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# Molar Pregnancy with False Negative $\beta$ -hCG Urine in the Emergency Department

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This case describes an atypical presentation of molar pregnancy in an emergency department patient with abdominal pain and vaginal bleeding. The patient demonstrated clinical features of hydatidiform mole, including acute discharge of a large, grape-like vesicular mass, despite multiple negative urine pregnancy tests. These false-negative qualitative human chorionic gonadotropin assays were likely caused by the “high-dose hook effect” and may have delayed proper care of the patient, who displayed pulmonary choriocarcinoma at the time of diagnosis. [West J Emerg Med. 2011;12(2):213-215.]

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## INTRODUCTION

Gestational trophoblastic disease encompasses a spectrum of tumors, including complete and partial hydatidiform mole (molar pregnancy) and locally invasive or disseminated choriocarcinoma.<sup>1</sup> Complete hydatidiform mole produces characteristic clinical features, including vaginal bleeding and uterine size beyond expected gestational age.<sup>1</sup> Many other clinical features of molar pregnancy, including hyperemesis gravidarum, hyperthyroidism and theca lutein ovarian cysts, are believed to be induced by markedly elevated serum human chorionic gonadotropin ( $\beta$ -hCG) levels produced by the trophoblastic tissue.<sup>1</sup> Thus, in addition to a complete physical and pelvic examination, complete blood count (CBC), blood chemistry and pelvic ultrasound, a hallmark of diagnosing hydatidiform mole is a positive  $\beta$ -hCG assay pregnancy test. Interestingly, sandwich chromatographic immunoassays, such as qualitative  $\beta$ -hCG assays, may produce false-negative results in the presence of excessively high antigen concentrations in a phenomenon known as the “high-dose hook effect.” We report a case of molar pregnancy and subsequent malignant choriocarcinoma presenting as abdominal pain and vaginal spotting with multiple false negative urine pregnancy tests, ultimately delaying care.

## CASE REPORT

A previously healthy 19-year-old Gravida 0 Para 0 female presented to the emergency department (ED) with seven weeks of abdominal pain, vaginal spotting, nausea and

vomiting. The abdominal pain was described as cramping in the mid-epigastric and pelvic regions. The patient denied fever, dysuria or diarrhea. She was sexually active without contraceptive use and described a history of irregular periods since menarche but no recent passage of tissue. Four weeks before presenting she took a home pregnancy test that was negative. Two weeks prior she was seen at a different facility where she had a negative urine pregnancy test and a pelvic examination that revealed tenderness. At that time she was treated with azithromycin and ceftriaxone for presumed cervicitis, but her symptoms continued.

The physical examination revealed an oral temperature of 98.3° F, heart rate of 99 beats/min, respiratory rate of 16 breaths/min, blood pressure of 169/96 mmHg and oxygen saturation of 100% on room air. She was alert and oriented but uncomfortable with pain and retching. The cardiac exam was normal, and the lungs were clear. The abdomen was diffusely tender but soft without rebound or guarding. In the lower abdomen, a firm, palpable uterus was present. Pelvic examination revealed a closed cervical os with blood clots in the vaginal vault and a 20-week sized uterus with cervical motion and adenexal tenderness. The patient was noted to have no tenderness at the costovertebral angles, no lower extremity edema, and no focal neurologic deficits. Point-of-care and laboratory qualitative urine  $\beta$ -hCG assays were negative. A pelvic ultrasound, CBC, blood chemistries and quantitative serum  $\beta$ -hCG were ordered. The patient was treated with analgesics and anti-emetics. As she was being

