



## Ectopic pregnancy until proven otherwise ... even with a negative serum hCG test: A case report



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### ABSTRACT

Ectopic pregnancy is commonly considered in the differential diagnosis for first-trimester vaginal bleeding and acute abdominal pain in women of reproductive age. Negative human chorionic gonadotropin (hCG) tests have been considered the gold standard to rule out this life-threatening diagnosis and appropriately rising hCG levels are thought to exclude it as well. In the unique case reported here, pathology confirmed ectopic pregnancy is identified in the setting of a negative serum hCG test. The patient was a 23-year-old woman (with one living child and one earlier miscarriage) who presented to the emergency department (ED) with sudden onset of abdominal pain, vaginal bleeding and syncope. She was tachycardic but normotensive and had both a negative serum hCG test and a negative urine hCG test. Imaging demonstrated a hemoperitoneum and right adnexal mass. She was taken for emergency exploratory surgery. The right fallopian tube had a tubal mass consistent with an ectopic pregnancy as well as 500 mL of blood. Pathology confirmed the ectopic pregnancy. A literature review revealed only two prior documented cases of pathology-confirmed ectopic pregnancy in the setting of a negative serum hCG test. The patient had experienced an abortion two months earlier without a documented intrauterine pregnancy. Her hCG levels were followed to <5 mIU/mL and she had not yet had return of menses at the time of her presentation. Perhaps a chronic ectopic could explain this unusual case. This case highlights that an ectopic pregnancy should never be excluded from the differential diagnosis in a woman of reproductive age. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### 1. Introduction

An ectopic pregnancy is defined as growth of an embryo outside the uterus. According to the American College of Obstetricians and Gynecologists (ACOG), the most common location of ectopic pregnancy is the fallopian tube: approximately 90% of cases occur there [1]. Other sites for implantation include the abdomen, cervix, ovary, and prior cesarean scar, each of which accounts for approximately 1–3% of cases [1]. Ectopic pregnancy accounts for approximately 2% of all pregnancies in the US and from 2011 to 2013, ruptured ectopic pregnancies accounted for

2.7% of all pregnancy-related deaths, primarily due to significant hemorrhage associated with rupture [1]. The prevalence of ectopic pregnancy among women presenting to an emergency department (ED) with first-trimester vaginal bleeding or abdominal pain, or both has been reported to be as high as 18% [1].

When evaluating for a possible ectopic pregnancy, risk factors such as a history of ectopic pregnancy, previous fallopian tube injury, prior fallopian tube surgery, and prior ascending pelvic infections are important to evaluate; however, 50% of women with ectopic pregnancies have no risk factors [1]. Evaluation starts with a transvaginal and transabdominal ultrasound scan to determine if there is an intrauterine pregnancy and the positive predictive value of ultrasound is 80% [1]. Determination of the human chorionic gonadotropin (hCG) level is also valuable in the assessment of an ectopic pregnancy. The expected rate of rise is 49% for an initial hCG level of less than 1500 mIU/mL, 40% for a level of 1500–3000 mIU/mL, and 33% for a level greater than 3000 mIU/mL [2]. In early pregnancy, an increase in serum hCG of less than a minimum threshold in 48 h is suggestive of an abnormal pregnancy [1]. hCG patterns consistent with a growing or resolving gestation do not eliminate the possibility of an ectopic pregnancy.

**Abbreviations:** hCG, Human chorionic gonadotropin; ACOG, American College of Obstetricians and Gynecologists; FAST, Focused assessment with sonography for trauma; ED, Emergency department; CT, Computed tomography; G, # of total pregnancies; P, # of full-term pregnancies, # of preterm pregnancies, # of miscarriages and/or abortion, # of living children.

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This is a unique case of an ectopic pregnancy with a negative serum hCG test after resolution of spontaneous abortion.

## 2. Case Presentation

A 23-year-old Caucasian woman, G2 [2 total pregnancies] P1011 [1 term pregnancy, 0 pre-term pregnancies, 1 miscarriage, and 1 living child], with a history of an uncomplicated term vaginal delivery 8 months prior presented to an emergency room for evaluation. Her initial complaint was sudden onset of abdominal pain and vaginal bleeding. During investigation of her history, she revealed that she had completed a spontaneous abortion two months prior. Her serum hCG levels were followed weekly until a value  $< 5$  mIU/mL was achieved. On initial exam she was awake and alert but visibly in pain. She was hemodynamically stable with a blood pressure of 106/69 mm Hg, heart rate of 104 beats per minute, respiration rate of 18 breaths per minute, temperature of 99F, and oxygenation at 99% on room air. On physical exam she had diffuse abdominal tenderness with voluntary guarding and rebound tenderness. Laboratory studies demonstrated a mild leukocytosis, with a white blood cell count of 16.5, and a mild anemia, with a hemoglobin of 10.9. Both serum qualitative hCG and serum quantitative hCG tests were reported as negative (serum quantitative value was  $< 5$  mIU/mL). A focused assessment with sonography for trauma (FAST) exam demonstrated free fluid in the abdomen and a computed tomography (CT) scan of the abdomen/pelvis confirmed a moderate-volume hemoperitoneum with a right para-ovarian lesion. While waiting for the return of her laboratory and imaging results, the patient had a syncopal episode walking to the bathroom. With the above findings, the emergency room physician consulted the gynecologic surgeon on call for a suspected ruptured right ovarian mass. The patient was transferred to a specialty hospital and was taken to the operating room for an exploratory laparotomy.

