Ticking timebombs: ectopic pregnancy **Twitter/Instagram: @emboardbombs**

Check out our other study guides as well as free podcasts and free board review quizzes at www.emboardbombs.com

Author: Blake Briggs, MD
Peer Reviewer: Iltifat Husain, MD

Objectives: the learner will recognize the board and clinically relevant presentation of ectopic pregnancy, the learner will be able pursue the proper diagnostic evaluation of ectopic pregnancy and general management plan of these patients.

Introduction

An ectopic pregnancy is simply an extrauterine pregnancy. They account for 2% of all pregnancies. The vast majority (96%) occur in the fallopian tube, however other sites include cervix, hysterotomy, ovary, or even abdomen. Very rarely, there can be both an intrauterine and ectopic pregnancy, which is coined a heterotopic pregnancy. Rates of ectopic pregnancies have been steadily increasing, however >40% of cases are initially misdiagnosed as a non-pregnancy condition or suspected intrauterine pregnancy (IUP). Failure to appropriately and quickly manage this common pathology leads to significant morbidity and mortality.

Risk factors

The boards love asking about these. The biggest risk factor is previous ectopic pregnancy (#obvious). Other major historical risk factors include uterine or tubal scarring from surgery (e.g. D&C, PID), increased maternal age, smoking, use of assisted reproductive techniques (ART) like in vitro fertilization.
Despite the popular misconception, IUD presence does *not* increase the overall risk of ectopic pregnancy, but a pregnancy with an IUD is more often an ectopic one.

Presentation

Most commonly, females will present with:
-Vaginal bleeding (76% of patients)
    -there is no measured amount of bleeding that is associated more with ectopics. Ranges from scant to heavy.
-Generalized abdominal pain (66%). Often non-focal tenderness on exam.
    -there is no pattern to the pain. No published data on one particular location of the pain either.
-Rupture in 18% of patients. Peritoneal signs are often present. Patient refuses to move.

A significant, and frightening, number of females may be asymptomatic as well.

Symptoms typically develop around 6-8 weeks after last menstrual period. Women may misinterpret their vaginal bleeding associated with the ectopic as their "normal menses".
Typical symptoms of pregnancy can also occur: breast tenderness, polyuria, nausea/vomiting.

Multiple resources state that the diagnosis of ectopic pregnancy should be considered in any female with vaginal bleeding or abdominal pain… let's expand that and make it easier.

You need to rule out ectopic pregnancy in ANY FEMALE OF REPRODUCTIVE AGE. We aren't saying you need to do major workups, but if a female of reproductive age presents to the ED, have a very low suspicion for ordering a urine point of care pregnancy test.

Therefore, here's some major complaints we *always* order a UPT for: syncope or near-syncopal symptoms, abdominal pain, chest pain, nausea/vomiting, dizziness, lightheadedness, any GU complaint.
There might be others we left out, but these are the classic ones.

BIG questions to ask patients with +UPT:
-Gravidity and parity, history of prior ectopics (duh), birth control status, usage of in vitro fertilization, prior history of STDs, PID, surgical history.

Pelvic exam should be performed but suffers from relatively poor specificity and sensitivity. Your goal is to assess for presence of bleeding, its quantity, and confirm that the uterus is the source of bleeding.

Diagnosis

Workup of ectopics can quickly get… algorithmic and tedious. Here's an overview to keep you grounded:

1) Confirm patient is pregnant (UPT) — If negative UPT this conversation is over.
2) Is the patient hemodynamically stable? — If not, then "hold on to your butts" (to quote Samuel L Jackson)
3) Order a serum hCG, blood type, CBC, CMP — The blood type is the most commonly forgotten test
4) Perform bedside US vs order formal study
    a. Determine intrauterine vs ectopic pregnancy
    b. Coordinate management strategy with Ob/gyn

Boring, but necessary stuff you must know…

Human chorionic gonadotropin (hCG) is secreted into maternal circulation after implantation (~6 days after ovulation). Normally, hCG should double ~48 hours during the first 30 days; decline is concerning for failed pregnancy. Slower rise is concerning for ectopic

pregnancy or early intrauterine demise, but hCG alone it is *not* confirmatory and there is no common predictable pattern of hCG in certain pathologies.
In short, a single serum hCG level has very limited utility and it alone should not be used to make decisions (more on that below).

Hemodynamically unstable and +UPT with no palpable fundal height: This is an ectopic pregnancy until proven otherwise. The workup is simple. Send the labs we discussed above.
Most critically, do not delay in performing a **Bedside Gyn US with FAST exam** to look for rupture, ovarian pathology, or intrauterine pregnancy (transvaginal likely needed to visualize if <4-6 weeks).
Follow aggressive resuscitation algorithms (2 IVs, blood products), and promptly alert Ob/Gyn consultant.

