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Clinical Communications: OB/GYN

CHRONIC ECTOPIC PREGNANCY—TWO CASES OF ACUTE RUPTURE DESPITE NEGATIVE βHCG

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□ **Abstract—We present the cases of two women with chronic ectopic pregnancies who presented with acute tubal rupture and hemoperitoneum despite negative β-human chorionic gonadotropin (βhCG) pregnancy tests. The appropriate screening use of βhCG assays to ascertain pregnancy status, the mechanisms by which ectopic pregnancy may be seen with negative βhCG tests, and the limitations of various assays are discussed. One patient, not initially believed to be pregnant, underwent computed tomography (CT) scan. Experience with use of CT scan in ectopic pregnancy diagnosis is limited; our case illustrates some of the possible CT scan findings. These cases illustrate the potential for ectopic pregnancy to rupture with low, if not undetectable βhCG hormone levels, and consequently why it is not recommended to rely on quantitative βhCG levels to guide the decision to proceed with ultrasound imaging.**

□ **Keywords—ectopic pregnancy; βhCG; diagnosis; computed tomography**

INTRODUCTION

Ectopic pregnancy is a common disorder, occurring in 1.6 to 2.0% of all pregnancies (1,2). Because of the potential for tubal rupture and serious maternal morbidity or mortality, Emergency Physicians (EPs) must look for ectopic pregnancy in all women of childbearing age with abdominal pain or vaginal bleeding (3). Accepted diagnostic strategies initially rely on βhCG testing to determine pregnancy status (4). The absence of this pregnancy hormone is usually very reliable in excluding pregnancy, regardless of gestation location. Rare cases of ectopic pregnancy with negative modern βhCG assays have been reported previously; these gestations were often felt to be chronic in nature (5–9). Two cases are presented that show the catastrophic potential of an acute presentation despite undetectable βhCG by qualitative assays. βhCG assays are not 100% sensitive; in unstable or high suspicion cases, further diagnostic efforts are warranted.

CASE PRESENTATION

Case 1

A 28-year-old woman presented to the Emergency Department (ED) with a 14-h history of right lower quadrant abdominal pain, which was progressively increasing in intensity and associated with nausea. She reported normal onset of menses 4 days prior. Past medical history was unremarkable.

Physical examination revealed normal vital signs, with blood pressure 104/64 mmHg, and pulse 94 beats/min. The abdomen was tender in the right lower quadrant

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(RLQ) with mild guarding but no rebound tenderness. Pelvic examination revealed scant old blood in the vault. There was no cervical motion tenderness, and no adnexal tenderness or mass was appreciated.

Laboratory evaluation demonstrated a negative qualitative serum βhCG (Abbott Testpack Plus hCG-Combo®; βhCG sensitivity ≥ 25 mIU/mL). The hemoglobin was 11.7 s *g*/dL and white blood cell (WBC) count was 13.7×10^3/mm. A computed tomography (CT) scan of the abdomen and pelvis was obtained to look for appendicitis. The radiologist's initial interpretation was a large amount of ascites within the entire abdomen and pelvis, without any other significant abdominal abnormalities noted.

The fluid was thought to be possible pyoperitoneum due to ruptured appendicitis. During surgery the fluid was found to be hemoperitoneum. More than 750 cc was evacuated after which a mass with active bleeding was noted in the right salpinx. A Gynecologist was consulted who performed a right salpingotomy with evacuation of the contents. Pathology identified the contents as an ectopic pregnancy with decidual tissue, and immature chorionic villi showing degeneration with hemorrhage. Later review of the CT scan also revealed a 1.5 cm hyperdense area, which was interpreted as a probable hemorrhagic focus in the region of the cul-de-sac (Figure 1). The patient had an uneventful postoperative course and was discharged 2 days later.

Case 2

A 23-year-old nulliparous woman presented to the ED with severe bilateral lower abdominal sharp cramping pain that radiated to her right shoulder. The patient had experienced intermittent pelvic pain over the prior 2 months, for which she had been seen several times by her private Obstetrician/Gynecologist who had presumptively diagnosed pelvic inflammatory disease. No pregnancy test was performed as the patient had denied sexual activity and reported normal menstrual periods. The patient was treated with oral azithromycin 2 weeks before presentation. This resulted in some improvement in her pelvic pain until 3 days before ED presentation when her pain returned and subsequently intensified. Work-up for sexually transmitted disease was ultimately negative. Menses were normal over the past several months with the last period ending 2 days before presentation. The patient had spotting 1 day before presentation with some increase in pain.

