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Vaginal Bleeding During the First 20 Weeks of Pregnancy: Guidelines for ED Evaluation and Management

Part I: Clinical Overview and Diagnostic Modalities for Detection of Ectopic Pregnancy

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Women frequently present to the emergency department (ED) for complications relating to pregnancy. In particular, vaginal bleeding is one of the most common presenting complaints of women during the first 20 weeks (or first half) of pregnancy. In fact, nearly 40% of women experience vaginal bleeding during the course of their pregnancy, and up to 15% of clinically recognized pregnancies terminate in miscarriage.

Pregnant patients presenting with bleeding complications require special attention because hemorrhage may represent life- or fetus-threatening complications. In this regard, the incidence of ectopic pregnancy (EP) has increased steadily over the past three decades, with ectopic pregnancies now accounting for about 2% of total identified pregnancies in the United States.[1]

The serious consequences of EP are well-known to emergency practitioners. It is the leading cause of death in the first trimester, and accounts for 9-13% of all pregnancy-related deaths.[2,3] Although EP is the second leading cause of maternal mortality among all races, it is the leading cause in African-American women.[4] Approximately 90% of these deaths are the result of uncontrolled maternal hemorrhage.[5]

To make matters worse, EP can be difficult to diagnose. One study suggests that up to 50% of patients with EP are misdiagnosed on their first ED visit.[6] Another recent study of misdiagnosed ectopic pregnancies found the correct diagnosis was not made until an average of eight days after initial presentation.[7] Once an EP has progressed to rupture, the only treatment option is surgery—either laparoscopically or by full laparotomy.

An important challenge in these patients is timely identification of those women with complicated ectopic pregnancies from the larger group of individuals with self-limiting, spontaneous miscarriage. In this regard, however, it should be emphasized that even among patients with spontaneous miscarriage, a significant subset will advance to serious complications such as uterine infection or prolonged bleeding, both of which may require aggressive management. Finally, a few patients with vaginal bleeding early in their pregnancies will suffer from such unusual conditions, among them, trophoblastic disorders such as hydatidaform mole and choriocarcinoma.

Of special significance is that medical management of EP has dramatically altered treatment of these patients, but use of nonin-

vasive management options requires early diagnosis to be successful. Accordingly, ED physicians are now under increasing pressure to diagnose EP very early in its course—and prior to complications—in order to take advantage of new medical advances in the management of this condition.

In the obstetrical literature, bleeding complications of pregnancy traditionally have been divided into those manifesting during the first half pregnancy, and those occurring in the second half of pregnancy. Generally speaking, vaginal bleeding in patients presenting before 20 weeks of gestation is associated with specific etiologies and treatments, whereas bleeding that occurs beyond 20 weeks is linked to an alternate differential diagnosis and management scheme.

From a clinical perspective, the work-up of patients in the first 20 weeks consists primarily of evaluation for EP or spontaneous miscarriage, whereas after 20 weeks, the most common serious causes of bleeding are placenta previa or abruption. Furthermore, it should be stressed that the fetus is considered viable after about 24 weeks gestation, which means the ED physician actually has two patients in most patients who present with bleeding during the second half of pregnancy.

With these issues in clear focus, the authors of this landmark series review the ED evaluation and management of vaginal bleeding encountered during the first 20 weeks of gestation. In this, the first of a three-part series, the authors provide a detailed discussion of detecting and assessing women suspected of having an EP. In part II of the series, a systematic approach to diagnostically challenging cases with suspected EP is outlined, new advances in medical therapy are discussed, and the approach to various types of spontaneous miscarriage that may present to the ED is discussed in detail. Finally, Part III of the series will consider pregnant patients who present to the ED with bleeding during the second half of pregancy.

Current diagnostic and management strategies recommended in these patients are presented so they can be applied in the ED setting, treatment tables are provided to streamline access to clinical information, and new advances in therapy are highlighted.

— The Editor

Ectopic Pregnancy: Overview and Epidemiology

Any pregnancy in which the embryo implants outside the uterine cavity is defined as an EP. With the extremely rare exception of an abdominal pregnancy that successfully reaches term, the presence of an EP presents the ED physician with the following dilemma: 1) a fetus located in an ectopic location cannot reach maturity; and 2) its continued presence in that location represents a potentially life-threatening condition for the mother. Stated simply, hemorrhagic shock secondary to EP accounts for 6-7% of all maternal deaths.[8]

Unfortunately, the incidence of EP in the United States has increased steadily over time. In 1983, 70,000 ectopic pregnancies were reported in the United States, with an incidence of 4.5 per 1000 pregnancies.[9] Since then, the incidence has continued to increase, with 19.7 ectopics reported per 1000 pregnancies in 1992.[10] The two principal explanations for this rise include the following: 1) an increase in the prevalence of risk factors for EP (especially pelvic inflammatory disease [PID]); and 2) an increase in the sensitivity for detecting the condition in its early stages (i.e., transvaginal ultrasound [TVU] and more sensitive serum pregnancy testing).

Confirmation of EP also has important implications for future fertility of the patient. Specifically, the chances for successful subsequent pregnancies are lowered; one study suggests that only 33% of patients with a history of EP will have a subsequent pregnancy progress to live birth.[11] A history of an EP is also a strong risk factor for occurrence of future ectopic pregnancies.

