CHAPTER 178

Acute Complications of Pregnancy

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Acute complications of pregnancy can appear in all trimesters and pose challenges in diagnosis and management for the emergency clinician. Life-threatening disorders, such as ectopic pregnancy in early pregnancy, pregnancy-induced hypertension in mid to late pregnancy, and abruptio placentae in late pregnancy, are relatively common. Emergency clinicians must consider the signs and symptoms, stage of pregnancy, and hemodynamic stability of the patient in developing diagnostic and treatment strategies.

PROBLEMS IN EARLY PREGNANCY

Miscarriage

Miscarriage, the most common serious complication of pregnancy, is defined as the spontaneous termination of pregnancy before 20 weeks of gestation. Fetal demise after 20 weeks of gestation or when the fetus is more than 500 g is considered premature birth. Loss of early pregnancy, defined as the detection of human chorionic gonadotropin (hCG) within 6 weeks of the last normal menstrual period, occurs in approximately 20% to 30% of pregnancies. Embryonic and fetal loss after implantation occur in up to one-third of detectable pregnancies. The risk of miscarriage rises with increasing maternal age (a fivefold increase in those >40 years compared with those 25–29 years), increasing paternal age, alcohol use, increased parity, history of prior miscarriage, poorly controlled diabetes mellitus and thyroid disease, obesity, low prepregnancy body mass index, maternal stress, and history of vaginal bleeding.[1,2] Approximately 80% of miscarriages occur during the first trimester; the rest occur before 20 weeks of gestation.

Approximately 25% of clinically pregnant patients experience some bleeding. It is estimated that up to 50% of all women who have bleeding during early pregnancy miscarry, although the risk is probably higher in the emergency department (ED) population.[3] Patients who have a viable fetus visualized on ultrasound examination have a much lower risk of miscarriage (3%–6%), although vaginal bleeding is a high-risk indicator, even when a viable fetus is present.[4] Those with a history of bleeding who do not miscarry may have otherwise normal pregnancies, although they have an approximately twofold increased risk of premature birth and low-birth-weight infants.[5]

Pathophysiology

Most miscarriages are due to uterine malformations or chromosomal abnormalities, which account for the majority that occur within 10 weeks of gestation. In some cases, the ovum never develops (anembryonic gestation). In most early miscarriages, fetal death precedes clinical miscarriage, often by several weeks. Although clinical symptoms of miscarriages are most common between 8 and 12 weeks of gestation, sonographic evidence in most cases demonstrates death before 8 weeks; if fetal viability can be demonstrated by cardiac activity and a normal sonogram, the subsequent risk of fetal loss decreases significantly.

Maternal factors that increase the risk of miscarriage include congenital anatomic defects, uterine scarring, leiomyomas, and cervical incompetence. Other conditions associated with increased miscarriage rates include toxins (eg, alcohol, tobacco, and cocaine), autoimmune factors, endocrine disorders including luteal phase defects, a prior history of miscarriage, and occasional maternal infections.[6]

Terminology

Miscarriage can be broadly divided into three categories. The first is a threatened miscarriage, in which the patient presents with vaginal bleeding but is found to have a closed internal cervical os. The risk of miscarriage in this population is estimated at 35% to 50%, depending on the patient's risk factors and severity of symptoms.[7] If the internal cervical os is open, the miscarriage is considered inevitable. If products of conception are present at the cervical os or in the vaginal canal, the miscarriage is termed *incomplete,* the second classification of miscarriage. The third classification is a termed a *completed* miscarriage, which occurs when the uterus has expelled all fetal and placental material, the cervix is closed, and the uterus is contracted. Establishing the diagnosis of completed miscarriage in the ED is difficult. A gestational sac should be visualized for diagnosis because the cervix may close after an episode of heavy bleeding and clot passage without or after only partial expulsion of the products of conception. Unless an intact gestation is passed and recognized, a completed miscarriage should be diagnosed only after dilation and curettage (D&C), with pathologic confirmation of gestational products, demonstration by sonography of an empty uterus with a prior known intrauterine pregnancy (IUP), or reversion to a negative pregnancy test result. This may take up to several weeks after the initial presentation.

Missed abortion is a relatively obsolete term referring to the clinical failure of uterine growth over time. The terms *anembryonic gestation* (when no fetus is visualized on ultrasound), *first-* or *second-trimester fetal death* (failure to see fetal cardiac activity with at least a 5-mm crown-rump length), and *delayed miscarriage* are more appropriate.

Clinical Features

Patient history should include the estimated length of the gestation, time since the last menstrual period, symptoms of pregnancy,

including evolution or loss of pregnancy symptoms, degree and duration of bleeding, presence of cramps, pain, or fever, and attempts by the patient to induce miscarriage. Although the history is important, it is not helpful in the classification of the type of miscarriage. In addition, the severity of symptoms does not correlate well with the risk of miscarriage, although cramping and passage of clots are thought more likely to occur as the miscarriage becomes inevitable.

The assessment of the patient who experiences first-trimester vaginal bleeding includes a careful abdominal examination to evaluate for tenderness or peritoneal irritation from a potential ectopic pregnancy and to determine the size of the uterus, which should not be palpable abdominally. A pelvic examination should be performed to evaluate whether the cervix is closed or open, look for clots or the products of conception, and determine the degree of vaginal bleeding, as well as uterine size and tenderness. The cervix should be gently probed with a ring forceps (not a cotton-tipped applicator) to determine whether the internal os (1.5 cm deep to the external os) is open or closed. This is unnecessary in the patient who has a clearly open os or visible products of conception but can be safely performed during the first trimester as long as the forceps are used gently and do not penetrate the cervix more than 2 or 3 cm. In the patient with second-trimester bleeding, probing should not be done because the uterus is more vascular, and the organized placenta may overlie the cervical os. Parous women normally have an open or lax external os, a finding of no significance. The adnexa may be enlarged, often unilaterally, because the corpus luteum is cystic or because the pregnancy is ectopic. Significant adnexal or uterine tenderness should always raise the possibility of an ectopic pregnancy. Much less commonly, pelvic infection can cause uterine and adnexal tenderness during early pregnancy.

Diagnostic Testing

A hemoglobin level is useful to provide a baseline measurement and evaluate the degree of blood loss in women whose bleeding persists. In addition, the Rh type should be determined. Ultrasonography is the primary means of evaluating the health of the fetus as well as its location (Table 178.1). Because historical and clinical estimations of gestational age are often inaccurate, ultrasonography is useful to provide an accurate measure of fetal age and viability (Box 178.1).

In the stable patient with threatened miscarriage, expectant management may be sufficient to determine when intervention is needed, as long as ectopic pregnancy has been excluded. Serial quantitative hCG levels are used to assess the health of the fetus if sonographic findings are indeterminate or if the gestational age is less than 6 to 7 weeks. The sonographic discriminatory zone is defined as the quantitative hCG level at which a normally developing IUP should reliably be seen. Discriminatory levels are operator- and equipment-dependent and vary by individual patient characteristics, but are usually considered to be 6500 mIU/mL for transabdominal ultrasonography and 1000 to 2000 mIU/mL for transvaginal ultrasonography.[8,9] Ultrasonography can be performed or repeated when hCG levels rise to 1500 to 3000 mIU/mL. If hCG levels are flat or decline, or if sonographic criteria for fetal demise are demonstrated (see Box 178.1), the patient should be referred to an obstetrician for follow-up to ensure miscarriage completion and to rule out subsequent complications.

Differential Diagnosis

Ectopic pregnancy can masquerade as a threatened miscarriage in the early stages of pregnancy and should always be considered in the differential diagnosis. Even in the patient with painless vaginal bleeding, the diagnosis of ectopic pregnancy must be considered. Early ultrasonography is imperative to locate the pregnancy in the patient who has bleeding or pain.

Other diagnoses should also be considered. A small amount of bleeding occurs at the time of implantation of the blastocyst into the endometrium and, occasionally, at the time of the first missed menses. Molar pregnancy is also characterized by vaginal bleeding, usually during the late first trimester or second trimester. This condition can be identified by ultrasonography. Cervical and vaginal lesions can also cause local bleeding and can usually be seen on vaginal inspection.

Management

After assessment of hemodynamic status and management of blood loss, a patient with a threatened miscarriage requires very little specific medical treatment. Anti-D immune globulin should be administered if the patient is Rh-negative. A 50-μg dose is used during the first trimester and a full 300-μg dose after the first trimester. Once ectopic pregnancy has been excluded, ultrasonography can be scheduled more routinely at a later time for the patient without significant pain. However, the patient should be made aware that the potential for ectopic pregnancy exists until it is excluded by identification of an IUP. In the patient who is planning pregnancy termination, prompt referral should be encouraged and chorionic villi confirmed at the time of uterine evacuation.

Unless an IUP is diagnosed, the patient with threatened miscarriage should be given careful instructions on discharge to return if she has signs of hemodynamic instability, significant

TABLE 178.1

Landmarks for Gestational Age and β-hCG Level by Transvaginal Ultrasonography

FINDING	WEEKS FROM LMP	β-hCG (mIU/mL)
Gestational sac (25 mm)	5	1000
Discriminatory zone	5–6	1000–2000
Yolk sac	6	2500
Upper discriminatory zone	6–7	3000
Fetal pole	7	5000
Fetal heart motion	6–7	7000

β-hCG, Beta subunit of human chorionic gonadotropin; *LMP*, last menstrual period.
Adapted from Ramsey E, Shilitto J: How early can fetal heart pulsations be detected reliably using modern ultrasound equipment? Ultrasound 16:193–195, 2008.

BOX 178.1

Sonographic Criteria for Abnormal Pregnancy With Transvaginal Ultrasonography

No gestational sac at β-hCG level of 3000 mIU/mL
No yolk sac with gestational sac of 13 mm (or at 32 days since last menstrual period)
5-mm crown-rump length, with no fetal heart tones
No fetus, with gestational sac of 25 mm mean diameter
No fetal heart tones after gestational age of 10–12 wk

β-hCG, Beta subunit of human chorionic gonadotropin.
Adapted from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310–320, 1999.

pain, or other symptoms that might indicate ectopic pregnancy (so-called ectopic precautions). In conjunction with gynecologic colleagues, an ED protocol is useful to determine when follow-up sonographic evaluation and serial hCG measurements should be obtained, because ultrasonography can be an inaccurate diagnostic tool if the hCG level is below 1500 mIU/mL, vaginal bleeding is significant, or sonographic findings do not include a fetal pole or yolk sac.[10,11]

Although 50% or more of women with threatened miscarriage who are seen in the ED ultimately miscarry, treatment to prevent miscarriage is not useful because most fetuses can be shown to be nonviable 1 to 2 weeks before symptoms occur. In most cases, spontaneous miscarriage is the body's natural method of expelling an abnormal or undeveloped (blighted) pregnancy. Thus, a major goal of early management should be patient education and support. Patients should be advised that moderate daily activities do not affect the pregnancy. Tampons, intercourse, and other activities that might induce uterine infection should be avoided as long as the patient is bleeding, and she should return immediately for fever, abdominal pain, or a significant increase in bleeding. Cramping from a known IUP can be safely treated with oral synthetic narcotics, if needed. If the patient passes tissue, it should be brought to a provider to be examined for products of conception because differentiation of fetal parts or villi from decidual slough or casts is difficult.

Patient counseling is paramount with threatened miscarriage.[12,13] Determination of fetal viability can be helpful in reassuring the mother or preparing her for probable fetal loss.[14] Miscarriages are associated with a significant grieving process, which is frequently more difficult because early pregnancy is unannounced, and early fetal death is not publicly recognized. Because many women consider that minor falls, injuries, or stress during the first trimester can precipitate miscarriage, patients should be reassured that they have done nothing to cause miscarriage. It is important to make them aware that miscarriage is common, grieving is normal, and counseling may be beneficial.[15,16] A follow-up appointment should be scheduled after miscarriage to support the patient in resolving such issues.

Treatment of the patient with incomplete miscarriage includes expectant management, medical management with misoprostol, or surgical evacuation.[15] When the miscarriage is incomplete, the uterus may be unable to contract adequately to limit bleeding from the implantation site. Bleeding may be brisk, and gentle removal of fetal tissue from the cervical os with ring forceps during the pelvic examination often slows bleeding considerably.

Management of patients with presumed completed miscarriage is more complicated. If the patient brings tissue with her, this should be sent to the pathology department for evaluation. Unless an intact gestational sac or fetus is visualized, it is rarely clear clinically whether miscarriage is complete. Studies have shown that in women with a history consistent with miscarriage who have minimal remaining intrauterine tissue as determined by ultrasonography, expectant management is safe, but only if ectopic pregnancy can be excluded.[17] If endometrial tissue is not seen with ultrasonography, bleeding is mild, and gestational age is less than 8 weeks, curettage is frequently unnecessary, and the patient can be safely observed by a gynecologist for serial hormonal assays. Up to 80% of women with first-trimester miscarriage complete the miscarriage without intervention.[17] However, the need for later visits and procedures may be decreased by uterine curettage, particularly if the fetal pole or a gestational sac is visible on the sonogram at the time of evaluation. Medical management with misoprostol instead of D&C is also an option and has a success rate of up to 96%.[15] The patient should be instructed to return if uncontrolled bleeding, severe pain or cramping, fever, or tissue passage occurs. Follow-up is recommended in 1 or 2 weeks to ensure that the miscarriage is complete.

After miscarriage, the patient should be advised that fetal loss, even during the first trimester, can cause significant psychological stress. Follow-up in 1 or 2 weeks with a gynecologist should be provided. Some physicians prescribe antibiotics after D&C or miscarriage (usually doxycycline or metronidazole), although there is no conclusive evidence to support this practice, and some evidence has suggested that the side effects of treatment may outweigh any potential benefit.[18,19] Ergonovine or methylergonovine (0.2 mg orally bid) can be used to stimulate uterine involution. The patient should be advised to return if signs of infection (eg, fever, uterine tenderness) occur, bleeding resumes, or further tissue is passed.

Ectopic Pregnancy

Principles

Ectopic pregnancy, or pregnancy implanted outside the uterus, is an increasingly frequent problem that poses a major health risk to women during the childbearing years. It is the third leading cause of maternal death, responsible for 4% to 10% of maternal mortality.[20] Ectopic pregnancy is estimated to account for approximately 2% of all pregnancies, although national estimates of incidence are difficult to determine.[21] Although the incidence of ectopic pregnancy is highest in women aged 25 to 34 years, the rate is highest among older women and women belonging to minority groups. Simultaneous intrauterine and extrauterine gestations (heterotopic pregnancy) have historically been rare, occurring in approximately 1 in 4000 pregnancies; more recently, women who have undergone assisted reproduction techniques with embryo transfer have a demonstrated risk of 4% or higher of one of the pregnancies being ectopic. The incidence of ectopic pregnancy among women presenting to the ED with vaginal bleeding or pain in the first trimester is consistently approximately 10%, but may be as high as 16%.[20]

Pathophysiology

Implantation of the fertilized ovum occurs approximately 8 or 9 days after ovulation. Risk factors for an abnormal site of implantation include prior tubal infection (50% of cases), anatomic abnormalities of the fallopian tubes, assisted reproduction (especially multiple embryo transfers), and abnormal endometrium (host factors). These result in failure of the embryo to implant in the endometrium. The risk of ectopic pregnancy increases approximately threefold after a patient has had pelvic inflammatory disease (PID). In recent studies, 25% of patients with ectopic pregnancies were found to have had tubal surgery, including tubal sterilization or removal of ectopic pregnancy.[22] If the patient is currently using an intrauterine device (IUD), increased risk can occur from a complicating PID or from failure of the IUD to prevent pregnancy while preventing endometrial implantation. All forms of contraception, except the IUD and tubal sterilization, decrease the incidence of ectopic pregnancy. After an ectopic pregnancy, the risk of a subsequent ectopic pregnancy can be as high as 22%, depending on the characteristics and treatment of the ectopic pregnancy (eg, location of implantation, surgical vs. medical management; Box 178.2).[22]

When abnormal implantation occurs in the fallopian tubes, on the ovaries, or in the cervix, the pregnancy usually grows at a less than normal rate, which can result in abnormally low or declining hCG production. Even if exceedingly low, there is no value in using a single hCG measurement to exclude the diagnosis of ectopic pregnancy. Blood leaks intermittently through the tubal wall or out the fimbrial ends, with spillage into the peritoneal cavity. Bleeding and other symptoms are usually intermittent. Three outcomes are possible—spontaneous involution of the

BOX 178.2

Risk Factors for Ectopic Pregnancy

Tubal surgery (for tubal sterilization or ectopic pregnancy)
Pelvic inflammatory disease
Smoking
Advanced age
Prior spontaneous abortion
Medically induced abortion
History of infertility
Intrauterine device

Adapted from Bouyer J, Coste J, Shojaei T, et al: Risk factors for ectopic pregnancy: A comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol 157:185–194, 2003.

pregnancy, tubal abortion into the peritoneal cavity or vagina, or rupture of the pregnancy with internal or vaginal bleeding. Implantation in the uterine horn (cornual pregnancy) is particularly dangerous because the growing embryo can use the myometrial blood supply to grow larger (10–14 weeks of gestation) before rupture occurs.