prepared for transport to the ultrasound suite, the patient discharged a large, fleshy, vesicular mass followed by profuse vaginal bleeding. Subsequent pathological examination of this mass found it to be a 777 gm, 20 x 15 x 16 cm aggregate of placental tissue mixed with abundant grape-like vesicular tissue and blood clot without fetal parts. Hemostasis was achieved with packing. Two large bores were placed intravenously, and a blood type and cross was performed for transfusion. An obstetrical/gynecological consult was called immediately. At this point the quantitative serum  $\beta$ -hCG level returned at 1,370,128 mIU/mL (normal <5-200,000). Initial complete blood count showed white blood cell count of 14.6 k/mm<sup>3</sup> and hemoglobin of 11.1 g/dL with a normal platelet count. Her coagulation and basic metabolic panels were within normal limits; however, her free thyroxine was elevated at 3.43 ng/mL (normal 0.00-0.05), with a corresponding low thyroid stimulating hormone level of 0.12 uIU/mL (normal 0.34-5.60). Once stabilized, she had an ultrasound showing enlarged uterus measuring 19.4 x 9.2 x 8.7 cm and a complex mass within the endometrium measuring 16.7 x 6.9 x 6.3 cm with small hypoechoic areas suspicious for molar pregnancy. There was also sonographic evidence of bilaterally enlarged ovaries with abundant cysts. She was taken to the operating room for emergent dilatation and curettage, which demonstrated hydatidiform mole. She was treated with blood transfusions for acute anemia, magnesium sulfate for pre-eclampsia and beta-blockers for hyperthyroidism. A subsequent work-up showed numerous pulmonary nodules in bilateral lungs likely due to metastatic choriocarcinoma. The patient had an uneventful hospital course and was discharged two days post operatively on Depo-Provera and Labetalol with instructions to follow up daily for methotrexate treatment. After completing chemotherapy, she was followed as an outpatient by the gynecological oncology team with serum  $\beta$ -hCG screening performed on a regular basis. One year after this presentation, the patient had complete remission of her choriocarcinoma.

## DISCUSSION

Molar pregnancy is an uncommon cause of abdominal pain and vaginal bleeding in the ED that may lead to serious disseminated disease and death if left untreated. Molar pregnancy occurs in approximately one in 1,000 pregnancies in the United States. It is most commonly associated with pregnancy in the early (15-20 years old) and late (>35 years old) reproductive periods.<sup>1-2</sup> Hydatidiform moles are an anomalous growth of trophoblastic tissue categorized as complete or partial. Complete moles have diploid karyotype of solely paternal origin and a complete absence of fetal tissue.<sup>1</sup> Partial moles are characterized by triploid karyotype of both maternal and paternal origin and the presence of fetal/embryonic tissue.<sup>1</sup> A retrospective analysis of molar pregnancies reported that 75% of patients present with vaginal bleeding, while 54% present with enlarged uterus for

gestational dates and 100% had excessively elevated  $\beta$ -hCG levels.<sup>2</sup> Here, we report a case of molar pregnancy and metastatic choriocarcinoma with multiple negative qualitative urine  $\beta$ -hCG pregnancy tests despite an extremely elevated serum  $\beta$ -hCG level.

Clinical decision-making regarding women of childbearing age with abdominal pain and vaginal bleeding is often dictated by pregnancy testing, specifically point-of-care qualitative urine hCG assays. These screening tools, along with over-the-counter home pregnancy tests, are chromatographic sandwich immunoassays in which two antibodies directed to different portions (for example, the  $\alpha$  and  $\beta$  subunits) of the hCG molecule sandwich a single antigen to produce color change. Our ED uses the Clinitest<sup>®</sup> hCG Pregnancy Test from Siemens Healthcare Diagnostic Inc. for point-of-care testing. This lateral flow, chromatographic assay is reported to produce positive results with hCG concentrations  $\geq 25$  mIU/mL. A urine sample placed on the membrane reacts with migratory colloidal gold particles coated with anti- $\beta$ -hCG antibodies. These antibody-bound particles then migrate by capillary action to the fixed detection line coated with either anti- $\alpha$ -hCG or goat-anti-mouse antibody (control). To induce color change a single hCG molecule must be bound by the antibodies to both subunits, forming a "sandwich" that attaches the gold particles for color change and binds the compound to the detection line. Despite the high sensitivity and specificity of the assay, our patient had repeatedly negative urine pregnancy tests at home, in an outside facility, and upon presentation to our ED. One explanation for the negative pregnancy test is the "high-dose hook effect," a rare phenomenon that occurs in sandwich immunoassays when the concentration of the antigen is sufficiently high to saturate both the solid migratory phase and fixed detection antibodies independently.<sup>3</sup> In this case, excessive levels of free antigen in the sample allow the anti- $\beta$ -hCG and anti- $\alpha$ -hCG antibodies to each bind subunits of different hCG molecules rather than subunits of the same molecule, preventing them from forming the "sandwich." As a result, the gold particle necessary for color change is never bound, leading to a false-negative test. A 1:10 to 1:1000 dilution of the antigen sample may overcome the hook effect by reducing the concentration and allowing the antibodies to properly bind to two portions of the same molecule.<sup>4-5</sup>