Risk Factors. Risk factors for development of EP are listed in Table 1. As many as 50% of patients with an EP will give history of one of more of these risk factors.[12] A common theme among all risk factors is scarring of the fallopian tubes. Damage to the

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Table 1. Risk Factors for Ectopic Pregnancy

LESSER RISK
Previous pelvic or abdominal surgery
Cigarette smoking
Vaginal douching
Age of 1st intercourse < 18 years
GREATER RISK
Previous genital infections (e.g., PID)
Infertility (In vitro fertilization)
Multiple sexual partners
GREATEST RISK
Previous ectopic pregnancy
Previous tubal surgery or sterilization
Diethystilbestrol exposure in utero
Documented tubal pathology (scarring)
Use of intrauterine contraceptive device

Adapted from Pisa MD, Carson SA. Ectopic pregnancy. In: Scott JR, et al, eds. *Danforth's Obstetrics and Gynecology*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 1999:155-172; and Mallett VT. Ectopic pregnancy. In: Pearlman MD, Tintinalli JE, eds. *Emergency Care of the Woman.* New York: McGraw Hill; 1998:21-28.

tubes often results from previous pelvic infection, especially from chlamydia and/or gonorrhea. In one study, the EP rate was 4% in women with salpingitis proven by laparoscopy, compared to 0.7% in women with healthy fallopian tubes.[13] In another study, 38% of tubes in women with EP had microscopic evidence of PID.[14]

The risk of repeated infection proportionally increases the likelihood of EP. For example, after two infections the risk for EP is about 35%, and after three or more prior infections the risk rose to about 75%.[13] It follows that pelvic surgery and previous sterilization procedures can lead to tubal scarring and, accordingly, increase in risk for EP. It should be stressed that a history of tubal ligation does not rule out the possibility of an EP. Reports of patients having EP after tubal ligation are not rare, and these patients are also at higher risk of rupture as EP is not always included in the differential of these patients.[15,16]

In the case of non-infectious risk factors, the link with an increased risk for EP is less clear. Cigarette smoking slightly increases the risk for ectopic implantation, but it is believed to be an association rather than a direct cause. It is theorized that impaired immune function found in smokers may predispose them to PID, alterations in tubal motility, or that it is associated with a lifestyle that is associated with acquisition of key risk factors.[17,18] Interestingly, use of vaginal douches is associated with increased an risk of EP, although the precise mechanism is not understood. Clearly, use of intrauterine devices (IUDs) for contraception increases risk of EP; interference with intrauterine implantation appears to be the mechanism. Finally, the use of diethylstilbestrol (DES) by a pregnant woman will produce fallopian tube deformities in her female offspring. Therefore, if a patient's mother used DES, she will be at higher risk for developing an EP.

Clinical Pathophysiology. Interestingly, the condition of EP appears to a uniquely human malady. No animal model is has been identified in which this condition has been documented. Consequently, much of what is known about the pathophysiology of EP is based on direct observation rather than animal testing.

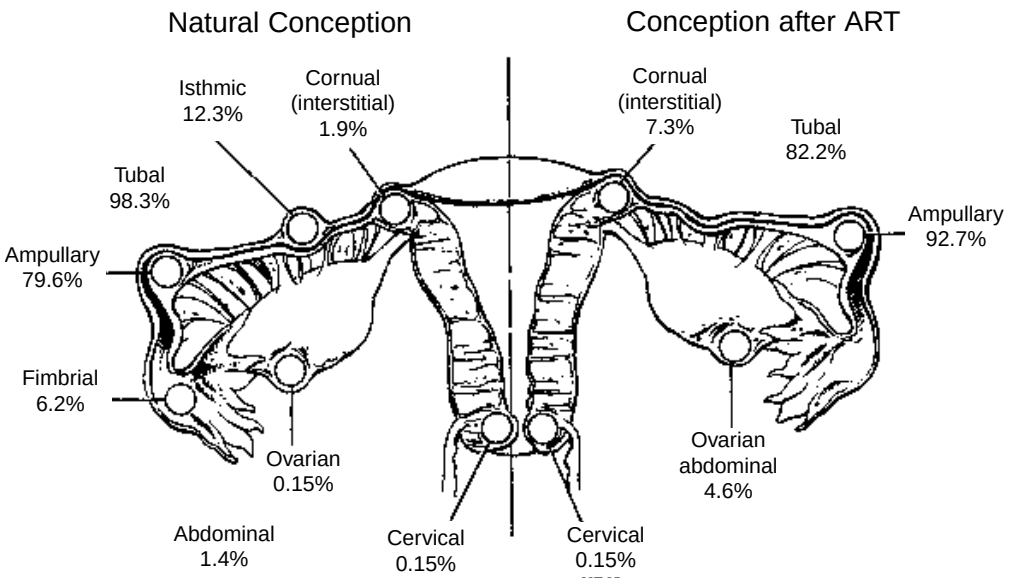
After fertilization, the trophoblast (pre-embryo) implants in an abnormal site, usually in the fallopian tube. When the trophoblast implants, it invades blood vessels in the tubal wall, thereby accessing a blood supply necessary for further growth. Although the embryo is growing, it does so at a slower rate than normal, since the tissue in which it has implanted is not designed to support its growth. Consequently, human chorionic gonadotropin (beta-hCG) levels may not rise at the normally predicted rate, a feature that is useful for diagnosis. However, once the embryo attains a certain size, three outcomes are possible: 1) The embryo may be aborted into the abdominal cavity where it will be reabsorbed or continue as an abdominal pregnancy (very rare); 2) the embryo may be spontaneously absorbed in the fallopian tube; or 3) the tubal wall may rupture and result in significant blood loss that may be life threatening.

Although researchers have tried to identify specific risk factors for rupture in EP, these have been very difficult to determine. In one series of 236 ectopic pregnancies, about 26% of ectopic pregnancies terminated in in rupture.[21] Interestingly, rupture occurred in some patients with beta-hCG levels as low as 100 mIU/mL.[21] In another series of 693 ectopic pregnancies, the mean gestational age for rupture was 7.2 ± 2 weeks.[22] No differences were detected in beta-hCG levels among women who did and did not have rupture. However, the rate of rupture in patients with beta-hCG levels lower than 100 mIU/mL was 11%.[22] Moreover, rupture was more common in patients with their first EP than in those with repeat cases, perhaps indicating that previous experience with the disease shortened the time to diagnosis.

