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Ectopic pregnancy

CLINICAL CASE

A 25-year-old woman reports that she had a positive home pregnancy test last week and now has spotting and low abdominal pain of 2 days' duration. Her last menstrual period was 6 weeks ago. Her abdomen is minimally tender in the left lower quadrant with no rebound tenderness. The pelvic examination is normal except for tenderness and a 4 cm mass in the left adnexa. Pelvic ultrasound shows an intact pregnancy consistent with her last period and a simple left ovarian cyst.

ECTOPIC PREGNANCY

An **ectopic** or **extrauterine pregnancy** is one in which the blastocyst implants anywhere other than the endometrial lining of the uterine cavity. Ectopic pregnancies account for approximately 1.5% of reported pregnancies in the United States. As shown in Figure 19.1, 98% of ectopic

pregnancies implant in the fallopian tube, with 80% occurring in the ampullary segment. Other locations include, but are not limited to, the ovary, cervix, and abdomen.

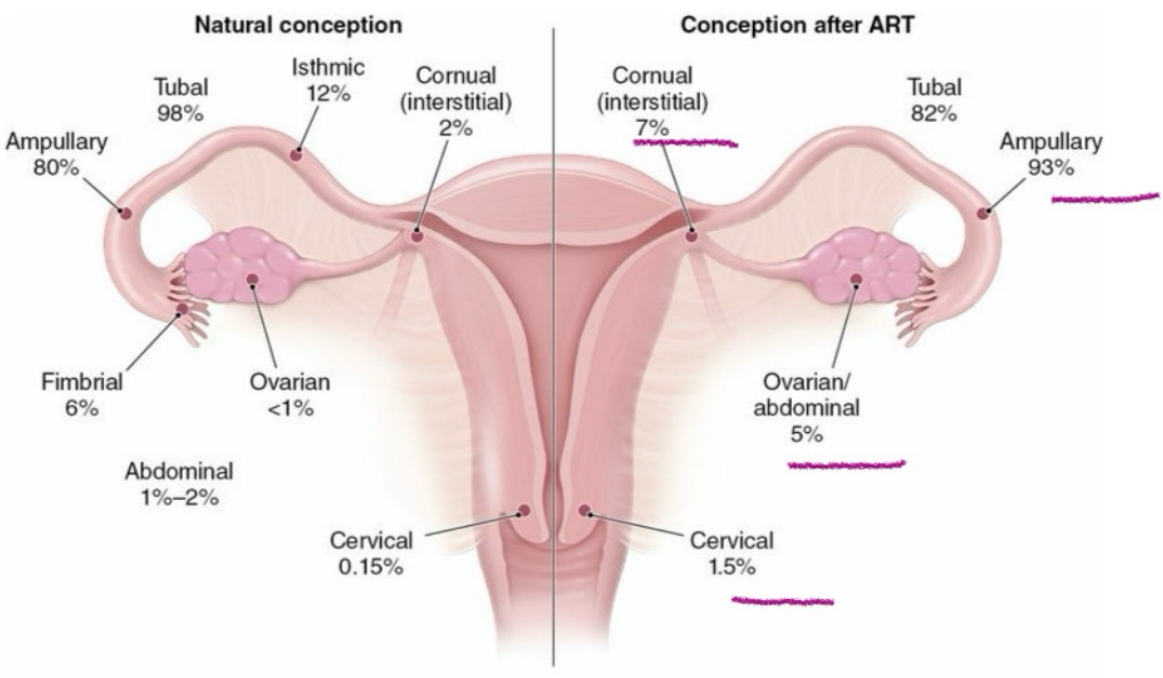


FIGURE 19.1. Incidence of types of ectopic pregnancy by location. ART, assisted reproductive technologies.

In the past, ectopic pregnancy was life threatening. Currently, earlier diagnosis made possible by the ability to detect the β-subunit of human chorionic gonadotropin (hCG), combined with high-resolution transvaginal sonography (TVS), has reduced this threat. Nevertheless, ectopic pregnancies remain an important cause of morbidity and mortality in the United States.

Tubal Ectopic Pregnancy

Without intervention, the natural course of a tubal pregnancy will result in any of three outcomes: tubal abortion, tubal rupture, or spontaneous resolution. **Tubal abortion** is the expulsion of the pregnancy through the fimbriated end. This tissue can then either regress or reimplant in the abdominal cavity. **Tubal rupture** is associated with significant intra-abdominal hemorrhage, often necessitating surgical intervention.

Pathophysiology and Risk Factors

An appreciation of risk factors for ectopic pregnancy can lead to making a more timely diagnosis resulting in both improved maternal survival and future reproductive potential. Inflammation resulting in tubal damage can disrupt the normal migration of a fertilized ovum through the tube, thereby predisposing to an ectopic pregnancy. Specific examples of an inflammatory process include **salpingitis** and **salpingitis isthmica nodosa**. An acute **chlamydial infection** causes intraluminal inflammation and subsequent fibrin deposition with tubal scarring. Despite negative cultures, persistent chlamydial antigens can trigger a delayed hypersensitivity reaction with continued scarring. Whereas endotoxin-producing *Neisseria gonorrhoeae* causes virulent pelvic inflammation with a rapid clinical onset, chlamydial inflammatory response is indolent and peaks at 7 to 14 days. The incidence of ectopic pregnancy has increased consistently with the rise in chlamydial infections.

