

Sahoko H. Little, MD;
Pamela G. Rockwell, DO
Department of Family
Medicine, University of
Michigan, Ann Arbor

✉ sahoko@med.umich.edu

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Ectopic pregnancy: Zero in on these lab and imaging clues

Quantitative β -hCG measurements and transvaginal ultrasound findings interpreted in light of a β -hCG “cutoff” can reliably guide clinical decisions.

PRACTICE RECOMMENDATIONS

› Administer a urine pregnancy test for women of childbearing age who present with abdominal pain or vaginal bleeding. **(C)**

› Initiate quantitative beta-human chorionic gonadotropin testing and order transvaginal ultrasound for women with abdominal pain or vaginal bleeding and a positive urine pregnancy test, but no confirmation of intrauterine pregnancy by abdominal ultrasound. **(B)**

› Refer hemodynamically stable patients with ectopic pregnancy for laparoscopic salpingostomy. For selected patients, an alternative is medical treatment with methotrexate. **(A)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE 1 ▶ Helen, who is 31 years old and G1P0, comes in to the office with a 10-day history of intermittent vaginal spotting without pelvic pain. A home pregnancy test 2 weeks earlier was positive, and this is a desired pregnancy. She has had no gynecologic disorders. It has been 6 weeks since her last menstrual period. Her vital signs are normal and her abdominal and pelvic exams are unremarkable. The cervical os is closed and there is a small amount of blood in the vaginal vault. Her family physician (FP) draws blood to measure the level of beta-human chorionic gonadotropin (β -hCG) and orders a transvaginal ultrasound (TVUS).

CASE 2 ▶ Mary is 28 years old and G2P1. She has experienced intermittent vaginal spotting and moderate pelvic discomfort for 3 days. She fears a return of pelvic inflammatory disease (PID). Her period is one week late and the office pregnancy test is positive. Her vital signs are normal. She has no cervical motion tenderness, but there is mild right adnexal tenderness to palpation. Her FP draws blood for a serum β -hCG level and orders a TVUS.

Assess physical and history findings for perspective

Abdominal or pelvic pain and vaginal bleeding in the first trimester are the most common presenting symptoms of ectopic pregnancies.¹ Physical examination will often elicit lateral or bilateral abdominal or pelvic tenderness, peritoneal signs, and cervical motion tenderness. But such findings (or their absence) cannot confirm (or exclude) the diagnosis with a high level of reliability.² A woman with a positive pregnancy test and pelvic pain or vaginal bleeding may instead have a normal pregnancy, spontaneous abortion (failing intrauterine preg-

nancy), or a disorder such as PID, acute appendicitis, tubo-ovarian abscess, or ovarian torsion.

In an early ectopic pregnancy, vital signs are usually normal. Even in cases of ruptured ectopic pregnancy, hypotension or tachycardia is present in <40% of cases.³

■ **Factors conferring a relative risk ratio >2 for ectopic pregnancy** are a previous ectopic pregnancy; documented tubal pathology or tubal instrumentation (eg, tubal sterilization or tubal corrective surgery); assisted reproductive technology such as in vitro fertilization; history of infertility; smoking; or a history of PID.⁴⁻¹¹

Proceed with a laboratory and imaging strategy

When a woman who has tested positive for pregnancy presents with abdominal pain or vaginal bleeding and a normal intrauterine pregnancy (IUP) has not been confirmed by abdominal ultrasound, request a quantitative measurement of the β -hCG level and arrange for urgent TVUS.^{12,13} If pregnancy has been unsuspected in a patient with these symptoms, perform a urine test for pregnancy immediately and follow up with ultrasound.¹⁴

If TVUS reveals either IUP or ectopic pregnancy, management is relatively straightforward. However, an inconclusive TVUS result indicates a “pregnancy of unknown location” (PUL) and necessitates further testing and follow-up to achieve a final diagnosis.¹⁵

Monitor β -hCG levels

Valuable diagnostic measures include documenting the initial serum level of β -hCG, monitoring the subsequent rise-or-fall pattern in the level, and making use of the “discriminatory cutoff” value.

