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Ectopic pregnancy

David Della-Giustina, MD, FACEP[a,b,c,d,*],
Mark Denny, MD[d,e]

[a]*Lieutenant Colonel, United States Army*
[b]*Military and Emergency Medicine, Uniformed Services University of the Health Sciences*
[c]*University of Washington School of Medicine*
[d]*Department of Emergency Medicine, Madigan Army Medical Center, Tacoma, WA 98431, USA*
[e]*Captain, United States Army*

Ectopic pregnancy should be one of the first thoughts that the emergency physician considers when evaluating a woman of reproductive age who presents to the emergency department with abdominal pain or vaginal bleeding. This concern is warranted, because the rate of ectopic pregnancy has continued to climb in the United States from less than 0.5% of all pregnancies in 1970 to 1.97% in 1992 [1,2]. Furthermore, despite a 90% drop in the mortality from ectopic pregnancy during this time period, ectopic pregnancy is still the leading cause of pregnancy-related death in the first trimester and accounts for 9% to 13% of all pregnancy related deaths [3,4]. Despite the increasing rates and the increased detection methods, ectopic pregnancy is misdiagnosed in more than 40% of patients on the initial emergency department visit [4]. Finally, missed ectopic pregnancy is one of the leading causes of emergency medicine malpractice risk. This article reviews the clinical, laboratory, and ultrasonographic findings that help the emergency physician diagnose an ectopic pregnancy. This review is followed by a discussion of an approach to the patient who presents to the emergency department with suspected ectopic pregnancy. Finally, the management of the patient diagnosed with an ectopic pregnancy is discussed.

The opinions and assertions contained herein are the private views of the authors and should not be construed as official or as reflecting the views of the Department of Army or the Department of Defense.

* Corresponding author. Department of Emergency Medicine, Madigan Army Medical Center, Tacoma, WA 98431.

E-mail address: David.Della-Giustina@nw.amedd.army.mil (D. Della-Giustina).

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Definitions

Ectopic pregnancy is defined as any pregnancy that occurs outside the uterine cavity. Approximately 97% of ectopic pregnancies occur in the fallopian tube, with 55% of these occurring in the ampulla, 25% in the isthmus, and 17% located in the fimbria. The remaining 3% of ectopic pregnancies are located in ovarian, cervical, abdominal, and intersitial (cornual) sites [1]. A heterotopic pregnancy is a coexistent intrauterine and ectopic pregnancy. The rate of heterotopic pregnancy varies from 1 in 3000 to 1 in 8000 in patients not treated with fertility agents to 1% to 3% in patients taking fertility agents or who undergo in vitro fertilization [2,3,5–12].

Clinical findings

The classic triad for the patient who presents with an ectopic pregnancy is amenorrhea, abdominal pain, and vaginal bleeding. Unfortunately, these findings are nonspecific and actually occur more commonly in the patient who has a threatened miscarriage than in an ectopic pregnancy [1]. Questioning the patient regarding previous ectopic pregnancy, history of pelvic inflammatory disease, use of an intrauterine device (IUD), and tubal surgery can increase one's level of suspicion when evaluating a patient with suspected ectopic pregnancy. The presence of any of these risk factors should increase one's suspicion for ectopic pregnancy. The absence of risk factors is not reassuring, however, because at least 40% to 50% of patients with proven ectopic pregnancies have no risk factors [1,3,13].

Most patients with ectopic pregnancy present to the emergency department with abdominal or pelvic pain. The nature of the pain may be mild to severe, and the pain may be located in the midline, laterally, or both. The absence of pain or pain that is mild is reassuring but is still seen in patients with ectopic pregnancy. Thus, one should not rely on these symptoms to rule out ectopic pregnancy clinically, especially because the goal is to diagnose the ectopic pregnancy before it ruptures [1,14]. Other important historical information is the amount of vaginal bleeding and the passage of tissue. Abnormal vaginal bleeding occurs in 50% to 80% of ectopic pregnancies and may range from scant to profuse. Although profuse or heavy vaginal bleeding is worrisome for ectopic pregnancy, it is more suggestive of an abnormal intrauterine pregnancy [1,14]. The passage of tissue may represent a miscarriage. One must consider, however, that the tissue passed may be a decidual cast formed by the endometrial response of the early hormonal changes of an ectopic pregnancy. Unless one evaluates the tissue under a microscope, a decidual cast can easily be mistaken for products of conception. Thus, the passage of tissue does not differentiate between an ectopic and an intrauterine pregnancy (IUP) [1,14].

The physical examination should focus on the vital signs and the abdominal and pelvic examination. Although hypotension and tachycardia

indicate a need to resuscitate the patient, they are not predictive of ectopic pregnancy. In fact, both of these findings occur more commonly with complications of IUP than with ectopic pregnancy [1,14]. Furthermore, the presence of normal vital signs does not rule out the presence of ectopic pregnancy [14]. The presence of peritoneal signs, cervical motion tenderness, and lateral or bilateral abdominal or pelvic tenderness increases the likelihood of ectopic pregnancy and are significant findings [1,14]. On the other hand, the absence of these finding does not rule out ectopic pregnancy [1,14]. Finally, the presence of an adnexal mass is not predictive of an ectopic pregnancy [1,14]. In the study by Dart et al [14], an adnexal mass was present in less than 10% of patients with diagnosed ectopic pregnancy. In one third of the cases in which a mass was noted, the ectopic pregnancy was actually found on the side opposite the side on which the mass was palpated. One must remember that the pelvic examination is completely normal in approximately 10% of patients who have an ectopic pregnancy [1].