Pregnancy after tubal sterilization is rare, but when it does occur, there

Pregnancy after tubal sterilization is rare, but, when it does occur, there is a substantial risk that the pregnancy will be ectopic due to the distorted tubal anatomy created by the tubal ligation. Previous concerns that intrauterine device use and pregnancy termination are predisposing risks for ectopic pregnancy have been dispelled. A history of infertility, independent of tubal disease, and ovulation induction also appear to be risk factors in ectopic pregnancy. Additional risk factors include prior ectopic pregnancy, smoking, prior tubal surgery, diethylstilbestrol exposure, and advanced age.

Symptoms

With the availability of early pregnancy testing, the ability to diagnose ectopic pregnancy before rupture—even before the onset of symptoms—is not unusual. The classic symptoms associated with ectopic pregnancy are amenorrhea followed by vaginal bleeding and abdominal pain on the affected side; however, there is no constellation of symptoms that are diagnostic.

Normal pregnancy symptoms, such as breast tenderness, nausea, and urinary frequency, may accompany more ominous findings. These include shoulder pain worsened by inspiration and caused by phrenic nerve

irritation from subdiaphragmatic blood as well as vasomotor disturbances, such as vertigo and syncope from hemorrhagic hypovolemia. As long as placental hormones are produced, there is usually no vaginal bleeding. Irregular vaginal bleeding results from the sloughing of the decidua from the endometrial lining. Vaginal bleeding in patients with an ectopic gestation may range from little or none to heavy, menstrual-like flow. In some patients, the entire "decidual cast" is passed intact, simulating a spontaneous abortion. Histologic evaluation of this tissue confirms whether placental villi are present. In any pregnant patient with no histopathologic confirmation of chorionic villi within the uterus, an ectopic implantation should be assumed to be present until proven otherwise.

Many women with a small unruptured ectopic pregnancy may have unremarkable clinical findings. Nevertheless, the diagnosis should be considered strongly when any of the above symptoms are reported by reproductive age women, especially those with risk factors for an extrauterine pregnancy.

Clinical Findings

Abdominal and pelvic findings are notoriously scant in many women before tubal rupture

before tubal rupture.

Prior to rupture, the diagnosis of an ectopic pregnancy is primarily based on laboratory and ultrasound findings. With rupture, however, nearly three-fourths of women will have marked tenderness on both abdominal and pelvic examination, and pain is aggravated with cervical manipulation. A pelvic mass, including fullness posterolateral to the uterus, can be palpated in about 20% of women. Initially, the ectopic pregnancy may feel soft and elastic, whereas extensive hemorrhage produces a firmer consistency. Many times, discomfort precludes palpation of the mass. Not performing a pelvic examination may actually help avert iatrogenic rupture.

Given the available technology and the natural course of an ectopic pregnancy, the role of physical examination in the diagnosis of this condition is minimal. Fever is not expected, although a mild elevation in temperature in response to intraperitoneal blood may occur. A temperature of 38°C may suggest an infectious cause of a patient's symptoms. Abdominal distention and tenderness, with or without rebound, rigidity, or

decreased bowel sounds may be seen in cases of intra-abdominal bleeding. Abdominal tenderness is present in 50% to 90% of patients with ectopic pregnancies. Cervical motion tenderness caused by intraperitoneal irritation and adnexal tenderness are commonly found.

An adnexal mass is present in roughly one third of cases, but its absence does not rule out the possibility of an ectopic implantation. The uterus may enlarge and soften throughout the first trimester, thus simulating an intrauterine pregnancy. A slightly open cervix with blood or decidual tissue may be found and mistaken for a threatened and/or spontaneous abortion.

Differential Diagnosis

Symptoms of ectopic pregnancy can mimic multiple entities. Early pregnancy complications (threatened, incomplete, or missed abortion), placental polyp, and hemorrhagic corpus luteal cyst are difficult to differentiate from ectopic pregnancy. Since early bleeding occurs in up to 20% of women with normal, intact pregnancies, the physician must take care to avoid any action that might compromise a possible ongoing pregnancy. A number of nonpregnancy-related disorders, such as appendicitis and renal calculi, can also mimic ectopic pregnancy.

The rapid and accurate diagnosis of ectopic pregnancy is imperative to reduce the risk of serious complications or death. Up to half of the women who have died as a result of ectopic pregnancy had a lag in treatment because of delayed or inaccurate diagnoses. Any sexually active woman in the reproductive age group who presents with pain, irregular bleeding,

and/or amenorrhea should have ectopic pregnancy as a part of the initial differential diagnosis.

Diagnostic Procedures

TVS and serial serum β-hCG measurements are the most valuable diagnostic aids to confirm a suspicion of ectopic pregnancy. The initial assessment in the otherwise hemodynamically stable patient must include a pregnancy test. A negative pregnancy test excludes the possibility of ectopic pregnancy. Urinary pregnancy tests, which detect hCG levels to 20 IU/L, are now commonly available. These tests detect hCG as early as 14 days after fertilization and are positive in more than 90% of cases of

ectopic pregnancy. Serum assays can detect the presence of hCG as early as 5 days after fertilization, that is, before the missed menstrual cycle; however, because they require additional time and expertise to perform, they are often not utilized in a potentially emergent clinical setting.