Vital signs were blood pressure of 126/67 mm Hg and pulse 81 beats/min. Abdominal examination revealed diffuse tenderness to light palpation, greatest in the right lower quadrant. Guarding and rebound were present. Pelvic examination revealed scant blood in the vault, significant right adnexal tenderness, but no cervical motion tenderness. Orthostatic blood pressure measurement resulted in a standing systolic blood pressure of 50 mm Hg with the patient becoming pale and diaphoretic. Subsequent blood pressure measurements were in the 110/50 mm Hg range after several liters of intravenous crystalloid.

Laboratory tests revealed a negative qualitative urine βhCG (Abbott Testpack Plus hCG-Combo®; βhCG sensitivity ≥ 25 mIU/mL). Hemoglobin concentration fell from 12.0 s *g*/dL initially to 9.0 s *g*/dL four hours later. Ultrasound examination revealed an $8.3 \times 6.8 \times 5.0$ cm complex solid mass in the right adnexal area and a moderately large amount of free intraperitoneal (i.p.) fluid (Figure 2). The uterus and left ovary were normal. There was diminished blood flow to the mass and the right ovary was not visualized.

Because of the ultrasound findings and the patient's hypotension, the patient was taken emergently to the operating room. Pre-operative differential diagnosis included tubo-ovarian abscess, ovarian torsion, ovarian tumor, endometrioma, and ectopic pregnancy. An estimated 500 mL of blood was found within the peritoneum, with clot within the cul-de-sac. A salpingectomy was performed on the enlarged and bleeding right tube. The right ovary appeared normal.

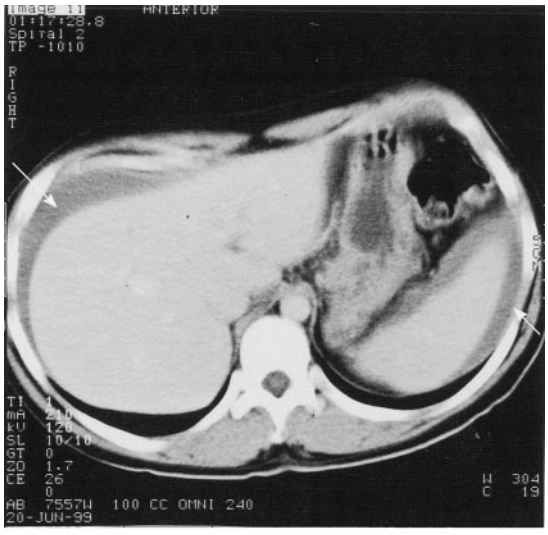
Grossly, the right fallopian tube specimen had clot and villi protruding from a $5 \times 2 \times 2$ cm rupture. Microscopic examination demonstrated immature chorionic villi with marked degeneration, hemorrhage within decidual tissue, and serosal adhesions. There were no fetal parts identified.

The patient had an uneventful post-operative course and was discharged home 3 days later.

DISCUSSION

These cases illustrate several important points to consider in the evaluation of acute abdominal pain in women of child bearing potential. These points include:

1. The inability to ascertain pregnancy status by menstrual or sexual history.
2. The occasional failure of qualitative βhCG assays to detect pregnancy.
3. The inability of low βhCG levels to exclude the presence of ectopic pregnancy, the inability to exclude catastrophic rupture, and the inability to predict the utility of imaging.
4. The utility of diagnostic imaging, including CT scan and ultrasound, in women with acute abdominal pain of unclear etiology.



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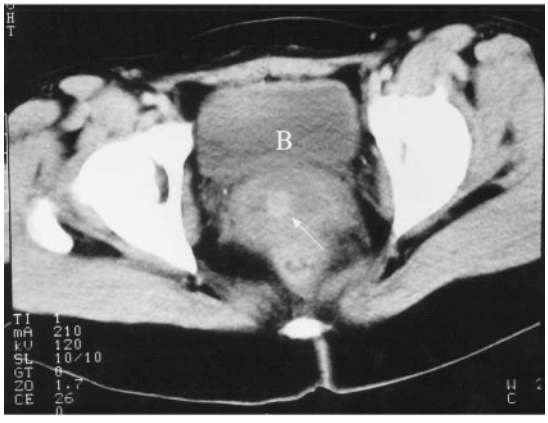