It is suspected that abnormalities in the fallopian tube (i.e., scarring) slow migration of the trophoblast through the tube and increase risk for ectopic implantation. While this may explain the majority of ectopic pregnancies, this does not explain those that implant in the cervix. Figure 1 illustrates various sites in which ectopic pregnancies are known to occur and the frequency of their occurrence. Note that in the case of natural reproduction, 98% of ectopic implantations occur in the fallopian tubes. With assisted reproduction, tubal pregnancies still account for 82% of all ectopic pregnancies.

Of clinical significance is the observation that two specific implantation sites are associated with a significantly higher maternal mortality rate (i.e., cornual and interstitial ectopic gestations). Because the myometrium is more distensible than the fallopian tube, these locations permit the embryo to grow to a much larger size before rupture. As a result, rupture may occur as late as 10-14 weeks during gestation, which produces more bleeding

Figure 1. Frequency and Sites of Ectopic Pregnancy Implantation



ART stands for assisted reproductive technology.

Reproduced with permission from Pisa MD, Carson SA. Ectopic pregnancy. In: Scott JR, et al, eds. *Danforth's Obstetrics and Gynecology.* 8th ed. Philadelphia: Lippincott Williams & Wilkins; 1999:156.

from the relatively vascular uterus.[23] Although cornual locations account for only 4.7% of ectopic pregnancies, they carry a 2.2% overall maternal mortality rate.[24]

Associated with the highest relative maternal risk, abdominal pregnancy carries a mortality rate that is about 7.7 times greater than all other forms of EP combined.[25] As Figure 1 indicates, abdominal pregnancies are diagnosed in only 1.4% of all ectopics produced through natural reproduction. If the fetus survives such a pregnancy, malformations are present in up to 40% of infants.

An especially problematic and high risk variation of EP is the heterotopic pregnancy. In this case, a normal uterine pregnancy coexists with an EP. In 1948, this was a very rare condition and was reported in only 1 in 30,000 pregnancies.[26] However, the ED physician should be aware that the heterotopic pregnancy is becoming increasingly common. In this regard, data from the 1980s show a rate of 1 in 10,000 pregnancies, and the most recent estimates vary from 1 in 3889 to 1 in 6778 pregnancies.[27-29] However, in the case of assisted reproduction, the heterotopic pregnancy rate soars to a staggering 1-8 per 100 pregnancies.[27]

As with isolated EP, the most common implantation site for the ectopic fetus is the fallopian tube (94%).[27] As one would expect, the presence of heterotopic pregnancy confounds the work-up and diagnostic evaluation of these patients. First, beta-hCG levels are not helpful since the concomitant intrauterine pregnancy will produce normal levels of beta-hCG. In addition, the pelvic ultrasound detects only about 50% of tubal heterotopic pregnancies.[30] As might be expected, few patients are diagnosed before the EP becomes symptomatic or ruptures, and almost 50% are admitted for emergency surgery after rupture occurs as the presenting symptom.[30]

Although case reports exist of normal delivery of the intrauterine pregnancy after rupture of the ectopic in a few patients, the most frequent outcome is loss of both fetuses when rupture occurs.[31] Finally, it is also important to know that there have been a few case reports of bilateral ectopic pregnancies. The essential clinical point concerning heterotopic pregnancies is that during a work-up for an EP, if the patient is found to have an intrauterine pregnancy, there is still a risk for presence of a coexisting ectopic.

Clinical Presentation

Although they may not compel the patient to seek medical attention, the first symptoms a woman with EP experiences are those associated with early pregnancy. As expected, these include nausea with or without vomiting, breast tenderness, and amenorrhea. However, because the vascularly compromised embryo is producing lower amounts of beta-hCG than if it were normally implanted, symptoms of pregnancy may not be as pronounced in some patients; in fact, no more than 25% of patients report pregnancy-related symptoms before diagnosis of their EPs.[33]

Symptoms precipitated by structural changes or hormonal perturbations are more typical, and frequently provide the first clue to diagnosis. In particular, as the embryo grows, myriad symptoms can be produced by distension of the fallopian tube. (*See Table 2*, which summarizes presenting signs and symptoms of EP.) Note that nonspecific abdominal pain or pelvic pain has been reported in 80% of patients with EP at 4-6 weeks gestation.[33] Patients may also report having "normal" periods, light periods, or spotting. This bleeding can occur at the time of an expected period, further confusing the patient about her pregnancy status. Up to 20% of patients do not report missing a period, and 15% of patients rupture prior to "missing" their first period.[20,34] Bleeding can sometimes be linked to insufficient beta-hCG levels, which cannot support the integrity of the uterine lining at these lower hormone levels. Furthermore, patients with cornual ectopics can progress to a later stage of pregnancy and may present with more severe symptoms as late as 12-14 weeks of gestation.

As an EP progresses, the greatest danger to the patient is risk of fallopian tube rupture. The symptoms of rupture produce the "classical" presentation of an EP. These symptoms include sud-

Table 2. Presenting Signs and Symptoms of Ectopic Pregnancy

SYMPTOM	PERCENTAGE OF WOMEN WITH SYMPTOM
Abdominal pain	80-100%
Amenorrhea	75-95%
Vaginal bleeding	50-80%
Dizziness, fainting	20-35%
Urge to defecate	5-15%
Pregnancy symptoms	10-25%
Passage of tissue	5-10%

SIGN	PERCENTAGE OF WOMEN WITH SIGN
Adnexal tenderness	75-90%
Abdominal tenderness	80-95%
Adnexal mass	50%
Uterine enlargement	20-30%
Orthostatic changes	10-15%
Fever	5-10%

Adapted from Weckstein LN. Current perspective on ectopic pregnancy. *Obstet Gynecol Surv* 1985;40:259-272.

den, severe unilateral abdominal pain, vaginal bleeding, and a history of amenorrhea. As one might expect, "classical" symptoms are uncommon and this particular history is neither sensitive nor specific.