Clinical Features

The classic clinical picture of ectopic pregnancy is a history of delayed menses, followed by abdominal pain and vaginal bleeding in a patient with known risk factors. Unfortunately, this history is neither sensitive nor specific. Risk factors for ectopic pregnancy are absent in almost half of patients. Of patients with symptomatic ectopic pregnancy, 15% to 20% have not missed a menstrual period, and occasionally the patient has no history of vaginal bleeding. Abdominal pain is usually severe, peritoneal in nature, and constant. Shoulder pain implies free fluid in the peritoneal cavity and is suggestive of an ectopic pregnancy with significant hemorrhage. The pain of ectopic pregnancy can also be crampy, intermittent, or even absent.

The physical findings in ectopic pregnancy are likewise variable. Vaginal bleeding, uterine or adnexal tenderness, or both in the patient with a positive pregnancy test result should trigger consideration of ectopic pregnancy. Tachycardia is not always present, even with significant hemoperitoneum; the hemoglobin level is usually normal, and hypotension may be seen. The presence of peritoneal signs, cervical motion tenderness, or lateral or bilateral abdominal or pelvic tenderness indicates an increased likelihood of ectopic pregnancy. If significant peritoneal irritation is present, pain can preclude an accurate bimanual examination. Adnexal masses are felt in only 10% to 20% of patients with ectopic pregnancy. Vaginal bleeding is often mild. Heavy bleeding with clots or tissue usually suggests a threatened or incomplete miscarriage, although the patient with an ectopic pregnancy who has decreasing hormonal levels may experience endometrial sloughing, which can be mistaken for passage of fetal tissue. Passed tissue should be examined, as with cases of miscarriage, in tap water or saline (or under low-power microscopy). Unless fetal parts or chorionic villi are seen, ectopic pregnancy should not be excluded in the patient with bleeding or passage of tissue.

Diagnostic Testing

Because the history and physical examination of the patient with ectopic pregnancy are insensitive and nonspecific, ancillary studies are essential to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result. Technologic advances have allowed accurate detection and exclusion of ectopic pregnancy in the assessment of the woman with first-trimester vaginal bleeding or pelvic pain. Ultrasonography and hormonal assays are the most commonly used ancillary tests. Laparoscopy may be the most efficient diagnostic tool in the hemodynamically unstable patient.

BOX 178.3

Sonographic Findings in the Patient With Suspected Ectopic Pregnancy

DIAGNOSTIC OF INTRAUTERINE PREGNANCY
"Double" gestational sac
Intrauterine fetal pole or yolk sac
Intrauterine fetal heart activity

DIAGNOSTIC OF ECTOPIC GESTATION
Pregnancy in fallopian tube (see Fig. 178.1)
Ectopic fetal heart activity (see Fig. 178.2)
Ectopic fetal pole

SUGGESTIVE OF ECTOPIC GESTATION
Moderate or large cul-de-sac fluid without intrauterine pregnancy
Adnexal mass without intrauterine pregnancy[a]

INDETERMINATE
Empty uterus (see Fig. 178.3)
Nonspecific fluid collections (see Fig. 178.4)
Echogenic material
Abnormal sac (see Fig. 178.5)
Single gestational sac

Adapted from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310–320, 1999.
[a]A complex mass is the most suggestive of ectopic pregnancy, but a cyst can also be seen with ectopic pregnancy.

Ultrasonography. Ultrasonography is the primary method used to locate early gestation, establish gestational age, and assess fetal viability. Transabdominal ultrasonography is most useful for identification of IUPs with fetal cardiac activity and exclusion of ectopic pregnancy, except in patients at high risk for heterotopic pregnancy because of infertility procedures. Transvaginal ultrasonography is more sensitive, recognizes IUP earlier than transabdominal ultrasonography, and is diagnostic in up to 80% of stable patients presenting in the first trimester.[23]

Sonographic findings in the patient with suspected ectopic pregnancy are listed in Box 178.3 and illustrated in Figures 178.1 to 178.5. In general, an indeterminate ultrasound study usually does not result in a diagnosis of normal pregnancy.[23] In one series of more than 1000 pelvic ultrasound examinations, 53% of indeterminate ultrasound studies resulted in a diagnosis of embryonic demise, 15% were ectopic pregnancies, and only 29% had an IUP. However, correlation of sonographic results with quantitative hCG measurements can add to the predictive value.[24] With hCG levels less than 1000 mIU/mL, the risk of ectopic pregnancy increases fourfold, and ultrasonography is still diagnostic in approximately one-third of these patients with ectopic pregnancy. Normal pregnancy is unlikely if no gestational sac is seen by transvaginal ultrasonography with an hCG level higher than 1000 to 2000 mIU/mL, depending on the institution's discriminatory zone, but the differential diagnosis includes miscarriage and ectopic pregnancy. Unfortunately, levels of approximately 1500 mIU/mL develop in only approximately 50% of patients with ectopic pregnancies (see Table 178.1).

Indeterminate sonograms, which demonstrate neither an IUP nor extrauterine findings suggestive of ectopic pregnancy, occur in approximately 20% of ED evaluations of women with

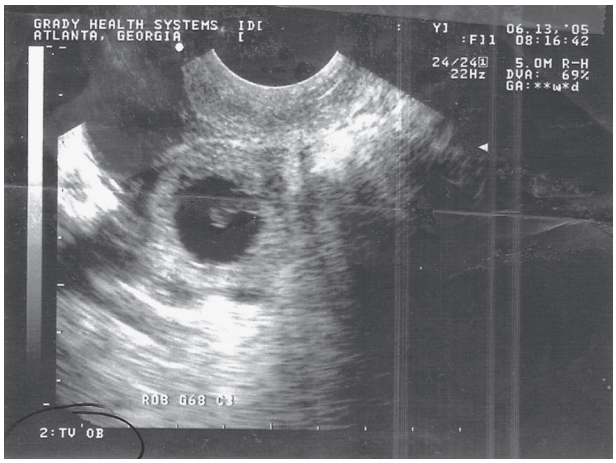

Fig. 178.1. Pregnancy in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

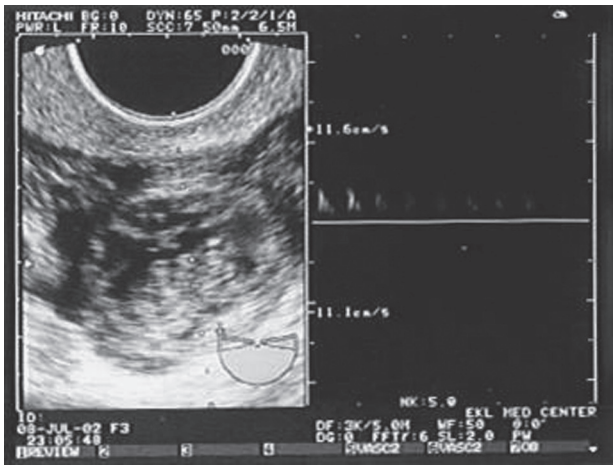

Fig. 178.2. Fetal heart movements detected by ultrasonography in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

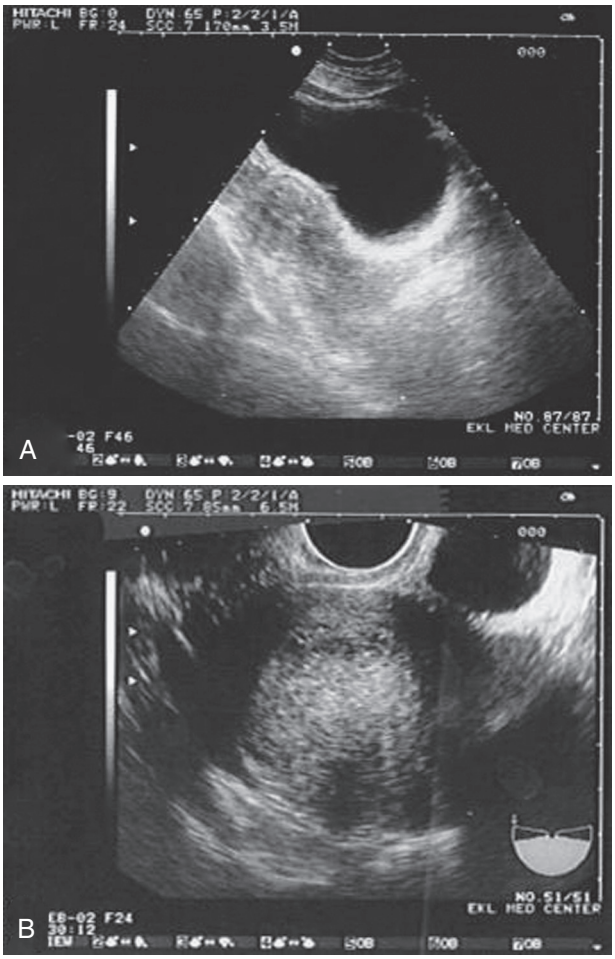

Fig. 178.3. Ultrasonogram showing an empty uterus, indeterminate for diagnosis of an ectopic pregnancy. (Courtesy Dr. Mary Ann Edens.)

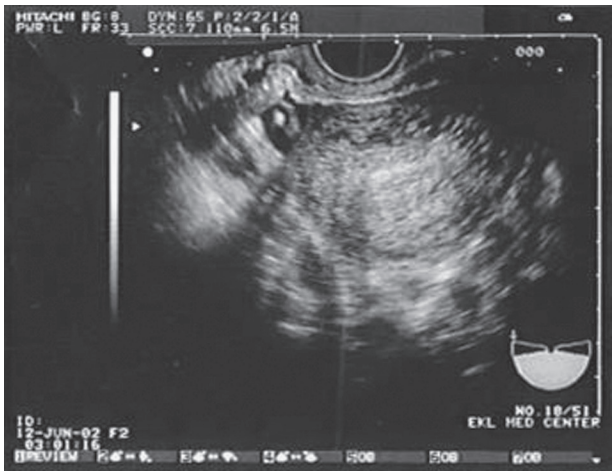

Fig. 178.4. Ultrasonogram showing fluid around the fallopian tube. (Courtesy Dr. Mary Ann Edens.)

first-trimester bleeding or pain. Ectopic pregnancy is more likely among this subgroup with indeterminate sonograms if the hCG level is less than 1000 mIU/mL and the uterus is empty. Endometrial debris and fluid in the uterus do not exclude ectopic pregnancy.[25]

Use of bedside ultrasonography in the ED for the diagnosis of IUP and exclusion of ectopic pregnancy has shown good sensitivity and negative predictive value in ruling out ectopic pregnancy, but it requires significant operator training.[26-28] In addition to operator-based limitations, the use of ultrasonography is also limited by device availability and quality.

Hormonal Assays. Quantitative hCG levels serve two primary functions—serial levels can be used in the stable patient who can be observed as an outpatient, and a single level can be correlated with sonographic results for improved interpretation. Serum hCG levels normally double every 1.8 to 3 days for the first 6 or 7 weeks of pregnancy, beginning 8 or 9 days after ovulation. An initial quantitative level can be measured at the time of the ED visit, particularly if the sonogram is indeterminate or gestational age is estimated as less than 6 weeks. A repeated level should be measured 48 to 72 hours later. Levels that fall or rise slowly are associated with abnormal pregnancy, intrauterine or ectopic. Of women with an ectopic pregnancy, 21% in one series had an initial rise in hCG at a rate consistent with an IUP.

Single quantitative hCG levels can also be useful in conjunction with ultrasonography; normal IUPs should be visible transvaginally at 1000 to 2000 mIU/mL hCG or higher (see Table 178.1). A benign course for ectopic pregnancy cannot be assumed with low hCG levels. Ruptured ectopic pregnancies requiring surgery have been reported with very low or absent levels of hCG.

Serum progesterone levels have been studied as an additional or alternative marker to determine which patients need further

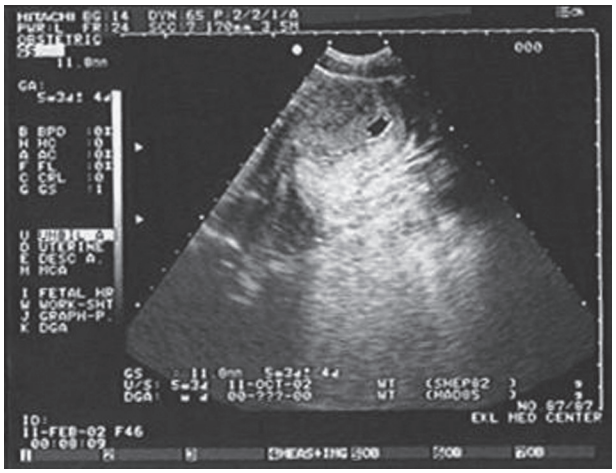

Fig. 178.5. Ultrasonogram showing a gestational pseudosac. (Courtesy Dr. Mary Ann Edens.)

evaluation and follow-up for possible ectopic pregnancy. The progesterone level rises earlier than hCG level in normal pregnancy and plateaus with levels higher than 20 ng/mL, so measurement of serial levels over time is not necessary. Levels below 5 ng/mL exclude viable IUP—with rare exceptions—and could be useful when the hCG levels are low, ultrasonography is indeterminate, and the emergency clinician is considering D&C or laparoscopy. The ability of a progesterone level to differentiate ectopic pregnancy from a failed IUP is limited, and it is not a standard tool for ED evaluation.

Other Studies. Dilation and evacuation can be used in patients without a viable IUP or ectopic pregnancy on ultrasonography to differentiate intrauterine miscarriage from ectopic pregnancy. Identification of chorionic villi in endometrial samples is seen in approximately 70% of patients and excludes ectopic pregnancy, except in patients undergoing assisted reproduction. Identification of chorionic villi can be made, even in 50% of women with an empty uterus on ultrasonography, and limits the need for laparoscopy to exclude ectopic pregnancy in this population.

Although it is invasive, laparoscopy is extremely accurate as a diagnostic (and therapeutic) procedure for possible ectopic pregnancy. It is the diagnostic treatment of choice in the unstable first-trimester patient with peritoneal signs and is also indicated in patients with significant peritoneal fluid or an ectopic gestation in the pelvic cavity. Medical alternatives for the management of ectopic pregnancy have resulted in decreased indications for laparoscopy in stable patients.[24]

Differential Diagnosis

The spectrum of clinical presentations in ectopic pregnancy is wide, so the differential diagnosis includes essentially all first-trimester complications. Threatened miscarriage, the most common alternative diagnosis, can be recognized by sonographic evidence of an IUP, healthy or failed. Hypovolemia may be seen, particularly in incomplete miscarriage, but hypotension without significant vaginal hemorrhage is highly suggestive of ectopic pregnancy. Identification of fetal parts or chorionic villi in tissue expelled or obtained during D&C is useful to confirm a complication of IUP, although this is not sufficient to exclude ectopic pregnancy in the patient with an increased risk of heterotopic gestation, such as the patient undergoing assisted reproduction treatment.

