in patients who are at risk of limb gangrene despite appropriate anticoagulation therapy. A systematic review of thrombolytic therapy for treatment of PE showed faster resolution of radiographic and hemodynamic abnormalities caused by acute PE. However, over time, there was no difference in radiographic outcomes compared with anticoagulant therapy alone, and there was no difference in clinical outcomes such as death or symptom resolution. Additionally, thrombolytic therapy is associated with a 1–2% risk of intracranial bleeding. For this reason, thrombolytic therapy is only recommended for acute treatment of patients with massive PE who are hemodynamically unstable and who are at low risk of bleeding.

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15 ⇦

Human papillomavirus vaccination

A 24-year-old woman comes to your office for her annual well-woman examination. She reports that she has regular painful menses that last 5 days but is otherwise healthy. She reports no prior sexual activity and no prior use of hormonal contraceptives. She is a nonsmoker. As her best gynecologic preventive health option, you recommend

(A) annual Pap testing
* (B) initiation of human papillomavirus (HPV) vaccine series
(C) Pap test with HPV cotesting
(D) HPV testing
(E) urine testing for gonorrhea and chlamydial infection

Annual cytologic testing by means of Pap testing has helped to reduce the incidence of cervical cancer in the United States by nearly 80%. However, true prevention of cervical cancer and other HPV-related cancer will be achieved only through primary prevention of HPV infection by vaccination of all eligible individuals and aggressive screening programs to identify and treat individuals with precancerous lesions. More than 140 HPV subtypes have been identified; of these subtypes, 40 are commonly associated with the anogenital tract, with HPV subtypes 16 and 18 accounting for 70% of cases of cervical cancer. In sexually active young women, HPV infection is nearly universal in prevalence, and approximately 87% of these infections are of an HPV subtype found in the commercial HPV vaccines. Penetrative intercourse is not required to spread HPV; rather, the infection can be spread through skin-to-skin or mucosal contact alone. Condom use reduces, but does not eliminate, the risk of HPV infection.

The requirement of persistent HPV infection for the development of a malignancy of the cervix, vagina, vulva, anus, penis, or oropharynx is well established. Infection with an oncogenic HPV subtype most often results in a low-grade lesion with high likelihood of spontaneous regression. Approximately 40–80% of women will have an HPV infection within 2 years after sexual debut. More than 90% of infected women will test negative for HPV by standard screening methods within 2 years, but only 60% of individuals develop type-specific antibodies rendering them immune to infection with the same HPV subtype. Highand low-risk HPV types can remain latent for many years, with immunologic tolerance to the HPV infection within an individual. Current screening methods only identify current viral shedding and help triage women at risk of serious cervical cancer precursors.

In the United States, two main HPV vaccines have been commercially available, both of which target HPV subtypes 16 and 18. These vaccines are approved for the vaccination of females aged 9–26 years to prevent HPV-associated genital tract cancer and precancer. The quadrivalent vaccine also has an indication for vaccination of males aged 9–26 years for the prevention of genital warts, anal cancer, and HPV-related precancerous disease. In phase III efficacy trials, the quadrivalent vaccine showed 100% efficacy in prevention of HPV subtype 6-, 1116-, and 18-related cervical intraepithelial neoplasia 3 in HPV-naïve individuals but 45% efficiency in the intention-to-treat group, who had previous exposure to HPV at enrollment. High-grade vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia were prevented in 95% and 75% of patients, respectively, regardless of prior HPV exposure. Similarly, the bivalent vaccine provided 100% efficacy in prevention of cervical intraepithelial neoplasia 3 in the HPV-naïve population and 46% efficacy in the total vaccinated group. Both vaccines show cross-protection to infection with other high-risk types, with the bivalent vaccine showing greater protection against HPV subtypes 31, 33, and 45. Neither was significantly protective against HPV subtypes 52 and 58. A nonavalent vaccine targeting nine HPV subtypes (6, 11, 16, 18, 31, 33, 45, 52, and 58) has been approved for clinical use. Studies have shown that protection conferred by the new vaccine decreased the risk of lower genital tract dysplasia and dysplasia-related procedures by more than 96% compared with the quadrivalent vaccine.

