Ectopic pregnancy accounts for approximately 2% of all pregnancies and is the most common cause of pregnancy-related mortality in the first trimester. Initial evaluation consists of hormonal assays and pelvic ultrasonography (US). A history of pelvic pain along with an abnormal β human chorionic gonadotropin level should trigger an evaluation for an ectopic pregnancy. The fallopian tube is the most common location for an ectopic pregnancy. An adnexal mass that is separate from the ovary and the tubal ring sign are the most common findings of a tubal pregnancy. Other types of ectopic pregnancy include interstitial, cornual, ovarian, cervical, scar, intraabdominal, and heterotopic pregnancy. Interstitial pregnancy occurs when the gestational sac implants in the myometrial segment of the fallopian tube. Cornual pregnancy refers to the implantation of a blastocyst within the cornua of a bicornerate or septate uterus. An ovarian pregnancy occurs when an ovum is fertilized and is retained within the ovary. Cervical pregnancy results from an implantation within the endocervical canal. In a scar pregnancy, implantation takes place within the scar of a prior cesarean section. In an intraabdominal pregnancy, implantation occurs within the intraperitoneal cavity. Heterotopic pregnancy occurs when an intrauterine and an extraterine pregnancy occur simultaneously. A spectrum of intra- and extraterine findings may be seen on US images. Although many of the US findings are nonspecific by themselves, when several of them are seen, the specificity of US in depicting an ectopic pregnancy substantially improves.
Introduction
Ectopic pregnancy occurs when a blastocyst abnormally implants outside the endometrium of the uterus. The incidence of ectopic pregnancy has increased from 0.37% of pregnancies in 1948 to approximately 2% of pregnancies in 1992 (1). Although mortality decreased by nearly 90% from 1979 to 1992, ectopic pregnancy remains the leading cause of death during the first trimester of pregnancy, with a 9%–14% mortality rate (1,2). The main risk factors for ectopic pregnancy include a history of ectopic pregnancy, tubal surgery, and pelvic inflammatory disease. Other risk factors are summarized in Table 1.

Early diagnosis and treatment of ectopic pregnancy are essential in reducing maternal mortality and preserving future fertility. Most patients who have an ectopic pregnancy present with a 5–9-week history of amenorrhea, mild pelvic pain, and vaginal spotting. These symptoms should trigger an evaluation for an ectopic pregnancy (3,4). Up to 50% of patients who have an ectopic pregnancy are asymptomatic. Therefore, some authors have advocated routine documentation of intrauterine pregnancies for all patients in their first trimester. Other clinicians limit first trimester ultrasonography (US) to high-risk and symptomatic patients.

As an ectopic pregnancy enlarges, its risk for rupture increases. The severity of pelvic pain does not necessarily correlate with the size of an ectopic pregnancy, and pain may even decrease or disappear following tubal rupture (4). Hypovolemic shock and shoulder pain secondary to diaphragmatic irritation are indirect signs of a ruptured ectopic pregnancy. Any clinical suspicion for a ruptured ectopic pregnancy in a patient in an unstable condition warrants emergent surgical intervention (4).

The initial evaluation of patients suspected to have an ectopic pregnancy entails a quantitative measurement of serum human chorionic gonadotropin (hCG), with or without evaluation of progesterone levels, and transvaginal US. The hormonal assays, findings seen on US images, and diagnostic criteria that can improve specificity in diagnosing ectopic pregnancies are briefly discussed in this article.

Laboratory Evaluation
Human chorionic gonadotropin is a glycoprotein hormone that contains both an alpha and a beta subunit. β-hCG levels begin to ascend in a curvilinear fashion early in pregnancy and continue until they reach a plateau at approximately 9–11 weeks (3). The plateau lasts for only a few days, and thereafter β-hCG levels begin to decline at 20 weeks. The average doubling time of β-hCG in a normal, viable intrauterine pregnancy is approximately 48 hours (range, 1.2–2.2 days) (4–7).

Because of the various impurities and contaminants that are found when determining hCG levels, standardized methods for measuring hCG levels have been established by the International Federation of Clinical Chemistry and the World Health Organization (8). The third International Standard (IS), or the first International Reference Preparation, is the most widely used standard and is the first IS to account for the alpha and beta subunits of hCG (8). The hCG level at which US can demonstrate an intrauterine gestational sac differs from one IS to another; the clinician should be aware of the IS used at his or her institution. Many earlier studies that investigated ectopic pregnancies were based on the second IS. The second IS can be converted to the International Reference Preparation by multiplying by a factor of 1.8. From here on, this article will refer to the third IS when discussing β-hCG levels.

