Ectopic pregnancy is a major health problem for women of childbearing age and a leading cause of pregnancy-related death in the first trimester. Untreated, ectopic pregnancy can lead to massive hemorrhage, infertility and death. With the advent of high-resolution transvaginal sonography, in conjunction with serum assays for the β-subunit of human chorionic gonadotropin (β-hCG), rapid and accurate diagnosis of this entity is now routinely possible.

Ectopic pregnancy is defined as implantation of a fertilized ovum outside the endometrial lining of the uterus. Based on data from the Centers for Disease Control and Prevention, ectopic pregnancy has an incidence of approximately 2% of all reported pregnancies and accounts for 9% of pregnancy-related deaths.1

First described in the 11th century, ectopic pregnancy was usually fatal. John Bard of New York City, NY, performed the first abdominal surgery for ectopic pregnancy in 1759. However, the survival rate for surgery was dismal in the 18th century and patients who were not treated surgically had a greater survival rate than those undergoing surgery.2 With subsequent improvements in anesthesia, antibiotics and blood transfusion during the 20th century, mortality rates have significantly declined. Between 1970 and 1989 the risk of death from ectopic pregnancy dropped from 35.5 to 2.6 deaths per 10,000 cases despite a fourfold increase in incidence.2

Although ectopic pregnancy can occur in any woman capable of becoming pregnant, certain patient populations are more predisposed to ectopic pregnancy. Risk factors include: history of prior pelvic inflammatory disease, prior tubal surgery or ligation, presence of an intrauterine device, infertility treatment, history of prior ectopic pregnancy, and older age. Ectopic pregnancy has also been found to be more common in smokers than nonsmokers, possibly secondary to altered tubal motility.3,4 These risk factors can be additive resulting in increased risk for women with multiple risk factors.

Ectopic pregnancy most commonly occurs in the fallopian tube with 90% to 95% occurring in the ampullary or isthmic portions (Figure 1). Less than 5% of ectopic pregnancies are interstitial in location. However, morbidity and mortality are higher for interstitial ectopic pregnancies due to later presentation and resultant massive hemorrhage. Cervical, ovarian and intra-abdominal ectopic pregnancies are rare and account for <1% of all ectopic pregnancies.5 Ectopic pregnancies can also occur in the scar from a previous caesarean section. These ectopic pregnancies are also rare, accounting for <1% of ectopic pregnancies. They can present with vaginal bleeding as early as 5 to 6 weeks gestational age and as late as

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16 weeks. These ectopic pregnancies, located in the anterior myometrium of the lower uterine segment, may rupture—resulting in severe hemorrhage and cardiovascular collapse.

Clinically, the classic triad of signs/symptoms of ectopic pregnancy consists of vaginal bleeding, abdominal or pelvic pain, and a tender adnexal mass. Unfortunately, this triad is only seen in about 50% of women presenting with ectopic pregnancy. In many patients, presenting signs and symptoms are often nonspecific and can overlap with findings common to normal early-intrauterine pregnancies or miscarriages. They can include nausea, fatigue, lower abdominal pain, cramping and shoulder pain. Because of the overlap with early pregnancy symptomatology, a high clinical index of suspicion for ectopic pregnancy is necessary.

How then does one approach the pregnant patient with pain and vaginal bleeding or the ubiquitous requisition for “rule out ectopic” from the Emergency Department? The primary differential diagnosis in such cases is fairly straightforward and includes: normal intrauterine pregnancy (IUP), abnormal IUP or spontaneous abortion, ectopic pregnancy, and molar pregnancy. The primary tools used to distinguish between these entities are high-resolution transvaginal sonography and serum assays for β-hCG.

Technique

Transvaginal sonography is performed at the authors’ institution with a curved 8-4 MHz array or a curved array 9-5 MHz endovaginal probe. The uterus is imaged in the sagittal and transverse planes. Measurement of the endometrial stripe is obtained on a midline sagittal image. The cervix is evaluated to determine if the os is open or closed and whether fluid is present in the endocervical canal. The adnexa are carefully evaluated and measurements of the ovaries are obtained in the sagittal and transverse planes. If a mass is identified within the adnexa, pressure is applied with the probe internally and by the

FIGURE 1. Locations of ectopic pregnancy. (A) ampullary/isthmic, (B) infundibulum, (C) fimbria, (D) interstitial, (E) intra-abdominal, (F) ovarian and (G) cervical.