A ruptured corpus luteum cyst should also be considered in the patient who has first-trimester bleeding associated with peritoneal pain or irritation. The corpus luteum normally supports the pregnancy during the first 7 or 8 weeks. Rupture causes pelvic pain and peritoneal irritation. Ultrasonography is helpful if it reveals an IUP (except in patients with in vitro fertilization). During early gestation, when ultrasonography is nondiagnostic, free fluid is usually visible by ultrasonography, and serial observation may be required (see Fig. 178.4). If the patient is unstable, especially if an IUP cannot be identified by ultrasonography, laparoscopy or, rarely, laparotomy may be required to differentiate between the two conditions.

Management

Classically, approximately 20% of women with ectopic pregnancies manifest signs and symptoms warranting immediate intervention. This includes patients with significant hypovolemia, large amounts of peritoneal fluid, or an open cervical os. For patients with significant signs of hypovolemia, rapid volume resuscitation should be instituted with intravenous (IV) fluids and blood products as necessary, and a baseline hemoglobin level and type and crossmatch should be obtained. A D&C or evacuation procedure with examination of the endometrial contents for products of conception can be performed urgently in the unstable patient with an open cervical os.

If the patient remains unstable, immediate surgery is warranted. Laparoscopy may be indicated for patients who stabilize with treatment or those who are hemodynamically stable but exhibit significant peritoneal signs on abdominal examination. One study has reported that identification of free fluid in Morison's pouch on bedside ultrasonography predicts the need for operative intervention in most cases in patients with suspected ectopic pregnancies. All patients with ectopic pregnancy who are Rh-negative should be given Rh immune globulin, 50 μg intramuscularly.

Most patients who seek treatment for bleeding or pain during the first trimester of pregnancy are stable. In these patients, the goal should be to exclude ectopic pregnancy in a timely manner. In the patient with significant pain by history or examination or significant risk factors for ectopic pregnancy, ultrasonography should be performed before discharge. If the results are indeterminate, a quantitative hCG level may be helpful in determining the patient's risk for ectopic pregnancy.

In low-risk patients with only minor symptoms or bleeding, ectopic pregnancy is still a possibility. Two general outpatient approaches can be considered. In most institutions, ultrasonography is the initial screening tool (Fig. 178.6). If an IUP is not seen, quantitative hCG levels help risk stratify these patients. In all cases, if the patient is discharged, careful instructions are given for symptoms that would require her earlier return (ectopic precautions). An alternative strategy uses hCG levels first. However, waiting times for the serum assay can increase ED length of stay. In addition, ultrasonography is usually diagnostic of IUP or ectopic pregnancy, even if the hCG level is less than 1000 mIU/mL. In most cases, the initial sonogram provides more rapid and accurate information.

A significant minority of patients have indeterminate sonographic results and hCG levels below 1000 mIU/mL. When the hCG levels never rise to the discriminatory zone, the differential diagnosis includes intrauterine fetal demise and ectopic pregnancy. Early D&C with identification of the products of conception can be useful in the patient with nonrising hCG levels to detect chorionic villi and confirm a failed IUP or strongly suggest ectopic pregnancy. Alternatively, hCG levels can be followed until they reach zero, particularly if initial levels are low.

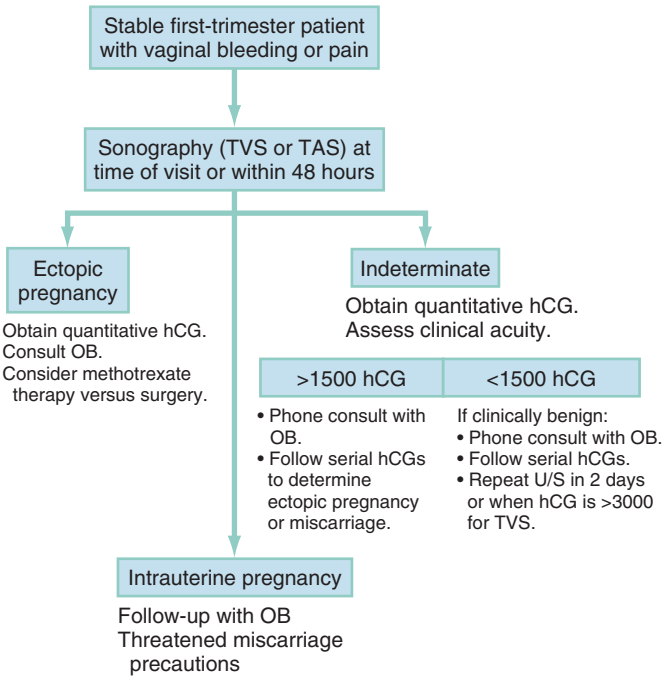

Fig. 178.6. Management of vaginal bleeding or pain in the stable first-trimester pregnant patient. *hCG,* Human chorionic gonadotropin; *OB,* obstetrics specialist; *TAS,* transabdominal sonography; *TVS,* transvaginal sonography; *U/S*, ultrasonography.

Although laparotomy may be required for patients who have an ectopic pregnancy, an increasing number of surgeries are being performed through the laparoscope. Salpingostomy is preferred to salpingectomy if the patient is stable and the procedure is technically feasible. Overall, the advent of transvaginal ultrasonography has resulted in a decreased number of surgeries and a trend toward nonoperative management.

Medical management is a safe and cost-effective treatment for the stable patient with minimal symptoms, especially when future fertility is desired.[22,29] Methotrexate is the drug most commonly used to treat early ectopic pregnancy. It interferes with fetal DNA synthesis and causes destruction of rapidly dividing fetal cells and involution of the pregnancy. Medical treatment is used most often for patients who are hemodynamically stable, with a tubal mass smaller than 3.5 cm in diameter, no fetal cardiac activity, and no sonographic evidence of rupture. Although there is no agreed on hCG cutoff for single-dose methotrexate, studies have suggested that increasing hCG levels are significantly correlated with methotrexate failure. Medical therapies are associated with an 85% to 93% success rate, with no significant difference between single- and multiple-dose protocols. Pelvic pain is common in patients receiving methotrexate (60%), even when it is used successfully. Indications of methotrexate failure and need for rescue surgery include decreasing hemoglobin levels, significant pelvic fluid, and unstable vital signs. All patients receiving methotrexate require close follow-up until the hCG level reaches 0, which may take 2 or 3 months.

Molar Pregnancy

Molar pregnancy, also known as a hydatidiform mole, comprises a spectrum of diseases characterized by disordered proliferation of chorionic villi. In the absence of fetal tissue, the pregnancy is termed a *complete hydatidiform mole*. Complete moles are caused by the fertilization of an ovum without maternal DNA and the subsequent duplication of the haploid genome. The term *incomplete mole* refers to a mole that is caused by the fertilization of a normal ovum by two sperm. The duplication of the triploid karyotype causes some fetal tissue to be present, along with focal trophoblastic hyperplasia. In approximately 19% of molar pregnancies, neoplastic gestational disease develops, with persistence of molar tissue after the pregnancy has been evacuated.[30] Metastatic disease can develop, requiring chemotherapy and intensive oncologic management.

Early molar pregnancy is usually not clinically apparent. The most well-described risk factor for the development of a molar pregnancy is extreme maternal age.[31] Many patients present with abdominal pain, nausea and vomiting, or vaginal bleeding, and it may be difficult to differentiate these patients from those with threatened miscarriage or ectopic pregnancy by historical features alone. Patients sometimes seek treatment for apparent persistent hyperemesis gravidarum from high circulating levels of hCG, bleeding or intermittent bloody discharge, or respiratory distress; failure to hear fetal heart tones during the second trimester is the usual initial clue to diagnosis. If molar pregnancy spontaneously aborts, it is usually in the second trimester (before 20 weeks), and the patient or physician may note the passage of grapelike hydatid vesicles. Uterine size is larger than expected by date (by >4 weeks) in approximately 30% to 40% of patients. Theca lutein cysts may be present on the ovaries as a result of excessive hormonal stimulation, and torsion of affected ovaries can be seen.

The characteristic sonographic appearance of hydropic vesicles within the uterus, described as a snowstorm appearance, is highly suggestive of a diagnosis of molar pregnancy (Fig. 178.7). Alternatively, cystic changes are seen in partial molar pregnancies. In some cases, a partial molar pregnancy is detected only on pathologic examination of abortion specimens. Complications of molar pregnancy include preeclampsia or eclampsia, which can develop before 24 weeks of gestation, respiratory failure or distress from pulmonary embolization of trophoblastic cells, hyperemesis gravidarum, and significant uterine bleeding, acute or chronic. Ultrasonography usually provides the diagnosis of a complete molar pregnancy in the second-trimester patient who has "threatened miscarriage" or during sonographic assessment for fetal well-being and size. However, ultrasonography is only 58% sensitive, and diagnosis of a partial mole is made in 17% of cases.[31] Up to two-thirds of molar pregnancies are diagnosed by pathologic specimens after miscarriage.

Following evacuation of a molar pregnancy, patients must be monitored in the outpatient setting for trophoblastic sequelae. Patients are at increased risk of an invasive mole, a benign tumor that invades the uterine wall and metastasizes to the lungs or vagina, or choriocarcinoma, a malignant tumor that invades the uterine wall and disseminates to the lungs, brain, and liver via the patient's vasculature. Patients who present to the ED with complications of bleeding metastases are managed with a combination of chemotherapy, radiation, and surgery.[32]

COMPLICATIONS OF LATE PREGNANCY

Vaginal Bleeding in Later Pregnancy

Bleeding during the second half of pregnancy occurs in approximately 4% of pregnancies. Only 20% of miscarriages occur after the first trimester, and the most important differential diagnoses after 12 to 14 weeks of gestation are abruptio placentae and placenta previa. The cause is often not determined, although occult marginal placental separations, which can be recognized only by placental inspection at delivery, are believed to come from a common source of bleeding above the cervix. Other causes of late

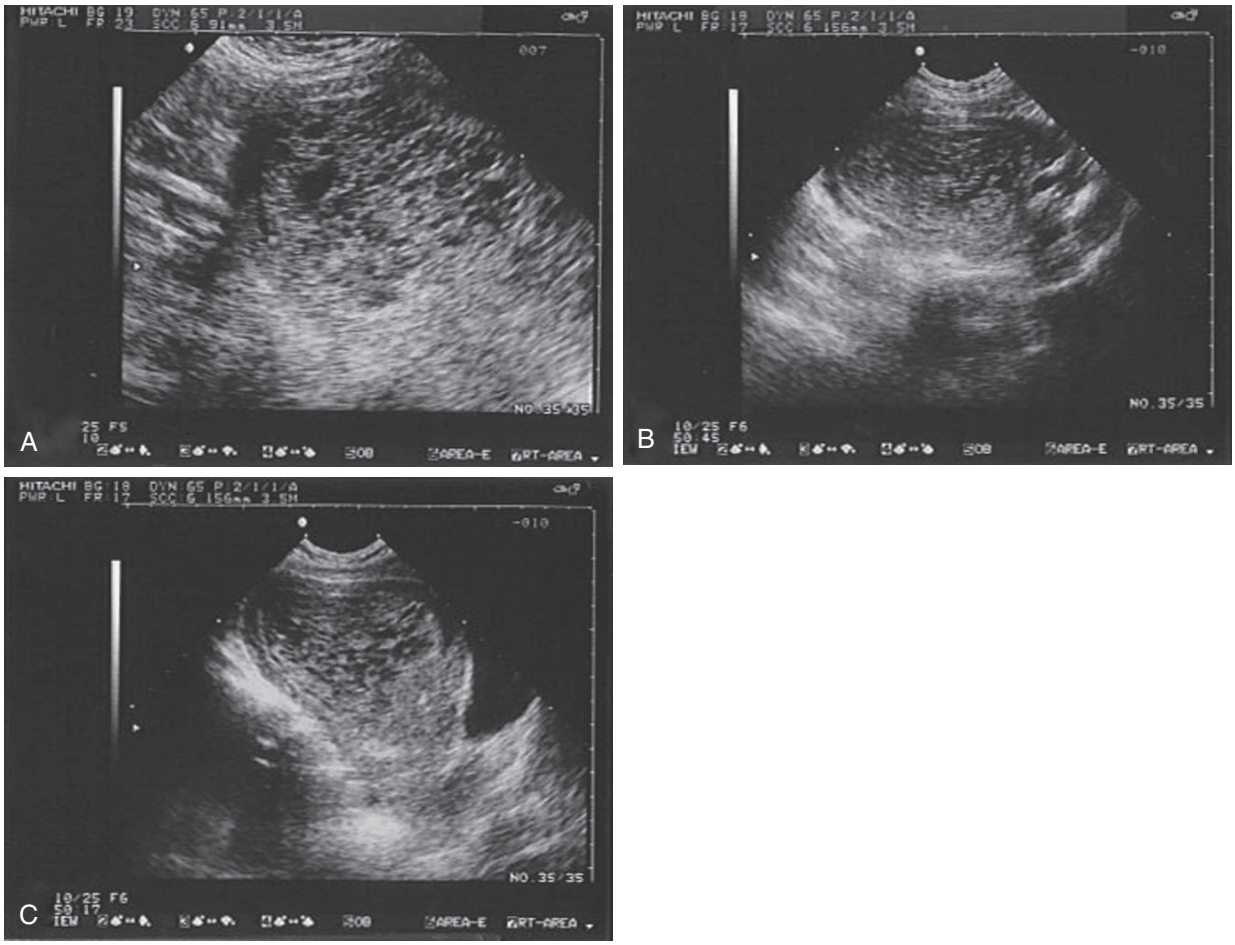

Fig. 178.7. Ultrasonogram showing molar pregnancy. (Courtesy Dr. Mary Ann Edens.)

vaginal bleeding include early labor, various cervical and vaginal lesions, lower genital tract infections, and hemorrhoids.

Bleeding during the second trimester before the fetus is potentially viable (14–24 weeks) is not benign. One-third of fetuses are ultimately lost when maternal bleeding occurs. Management is supportive and expectant because fetal rescue is impossible at this level of fetal immaturity. In the third trimester, vaginal bleeding is still associated with significant morbidity in approximately one-third of women; treatment includes consideration of urgent delivery.[33]

Abruptio Placentae

Abruptio placentae, or separation of the placenta from the uterine wall, is believed to account for approximately 30% of episodes of bleeding during the second half of pregnancy, 10% of preterm births, and 10% to 20% of perinatal deaths.[25] Small subclinical or marginal separations may go undetected until the placenta is examined at delivery and probably account for many of the other self-limited episodes of bleeding for which no diagnosis is made. In cases of nontraumatic abruptio placentae, apparently spontaneous hemorrhage into the decidua basalis occurs, causing separation and compression of the adjacent placenta. Small amounts of bleeding may be asymptomatic and remain undetected until delivery. In other cases, the hematoma expands and extends the dissection. Bleeding may be concealed or may be clinically apparent if dissection occurs along the uterine wall and through the cervix. Placental separation may be acute or may be an indolent problem throughout late pregnancy.