In ectopic pregnancies, serum hCG levels often rise at a much slower rate. If β-hCG levels increase by less than 50% during a 48-hour period, there is almost always a nonviable pregnancy associated, be it intra- or extraterine (3). Eighty-five percent of viable intrauterine pregnancies reflect an increase in β-hCG levels of 66% or more during a 48-hour period (7). However, up to 21% of ectopic pregnancies demonstrate a β-hCG doubling time identical to that of intrauterine pregnancies (9). Arriving at a β-hCG plateau early in the pregnancy is highly suggestive of an ectopic pregnancy.

### Table 1: Risk Factors of Ectopic Pregnancy

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Prior ectopic pregnancy</td>
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<tr>
<td>History of pelvic inflammatory disease</td>
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<tr>
<td>History of gynecologic surgery</td>
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<tr>
<td>Infertility</td>
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<tr>
<td>Use of intrauterine device</td>
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<tr>
<td>History of placenta previa</td>
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<tr>
<td>Use of in vitro fertilization</td>
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<tr>
<td>Congenital uterine anomalies</td>
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<tr>
<td>History of smoking</td>
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<tr>
<td>Endometriosis</td>
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<tr>
<td>Exposure to diethylstilbestrol</td>
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A normal serum progesterone level in viable pregnancies is typically more than 25 ng/mL. Ninety-nine percent of nonviable pregnancies have a progesterone level of less than 5 ng/mL (10,11). The combination of a low serum progesterone level and an abnormal rise in serum β-hCG is nearly diagnostic of a nonviable pregnancy. However, progesterone levels often take several days to process. If a laboratory is unable to report a value within 24 hours, the test has limited use. Because of the delay in measuring progesterone levels, clinical management often relies on measuring β-hCG levels and on the patient’s clinical picture.

**US Evaluation**

When a patient presents with symptoms that suggest an ectopic pregnancy or when hormonal assays indicate an abnormal pregnancy, pelvic US should be performed to determine the location of an intra- or extrauterine pregnancy. Transvaginal US is the preferred method of evaluation. Transvaginal US should be able to demonstrate a gestational sac when β-hCG levels are greater than 2000 mIU/mL, which is the discriminatory level of β-hCG (12). However, some institutions may use a higher threshold. Transabdominal US can demonstrate an intrauterine pregnancy when β-hCG levels reach 6500 mIU/mL (4).

The goal of first-trimester screening is to document the presence of an intrauterine pregnancy, be it normal or abnormal. US is very sensitive and specific in differentiating between normal and abnormal pregnancies in the first trimester (13). In normal pregnancies, transvaginal US can demonstrate an intradecidual sign approximately 4.5 weeks after the last menstrual period (12). The intradecidual sign is a small collection of fluid that is eccentrically located within the endometrium and is surrounded by a hyperechoic ring. At approximately 5 weeks, the double decidual sac sign can be visualized. The double decidual sac sign consists of two concentric hyperechoic rings that surround an anechoic gestational sac in a normal intrauterine pregnancy (13). The secondary yolk sac may be identified at transvaginal US at approximately 5.5 weeks, when the gestational sac reaches 10 mm (14,15). Embryonic cardiac activity should also be visualized at transvaginal US at approximately 5–6 weeks, when the gestational sac measures more than 18 mm or when the embryonic pole measures 5 mm or more (16).

When neither an intrauterine pregnancy nor specific findings of an ectopic pregnancy can be documented in a patient with a subthreshold β-hCG level, the patient should be closely monitored with serial US examinations, and β-hCG levels should be continually tested until either an ectopic or an intrauterine pregnancy is identified (17).

When an abnormal pregnancy is suspected because of hormonal assays, a spectrum of abnormalities can be detected at pelvic US (16). The absence of an intrauterine gestational sac should trigger a detailed search for an ectopic pregnancy. In addition, up to 35% of ectopic pregnancies may not display any adnexal abnormalities (12,14). Possible locations of ectopic pregnancy are illustrated in Figure 1.

**US Findings by Location**

**Tubal Pregnancy**

Ninety-five percent of ectopic pregnancies are tubal; they occur mostly in the ampulla (70%)
Figure 2. Transvaginal gray-scale US image obtained with M-mode scanning demonstrates a left tubal ring with a yolk sac and a live embryo (arrowhead), which is suggested by the presence of cardiac activity. A live tubal pregnancy was confirmed at surgery.