Ultrasound
Transvaginal (TVUS): the best test to effectively exclude an ectopic pregnancy. There are only 3 possible options that can occur:

Option 1: Gestational sac *with* a yolk sac or embryo in the uterus = intrauterine pregnancy
Option 2: Gestational sac with or without yolk sac outside the uterus = ectopic pregnancy
Option 3: No pregnancy is identified = nondiagnostic

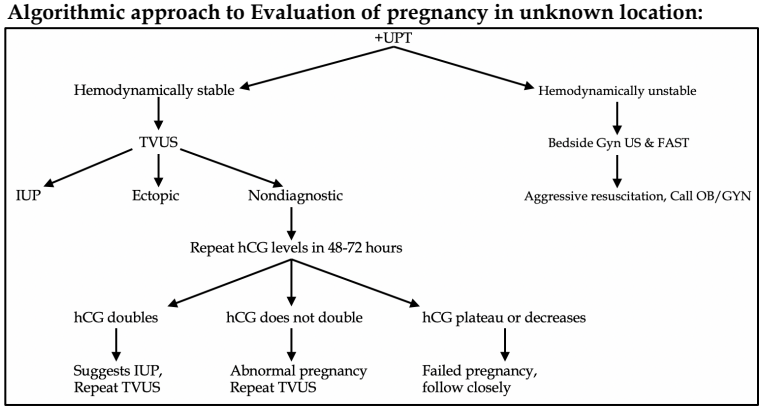
In confirmed ectopic cases, the most common finding is an extraovarian adnexal mass, at 89% of the time.
Presence of an intrauterine gestational sac alone does *not* confirm an IUP! In fact, an intrauterine "sac-like" structure (including a "double sac sign") could be a pseudogestational sac, which is a collection of blood and hypoechoic fluid in the uterine cavity that can be seen in ectopic pregnancy.
A small amount of clear fluid in the pelvis is physiologic, but echogenic free fluid in a woman with +UPT is highly associated with ectopic pregnancy. In a prospective study, finding echogenic fluid has a sensitivity of 56% and specificity of 96% for predicting ectopic pregnancy.

Option 1: ectopic pregnancy is effectively ruled out.

Option 2: move forward with medical or surgical management of ectopic pregnancy.

Option 3: if no pregnancy is identified (either IUP or ectopic), it is likely because gestation is too early to be visualized on ultrasound. This is a pregnancy of unknown location, and 8-40% turn out to be ectopic. Serial measurements of hCG should occur with a discussion to repeat TVUS in the future. See algorithm below for details.

Algorithmic approach to Evaluation of pregnancy in unknown location:



What about the magical "discriminatory zone"?
The discriminatory zone is defined as the hCG level above which one should see an IUP via US. On average, this is about 2000 mIU/mL for TVUS (about 6000 for Transabdominal US). Traditional teaching was that if a patient's serum hCG was below the cut-off value and the US showed no IUP, there was a "decreased risk" for EP. This has been found to simply not be accurate and there are even some studies to suggest the opposite (i.e. increased risk for ectopic pregnancy).
Therefore, we recommend not using the discriminatory zone alone to rule out ectopic pregnancy. There is no standard hCG level ectopic pregnancies are expected to present at. Remember, a single serum hCG level has very limited utility.

For patients with an elevated hCG, but a nondiagnostic US, this is a *pregnancy of unknown location*, and a wide range (8-40%) turn out to be ectopic. Repeat hCG measurement in about 48 hours should occur with a discussion to repeat TVUS (Figure 3). Serial hCGs that do not rise by about 66% in 48 hours is coined an *abnormal pregnancy* (ectopic or nonviable IUP). Besides stressing close Ob/Gyn follow up, very strict return precautions should be given.

What about the heterotopic pregnancy?
This is a feared pathology that very rarely occurs. In fact, its estimated to occur in 1 in 30,000 pregnancies. Therefore, in a female that has a confirmed IUP with no assisted reproductive techniques being used (ART), no further workup for heterotopic pregnancy needs to occur.

The risk of heterotopic pregnancy in those using ART is 1.5 per 1000 pregnancies. Expect similar nonspecific symptoms of ectopic pregnancy. High index of rupture due to misdiagnosis.
In these patients, besides an IUP, signs of heterotopic pregnancy are complex adnexal mass or fluid. Often falsely labeled as a corpus luteum cyst. In stable patients, laparoscopy is the treatment of choice.

