Diagnostic Keys to Ectopic Pregnancy

Abdominal pain, vaginal bleeding, and missed menses can mean many things, but it's important to rule out the life-threatening possibility of ectopic pregnancy.

By Matthew R. Martin del Campo, MD, and Bruce M. Lo, MD

The incidence of ectopic pregnancy has risen dramatically over the years—between 1970 and 1989, by more than 400%—to almost 20 in 1000 pregnancies. In part the rise is due to an increase in risk factors, such as sexually transmitted diseases (STDs), and in part to better detection. But ectopic pregnancy is still the number-one cause of pregnancy-related deaths in the first trimester. And although overall survival has improved, ectopic pregnancy is still the cause of 10% to 15% of all maternal deaths, with minorities facing an increased mortality risk.

Many women present to the emergency department with abdominal pain, vaginal bleeding, and missed menses. When is it a real emergency? It can be hard to tell; as many as half of ectopic pregnancies are misdiagnosed at the initial visit. The two cases discussed here demonstrate very different presentations and courses for an ectopic pregnancy. The first, a ruptured ectopic pregnancy, could have been mistaken for gastroenteritis. The second patient's early ectopic pregnancy was successfully managed with outpatient methotrexate therapy. Both cases underscore the importance of identifying ectopic pregnancy before it becomes life-threatening.

DANGEROUSLY DECEPTIVE

Ms. K, 20 years-old, presented to the emergency department with nausea, vomiting, diarrhea, and abdominal pain, all of which had developed suddenly six hours earlier. She denied any fevers, chills, previous episodes of abdominal pain, or sick contacts, as well as new foods or travel. Her last menstrual period had been approximately three weeks before, but she said the period was shorter and lighter than normal. She had never been pregnant, nor did she have any history of STDs or pelvic surgery.

On examination, Ms. K had no fever. Her heart rate was 54; blood pressure, 96/45; and pulse oximetry, 100% on room air. She appeared mildly ill but was awake, alert, and oriented. The physical exam was normal except for the abdominal exam, which was significant for diffuse abdominal tenderness to

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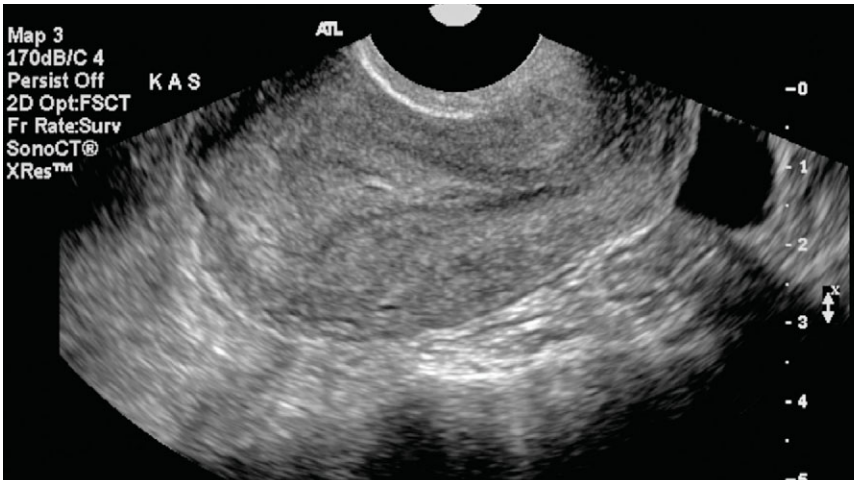

>Empty uterus. No intrauterine pregnancy is seen in this image.

palpation and decreased bowel sounds. No mass, rebound, or guarding was noted. Pelvic exam revealed a closed cervical os with no blood or tissue and no cervical motion tenderness. There was no tenderness over the uterus, but mild tenderness in the right adnexa was noted; no palpable masses were identified.

Lab values showed an elevated white blood cell count of 21,000/mm^3. Her hemoglobin level was 8.5 g/dl; hematocrit, 25.1%; and platelet count, 331,000/mm^3. Her basic metabolic profile and liver function tests were within normal limits.

The patient had a positive urine pregnancy test. The quantitative serum beta human chorionic gonadotropin (ß-hCG) was 15,000 mIU/ml. Transabdominal and transvaginal ultrasound showed a complex mass in the right adnexa with positive cardiac activity and a moderate amount of complex fluid in the pelvis, consistent with a ruptured ectopic pregnancy.