Initiation of the HPV vaccination series as a primary prevention strategy constitutes the best gynecologic preventive health option for the

described patient. The number of potential HPV infections increases with age and number of lifetime sexual partners. Despite the fact that most women between ages 20 years and 25 years will be exposed to HPV, only 21% of women aged 19–26 years have received at least one dose of HPV vaccine. Penetrance of HPV vaccination in teenagers is improving but is still low. The 2010 National Immunization Survey–Teen data found that 32% of teenagers completed a 3-dose HPV vaccination series, and almost one half of teenagers received one or more doses.

Current American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines call for triennial screening with cytology alone for women aged 21–29 years; HPV reflex testing with atypical squamous cells of unknown significance is acceptable for women aged 21–24 years and recommended for women aged 25–29 years. For women aged 30 years and older, screening with cytology and HPV cotesting every 5 years is preferred, although cytology alone every 3 years is acceptable. Notably, these screening procedures are carried out regardless of HPV vaccination status.

As previously shown, primary prevention of HPV infection occurs most reliably when a vaccinated individual is HPV naïve. Testing for HPV should not be performed before vaccination, nor should vaccine be withheld if a woman has a history of HPV infection. This healthy woman, with no prior sexual activity, is likely to be HPV naïve and should be offered an HPV vaccine series. The ASCCP guidelines call for cytology screening only beginning at age 21 years, regardless of time of sexual debut, because the prevalence of HPV infection in sexually active women younger than 30 years is very high. Cytology screening for this sexually naïve woman would be of low yield. Annual Pap test or HPV testing would not be appropriate. Given that she is not sexually active, a urine test for gonorrhea and chlamydial infection for a routine well-woman examination is not useful.

As of April 2014, the U.S. Food and Drug Administration has approved a primary HPV screening test for women 25 years and older, with cytology used as a triage for women who test positive for HPV subtypes 16 and 18. A new screening algorithm using primary HPV testing has been endorsed by the Society of Gynecologic Oncology, ASCCP, American College of Obstetricians and Gynecologists, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology. After primary screening is performed, if high-risk HPV such as subtype 16 or 18

is identified, colposcopy is recommended. If testing shows the presence of one of the other 12 high-risk HPV types, cytology is recommended, and if negative for high-risk HPV, routine screening is recommended.

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16 ⇦

Necrotizing fasciitis

A 28-year-old woman, gravida 2, para 2, comes to your office with fever and severe incisional pain 4 days after a primary cesarean delivery. Her pregnancy was complicated by insulin-requiring gestational diabetes mellitus, prolonged rupture of membranes, and cesarean delivery for second-stage failure of fetal descent. She has a temperature of 39.5°C (103.1°F), pulse of 125 beats per minute, and blood pressure of 100/50 mm Hg. Her lungs are clear, abdomen is soft, uterus is tender with the fundus at the umbilicus, and her extremities have 1+ edema. The abdominal incision is erythematous and edematous, leaking a cloudy serous discharge, and is exquisitely tender. In addition to starting antibiotics, the next step in patient management is

* (A) debridement of incision
(B) wound packing with calcium alginate
(C) aspiration and culture of wound
(D) computed tomography (CT) scan of abdomen

The described patient has clinical features and history worrisome for necrotizing fasciitis, including an exquisitely tender, erythematous, edematous incision after a cesarean delivery. She has an additional risk

factor: having had glucose intolerance during pregnancy requiring insulin. Her fever and relative hypotension speak to systemic illness, but the differential diagnosis includes endometritis, wound cellulitis, and necrotizing fasciitis. Because of her systemic symptoms and clinical presentation, surgical debridement of her wound is the preferred first step in management. Culture of the wound or observation with antibiotics would delay definitive therapy and increase her risk of death. Although a CT scan can be helpful in detecting necrotizing fasciitis, given that she exhibits the classic signs and symptoms of the disease, giving her a CT scan would delay her definitive management. She should begin broad-spectrum antibiotics to prevent additional systemic infection and be taken emergently to the operating room, and subsequently to the intensive care unit for supportive care. In patients with severe necrotizing soft tissue infections, other nosocomial infections are seen in approximately 76% of patients, ventilator-dependent respiratory failure and adult respiratory distress syndrome in 30%, and renal failure in 30%. Prompt recognition of a necrotizing soft tissue injury may be lifesaving.