Loss of blood into the peritoneal cavity usually will produce symptoms of peritoneal irritation, but the quantity and location of the blood will greatly influence the symptom complex. For example, smaller amounts of bleeding may only produce tenderness, rebound, and guarding in the pelvic area, and the patient's abdominal exam may not yield any significant findings. At least one study suggests that absence of pain and tenderness is not an absolutely reliable negative predictor for rupture, since about 4% of women with hemoperitoneum secondary to a ruptured ectopic are pain free.[8,20]

Another recent study of an inner city population found almost 10% of EP patients with rupture had no pain and 36% had no adnexal tenderness on pelvic exam.[6] Therefore, absence of pain and tenderness will not always alert the clincian to patients with a life-threatening rupture. However, with larger amounts of blood loss, the patient will exhibit signs of hypovolemia, including orthostasis, syncope, tachycardia, and hypotension. Syncope is common in these patients, and EP should be in the differential for any woman of reproductive age who presents to the ED with syncope. Even in the absence of significant pain or other symptoms, a woman with syncope and a positive pregnancy test in the ED should have an ultrasound to rule out the possibility of ectopic rupture.

In the past, a patient presenting with an adnexal mass and hypotension was considered typical of EP. As detection methods have improved, patients presenting in shock now make up fewer than 5% of cases.[20] The two most common complaints are of lower abdominal pain and vaginal bleeding, but the patient may have only one or the other symptom. In contrast to the case of spontaneous miscarriage, vaginal bleeding in EP is often mild.

Although up to 80% of patients will complain of vaginal bleeding, not all will have blood present in the vaginal vault on pelvic exam. Heavier bleeding with passage of clots is more likely to be associated with miscarriage. One should take care to examine any tissue that may have been passed and assumed to be from a miscarriage. Endometrial sloughing can also cause heavy bleeding in women with an EP, due to falling beta-hCG levels. If fetal parts or chorionic villi are seen, an ectopic is highly unlikely, with the exception of a heterotopic pregnancy.

In addition to abdominal tenderness, which frequently is a non-specific finding in patients of child-bearing years, the pelvic exam may reveal useful clues that suggest the presence of an EP. As useful as these findings are, they too can be nonspecific and obfusacte the clinical picture. Up to 66% of women with EP have cervical motion tenderness, which may suggest the diagnosis of PID. Although the presence of an adnexal mass is an important sign of EP, this finding is present in only up to 60% of cases, even in those patients who are under general anesthesia.[37] Moreover, up to 20% of patients will have adnexal masses on the opposite side, presumably from a corpus luteum cyst on the uninvolved ovary.[38]

The uterus in a patient with suspected EP should be softened and normal size, or slightly enlarged but smaller than expected by gestational dates. This finding is reported in up to 70% of cases, although one study found that 26% of patients were thought to have a 6-8 week uterus.[20,39] Because the uterus will be enlarged consistent with the gestational period in the case of heterotopic pregnancy, finding a normal sized uterus will not rule out presence of an ectopic.

The authors of one review went so far as to suggest that a pelvic digital and speculum exam should not be performed in these patients.[36] In a series of 382 patients with EP, they found that these exams did not yield any information that changed management of these patients. While this may be the case in women who ultimately are found to have EP, the pelvic exam is still useful in diagnosing conditions that can be confused with EP. And it is especially helpful to identify patients who have an open os, as this subgroup is much more likely to have a spontaneous miscarriage than EP.

Diagnostic Strategy: Multi-Modal Synthesis

The ED evaluation of a patient with suspected EP primarily relies on the determination of serum hormone levels and the use of ultrasound imaging. Culdocentesis and diagnostic laparoscopy are still indicated in certain situations, and will also be discussed. However, these techniques are adjuncts to the primary modalities and are indicated in difficult-to-diagnose subgroups. It should be emphasized that Rh status must be verified in every patient with vaginal bleeding to avoid the failure to treat Rh-negative mothers with Rhogam.

Human Chorionic Gonadotropin. Beta-hCG is a glycoprotein hormone produced by both ectopic and normally implanted

trophoblastic cells. Currently available monoclonal antibody assays can detect the presence of beta-hCG as soon as 2-3 days postimplantation. In a normal pregnancy, the level of this protein doubles about every two days up to a value of 10,000 mIU/mL. After this level, doubling no longer occurs, and serial beta-hCG measurements are not clinically helpful.

Specifically, the beta-hCG level should increase by 66% every 1.8-3 days for the first 6-7 weeks beginning 8-9 days after ovulation.[49] After 9-10 weeks gestation, the levels decline. This is an important clinical distinction. In the majority of ectopic pregnancies (or conditions associated with an abnormally developing fetus), beta-hCG levels will not consistently rise at the expected rate. The trophoblastic tissue does not obtain an adequate blood supply when implanted ectopically, and therefore, it does not grow at the expected rate. Abnormal beta-hCG levels are defined as those that fall, plateau, or fail to reach the predicted slope before 9-10 weeks gestation.