FIGURE 2. Intradecidual sign. Sagittal transvaginal images (A, B) of the uterus demonstrate an eccentrically located small gestational sac with echogenic rim (arrows).

FIGURE 3. Double decidual sac sign. Transvaginal images (A, B) of the uterus demonstrate gestational sac surrounded by 2 hyperechoic curvilinear lines. The inner line (long arrows) represents decidua capsularis, the outer line (arrowheads) represents decidua vera (parietalis). Also note the yolk sac and small fetal pole.
hand externally on the anterior abdominal wall to determine if the mass is arising from the ovary or is separate from it. The cul-de-sac is imaged for any evidence of free fluid. Color and spectral Doppler waveforms are obtained from both ovaries with a resistive index (RI) calculated. Spectral and color Doppler imaging is also obtained of any abnormalities seen in the adnexal regions with calculation of RIs.

Transabdominal imaging of the pelvis is performed if no ectopic pregnancy is identified transvaginally to give a broader overview of the pelvis and to detect any possible intra-abdominal location of the ectopic pregnancy. Transabdominal imaging is also performed to evaluate for fluid in the pelvis and in Morison’s pouch. The area of the patient’s pain should also be examined by transabdominal imaging if not adequately visualized on the transvaginal examination.

Serum ß-hCG

Human chorionic gonadotropin is produced by the placenta and can be detected in the serum approximately 9 days after conception (23 days after the last menstrual period [LMP]). A negative serum ß-hCG result essentially excludes the diagnosis of a live pregnancy. It is important to note that several reference standards are used in reporting the results of a serum ß-hCG level and it is essential to know which standard is used by your institution. The third international standard (IS) or international reference preparation (IRP) is now used most commonly. However, early studies and papers on ectopic pregnancy utilized the second IS. Conversion from the second IS to the IRP can be achieved by multiplying the second IS by a factor of 1.8.

Utilizing the IRP standard, a gestational sac should be seen on transvaginal sonography if the serum ß-hCG level is 1800 to 2000 mIU/mL. In early healthy intrauterine pregnancies, the ß-hCG level should double approximately every 2 days.

Normal intrauterine pregnancy

To evaluate for an ectopic pregnancy or abnormal pregnancy, it is necessary to recognize the ultrasound findings of an early normal intrauterine pregnancy (IUP). Documentation of an IUP significantly decreases the likelihood for an ectopic pregnancy in most patients. The earliest sonographic finding of an early IUP is the intradecidual sign first described by Yeh et al. in 1986. Seen at approximately 4.5 weeks after the LMP, the intradecidual sign consists of a small fluid collection with an echogenic rim eccentrically located adjacent to, but separate from, the central linear echogenic complex (Figure 2). The presence of an echogenic rim aids in distinguishing this entity from a decidual cyst. The accuracy of this sign is variable with reported sensitivities ranging from 48% to 68% and specificities from 66% to 100%.

By 5 weeks gestational age, a more clearly defined gestational sac should be observed with a double decidual sac sign present. The double decidual sac sign consists of 2 hyperechoic curvilinear lines at the margin of the developing gestational sac separated by hypoechoic material (Figure 3). The 2 hyperechoic interfaces result from: the inner decidua capsularis, forming the “free” edge of the enlarging gestational sac; and, the outer decidua vera (Figure 4). The hypoechoic region represents fluid between the 2 structures within the endometrial canal. The double decidual sac sign is a highly accurate
indicator of an early IUP. Absence of this sign does not necessarily exclude an early IUP. Other characteristics of a normal intrauterine gestational sac include: continuous echogenic rim of at least 2 mm thickness, spherical or ovoid shape, location in the upper or middle portion of the uterus, and growth >1.2 mm per day.