Necrotizing soft tissue infection is a potentially life-threatening, rapidly progressive disease associated with mortality of approximately 25–35%. Fascial necrosis is the defining hallmark of necrotizing fasciitis and requires early clinical suspicion, appropriate antimicrobials, and surgery to prevent overwhelming sepsis. The speed of development of clinical features of necrotizing fasciitis and risk of death are dependent on the causative organism. Most commonly, necrotizing fasciitis is a polymicrobial disease, often including bowel flora and *Clostridium septicum* or *tertium*. *Clostridium sordellii* infection is more commonly associated with a gynecologic infection. Group A streptococcal infections and *Staphylococcus aureus* infections account for approximately 25% of necrotizing soft tissue infections but often progress more rapidly. The distinguishing clinical features of necrotizing fasciitis are “dishwater fluid” due to serous fluid and lysed inflammatory cells being produced in an area of fascial necrosis, myositis, and myonecrosis, plus rapidly worsening pain, caused by infarction of nerves in the subcutaneous space followed by anesthesia. The earliest clinical feature is pain out of proportion to the external wound. As nerves supplying the necrotizing area of skin die, the central area becomes anesthetic, whereas the lateral tissues remain exquisitely tender. As underlying infection ascends to the skin, the epidermis and dermis become edematous (woody) and can progress to cutaneous necrosis.

Type I polymicrobial infections occur more often in the perineum and trunk, commonly in immunocompromised patients, such as patients with diabetes mellitus. Other risk factors for infection include obesity, chronic renal failure, human immunodeficiency virus (HIV) infection, intravenous drug use, surgical incision, blunt or penetrating trauma, or intra-abdominal abscess. Type II group A streptococcal infections with or without associated *S aureus* infection occur in young immunocompetent patients, usually beginning on the extremities, or if occurring on the trunk, after recent surgery. Methicillin-resistant *S aureus* (MRSA) and group A streptococcal infections have been observed in up to 40% of cultures taken from intravenous drug users, athletes, and institutionalized patients.

Early complete debridement of devitalized tissue is the mainstay of treatment. Incomplete initial debridement has been associated with a 7.5-fold increase in mortality, and a delay of more than 24 hours in debridement is associated with a ninefold increase in mortality. Initial boundaries of excision should be inclusive of the area of erythema and edema and should reach healthy bleeding tissue. Serial debridement often is required when an area of residual tissue demarcates with erythema and edema. Combination antibiotic therapy to cover gram-positive and gram-negative aerobes as well as anaerobic organisms should be continued until the patient has no signs of systemic infection. Empiric addition of an antibiotic for MRSA is also reasonable, considering the rapid increase in MRSA infections seen with group A streptococcal infection necrotizing fasciitis.

Because local erythema, edema, and tenderness are the most common findings of necrotizing fasciitis, many patients are initially diagnosed erroneously with simple cellulitis. Even in cases of documented necrotizing fasciitis, fever and hypotension are present at the time of initial diagnosis less than 50% of the time. A high level of clinical suspicion, close observation of the patient, and willingness to proceed with operative exploration are critical to the care of a necrotizing fasciitis patient. A CT scan provides approximately 80% sensitivity for diagnosis with an ability to identify thickened fascial planes and subcutaneous gas or fluid collections.

After debridement, this patient is likely to be left with a large abdominal wound, and closure by secondary intention is appropriate. A vacuum-assisted closure device can be used to facilitate closure after all necrotic and non-viable tissue has been removed. Until a vacuum-assisted closure device can be placed, other wound care options include saline wet-

to-dry dressings, charcoal-based dressings, or alginate-based dressings. Charcoal dressings are used for malodorous wounds, including surgical, traumatic, and gangrenous wounds or pressure sores. Charcoal dressings are pliable, comfortable, and smooth and are nonadhesive. Alginate dressings are derived from seaweed and are highly absorbent and biodegradable. They are used for moderately secreting wounds. The high absorption is achieved via strong hydrophilic gel formation, which limits wound secretions and minimizes bacterial contamination. The dressing maintains a physiologically moist microenvironment that promotes healing and the formation of granulation tissue. Alginates can be rinsed away with saline irrigation, so removal of the dressing does not interfere with healing granulation tissue.