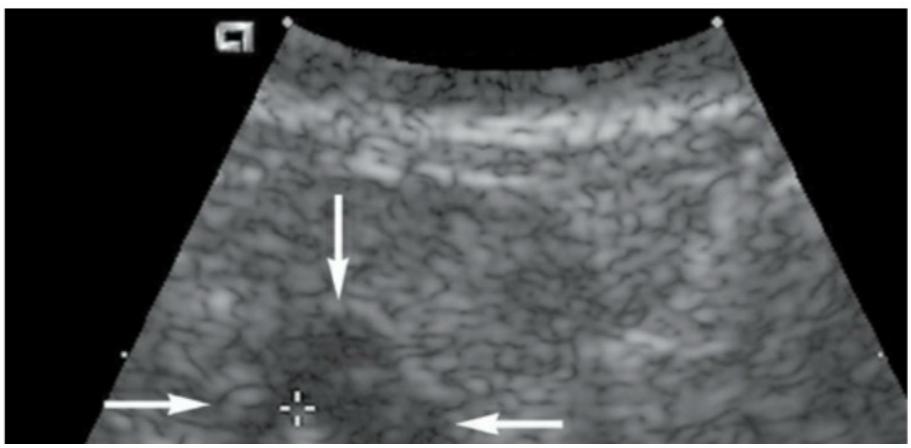
Serum Human Chorionic Gonadotropin Levels

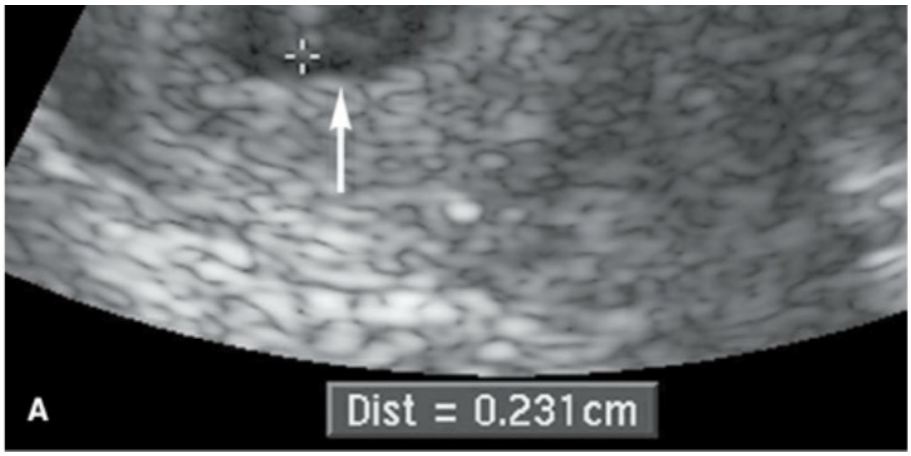
If a positive pregnancy test is found when ectopic pregnancy is suspected, the remainder of the workup should focus on evaluating the viability and location of the pregnancy. In normal pregnancies, serum β-hCG levels rise in a log-linear fashion until 60 or 80 days after the last menses, at which time levels plateau at about 100,000 IU/L. During this early phase of pregnancy, a 53% or greater increase in serum β-hCG levels should be observed every 48 hours. A rise of hCG levels less than this should raise suspicion for an abnormal gestation, either intrauterine or ectopic. Complicating this scenario is the recognition that approximately 15% of normal intrauterine pregnancies are associated with less than a 53% increase in hCG, and 17% of ectopic pregnancies have normal hCG doubling times. Although inappropriately rising serum β-hCG levels suggest (but do not diagnose) an abnormal pregnancy, they do not identify its location.

Transvaginal Ultrasonography

A key adjunct to serial quantitative levels of hCG is transvaginal pelvic ultrasonography (Fig. 19.2). Using TVS, a gestational sac is usually visible between 4½ and 5 weeks from the last menstrual period (LMP). The yolk sac appears between 5 and 6 weeks, and a fetal pole with cardiac activity is first detected at 5½ to 6 weeks. With transabdominal sonography, these structures are visualized slightly later. Each institution must define a β-hCG **discriminatory value** (i.e., the lower limit of serum hCG at which a TVS can reliably visualize pregnancy). It is not uncommon for TVS to demonstrate an intrauterine pregnancy by the time the hCG level is 1,000 to 2,000 IU/L. Transabdominal ultrasonography should be able to identify an intrauterine gestation by the time the hCG level reaches 5,000 to 6,000 IU/L. The absence of an intrauterine pregnancy with β-hCG levels above the discriminatory value signifies an abnormal pregnancy—ectopic, incomplete abortion, or resolving completed abortion. Care must be taken

to differentiate between a uterine gestation and a **pseudogestational sac**. This one-layer sac is the result of an intracavitary fluid collection caused by sloughing of the decidua typically situated in the midline of the uterine cavity, whereas a normal gestational sac is eccentrically located (Fig. 19.3).