In summary, several historical and physical examination findings raise the suspicion for ectopic pregnancy. There is, however, no combination of findings that can allow the emergency physician to exclude ectopic pregnancy reliably on clinical findings alone.

Laboratory findings

The emergency physician uses beta-human chorionic gonadotropin (β-hCG) to diagnose the pregnancy and to assist in determining the potential of the patient having an ectopic pregnancy. Beta-human chorionic gonadotropin is produced by the trophoblasts and may be detectable in the serum as early as 1 week before expected menses. Most laboratories test for serum levels as low as 5 mIU/mL and urine levels in the 20 mIU/mL to 50 mIU/mL range. False-negative results can occur with the urine testing, especially if the urine is not very concentrated. When there is a high suspicion of pregnancy, a negative urine β-hCG test should be followed with a more definitive serum β-hCG test. If the serum β-hCG test is negative, pregnancy is extremely unlikely. There are a few case reports in which a patient had a negative serum β-hCG test and an ectopic pregnancy; however, those were rare cases and usually involved the older, less sensitive assays [1]. Normal dynamics for β-hCG are that it doubles approximately every 1.4 to 2.1 days until it peaks above 100,000 mIU/mL. This doubling rate slows somewhat after reaching 10,000 mIU/mL; however, at that time ultrasonography should be diagnostic [1,3].

Although a single quantitative β-hCG test is useful in diagnosing pregnancy, it is not helpful in differentiating between ectopic and IUP. A common misconception is that a single quantitative level below 1500 mIU/mL to 2500 mIU/mL is useful in ruling out an impending rupture of an ectopic pregnancy. This erroneous concept stems from the use of 1500

mIU/mL as the discriminatory zone where transvaginal ultrasound findings of an IUP should be present. Ruptured and unruptured ectopic pregnancies have been identified at β-hCG levels below 100 mIU/mL and greater than 50,000 mIU/mL, however [1]. In one study, 10% of ectopic pregnancies with β-hCG levels below 100 mIU/mL were ruptured [1]. Furthermore, 7% of all ruptures in this series occurred at levels below 100 mIU/mL. Thus, a single quantitative level is not useful in ruling out an ectopic pregnancy or an impending rupture of an ectopic pregnancy.

Serial quantitative β-hCG testing is a common method of following pregnant patients who do not have a definitive IUP. This method involves drawing serial quantitative β-hCG levels approximately every 48 hours and monitoring for an appropriate rise. Normal dynamics allows for a greater than 66% increase in this time period. This rise is seen in approximately 85% of patients with a normal IUP but unfortunately still occurs in 15% of ectopic pregnancies, especially early in the pregnancy [1,3,6]. On the other hand, an abnormal rise ($<66\%$) is strongly suggestive of an abnormal pregnancy, including 85% of ectopic pregnancies. Regrettably, this abnormal rise is still seen with 15% of normal IUPs [1,3,6]. Declining β-hCG levels are indicative of a nonviable pregnancy, either intrauterine or ectopic [1,3,6]. The best method for employing serial β-hCG testing is in conjunction with ultrasonography in follow-up of patients with indeterminate evaluations in the emergency department, as described later.

Serum progesterone is another hormonal marker that has been used in an attempt to determine whether the patient has a viable IUP. In distinction to serum β-hCG, serum progesterone levels are not gestational age-specific and remain relatively constant during the first trimester whether the pregnancy is normal or abnormal [3]. Multiple researches have evaluated the use of serum progesterone. Generally, the research shows that a progesterone level greater than 20 ng/mL to 25 ng/mL is highly predictive (95%–100%) of a normal IUP and that levels below 5 ng/mL are nearly 100% predictive of an abnormal pregnancy [1,3,15,16]. In these cases, an abnormal pregnancy includes both ectopic pregnancy and abnormal IUP. Although the utility of a single serum progesterone level seems promising, some problems are associated with its use. First, most patients have levels that are in the gray zone between 5 ng/mL and 25 ng/mL. In this range, there is too much overlap between ectopic and normal pregnancies for the marker to be of any use [1,15]. Furthermore, most laboratories do not perform rapid serum progesterone testing, so the results are not readily available for use in the emergency department [1,17].

Ultrasound testing

Over the decade, physicians in the emergency department have increasingly used ultrasonography in the evaluation of first trimester

complications of pregnancy. Several studies have validated the ability of emergency physicians to complete pelvic ultrasound evaluations with minimal training [18–21]. One major impact of ultrasonography performed by the emergency physician is that the length of stay in the emergency department has been shown to decrease by as much as 120 minutes [22], because as many as 75% of patients presenting to the emergency department for first trimester complications of pregnancy can be diagnosed by the initial transvaginal ultrasound test as having either an IUP or an ectopic pregnancy, making the disposition of these patients quick and easy [4]. Furthermore, there is decreased morbidity when emergency physicians perform ultrasound testing before discharge, instead of having the patient follow up for an outpatient ultrasound test [23].