Abruptio placentae is most clearly associated with maternal hypertension and preeclampsia. It is also more common with maternal age younger than 20 or 35 years of age or older, parity of three or more, unexplained infertility, history of smoking, thrombophilia, prior miscarriage, prior abruptio placentae, and cocaine use.[25,34] Placental separation can also be associated with blunt trauma to the abdomen. In such cases, the cause appears to be shearing of a nonelastic placenta from the easily distorted elastic uterine wall at the time of traumatic impact. Women who reported physical violence during pregnancy were found to be twice as likely as women who did not report violence to have an abruption.[35]

Clinical Features. Vaginal bleeding occurs in 70% of patients with abruptio placentae. Blood is characteristically dark and the amount is often insignificant, although the mother may have hemodynamic evidence of significant blood loss. Uterine tenderness or pain is seen in approximately two-thirds of women; uterine irritability or contractions are seen in one-third. With significant placental separation, fetal distress occurs, and the maternal coagulation cascade may be triggered, causing disseminated intravascular coagulation (DIC).[33]

There is a wide spectrum of severity of symptoms and risk in placental separation. Up to 20% of women will have no pain or vaginal bleeding.[36] Assessment is generally based on clinical features, coagulation parameters, and signs of fetal distress. Slight vaginal bleeding, little or no uterine irritability, absence of signs of fetal distress, and normal coagulation characterize mild abruption. As the separation becomes more extensive, it is associated

with more vaginal bleeding (or hidden maternal blood loss), increased uterine irritability, with or without tetanic contractions, declining fibrinogen levels, and evidence of fetal distress and maternal tachycardia. In severe abruptio placentae (15% of cases), the uterus is tetanically contracted and very painful, maternal hypotension results from visible or concealed uterine blood loss, fibrinogen levels are less than 150 mg/dL, and fetal death can occur. Ultrasonography is insensitive in the diagnosis of abruptio placentae, often because the echogenicity of fresh blood is so similar to that of the placenta. Symptomatic or even fetus-threatening abruption can occur in the presence of a normal sonogram.[36]

Fetal distress and death occur in approximately 15% of patients with abruptio placentae by interruption of placental blood and oxygen flow. Risk of fetal death increases in proportion to the percentage of the placental surface involved and rapidity of separation. Fetal distress may result from the loss of placental blood flow, associated maternal hemorrhage (into the uterine cavity or externally), increased uterine tone, or resultant DIC. Maternal death can result, usually from coagulopathy or exsanguination. Fetomaternal transfusion occurs in a significant minority of patients. Placental separation also predisposes the mother to amniotic fluid embolism.

Differential Diagnosis. The main alternative diagnosis in the woman with late-pregnancy bleeding is placenta previa, which is usually associated with painless, bright red bleeding and is excluded with ultrasonography. Lower genital tract or rectal lesions and bloody show (blood-tinged cervical mucous plug) are also considerations.

In the patient with abdominal pain but no vaginal bleeding, abruptio placentae with concealed hemorrhage must be distinguished from other causes of abdominal pain in later pregnancy—complications of preeclampsia, pyelonephritis, various liver diseases, gallbladder disease, appendicitis, and ovarian torsion. Uterine irritability caused by abruptio placentae can also be confused with early labor; in one series, almost 25% of patients were misdiagnosed as having premature labor until fetal distress occurred. If the patient has acute catastrophic hypotension, amniotic fluid embolus, with or without abruptio placentae, and uterine rupture must be considered.

Placenta Previa

Placenta previa, or implantation of the placenta over the cervical os, is the other major cause of bleeding episodes during the second half of pregnancy. The risk of placenta previa is increased with maternal age, smoking, multiparity, cesarean section, prior miscarriage or induced abortions, and preterm labor.[37,38] Bleeding occurs when marginal placental vessels implanted in the lower uterine segment are torn, either as the lower uterine wall elongates or with cervical dilation near the time of delivery. Early bleeding episodes tend to be self-limited unless separation of the placental margin is aggravated by iatrogenic cervical probing or the onset of labor.

Clinical Features. Painless, fresh vaginal bleeding is the most common symptom of placenta previa. In approximately 20% of cases, some degree of uterine irritability is present, but this is generally minor. Vaginal examination usually reveals bright red blood from the cervical os. All patients with painless, second-trimester vaginal bleeding should be assumed to have placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis is excluded via ultrasound. Injudicious vaginal examination can precipitate severe hemorrhage in the patient with an asymptomatic or minimally symptomatic placenta previa. Speculum examination of the vagina and cervix should be performed only in those settings in which obstetric consultation is not readily available. It should be limited to an atraumatic partial speculum insertion to identify whether the bleeding is coming from the cervical os (and a presumed placenta previa), hemorrhoids, or a vaginal lesion that might not require urgent management.

Most cases of placenta previa identified during the midtrimester resolve by the time of delivery as the lower uterine segment elongates and the placenta no longer overlaps the cervical os. Central or total previa, which occurs in approximately 20% of cases, can, however, cause severe hemorrhage, with the risk of exsanguination for the fetus and mother.

Diagnostic Testing. Ultrasonography is the diagnostic procedure of choice for localization of the placenta and diagnosis of placenta previa. Accuracy is excellent, but visualization of the placenta and of the internal cervical os is required. The bladder should be emptied before examination for suspected placenta previa to avoid overdiagnosis of placenta previa. Transvaginal ultrasonography is safe and even more accurate for visualization of the relationships between the placenta and internal os.[38]

Management. Patients who experience vaginal bleeding during late pregnancy should have immediate obstetric consultation and arrangements for safe transfer to an appropriate obstetric facility. Initial management consists of maternal stabilization, with establishment of two large-bore IV lines and fluid resuscitation, as well as continuous fetal monitoring, if available. A baseline hemoglobin level should be determined, and blood should be sent for type and crossmatch. Baseline coagulation studies, including platelet count, prothrombin time, and partial thromboplastin time, should be performed, and the fibrinogen level and presence of fibrin split products should be determined. The normal fibrinogen level in pregnancy is 400 to 450 mg/dL; values below 300 mg/dL indicate significant consumption of coagulation factors.

Blood loss requiring transfusion can occur in patients with placenta previa or abruptio placentae. Fresh-frozen plasma or fresh whole blood may be needed because of the coagulopathy associated with significant abruptio placentae. Fetomaternal hemorrhage can occur with abruption. If the Rh-negative patient has not yet received her routine Rh immune globulin prophylaxis at 28 weeks, 300 μg of Rh immune globulin should be administered within 72 hours. Transfer to the obstetric unit should be expedited if the patient is stable, or it should be done after initiation of resuscitation if she is unstable. If transfer to another hospital is required, a high-risk transfer team should be used if bleeding is significant or the fetus is in distress. Although the bleeding source may not be identified or may be relatively benign, assessment is best accomplished by obstetricians who are accustomed to the evaluation of late-pregnancy complications and who can perform emergent cesarean section, if needed.

In the obstetrics unit, fetal monitoring is continued. Ultrasonography is used primarily to locate the placenta and diagnose placenta previa, but it may not be reliable in confirming the diagnosis of abruptio placentae. On occasion, subplacental hemorrhages of abruptio placentae can be seen, and changes in size of the collection can be monitored. If evidence of placenta previa is absent or equivocal, a vaginal examination is performed in the delivery suite, where an emergency cesarean section can be performed if uncontrolled bleeding is encountered.

Patients who have significant abruptio placentae may require early delivery—vaginal or surgical, depending on fetal status. If placenta previa is diagnosed or if abruptio placentae is considered mild, the patient is admitted for close monitoring. The goal is to support the patient, ideally until fetal maturity is demonstrated and a successful delivery can be accomplished.

Pregnancy-Induced Hypertension (Preeclampsia and Eclampsia)

Hypertension is observed in up to 8% of pregnancies and is generally divided into several categories[39,40]:

- Gestational hypertension occurs during pregnancy, resolves during the postpartum period, and is recognized by a new blood pressure reading of 140/90 mm Hg or higher.
- Preeclampsia is gestational hypertension with proteinuria (>300 mg/24 hr).
- Eclampsia is the occurrence of seizures in the patient with signs of preeclampsia. Progression of preeclampsia to eclampsia is unpredictable and can occur rapidly.
- Pregnancy-aggravated hypertension is chronic hypertension, with superimposed preeclampsia or eclampsia.
- Chronic or coincidental hypertension is present before pregnancy or persists more than 6 weeks postpartum.[40]

Approximately 2% to 7% of pregnancies are complicated by pregnancy-induced hypertension. The incidence of actual eclampsia has progressively declined but is still one of the major causes of maternal mortality. The risk of pregnancy-induced hypertension is greatest in women younger than 20 years, primigravidas, those with twin or molar pregnancies, those with hypercholesterolemia, pregestational diabetes, or obesity, and those with a family history of pregnancy-induced hypertension.[40]

Pathophysiology

Gestational hypertension or preeclampsia is a vasospastic disease of unknown cause unique to pregnant women. Vasospasm, ischemia, and thrombosis associated with preeclamptic changes cause injury to maternal organs, placental infarction and abruption, and fetal death from hypoxia and prematurity. The cause of eclampsia is unknown, but recent studies have centered on vascular responsiveness to endogenous vasopressors in the preeclamptic woman. Vascular responsiveness is normally depressed during pregnancy, which is a high-output, low-resistance state. Gestational hypertension is characterized by an even greater elevation in cardiac output, followed by an abnormally high peripheral resistance as clinical manifestations of the disease develop. In patients with preeclampsia, the cardiac output eventually drops as peripheral resistance rises.[41] The cause of these changes is not known, but endothelial dysfunction is purported to release vasoactive mediators and result in vasoconstriction. Antiplatelet agents during pregnancy have been reported to reduce the risk of development of preeclampsia, supporting the premise of an imbalance between levels of thromboxane and prostacyclin in preeclampsia.[42]

The vasospastic effects of gestational hypertension and preeclampsia are protean. The intravascular volume is lower than in normal pregnancy, central venous pressures are normal, and capillary wedge pressures are variable. Liver effects are believed to be due to hepatocellular necrosis and edema resulting from vasospasm. Renal injury causes proteinuria and may result in decreased glomerular filtration. Microangiopathic hemolysis may result from vasospasm, causing thrombocytopenia. Central nervous system (CNS) effects include microvascular thrombosis and hemorrhage, as well as focal edema and hyperemia.[40]

Clinical Features

Signs and Symptoms. The patient with gestational hypertension has mild systolic or diastolic blood pressure elevation, no proteinuria, and no evidence of organ damage. Mental status assessment, testing of reflexes, abdominal examination, liver function studies, and coagulation studies yield normal results. Preeclampsia is associated with kidney changes and, in severe cases, other end-organ symptoms. Edema is often difficult to assess because pregnancy is normally associated with excess extracellular fluid and dependent edema, and it is no longer used as a criterion for preeclampsia. Proteinuria (300 mg/24 hr) is variable at any given time and may not be detectable in a random urine specimen.[39]

In cases of severe preeclampsia, the diastolic blood pressure can exceed 110 mm Hg, proteinuria is more severe, and there is evidence of vasospastic effects in various end organs. CNS effects commonly include headache or visual disturbances. Thrombocytopenia may be present, liver function test findings may be elevated, and the liver is often tender. Renal dysfunction may be indicated by oliguria and elevated creatinine levels in addition to proteinuria.

Complications

The HELLP syndrome, a particularly severe form of preeclampsia that develops in 5% to 10% of women who have preeclamptic symptoms, is characterized by ***h***emolysis, ***e***levated ***l***iver enzyme levels (alanine transaminase [ALT] and aspartate transaminase [AST] > 70 U/L), and ***l***ow ***p***latelet count (<100,000/mL). Prothrombin time, partial thromboplastin time, and fibrinogen level are normal, and blood studies reveal microangiopathic hemolytic anemia. Other complications of preeclampsia include spontaneous hepatic and splenic hemorrhage and abruptio placentae.

The most dangerous complication is eclampsia, which is the occurrence of seizures or coma in the setting of signs and symptoms of preeclampsia. Warning signs for the development of eclampsia include headache, nausea and vomiting, and visual disturbances. Elevated total leukocyte count, and creatinine and AST levels are also predictive of increased morbidity for the patient with severe preeclampsia. Particularly in early eclampsia before 32 weeks of gestation, seizures may develop abruptly, and hypertension may not be associated with edema or proteinuria.[40] In postpartum women who have eclampsia, more than half (55%) have not been previously diagnosed with preeclampsia, and patients may present with headache, vision changes, elevated blood pressure, and/or seizures up to 4 weeks after delivery.[43] After 48 hours postpartum and without predelivery signs of preeclampsia, other diagnoses, such as intracranial hemorrhage, should be considered. Maternal complications of eclampsia include permanent CNS damage from recurrent seizures or intracranial bleeding, renal insufficiency, and death.

The maternal mortality rate from eclampsia has been reduced to less than 1% with modern management. Perinatal mortality has also decreased, although it remains at 4% to 8%.[40] Causes of neonatal death include placental infarcts, intrauterine growth retardation, and abruptio placentae. In addition, fetal hypoxia from maternal seizures and the complications of premature delivery contribute significantly to fetal morbidity and mortality.

Diagnostic Testing

The patient who has severe preeclampsia should have an IV line and fetal monitoring initiated. Blood testing should include complete blood cell count, renal function studies, liver function tests, platelet count, and coagulation profile. A baseline magnesium level should also be determined. In the patient with actual seizures, the serum glucose concentration should be determined. If a history of preeclampsia is not obtained or the symptoms are refractory to magnesium sulfate therapy, a computed tomography (CT) scan of the head should be performed to exclude cerebral venous thrombosis or an intracranial bleed, either of which can occur in pregnancy—with or without pregnancy-induced hypertension—and may require specific treatment. CT scan abnormalities can be seen in 50% of patients with eclampsia. Patchy hemorrhage and microinfarcts of the cortex are

characteristic and may be due to loss of cerebral autoregulation in patients with severe pregnancy-related hypertension. Diffuse cerebral edema can also be seen.

Differential Diagnosis

Peripheral edema is common in normal pregnancy, and it may be difficult to differentiate normal edema from that of early preeclampsia. Differentiation of gestational hypertension from preexistent hypertension is often impossible if no record of normal blood pressure is available. Seizures during pregnancy may be due to epilepsy as well as other intracranial catastrophes, such as thrombosis or hemorrhage.

Management

The management of patients with mild preeclampsia includes documentation of blood pressure and reflexes, weight, and testing to ensure normal end-organ function. Accurate determination of gestational age by ultrasonography is needed to allow optimal management if symptoms progress. Limitation of physical activities, including bed rest, is the only demonstrated means of reducing blood pressure and allowing the pregnancy to be sustained longer. Definitive treatment is delivery of the fetus, although expectant management is standard in women at less than 34 weeks of gestation. Arrangement for close follow-up is important for patients who are not hospitalized.

Hospitalization is usually required for patients with sustained hypertension above 140/90 mm Hg and signs of severe preeclampsia. Baseline laboratory studies should be carried out to identify end-organ effects in the liver, kidney, and hematologic systems. Both diuresis and antihypertensive therapy have been remarkably unsuccessful in improving fetal outcome and/or prolonging pregnancy. Admission does, however, allow the obstetrician to assess fetal age and well-being accurately, maternal organ function, and effect of bed rest on blood pressure before the optimal timing of delivery is decided.[39]

Fulminant or severe preeclampsia, with marked blood pressure elevation (≥160/110 mm Hg) associated with epigastric or liver tenderness, visual disturbance, or severe headache, is managed in the same way as eclampsia (Box 178.4). The goal is prevention of seizures and permanent damage to maternal organs. Magnesium sulfate is given for seizure prophylaxis.

BOX 178.4

Management of Eclampsia and Severe Preeclampsia

Control seizures with magnesium sulfate.
Control hypertension after seizure control if diastolic blood pressure >105 mm Hg.
Obtain initial laboratory studies to assess organ injury:
- Complete blood count and platelet count
- Liver function tests
- Blood urea nitrogen, creatinine

Monitor urine output; maintain at <25 mL/hr.
Limit intravenous fluid administration unless significant losses occur.
Avoid diuretics and hyperosmotic agents.
Perform a computed tomography scan of the head if consciousness is decreased or seizures persist, lateralizing signs are present, or there are other concerns.
Initiate steps to delivery.

Adapted from Pritchard JA, Cunningham FG, Pritchard SA.: The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol 148:951–963, 1984.