One should keep in mind that there are exceptions to this rule, that is, 10% of normal pregnancies can manifest abnormal doubling times, and similarly, up to 15% of ectopic pregnancies can have a normal doubling time.[44] Even accounting for such variations, most obstetrical texts take the position that documented failure of beta-hCG levels to double in 48 hours is diagnostic of a nonviable pregnancy and permits uterine curettage to empty the uterus.[19]

Typically, a urine pregnancy test is ordered to verify the presence of beta-hCG in the urine and, if positive, a serum quantitative level may then be obtained in order to verify if the level is above the discriminatory level for ultrasound. Alternatively, one may proceed directly to ultrasound, and if an intrauterine pregnancy is seen, a quantitative level may not be required. However, if no intrauterine pregnancy is identified, the quantitative level will be needed to interpret the ultrasound results. *(See section on Ultrasound.)* Even though normally rising levels can be seen early in ectopic pregnancies, nearly 90% of patients with documented EP will have low, plateauing, or declining levels on their initial visit.[50]

As outlined, the quantitative level of beta-hCG is useful in management decisions and for interpreting results of the ultrasound. With current ultrasound technology, most series state that early evidence of intrauterine pregnancy should be seen by transabdominal ultrasound with beta-hCG levels of 6500 mIU/mL, or at 1500 to 2000 mIU/mL using TVU.[9,23] Consequently, absence of a gestational sac in a patient whose beta-hCG indicates that a pregnancy should be detectable by these ultrasonographic modalities increases the likelihood for EP. Clinically, the beta-hCG level can be followed in stable patients in whom the level is too low to expect ultrasound visualization of a normal intrauterine pregnancy. The level should be rechecked in 48 hours; the importance of this repeat test should be communicated to the patient, and it should documented that this was stressed to the patient.

Although beta-hCG levels are a cornerstone in the diagnosis of EP, caution is advised when interpreting the results in specific patients, inasmuch as some patients with EP never attain beta-hCG levels greater than 1500 mIU/mL. Low levels, however, do not predict a benign course in every patient. A recent study of 1263 patients with suspected EP found that 60% of women with EP never had beta-hCG levels rise to greater than 1500 mIU/mL.[51] Another study found a four-fold increase in risk of EP in women with beta-hCG levels less than 1000 mIU/mL, with rupture occurring in 29% of these patients.[6]

In conjunction with these results, the ED physician should be aware that ectopic rupture requiring surgery is well documented in patients with low (< 100 mIU/mL) or even absent beta-hCG levels (rupture at < 10 mIU/mL), and that it is imprudent to believe that there is no danger of rupture at levels below 1500 mIU/mL.[21,52,53] In other words, if a patient has a beta-hCG below 1500 mIU/mL and is in shock without other obvious cause, ruptured EP has not been ruled out and the patient should be treated accordingly.

Progesterone. As early as the mid 1980s, use of a single, quantitative serum progesterone level has been reported in the literature to be of use in the diagnosis of EP.[40] Progesterone is produced by the corpus luteum in response to the presence of a pregnancy. In contrast to beta-hCG levels, progesterone levels change little in the first 8-10 weeks of gestation. An important point is that progesterone levels normally fall after 10 weeks gestation. When dates are unclear, a low level can be misleading if the patient has a normal pregnancy advanced beyond 10 weeks.[41] Otherwise, when a pregnancy fails during the first 8-10 weeks, progesterone levels fall.

Current data suggest that a single progesterone level higher than 25 ng/mL is consistent with a viable intrauterine pregnancy, and that this level was found to exclude EP with a 97.5% sensitivity.[19,20] Moreover, 25% of viable intrauterine pregnancies have levels below 25 ng/mL.[12] Many authors report that a level below 5 ng/mL is 100% diagnostic of a non-viable pregnancy.[19] However, a low level does not correlate with the location of the pregnancy.[42]

The American College of Obstetrics and Gynecology (ACOG) currently recommends that "no single progesterone value will definitively confirm the viability or nonviability of an intrauterine pregnancy or the presence of an EP."[43] Most authors still suggest that when beta-hCG levels fail to rise as predicted, a progesterone value below 5 ng/mL permits diagnostic evacuation of the uterus in cases in which an EP cannot be distinguished from a spontaneous miscarriage.[44,45] It is important to realize that variation can be present; the lowest progesterone level associated with an EP reported thus far is 5.1 ng/mL.[46] Furthermore, 2% of ectopic pregnancies have been reported to have levels higher than 25 ng/mL.[47]

Because of these inconsistencies and imperfect sensitivities for detection of EP, use of progesterone levels to diagnose EP is currently controversial. A recent meta-analysis of 26 studies found that serum progesterone levels are not sensitive enough to distinguish between EP and non-EP.[45] This study, however, did confirm that low serum levels are sufficiently accurate to distinguish between pregnancy failure and a viable pregnancy. Although current ACOG guidelines state that no single level can

identify a failed pregnancy, current recommendations from the literature are as follows: A single progesterone level greater than 25 ng/mL is highly suggestive of a viable intrauterine pregnancy, but is not considered sufficient evidence by ACOG to discontinue a work-up for EP.[20]

One recent study found use of a progesterone level in patients with beta-hCG less than 1000 mIU/mL increased the accuracy of diagnosis.[48] When the progesterone level was less than 5 ng/mL in patients with a beta-hCG less than 1000 mIU/mL, abnormal pregnancy was diagnosed with a specificity of 94% and sensitivity of 100%.[48] When the level is less than 5 ng/mL, a patient may undergo uterine curettage if chorionic villi are found and EP is ruled out. However, if no villi are found, laparoscopy is indicated to exclude EP.[44] Levels between 5 ng/mL and 25 ng/mL are indeterminate. Although serum progesterone levels are inexpensive, they are not always available in every ED within a useful time frame. If and when the value of progesterone levels are clarified, they may add utility to the other modalities used for evaluation of EP.

Ultrasound. From a clinical, patient assessment perspective, TVU has become the single most valuable modality for the work-up of patients suspected of having an EP. It is the only technique available, other than laparoscopy, that permits the physician to identify the specific location of the pregnancy.