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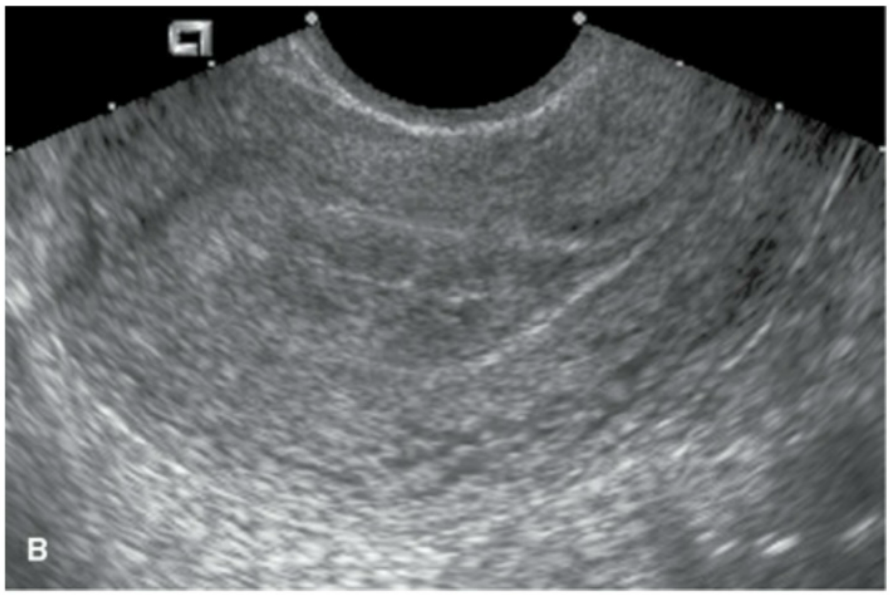


FIGURE 19.2. Ectopic pregnancy with an extrauterine gestational sac containing a live embryo. (A) Coronal transvaginal view of the right adnexa demonstrates an extrauterine sac (*arrows*) containing an embryo (calipers). (B) Sagittal transvaginal view of the uterus reveals no evidence of a gestational sac. (From Doubilet PM, Benson CB. *Atlas of Ultrasound in Obstetrics and Gynecology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:319.)

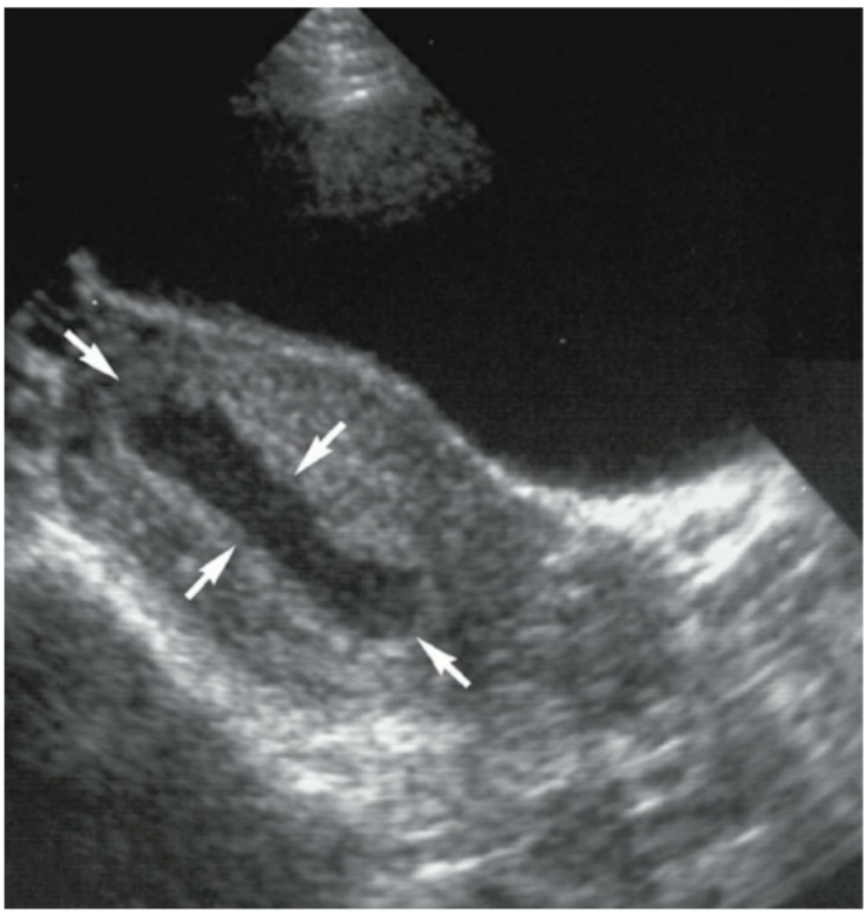


FIGURE 19.3. Pseudogestational sac. Sagittal transabdominal view of the uterus demonstrates a pseudogestational sac, a collection of fluid within the uterus. (From Doubilet PM, Benson CB. *Atlas of Ultrasound in Obstetrics and Gynecology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:320.)

Serum Progesterone Level

Serum progesterone concentration is higher in a viable pregnancy than an ectopic pregnancy. There is minimal variation in serum progesterone concentration between 5 and 10 weeks of gestation; thus a single value is sufficient. A serum progesterone level of <5 ng/mL has been used to identify a nonviable pregnancy with 98% specificity and with a sensitivity of 75%. Conversely, a serum progesterone of >20 ng/mL has a sensitivity of 95%, with a specificity of approximately 40% to identify a healthy pregnancy. Serum progesterone values cannot differentiate between an ectopic and an intrauterine pregnancy.