Seizures and coma are the hallmarks of eclampsia, the ultimate consequence of preeclampsia. As in all seizure patients, hypoglycemia, drug overdose, and other causes of seizures should be excluded with appropriate tests. Eclamptic seizures are controlled in almost all patients by adequate doses of magnesium sulfate, although the mechanism of action remains elusive. Magnesium has little antihypertensive effect but is the most effective anticonvulsant, preventing recurrent seizures while maintaining uterine and fetal blood flow. The goals of magnesium sulfate therapy are to terminate ongoing seizures and prevent further seizures. An IV loading dose of 4 g magnesium, followed by 2 g/hr IV, is recommended. Magnesium administration should be accompanied by clinical observation for loss of reflexes (which occurs at ≈10 mg/dL) or respiratory depression (which occurs at levels of 12 mg/dL, although actual serum magnesium levels are rarely monitored). The infusion should be stopped if signs of hypermagnesemia are seen, because such patients may require assisted ventilation. IV calcium gluconate, 1 g given slowly, will reverse the adverse effects of hypermagnesemia.[40]

Despite ongoing controversy, the familiarity with magnesium sulfate and its physiologic advantages to the fetus, wide margin of safety, and high success rate in controlling seizures make it the first-line drug in patients with eclampsia. A Cochrane review has found that magnesium sulfate is more effective than other anticonvulsants and diazepam for prophylaxis against or treatment of eclamptic seizures, more than halving the risk.[44] If seizures persist after the recommended doses of magnesium sulfate have been administered, diazepam or phenytoin may be given as alternative regimens in conjunction with obstetric consultation, and a careful search for other causes of seizures (eg, hypoglycemia and intracranial bleed) should be instituted.[45]

Although magnesium sulfate is not a direct antihypertensive, the hypertension associated with eclampsia is often controlled adequately by stoppage of the seizures. Rapid lowering of blood pressure can result in uterine hypoperfusion, so specific antihypertensive treatment is initiated only if the diastolic blood pressure remains above 105 mm Hg after control of seizures. Many patients do not require specific antihypertensive treatment after treatment with magnesium sulfate. The antihypertensive used most often by obstetricians is hydralazine, 5 mg IV, with repeated doses of 5 to 10 mg IV every 20 minutes as needed to keep the diastolic blood pressure below 105 mm Hg. Nimodipine and labetalol have also been reported to be safe and effective, although they are less widely used. Other antihypertensive agents have not been well studied in this population because there are specific risks to uncontrolled lowering of blood pressure and loss of uteroplacental blood flow.

Although total body water in the eclamptic patient is excessive, intravascular volume is contracted, and the eclamptic patient is sensitive to further volume changes. Hypovolemia results in decreased uterine perfusion. Thus, diuretics and hyperosmotic agents should be avoided in these patients. Invasive monitoring has demonstrated that vasospasm is not reversed with IV fluid administration. Rather, excessive IV fluids increase extravascular fluid stores that are difficult to mobilize postpartum, resulting in a higher incidence of pulmonary edema in patients treated aggressively with fluid therapy. Invasive pulmonary artery pressure monitoring may be required for accurate fluid management in the eclamptic patient.

Amniotic Fluid Embolus

Amniotic fluid embolus is the release of amniotic fluid into the maternal circulation during intense uterine contractions or uterine manipulation at areas of placental separation from the uterine decidua basalis (abruptio placentae), triggering a rapidly fatal, anaphylactoid-type maternal response. Although amniotic

fluid embolus usually occurs during labor, with the maternal mortality rate at 25% or higher, it can also occur after induced abortions and miscarriages and spontaneously during the second and third trimesters. Amniotic fluid embolus can also occur after amniocentesis or in association with abruptio placentae after abdominal trauma. Although it is a rare syndrome, amniotic fluid embolus is the leading cause of cardiovascular collapse during labor.[46]

Clinical Features

Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden hypotension, hypoxia, and coagulopathy. The embolization of amniotic fluid and the particulate matter suspended in it triggers a profound immunologic response when it enters the maternal circulation. The list of proposed mediators is extensive and includes histamine, endothelin, and leukotrienes.[46] In survivors, DIC, acute respiratory distress syndrome, and left ventricular dysfunction develop. An initial seizure is seen in approximately 20% of patients. Bleeding diathesis may be the initial sign in some women, and DIC occurs in approximately 50%.

Diagnostic Testing

When amniotic fluid embolus is suspected, a complete blood cell count, coagulation studies, arterial blood gas analysis, and chest radiograph should be obtained. Urine output should be monitored after urinary catheter placement. The diagnosis is usually made with certainty only at autopsy, with the finding of fetal hairs, squamous cells, and debris in the maternal circulation. Because squamous epithelial cells can be seen normally in the maternal pulmonary circulation, the typical clinical syndrome is also required for diagnosis.

Differential Diagnosis

Catastrophic pulmonary embolus, drug-induced anaphylaxis, and septic shock must be considered in the differential diagnosis. Seizures occur in patients with eclampsia, but hypertension rather than cardiovascular collapse is usually observed in that condition. Coagulopathy may be seen in patients with preeclampsia (HELLP syndrome), abruptio placentae, or other chronic coagulopathies seen in the nonpregnant patient.

Management

Amniotic fluid embolus is uncommon, so treatment recommendations are anecdotal and have been based on animal studies. The most helpful modalities appear to be high-flow oxygen, support of ventilation and oxygenation with intubation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy. Adequate treatment usually requires invasive hemodynamic monitoring in an intensive care unit.

Rh (Anti-D) Immunization in Pregnancy

Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. Small numbers of fetal cells enter the maternal circulation spontaneously throughout pregnancy, but the maternal immune system is triggered only by significant loads of fetal cells, which can occur during the third trimester and at delivery. Sensitization occurs in up to 15% of Rh-negative women carrying Rh-positive fetuses. To prevent this, anti-D immune globulin (RhoGAM) is routinely administered to Rh-negative mothers—if the father is Rh positive or his status is unknown—at approximately the 28th week of gestation to protect the mother from spontaneous sensitization, which occurs during the third trimester. Transplacental hemorrhage can also occur during uterine manipulation, threatened miscarriage (even without fetal loss), spontaneous miscarriage, surgery for ectopic pregnancy, and amniocentesis, although the risk is not clear. Anti-D immune globulin should be administered when these events occur. A dose of 50 μg can be used if the patient is at less than 12 weeks of gestation, although many pharmacies carry only the 300-μg dose, which can also be given. After 12 weeks, a 300-μg dose should be given. The half-life of immune globulin is 24 days, and it needs to be administered within 72 hours of a sensitization event to prevent antibody development.

The Kleihauer-Betke test of maternal blood has been used to detect fetal cells in the maternal circulation. Unfortunately, the test is difficult to perform, not immediately available in most emergency laboratories, and only sensitive enough to detect 5 mL of fetal cells in the maternal circulation. Because only 0.1 mL of fetal cells is required to sensitize the mother, routine immune globulin administration has been recommended in situations likely to result in sensitization. Patients with third-trimester bleeding are not at increased risk of sensitization compared with patients with normal pregnancy. Thus, RhoGAM should be administered only if the patient did not receive her prophylactic dose at 28 weeks. In cases of significant blunt trauma to the uterus, the Kleihauer-Betke test should be ordered to detect the rare, large fetal transfusions that may require specific fetal blood therapy or administration of additional immune globulin to the mother. The standard dose (300 μg) is sufficient to prevent maternal immunization for fetal transfusions of up to 15 mL of red blood cells or 30 mL of whole blood.

MEDICAL AND SURGICAL PROBLEMS IN THE PREGNANT PATIENT

Clinicians should be aware of a variety of illnesses, related and unrelated to pregnancy, that may have altered symptoms, risk, and treatment in the pregnant patient (Tables 178.2 and 178.3). See also Chapter 179.

Abdominal Pain

Appendicitis

Appendicitis is the most common surgical emergency in pregnant patients. The incidence of appendicitis in pregnant patients is the same as that in nonpregnant patients, but delays in diagnosis contribute to an increased rate of perforation, which results in significant fetal mortality and maternal morbidity.[47] There is also an increased rate of complications of appendicitis in pregnancy. A large, population-based study has found an almost twofold increase in sepsis and septic shock, transfusion, pneumonia, bowel obstruction, postoperative infection, and length of stay longer than 3 days.[48] During the first half of pregnancy, diagnostic findings are usually similar to those in the nonpregnant woman, but the clinical picture becomes more atypical during the second half of pregnancy.

Traditionally, the appendix was thought to be displaced counterclockwise out of the right lower quadrant after the third month of gestation, with its ultimate location deep in the right upper quadrant, superior to the iliac crest (Fig. 178.8). However, one study has found that in only 23% of pregnant patients does the location change from the right lower quadrant, even in the third trimester. Displacement of the abdominal wall away from the abdominal viscera can result in difficulty in palpation of organs and loss of signs of parietal peritoneal irritation. The physiologic

TABLE 178.2

Differential Diagnosis of Abdominal Pain in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
GYNECOLOGIC		
Miscarriage	<20 wk; 80% <12 wk	Ultrasonography to confirm location
Septic abortion	<20 wk	Fever, uterine tenderness
Ectopic pregnancy	<14 wk	Must always be considered in first trimester until intrauterine pregnancy confirmed
Corpus luteum cyst	<12 wk	Sudden focal peritoneal pain; no fever
Ovarian torsion	Especially <24 wk	Ischemic pain
Pelvic inflammatory disease	<12 wk	Very rare
Chorioamnionitis	>16 wk	Tender uterus, fever; amniocentesis reveals white blood cells
Abruptio placentae	>16 wk	Focal uterine tenderness, fetal distress, variable bleeding
Preeclampsia	>20 wk	Hypertension, proteinuria, edema, right upper quadrant pain
NONGYNECOLOGIC		
Appendicitis	Throughout	Guarding may be less prominent; location changes
Cholecystitis	Throughout	Confirm with ultrasonography
Hepatitis	Throughout	Confirm with liver function tests
Pyelonephritis	Throughout	Flank pain, fever, positive catheterized urinalysis

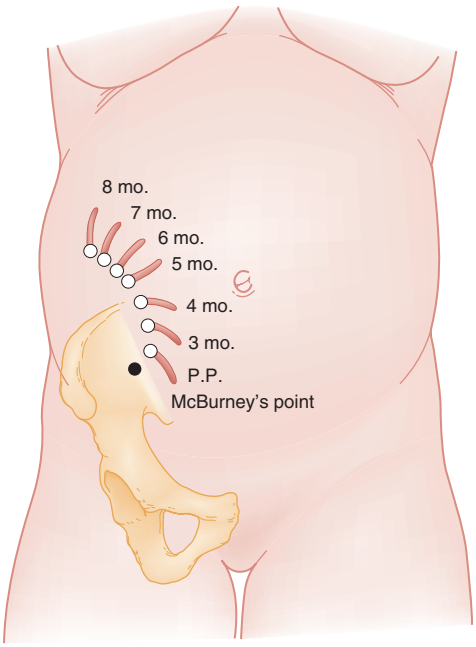

Fig. 178.8. Locations of the appendix during succeeding months of pregnancy. In planning an operation, it is better to make the abdominal incision over the point of maximal tenderness unless there is great disparity between that point and the theoretic location of the appendix. *P.P.,* postpartum. (From Gabbe SG, Niebyl JR, Simpson JL, Galan HL: Obstetrics: normal and problem pregnancies, New York, 2007, Churchill Livingstone.)

increase in white blood cell count and erythrocyte sedimentation rate in pregnancy should also be considered in the evaluation of the patient with possible appendicitis because these may confuse the overall clinical picture.

Clinical Features. The gastrointestinal symptoms of appendicitis, such as anorexia, nausea, and vomiting, mimic those of pregnancy, particularly during the first trimester, making such symptoms relatively nonspecific. Right-sided abdominal pain is the most constant finding, although this is less reliable later in pregnancy. Peritoneal signs are also most common during the first trimester. The absence of fever, leukocytosis, or tachycardia has been reported. The lack of these clinical findings in pregnant patients with appendicitis may be the result of a blunted inflammatory response caused by elevated maternal levels of pregnancy-related steroids. Pyuria without bacteriuria is seen in up to 58% of patients.

Because of confounding factors, the misdiagnosis rate for appendicitis is 30% to 35% overall in pregnancy, with a 40% to 50% rate of removal of normal appendix during the third trimester. In contrast to the relative safety of performing an exploratory laparotomy or laparoscopy during pregnancy, the risk of fetal loss and maternal morbidity from failure to diagnose appendicitis and perforation is considerable, so clinical vigilance is required, even in the absence of classic signs. In later pregnancy, when peritoneal signs are often absent and the uterus obscures normal physical findings, diagnosis is frequently delayed, and the perforation rate may approach 25%.

Differential Diagnosis. Pyelonephritis, cholecystitis, nephrolithiasis, and pregnancy-related diseases such as ectopic pregnancy, broad ligament pain, corpus luteum cyst leakage, and ovarian torsion should be considered in the patient who has right-sided abdominal pain. Pyelonephritis is the most common condition that is confused with appendicitis. During its migration, the appendix is located very near the kidney, resulting in a high incidence of pyuria and flank pain (see Fig. 178.8). In cases of appendicitis, unless there is coincident urinary tract infection, the urine is free of bacteria, a feature distinguishing it from pyelonephritis. Salpingitis, another common misdiagnosis, is very rare in pregnancy, although it can occur before 12 weeks of gestation.

Diagnostic Testing. Leukocytosis is common in pregnant patients with appendicitis, although it is rarely high enough to distinguish it from the physiologic leukocytosis of pregnancy. Pyuria in a catheterized urine specimen suggests pyelonephritis,

TABLE 178.3

Differential Diagnosis of Common Symptoms in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
VAGINAL BLEEDING		
Miscarriage	<20 wk	Usually no fetal heart activity at 8 wk; decreasing hCG level
Ectopic pregnancy	<14 wk	Evaluate with ultrasonography
Molar pregnancy	12-24 wk	No fetal heart tones, characteristic sonogram
Cervical lesions	Throughout	Perineal and vaginal inspection
Vaginitis, cervicitis	Throughout	White blood cells on wet mount, with culture
Placenta previa	>16 wk	Ultrasonography to localize placenta
Abruptio placentae	>16 wk	Ultrasonography to exclude previa; fetal distress, tenderness
SEIZURE		
Eclampsia	>24 wk	Blood pressure > 140/90 mm Hg; usually history of PIH, edema, proteinuria
Amniotic fluid embolus	>12 wk	Hypotension, respiratory distress, DIC
Epilepsy	Throughout	History; lack of PIH findings
DYSPNEA		
Pulmonary embolus	Especially 6 wk prepartum and postpartum	Usual diagnostic studies
Dyspnea of pregnancy	>24 wk	Exclude other causes
Pulmonary infection	Throughout	Examination; radiography
Amniotic fluid embolus	>12 wk	Uterine manipulation, bleeding diathesis, hypotension
JAUNDICE		
Cholestasis of pregnancy	>24 wk	Well patient; itching and jaundice
Hepatitis	Throughout	Abnormal liver function test results
Acute fatty liver	>24 wk	Rapid liver failure; coma, seizures, hypoglycemia
BLEEDING DIATHESIS		
Eclampsia	>24 wk	Blood pressure > 140/90 mm Hg; proteinuria, edema, HELLP syndrome
Amniotic fluid embolus	>12 wk	Respiratory distress, cardiovascular collapse
Abruptio placentae	>20 wk	Uterine tenderness; vaginal bleeding; fetal distress

DIC, Disseminated intravascular coagulation; *hCG,* human chorionic gonadotropin; *HELLP,* hemolysis, elevated liver enzyme levels, low platelets; *PIH,* pregnancy-induced hypertension.

but it is also seen in 20% of patients with appendicitis. Bacteriuria is uncommon. Ultrasonography with a graded compression technique may reveal a noncompressible tubular structure in the right lower quadrant consistent with appendicitis. Studies of the diagnostic value of ultrasonography in the diagnosis of appendicitis are limited but have suggested that it has a high positive predictive value but a low negative predictive value.[49] Butala and colleagues have recommended abdominal ultrasonography as the first imaging modality, followed by CT when ultrasound findings are inconclusive.[50] Surgical, obstetric, and radiologic society guidelines agree.[49] When available, magnetic resonance imaging (MRI) is also useful in the evaluation of pregnant patients with suspected appendicitis (see Chapter 83). Otherwise, laparoscopy or laparotomy is the diagnostic procedure of choice in the pregnant patient thought to have appendicitis. Early exploration is highly encouraged in pregnant patients because of the variability of clinical signs and increased fetal risk if diagnosis is delayed.