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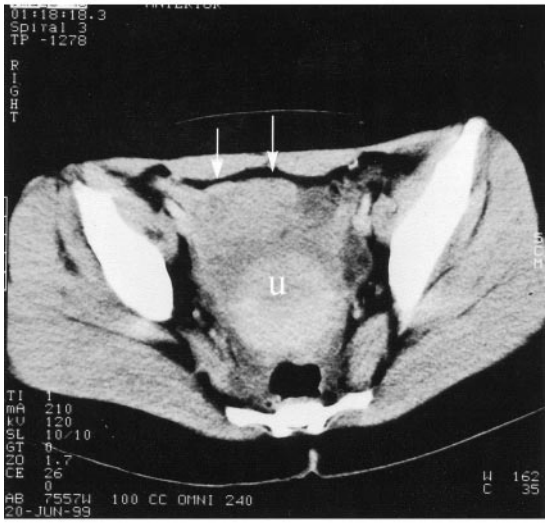

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Figure 1. Computed tomography scan from Case 1. Figure 1A: Significant free intraperitoneal fluid around liver (long arrow) and spleen (short arrow). Figure 1B: Hyperdense 1.5 cm focus (arrow) in the region of the cul-de-sac (B = bladder). Figure 1C: Mass (arrows) anterior to uterus (u).

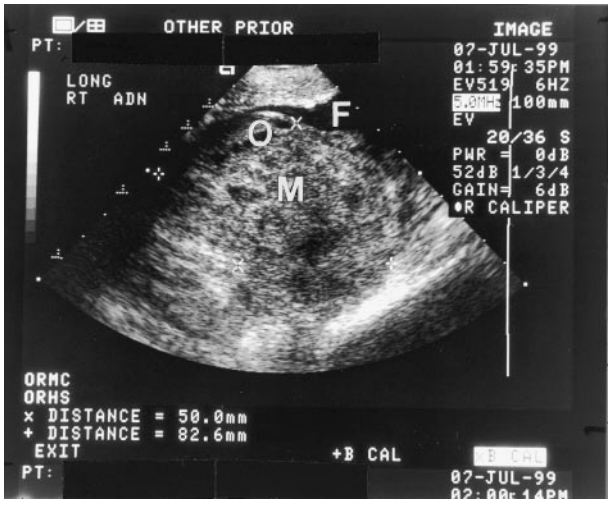

Figure 2. Sonogram from Case 2: Endovaginal longitudinal view of right adnexa, showing free fluid (F) and an 8.3 × 6.8 × 5.0 cm complex right adnexal mass (M) outlined by cursor [x +]. Ovary (O) at top.

Clinical errors in medicine often result from inappropriate reliance on clinical features to exclude a potentially serious disorder such as ectopic pregnancy. In our second case, the premature exclusion of pregnancy from diagnostic consideration appears to be based partially on the history of regular menses. Menstrual histories are notoriously unreliable in excluding pregnancy or for dating gestational age. Any menstrual history is possible in patients with ectopic pregnancy, with amenorrhea of less than 4 weeks or more than 12 weeks seen in 15% of cases, including those with rupture (10–12). In addition, reliability of sexual history may be problematic if relied upon to exclude pregnancy risk. For example, Ramoska et al. found at least a 10% chance of pregnancy in women reporting normal menses and in those who reported "no chance [they] could be pregnant." They found no combination of historical criteria successful in excluding pregnancy in ED patients (13). Lastly, errors may arise from lack of consistency in diagnostic thinking. In this case, the denial of sexual activity was relied upon to exclude pregnancy, but ignored in making a diagnosis of a sexually transmitted infection.