Endometrial Curettage

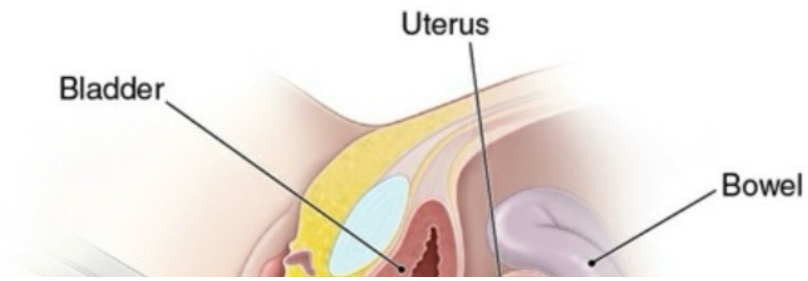
Curettage of the uterine cavity can also help rule out ectopic pregnancy but should only be undertaken after the possibility of interrupting an intact pregnancy has been considered. Although intrauterine and ectopic pregnancies can exist simultaneously in rare cases (heterotopic pregnancy), identification of chorionic villi in tissue samples identifies an intrauterine location of the pregnancy and essentially rules out ectopic pregnancy. The presumptive diagnosis of ectopic pregnancy is reportedly inaccurate in nearly 40% of cases without histologic exclusion of a spontaneous pregnancy loss. The **Arias-Stella reaction**, a hypersecretory endometrium of pregnancy seen on histologic examination, occurs with both ectopic and intrauterine pregnancies and, therefore, is not useful in identifying an ectopic pregnancy.

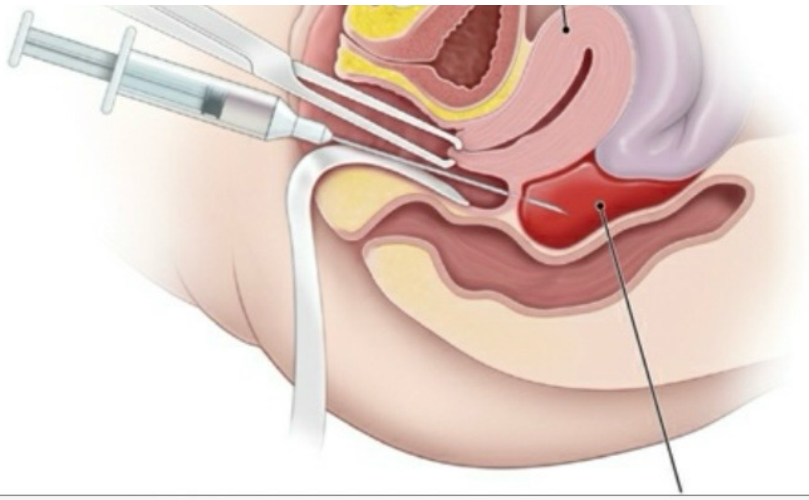
Culdocentesis

Culdocentesis can identify **hemoperitoneum** (blood in the peritoneal cavity), which may indicate a ruptured ectopic pregnancy, although it is also consistent with other causes, such as a ruptured corpus luteum cyst. An 18G needle is inserted posterior to the cervix, between the uterosacral ligaments, and into the cul-de-sac of the peritoneal cavity (Fig. 19.4). Aspiration of clear peritoneal fluid (negative culdocentesis) indicates no hemorrhage into the abdominal cavity but does not rule out an unruptured ectopic pregnancy. Aspiration of blood that clots can indicate either penetration of a vessel or such rapid blood loss into the peritoneal cavity that the blood clot has not had time to undergo fibrinolysis. Aspiration of nonclotting blood is evidence of hemoperitoneum (positive culdocentesis), in which the blood clot has undergone fibrinolysis. If nothing is aspirated (equivocal or nondiagnostic culdocentesis), no information is obtained. Purulent fluid suggests a number of infection-related causes, such as salpingitis and appendicitis. Because none of the possible findings on culdocentesis can definitively confirm the presence or absence of ectopic pregnancy, its use in clinical practice is limited.

When used, the principal useful result is that a positive culdocentesis identifies blood in the peritoneal cavity and confirms the need for further evaluation to identify the source of the bleeding. With the availability of

other diagnostic technology, particularly ultrasound, in many regions the use of culdocentesis has become almost obsolete.





Laparoscopy

The most accurate technique of identifying an ectopic pregnancy is by ***direct visualization****, which is done most commonly via* ***laparoscopy****.* Even laparoscopy, however, has a 2% to 5% misdiagnosis rate. For example, an extremely early tubal gestation may not be identified because it may not distend the fallopian tube sufficiently to be recognized as an abnormality (false negative). Conversely, a false-positive diagnosis may result from a **hematosalpinx** (blood in the fallopian tube) being misinterpreted as an unruptured ectopic pregnancy or tubal abortion.

Management

Management may be either surgical or medical, depending on a variety of factors. In any individual case, surgery can be a simple procedure, but it

can also be far more extensive, depending on the location of the ectopic pregnancy, whether or not it is ruptured, the gestational age of the pregnancy, and the patient's desire for future fertility.