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Chlamydial and gonorrheal infections can double the risk of ectopic pregnancy.

An ob/gyn consult was obtained and the patient was taken emergently to surgery. Exploratory laparotomy revealed a ruptured ectopic pregnancy with more than a liter of blood in the abdomen. A right salpingectomy was performed and the patient was discharged home in good condition two days later.

LOOK BEYOND A "NORMAL" EXAM

Ms. L, also 20 years old, came to the emergency department after one day of vaginal spotting. She had not passed clots or tissue. She had not had any abdominal or pelvic pain. She'd had a positive home pregnancy test; her last menstrual period was seven weeks earlier. A previous pregnancy ended in a spontaneous abortion. She had no history of STDs or pelvic surgery.

On exam, the patient was afebrile and had vital signs within normal limits. Her physical exam was normal, including no pain on palpation. Speculum and bimanual exams were unremarkable, with no evidence of vaginal bleeding, adnexal masses, or tenderness.

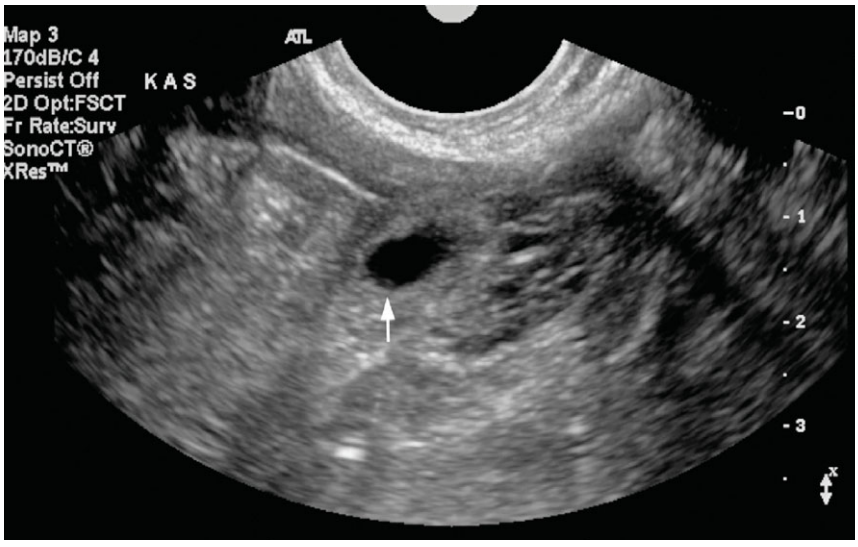
Lab values included a complete blood count and basic metabolic profile within normal limits and a quantitative ß-hCG of 6500 mIU/ml. Transabdominal and transvaginal ultrasound showed an empty uterus (see image) with a complex mass noted in the left ovary (see image on page 13) measuring 1.4 x 1.2 x 1.6 cm with a 6.6-mm anechoic center consistent with an ectopic pregnancy. A small amount of fluid was noted in the pelvis.

An ob/gyn physician was consulted and saw the patient in the emergency department. Ms. L elected to be treated with methotrexate and was scheduled for follow-up as an outpatient on days 4 and 7. Her quantitative ß-hCG increased to 11,700 mIU/ml on day 4 and then declined to 8300 mIU/ml on day 7. She did well and did not require surgery.

KNOW THE RISK FACTORS

The most common site for an ectopic pregnancy is within the fallopian tube, the most common reason is fallopian tube pathology, and the most common risk factor is pelvic inflammatory disease (see box on page 14). Chlamydial and gonorrheal infections can double the risk of ectopic pregnancy. Studies have shown that with subsequent infections more damage is done to the fallopian tubes.

Other major risk factors for ectopic pregnancy include previous ectopic pregnancy and a history of tubal surgery. In one study of 10,000 women who



>Ectopic pregnancy. Complex mass in left adnexa.

underwent tubal sterilization, the ectopic pregnancy rate was 7.3 per 1000 cases over 10 years. The probability of pregnancy over 10 years after tubal sterilization was 18.5 per 1000 cases. Although pregnancy is uncommon after a sterilization procedure, a high percentage of those cases are ectopic.