Ultrasonography measures returning echoes using a piezoelectric transducer. As the transducer frequency increases, the resolution of the image improves, but the depth of penetration is reduced. This characteristic makes transvaginal ultrasonography more sensitive than transabdominal ultrasonography when imaging the pelvic organs [24]. Technologic improvements and transvaginal ultrasonography have allowed the discriminatory level of β-hCG (the lowest level at which a gestational sac should be visible) to decrease from the 6500 mIU/mL, as originally described for the transabdominal technique, to between 1000 mIU/mL and 1500 mIU/mL for the transvaginal technique [24–32]. Thus, using a noninvasive technique, one may diagnose intrauterine and ectopic pregnancies earlier in the disease process, allowing more conservative management and decreased morbidity.

To interpret ultrasound findings, it is important to understand the ultrasound findings in normal pregnancy. A number of studies have been published in an attempt to correlate β-hCG levels, transvaginal ultrasound findings, and menstrual dates. A gestational sac should be visualized with β-hCG levels between 1000 mIU/mL to 1500 mIU/mL, which correlate with 4.5 to 5 weeks' gestation [24–29,31–35]. A clearly defined yolk sac should be visualized at approximately 2500 mIU/mL, which correlates with 5 to 6 weeks' gestation; however, the yolk sac is sometimes not seen until the β-hCG level is 6000 mIU/mL to 7000 mIU/mL [27,34]. With a β-hCG level between 5000 mIU/mL and 17,000 mIU/mL, one should be able to visualize a fetal pole and fetal heart beat, respectively. This level corresponds to approximately 7 weeks' gestation [24,29,36,37]. These guidelines are rough indications as to when one should expect certain findings. Because ultrasonography is user-dependent, the individual ultrasonographer should set the discriminatory zone gray use, based on previous experience.

The literature is varied on how and when to use transvaginal ultrasonography in the diagnostic algorithm for first trimester pregnancy complications. Furthermore, there is disagreement about the categorization of ultrasound findings. Because of these issues, it is difficult to interpret many of the studies clearly. This article presents a diagnostic algorithm and a classification system for findings that can help the emergency physician

interpret results and treat the patient appropriately. Ultrasound findings in the evaluation of the pregnant patient are categorized as diagnostic of IUP, diagnostic or suggestive of ectopic pregnancy, or indeterminate. The ultrasound findings in each category are discussed in the following sections, and β-hCG levels are integrated into the discussion when pertinent.

Findings diagnostic of IUP

The primary objective for the emergency physician is to attempt to demonstrate an IUP. The demonstration of an IUP effectively rules out ectopic pregnancy because the risk of heterotopic pregnancy is relatively uncommon. Caution must still be used in the patient who is undergoing reproductive assistance, because of the higher risk of heterotopic pregnancy. Diagnosing an IUP in a patient with abdominal pain, vaginal bleeding, or both allows the emergency physician to focus on alternate diagnoses or allows the disposition of the patient under the category of threatened miscarriage. Furthermore, ultrasonography allows one to educate the patient about the prognosis of the pregnancy in cases of threatened miscarriage, because approximately 90% of symptomatic patients who have an IUP with fetal cardiac activity detected on ultrasound testing ultimately deliver a viable infant [38].

The definition of an IUP has not been agreed upon in the literature. Some claim that a fetal pole with cardiac activity should be visualized before definitively diagnosing an IUP. Most authorities conservatively state that demonstrating a gestational sac with a clearly defined yolk sac is the earliest finding diagnostic of an IUP [27,39]. Others, however, feel that IUP can be diagnosed with just the presence of a gestational sac, as long as it has certain properties [40,41]. Although earlier findings, such as a double decidual sign or intradecidual sign, may be consistent with an IUP, these findings are more subjective, and the emergency physician should use caution in interpreting these findings as definitive [13,42]. These findings are discussed in the indeterminate ultrasound section.

In attempting to define an IUP, one must first search for and evaluate the gestational sac. The gestational sac should appear as a round, black (anechoic) structure in the endometrial cavity. Depending on the maturity of the sac, it may have an echogenic border with internal structures such as a yolk sac and fetal pole. One should measure the sac diameter with three separate measurements, because the mean gestational sac diameter may be diagnostically important. A yolk sac should be visible by the fifth to sixth week of gestation and in all patients in whom the mean gestational sac diameter is greater than 6 to 8 mm [27,36,37,44]. A gestational sac greater than 10 mm in diameter without a yolk sac is strongly suggestive of an abnormal pregnancy [27,43–45]. A fetal heartbeat should be seen by 5.5 to 7 weeks' gestation and in all patients with a mean gestational sac diameter of 9 to 16 mm [27,36,37,44]. Although the finding of a gestational sac without

a yolk sac is considered an indeterminate ultrasound finding, these measurements can suggest whether the pregnancy seems to be progressing normally. If present, the measurement of the yolk sac diameter and the fetal pole length is also of prognostic benefit. A normal yolk sac measures 3 to 5 mm in diameter, and a diameter greater than 7 mm suggests a nonviable pregnancy [46]. By the time the fetal pole is 5 mm in length, the fetal heartbeat should be visible [44]. The absence of a fetal heartbeat in a fetal pole greater than 5 mm in length is the most reliable finding of a nonviable pregnancy [47].