Management. The pregnant patient with suspected appendicitis should be hospitalized after appropriate consultation with a surgeon and obstetrician. Ultrasonography, MRI, or CT scan are diagnostic options. The patient should be kept on nothing by mouth (NPO) status, with IV fluid hydration to maintain intravascular volume. Although prompt surgery is required if the diagnosis is clear, in unclear cases the patient should undergo observation to allow for clarification of signs and symptoms.

Gallbladder Disease

Cholelithiasis is present in approximately 5% of pregnant women and is the second most common nonobstetric surgical condition in pregnant patients. The natural history of asymptomatic cholelithiasis is believed to be similar to that in nonpregnant women, with less than 50% of patients with gallstones developing symptoms.

Changes in gallbladder kinetics are believed to be due to high pregnancy-related steroid levels. Progesterone decreases smooth muscle tone and induces gallbladder hypomotility and cholestasis, causing an increased risk of stone formation. In addition, pregnancy induces changes in bile composition and increased cholesterol secretion, thus increasing the incidence of cholesterol stone formation.

Clinical Features

The signs and symptoms of acute cholecystitis during pregnancy are the same as those in nonpregnant women. Epigastric or right upper quadrant pain and tenderness and nausea predominate. Leukocytosis must be interpreted carefully because of the increased white blood cell count seen normally in pregnancy. Likewise, a slightly elevated amylase level can be normal during pregnancy, and alkaline phosphatase, which is produced by the placenta, may be twice the nonpregnant level. A history of self-limited pain episodes associated with food intake suggests the diagnosis.

Diagnostic Testing

Ultrasonography is a reliable means of recognizing stones in the gallbladder, although it may not differentiate symptomatic from asymptomatic stones. In the patient with right upper quadrant pain, simultaneous sonographic evaluation of the liver is useful but technically difficult, particularly during the third trimester, when subcapsular liver hematomas and other intrinsic hepatocellular disease can occur but the liver may be obscured under the ribs.

Differential Diagnosis

Pyelonephritis should be considered in the patient with right upper quadrant pain, with or without fever. During the third trimester, appendicitis can also be associated with right upper quadrant pain. Hepatitis and fatty liver infiltration occur in pregnancy; liver distention and inflammation associated with pregnancy-induced hypertension can also cause right upper quadrant pain. In addition, spontaneous intrahepatic bleeding can occur during late pregnancy, mimicking cholecystitis. Because of the potential for other serious diseases, diagnostic studies should be performed to verify a clinical diagnosis of symptomatic cholelithiasis and cholecystitis in pregnancy.

Management

The patient who has fever, leukocytosis, prolonged pain, or evidence of cholecystitis should be made NPO and given IV fluid hydration, adequate pain control, and broad-spectrum antibiotics. Some patients with uncomplicated cholecystitis can be managed medically. Patients with obstructive jaundice, gallstone pancreatitis, sepsis or failure to respond to conservative management are candidates for surgery (optimally, during the second trimester, if possible[51]).

Discharge should be considered only for patients with uncomplicated and sonographically proven cholelithiasis who are not otherwise candidates for admission after consultation with an obstetrician. Pregnant patients with symptomatic cholelithiasis have a high rate of symptomatic relapse and increased severity of disease with each relapse. Early follow-up should be arranged, and the patient should be given careful instructions to return if she experiences fever, vomiting, or persistent pain. In one study, patients who were observed during pregnancy had a higher rate of pregnancy-related complications (36%) in contrast to much lower rates of complications in those who had a laparoscopic cholecystectomy.[52]

Liver Disorders

Pregnancy is associated with several unique liver abnormalities in addition to more usual hepatic diseases. Emergency clinicians should recognize the various symptoms of liver disease during pregnancy, as well as the hepatic diseases unique to pregnant women. Liver metabolism increases during pregnancy, but hepatic blood flow is unchanged, and little change occurs in liver function. Bilirubin, transaminase, and lactate dehydrogenase levels and prothrombin times are unchanged from those in the nonpregnant state. Albumin levels decrease secondary to an increase in maternal circulating plasma volume. Alkaline phosphatase levels may be up to double the nonpregnant values, and amylase levels may also be slightly elevated.

Hepatitis

Hepatitis is the most common cause of liver disease in pregnancy, accounting for 40% of cases of jaundice in pregnancy. Management and treatment are supportive and unchanged from those for nonpregnant patients. Hepatitis E, however, has been reported to have a more aggressive course in pregnancy, with an increased maternal mortality rate and rate of fetal loss.[53] Maintenance of adequate nutrition is a priority. Vertical transmission of hepatitis B can occur if the disease is not recognized. Pregnant women should be vaccinated. Prophylaxis should be administered to the newborn.[54]

Acute Fatty Liver

Acute fatty liver of pregnancy is a disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. The disease is rare, occurring most often in primiparous patients and patients with twin gestations.

The cause of acute fatty liver of pregnancy is unknown, although studies have suggested that a deficiency in the fetus's fatty acid metabolism leads to an accumulation of hepatotoxic metabolites in the maternal circulation. On microscopic examination, fatty infiltration of the hepatocytes with edema and vacuolization can be seen, but there is no necrosis or inflammation. Liver function returns to normal after delivery if the patient can be supported through the acute phase. Although up to 50% of patients have signs of preeclampsia, the two are not clearly related. The diagnosis must be differentiated from viral hepatitis and HELLP syndrome, which have similar disease presentations and laboratory findings but, again, are not clearly related.

Clinical Features. Nausea and vomiting associated with malaise or jaundice during the third trimester should trigger consideration of a diagnosis of acute fatty liver.[55] The right upper quadrant or epigastrium is usually tender. The disease may progress to coagulopathy, jaundice, seizures, DIC and hepatic encephalopathy. Hemorrhage from coagulopathy is the most common complication at delivery.[56] The diagnosis is often delayed secondary to the multiple differential considerations.

Diagnostic Testing. Typically, leukocytosis is present, the platelet count and fibrinogen level are low, prothrombin and partial thromboplastin times are elevated, and fibrin split products are present. In a series of 11 patients, increased transaminase and serum bilirubin concentrations were found in all patients, hypoglycemia was found in 18%, and hypoproteinemia was found in 46%.[55,56] In contrast to Reye's syndrome, the serum ammonia level is only mildly elevated. Hyperuricemia is usually present. The bilirubin level is elevated late in the course of the disease. The CT scan and sonogram may be normal, so liver biopsy is used to make the definitive diagnosis.

Differential Diagnosis. Liver tenderness and coagulopathy usually suggest preeclampsia during the third trimester. Jaundice and increases in the ALT level are distinguishing features because they are unusual in cases of liver disease associated with pregnancy-induced hypertension. Similarly, rapid progression of hepatic failure, hypoglycemia, and coagulopathy is unlikely in cases of

preeclampsia. Elevations in the creatinine level are more common in acute fatty liver of pregnancy.[56] The patient with viral hepatitis is likely to have more marked elevations in transaminase levels. Drug-induced hepatic failure should be excluded by history and toxicologic screening for acetaminophen or other toxins, if appropriate. Cholecystitis may be distinguished by ultrasound examination, but may also be characterized by right upper quadrant pain; it is not associated with coagulopathy or progressive liver failure.

Management. The patient with acute fatty liver of pregnancy may require acute stabilization for seizures or coma. Hypoglycemia may occur, which should be rapidly corrected with dextrose. Coagulation parameters should be assessed. Fluid resuscitation and replacement of clotting factors may be required, and the patient should be admitted to an obstetric service capable of managing this serious disease. The diagnosis is usually made with liver biopsy if the disease has not progressed to severe coagulopathy. Rapid delivery is usually advisable when the diagnosis has been established. Fresh-frozen plasma, platelet transfusions, and glucose may be needed to sustain the patient until delivery can be accomplished.

Intrahepatic Cholestasis

Intrahepatic cholestasis of pregnancy, also termed *idiopathic jaundice of pregnancy*, *icterus gravidarum*, or *pruritus gravidarum*, is a rare syndrome that occurs during the third trimester of pregnancy. It is the second most common cause of jaundice in pregnancy, after hepatitis. On histologic examination, the disease is characterized by cholestasis and dilated canaliculi in the biliary tree. The liver is normal. It is more common with increasing maternal age, with multiple gestations, and in the winter months.

Clinical Features. Generalized pruritus and mild jaundice are the hallmarks of intrahepatic cholestasis of pregnancy. Only 20% of patients present with this combination, however, and 80% present with pruritus alone. The pruritus usually begins in the palms and soles and ascends to the trunk. Although insomnia and fatigue occasionally accompany the pruritus, the patient appears nontoxic, without fever, vomiting, diarrhea, or significant malaise. The bilirubin level is rarely above 5 mg/dL, the alkaline phosphatase level can be elevated sevenfold to tenfold, and transaminase levels are in the normal range. Resolution occurs when the woman delivers. Although maternal outcome is favorable, women with intrahepatic cholestasis of pregnancy are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.

Differential Diagnosis and Management. Exclusion of more serious entities, such as viral hepatitis, acute fatty liver, drug-induced cholestasis, and complicated cholecystitis, is required. Outpatient management is appropriate, provided the diagnosis is clear and the patient has close obstetric follow-up. Some have advocated aggressive fetal surveillance and delivery after fetal lung maturity to improve the fetal outcome. Symptomatic treatment with antihistamines, ursodeoxycholic acid, bile salts, guar gum, benzodiazepines, and other medications has been tried, with variable success.[57]

Nausea and Vomiting

Normal Pregnancy

Nausea and vomiting are common in pregnancy, particularly from 6 to 20 weeks of gestation. Symptoms are usually self-limited and often resolve with lifestyle changes, such as diet modification and avoidance of environmental triggers. Although evidence supporting nonpharmacologic agents is mixed, in several randomized trials ginger has been found to be effective.[58,59] Treatment is recommended at a dose of 250 mg qid, in capsule or syrup form.

In women who fail conservative management, pharmacologic therapy may be initiated. The American College of Obstetricians and Gynecologists has recommended Diclegis,[60] a delayed-release combination of doxylamine, 10, mg and pyridoxine, 10 mg (vitamin B_6), as the first-line pharmacologic agent for the treatment of nausea and vomiting in pregnancy.[58,61] A combination of the same medications, known as Bendectin, was previously available from 1976 to 1983, but was voluntarily withdrawn from the market due to financial repercussions of litigation alleging the teratogenicity of the drug.[62] Multiple studies and the Centers for Disease Control and Prevention (CDC) Birth Defect Monitoring Program data have since demonstrated the safety of the drug. Diclegis is now approved by the US Food and Drug Administration (FDA) for use in pregnancy.

If there are circumstances preventing the prescription of Diclegis, or in case of treatment failure, other antiemetics may be considered. Although the FDA has not explicitly approved metoclopramide or promethazine for the treatment of nausea and vomiting in pregnancy, both drugs have been widely used and are generally considered safe.[63-65] Ondansetron has been widely used for the treatment of nausea and vomiting in pregnancy. However, recent studies have suggested that ondansetron may be associated with an increased risk of fetal anomalies.[61,66] Some experts recommend that ondansetron be used only when alternative antiemetics have failed.[59]

Hyperemesis Gravidarum

Hyperemesis gravidarum occurs in approximately 1% of pregnant patients and is defined by nausea and vomiting that cause starvation metabolism, weight loss greater than 5% of total body weight, dehydration, and prolonged ketonemia and ketonuria.[62] Without treatment, there is an increased risk of micronutrient deficiency and their respective sequelae to the patient (eg, vitamin B_1 deficiency, Wernicke encephalopathy) and fetus (eg, vitamin K deficiency, bleeding diatheses).[58,67,68]

The cause of hyperemesis gravidarum is not clear; associations have been made with increasing estradiol and hCG levels, as well as with maternal cytokines. Several studies have suggested an increased infection rate with *Helicobacter pylori* in patients with hyperemesis gravidarum; a nonteratogenic regimen for *H. pylori* treatment has been shown to decrease vomiting in hyperemesis patients.[69] Studies have also suggested that early treatment of nausea and vomiting of pregnancy may prevent progression to hyperemesis gravidarum.[58]

Diagnostic Testing. Laboratory studies should assess volume status and reversible electrolyte abnormalities. A urinalysis should look for the presence of ketosis, elevated specific gravity, and infection. Serum chemistry should be tested to assess the presence of hypokalemia, contraction alkalosis, elevated anion gap, and/or other metabolic abnormalities. Bilirubin and alkaline phosphatase levels can be mildly elevated but should return to normal after delivery. Hyperemesis may be complicated by liver disease and abnormal liver function test results, which are expected to resolve with supportive treatment.

Management. Initial management involves rehydration with IV fluids, antiemetics, and demonstration of ability to take oral hydration. Expert consensus favors the addition of dextrose and vitamins to IV fluids and the administration of thiamine before dextrose to prevent progression to Wernicke encephalopathy.[58] Antiemetics may be used, as for nausea and vomiting in pregnancy. A short course of oral prednisolone has been reported

to be therapeutic for intractable hyperemesis; however, it is considered a last-line agent and its risk profile should be weighed carefully before administration.[58]

In women who cannot maintain their weight despite medical therapy, enteral nutrition via a nasogastric (NG) tube should be considered.[58]

Thromboembolic Disease

Thromboembolic disease accounts for almost 20% of obstetric mortality, making it the leading cause of death in pregnancy.[70] Pregnancy is a hypercoagulable state, with increased coagulation factors and stasis as pregnancy progresses and significant vascular trauma at the time of delivery. The risk of venous thrombosis increases during pregnancy to five or six times that of nonpregnant women. Although the risk is increased throughout pregnancy, it is highest during the puerperium. Risk factors include smoking, obesity, age older than 35 years, hypercoagulable state, varicose veins, and prior superficial venous thrombosis. Women who deliver prematurely or have postpartum hemorrhage are also at higher risk.[71,72]

Clinical Features

As in nonpregnant patients, clinical signs of pain, tenderness, and swelling are poor predictors of deep venous thrombosis (DVT) in pregnancy. The clinical diagnosis of pulmonary embolus (PE) is also difficult. Although tachypnea, tachycardia, dyspnea, and pleuritic pain are commonly associated with PE, the symptoms are nonspecific and may be associated with such diverse diseases as hepatic inflammation, pyelonephritis, and diaphragmatic impingement from a normal gravid uterus.

Diagnostic Testing

Deep Venous Thrombosis. Because of its widespread availability, Doppler ultrasonography is the first-line test for the diagnosis of DVT. An abnormal study result is usually sufficient reason to treat the pregnant patient. However, normal leg study results can be seen with isolated iliac vein disease, which is common in pregnancy and requires imaging with MRI or CT for diagnosis. If thromboembolic disease is suspected, serial indirect Doppler testing or CT may be required.[72] The risk of anticoagulation usually outweighs the risk of definitive studies when the diagnosis is equivocal.

Pulmonary Embolism. Currently, studies do not support D-dimer tests in pregnancy to exclude the diagnosis of PE because this test may lack sufficient sensitivity in pregnant patients.[72,73] Imaging with lung scintigraphy or CT angiography is recommended. Both have comparable performances for PE diagnosis during pregnancy, although CT angiography delivers a higher maternal radiation dose.[74] Pulmonary angiography may be required if the diagnosis of PE is unclear after less invasive studies have been performed.

Chest radiography (shielding the pelvis and uterus) should be performed to exclude other disease processes that may mimic a PE. The diaphragm is normally symmetrically elevated during late pregnancy.