Due to the inherent risks of each, medical therapy is preferred over surgery in appropriate patients.

Medical Management

Methotrexate is the medical treatment usually used as an alternative to surgical therapy. Methotrexate is a folic acid antagonist that competitively inhibits the binding of dihydrofolic acid to dihydrofolate reductase, which, in turn, reduces the amount of the active intracellular metabolite, folinic acid. It stops the growth of rapidly dividing placental, embryonic, and fetal cells.

An appropriate candidate for medical therapy is the woman who is asymptomatic, motivated, and has resources to be compliant with follow-up. Relative and absolute contraindications for medical management are listed in Box 19.1.

BOX 19.1 Contraindications to Medical Therapy for Ectopic Pregnancy

Absolute

- Breastfeeding
- Overt or laboratory evidence of immunodeficiency
- Known sensitivity to methotrexate
- Active pulmonary disease
- Peptic ulcer disease
- Hepatic, renal, pulmonary, or hematologic dysfunction
- Heterotopic pregnancy with viable intrauterine gestation
- Unable to comply with management protocol

Relative

- Gestational sac greater than 3.5 cm
- Embryonic cardiac motion
- Free peritoneal fluid (possible hemoperitoneum)

Modified from American Society of Reproductive Medicine. Medical Treatment of Ectopic Pregnancy: a committee opinion. Fertility and Sterility, Vol 100(3); September, 2013.

Factors that can be assessed in predicting the success of medical therapy include the initial β-hCG level, the size of ectopic pregnancy as determined by TVS, and presence or absence of fetal cardiac activity. The initial serum β-hCG level is the best prognostic indicator of treatment success in women managed with a single-dose methotrexate protocol. An initial serum value <5,000 IU/L is associated with a success rate of 92%, whereas an initial concentration >15,000 IU/L has a success rate of 68%. Ectopic pregnancy size also appears to have an effect on methotrexate success rates. Success rates are reported as high as 93% in cases with ectopic masses <3.5 cm. A diameter >3.5 cm and the presence of cardiac activity are considered relative contraindications to medical management because these findings are associated with a lower success rate.

The most common side effects of methotrexate include nausea, vomiting, diarrhea, gastric distress, dizziness, and stomatitis. Intramuscular methotrexate given as part of a single-dose protocol has been the most widely used medical treatment of ectopic pregnancy. Close monitoring is imperative. A serum β-hCG level is determined before administering methotrexate and is repeated on days 4 and 7 following injection. Levels may continue to rise until day 4. Comparison is then made between the day 4 and the day 7 serum values. If there is a decline by 15% or more, serum β-hCG levels are measured weekly until they are undetectable. If the β-hCG level does not decline, the patient may require either surgery or a second dose of methotrexate if no contraindications exist. Surgical intervention may be required for patients who do not respond to medical therapy.

During the first few days following methotrexate administration, up to half of women experience abdominal pain that can be controlled with nonsteroidal anti-inflammatory drugs. This pain presumably results from tubal distention, tubal abortion, and/or hematoma formation.

Methotrexate given in a multidose protocol has also been used successfully, but the single-dose protocol described appears to reduce the amount of potential complications while achieving similar success rates. Other medical treatments that have been used include hyperosmolar glucose, potassium chloride, prostaglandins, and the progesterone receptor

antagonist mifepristone (formerly referred to as *RU-486*). In some cases, an agent may be administered systemically, but sometimes it may be injected directly into the ectopic pregnancy.

Surgical Management

Women who are hemodynamically stable and in whom there is a small ectopic diameter, no fetal cardiac activity, and serum β-hCG concentrations <5,000 IU/L have similar outcomes with medical or surgical management. Conservative surgical techniques have been developed that maximize preservation of the fallopian tube. If removal is done through the laparoscope, definitive diagnosis as well as treatment can be accomplished at the same operation with minimal morbidity, cost, and hospitalization. In a **linear salpingostomy**, the surgeon makes an incision on the fallopian tube over the site of implantation, removes the pregnancy, and allows the incision to heal by secondary intention. A **segmental resection** is the removal of a portion of the affected tube (Fig. 19.5). **Salpingectomy** is removal of the entire tube, a procedure reserved for those cases in which little or no normal tube remains.