The beta-hCG level at which signs of pregnancy can first be seen ultrasonographically is called the discriminatory threshold. Although the precise beta-hCG value varies among institutions, a recent study reported that with TVU, a gestational sac was visible with beta-hCG levels of 1398 ± 155 mIU/mL.[54] Another study found that a level greater than 1500 mIU/mL was associated with 94% EP diagnosis rate on TVU.[55] However, in another study, only 33% of patients with EP were identified when the levels were less than 1000 mIU/mL.[56]

Consistent with these data is the fact that most authors report a discriminatory beta-hCG threshold of between 1000 mIU/mL and 2000 mIU/mL. These levels corresponded with beta-hCG determinations made only 34.8 ± 2.2 days from the patient's last menstrual period.[56] Accordingly, TVU has the capability, assuming sufficiently high and "discrminatory" beta-HCG levels are detected, to identify a pregnancy location as soon as one week after missing a menstrual period.

An important exception to the discriminatory level is the case of multiple gestations. With twins, the beta-hCG level can be greater than 2000 mIU/mL and there may be no ultrasonogrpahic findings of intrauterine pregnancy as would be expected in a single gestation.[57] Transabdominal ultrasound is less sensitive and is reported to identify a gestational sac in patients with beta-hCG values of 6500 mIU/mL. Clearly, transabdominal ultrasound is less accurate, and it should be no surprise that up to 50% of cases of EP have indeterminate transabdominal ultrasound results.[58] In addition, a level of 6000 mIU/mL level is attained in only 25% of ectopic pregnancies, further reducing the usefulness of transabdominal ultrasound.[58]

Departmental Ultrasonography. Increasingly, ED physicians are performing their own ultrasonographic studies in the ED, with recent studies confirming the safety and effectiveness of this practice. One investigator found that when properly trained, ED physicians performing an ultrasound had a 90% sensitivity and 88% specificity in their diagnosis of EP.[59] A second study found that readings by gynecologists agreed with 93% of ultrasonographic studies performed by ED physicians.[60] In addition, the waiting time for ED patients was reduced by an average of 70 minutes when the ED physician performed the ultrasound as compared to those seen in consultation by Ob/Gyn residents.[61] The number of patients requiring consultation was reduced 85%.[61]

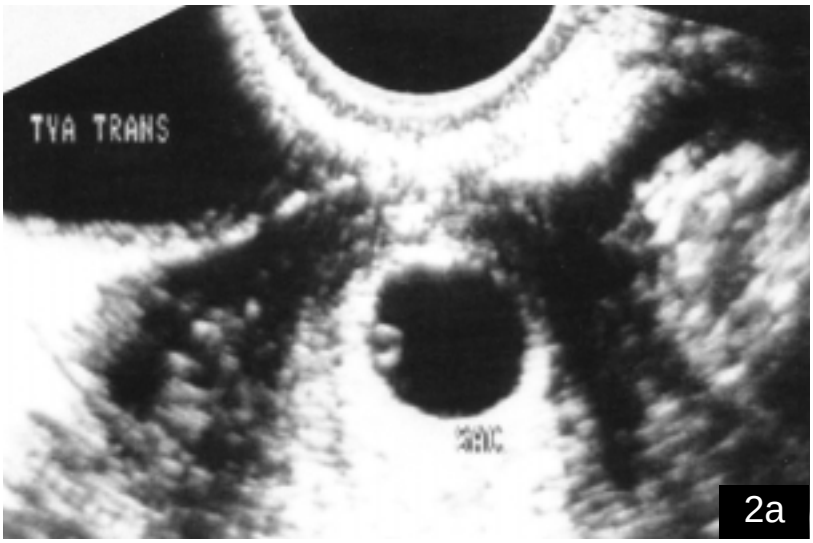
Because an increasing percentage of ED physicians are learning to use ultrasonographic techniques for evaluation of EP as well as other conditions, the ultrasonographic findings in early pregnancy will be discussed in this review. The first sign of pregnancy with TVU is a gestational sac, which appears as a round hypoechogenic collection of fluid surrounded by a hyperechogenic rim representing the trophoblast. A gestational sac can be seen as early as 2-3 weeks after implantation in a normal pregnancy. *(See Figure 2a.)* It is important to note that a pseudogestational sac also can be seen, and may be confused with a normal pregnancy.

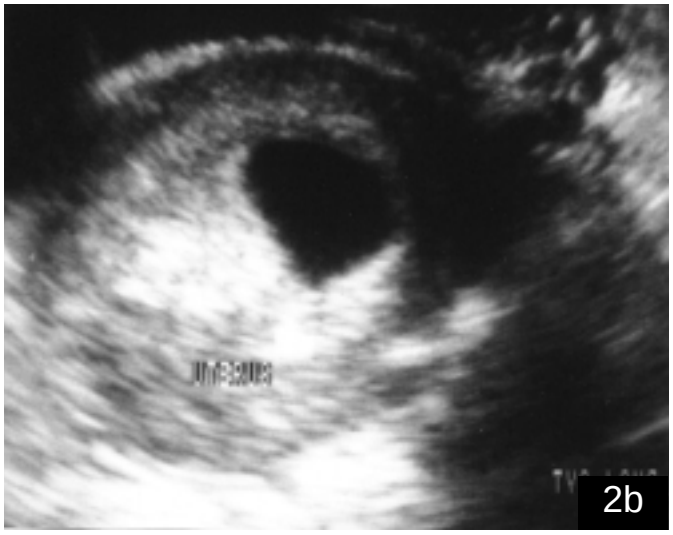
A pseudogestational sac is actually a fluid collection inside the endometrial cavity. *(See Figure 2b.)* This is the result of bleeding of the endometrium caused by the extrauterine pregnancy, and it will conform to and fill the endometrial cavity. A gestational sac is eccentrically placed within the uterine wall, as it is implanted in the endometrium. A normal gestational sac has (or will develop) a yolk sac within it (see Figure 2a), whereas a pseudogestational sac will not. Because the yolk sac may not always be visible at the time of first ultrasound, care must be taken in interpreting these early findings of pregnancy on ultrasound.