A yolk sac is usually visualized by 5.5 weeks and confirms the presence of an intrauterine pregnancy. The upper limit for normal size for the yolk sac is 5 to 6 mm. By 11 weeks, the yolk sac starts to involute. By 6 weeks, an embryonic pole should be identifiable and by 6.0 to 6.5 weeks, cardiac activity should be visualized on real-time imaging (Figure 5).

Concomitant with the developing intrauterine gestational sac is the development of the corpus luteum. From the Latin meaning “yellow body,” the corpus luteum forms from the ovarian follicle after ovulation. Signaled by hCG from the developing pregnancy, the corpus luteum secretes progesterone to maintain the pregnancy until the placenta assumes this role. If no pregnancy develops during the normal menstrual cycle, the corpus luteum involutes becoming the corpus albicans.

Sonographically, the corpus luteum can have a wide range of appearances. The corpus luteum can appear as an ill-defined, hypoechoic, homogeneous structure, a thick-walled cystic structure, a complex cystic lesion with internal echoes; and less commonly, as a thin-walled cyst. Color Doppler imaging generally demonstrates a peripheral ring of flow around the corpus luteum (Figure 6). Spectral Doppler interrogation usually demonstrates a low-resistance waveform with an RI of 0.4 to 0.7. Unfortunately, as will be discussed below, the appearance of the corpus luteum can mimic an ectopic pregnancy. Differentiation of this normal structure from an ectopic pregnancy is essential.

**Abnormal intrauterine pregnancy**

As noted earlier, spontaneous abortion or abnormal pregnancy is part of the differential diagnosis for a pregnant patient with pain and bleeding. Certain threshold measurements of mean sac diameter (MSD):

\[ MSD = \frac{(L + W + H)}{3} \]

These measurements can be employed to aid in diagnosing a failed pregnancy. The literature reports that there should be visualization of a yolk sac with MSD >8 mm, visualization of an embryo with MSD >16 mm, and visualization of cardiac activity by the time the embryo is 5 mm in length or MSD >18 mm. Failure to meet these thresholds is consistent with a nonviable pregnancy in most cases, especially if the β-hCG level is not rising normally. To ensure greater specificity, Levine suggests using a higher threshold of 13 mm for nonvisualization of a
yolk sac and 18 mm for nonvisualization of an embryo.4

In an abnormal pregnancy, the gestational sac may have a distorted nonovoid contour. Location in the lower uterine segment may be seen in spontaneous abortion (Figure 7). With a low-lying gestational sac, one should carefully evaluate for a fundal fibroid, which may displace a viable gestational sac towards the lower uterine segment. A thin (<2 mm) decidual reaction around a gestational sac is a worrisome sign, as it is an enlarged or calcified yolk sac. An open cervix is consistent with an impending abortion.

Gestational trophoblastic neoplasia should also be considered in the pregnant patient with pain and vaginal bleeding. Although this entity may have differing sonographic appearances, depending on whether it is a complete mole, partial mole or choriocarcinoma, early sonographic findings with molar pregnancy are generally a thickened endometrial stripe with or without an endometrial mass, and variable cystic changes (Figure 8). Evaluation of the adnexa may demonstrate theca lutein cysts involving the ovaries. Correlation with serum β-hCG levels is helpful with the value generally exceeding 100,000 mlU/mL.

Ectopic pregnancy

No specific endometrial findings are diagnostic of ectopic pregnancy. Decidual cysts are more common in ectopic pregnancy but can also be seen with normal pregnancies. These cysts, which are located at the endometrial-myometrial junction, have a thin wall without a surrounding echogenic rim (Figure 9). The lack of an echogenic rim helps to distinguish these cysts from the gestational sac seen with the intradecidual sign of an early IUP. In addition, these cysts may be multiple, in distinction to a gestational sac, which is usually a single cystic structure.

A pseudogestational sac may be seen in 10% to 20% of ectopic pregnancies.4,14 This fluid collection is centrally located within the endometrial canal and is surrounded by a single echogenic rim as opposed to the double echogenic rim seen with the double decidual sac sign.14 The fluid is secreted by the decidualized endometrium and can be anechoic to echogenic/hemorrhagic in nature (decidual cast, Figure 10).