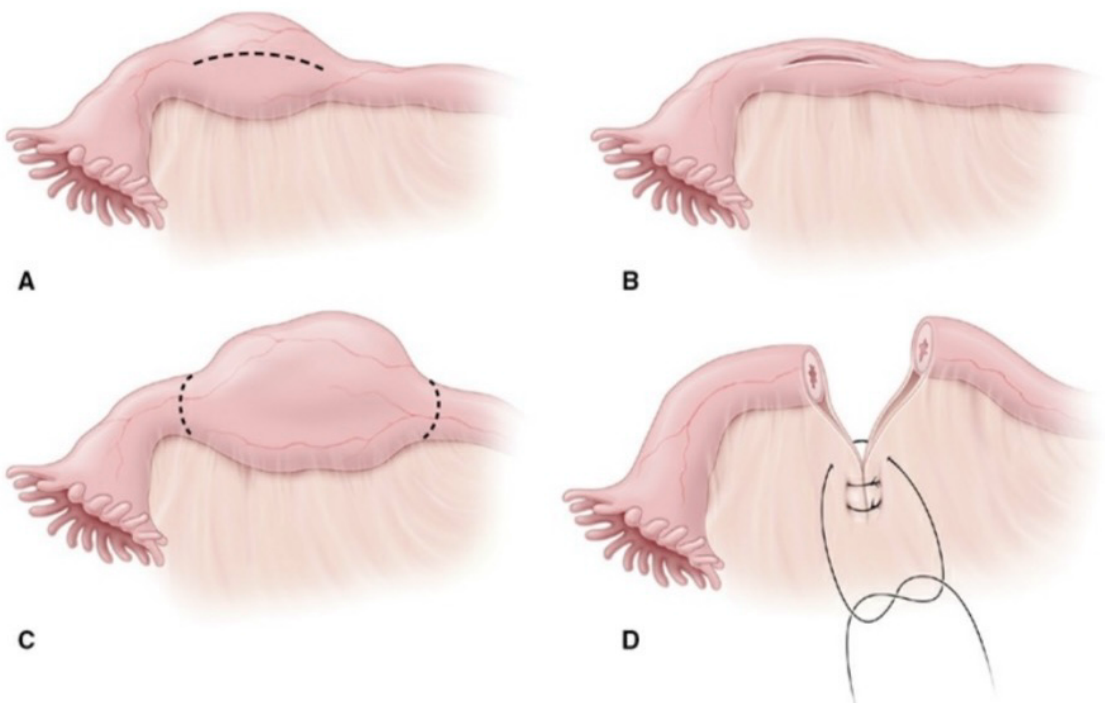


FIGURE 19.5. Surgical management of ectopic pregnancy. (A) Site of linear incision for linear salpingostomy. (B) Linear incision. (C)

Segmental resection. (D) Tubal reanastomosis.

When conservative surgery or nonsurgical treatment is used, the patient must be followed post-therapy with serial quantitative β-hCG levels to monitor regression of the pregnancy. Subsequent surgery or methotrexate therapy is needed if trophoblastic function persists as evidenced by persistent or rising levels of hCG. *Rh-negative mothers with ectopic pregnancy should receive* ***Rh immunoglobulin*** *to prevent Rh sensitization (see Chapter 23).*

Non–Fallopian Tube Ectopic Pregnancy

Ovarian Pregnancy

Ectopic implantation of the fertilized egg in the ovary is rare. Improved imaging modalities have facilitated this diagnosis being made. Risk factors are similar to those for tubal pregnancies, although ovarian pregnancies are not associated with a history of salpingitis. Diagnosis is based on the classic sonographic description of a cyst with a wide echogenic vascular outer ring located on or within the ovary.

Medical management as well as surgery can be used to conserve the ovary.

Interstitial Pregnancy

Also termed **cornual pregnancy**, interstitial pregnancies implant in the proximal tubal segment that lies within the muscular uterine wall. Swelling lateral to the insertion of the round ligament is the characteristic anatomic finding. A pregnancy that implants in the cornual segment of the tube tends to present several weeks later in pregnancy, because the muscular cornu of the uterus is better able to expand and accommodate an enlarging pregnancy. As a result, rupture of a cornual pregnancy typically occurs between the 8th and 16th gestational weeks and is often associated with massive hemorrhage, sometimes requiring hysterectomy.

Mortality rates are quoted as high as 2.5%. If detected prior to rupture, medical management is potentially successful. If surgery is needed, resection of the cornual region is performed.

Cervical Pregnancy

Cervical pregnancy occurs in 1 in 9,000 to 12,000 pregnancies, when the ovum implants in the cervical mucosa below the level of the histologic cervical internal os. Two diagnostic criteria are necessary for confirmation of cervical pregnancy: (1) the presence of cervical glands opposite to the

of cervical pregnancy: (1) the presence of cervical glands opposite to the placental attachment site and (2) a portion of or the entire placenta must be located below either the entrance of the uterine vessels or the peritoneal reflection on the anterior and posterior uterine surface. Both medical and surgical management have been used successfully to preserve the cervix in cases where future fertility is desired.

Heterotopic Pregnancy

Heterotopic pregnancy (coincident or combined pregnancy) is the coexistence of an ectopic and an intrauterine pregnancy. The incidence was previously estimated to be 1 in 30,000 pregnancies. As a result of assisted reproduction, however, the rate of heterotopic pregnancies has increased to as high as 1 in 100 pregnancies in some series. Mechanisms that have been proposed to explain this include (1) hydrostatic forces delivering the embryo into the cornual or tubal area, (2) the tip of the catheter directing transfer toward the tubal ostia, or (3) reflux of uterine secretions leading to retrograde tubal implantation. In addition to the option of surgical management of the ectopic pregnancy while attempting to preserve the intrauterine pregnancy, medical therapy in which potassium chloride can be injected into the pregnancy sac is another option. Methotrexate is contraindicated due to potential detrimental effects on the normal pregnancy.