Risk factors also include a history of smoking and multiple sexual partners, which increases the risk of pelvic inflammatory disease. Women who use an intrauterine device (IUD) have an overall lower incidence of ectopic pregnancy than those who do not use such a device, but that is due to the overall lower incidence of pregnancy. Women who use an IUD and do get pregnant actually have a higher incidence of ectopic pregnancy.

A woman older than 35 also has a higher risk of ectopic pregnancy, most likely from the cumulative effects of infections and damage to the fallopian tubes. Women aged 35 to 44 have three to four times the risk of women aged 15 to 24.

A newly emerging risk factor for ectopic pregnancy comes from recent advances in the field of fertility and assisted reproductive techniques. There appears to be a two- to threefold increase in ectopic pregnancy and an increased risk of heterotopic pregnancy (a simultaneous intrauterine pregnancy [IUP] and an ectopic pregnancy) in women undergoing fertility treatment. Heterotopic pregnancy occurs in 1 in 4000 pregnancies in the general population, but in women receiving reproductive assistance, the rate of heterotopic pregnancy is reported as high as 1%.

SPECTRUM OF SYMPTOMS

Women can present to the emergency department with a wide range of symptoms, from the classic triad of abdominal pain, vaginal bleeding, and a recent history of amenorrhea to hypovolemic shock. Most women with an ectopic pregnancy have some abdominal pain or discomfort; however, about 10% have no abdominal discomfort at all. About half have vaginal bleeding.

In a study involving first-trimester women who presented to the emergency department with abdominal pain or vaginal bleeding, those who had moderate to severe "sharp" pain in a lateral or bilateral abdominal location were more likely to have an ectopic pregnancy. Pain in the midline correlated with a reduced risk for ectopic pregnancy. The study did not find any significant predictive risk in the amount of vaginal bleeding, passing of tissue, or vital signs, including tachycardia or hypotension, in patients with ectopic pregnancy. Interestingly, however, if an IUP is not detected by ultrasound, then mild to no vaginal bleeding is a greater risk for ectopic pregnancy compared with moderate to severe vaginal bleeding.

On physical exam, vital signs are a poor predictor for ectopic pregnancy, even ruptured ectopic pregnancy. There are case reports in which a patient presented with a normal heart rate or even bradycardia while having a large amount of blood in the peritoneum from a ruptured ectopic pregnancy. The bradycardia response seen in ectopic pregnancy is thought to be due to an increase in vagal stimulation.

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Risk Factors for Ectopic Pregnancy

- history of pelvic inflammatory disease
- previous ectopic pregnancy
- history of pelvic or tubal surgery
- in utero exposure to diethylstilbestrol
- age over 35
- smoking

With such a variety of possible signs and symptoms, it is imperative to maintain a low threshold of suspicion to investigate for ectopic pregnancy. For all women of childbearing age, ectopic pregnancy must be in the differential diagnosis and ruled out, if possible. A thorough physical exam should be performed on all patients with suspected ectopic pregnancy, including a pelvic exam. Although more than a third of patients have no adnexal mass or tenderness, cervical motion tenderness or abdominal peritoneal signs should heighten suspicion for ectopic pregnancy, including a ruptured ectopic pregnancy.

FOLLOW-UP TESTS AND IMAGING STUDIES

Ideally, the diagnosis of ectopic pregnancy should be made on the patient's first visit to the emergency department. However, many cases are not clear-cut, and even in the stable patient follow-up tests and imaging studies are necessary.

Any woman of reproductive age presenting to the emergency department with vaginal bleeding and pelvic or abdominal symptoms needs to have a urine pregnancy test. If positive, further investigation is needed to confirm a normal IUP. Women with a positive urine pregnancy test should also have a quantitative serum ß-hCG; blood type with Rh factor; and pelvic ultrasound, including transvaginal and transabdominal studies.

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A small amount of anechoic pelvic fluid is a normal ultrasound finding.

Bedside transabdominal ultrasound can be performed by the emergency physician trained in ultrasonography to detect later intrauterine pregnancies with fetal movement and cardiac activity. However, unlike transvaginal ultrasound, it is a suboptimal study in looking for an IUP in early pregnancy, as well as in looking for adnexal masses or abnormalities that would be consistent with an ectopic pregnancy.

