



Abnormally low hCG in a complete hydatidiform molar pregnancy: The hook effect

James L. Nodler^a, Kenneth H. Kim^{b,*}, Ronald D. Alvarez^b

^a Department of Obstetrics and Gynecology, The University of Alabama at Birmingham, AL, USA

^b Division of Gynecologic Oncology, The University of Alabama at Birmingham, AL, USA

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Introduction

Hydatidiform molar pregnancy occurs as a proliferative disorder of trophoblastic cells. Complete hydatidiform moles present with abnormally high levels of human chorionic gonadotropin (hCG); more than 40% of patients have levels greater than 100,000 (Berkowitz & Goldstein, 2009). Serum hCG may be misreported in cases of extremely high levels due to the “hook effect,” where falsely low or negative results occur from oversaturation of the signaling antibodies employed to detect hCG by the testing equipment. Herein we describe a case where the hook effect was noted in a patient with a complete hydatidiform mole.

Case

A 27-year-old Latin-American female, P1001, presented to the emergency department complaining of abdominal pain, persistent nausea and vomiting for two weeks, and a twenty-pound weight loss. The patient reported a positive home pregnancy test 16 weeks prior to presentation, but had not presented for obstetric care. She thought she had miscarried four weeks prior, with passage of a profuse amount of “jelly-like” substance, which had persisted.

* Corresponding author at: Division of Gynecologic Oncology, University of Alabama at Birmingham, 176F, Rm 10250, 619 19th Street South, Birmingham, AL 35249, USA. Fax: +1 205 975 6471.

E-mail address: kkim@uabmc.edu (K.H. Kim).

Her obstetric history was significant for an uncomplicated vaginal delivery at 40 weeks gestation, three years prior to presentation. She had no other medical problems. The patient appeared cachectic upon arrival to her local hospital, and abdominal exam was consistent with a 20-week size uterus. Ultrasound revealed an enlarged uterus filled with echogenic material. Serum β hCG was found to be 900 mIU/mL. The patient was transferred to our university hospital with findings concerning for a complete molar pregnancy.

Upon transfer, ultrasound findings were confirmed and serum β hCG was repeated, revealing a value of 882 mIU/mL. The patient was found to be thrombocytopenic with a platelet value of 95.1, anemic with a hemoglobin value of 7.5, and coagulopathic with an INR of 2.2. After transfusion of packed red blood cells and fresh frozen plasma, the patient was taken to the operating room for suction evacuation of uterine contents. Pathology was consistent with a complete hydatidiform mole. The patient developed preeclampsia with blood pressures as high as 162/90, requiring magnesium prophylaxis. She also developed hyperthyroidism with a TSH of <0.01 and free T4 of 2.97, requiring therapy with metoprolol.

The hospital laboratory was contacted and asked to perform serial dilutions of the original β hCG sample, reported as 882 mIU/mL. Dilutions were performed to 1:1600 and the β hCG result was recalculated to be over 1,300,000 mIU/mL. On postoperative day 1, the β hCG fell to 326,175 mIU/mL, and was 13,035 mIU/mL on postoperative day 8. In the days following evacuation, the patient's hyperemesis resolved and hematologic parameters normalized. No evidence of metastasis was seen on CT scans of the head, chest, abdomen, and pelvis. The patient's β hCG continued to fall, but subsequently plateaued between 456 and 489 mIU/mL after approximately ten weeks, requiring ten cycles of weekly methotrexate therapy dosed at 40 mg/m². She has now achieved a negative β hCG value, and has shown no evidence of recurrence or metastasis.

Discussion

Human chorionic gonadotropin (hCG) is commonly used as a marker for gestational trophoblastic disease. Total hCG levels greater than 100,000 are highly suggestive of a complete hydatidiform mole (Berkowitz & Goldstein, 2009). High hCG concentrations can give low results, as the sensitivity of most hCG tests is set to the pregnancy range of 27,300 to 233,000 at 8 to 11 weeks gestational age (Cole, 1997). Laboratory errors can occur with β hCG levels higher than 500,000 (Cole, 1997). Patients with hydatidiform molar pregnancies often can present with extremely high HCG levels, reaching as high as 3,000,000 (Muller & Cole, 2009). Serum testing is performed

using two antibodies to the beta subunit of hCG molecules. When hCG is present, it is immobilized by a capture antibody, and labeled by a tracer antibody, resulting in an immobilized antibody-hCG-tracer sandwich. When hCG levels are high, both the capture and tracer antibodies saturate, and the signal response is decreased. The “hook effect” occurs when non-sandwiched tracer antibodies are washed away with the excess material resulting in a falsely low or negative test (Grenache et al., 2010). This may delay diagnosis and lead to mismanagement of patients. If molar pregnancy is suspected, the lab should be asked to perform a 1:1000 dilution, with which an accurate value should be obtained (Muller & Cole, 2009). This hook effect was first described by Miles et al. in 1976, and is more commonly seen in assays for prolactin and thyroid stimulating hormone. The Advia Centaur assay is used at our hospital, and has been shown in previous studies to have dose-dependent falsely decreased results at hCG concentrations greater than 940,000 (Grenache et al., 2010); this effect is usually not significant until concentrations are greater than those typically seen in malignancy. Current hCG assays measure non-nicked (biologically active) hCG and one of seven other combinations of hCG-related molecules, attributing to variation in different hCG assays (Cole, 1997).

While rare, the hook effect can lead to delayed therapy or mismanagement of care. Nevertheless, clinicians should be aware of the limitations of laboratory measurements of extremely high levels of hCG, understanding that falsely low or negative tests may arise due to a hook effect, particularly in situations where a clinical scenario may not correspond to a potentially falsely low laboratory value.

Conflict of interest statement

The authors declare that there are no conflicts of interest. This study received no financial support.

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