Pregnancy Testing

Detection of βhCG produced by the developing trophoblasts is the mainstay of pregnancy testing. By the time of missed menses (13–14 days after conception) the zygote is < 1 mm in size and βhCG levels are 50 to 300 mIU/mL, rendering virtually all clinically used βhCG pregnancy tests positive (14). Normally βhCG rises from

about 100 mIU/mL at four weeks to > 100,000 mIU/mL at the end of the first trimester (3). Surgically proven ectopic pregnancy with negative βhCG assay may rarely occur via the following (5–9):

1. Use of an older, less sensitive assay
2. Presence of chronic ectopic pregnancy, with inactive trophoblasts
3. Deficient production of hCG (rare)

Both serum and urine qualitative βhCG tests in our healthcare system are performed using the Abbott Testpack Plus hCG-Combo®. This is a modern immunoassay that uses both monoclonal and polyclonal antibodies. The stated threshold for this test is a βhCG level of 25 mIU/mL or greater. In clinical tests for determining pregnancy, the immunoassay was determined to have a sensitivity of 99.4% and a specificity of 99.8% for urine, and a sensitivity of 99.8% and a specificity of 99.4% for serum (15). We believe our test results to be accurate. Unfortunately, neither of our patients had confirmatory serum quantitative levels, as this was not needed in their care. However, we do not believe the test kits were faulty as the cases were seen at two separate facilities 18 days apart. The tests (one serum, the other urine [specific gravity = 1.020]) were performed by hospital laboratory technicians with appropriate positive and negative controls.

Quantitative serum βhCG testing. Although ectopic pregnancies tend to produce less βhCG than intrauterine pregnancies of comparable gestational age, a single βhCG level is not diagnostic due to the difficulty in establishing gestational age precisely as well as the range (0–100,000 mIU/mL) and variation of βhCG produced by both intrauterine and ectopic pregnancies (16–18). Similarly, quantitative βhCG information is not helpful in predicting tubal status. Although βhCG levels correlate with ectopic size and risk of rupture, there is so much overlap between ruptured (βhCG = 12,590 ± 4499 mIU/mL) and unruptured (βhCG = 2968 ± 909 mIU/mL) ectopic pregnancies that this finding is not useful clinically. Both ruptured and unruptured ectopic pregnancies are seen in the βhCG < 100 and > 50,000 mIU/mL ranges. Although one can be somewhat reassured that tubal rupture is less likely at low βhCG levels, rupture can certainly be seen at low levels. In DiMarchi's series, 10% of ectopic pregnancies with βhCG < 100 mIU/mL were ruptured and 7% of ruptures occurred at βhCG < 100 mIU/mL (7). Furthermore, significant hemoperitoneum (>500 mL) can occur without tubal rupture (in 6 of 102 unruptured ectopic pregnancies) (7). Our cases further illustrate that rupture and significant hemoperitoneum can be seen with low levels of βhCG; although neither patient underwent quantitative βhCG testing, both had undetectable levels by qualitative assays, corresponding to βhCG levels < 25 mIU/mL.

With regard to the utility of imaging, many have proposed limiting sonography to the subset of women with high βhCG levels, where sonography is more likely to be diagnostic (19–22). Although most normal intrauterine pregnancies (IUPs) will not be detectable very early, at low βhCG levels some are demonstrable below the discriminatory zone of 1200 to 1500 mIU/mL (23). The discriminatory zone is defined as the βhCG level above which all normal IUPs should be seen; the possibility of visualizing many at lower levels is not excluded (24). Furthermore, the visualization of many abnormal IUPs and ectopic pregnancies may be possible at lower levels (25,26). Dart et al. reported that 15% of potential ectopic pregnancy patients presented with βhCG levels below 1000 mIU/mL. Although sonography in this subset was far from uniformly helpful, they were able to sonographically diagnose 9 of 23 ectopic gestations (39%) despite low βhCG levels (26). Imaging demonstrated significant hemoperitoneum and suspicious adnexal masses in our cases, lending further credence to a liberal imaging policy.

In summary, a single quantitative βhCG level is a poor predictor of ectopic pregnancy size and tubal rupture risk (7). As a result, we conclude, as have others, that imaging is indicated despite low βhCG levels (4,26). In cases of indeterminate sonograms, serial quantitative values are useful to define βhCG dynamics and single values help interpretation when they exceed the discriminatory cutoff. (3,4)

Chronic Ectopic Pregnancy

Chronic ectopic pregnancy is a term used more commonly in the past to describe an ectopic pregnancy that often, but not exclusively, was associated with a negative pregnancy hormone assay and in which the gestation was marked by degeneration, an inflammatory mass of organized hematoma, and perigestational adhesions (27–29). Early reports focused on the likelihood of negative pregnancy assays, but more recent references describe the presence of inflammatory adhesions and mass formation as the most salient features of this disorder (28–34).