The emergency physician must be meticulous in visualizing a clearly defined yolk sac or fetal pole within a gestational sac that is intrauterine. There are numerous instances in which physicians visualized a yolk sac or a fetal pole by ultrasonography, and the patients were subsequently found to have ectopic pregnancies. Such missed diagnoses most likely result from the failure to determine that the yolk sac or fetal pole are within a true intrauterine gestational sac or from the identification of a pseudogestational sac in the endometrial cavity. A pseudogestational sac is a collection of material, probably blood and clot, which mimics the appearance of a gestational sac. Echogenic structures located in the center of the sac may lead to misinterpretation. This possibility is one of the most worrisome of the potential diagnostic errors, because it can be falsely reassuring and lead to morbidity from delayed diagnosis. Education, practice, and knowledge of the normal measurements of the gestational sac, yolk sac, and fetal pole and when to expect to visualize a fetal heartbeat should help minimize this possibility.

Findings diagnostic or suggestive of ectopic pregnancy

The only true ultrasonic finding diagnostic of an ectopic pregnancy is visualization of a gestational sac with yolk sac or fetal pole outside the endometrial cavity. Numerous other findings are highly suggestive but not diagnostic of ectopic pregnancy. These findings include a β-hCG level above the discriminatory zone with an empty uterus, an adnexal mass that is anything other than a simple cyst and is separate from the ovary, any echogenic fluid in the cul-de-sac, and a moderate to large amount of fluid in the cul-de-sac.

Numerous studies have shown that the finding of a nondiagnostic ultrasound study and a β-hCG level that exceeds the discriminatory zone is highly specific for ectopic gestation [25,28,48–50]. Cacciatore et al [28] prospectively tested 200 pregnant women suspected of having an ectopic pregnancy with transvaginal ultrasonography and β-hCG measurements. They found that all women with a β-hCG level greater than 1000 mIU/mL and an empty uterus had confirmed ectopic pregnancies (specificity 100%, positive predictive value 100%, sensitivity 67%). In a retrospective review,

Dart and Howard [51] found that the frequency of ectopic pregnancy in patients with an empty uterus detected by transvaginal ultrasonography and a β-hCG level greater than 1000 mIU/mL was only 22%. One likely reason for the difference in the frequency of ectopic pregnancy is that the prevalence of ectopic pregnancy in the studies was 34% and 14%, respectively. Despite the large difference in the rates of ectopic pregnancy in these studies, the importance of these studies is to recognize that the finding of an empty uterus on ultrasound testing with a β-hCG level greater than 1000 mIU/mL is suggestive of ectopic pregnancy. One other major reason for a patient's having an empty uterus with β-hCG levels greater than 1000 mIU/mL is that she recently may have had a complete abortion. Using a higher quantitative β-hCG level, Mateer et al [23] found that 57% of patients with no definite IUP detected on transvaginal ultrasonography and a β-hCG level above 2000 mIU/mL had the final diagnosis of ectopic pregnancies; only one patient had a normal IUP. Until further research clarifies this discrepancy, an empty uterus with a β-hCG level greater than the discriminatory level set by the ultrasonographer should be considered highly suggestive but not diagnostic of ectopic pregnancy.

An adnexal mass that resembles an extrauterine gestational sac without a yolk sac or fetal pole (ie, a thick-walled mass with an anechoic center or tubal ring) has a 95% chance of being an ectopic pregnancy [52]. Any adnexal mass other than a simple cyst or an intraovarian lesion has a 92% likelihood of being an ectopic pregnancy. Cacciatore et al [28] found that a complex adnexal mass or gestational saclike adnexal ring separate from the ovary is highly suggestive of ectopic pregnancy with a sensitivity of 93%, specificity of 99%, and a positive predictive value (PPV) of 98%. Braffman et al [26] also found a complex adnexal mass to have a high specificity (92%) for diagnosing ectopic pregnancy. Finally, in a prospective study of extrauterine findings on transvaginal ultrasonography in patients with suspected ectopic pregnancy, Nyberg [53] found that a solid or complex adnexal mass is associated with an ectopic pregnancy with a specificity of 93% and PPV of 70%. False-positive results in the Nyberg study were caused by hemorrhagic cysts, hydrosalpinx, or ovarian masses. In summary, the accuracy of transvaginal ultrasonography in visualizing adnexal ringlike structures or nonhomogeneous adnexal masses justifies immediate obstetric consultation and possibly laparoscopic intervention [54].

Nyberg's study [53] found that characterizing the amount and appearance of pelvic fluid is helpful diagnostically. The presence of a moderate to large amount of fluid in the cul-de-sac or the presence of any echogenic fluid had 96% specificity for diagnosing ectopic pregnancy. Echogenic fluid in the cul-de-sac was the only extrauterine finding in 15% of confirmed ectopic pregnancies. On the other hand, the presence of a small amount of anechoic fluid is not useful diagnostically, because it may be found in patients with ectopic pregnancies and in patients with intrauterine pregnancies [53,55].