There have been reports of false-negative urine, serum and both urine and serum  $\beta$ -hCG pregnancy tests in hydatidiform mole.<sup>6-11</sup> In each of these reports, the serum  $\beta$ -hCG levels were determined to be greater than 1,000,000 mIU/mL, and the likely cause for false negative results were reported to be the "high-dose hook effect."<sup>6-11</sup> Those cases with false-negative serum assays required dilution of the samples and re-testing after ultrasound demonstrated sonographic evidence of molar pregnancy.<sup>9-11</sup> In some reports, the diagnosis of molar pregnancy was already suspected prior to the false-negative test because of ultrasound evidence or a

previous positive pregnancy test.<sup>6,7,10,11</sup> In our case, the patient discharged a large, vesicular mass characteristic of hydatidiform mole prior to the completion of quantitative  $\beta$ -hCG testing or ultrasound evaluation. A retrospective analysis has suggested that the positive predictive value of transvaginal ultrasound for molar pregnancy is 100%.<sup>2</sup> However, often this procedure is delayed or not considered when a pregnancy test is negative, as was likely the case when our patient was initially seen at an outside facility. Since her screening pregnancy test was negative, an ultrasound was never performed, making the correct diagnosis difficult. These rare reports underscore the importance of quantitative  $\beta$ -hCG assays and sonographic evaluation in patients with negative pregnancy tests where clinical suspicion of pregnancy remains high.

Management of molar pregnancy in the ED is largely supportive and dependent on disease severity. Abdominal pain and vaginal bleeding are caused by the mass of trophoblastic tissue and fragile surrounding blood vessels.<sup>1</sup> Hyperemesis, hyperthyroidism and ovarian cysts are thought to be derived from excessive serum  $\beta$ -hCG levels secreted from trophoblastic tissue.<sup>1</sup> Therefore, the definitive treatment is either hysterectomy or dilation and curettage. Initial therapy consists of stabilization, hemostasis if indicated, analgesics and anti-emetics. Beta-blockers may be used for symptoms of hyperthyroid state. Some molar pregnancies will induce pre-eclampsia, which should be managed with magnesium sulfate, but true eclampsia is extremely rare in this patient population.<sup>1</sup> Choriocarcinoma may present as locally invasive non-metastatic or diffuse metastatic disease.<sup>1</sup> The World Health Organization (WHO) prognostic index score is used to determine severity of disease and likely response to treatment.<sup>12</sup> Nine prognostic factors are scored from zero to four to determine low, intermediate or high-risk gestational trophoblastic disease.<sup>12</sup> A WHO score of less than seven is usually treated with single agent chemotherapy, most commonly methotrexate.<sup>12</sup> A score of seven or higher requires combination therapy, typically the EMA-CO regime, including etoposide, methotrexate and actinomycin D administered in the first week of a two-week cycle, then cyclophosphamide and vincristine.<sup>12</sup> Post-treatment surveillance includes weekly serum  $\beta$ -hCG monitoring until levels become negative, and then monthly for six months.<sup>12</sup> With appropriate therapy survival approaches 100%.<sup>1,12</sup>

## CONCLUSION

Molar pregnancy is an uncommon yet serious condition that may cause significant pain, hyperemesis, pre-eclampsia, hyperthyroidism and possibly metastatic disease. In addition to vaginal bleeding and excessive uterine size, a hallmark of diagnosis is elevated  $\beta$ -hCG. However, qualitative  $\beta$ -hCG assays may be falsely negative due to the high-dose hook effect if serum levels are extremely elevated. When suspicion

exists for molar pregnancy, sonographic evaluation and quantitative  $\beta$ -hCG levels are necessary in the work-up. The ED therapy for molar pregnancy is supportive along with prompt gynecologic consultation with definitive treatment being operative.

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**Conflicts of Interest:** By the WestJEM article submission agreement, all authors are required to disclose all affiliations, funding sources, and financial or management relationships that could be perceived as potential sources of bias. The authors disclosed none.

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