β -hCG, made by placental cells, can be detected in the mother’s blood approximately 11 days after conception, and in the urine 12 to 14 days after conception. The serum β -hCG level normally doubles every 48 to 72 hours until it reaches its peak in the first 8 to 11 weeks of pregnancy. The level then declines and plateaus.

■ **“Discriminatory cutoff”** is a widely accepted concept signifying the level of β -hCG

at which a normal IUP can be visualized by ultrasonography with sensitivity approaching 100%.¹⁶ Generally an intrauterine sac can be visualized by abdominal ultrasound when the serum β -hCG level is >6500 mIU/mL.¹⁷ Visualization with TVUS (the preferred modality) has been demonstrated when the serum β -hCG level is as low as 1000 mIU/mL.¹⁷ However, the generally accepted cutoff range is 1500 to 2500 mIU/mL, based on several studies.^{13,18-20} The absence of an IUP in a pregnant woman with pain or bleeding and a β -hCG level above the cutoff implies an ectopic pregnancy¹⁸ or a failing IUP (spontaneous abortion).

■ **Serial β -hCG levels.** When the β -hCG level is below the discriminatory cutoff, serial β -hCG measurements every 2 to 3 days are needed to assess viability of the pregnancy. A “normal rise” of β -hCG indicates early viable pregnancy and “normal fall” indicates spontaneous abortion. An analysis of 287 women with abdominal pain or vaginal bleeding who ultimately had normal uterine pregnancies found that the median slope for rise of β -hCG was 1.5 times (50% increase) in 1 day, and 2.24 times (124% rise) in 2 days.²¹ A rapid fall in β -hCG is consistent with a miscarriage that may resolve spontaneously. However, if the β -hCG level does not decline by 21% to 35% in 2 days, suspect ectopic pregnancy.²¹

Arrange for transvaginal ultrasound

TVUS is the imaging modality of choice for diagnosis of ectopic pregnancy, with a sensitivity of 87.0% to 99.0% and specificity of 94.0% to 99.9%.²² Arrange for TVUS when a woman has abdominal pain or vaginal bleeding and a positive urine pregnancy test, even if the β -hCG level is lower than the discriminatory cutoff of 1500 to 2500 mIU/mL.^{13,18-20} Ordering TVUS and β -hCG level at the same time yields the best outcome for diagnosis,¹⁹ while varying the discriminatory zone alone has not improved diagnosis.^{18,23}

Other novel markers

The use of serum progesterone and other novel markers such as inhibin A, activin A, creatinine kinase, vascular endothelial growth factor, and cancer antigen 125 in the diagnosis of ectopic pregnancy has been



A woman with a positive pregnancy test and pelvic pain or vaginal bleeding may have a normal pregnancy, a spontaneous abortion, or a disorder such as PID.

➤ **An analysis of 287 women with abdominal pain or vaginal bleeding who ultimately had normal uterine pregnancies found that the median slope for rise of β -hCG was 1.5 times in 1 day and 2.24 times in 2 days.**

studied extensively. To date, no single marker has demonstrated high sensitivity and specificity in differentiating ectopic pregnancy.²⁴ However, when the initial progesterone level is ≤ 10 nmol/L (equivalent to 31.4 ng/mL) in a woman with a PUL, the probability that she will require any intervention is reported to be low (4 cases out of 227 PUL cases).²⁵ Multiplex tools to combine multiple biomarkers may become available in the future.

Evacuation of uterine contents

When the β -hCG level is above the discriminatory cutoff but no evidence of an extrauterine or intrauterine pregnancy can be found by TVUS, the patient likely has a failing IUP or impending abortion. Some experts suggest considering evaluation of the uterine contents by dilation and curettage (D&C) or manual vacuum extraction at this time, to differentiate an abnormal intrauterine gestation from an ectopic pregnancy. Barnhart found that more than one-third of such cases were due to a failed uterine pregnancy, not ectopic pregnancy.²⁶

If, after a D&C or manual extraction, chorionic villi are not confirmed by pathologic examination of the uterine contents, then treat as an ectopic pregnancy. Some clinicians alternatively recommend checking the β -hCG level again in 12 to 24 hours, expecting $\geq 15\%$ decline with a spontaneous abortion.²⁷ Alternatively, some recommend using methotrexate (MTX) without D&C to avoid unnecessary medical and surgical treatment.²⁶

CASE 1 ▶

Helen's serum β -hCG level is 4500 mIU/mL, and the TVUS image the next day shows an echogenic mass next to the right ovary—highly suspicious for ectopic pregnancy.