The indeterminate ultrasound finding

The indeterminate ultrasound finding is any ultrasound finding within the endometrial cavity that is neither diagnostic nor suggestive of an ectopic pregnancy or an IUP. About 15% to 20% of all ultrasound tests completed are indeterminate [4,26]. Indeterminate ultrasound findings are not reassuring, and these patients require close follow-up. Fifteen percent to 24% of these patients ultimately have a final diagnosis of ectopic pregnancy [4,26,56]. Aggressive intervention is not advised in this group of patients, however, because 10% to 26% will have normal IUPs [4,26,56]. Dart and Howard [51] developed a subclassification system consisting of five categories to stratify better the risk represented by these indeterminate ultrasound findings. The subclasses are an empty uterus, a normal-appearing sac within the uterus, an abnormal-appearing sac within the uterus, a nonspecific fluid collection within the uterus, and echogenic material within the uterus. These subclasses have different prognostic implications and may help guide subsequent interventions.

The finding of an empty uterus is highly suggestive of an ectopic pregnancy when the β-hCG level is above the ultrasonographer's discriminatory zone. Regardless of the β-hCG level, however, Dart and Howard [51] found that 25% of patients with an empty uterus and no other findings had the final diagnosis of ectopic pregnancy. Six percent of these patients had a final diagnosis of normal IUP. The thickness of the endometrial stripe is also predictive. Early in pregnancy, and before a gestational sac is apparent, the endometrial stripe is thickened and well visualized with transvaginal ultrasonography. Patients with an endometrial stripe thicker than 8 mm often have a normal IUP, and those with a thickness less than 8 mm are at the greatest risk for ectopic pregnancy. Seventy-one percent of the pregnancies with an endometrial stripe thickness less than or equal to 8 mm were ectopic, and only 3% were normal IUPs [57]. No patient with a stripe thickness greater than 13 mm had an ectopic pregnancy. Accordingly, endometrial stripe thickness may aid in stratifying the risk of ectopic pregnancy for the patient with an empty uterus detected on ultrasonographic evaluation. If the emergency physician is not the ultrasonographer, then he or she must be able to interpret fully the official reading of the study. There can be significant confusion if the report reads "normal" or "negative for ectopic." One study showed that no ultrasound abnormalities were seen in 28% of patients with subsequently confirmed ectopic pregnancies [26].

The second subclass is the abnormal gestational sac, which is defined as an anechoic intrauterine fluid collection (ie, no yolk sac or fetal pole) greater than 10 mm in mean diameter or with a grossly irregular border. In a normal gestation, a yolk sac should be apparent once the gestational sac is 6 to 8 mm in mean diameter [27,44]. In this subclass, only 3% have the final diagnosis of ectopic pregnancy, and there were no subsequent normal IUPs. The

abnormal sac may be a pseudogestational sac or the result of a blighted ovum [28]. Although there are reports of normal IUPs after finding a gestational sac greater than 10 mm in diameter, most other studies have shown that a normal IUP can be excluded [27,43–45,58].

The third subclass is the normal sac, defined as an anechoic intrauterine fluid collection (ie, no yolk sac or fetal pole) with an echogenic border and none of the previously described characteristics of an abnormal gestational sac. No ectopic pregnancies were found in this group, and 30% were ultimately diagnosed as normal IUPs. This group probably encompasses two signs that are considered diagnostic of an IUP by some authors, the double decidual sac and the intradecidual sign [25,31,36,40,41]. The early sac should be embedded in the endometrium, and therefore eccentrically located, whereas free blood in the endometrial cavity should be midline in the endometrial cavity. The intradecidual sign is thought to represent an early sac embedded completely within the endometrial lining. The double sac sign is thought to represent a slightly later stage of development in which part of the sac is beginning to protrude into the endometrial cavity. Neither of these findings is 100% reliable in excluding ectopic pregnancy [39,59]. Because of the low likelihood of ectopic pregnancy, this subclass of patients is suitable for outpatient follow-up and expectant management.

The fourth subclass is the nonspecific fluid collection, defined as an anechoic intrauterine fluid collection greater than 10 mm in mean diameter without an echogenic border. Thirteen percent of these patients were found to have ectopic pregnancies, and 20% had normal IUPs [51]. This fluid collection probably represents pseudogestational sacs in the ectopic cases and early gestational sacs in subsequent normal pregnancies. Gestational sacs less than 5 mm in diameter frequently do not have an echogenic rim, and many do not demonstrate the double decidual sac sign [60]. Because of the high incidence of ectopic pregnancies in this subclass, close monitoring is advised.

The final subclass described by Dart and Howard [51,61] is the finding of echogenic material within the endometrial cavity without a defined sac or of multiple discrete anechoic collections of varying sizes divided by echogenic septations. This material is probably clotted blood or retained products of conception. Three percent to 10% of patients with this finding have an ectopic pregnancy. None of these patients had a normal IUP. The caveat in this case is that the ultrasonographer must be able to distinguish the normal, uniform, thick endometrial stripe from the abnormal, nonuniform, heterogeneous echogenic material.