A Pfannenstiel incision was made and a significant hemoperitoneum was encountered upon entry into the abdominal cavity. The right fallopian tube and ovary were elevated out of the incision and a right tubal mass was identified (Fig. 1). This mass was consistent with a tubal ectopic pregnancy with active bleeding from the tubal ostia and friable edematous tubal tissue. A right salpingectomy was performed and the specimen was sent for pathological examination. Approximately 500 mL of blood was evacuated from the abdomen.

The patient had an uncomplicated post-operative course and was discharged on post-operative day two. Pathologic evaluation of the specimen confirmed the presence of chorionic villi consistent with an ectopic/tubal pregnancy.



Fig. 1. Intra-operative visualization of a right tubal mass. A right salpingectomy was performed and pathological examination confirmed the mass was an ectopic pregnancy.

## 3. Discussion

The diagnosis of an ectopic pregnancy in the setting of a negative serum hCG test is exceedingly rare. Most often, in a patient with a similar presentation to the ER and a negative hCG, the likely cause is a ruptured hemorrhagic cyst with active bleeding. It would be reasonable to lower ectopic pregnancy in the differential for a patient with this presentation given that the diagnosis of an ectopic pregnancy is clinically made on the basis of serial hCG testing in conjunction with the use of transvaginal ultrasound [1,2]. During pregnancy, one can anticipate that hCG levels rise at least 50% in 48 h or double in 72 h, with a peak around 60–90 days after conception [2]. An intrauterine pregnancy should be visualized on transvaginal or abdominal ultrasound, with an hCG value of 3500 mIU/mL [2]. Decreasing hCG concentration more likely represents a failed intrauterine pregnancy.

A thorough literature review revealed a handful of prior case reports with confirmed ectopic pregnancies in the setting of a negative urine hCG test [3,4]; however, only two of these cases had a negative serum hCG test [5]. Both of those cases had presentations with varying degrees of stability, and abdominal pain and vaginal bleeding were the primary complaints. Unlike both of those cases, this patient had a previous completed abortion which may have been a confounding factor.

When contemplating how a patient had a pregnancy with a negative hCG test, it is important to understand how hCG is produced and maintained during early gestation. hCG consists of an alpha subunit (92-amino-acid) and a structurally similar but slightly different beta subunit (30-amino-acid tailpiece) [6]. It is produced from the extravillous cytotrophoblast, which is the principal form of hCG during implantation of a fertilized embryo [7]. The production is then passed to the syncytiotrophoblast of the placenta, which produces hCG to maintain the corpus luteum in pregnancy. The maximum hCG value is achieved at approximately week 8 of gestation and falls by week 13 to reach a low steady state [7]. When considering this case of a confirmed ectopic pregnancy by pathology in the setting of a negative serum hCG test, a potential cause for low or absent hCG values is degeneration of the trophoblastic tissue or low mass of chorionic villi, both of which are sources of hCG production. It is also possible that this particular patient had enhanced hCG clearance by an unknown mechanism that allowed what would be an otherwise abnormal but detectable hCG level to be absent. Another possibility is that the patient had synthesis of abnormal hCG molecules that the serum screens failed to detect. Additionally, the patient could have produced the alpha subunit of hCG rather than the beta subunit, which would render the pregnancy undetectable; however, these theories are less likely given that the patient had previous gestations with the same partner and a detectable hCG resulting in a term vaginal delivery. When considering the specimen itself, final pathology of the surgical specimen returned with no gross abnormalities, but no further genetic evaluation was performed. While it is possible an unknown and never before reported genetic mutation could have led to undetectable hCG production, this is considered unlikely.

A final and most likely explanation of her ectopic pregnancy in the setting of a negative hCG test is an undiagnosed chronic ectopic pregnancy. It is possible that the patient's presumed completed abortion that had been followed to an hCG value of  $< 5$  mIU/mL was actually an ectopic pregnancy. This is supported by documentation that her complete abortion two months prior never had an intrauterine pregnancy documented by ultrasound and there was no pathology to confirm the presence of chorionic villi in the uterine cavity. It is unknown how long this ectopic pregnancy may have gone undiagnosed had it not ruptured and prompted the patient's presentation to the ED.

## 4. Conclusion

In the setting of a negative pregnancy test and an acute abdomen, standard workup for intra-abdominal pathology should be carried out

with abdominal ultrasound and abdominal/pelvic CT as well as laboratory examinations for blood counts and coagulopathies. If there is concern regarding an ectopic pregnancy, appropriate consultation with the gynecologic surgical service is necessary. This case is an excellent example of the ongoing struggle to use diagnostic tools to narrow a differential diagnosis and highlights the need to investigate rare cases to expand awareness so that a potentially life-threatening diagnosis is never excluded from the differential. As this case proves, never exclude the diagnosis of an ectopic pregnancy from the differential in a woman of reproductive age, even when all tests and examinations may indicate otherwise.

### Contributors

Zachary A. Kopelman drafted the paper and is the lead author.

Erin A. Keyser contributed to critical revision of the paper.

Kelly J. Morales contributed to critical revision of the paper.

The views expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, or the Department of Defense, or the U.S. Government.

### Conflict of Interest

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