Figure 3. Transvaginal gray-scale US image of the right adnexa reveals an extraovarian adnexal mass with a hyperechoic tubal ring (arrow). A tubal pregnancy was confirmed at surgery. OV = right ovary.

Figure 4. Tubal ring sign. Transvaginal US image of the left adnexa reveals an extraovarian gestational sac with a yolk sac (arrow). The yolk sac is surrounded by a thick echogenic ring (arrowhead).

Figure 5. Ring of fire sign. Transvaginal color Doppler US images of a tubal pregnancy show peripheral hypervascularity surrounding the extrauterine gestational sac (a) and a hemorrhagic ovarian cyst (b), a finding that is a mimic of the ring of fire sign.
or fimbria (11.1%) (18,19). An adnexal mass that is separate from the ovary is the most common finding of a tubal pregnancy and is seen on US images in up to 89%–100% of patients (20,21). An adnexal mass is more specific for an ectopic pregnancy when it contains a yolk sac or a living embryo (Fig 2) or when it moves independently from the ovary (Fig 3) (22). However, an extrauterine mass may not be detected at transvaginal US in 15%–35% of patients with an ectopic pregnancy (12).

The tubal ring sign is the second most common sign of a tubal pregnancy. The tubal ring sign describes a hyperechoic ring surrounding an extrauterine gestational sac (Fig 4). A related finding is the “ring of fire” sign, which is recognized by peripheral hypervascularity of the hyperechoic ring. The term ring of fire was used by Pellerito et al (23) to describe the high-velocity, low-impedance flow surrounding an ectopic adnexal pregnancy. Peripheral hypervascularity is a nonspecific finding of the ring of fire sign and may also be seen surrounding a normal maturing follicle or a corpus luteal cyst (Fig 5) (24). Therefore, the ring of fire sign should not be used to describe the corpus luteum. Determining the location of this type of flow, whether it is within the ovary or outside the ovary, is most important to distinguish between an ectopic pregnancy and a corpus luteum. However, the ring of fire sign is most helpful when no definite ectopic pregnancy is seen on gray-scale images. Color Doppler images of the adnexa may demonstrate the ring-of-fire flow in an otherwise nondescript adnexal lesion and thereby may improve confidence in the diagnosis of ectopic pregnancy.

Intrauterine findings of an ectopic pregnancy include a “normal endometrium,” a pseudogestational sac, a trilaminar endometrium, and a thin-walled decidual cyst. A pseudo–gestational sac represents a thick decidual reaction surrounding intrauterine fluid (Fig 6). Ten percent of patients with an ectopic pregnancy demonstrate a pseudo–gestational sac (25). The absence of the double decidual sac sign helps distinguish a pseudo–gestational sac from a true viable gestational sac (Fig 7) (26). In addition, a pseudo–gestational sac is located centrally within the endometrial canal, whereas a normal gestational sac

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**Figure 6.** Pseudo–gestational sac. Transvaginal gray-scale US image obtained along the longitudinal axis shows an intrauterine pseudo–gestational sac (arrow); there is no yolk sac or fetal pole. Free fluid is seen in the cul-de-sac (*). The patient also had a tubal ectopic pregnancy, which is shown in Figure 4.

**Figure 7.** Diagrams show a pseudo–gestational sac in an ectopic pregnancy (a) and a double decidual sac sign in a normal intrauterine pregnancy (b).
hemorrhage is a more specific finding, with an 86%–93% positive predictive value when \( \beta \)-hCG levels are abnormal (14,28). The presence of echogenic fluid within the right posterior subhepatic space (Morrison pouch) and within the cul-de-sac should raise concern for a ruptured ectopic pregnancy.

**Interstitial Pregnancy**

Interstitial pregnancies are uncommon, accounting for 2%–4% of all ectopic pregnancies (19). Risk factors for interstitial pregnancy include prior salpingectomy and in vitro fertilization. Interstitial pregnancies occur when the gestational sac implants in the intramyometrial segment of the fallopian tube (29). Because of the increased distensibility of this segment of the fallopian tube, interstitial pregnancies may be seen as late as the 16th week of gestation (30). Rupture of an interstitial pregnancy can lead to life-threatening hemorrhage because of the proximity of the uterine artery to the fallopian tube (30).
of the intramural gestational sac” (Fig 8) (31). This echogenic line most likely represents the interstitial portion of the fallopian tube (31). In the study by Ackerman et al (31), the interstitial line sign was 80% sensitive and 98% specific for an interstitial pregnancy.