If an IUP is seen without any adnexal abnormalities, ectopic pregnancy is ruled out. The exception, while rare, is a heterotopic pregnancy. For a patient involved in reproductive assistance, a thorough investigation of the adnexa is needed to rule out heterotopic pregnancy; alert her obstetrician for close follow-up. If no IUP is seen, the use of the serial quantitative ß-hCG is critical.

Advances in ultrasound technology have led to very detailed and high-resolution pictures of the adnexa and uterus. Intrauterine pregnancies should be seen on transvaginal ultrasounds with a quantitative serum ß-hCG of 1500 to 1800 mIU/ml. A gestational sac should be seen on transvaginal ultrasound with a ß-hCG over 1500 mIU/ml and about five weeks after the last menstrual period. A yolk sac should be seen on transvaginal ultrasound with a ß-hCG of 2500 mIU/ml and about five to six weeks after the last menstrual period. A fetal pole should be seen on transvaginal ultrasound with a ß-hCG of 5000 mIU/ml with cardiac activity around six to seven weeks after the last menstrual period. Note that patients with multiple gestations could have a significant delay in reaching these ß-hCG levels.

Patients with a low quantitative serum ß-hCG should still have a transvaginal ultrasound to evaluate the adnexa and pelvis for free fluid. Although a corpus luteal cyst can be seen in the adnexa in a normal pregnancy, 66% of ectopic pregnancies will have abnormal adnexal findings. The most common adnexal findings include a tubal ring, complex mass, or live extrauterine embryo. A small amount of anechoic pelvic fluid is a normal ultrasound finding; however, a moderate to large amount of echoic fluid should warrant concern for clotted blood and a ruptured ectopic pregnancy.

Pregnant women presenting to the emergency department with ultrasound findings of an empty uterus and abnormal adnexa findings should have an immediate ob/gyn consult for an ectopic pregnancy. Women with quantitative ß-hCG levels greater than 1500 mIU/ml, an empty uterus, and normal adnexa should have a consult and close follow-up with an ob/gyn physician or return to the emergency de-

partment in 48 hours. A repeat ultrasound should be ordered; the patient's ß-hCG should increase by 66% to 100% within two days. If an IUP is not seen on repeat exam, an immediate ob/gyn consult should be ordered for suspected ectopic pregnancy. Women with declining ß-hCG levels most likely had a spontaneous abortion, but should still follow up with an ob/gyn until the ß-hCG reaches zero or below a detectable level. All women with unstable vital signs and possible ectopic pregnancy should have immediate consultation and surgery.

Women presenting with quantitative ß-hCG levels below 1500 mIU/ml present a unique diagnostic dilemma. Those who have vaginal bleeding or pelvic pain may have a normal early pregnancy, spontaneous abortion, or ectopic pregnancy. Again, abnormal adnexal findings should prompt an immediate ob/gyn consult. Women with no abnormal adnexal findings and a minimal amount of pelvic fluid can be followed up by an ob/gyn or in the emergency department for repeat ß-hCG and ultrasound in 48 hours.

Women at risk for an ectopic pregnancy who do not wish to continue the pregnancy have one more diagnostic test available to them. If they have vaginal bleeding and no conclusive signs of either an IUP or ectopic pregnancy, they can undergo dilation and curettage by an ob/gyn. The presence of chorionic villi confirms a failed IUP and ends the workup for ectopic pregnancy. No chorionic villi on pathology requires further investigation or treatment for possible ectopic pregnancy.

TREATMENT: MEDICAL OR SURGICAL?

Women with ectopic pregnancy have two basic treatment options—medical and surgical. Conservative medical treatment involves single or multiple injections with methotrexate, an antimetabolite that interferes with DNA synthesis. The easiest regimen is a one-time intramuscular dose (50 mg/m^2 of body surface area).

Typically, it takes a couple of days for the patient's quantitative ß-hCG to drop after medical therapy. Patients are required to follow up with a ß-hCG on days 4 and 7 after treatment. If ß-hCG does not decline by at least 15% between days 4 and 7, a second dose of methotrexate should be given. If ß-hCG drops by more than 15%, weekly blood tests should be ordered until it is less than 10 mIU/mL.