Management

Warfarin (Coumadin) is contraindicated during pregnancy because of its teratogenic effects, high risk of abortions, and fetal hemorrhage. Heparinoids are used to treat thromboembolic disease during pregnancy.[72] Unfractionated heparin carries a poorly understood risk of fetal osteoporosis, thrombocytopenia, prematurity, or miscarriage. In general, acute anticoagulation with IV heparin is followed by subcutaneous heparin bid, usually continued for 3 to 6 months postpartum in patients who have DVT or PE during pregnancy. Patients receiving this treatment require laboratory testing every 1 or 2 weeks, and the efficacy of anticoagulation may be variable during pregnancy. Low-molecular-weight heparin is considered safe in pregnancy and offers several advantages over unfractionated heparin, including decreased bleeding risk, reliable pharmacokinetics, decreased risk of heparin-induced thrombocytopenia, fixed dosages, less frequent dosing, and decreased risk of osteoporosis and thrombocytopenia. In patients with a history of DVT or PE, prophylaxis for subsequent gestations is usually recommended.

Genitourinary Infections

Urinary Tract Infection

Asymptomatic bacteriuria in pregnancy predisposes the patient to the development of symptomatic lower and upper tract genitourinary infections. This has led to the US Preventive Services Task Force recommendation to screen for asymptomatic bacteriuria with urine culture in pregnant women at 12 to 16 weeks' gestation or at the first prenatal visit, if later (grade A recommendation). Uterine pressure exerted on the bladder and ureters, poor emptying of the bladder with voiding, and progesterone-induced smooth muscle relaxation that inhibits ureteral peristalsis appear to contribute to an increased risk of infection during pregnancy.

Prenatal screening of patients with asymptomatic bacteriuria in early pregnancy identifies approximately 95% of those at risk for subsequent bacteriuria during the pregnancy. Because up to 30% of women who have asymptomatic bacteriuria will have pyelonephritis if they are untreated, the treatment of bacteriuria is cost-effective and important.

Clinical Features and Diagnostic Testing. The pregnant patient who presents with lower urinary tract symptoms (eg, dysuria, frequency, urgency) or upper tract symptoms (eg, fever, malaise, back pain) should have a pelvic examination and evaluation of an uncontaminated urine specimen, preferably catheterized. There is a predominance of right-sided symptoms during pregnancy, probably the result of increased mechanical forces on the right ureter, but left-sided flank pain or bilateral symptoms may be caused by pyelonephritis. Rarely, urinalysis may yield normal results or cultures may produce negative findings because of failure to report lower colony counts or because of complete obstruction of the involved ureter.

The major risk of asymptomatic and lower urinary tract infection is spread to the renal parenchyma. Acute pyelonephritis carries considerable morbidity in pregnancy, including maternal sepsis, permanent renal injury, and premature labor. The risk of prematurity can be minimized by effective treatment and continued monitoring for recurrence. The development of premature labor in the woman who has pyelonephritis is ominous; it can be prevented only by aggressive recognition and treatment earlier in pregnancy.

Differential Diagnosis. Vaginitis, herpes genitalis, chlamydial infection of the urethra, and ovarian torsion can masquerade as urinary tract symptoms. A history of external dysuria (burning at the perineum with urination) suggests herpes or vaginitis. A pelvic examination should be performed to obtain cervical culture specimens and identify perineal or vaginal causes of dysuria. Appendicitis, cholecystitis, pancreatitis, and liver diseases in pregnancy must be considered in the differential diagnosis of an upper urinary tract infection. Back pain may also be a sign

of premature labor. Careful evaluation of an uncontaminated catheterized urine specimen is essential to the correct diagnosis.

Management. Patients with asymptomatic bacteriuria or lower urinary tract signs and symptoms should be treated with 7 to 10 days of an antibiotic that is active against usual urinary pathogens and safe in pregnancy. The most common choices are a cephalosporin, such as cephalexin, 500 mg orally qid for 3 to 7 days); nitrofurantoin, 100 mg orally bid for 3 to 7 days; or a sulfonamide, such as trimethoprim-sulfamethoxazole, 800/160 mg bid for 3 days (except during the third trimester). Emergency clinicians should consider factors such as cost, local availability, and side effects when selecting the best treatment option.[75,76]

Patients with fever, back pain, and evidence of acute pyelonephritis in pregnancy are usually admitted for IV antibiotic administration, although outpatient parenteral therapy can be effective and safe in selected patients.[77] In such cases, aggressive IV hydration, obstetric consultation, and testing of urine cultures should be initiated. At least one parenteral dose of antibiotics should be given, with antibiotic coverage guided by known organism susceptibilities in a given hospital. Because the resistance of *Escherichia coli* to ampicillin is considerable in most regions, a cephalosporin, such as ceftriaxone, 1 g IV bid, is usually administered. Culture testing must be performed to ensure that the original choice of antibiotic was correct, and the patient must have a repeated culture and be observed closely after treatment.

Vaginitis

Bacterial Vaginosis. Bacterial vaginosis (formally known as *Gardnerella* vaginitis or *Haemophilus vaginalis* vaginitis) is an overgrowth of multiple endogenous vaginal bacteria, in some cases producing excessive discharge and vaginal malodor. Prevalence rates for bacterial vaginosis in pregnancy are estimated at 15% to 20%. Bacterial vaginosis is associated with an increased risk of chorioamnionitis, subclinical PID, premature rupture of membranes, fetal prematurity, and postpartum endometritis after vaginal delivery. However, treatment of bacterial vaginosis is directed toward symptomatic relief for the patient and does not necessarily improve fetal outcomes. Management includes a 7-day course of metronidazole or 7-day course of clindamycin. Intravaginal treatment is not recommended in pregnant patients.[78]

***Candida albicans* Vaginitis.** The incidence of vulvovaginal candidiasis is increased during pregnancy by high levels of estrogen and other steroids. Oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes. Treatment with vaginal azoles for 7 days during pregnancy is considered safe, with an estimated 85% to 100% cure rate.[78] Recurrent disease may require a vaginal culture to confirm diagnosis and identify unusual candidal species (eg, *Candida glabrata*) that may be resistant to conventional treatment. Longer treatment or treatment of a potential *Candida* reservoir in the patient's sexual partner(s) may also be required. However, there is no association of *Candida* colonization with adverse pregnancy outcomes, and treatment is for relief of symptoms only.

***Trichomonas* Vaginitis.** Trichomoniasis is a sexually transmitted vaginitis caused by a protozoan parasite, *Trichomonas vaginalis*. Of patients who have trichomoniasis, 50% are asymptomatic. Symptoms include vaginal itching, malodorous discharge, and vaginal irritation. Diagnosis is made by direct visualization or protozoans on wet mount. The recommended treatment is metronidazole, a one-time dose of 2 g, for symptomatic patients only.[78] Although trichomoniasis has been associated with increased prematurity, treatment with metronidazole has not been shown to improve fetal outcomes, so emergency clinicians should counsel patients and consider deferment of treatment in asymptomatic pregnant women until after 37 weeks' gestation.

Sexually Transmitted Disease

Sexually transmitted diseases are treated in pregnant patients according to the latest CDC guidelines. In general, the tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important in preventing preterm labor and decreasing transmission to the infant.

Chlamydia trachomatis. *Chlamydia trachomatis* infection is the most common sexually transmitted disease in the United States and worldwide. Its prevalence is currently three to five times that of *Neisseria gonorrhoeae* infection. Clinical diagnosis is difficult during pregnancy because cervical mucus is usually cloudy and contains white blood cells, but urine sampling can be done and is equivalent to endocervical sampling in pregnancy infections.[79] Routine chlamydial screening during pregnancy is important to prevent complications of preterm labor and postpartum endometritis, both of which are more common in patients who have chlamydial cervical infections. Chlamydial infections of infants born to infected mothers include conjunctivitis and pneumonitis. Treatment during pregnancy or breast-feeding is azithromycin (single 1-g dose), which improves compliance and decreases gastrointestinal side effects; a 7-day course of amoxicillin is an acceptable alternative.[78]

Herpes Simplex. Herpes simplex virus infections pose a significant risk in pregnancy to the mother and newborn. Women who have genital herpes during the third trimester have a 30% to 50% increased risk of transmission compared with women with herpes simplex virus infection in the first trimester (1%). The virus can be transmitted prenatally through transplacental infection or ascending vaginal infection and by vaginal delivery, particularly when herpetic lesions are present. Infections in the neonate often are disseminated or involve the CNS, causing significant morbidity and mortality. In the ED, culture of new suspected herpetic lesions of the cervix, vagina, or perineum identifies patients at risk for perinatal complications. Although the risk of oral acyclovir and valacyclovir use in pregnancy is not well known, it is recommended for first-episode genital herpes. Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital herpes simplex occurred during pregnancy but may not eliminate the need for cesarean section in women with recurrent herpes simplex. Treatment should be undertaken with obstetric consultation and careful patient monitoring.

Neisseria gonorrhoeae. Gonococcal infection of the cervix occurs during pregnancy in 1% of women. Symptoms are similar to those in nonpregnant women. Salpingitis is rare but may develop during the first trimester from upper genital extension of cervical infection. Some practitioners believe that the incidence of the disseminated infection is increased in pregnant patients because of elevated progesterone levels and increased vascularity in the area of the cervix. Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy; treatment includes cephalosporins or azithromycin.[78] Treatment of possible coexistent chlamydial infection is recommended for pregnant and nonpregnant women. The major complications of third-trimester gonococcal infection are neonatal gonococcal ophthalmia and sepsis.[78,80]

Upper Genital Tract Infection

Pelvic Inflammatory Disease. PID is very rare in pregnancy and does not occur after the first trimester. The differential diagnosis includes ectopic pregnancy, septic abortion, and appendicitis, all of which are more common. In the patient with suspected infection, smears or cultures for *Chlamydia* and gonorrhea should be performed. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospitalization and IV antibiotics.[78]

Chorioamnionitis. Chorioamnionitis is the infection or inflammation of the placenta and fetal membranes. After 16 weeks of pregnancy, the chorioamniotic membranes adhere to the cervical os and may become infected. The risk is increased in women with preterm labor. Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy.[81] Leukocytosis can be suggestive of chorioamnionitis but is not diagnostic. Patients should have blood specimens drawn for culture. Vaginal and cervical culture specimens for group B streptococci, *E. coli,* chlamydia, and gonorrhea should also be obtained. Urgent obstetric consultation should be obtained, and hospitalization for IV administration of antibiotics is required. Patients are usually treated with IV ampicillin and gentamicin. In addition, a study has reported that antenatal steroids may reduce adverse neonatal outcome after a preterm birth associated with chorioamnionitis.[82]

Thyroid Disorders

Thyroid disorders are common in women of childbearing age. During pregnancy, however, this is associated with a range of adverse maternal and fetal outcomes, including spontaneous miscarriage, preeclampsia, heart failure, preterm delivery, intrauterine growth restriction, and stillbirth.[33,83] The evaluation and management of pregnant women with thyroid dysfunction parallel those of nonpregnant women, but require attention to the physiologic changes to the thyroid gland that occur during pregnancy.

Normal pregnancy exerts a significant amount of stress on the thyroid gland. During pregnancy, the thyroid gland increases in size, requires more iodine, and produces more thyroid hormone than in the nonpregnant state. Moreover, maternal and fetal thyroid function are strongly linked, with maternal thyroxine accounting for a substantial portion of fetal thyroid function at birth.[33] Thyroid dysfunction in pregnancy can occur during pregnancy or the postpartum state.

Hyperthyroidism, characterized by suppressed TSH levels, elevated T_4 and/or T_3 occurs in only 0.1 to 0.4% of all pregnancies.[84] Hyperthyroidism in pregnancy can be a result of any cause, but Graves' disease and hCG-mediated hyperthyroidism are the most common causes. Graves' disease is an autoimmune process associated with thyroid-stimulating antibodies and usually becomes less severe during the later stages of pregnancy.[33] hCG, which is homologous to thyroid-stimulating hormone (TSH), has some thyroid-stimulating activity and may transiently cause hyperthyroidism in the first half of gestation. hCG-mediated hyperthyroidism is typically less severe than Graves' disease–associated hyperthyroidism.

Hypothyroidism complicates 2% to 3% of pregnancies. Although nutritional iodine deficiency is a common cause of hypothyroidism globally, it is rare in the United States. When US women are diagnosed with hypothyroidism, the most common cause is Hashimoto's (autoimmune) thyroiditis, in which autoantibodies cause destruction of the thyroid gland. Hypothyroidism is associated with adverse pregnancy effects, including preeclampsia, placental abruption, low birth weight, and an increased risk of stillbirth.

Postpartum thyroiditis is characterized by transient hyperthyroidism and/or hypothyroidism in the postpartum period. It is estimated that 5% to 10% of women have postpartum thyroiditis. Most women return to a euthyroid state within 1 year postpartum, but approximately 25% of these women develop permanent hypothyroidism in the subsequent 10 years. The diagnostic triad consists of the lack of previous history of thyroid disorder, an abnormal TSH concentration during the first postpartum year, and the absence of TSH receptor antibodies (Graves' disease) or a toxic nodule.

Clinical Features

The diagnosis of thyroid dysfunction during pregnancy is difficult because pregnancy itself can mimic the findings in mild to moderate hypothyroidism and hyperthyroidism.

Hyperthyroidism in pregnancy should be suspected when the patient exhibits disproportionate tachycardia, thyromegaly, exophthalmos, weight loss, or inadequate weight gain during pregnancy. Hyperthyroidism may be associated with a hydatidiform mole and usually resolves with evacuation of the mole. Patients may present with signs of thyroid storm, including altered mental status, severe tachycardia, and signs of high-output heart failure (eg, edema, dyspnea, orthopnea).

Like hyperthyroidism, hypothyroidism in pregnancy is difficult to diagnose. Signs such as edema, fatigue, and/or weight gain may be attributed to the pregnancy rather than thyroid dysfunction. Enlargement of the thyroid gland may be absent depending on the cause of the hypothyroidism. The diagnosis of hypothyroidism during pregnancy should be suspected when the patient exhibits edema, dry skin, hair loss, and a prolonged relaxation phase of deep tendon reflexes.

Patients with postpartum thyroiditis classically present with thyrotoxicosis 6 weeks to 6 months postpartum, followed by a hypothyroid state lasting up to 6 months. A euthyroid state returns by the end of the first postpartum year. However, most patients present with hyperthyroidism alone or lone hypothyroidism. The recurrence rate in subsequent pregnancy is estimated at 69%, and 25% of women eventually develop permanent hypothyroidism.

Diagnostic Testing

Normal values of thyroid hormones vary based on stage of pregnancy. The diagnosis of hyperthyroidism is confirmed by a low (<0.1 mU/L) or undetectable (<0.01 mU/L) serum TSH level and levels of free triiodothyronine (T_3) and thyroxine (T_4) that exceed the normal range for pregnancy. Confirmation of hypothyroidism is based on an elevated serum TSH level, relying on trimester-specific TSH reference ranges.[83] Overt hypothyroidism is defined as an elevated trimester-specific TSH, along with a decreased, trimester-specific free T_4 concentration. Subclinical hypothyroidism is defined as an elevated trimester-specific serum TSH concentration and a normal free T_4 concentration.

Differential Diagnosis

Thyroid dysfunction should be considered in the patient with nonspecific symptoms, including fatigue, anxiety, depression, and unexplained weight loss or weight gain. When a diagnosis of hypothyroidism or hyperthyroidism is recognized, their respective causes and differential diagnoses should be considered (see Chapter 120 for more detailed information).

Management

No treatment is usually required for hCG-mediated hyperthyroidism. Treatment of pregnant women with overt hyperthyroidism due to Graves' disease is of utmost importance because good fetal and maternal outcomes depend on controlling the mother's hyperthyroidism. Although thyroid ablation with radioactive iodine is contraindicated in pregnancy, medical treatments are available. Propylthiouracil (PTU) is the preferred treatment of hyperthyroidism in the Unites States. Methimazole is equally effective at treating hyperthyroidism in pregnancy but may be associated with fetal anomalies such as aplasia cutis, esophageal atresia, and choanal atresia. It is therefore not recommended as first-line treatment for hyperthyroidism in pregnancy.