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17 ⇦

Fibrocystic changes and risk of breast cancer

A 47-year-old woman comes to your clinic for routine bilateral screening mammography. She is found to have fibrocystic changes and a small mass that, on biopsy, is consistent with ductal hyperplasia without atypia. The most appropriate next step is

(A) breast ultrasonography
(B) breast magnetic resonance imaging
(C) excisional breast biopsy
(D) tamoxifen citrate
* (E) observation

Histologically, benign epithelial breast lesions are classified into three groups, depending on the degree of cellular atypia and proliferation:

1. Nonproliferative
2. Proliferative without atypia
3. Atypical hyperplasia

Nonproliferative breast lesions include fibrocystic changes, fibrocystic disease, chronic cystic mastitis, mammary dysplasia, and breast cysts. These lesions are not associated with an increased risk of breast cancer. Breast cysts are more common in women aged 35–50 years and may be observed as breast masses on physical examination or seen as abnormalities on breast mammography. Such breast cysts can be painful and may require aspiration to alleviate the discomfort.

Proliferative breast lesions without atypia may be associated with a small increased risk of developing breast cancer, estimated to be 1.5–2 times greater than the general population risk. Such lesions include ductal hyperplasia, intraductal papillomas, sclerosing adenosis, radial scars, and fibroadenomas. Although simple fibroadenomas are not associated with an increased risk of breast cancer, the risk is slightly higher in patients with complex fibroadenomas, a family history of breast cancer, or a fibroadenoma adjacent to proliferative disease. Ductal hyperplasia without atypia is another proliferative breast lesion. It is often a pathologic diagnosis or an incidental finding made histologically at the time of tissue biopsy done as part of the evaluation of a mammographic abnormality or a breast mass. Histologically, it is characterized by an increased number of cells within the ductal space that can vary in shape and size but retain the cytologic characteristics of benign cells. Patients with ductal hyperplasia, such as the described patient, require no further evaluation or treatment given that the risk of developing breast cancer is small. Thus, chemoprevention is not indicated.

Proliferative lesions with atypical hyperplasia include atypical ductal hyperplasia and atypical lobular hyperplasia. These lesions typically are found at the time of tissue biopsy in the evaluation of a breast mass or a mammographic abnormality and are associated with increased risk of breast cancer (relative risk, 3.7–5.3). Women with atypical hyperplasia may benefit from risk-reducing strategies. Semiannual breast examinations and yearly mammographic examinations are recommended.

Primary chemoprevention with a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or with an aromatase inhibitor may be appropriate risk-reduction strategy for some of these patients. Given that ductal hyperplasia without atypia usually represents an incidental finding

and requires no further treatment, this patient requires no further intervention and observation is the most appropriate next step.

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18 ⇦

Blood product selection after massive hemorrhage

A 70-year-old woman in whom stage III ovarian cancer is diagnosed has a medical history that is significant for diabetes mellitus and hypertension. During cytoreductive surgery, there is an estimated 1,500-mL blood loss with ongoing bleeding due to extensive peritoneal stripping. Her temperature is 36.1°C (97.0°F), pulse is 140 beats per minute, and blood pressure is 96/64 mm Hg. Laboratory testing shows a hemoglobin level of 6.8 g/dL, platelet level of 75,000/mm^3, and prolonged prothrombin time and partial thromboplastin time. The best management for this patient is

(A) warmed crystalloid solution, 5 mL per 1 mL blood loss
(B) intravenous colloid, packed red blood cells (RBCs), 1 mL of colloid and packed RBCs per 1 mL blood loss
(C) fresh frozen plasma, cryoprecipitate, crystalloid, 1 unit each to 1 L crystalloid
(D) packed RBCs, platelets and crystalloid in 1 unit of packed RBCs and platelets to 1 L crystalloid
* (E) packed RBCs, fresh frozen plasma, platelets, balanced as 1:1:1 units transfused

During surgery, blood loss of 1,000 mL or blood loss that requires transfusion is considered intraoperative hemorrhage. Intraoperative hemorrhage is an uncommon complication of gynecologic surgery. Risk factors for intraoperative hemorrhage include obesity, poor visibility,

distorted anatomy, surgical factors (such as surgeon's experience and surgical volume), and patient's use of supplements or prescribed platelet inhibitors. Dissection outside the central pelvis puts fragile high-volume veins at risk of injury, particularly with extensive blunt dissection. Surgery that requires peritonectomy and extensive cytoreduction has a 40–80% risk of intraoperative transfusion.