Although early investigators found 36–60% of chronic ectopic pregnancies presented with negative pregnancy tests, this false negative rate was found to be as low as 6.8–8% in more recent series, reflecting the advances in pregnancy detection offered by the adoption of βhCG assays in the early 1980s (28,30–33,35). The pathophysiology of ectopic pregnancy is thought to involve growth of trophoblasts into the tubal mucosa, often

eroding into tubal vessels with resultant hematoma formation, tubal swelling, and pain. However, a subset of ectopic pregnancies may persist without rupture long enough for the trophoblasts to degenerate, cease production of βhCG, and present with negative sensitive βhCG assays, as in our cases (29,33,34). Chronic ectopic pregnancy is thought to be a tubal gestation that has undergone abortion or repetitive minor bleeding episodes, resulting in degeneration of trophoblasts but with resultant inflammatory reaction to the tubal hematoma.

Clinical features. Clinical features of chronic ectopic pregnancy differ little from acute ectopic pregnancy in most series, with amenorrhea, abdominal pain, and abnormal vaginal bleeding being common (30–32,35). One feature setting chronic ectopic pregnancy apart from acute ectopic pregnancy is the frequent presence of a mass on physical examination or ultrasound study (28,30–33,35). In addition, duration of symptoms is often longer in chronic ectopic pregnancy, with longer amenorrhea and more remote onset of pain in general (30,33). Although acute ectopic pregnancy with tubal rupture may often present dramatically with abrupt symptoms and shock, chronic ectopic pregnancy will typically present in a manner similar to an acute but unruptured tubal pregnancy. The most reliable differentiating feature of chronic ectopic pregnancy seems to be the operative findings of hematocele and adhesion formation (28). Because chronic ectopic pregnancies also have the potential for acute tubal rupture with free i.p. bleeding, the timely clinical diagnosis of both disorders is important. In reality, ectopic pregnancy is one illness that may have a varied presentation depending on the complex interaction of trophoblastic growth, tubal bleeding, and the patient's response.

Use of CT scan in Ectopic Pregnancy

Based upon a search of the literature, experience with CT scan in the evaluation of ectopic pregnancy is very limited. CT scan or Magnetic Resonance Imaging (MRI) may have some use in abdominal ectopic pregnancy, especially in planning the surgical approach (20,36,37). No previous reports of CT findings in an ectopic pregnancy with a negative βhCG test were found. There have been rare reports of an ectopic pregnancy seen on CT scan with a positive βhCG, or in cases where a βhCG was not performed (36,38–40). Harris et al. reported the utility of CT scan in delineating the anatomy in a rare intrahepatic abdominal ectopic pregnancy. The ectopic pregnancy was well defined and well differentiated from the hepatic tissue (38). In another study, a ruptured ectopic pregnancy was misdiagnosed on CT scan as a malignant ovarian tumor. The findings of the CT scan in this case were described as "a mixed cystic-solid mass with papillary projections and marked contrast enhancement." In addition, free fluid in the pouch of Douglas was noted. A pregnancy test was not performed (39).

In our first case of a young woman with RLQ pain and negative pregnancy test, the CT scan was obtained to evaluate for possible acute appendicitis. The role of CT scan in evaluating nongravid patients for suspected acute appendicitis has been well-documented (41). In this instance, the CT scan did not reveal appendicitis but did detect abnormal findings. In addition, the official reading of the CT scan revealed a 1.5-cm hyperdense focus that could not be localized to the right adnexa or uterus due to poor tissue margin definition. Hemoperitoneum was also noted. This correlated with the intraoperative findings. Bleeding from the right distal fallopian tube was noted with a 1.5 cm area in the mid-segment bulging with a bluish discoloration. An ectopic pregnancy was not confirmed until the pathology results were obtained.

CONCLUSIONS

Ectopic pregnancy is rare but possible with negative qualitative βhCG results. Unstable patients presenting with abdominal pain must be resuscitated while appropriate evaluation for hemoperitoneum is pursued. In more stable patients with negative βhCG results, other tests including CT scan may be used to evaluate abdominal pain, especially in the setting of suspected appendicitis. CT scan may inadvertently reveal findings suspicious for ectopic pregnancy, allowing appropriate treatment even when this condition is clinically unsuspected. Most importantly, low quantitative βhCG levels cannot reliably predict the utility of sonography, nor eliminate the risk of tubal rupture.

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