In summary, the patients with an empty uterus and nonspecific fluid collection have the highest risk for ectopic pregnancy. An abnormal gestational sac and echogenic material encompass a second tier of risk, and the patient with a normal-appearing sac is at the lowest risk. Also, patients with an abnormal gestational sac or echogenic intrauterine material are unlikely to have normal IUPs. Interpreting these ultrasound

results with the addition of the β-hCG level helps guide therapy and disposition.

Clinical approach

The approach to ectopic pregnancy (Fig. 1) begins with developing a clinical suspicion for the entity. History and physical examination characteristics are poor predictors [1,43]. Any woman of reproductive age who presents to the emergency department with vaginal bleeding, abdominal pain, syncope, hypotension, or altered mental status should have a pregnancy test.

If the patient is pregnant, then hemodynamic instability, a low hematocrit, or an acute abdomen warrants immediate obstetric consultation for concern of a ruptured ectopic pregnancy. These patients should have two large-bore intravenous lines inserted and should be placed on a cardiac monitor. Blood should be sent for hematocrit, typing and cross matching, Rh status, and a quantitative β-hCG. The quantitative β-hCG will help the obstetrician monitor resolution of the ectopic pregnancy after surgical intervention. Blood transfusion should be initiated for hypotension that does not respond to a repeated fluid bolus. Any Rh-negative mother with

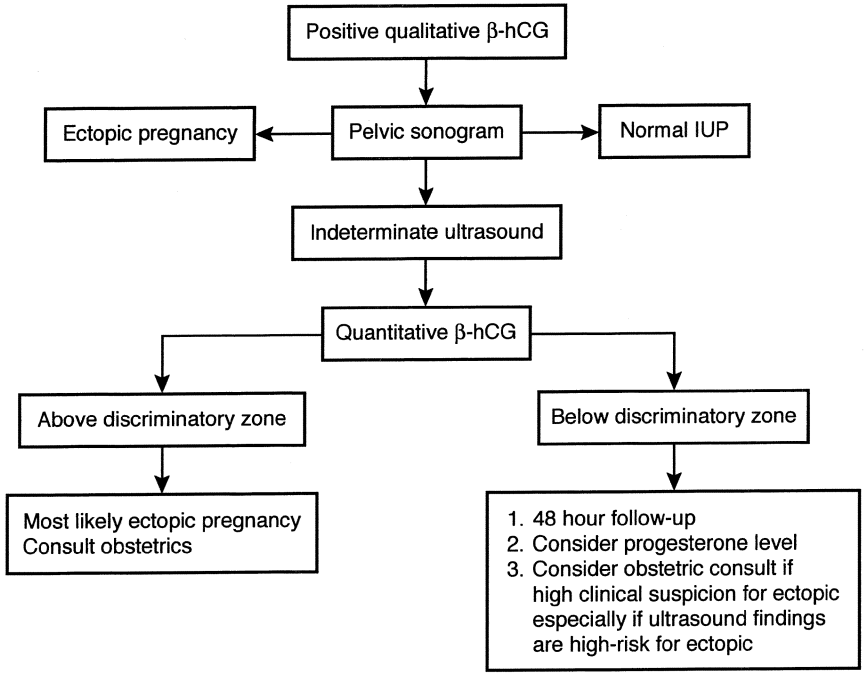

Fig. 1. Clinical approach for ectopic pregnancy.

vaginal bleeding or a diagnosed ectopic pregnancy should have Rh_o (D) immune globulin (RhoGAM) administered.

In the stable pregnant patient, pelvic sonography is the next step. If an IUP is definitively identified, the patient can be counseled appropriately for threatened miscarriage, discharged with follow-up, and managed expectantly.

Finding an obvious ectopic gestation or demonstrating sonographic evidence that is highly suggestive of ectopic pregnancy mandates obstetric consultation in the emergency department. Blood should be sent for hematocrit, typing and cross matching, and determination of Rh status. These patients may undergo confirmatory laparoscopy and treatment or be treated with methotrexate, depending on the exact ultrasonographic findings. When the ultrasound evaluation is indeterminate, a quantitative β-hCG should be measured. Previous recommendations have been to check the quantitative level before ultrasonographic evaluation and to forego the imaging if the level is below the discriminatory zone. The argument offered for this pathway is that, if the quantitative level is below the discriminatory zone, the ultrasonographer will be unable to visualize the pregnancy. This practice, however, is inaccurate and dangerous. In Kaplan's study [4], 38% of the confirmed ectopic pregnancies had β-hCG levels less than 1000 mIU/mL, and 29% of these were ruptured. Six of the 11 ectopic pregnancies in Fleischer's study [62] had β-hCGs below 1000 mIU/mL [62]. Thirty of 38 (79%) ectopic pregnancies in Mol's study [63] had β-hCG levels below 1000 mUI/mL, and 17 (44%) were below 500 mUI/mL. Dart [64] found that 39% of ectopic pregnancies in patients with a β-hCG level below 1000 mIU/mL were identifiable at initial ultrasound evaluation. In fact, 56% of those identified at initial ultrasound evaluation had β-hCG values below 500 mIU/mL. This strong evidence indicates that clinicians should not defer ultrasound evaluation based on the quantitative β-hCG level.