The described patient has had significant blood loss and has developed a consumptive coagulopathy. She has hypothermia, which will contribute to the severity of her coagulopathy, as well as signs of volume depletion with elevated heart rate and low blood pressure. She needs rapid resuscitation of blood volume and blood products to reverse her coagulopathy and avoid the sequelae of shock-impaired organ function and death. The surgical team should alert the blood bank, transfusion medicine service, or both to the situation and activate the hospital's massive transfusion protocol. All hospitals should have an algorithm that allows for rapid release of blood and blood components in critical situations (Fig. 18-1).

Traditional paradigms for management of intra-abdominal hemorrhage called for rapid infusion of large amounts of crystalloid solution to expand the intravascular space and transfusion of RBCs to maintain a hemoglobin level of 7 g/dL. Additional blood components such as fresh frozen plasma and platelets were given only after transfusion of 6 or more units of RBCs. Fresh frozen plasma contains all of the factors of the soluble coagulation system, including the labile factors V and VIII. This traditional management of hypovolemia and shock resulted in dilution of coagulation factors and worsening coagulopathy. Intraoperative hemorrhage and coagulopathy should be managed with restricted use of crystalloid solution and aggressive transfusion of RBCs, fresh frozen plasma, and platelets to rapidly correct coagulopathy. Such balanced transfusion practices have been associated with improved outcomes in trauma settings, and recent studies support such practices in the general population.

A patient with hypovolemic shock from large intraoperative blood loss has inadequate tissue perfusion and lactic acidosis. A pH of 7.2 will decrease factor Xa and prothrombin activity by 50%, and temperatures between 33°C and 37°C (91.4°F and 98.6°F) will impair tissue factor activity and platelet function. Coagulopathy occurs when coagulation factors are consumed, are diluted to inactive concentrations in vivo, or when there is tissue injury or hypoperfusion. Coagulopathy also arises in patients who have undergone massive transfusion as a result of the

dilutional effect of packed RBCs rather than whole-blood administration. Massive hemorrhage also can cause a consumptive coagulopathy, which further increases the severity of the clotting disorder. Coagulopathy is demonstrated by thrombocytopenia (platelets less than 50,000/mm^3), low fibrinogen (less than 100 mg/dL), and prolonged prothrombin time and partial thromboplastin time.

The described patient should have resuscitation tailored to her vital signs and laboratory values supporting coagulopathy. Warmed crystalloid as well as warm irrigation and forced warm air blankets will help raise her core temperature. Intravenous pressors will help to support her blood pressure. Her anemia and coagulopathy are best treated with blood component therapy. Most blood banks do not store whole blood but immediately separate RBCs from plasma. The RBCs and plasma from an individual donor are frozen separately in units. Although some blood banks pool platelets from many donors together, most institutions prefer to obtain donor platelets from pheresis of a single donor. Previous guidelines called for transfusion of fresh frozen plasma and platelets after transfusion of 6 units of RBCs. This does not sufficiently restore adequate concentrations of coagulation factors that have been lost by hemorrhage or diluted by RBC and crystalloid transfusion. Recent trauma and military studies support a transfusion ratio of 1:1:1 of RBCs, fresh frozen plasma, and platelets as soon as resuscitation begins, regardless of anticipated blood component needs. An early and aggressive transfusion protocol can prevent coagulopathy and has been shown to decrease mortality by 15–25% in trauma patients who require massive transfusion. Restrictive transfusion protocols improve the 30-day in-hospital mortality rate of critically ill patients. In a typical community hospital setting, however, it can be difficult to achieve an appropriate ratio because thawing times for fresh frozen plasma can be longer than 1 hour compared with 20 minutes for packed RBCs.