Misinterpretation of the pseudogestational sac as a sign of intrauterine pregnancy is one of the most common causes of misdiagnosis of EP by TVU.[62] To complicate matters, in a study on misdiagnosis of EP, pseudogestational sacs were seen in 20% of patients initially misdiagnosed on their first ED visit.[63] The next finding after development of the yolk sac is visualization of the embryonic pole followed by actual cardiac motion. Caution is urged in interpretation of these ultrasound images because interstitial pregnancies can be very hard to distinguish from normal implantations. In addition, implantation of the embryo in the horn of a bicornuate uterus can be difficult to interpret with discriminating accuracy on ultrasound, as can cervical implantation. Furthermore, abnormally developing pregnancies or spontaneously reabsorbing pregnancies may also present problems in interpretation. In the case of interstitial, cervical, or bicornuate uterus, additional diagnostic information may be obtained with magnetic resonance imaging (MRI), provided that the patient is stable enough to undergo this type of testing.

Ultrasonograhic evidence of EP requires observation of a definite pregnancy outside the uterine boundary (most often in the fallopian tubes), or finding a complex adnexal mass that

Figures 2a and 2b. Ultrasound Images of a Normal Gestational Sac and Pseudogestational Sac





In Figure 2a, the yolk sac is seen an a small hyperechogenic circle on the left margin of the gestational sac. **In contrast, Figure 2b** shows a pseudogestational sac where the sac is irregular in shape, has no yolk sac, and represents fluid in the endometrial cavity. One can see how a early gestational sac without yolk sac development can be confused with a pseudogestational sac.

represents an EP. When a gestational sac is seen in the tube, one will be able to visualize a hypoechogenic fluid collection surrounded by a hyperechogenic ring. The ring consists of a decidual reaction of the fallopian tube, and is termed the "tubal ring" sign or "ring of fire." This finding is common and is seen in 60-70% of ectopic pregnancies.[64] In one series, the presence of a tubal ring correlated with a mean beta-hCG of 4300 mIU/mL.[65]

Inasmuch as the fallopian tube is an inhospitable location for pregnancy development, many tubal pregnancies do not develop normally. For example, in the largest series to date (380 surgically confirmed ectopic pregnancies) cardiac motion was only seen in 4% of patients with EP, and this finding correlated with an average beta-hCG level of 10,744 mIU/mL.[66] Bleeding into the gestational sac is common, however, and can lead to thrombus formation inside the sac. This may produce a confusing ultrasound picture, with visualization only of a complex adnexal mass. Presence of such a mass is, however, still suggestive of EP and should heighten suspicion of the diagnosis in the appropriate clinical setting. Additional caution is urged in the case of ovarian pregnancies because the EP can be very difficult to distinguish from a normal ovarian cyst. Serial ultrasonographic studies may be necessary to identify an enlarging gestational sac.

The ED physician must be familiar with the limitations of ultrasonographic technology. First, the usefulness and predictive value of the ultrasound generally depends as much on the skill level and experience of the operator. For ED physicians performing their own ultrasound, the primary utility of TVU is to identify an empty uterus (or a normal intrauterine pregnancy) in a patient whose beta-hCG level is above the discriminatory threshold. Indeed, a recent study found patients suspected of EP whose first ultrasound study showed an empty uterus were at highest risk compared to other patients whose ultrasound showed intrauterine fluid or debris.[67] In other words, if the level is between 1000 mIU/mL and 2000 mIU/mL and no signs of intrauterine pregnancy are seen, the patient is assumed to have an EP.

Therefore, definitive failure to identify an intrauterine pregnancy and absent ultrasound findings of an EP are sufficient to maintain a high suspicion of an ectopic when the beta-hCG is above the discriminatory threshold. If ultrasound findings indicate definitive evidence of an EP (an identified ectopic fetus), the diagnosis is certain. If suspicious but indeterminate findings (fluid in the cul-de-sac without intrauterine pregnancy [IUP], adnexal mass without IUP), then the diagnosis is strengthened but not certain.

Numerous studies have shown that use of TVU does reduce indeterminate ultrasound findings compared to transabdominal ultrasound, but it is not 100% accurate in every case. Even with a definitive adnexal mass or cul-de-sac fluid, the positive predictive value for EP is reported to be about 94%.[68] Other studies show that adnexal masses are seen in only 15-35% of patients with an EP.[69,70] Another recent study found that among patients with beta-hCG greater than 1500 mIU/mL, about 24% of those who had indeterminate TVU findings eventually had an EP confirmed.[71] A novel suggestion by one author was to subdivide indeterminate ultrasound findings into high-, medium-, and low-risk patients. High-risk patients were defined as those having an empty uterus, medium-risk patients had non-specific intrauterine fluid collections, and low-risk patients had intrauterine echogenic debris (blood clots).[72] One study of 132 patients with EP found there were no definitive ultrasound findings for the presence of rupture.[73]

Recently, there has been debate in the literature about the usefulness of the thickness of the endometrial stripe as seen on TVU. Some authors suggest that the thickness of the stripe in the uterine cavity alone can be predictive the location of the pregnancy. In a 1996 retrospective study of 47 women with ectopic pregnancies, one author found that the endometrial stripe was always less than 6 mm.[74] In comparison, 37 women who ultimately were proven to have normal intrauterine pregnancies had stripe thickness greater than 6 mm.[74] However, a more recent study of 676 patients (42 with EP) found that a thin endometrial stripe alone was not predictive of EP.[75] Another study found that there was predictive value of the endometrial stripe, but that it was limited to patients with beta-hCG levels less than 1000 mIU/mL.[76] Finally, one author found that gestation age and endometrial stripe thickness could not distinguish between patients with and without EP.[77] Larger studies will likely be needed to clarify this issue.