**Cornual Pregnancy**

Although it is often used interchangeably with interstitial pregnancy, *cornual pregnancy* specifically refers to the implantation of a blastocyst within the cornua of a bicornuate or septate uterus (20,32). Cornual pregnancies are rare and account for less than 1% of all ectopic pregnancies (33). Rupture of a cornual pregnancy also results in catastrophic hemorrhage.

In a cornual pregnancy, the gestational sac is surrounded by a thin rim (<5 mm) of myometrium (34). In addition, the sac is in an eccentric position and is more than 1 cm from the lateral wall of the endometrial cavity (34).

**Ovarian Pregnancy**

An ovarian pregnancy occurs when an ovum is fertilized and is retained within the ovary. Ovarian pregnancies account for 3% of ectopic pregnancies (18); sometimes they manifest as part of a heterotopic pregnancy (35,36). Ovarian pregnancies are strongly associated with the use of intrauterine devices (37) and often manifest at the same time as tubal pregnancies (18).

The presence of a gestational sac, chorionic villi, or an atypical cyst with a hyperechoic ring within the ovary, along with the normal fallopian tubes, is suggestive of an ovarian pregnancy (38,39).

**Cervical Pregnancy**

Cervical pregnancy occurs when implantation takes place within the endocervical canal. It is rare (<1% of ectopic pregnancies) and is likely associated with in vitro fertilization and a history of prior curettage (41). Diagnosis is typically made at US.

In a cervical pregnancy, the uterus may be shaped like an hourglass or a figure eight as the fetus expands within the cervix (Fig 9) (41,42). In addition, cardiac activity below the internal os is highly suggestive of a cervical pregnancy (42). When a gestational sac is visualized in the region of the cervix, gentle manipulation of the gestational sac should be attempted to differentiate a cervical pregnancy from an abortion in progress (Fig 10) (43). If the sliding sign is seen (if the transducer probe can manipulate the gestational...

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**Figure 9.** Cervical pregnancy. Transvaginal US image of the uterus obtained along the longitudinal axis reveals a gestational sac that contains the fetal pole (arrow) within the cervix. *Fu* = uterine fundus. (Reprinted, with permission, from reference 25.)

**Figure 10.** Abortion in progress in a patient with a history of vaginal bleeding. Transvaginal US image of the uterus demonstrates a low-lying gestational sac (arrow) with mixed hyper- and hypoechoic contents in the endometrial cavity of the fundus (arrowheads), which represent decidual reaction and hemorrhage. The patient experienced a complete spontaneous abortion a few hours after the US examination. (Reprinted, with permission, from reference 16.)
sac), this confirms that the gestational sac is not adherent to the cervix (excluding cervical pregnancy), which indicates that an abortion is in progress (43).

**Scar Pregnancy**

Caesarean scar pregnancies are also rare and are estimated to occur in less than 1% of all pregnancies (44). Implantation takes place within the scar of a prior cesarean section, separate from the endometrial cavity (44). Within the scar, the blastocyst is surrounded by myometrium and fibrous tissue (45). A suggested mechanism is that a tract connects the endometrial canal and the uterine myometrium; this tract facilitates implantation within the scar (45). Patients who have a scar pregnancy may present with vaginal bleeding as early as 5–6 weeks and as late as 16 weeks. Scar pregnancies may also rupture, which can result in severe hemorrhage and hemodynamic collapse.

In a scar pregnancy, a gestational sac may be visualized within the anterior wall of the inferior aspect of the uterus (Fig 11) (46). Secondary to compression by the gestational sac, the myometrium may also be thinned anteriorly (46). Thinning of the myometrium may predispose a patient to uterine rupture (21).

**Intraabdominal Pregnancy**

In an intraabdominal pregnancy, implantation occurs within the intraperitoneal cavity (Fig 12), excluding tubal, ovarian, and intraligamentous locations. This is a rare cause of ectopic pregnancy, but it is more common in patients who undergo assisted reproduction (48), and it may represent 1.4% of ectopic pregnancies. Because of significant hemorrhage, maternal mortality associated with intraabdominal pregnancy is 7.7 times that of other locations of ectopic pregnancy (49).

**Figure 11.** Scar pregnancy in a patient with a history of cesarean section. Transvaginal gray-scale US image of the uterus, obtained with M-mode scanning along the longitudinal axis, reveals a gestational sac with a fetal pole (arrowhead) in the anterior wall of the uterus. There was no fetal cardiac activity, a finding suggestive of fetal demise.