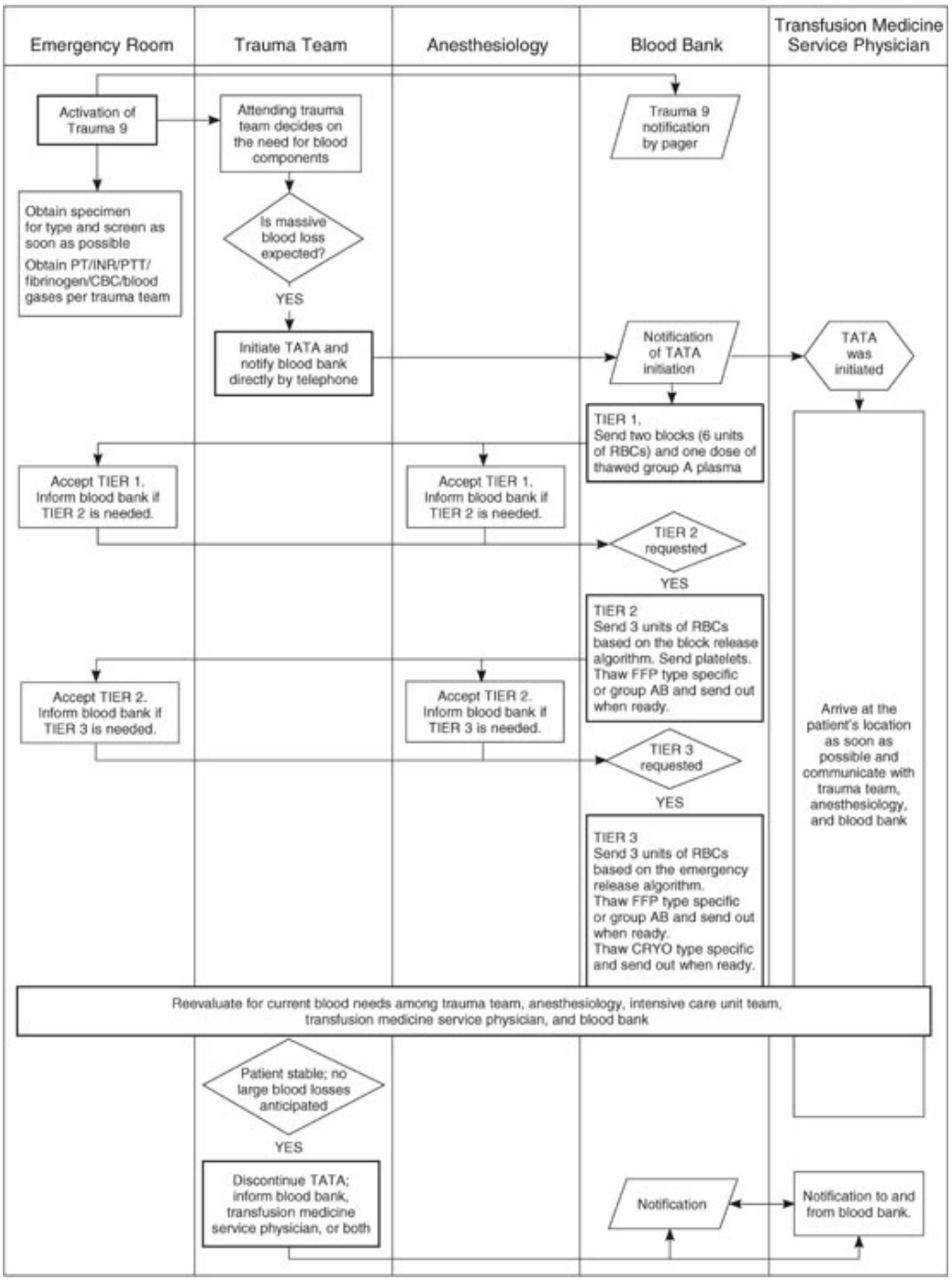

FIG. 18-1. Algorithm for hospital use in cases of severe trauma (ie, trauma 9 or greater) when massive transfusion is needed. Abbreviations: CBC, complete blood count; FFP, fresh frozen plasma; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; RBCs, red blood cells; TATA, trauma-activated transfusion algorithm. (Courtesy, Leslie DeMars, M.D., Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.) ⇦

The practice of low transfusion ratios remains controversial for the civilian and nontrauma population because of the lack of prospective trials and the emphasis of existing literature on trauma patients. A prospective study of patients undergoing extensive debulking, with anticipated large blood loss and RBC transfusion requirements, demonstrated that early fresh frozen plasma administration with restrictive crystalloid resuscitation reduced overall RBC units transfused.