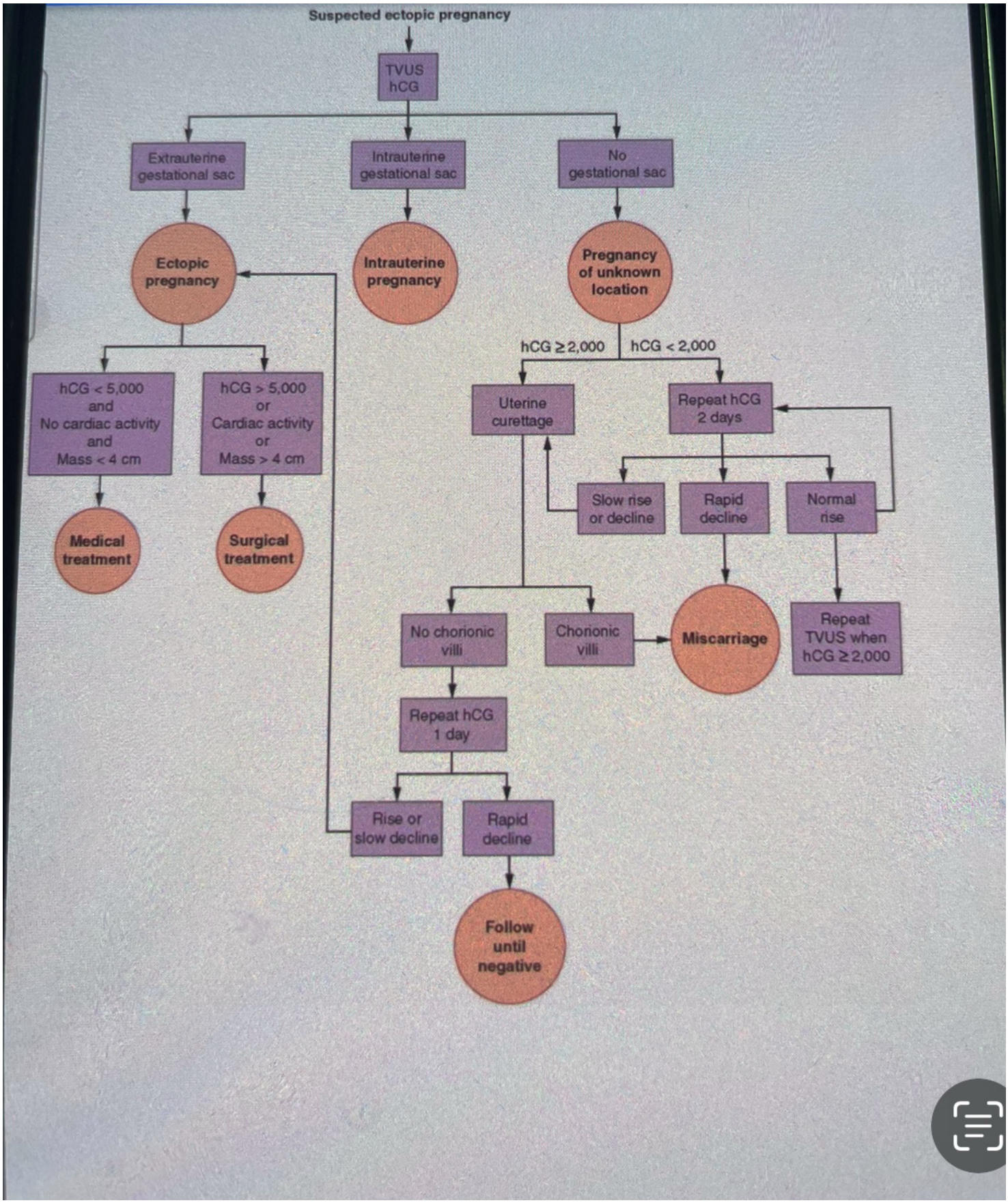
Abdominal Pregnancy

The estimated incidence of **abdominal pregnancy** ranges from 1 in 10,000 to 1 in 25,000 live births. Abdominal pregnancies may result from primary implantation onto the peritoneal surface or secondary implantation via tubal rupture or tubal abortion. Physical findings and symptoms are widely variable, depending on gestational age and site of implantation. Diagnosis is confirmed primarily by ultrasonography. Abdominal pregnancy is usually discovered long before fetal viability, and removal of the pregnancy is the mainstay of therapy.

Survival of the fetus occurs in only 10% to 20% of cases; up to one half

of those surviving have significant deformity. The patient is given the option of continuing the pregnancy to fetal viability with operative delivery or operative termination of the pregnancy at the time of diagnosis. In either case, removal of the placenta is usually not attempted because of

In either case, removal of the placenta is usually not attempted because of the risk of uncontrollable hemorrhage. Allowing the placenta to spontaneously regress is often the management chosen. Alternative treatments include administration of methotrexate and embolization of placental vessels.


Suspected ectopic pregnancy
TVUS
hCG
Extrauterine gestational sac
Intrauterine gestational sac
No gestational sac
Ectopic pregnancy
Intrauterine pregnancy
Pregnancy of unknown location
hCG < 5,000 and No cardiac activity and Mass < 4 cm
hCG > 5,000 or Cardiac activity or Mass > 4 cm
hCG ≥ 2,000
hCG < 2,000
Uterine curettage
Repeat hCG 2 days
Slow rise or decline
Rapid decline
Normal rise
Medical treatment
Surgical treatment
No chorionic villi
Chorionic villi
Miscarriage
Repeat TVUS when hCG ≥ 2,000
Repeat hCG 1 day
Rise or slow decline
Rapid decline
Follow until negative