When a pregnancy test is positive and there is no evidence for an IUP, any adnexal finding other than a corpus luteum should be considered suspicious for an ectopic pregnancy until proven otherwise. Adnexal ultrasound findings with a high positive predictive...
value (PPV) for ectopic pregnancy can be categorized into 4 groups: live embryo in an extrauterine gestational sac (PPV = 100%, Figure 11), adnexal mass with yolk sac or nonliving embryo (PPV close to 100%), complex or solid adnexal mass (PPV = 95%, Figure 12), and echogenic tubal ring/donut that is separate from the ovary (PPV = 90% to 95%, Figure 13). The finding of an extraovarian mass with a living embryo or yolk sac has the highest specificity (100%) but the lowest sensitivity (20% to 64%). Identification of a complex adnexal mass or tubal ring has a higher sensitivity (84%) but a slightly lower specificity and PPV (98%).15-17 It should be noted that in 15% to 35% of cases, no adnexal mass will be identified on initial transvaginal scan.16 Therefore, a “negative” transvaginal US examination does not exclude the possibility of ectopic pregnancy and follow-up US examination and B-hCG levels should be performed to distinguish an ectopic pregnancy from an early IUP or miscarriage.

A potential pitfall in the diagnosis of ectopic pregnancy is the corpus luteum, which can mimic the US appearance of a tubal ring or other adnexal mass seen with ectopic pregnancy. Demonstrating that an adnexal “mass” is within the ovary, or arising from it, in an exophytic manner virtually excludes the possibility of it representing an ectopic pregnancy as intraovarian ectopic pregnancies are very rare (<1%). A differential feature is that the corpus luteum should move with the ovary when pressure is applied by the vaginal probe internally and by manual compression externally on the anterior abdominal wall. Lack of independent movement of an adnexal “mass” and ovary is strongly associated with absence of ectopic pregnancy (negative predictive value = 96%).18 An ectopic pregnancy will move separately from the ovary or can be pushed away from it.

The tubal ring of an ectopic pregnancy is usually more echogenic than the ovarian parenchyma, whereas the wall of the corpus luteum is usually less echogenic.19 It has also been recently reported by Stein et al. that the wall of the corpus luteum is typically less echogenic than the endometrium and that an anechoic cystic structure with a thin wall is significantly more likely to be the corpus luteum cyst rather than an ectopic pregnancy.20

It has been reported in the literature that spectral Doppler examination can also aid in the differentiation of a corpus luteum from an ectopic pregnancy. Resistive indices <0.4 and >0.7 have been reported to have 100% specificity for ectopic pregnancy but low sensitivity (15% and 31%, respectively).21 However, experience at the authors’ institution has not found spectral Doppler examination to be as helpful.

**FIGURE 11.** Ectopic pregnancy. Transvaginal ultrasound (A, B) demonstrating a right adnexal mass with a fetal pole and yolk sac (calipers depict the fetal pole, OV marks the ovary, and UT marks the uterus). M-mode imaging (C) demonstrates a fetal heart beat associated with the fetal pole in the right adnexal mass.
for this distinction since the corpus luteum may also demonstrate a low-resistance waveform. Color Doppler flow imaging may demonstrate a peripheral ring of color surrounding an ectopic pregnancy, the so-called “ring of fire.” However, in our experience this finding is more commonly observed with the corpus luteum and is therefore less helpful distinguishing criterion.

Free fluid demonstrating low-level echoes is consistent with hemoperitoneum (Figure 14). Hemoperitoneum with a positive β-hCG level has been shown to have a PPV of 86% to 93% in the diagnosis of ectopic pregnancy.22 However, it is a nonspecific finding as other conditions can cause echogenic pelvic fluid including ruptured hemorrhagic corpus luteum cyst, spontaneous abortion, ovarian torsion and PID. If hemoperitoneum is demonstrated in the cul-de-sac, it is important to image Morison’s pouch to help ascertain the quantity of fluid present (Figure 15).