CASE 2 ▶

Mary's TVUS does not show any evidence of IUP or any abnormality in either adnexa. Her serum β -hCG level is 650 mIU/mL. She has a PUL. Her FP informs her that she may have an early normal pregnancy, a failed IUP, or an ectopic pregnancy. She agrees to have her serum β -hCG measured every 2 days. Her β -hCG level increases to 1100, 2000, and 3500 mIU/mL,

in 2, 4, and 6 days, respectively. TVUS on the sixth day is still nondiagnostic.

Treatment of ectopic pregnancy: Surgical vs medical

For hemodynamically unstable patients, laparotomy is still the mainstay of therapy. However, with early diagnosis and a stable patient, options are minimally invasive surgical intervention via laparostomy or medical management with MTX in a single or multidose regimen. Surgical and medical treatments have comparable outcomes, as documented by a Cochrane review.²⁸

The risk of recurrent ectopic pregnancy after MTX treatment and salpingostomy is similar—about 10%.²⁹ Ipsilateral tubal patency as documented by hysterosalpingography after MTX treatment or salpingostomy was reported to be equal.²⁸ Reproductive outcomes after either treatment were similar, as well.³⁰

■ **We recommend urgent referral** for OB/GYN consultation if the diagnosis of ectopic pregnancy is made by TVUS, since the recommended treatment is laparoscopic salpingostomy. In the case of a PUL, we recommend referral to an OB/GYN when the serum β -hCG level is above the discriminatory cutoff of 1500 to 2500 mIU/mL without signs of IUP as seen by a gestational sac via TVUS. When an urgent referral is not possible, initiate medical treatment. Regardless of the treatment method, give anti-D immunoglobulin to any woman whose blood is Rh negative (no D-antigen) and who has not been sensitized to D-antigen.

Surgical management

Laparoscopic salpingostomy is the preferred surgical treatment for ectopic pregnancy. A Cochrane review meta-analysis of 35 randomized controlled trials (RCTs) on intervention of ectopic pregnancy concluded that, compared with laparotomy, laparoscopy results in shorter operative time, less blood loss, less analgesia, shorter hospital stays, and greater cost effectiveness.²⁸ Another meta-analysis of 15 RCTs concluded that laparoscopic salpingostomy is the most cost-effective treatment for ectopic pregnancy.³¹

CONTINUED ON PAGE 684

CONTINUED FROM PAGE 680

TABLE

Monitoring methotrexate therapy for ectopic pregnancy

Obtain a complete blood count with differential and liver and renal function tests before starting any regimen.

Regimen	Surveillance
Single dose* Methotrexate, 50 mg/m ² IM	Measure β -hCG level on Days 4 and 7: If difference $\geq 15\%$, repeat weekly until undetectable If difference $< 15\%$, repeat methotrexate dose and begin new Day 1 If fetal cardiac activity present on Day 7, repeat methotrexate dose and begin new Day 1 Refer for surgical treatment if β -hCG level is not decreasing or fetal cardiac activity persists after 3 methotrexate doses
2 dose Methotrexate, 50 mg/m ² IM, Days 0, 4	Follow up as for single-dose regimen
Multidose (up to 4 doses) Methotrexate, 1 mg/kg IM, Days 1, 3, 5, 7 Leucovorin, 0.1 mg/kg IM, Days 2, 4, 6, 8	Measure β -hCG level on Days 1, 3, 5, and 7 Continue alternate-day injections until β -hCG level decreases $\geq 15\%$ in 48 hours or 4 doses of methotrexate have been given. Then, weekly β -hCG measurement until undetectable

β -hCG, beta-human chorionic gonadotropin; IM, intramuscularly.