The quantitative β-hCG level in conjunction with the ultrasound results can be extremely helpful in stratifying the risk of ectopic pregnancy and determining the course of treatment. For instance, a β-hCG level greater than the discriminatory zone with an empty uterus detected on ultrasound evaluation places the patient at high risk for an ectopic gestation [26,30,38,48–50]. Of course, this situation could just be a completed spontaneous abortion in which the patient missed the passing of tissue, but the emergency physician should be cautious in making this determination. A number of studies have demonstrated that β-hCG thresholds ranging from 1000 to 2000 mIU/mL can exclude the diagnosis of normal IUP in patients without gestational sac detected by transvaginal ultrasound [28,50,65]. Excluding a normal IUP allows the consultant to consider curettage as a diagnostic procedure. On the other hand, a low β-hCG level with an empty uterus is a meaningless finding that could be an ectopic pregnancy, an abnormal IUP, or an early normal IUP.

A few further diagnostic modalities may help differentiate the ectopic or abnormal gestation from a normal IUP. Culdocentesis, laparoscopy,

progesterone levels, curettage, and serial β-hCG levels have been evaluated. The use of culdocentesis for diagnosing and analyzing free pelvic fluid should be considered only in emergent situations when ultrasound is unavailable.

Laparoscopy has been used for decades as a diagnostic tool in the evaluation of ectopic pregnancy. This procedure should still be considered in patients with uncontrollable pain, unreliable follow-up, or certain higher-risk indeterminate ultrasound findings such as a nonspecific fluid collection in the uterus. There are no guidelines or studies that indicate which indeterminate ultrasound findings necessitate laparoscopy. Furthermore, no prospective studies have been completed using β-hCG levels in combination with specific indeterminate ultrasound findings (except for the empty uterus) to guide therapy. By defining specific indeterminate ultrasound findings in conjunction with β-hCG levels, future studies may be able to identify those patients needing laparoscopy.

A progesterone level may help if it is either very low or very high. A progesterone level above 25 ng/mL is associated with a viable IUP, but a level less than 5 ng/mL is highly suggestive of a nonviable pregnancy. Performing curettage in the patient with a progesterone level less than 5 ng/mL provides the clinician with the probable location of the pregnancy and decreases the time to diagnosis [66]. Absence of chorionic villi in the histologic material indicates a diagnosis of ectopic pregnancy. A frozen section can accurately confirm the diagnosis within minutes and allow further intervention (ie, laparoscopy) while the patient is still anesthetized in the operating room [67]. Unfortunately, very few abnormal pregnancies have a progesterone level this low, making this test only infrequently useful. Some authors have suggested a higher discriminatory level for progesterone, but progesterone levels above 5 ng/mL can occur in too many normal IUPs to make these higher cutoff values clinically useful [68].

The final method, which is the most frequently applied, is the serial measurement of β-hCG levels at 48-hour intervals. With a normal rise in β-hCG level of at least 66%, most pregnancies are found to be intrauterine [6]. Mol [63] found similar results using a rise of greater than 50% as the cutoff. Twelve percent to 35% of ectopic pregnancies will have a normal rise in β-hCG levels, however [6,63,69]. Patients with a normal rise and an empty uterus detected on ultrasound testing still have a 22% chance of having an ectopic pregnancy [6]. These patients need to be followed closely until the β-hCG level has risen above the discriminatory zone, at which time they should have a repeat ultrasound evaluation.

An increase of less than 66% in β-hCG level after 48 hours frequently indicates an abnormal pregnancy, although this increase still characterizes up to 27% of normal IUPs [6]. An abnormal pregnancy is not necessarily an ectopic pregnancy, and repeating the ultrasound evaluation after the level is above the discriminatory zone may therefore be helpful. Determining the progesterone level may be helpful if it was not checked initially. Using curettage in this setting would lead to an unacceptably high rate of aborting

normal IUPs. In this population the finding of an empty uterus on ultrasound examination increases the risk of ectopic pregnancy substantially, with an odds ratio of 25 [6].

A decrease in β-hCG level by greater than 50% at 48 hours is good evidence for abnormal pregnancy and a decreased risk of ectopic pregnancy [6,63,70]. Only 2 of 170 patients in this category were found to have an ectopic pregnancy, and there were no normal IUPs in this group [6,63]. Therefore, curettage would be safe in this population but may not be cost effective. The two ectopic pregnancies in this group also had an empty uterus detected on ultrasound examination, but so did 60% of the spontaneous miscarriages [6]. Using selective curettage in patients with decreasing β-hCG levels and empty uteri detected on ultrasound evaluation may prove efficacious. For the most part, however, these patients are managed expectantly.

A decrease β-hCG level by less than 50% at 48 hours is also good evidence for an abnormal pregnancy. Kadar [70] found that slowly decreasing β-hCG values were present in 86% of the ectopic pregnancies in that study. In two other studies, only 1 of 117 patients had a normal IUP, but 16% had ectopic pregnancies [6,63]. Of the patients diagnosed with ectopic pregnancy who were tested by ultrasonography, all had empty endometrial cavities [6]. The natural history of some ectopic pregnancies is spontaneous resolution; however, there are case reports of slowly declining β-hCG levels with subsequent rupture weeks later [71]. Therefore, the authors believe that expectant management is not indicated, and another modality should be used to make the diagnosis.