Atypical locations for an ectopic pregnancy include the cornua, the cervix and the abdomen. Interstitial (cornual) ectopic pregnancies are uncommon, comprising 2% to 4% of all ectopic pregnancies. Clinically, they are of greater concern as they present later in the pregnancy resulting in massive hemorrhage with greater morbidity and mortality. Interstitial ectopic pregnancies, which are located in the interstitial portion of the fallopian tube, present as an eccentric intrauterine gestational sac, high in the fundal region, that is surrounded by <5 mm of myometrium in all imaging planes (Figure 16).6 The “interstitial line sign,” described by Ackerman et al., is a more specific finding for interstitial ectopic pregnancy. Ultrasonographically, an echogenic line, which is felt to represent the interstitial portion of the fallopian tube, is seen extending into the cornual region and abutting the midportion of the eccentric gestational sac.23 In the authors’ experience, if myometrium can be documented between the edge of the

**FIGURE 12.** Ectopic pregnancy. Transvaginal ultrasound (A) demonstrates a solid right adnexal mass adjacent to the right ovary. Color Doppler flow imaging (B) demonstrates a peripheral ring of vascularity. Complex left adnexal mass (C) is oriented medial to the left ovary and lateral to the uterus.
gestational sac and the endometrium, such that the endometrial stripe is clearly separate from the gestational sac, the ectopic pregnancy is likely interstitial in location.

Cervical ectopic pregnancies constitute <1% of ectopic pregnancies. Risk factors predisposing to this condition include prior uterine curettage, fibroids, indwelling IUD and in vitro fertilization. Detection of cardiac activity or trophoblastic flow related to the gestational sac aid in distinguishing this entity from abortion in progress. Change in the position and shape of the gestational sac on serial exams is more consistent with a spontaneous abortion. Caesarean-scar ectopic pregnancies located within the anterior wall of the lower uterine segment, as discussed earlier, are rare but can rupture resulting in massive hemorrhage and cardiovascular collapse (Figure 17).

As noted earlier, documentation of an intrauterine pregnancy greatly diminishes the likelihood of an ectopic pregnancy. Heterotopic pregnancies (concurrent intra- and extraterine pregnancies) have been reported to occur in the general population with a frequency of approximately 1 in 7000 to 1 in 30,000 pregnancies. A higher incidence (1% to 3%) has been reported for patients undergoing ovulation induction. Therefore, careful examination of the pelvis must be performed in patients undergoing infertility treatments to exclude the possibility of heterotopic pregnancy.

**Treatment**

With the advent of high-resolution sonography (and the resultant earlier detection of ectopic pregnancy) and readily available serum β-hCG levels in recent years, the management of ectopic pregnancy has changed. Although surgical intervention such as laparotomy or laparoscopy used to be the main stay of treatment, earlier detection has allowed a shift towards more conservative nonsurgical management.

For unstable patients, surgery is still the treatment of choice. Surgery is also typically indicated for patients with a live ectopic pregnancy demonstrating

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**FIGURE 13.** Ectopic pregnancy. Transvaginal ultrasound (A, B) demonstrates tubal ring (calipers in A, arrow in B) adjacent to left ovary (arrowhead).

**FIGURE 14.** Sagittal (A) and transverse (B) transvaginal ultrasound images demonstrating echogenic fluid in the cul-de-sac posterior to the uterus.
cardiac activity, an adnexal mass >4 cm, and/or active bleeding or hemoperitoneum. For stable patients with an ectopic pregnancy detected at an early gestational age, treatment with methotrexate (MTX) has become the mainstay of care. In select patients, expectant management is now also considered an option.

MTX, an antimetabolite chemotherapy agent/folate anatagonist, disrupts purine nucleotide synthesis and subsequently DNA synthesis and cell replication. Although criteria may vary from institution to institution, a patient generally is considered a candidate for MTX treatment if they are hemodynamically stable, the gestational sac is <3.5 cm, and there is no detectable cardiac activity. Serum β-hCG levels <5,000 mIU/mL are also correlated with a higher likelihood of successful treatment. MTX treatment is an attractive option for interstitial, ovarian or cervical ectopics where surgical treatment has a higher rate of hemorrhagic complications resulting in possible hysterectomy or oophrectomy and loss of reproductive capability.