Single-dose methotrexate therapy should be reserved for cases of early ectopic pregnancy with serum quantitative ß-hCG less than 5000 mIU/ml. Those patients have a 97% rate of success. When the ß-hCG is greater than 5000 mIU/ml, single-dose therapy is 14% more likely to fail.

Methotrexate should not be used in patients with a large adnexal mass, fetal cardiac activity, or signs of a ruptured ectopic pregnancy on ultrasound, nor in patients who have liver, renal, or peptic ulcer disease or are unlikely to adhere to treatment.

Although side effects are usually mild and transient at the low dosage used in patients with ectopic pregnancies, it's important to remember that methotrexate has many known adverse effects that can be confused with failed treatment or ruptured ectopic pregnancy. Patients can expect to experience nausea, vomiting, and diarrhea. A small elevation in liver enzymes is not uncommon (it's standard practice for a gynecologist to obtain baseline liver enzymes prior to initiating methotrexate therapy).

The most common adverse effects seen with methotrexate therapy are abdominal pain, stomatitis, and conjunctivitis. Pain may simply be an anticipated treatment effect, but a ruptured ectopic pregnancy must also be considered. Close ob/gyn follow-up is crucial. The patient may need repeat ultrasound and abdominal exams if abdominal pain becomes more severe or changes in quality. She also may need to be admitted to the hospital for close observation if abdominal pain increases after she starts methotrexate treatment. Abnormalities in vital signs also may indicate a ruptured ectopic pregnancy and should not be attributed simply to treatment side effects.

Surgery is the gold standard for diagnosis and treatment. Various surgical techniques are available, ranging from laparoscopy with salpingostomy to exploratory laparotomy with salpingectomy. Surgeons can take a minimally invasive approach with laparoscopy to treat ectopic pregnancy. However, if immediate treatment is required in the case of a ruptured ectopic pregnancy or better exposure is needed, exploratory laparotomy is the approach of choice.

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Once inside the pelvis, the surgeon has two options: salpingectomy or salpingostomy. The patient's

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desire for future pregnancy is an important discussion that should take place prior to surgery. If the contralateral fallopian tube appears healthy and the diseased tube appears severely damaged, salpingectomy is the treatment of choice. It has a success rate near 100%, since the whole fallopian tube is removed, leaving a good fallopian tube with fertility intact. In theory, salpingostomy helps preserve fertility, although the risk of residual ectopic pregnancy is 8%.

RISKY SCENARIOS, SAFER OUTCOMES

Ectopic pregnancy is a deadly condition that can present to the emergency department in a wide variety of clinical scenarios. With a high level of suspicion, the astute physician should be able to diagnose ectopic pregnancy on the first visit or at least set up appropriate follow-up to rule it out. With the use of quantitative serum ß-hCG and transvaginal ultrasound, it has become easier to identify ectopic pregnancy early on and provide more treatment options. And that means your patient may have to stay only a short time in the hospital, with a quick recovery or even go home directly from the emergency department. □

SUGGESTED READING

Adhikari S, et al.: Diagnosis and management of ectopic pregnancy using bedside transvaginal ultrasonography in the ED: a 2-year experience. *Am J Emerg Med* 25(6):591, 2007.

Centers for Disease Control and Prevention: Current trends in ectopic pregnancy – United States, 1990-1992. *MMWR Morb Mortal Wkly Rep* 44:46, 1995.

Dart RG, et al.: Predictive value of history and physical examination in patients with suspected ectopic pregnancy. *Ann Emerg Med* 33(3):283, 1999.

Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. *Ann Emerg Med* 33(3):310, 1999.

Kaplan BC, et al.: Ectopic pregnancy: prospective study with improved diagnostic accuracy. *Ann Emerg Med* 28(1):10, 1996.

Kohn MA, et al.: Beta-human chorionic gonadotropin levels and the likelihood of ectopic pregnancy in emergency department patients with abdominal pain or vaginal bleeding. *Acad Emerg Med* 10(2):119, 2003.

Peterson HB, et al.: The risk of ectopic pregnancy after tubal sterilization. *N Engl J Med* 336(11):762, 1997.

Somers MP, et al.: Ruptured heterotopic pregnancy presenting with relative bradycardia in a woman not receiving reproductive assistance. *Ann Emerg Med* 43(3):382, 2004.

Walker JJ: Ectopic pregnancy. *Clin Obstet Gynecol* 50(1):89, 2007.