**Figure 12.** Intraabdominal pregnancy in a patient who went to the hospital for an abortion. The intraabdominal pregnancy was missed because US was not performed before dilation and curettage. She presented with pain and fever secondary to pyometra 1 week later. (a) Transabdominal US image reveals an extraterine gestational sac with a fetal head (arrow). Laparotomy was performed, and only the fetal head was found in a pocket of pus in a retrocecal location. No other fetal parts were identified. (b) Photograph shows the surgically removed extraterine gestational sac with the fetal head. (Scale is in centimeters.) (Reprinted, with permission, from reference 47.)
a known heterotopic pregnancy can potentially undergo US-guided ablation or laparoscopic removal of the extrauterine fetus to permit the intrauterine pregnancy to continue normally. If a patient undergoes an abortion of an intrauterine pregnancy and continues to experience persistent adnexal pain with abnormal \(\beta\)-hCG levels, heterotopic pregnancy should be suspected.

Table 2

<table>
<thead>
<tr>
<th>Type of Pregnancy</th>
<th>Findings on US Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubal pregnancy</td>
<td>Living extrauterine gestation, adnexal mass, tubal ring sign, ring of fire sign, pelvic hemorrhage</td>
</tr>
<tr>
<td>Interstitial pregnancy*</td>
<td>Eccentrically located gestational sac, gestational sac surrounded by a thin myometrium (&lt;5 mm), interstitial line sign</td>
</tr>
<tr>
<td>Ovarian pregnancy†</td>
<td>Serum (\beta)-hCG level &gt;1000 mIU/mL; normal fallopian tubes; gestational sac, chorionic villi, or atypical cyst within the ovary; normal (\beta)-hCG level after therapy</td>
</tr>
<tr>
<td>Cervical pregnancy‡</td>
<td>Trophoblastic flow surrounding the gestational sac within the cervix, normal endometrial stripe, gestational sac within the cervix with cardiac activity, hourglass-shaped uterus, cardiac activity below the internal os</td>
</tr>
<tr>
<td>Cesarean scar pregnancy</td>
<td>Gestational sac located within the lower anterior segment of the uterus at the site of a prior cesarean section, thinning of myometrium anterior to the gestational sac</td>
</tr>
<tr>
<td>Abdominal pregnancy</td>
<td>Absence of a normal intrauterine gestational sac, gestational sac located within the intraperitoneal cavity, abdominal or pelvic hemorrhage</td>
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* Reference 37.
† References 48 and 49.
‡ Reference 40.

Heterotopic Pregnancy

Heterotopic pregnancy occurs when an intrauterine and an extrauterine pregnancy occur simultaneously (Fig 13). Knowledge of heterotopic pregnancy is becoming increasingly important as more women undergo assisted reproduction, particularly ovulation induction. The prevalence of heterotopic pregnancy in women who undergo assisted reproduction has been reported to be 1%–3% (50). Heterotopic pregnancy remains a diagnostic challenge and should be kept in mind when a patient who has undergone assisted reproduction presents with pelvic pain. US images can demonstrate the presence of an intrauterine and an extrauterine pregnancy. Patients who have
Conclusions

Although mortality has significantly decreased over the past two decades because of earlier detection and intervention, ectopic pregnancy remains the leading cause of death of women in the first trimester of pregnancy. Work-up of a patient who presents with pelvic pain, amenorrhea, and vaginal spotting entails hormonal assays and pelvic US. When results of laboratory evaluation suggest an abnormal pregnancy, a detailed search for an intra- or extraterine pregnancy should be performed.

The most common location of an ectopic pregnancy is the fallopian tube. US findings of ectopic pregnancy can be categorized by location (intra- or extraterine). Although many of these findings are nonspecific when they are seen singly, when several of them are seen, the specificity of US in depicting an ectopic pregnancy substantially improves. Use of these diagnostic criteria, as was outlined previously, may therefore improve diagnostic accuracy when abnormal β-hCG or progesterone levels suggest an ectopic pregnancy.

References

Diagnostic Clues to Ectopic Pregnancy

Edward P. Lin, MD, Shweta Bhatt, MD, and Vikram S. Dogra, MD

Ectopic pregnancy remains the leading cause of death during the first trimester of pregnancy, with a 9%–14% mortality rate.

The absence of an intrauterine gestational sac should trigger a detailed search for an ectopic pregnancy.

In addition, up to 35% of ectopic pregnancies may not display any adnexal abnormalities.

Ninety-five percent of ectopic pregnancies are tubal.

Although many of the intra- and extrauterine findings are nonspecific when they are seen in isolation, the use of diagnostic criteria may improve specificity when several findings are identified in a patient suspected of having an ectopic pregnancy.