US post MTX treatment is indicated only when there is concern for rupture as manifested by hemodynamic instability or increasing abdominal pain. Failure of medical management as indicated by rising or a plateau in β-hCG levels, also warrants further sonographic investigation. US of successful MTX treatment is somewhat complex in course. Atri et al. have reported that the fallopian tube/ectopic pregnancy may increase in size initially post treatment and that vascularity may increase on color Doppler flow imaging. The ultrasonographic resolution of the ectopic pregnancy may also lag behind the laboratory resolution of detectable β-hCG levels. Bixby et al. have reported that the presence of a yolk sac detected by transvaginal sonography post treatment was the most reliable ultrasonographic predictor of single-dose MTX treatment failure.

With the recognition that some ectopic pregnancies may resolve spontaneously, and with the understanding that some of these otherwise subclinical pregnancies are now detected because of increased imaging of early pregnancy with high-resolution transvaginal US, expectant management is now considered a treatment option in select patients. The reported incidence of spontaneous resolution of ectopic pregnancies varies from 4% to 24%. Patients who are hemodynamically stable, have a low initial β-hCG, (<1,000 mIU/mL), and have declining β-hCG levels, are considered candidates for expectant management. It has also been reported that lack of a gestational sac on initial sonography, longer time interval from LMP to time of presentation (>6.5 weeks), and higher RI of blood flow surrounding the ectopic pregnancy (>0.6) are also independent predictors of spontaneous resolution. Patients treated by expectant management are followed closely with sequential β-hCG levels and serial US.

**Algorithm**

For the patient who presents in the emergency department with a positive pregnancy test and any other symptomatology worrisome for ectopic pregnancy, a simple algorithm can be followed. A serum β-hCG level should be drawn and a transvaginal US obtained. If the US demonstrates an IUP, one can feel fairly comfortable that an ectopic pregnancy is unlikely. A careful assessment of the adnexa and pelvis should be performed to exclude any possibility of heterotopic pregnancy, especially if the patient is undergoing ovulation induction/infertility treatment.

If no IUP is identified, knowledge of the β-hCG level is essential. If the β-hCG level is <2000 mIU/mL (IRP) one is left with essentially 3 diagnostic options: early IUP, ectopic pregnancy or abnormal IUP/spontaneous abortion. If the adnexa are unremarkable, early IUP or ectopic pregnancy are still possible and the patient should be fol-
lowed up with repeat US in 5 to 7 days and serial β-hCG levels obtained. History and physical exam findings are also helpful as lack of vaginal bleeding makes the diagnosis of miscarriage less likely, whereas a large amount of vaginal bleeding is more consistent with spontaneous abortion. If any abnormality is identified in the adnexal regions, ectopic pregnancy should be the presumptive diagnosis until proven otherwise.

If the β-hCG level is >2000 mIU/mL, an intrauterine gestational sac should be seen. If no intrauterine gestational sac is identified, ectopic pregnancy should be strongly considered. If an adnexal abnormality is identified, the presumptive diagnosis is ectopic pregnancy until proven otherwise. If no adnexal abnormality is seen, close follow-up US and serial β-hCG levels should be performed.

Patients with an abnormal IUP or who are undergoing a spontaneous abortion should demonstrate abnormal findings within the endometrial cavity. Findings include abnormal gestational sac or avascular heterogenous material consistent with blood clot. Heterogeneous material/endometrial thickening with trophoblastic flow is consistent with retained products of conception.

Conclusion
Transvaginal sonography and serum β-hCG level assays have changed the course and management of ectopic pregnancy. Once considered to be a surgical emergency, earlier and more expeditious diagnosis with transvaginal sonography has changed the management approach to ectopic pregnancy, such that maintaining fertility with medical and expectant management is now possible. Knowledge of the US findings of normal early IUP, abnormal intrauterine pregnancy/spontaneous abortion, and ectopic pregnancy is essential. Correlation with serum β-hCG levels and physical findings allows the radiologist to formulate a quick and accurate diagnosis and recommend the appropriate follow-up and treatment.
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REFERENCES