In a patient who has large intraoperative blood loss and life-threatening coagulopathy, infusion of crystalloid will only exacerbate her coagulopathy by further diluting her coagulation factors. Use of albumin or other colloid to expand intravascular volume and transfusion of packed RBCs also will increase her coagulopathy. The described patient is in shock and has thrombocytopenia. To give her fresh frozen plasma and cryoprecipitate with no platelets will not adequately correct her coagulopathy. Cryoprecipitate contains a concentrated subset of fresh frozen plasma components, including fibrinogen, factor VIII coagulant, von Willebrand factor, and factor XIII. Only a balanced transfusion of RBCs, platelets, and fresh frozen plasma will correct the patient's life-threatening coagulopathy.

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19 ⇦

Human chorionic gonadotropin

A 47-year-old woman is referred to you for a diagnosis of amenorrhea for 2 years and recurrent cervical intraepithelial neoplasia 3 by colposcopic biopsy. You plan a loop electrosurgical excision procedure conization, but on review of her records, you note follicle-stimulating hormone (FSH) and luteinizing hormone levels of 75 mIU/mL. Her referring primary physician found a quantitative human chorionic gonadotropin (hCG) level of 10 mIU/mL on two separate tests. She has no other medical issues. The best next step in management is to

(A) proceed with the planned procedure
(B) perform computed tomography scan of abdomen, chest, and pelvis
(C) perform dilation and curettage plus hysteroscopy
* (D) prescribe oral contraceptives and recheck hCG level

A small number of perimenopausal and postmenopausal women will be found to have positive hCG at very low levels. Approximately 1% of perimenopausal women and 7% of postmenopausal women have a serum hCG concentration above the conventional cutoff level of 4–5 mIU/mL. Serum FSH and hCG levels are known to increase with age. One study suggested that women older than 55 years should have a reset hCG cutoff value of 14 mIU/mL to minimize the possibility of such a false-positive result. These false-positive results are due to a cross reaction of elevated pituitary FSH or luteinizing hormone levels and possibly benign low-level pituitary hCG production. If pituitary in origin, the hCG titer can be suppressed with a small dose of oral contraceptives over a 1-week period.

False-positive hCG levels also are caused by circulating heterophilic antibodies. Approximately 2% of reproductive-aged women will have a low-level positive conventional hCG test without trophoblast production. The levels are generally less than 300 mIU/mL. This false-positive test is usually the result of nonspecific heterophile antibodies in the patient's serum because of childhood smallpox immunization, poorly defined

antigens, or foreign proteins. These heterophilic antibodies are frequently reactive to animal proteins from mice, rats, rabbits, and other animals. The antibodies and antianimal antibodies have the potential to interfere with hCG assays, which cause them to return false-positive results. Most of the currently available hCG platforms correct for heterophilic antibodies.

Because there is only a remote chance that a patient may have hCG production from a nonphysiologic source or tumor, oral contraceptive suppression is a reasonable first option for management. A computed tomography scan of the chest, abdomen, and pelvis would not be cost-effective at this point but could be useful if oral contraceptive suppression is not successful in decreasing the hCG level. Dilation and curettage plus hysteroscopy would not be necessary given that the patient does not have bleeding. Hyperglycosylated levels are useful in managing patients who have gestational trophoblastic neoplasia and, therefore, are not indicated for this patient. To proceed with the planned procedure would not be the best next step.

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20 ⇦

Preoperative cardiac risk assessment

A 70-year-old woman comes to your clinic for evaluation of a 10-cm complex pelvic mass. Her medical history is significant for diabetes mellitus controlled with metformin hydrochloride and hypertension controlled by means of hydrochlorothiazide. She can walk approximately four blocks but then stops because of cramps in her legs. She states that she does not experience chest pain or shortness of breath with activity. You