Treatment

Once the diagnosis of ectopic pregnancy has been definitively established, the next decision is between surgical and medical management. Although the obstetrician makes this decision, some of the recent changes in the management of ectopic pregnancy are presented here. Surgery has long been the criterion standard for the diagnosis and treatment of ectopic pregnancy. Initially, the procedure was laparotomy with salpingectomy. In the early 1950s, Stromme [72] reported the first laparotomy with salpingostomy (tube conserving surgery), and the first laparoscopic salpingostomy was completed in 1978 [73]. Since this time, laparoscopic diagnosis and treatment have been the criterion standard. The benefits of laparoscopic treatment over laparotomy are lower cost, blood loss, and pain, as well as a shorter postoperative recovery [74–76]. In a review of 32 studies of laparoscopic intervention for ectopic pregnancy, Pisarska [2] found that 93% of patients needed no further therapy. Fifty-seven percent of patients went on to have normal subsequent IUPs, and 13% had further ectopic pregnancies. Laparotomy is still indicated in the hemodynamically unstable patient and

when surgery is indicated, but the surgeon is not adequately trained for laparoscopic intervention.

In the early to mid-1980s, several studies used methotrexate in the treatment of ectopic pregnancy [77–79]. Success rates, tubal patency rates, and subsequent fertility rates have been found to be equivalent to those following surgical therapy [2,17,65,80]. In a randomized comparison between variable-dose methotrexate and laparoscopic salpingostomy, Hajenius et al [81] found comparable success rates for the two interventions. In fact, the primary treatment in many centers has become medical management with methotrexate and close monitoring. The commonly accepted indications for methotrexate therapy are an adnexal mass less than 3 cm to 4 cm in diameter, hemodynamic stability, desire for future fertility, and a stable or rising β-hCG level after curettage that is less than 15,000 mIU/mL [82]. There is no consensus on which selection criteria are the best predictors of successful medical therapy, but most studies suggest that failure rates are higher with larger ectopic pregnancies, evidence of fetal cardiac activity, and higher β-hCG levels [83].

Success rates with single-dose methotrexate are promising, ranging from 63% to 94% [82,84–89]. A discussion of the details of methotrexate protocols or of other potential medical therapies, such as direct injections of methotrexate, prostaglandins, and hyperosmolar glucose into the ectopic gestation, is beyond the scope of this article.

Unless the affected tube is completely removed, there is a risk of residual trophoblastic tissue continuing to grow. The risk of persistent ectopic gestation is similar in surgically and medically treated patients, ranging from 5% to 20% [82,86,88,90–97]. Therefore, most protocols for conservative management of ectopic pregnancies follow serial β-hCG levels in the outpatient setting until the hormone is undetectable. A patient with a persistent ectopic pregnancy will need surgical rescue or further treatment with methotrexate. A diagnostic dilemma for the emergency physician arises when the patient with a known ectopic pregnancy undergoing outpatient medical therapy presents to the emergency department with abdominal pain. The difficulty lies in determining whether the abdominal pain results from rupture of the ectopic pregnancy or the normal course of therapy, because most patients who receive methotrexate experience abdominal pain and cramping by day 3 to 7 of therapy. It is recommended that one not perform a bimanual examination on these patients, because the procedure will not offer additional clinical information but may potentially cause rupture of the ectopic pregnancy. One should perform a pelvic ultrasound evaluation looking for free fluid in the pelvis. Some authors recommend admission for serial hematocrits and observation in some cases, even if free fluid is not identifiable on ultrasound evaluation. This decision should be made in consultation with the patient's obstetrician. Furthermore, the social situation and immediacy of access to care may be important factors in the decision-making process.

Maternal death from the use of methotrexate has not been reported, and significant side effects are uncommon. Contraindications to methotrexate use include renal insufficiency, liver dysfunction, active peptic ulcer disease, leukopenia, thrombocytopenia, and blood dyscrasias. Screening patients with baseline laboratory measurements and following these laboratory results during therapy is recommended.

In summary, as physicians have become more adept at making the diagnosis of ectopic pregnancy with the early use of ultrasound testing, it has been found that many patients can be managed by an entirely noninvasive approach. With the increasing use of ultrasound testing by emergency physicians and the increasing evidence that single-dose intramuscular methotrexate is efficacious, a certain subset of patients with ectopic pregnancy may be diagnosed, treated, and followed in an entirely outpatient setting.

Summary

Ectopic pregnancy is a high-risk diagnosis that is increasing in frequency and is still commonly missed in the emergency department. The emergency physician needs a high index of suspicion and must understand that the history, physical examination, and a single quantitative β-hCG level cannot reliably rule out an ectopic pregnancy. Most pregnant patients who present to the emergency department during the first trimester with abdominal or pelvic pain, regardless of the presence of vaginal bleeding, should undergo further evaluation with ultrasonography. Ultrasound findings in conjunction with quantitative β-hCG levels guide the management of the patient.

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