Patients with symptoms of thyroid storm should be managed in an intensive care setting. Treatment with PTU should be initiated early. Dexamethasone is recommended to block the peripheral conversion of T_4 to T_3.[33] Beta blockers should be considered to control tachycardia; labetalol, esmolol, and propranolol have been used intrapartum.[33] A subtotal thyroidectomy may be considered once the symptoms of thyrotoxicosis are managed medically.

Hypothyroidism in pregnancy is managed with levothyroxine supplementation (2 μg/kg/day). Patients in the hypothyroid phase of postpartum thyroiditis require levothyroxine when they have a TSH level higher than 10 mU/L or between 4 and 10 mU/L with symptoms or active pregnancy attempt. The hyperthyroid phase of postpartum thyroiditis is usually managed with limited course of beta blockers.

Disorders of the Hypothalamic-Pituitary Axis

The pituitary is normally enlarged in pregnancy due to estrogen stimulation. Disorders of the hypothalamic-pituitary axis may increase the incidence of maternal and fetal morbidity and mortality.

Pregnancy profoundly affects the hypothalamic-pituitary axis, resulting in increased circulating levels of cortisol and adrenocorticotropic hormone due to increased estrogen production. In contrast, levels of growth hormone decrease in pregnancy. Disorders of the hypothalamic-pituitary axis in pregnancy can result in adrenal insufficiency, Cushing's syndrome, acromegaly, diabetes insipidus, and prolactinomas. Although these disorders are rare, they are associated with maternal morbidity (eg, hypertension, hyperglycemia, eclampsia) and up to 20% fetal mortality.

Clinical Features

Disorders of the hypothalamic-pituitary axis usually present as an insidious set of chronic symptoms, many of which can mimic normal pregnancy, making diagnosis difficult. Symptoms vary depending on the specific disease but include fatigue, malaise, vomiting, weight gain or loss, amenorrhea, galactorrhea, and hyperprolactinemia. Normal pregnancy can be associated with slight decreases in the serum sodium level; more severe decreases in the serum sodium level may be signs of diabetes insipidus or adrenal insufficiency.

Diabetes insipidus may also be caused by pituitary infarction in the setting of severe obstetric hemorrhage (Sheehan's syndrome). Advancements in the management and resuscitation of obstetric hemorrhage have made Sheehan's syndrome increasingly rare, but it remains an important clinical consideration. The symptoms of Sheehan's syndrome are dependent on the degree of the patient's hypopituitarism. Patients present with signs and symptoms that vary, according to the deficient hormones. The failure of postpartum lactation and resumption of normal menstruation are strongly suggestive of Sheehan's syndrome.[85] Following postpartum hemorrhage, patients may have persistent tachycardia, hypotension, and latency between hemorrhage, and the onset of symptoms can vary, from months to years after pregnancy.[33]

Diagnostic Testing

Diagnostic considerations vary according to the patient's presentation. Growth hormone levels are elevated in patients with acromegaly. Patients with adrenal insufficiency may present with hyponatremia and hyperkalemia, although these may be absent in many patients. MRI is helpful in the detection of prolactinoma or Sheehan's syndrome.

Differential Diagnosis and Management

Stabilization consists of treatment of serious manifestations, such as hyperkalemia, tachycardia, and hypotension. Outpatient management is appropriate in the stable patient, provided there is urgent endocrinology follow-up.

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KEY CONCEPTS

Ectopic Pregnancy

- An ectopic pregnancy can masquerade as a threatened miscarriage in the early stages of pregnancy and should always be considered in the differential diagnosis.
- Because the history and physical examination of the patient with ectopic pregnancy are insensitive and nonspecific, pelvic ultrasonography and determination of serum hCG levels are essential to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result.

Bleeding in Late Pregnancy

- Bleeding during the second trimester (14–24 weeks) is not benign and is associated with a 33% risk of fetal loss. Management is supportive and expectant because fetal rescue is impossible at this level of fetal immaturity.
- The major conditions associated with vaginal bleeding in the second half of pregnancy include abruptio placentae and placenta previa. Patient history, physical examination, and results of ultrasonography can be used to distinguish them.
- All patients with painless, second-trimester vaginal bleeding should be assumed to have placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis has been excluded via ultrasound.
- Abruptio placentae has consists of a wide spectrum of severity of symptoms and risk. Up to 20% of women will have no pain or vaginal bleeding. Assessment is generally based on clinical features, coagulation parameters, and signs of fetal distress.

KEY CONCEPTS—cont'd

Hypertension in Pregnancy

- Gestational hypertension occurs during pregnancy, resolves during the postpartum period, and is recognized by a new blood pressure reading of 140/90 mm Hg or higher.
- Preeclampsia is gestational hypertension with proteinuria (>300 mg/24 hr); eclampsia is the occurrence of seizures in the patient with signs of preeclampsia.
- The HELLP syndrome is a particularly severe form of preeclampsia characterized by ***h***emolysis, ***e***levated ***l***iver enzyme levels (ALT and AST > 70U/L), and ***l***ow ***p***latelet count (<100,000/mL).
- Because progression of preeclampsia to eclampsia is unpredictable and can occur rapidly, blood pressure control in the pregnant patient is of utmost importance.

Amniotic Fluid Embolism

- Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden hypotension, hypoxia, and coagulopathy.
- Treatment of amniotic fluid embolus consists of support of oxygenation and ventilation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy.

Rh Immunization

- Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. To prevent this, a dose of 50 μg of Rh immune globulin can be used if the patient is at less than 12 weeks of gestation. After 12 weeks, a 300-μg dose should be given.

Abdominal Pain in Pregnancy

- Appendicitis is the most common surgical emergency in pregnancy. Clinical presentations may be atypical, leading to a misdiagnosis rate of 30% to 35% in pregnant patients. Right lower quadrant pain is the most common finding, especially early in pregnancy. Ultrasound, CT, and MRI are useful for the diagnosis.
- Cholelithiasis presents with similar symptoms to those in nonpregnant women and is similarly diagnosed through ultrasound. Surgery, if required, is optimally done during the second trimester.
- During pregnancy, albumin levels decrease while alkaline phosphatase levels may increase up to double; amylase levels may also be slightly elevated.
- Hepatitis is the most common cause of liver disease in pregnancy; the increased incidence of hepatitis E has increased maternal mortality and rate of fetal loss.
- Acute fatty liver of pregnancy is a rare disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. Coagulopathy, jaundice, seizures, DIC, and hepatic encephalopathy may also result.
- Intrahepatic cholestasis of pregnancy typically presents with generalized pruritus and mild jaundice. Resolution occurs with delivery. Women are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.

Nausea and Vomiting in Pregnancy

- Nausea and vomiting in pregnancy is common and may be treated with conservatively with diet modification and avoidance of environmental triggers. If conservative measures fail, Diclegis, a delayed-release combination of doxylamine, 10 mg, and pyridoxine (vitamin B_6), 10 mg, is the first-line pharmacologic agent for the treatment of nausea and vomiting in pregnancy.
- Hyperemesis gravidarum is defined as nausea and vomiting that cause starvation metabolism, weight loss, dehydration, and prolonged ketonemia and ketonuria. Initial management involves rehydration with IV fluids, antiemetics, and demonstration of ability to take oral hydration.

Thromboembolism in Pregnancy

- Thromboembolic disease accounts for almost 20% of obstetric mortality, making it the leading cause of death in pregnancy.
- Doppler ultrasonography is the first-line test for the diagnosis of DVT. CT angiography and lung scintigraphy are used for the diagnosis of PE.
- Low-molecular-weight heparin is preferred for anticoagulation.

Vaginal and Urinary Tract Infections

- Asymptomatic bacteriuria in pregnancy predisposes the patient to the development of symptomatic lower and upper tract genitourinary infections. Because up to 30% of women who have asymptomatic bacteriuria will have pyelonephritis if they are untreated, treatment of bacteriuria is cost-effective and important.
- Treatment of bacterial vaginosis is directed toward symptomatic relief for the patient and does not necessarily improve fetal outcomes. Management includes a 7-day course of metronidazole or 7-day course of clindamycin.
- For the treatment of vulvovaginal candidiasis, oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes. Treatment with vaginal azoles for 7 days during pregnancy is considered safe, with an estimated 85% to 100% cure rate.
- Of patients who have trichomoniasis, 50% are asymptomatic. Diagnosis is made by direct visualization of protozoans on wet mount. The recommended treatment is metronidazole, a one-time dose of 2 g, for symptomatic patients only.
- Regarding the treatment of sexually transmitted diseases, in general, the tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important for preventing preterm labor and decreasing transmission to the infant.
- *Chlamydia trachomatis* infection is the most common sexually transmitted disease in the United States and worldwide. Treatment during pregnancy or breast-feeding is azithromycin (single 1-g dose); a 7-day course of amoxicillin is an acceptable alternative.
- Women who have genital herpes during the third trimester have a 30% to 50% increased risk of transmission compared with women with herpes simplex virus (HSV) infection in the first trimester (1%).
- Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital HSV occurred during pregnancy.
- Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy; treatment includes cephalosporins or azithromycin.
- PID is very rare in pregnancy and does not occur after the first trimester. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospitalization and IV antibiotics.
- Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy. Patients are usually treated with IV ampicillin and gentamicin.

Thyroid Disease

- During pregnancy, the thyroid gland increases in size, requires more iodine, and produces more thyroid hormone than in the nonpregnant state.
- Hyperthyroidism, characterized by suppressed TSH levels and elevated T_4 and/or T_3 levels occurs in only 0.1% to 0.4% of all pregnancies. Graves' disease and hCG-mediated hyperthyroidism are the most common causes.
- When US women are diagnosed with hypothyroidism, the most common cause is Hashimoto's (autoimmune) thyroiditis.
- Postpartum thyroiditis is characterized by transient hyperthyroidism and/or hypothyroidism in the postpartum period. Approximately 25%

Continued

KEY CONCEPTS—cont'd

of these women develop permanent hypothyroidism in the subsequent 10 years.
- Hyperthyroidism may be associated with a hydatidiform mole and usually resolves with evacuation of the mole.
- The diagnosis of hyperthyroidism is confirmed by a low (<0.1 mU/L) or undetectable (<0.01 mU/L) serum TSH level and levels of free T_3 and T_4 that exceed the normal range for pregnancy.
- Confirmation of hypothyroidism is based on an elevated serum TSH level, relying on trimester-specific TSH reference ranges.
- Propylthiouracil (PTU) is the preferred treatment of hyperthyroidism in the Unites States. For thyroid storm, dexamethasone and beta blockers are added, with the patient under observation in the intensive care unit.
- Hypothyroidism in pregnancy is managed with levothyroxine supplementation (2 μg/kg/day).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 178: QUESTIONS & ANSWERS

178.1. An 18-year-old G1P0 at 8 weeks of gestation presents with abdominal pain and vaginal bleeding for 1 day. Her serum human chorionic gonadotropin (hCG) level is 3,700 IU/L. Transvaginal ultrasonography does not reveal an intrauterine pregnancy (IUP) or mass. The pelvic examination is remarkable for a closed cervical os and a small amount of blood. Which of the following should be the next step?
A. Coagulation panel
B. Gynecologic consultation
C. RhoGAM, 300 μg intramuscularly
D. Repeat hCG in 2 days
E. Serum progesterone level

Answer: A. Ultrasonographic detection of an IUP is likely at hCG levels higher than 1500 to 2000 IU/L. A negative ultrasound, with an hCG level of 3700 IU/L, is concerning for an ectopic pregnancy or miscarriage. β-hCG levels should peak at the 7- to 10-week range, with mean values of 50,000 IU/L. A persistently low hCG level is even more suspicious for ectopic pregnancy, and gynecologic consultation is warranted.

178.2. A 36-year-old G3P2 presents with painless vaginal bleeding during the past hour. She is at 33 weeks of gestation, and her pregnancy has been uncomplicated. Her bleeding lasted approximately 20 minutes. Appropriate management includes all of the following except which one?
A. Baseline hemoglobin level and platelet count
B. Immediate complete pelvic examination
C. Immediate obstetric consultation
D. Intravenous fluid resuscitation
E. Transvaginal ultrasound

Answer: B. Painless late pregnancy bleeding is placenta previa until proven otherwise. Digital or instrumental probing of the cervix should be avoided until the diagnosis is excluded via ultrasound. An injudicious vaginal examination can precipitate severe hemorrhage in the patient with an asymptomatic or minimally symptomatic placenta previa.

178.3. In pregnancy, treatment is indicated in each of the following sexually transmitted diseases except which one?
A. *Chlamydia trachomatis*
B. Herpes simplex virus
C. *Neisseria gonorrhoeae*
D. Pelvic inflammatory disease (PID)
E. *Trichomonas vaginalis*

Answer: E. Although trichomoniasis has been associated with increased prematurity, treatment with metronidazole has not been shown to improve fetal outcomes, so emergency clinicians should counsel patients and consider deferring treatment in asymptomatic pregnant women until after 37 weeks' gestation.

178.4. A 28-year-old G3P0 at 34 weeks of gestation presents with new-onset seizures. The patient has multiple seizures in the emergency department (ED) and is noted to be hypertensive at a blood pressure of 164/87 mm Hg. Which of the following should be administered next?
A. Benzodiazepines
B. Calcium gluconate
C. Labetalol
D. Magnesium sulfate
E. Pralidoxime

Answer: D. Magnesium sulfate has little antihypertensive effect but is the most effective anticonvulsant, preventing recurrent seizures while maintaining uterine and fetal blood flow. A loading dose of 4 g intravenous (IV) magnesium, followed by 2 g IV/hr, is recommended.

178.5. A 36-year-old G5P4 at 8 weeks of gestation presents to the ED with painless vaginal bleeding. Ultrasonography shows products of conception in the uterus. The pelvic examination shows a dilated cervix and a moderate amount of blood in the vaginal vault. Which of the following is appropriate management?
A. All of these
B. Expectant management
C. Medical management with misoprostol
D. None of these
E. Surgical evacuation

Answer: A. All of these are appropriate management options for an incomplete miscarriage.

178.6. Which of these is the most commonly observed surgical emergency in pregnancy?
A. Abruptio placentae
B. Appendicitis
C. Cholecystitis
D. Ovarian torsion
E. Ruptured peptic ulcer

Answer: B. Appendicitis is the most common surgical emergency in pregnancy. Clinical presentations may be atypical, particularly during the second half of pregnancy.

178.7. For the treatment of nausea and vomiting in pregnancy, which of the following has been found to have some associated risk of fetal abnormalities?
- **A.** Diclegis (delayed-release combination of doxylamine and pyridoxine)
- **B.** Ginger
- **C.** Metoclopramide
- **D.** Ondansetron
- **E.** Promethazine

Answer: D. Ondansetron has been shown in studies to be linked with fetal cardiac abnormalities, as well as cleft lip and palate. Diclegis is first-line pharmacologic treatment of nausea and vomiting in pregnancy; metoclopramide and promethazine are alternatives if it fails. Ginger, a nonpharmacologic treatment, has been shown to be safe and effective at a dose of 250 mg qid.

178.8. Which of the following is not considered a normal physiologic change in pregnancy?
- **A.** Decreased albumin level
- **B.** Increased D-dimer level
- **C.** Increased serum amylase level
- **D.** Increased serum bilirubin level
- **E.** Increased WBC count

Answer: D. Bilirubin, transaminase, and lactate dehydrogenase levels and prothrombin times are unchanged from the nonpregnant state. Albumin levels decrease secondary to an increase in maternal circulating plasma volume. Alkaline phosphatase levels may be up to double the nonpregnant values, and amylase levels may also be slightly elevated. The D-dimer level can be substantially elevated, even in normal pregnancy.