Treatment overview
If an ectopic pregnancy is confirmed, treatment discussion should obviously involve Ob/Gyn. We briefly review it here for completeness sake and to educate the emergency provider.

All patients that are hemodynamically unstable, have significant free fluid on US, or have symptoms of rupture go to emergency surgery. That's easy enough.

Who qualifies for Methotrexate (MTX) therapy? This form of medical therapy has been found to be quite beneficial at reducing surgical exposure and its associated complications. You do *not* need to memorize these for exams but need to be familiar with them as you discuss care with Ob/Gyn.

-hCG <5000 mIU/mL
-No fetal cardiac activity
-No heterotopic pregnancy,
-Not currently breastfeeding
-No lab abnormalities to MTX
-Patient is willing and able to follow up

If ANY are not present, patients will require surgery.

References

1. Bouyer J, Coste J, Fernandez H, et al. Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. Hum Reprod 2002; 17:3224.
2. Alkatout I, Honemeyer U, Strauss A, et al. Clinical diagnosis and treatment of ectopic pregnancy. Obstet Gynecol Surv 2013; 68:571.
3. Zou S, Li X, Feng Y, et al. Comparison of the diagnostic values of circulating steroid hormones, VEGF-A, PIGF, and ADAM12 in women with ectopic pregnancy. J Transl Med 2013; 11:44.
4. Casanova BC, Sammel MD, Chittams J, et al. Prediction of outcome in women with symptomatic first-trimester pregnancy: focus on intrauterine rather than ectopic gestation. J Womens Health (Larchmt) 2009; 18:195.
5. Daya S. Human chorionic gonadotropin increase in normal early pregnancy. Am J Obstet Gynecol 1987; 156:286.
6. Jackson HT, Diaconu SC, Maluso PJ, et al. Ruptured splenic artery aneurysms and the use of an adapted fast protocol in reproductive age women with hemodynamic collapse: case series. Case Rep Emerg Med 2014; 2014:454923.
7. Nahum GG. Rudimentary uterine horn pregnancy. The 20th-century worldwide experience of 588 cases. J Reprod Med 2002; 47:151.
8. Dogra V, Paspulati RM, Bhatt S. First trimester bleeding evaluation. Ultrasound Q 2005; 21:69.
9. Doubilet PM, Benson CB, Bourne T, et al. Diagnostic criteria for nonviable pregnancy early in the first trimester. N Engl J Med 2013; 369:1443.
10. Barnhart KT, Sammel MD, Rinaudo PF, et al. Symptomatic patients with an early viable intrauterine pregnancy: HCG curves redefined. Obstet Gynecol 2004; 104:50.
11. Zee J, Sammel MD, Chung K, et al. Ectopic pregnancy prediction in women with a pregnancy of unknown location: data beyond 48 h are necessary. Hum Reprod 2014; 29:441.
12. Seeber BE, Barnhart KT. Suspected ectopic pregnancy. Obstet Gynecol 2006; 107:399.
13. Pisarska MD, Carson SA. Incidence and risk factors for ectopic pregnancy. Clin Obstet Gynecol 1999; 42:2.
14. Barrenetxea G, Barinaga-Rementeria L, Lopez de Larruzea A, et al. Heterotopic pregnancy: two cases and a comparative review. Fertil Steril 2007; 87:417.e9.
15. Hassiakos D, Bakas P, Pistofidis G, Creatsas G. Heterotopic pregnancy at 16 weeks of gestation after in-vitro fertilization and embryo transfer. Arch Gynecol Obstet 2002; 266:124.
16. Tal J, Haddad S, Gordon N, Timor-Tritsch I. Heterotopic pregnancy after ovulation induction and assisted reproductive technologies: a literature review from 1971 to 1993. Fertil Steril 1996; 66:1.
17. Clayton HB, Schieve LA, Peterson HB, et al. A comparison of heterotopic and intrauterine-only pregnancy outcomes after assisted reproductive technologies in the United States from 1999 to 2002. Fertil Steril 2007; 87:303.
18. Cole LA, Ladner DG, Byrn FW. The normal variabilities of the menstrual cycle. Fertil Steril 2009; 91:522.
19. Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. N Engl J Med 1999; 340:1796.
20. Mahendru AA, Daemen A, Everett TR, et al. Impact of ovulation and implantation timing on first-trimester crown-rump length and gestational age. Ultrasound Obstet Gynecol 2012; 40:630.
21. Johnson SR, Godbert S, Perry P, et al. Accuracy of a home-based device for giving an early estimate of pregnancy duration compared with reference methods. Fertil Steril 2013; 100:1635.