Other Diagnostic Tests: Uterine Curettage, Culdocentesis, and Laparoscopy. Three other diagnostic tests may be useful in the diagnosis of EP: 1) uterine curettage; 2) culdocentesis; and 3) laparoscopy. While these procedures are beyond the purview of the ED physician (with the exception of culdocentesis), it is important to understand when these tests are indicated and what their limitations are.

Uterine curettage involves physically scraping the uterine cavity in an effort to obtain evidence of a intrauterine pregnancy. This is performed only when serum hormones indicate a non-viable pregnancy (progesterone < 5 ng/mL or falling/plateauing beta-hCG). Typically, chorionic villi are identified (by floating tissue obtained in saline) when a failed intrauterine pregnancy is present. When villi are not seen, diagnosis of completed miscarriage can still be made if the beta-hCG level falls 15% or more 8-12 hours after the procedure.[44] When no villi are seen and beta-hCG levels do not fall, EP is highly suspected. Ectopic pregnancy is diagnosed in this situation if the beta-hCG plateaus or continues to rise after the procedure.[44] Curettage is most useful in patients with an indeterminate ultrasound. In one study of patients with indeterminate scans, the incidence of EP was 40% when no villi were seen on curettage.[78]

Culdocentesis was used much more often before widespread availability of TVU. It is still indicated in situations where ultrasound is unavailable and EP is highly suspected, or in an unstable patient where time is critical. It can be accurate in the case of ruptured ectopic. Up to 90% of patients with a ruptured ectopic will have a positive culdocentesis result.[34] As one might expect, the results are not as good with unruptured ectopics. Only 65% of these patients will have a positive culdocentesis result.[79] In culdocentesis, a tenaculum is used to elevate the cervix anteriorly and a 20-gauge spinal needle is inserted below the cervix to obtain fluid from the cul-de-sac.

Caution is urged in interpreting indeterminate results, as they can be difficult to decipher. A positive result is determined when nonclotted blood (> 0.5 cc) is obtained.[79] Indeterminate results are when a dry tap, clotting blood (> 0.5 cc), or serous fluid (> 5 cc) is obtained. Presumably, clotting blood is from pelvic veins, as defibrinators in the peritoneum should prevent clotting of free peritoneal blood. One needs to remember, though, that rapid bleeding into the peritoneum can produce clotting blood on a culdocentesis, but that the patient's condition should clue one to the severity of the blood loss. Bloody culdocentesis fluid can also be obtained from a hemorrhagic corpus luteum cyst, but the fluid normally has a hematocrit of less than 12%.[80]

Dry taps are seen in 10-20% of culdocentesis procedures, and can be obtained in patients who actually have peritoneal blood from a ruptured ectopic.[34] Thus, a dry tap should not be confused with a negative result. Aspiration of only small amounts of serous fluid (0.3-5.0 cc) is a negative culdocentesis result. These can be seen in the case of a non-hemorrhagic corpus luteum cyst rupture, but are found in up to 5% of women with EP as well.[34] As culdocentesis is not a technically difficult procedure, the key is to know how to interpret the results correctly if one is forced to rely on this in patient work-up for EP.

Finally, laparoscopy can be both diagnostic and therapeutic for EP. Use of laparoscopy is indicated in patients with peritoneal signs and equivocal results from previous testing with ultrasound, culdocentesis, or uterine curettage. It can also used alone for treatment when the diagnosis has been made by other means, although many patients are now managed medically.

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Physician CME Questions

97. What level of serum progesterone, when the patient has a beta-hCG less than 1000 mIU/mL, is associated with an abnormal pregnancy?
    A. 25 ng/mL
    B. 30 ng/mL
    C. < 5 ng/mL
    D. 15 ng/mL

98. Damage to a woman's fallopian tubes often results from previous pelvic infection, especially from which of the following?
    A. Chlamydia
    B. Gonorrhea
    C. Klebsiella
    D. Both A and B are correct

99. The most common presenting symptom of ectopic pregnancy is:
    A. pain.
    B. vaginal bleeding.
    C. syncope.
    D. passage of tissue.

100. What is *not* a sign of viable pregnancy on ultrasound?
    A. Gestational sac with yolk sac
    B. Visualization of the embryonic pole
    C. Large gestational sac (> 20 mm) without a fetal pole
    D. Fetal cardiac flicker

101. Ultrasound signs of ectopic pregnancy include which of the following?
    A. Complex adnexal mass
    B. "Tubal ring sign"
    C. "Ring of fire"
    D. All of the above

102. Patients who present with ectopic pregnancy and are misdiagnosed often:
    A. have non-diagnostic ultrasound on initial exam.
    B. are most commonly diagnosed with threatened miscarriage.
    C. report passage of tissue.
    D. have no complaints of pain.
    E. All of the above.

103. Most obstetrical texts take the position that documented failure of beta-hCG levels doubling in how many hours is diagnostic of a non-viable pregnancy?
    A. 24 hours
    B. 48 hours
    C. 36 hours
    D. 12 hours

104. According to current data, a viable intrauterine pregnancy is suggested by a single progesterone level of:
    A. higher than 5 ng/mL.
    B. 1 ng/mL.
    C. 2.5 ng/mL.
    D. None of the above

In Future Issues:

Bleeding in the First 20 Weeks of Pregnancy: Part II