*Preferred treatment if low initial β -hCG level.

Adapted from: Seeber BE, et al. *Obstet Gynecol.* 2006.²⁷

Medical management with methotrexate

This folic acid antagonist is highly effective in treating ectopic pregnancy, and is usually given intramuscularly for this indication. Clinicians who use this chemotherapeutic agent must be familiar with its dosing regimen, contraindications, and possible adverse effects. Multidose MTX is more effective than surgery, but more expensive.³² Single-dose MTX has a higher failure rate than laparoscopic salpingostomy, especially in patients with higher β -hCG levels.³²

■ **The best candidate for medical therapy** is the woman who is asymptomatic, motivated, and compliant. Absolute contraindications to single-dose MTX include the following:

- breastfeeding
- overt or lab evidence of immunodeficiency
- alcoholism, alcoholic liver disease, or other chronic liver disease
- preexisting blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia, or significant anemia
- known sensitivity for methotrexate

- acute pulmonary disease
- peptic ulcer disease
- hepatic, renal, or hematologic dysfunction, and several metabolic diseases.³³

■ **Dosing regimen.** The 3 general dosing schemes of single dose, 2-dose, and multidose (up to 4 doses) are shown in the TABLE. These were recommended by the American College of Obstetrician and Gynecologists (ACOG).³³

■ **Single dose vs multidose.** The single-dose treatment is easier to administer and monitor and is most cost effective, but it may have a higher failure rate than the multidose regimens.²⁸ The best prognostic indicator of successful treatment with single-dose MTX is the initial β -hCG level. The lower the initial level, the higher the success rate. The reported failure rate is 1.5% if the initial β -hCG level is < 1000 mIU/mL; 5.6% with 1000 to 2000 mIU/mL; 3.8% with 2000 to 5000 mIU/mL; and 14.3% with 5000 to 10,000 mIU/mL.³⁴ ACOG has outlined relative contraindications to single-dose MTX: ectopic pregnancy larger than 3.5 cm and the presence of fetal cardiac activity. Both cor-

relate with an increased failure rate. Patients with PUL and low β -hCG levels are good candidates for single-dose MTX treatment.

Monitoring efficacy of treatment

Serum β -hCG levels indicate response to medical and surgical therapy. After salpingostomy, the serum β -hCG level declines rapidly within the first 4 days, and then more gradually, with mean resolution occurring at about 20 days. In contrast, after single-dose MTX, the mean serum β -hCG level increases for the first 4 days and then gradually declines, with a mean resolution at 27 days.³⁵ The guideline for surveillance is shown in the TABLE.

CASE 1 ▶

The FP counsels Helen on the risks and benefits of surgery and MTX treatment for her ectopic pregnancy, and she elects to have a laparoscopic salpingostomy. The FP refers Helen to an OB/GYN via the emergency department on the same day. Helen does well.

After the surgery, her β -hCG is monitored every 2 days until it decreases to 1000 mIU/mL, then every week until it is negative.

CASE 2 ▶

The FP advises Mary that an OB/GYN would likely recommend a D&C for her PUL, as her β -hCG level is above the discriminatory cutoff and the TVUS does not show a viable IUP. After discussing MTX treatment and manual vacuum aspiration of the uterine contents, Mary elects to have the MTX treatment and receives the 2-dose protocol. Her β -hCG level is 4210 mIU/mL on Day 1—higher than her level prior to the methotrexate treatment, but expected. Levels drop to 3635, 3102, and 2214 mIU/mL on Days 4, 7, and 10, respectively. Mary receives weekly surveillance until her level decreases to 0, which it did in a month. **JFP**

CORRESPONDENCE

Sahoko H. Little, MD, Room 2300, Lobby H, 24 Frank Lloyd Wright Drive, Ann Arbor, MI 48105-9755; sahoko@med.umich.edu

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▶ The single-dose treatment is easier to administer and monitor and is most cost effective, but it may have a higher failure rate than the multidose regimens.

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