



## Case Report

# Molar pregnancy with false negative urine pregnancy test, the hook effect

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## ABSTRACT

Molar pregnancy is characterized by high level of serum β hcg which can be usually detected by urine pregnancy test as a first screening test. Urine pregnancy test is also used as the first screening test for patients of reproductive age presenting with gynecological problem in order to exclude pregnancy. Rarely large amounts of β human chorionic gonadotrophin (hcg) may cause a false negative result due to over saturation of the assay system, known as, 'the hook effect'. This can result clinical dilemma in the diagnosis and delay in the management. When there is clinical features of molar pregnancy, the knowledge of "The Hook Effect" will help at arriving at the diagnosis.

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## 1. Introduction

Molar pregnancy occurs in 1 in 1000 pregnancies in the United States. It is most commonly associated with pregnancy in early (15-20 years old) and late > 35 years.<sup>1</sup> Hydatidiform mole have abnormal growth of trophoblastic tissue, categorized as complete or partial mole. Urine pregnancy test is a screening tool which is a chromatographic sandwich immunoassay in which two antibodies directed to different portion (α and β subunit) of βhCG molecule sandwich a single antigen and produce colour change.<sup>2</sup> The assay system can detect β hcg >25mIU/ml. However large levels of serum hcg can cause oversaturation of the assay system, resulting in false negative result in urine pregnancy test.<sup>3</sup> However the gynecologist must be aware of this clinical entity and this can be resolved by further evaluation of serum quantification of β hcg by DPC immulite assay to detect serum β hcg and urine sample with 1:10 dilution for pregnancy test.<sup>3,4</sup>

## 2. Case Report

A middle aged multiparous woman aged 35 years presented in the casualty with complaints of bleeding per vagina on and off since 2 months; pain abdomen, fever, vomiting since 2 days. Patient was P2L2, not sterilized and not using any contraception. There was no h/o amenorrhea or intervention. Her past menstrual cycles were regular lasting for 3-4 days. There was no significant medical, surgical, personal and family history.

### 2.1. Examination

On general examination patient was pale, afebrile, and normotensive, with tachycardia. The cardiovascular examination revealed haemic murmur; respiratory system was normal. On per abdomen examination a firm, globular, mass corresponding to uterus of 22 weeks was felt in the lower abdomen occupying the hypogastrium, umbilical, right and left iliac fossa. The lower pole of the mass was not felt. On per speculum examination cervix appears hypertrophied, altered colored blood was seen through the os. On per vaginal examination uterus corresponding to 20-22 weeks, firm and mobile was felt, fornices were free and non tender.

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The cervical os was closed.

## 2.2. Investigation

Urine pregnancy test was repeated twice and conspicuously negative on repeated examination. Hb% was 4.2gm%; LFT, renal function test, coagulation profile were within normal limits. Ultrasound examination was suggestive of hydatidiform mole and suggested clinical correlation, hence serum  $\beta$ -hcg evaluation was sent. Meanwhile, the reports were awaited; patient party was advised to arrange blood for the correction of anemia. As urine pregnancy test was negative considerable time was lost in the diagnosis. Due to the discrepancy in the reports, the patient was subjected to further investigation.

## 2.3. Management

Patient developed excessive bleeding per vagina on the third day of admission with passing of jelly like vesicles. Emergency suction and evacuation was done in the emergency hours, the products were sent for histopathology and 2 unit whole blood was transfused after the procedure. The serum  $\beta$ -hcg report of 2,25000miu/ml was received on day 4 of admission. After a discussion with the pathologist with a high degree of suspicion of the Hooking effect, urine pregnancy test was repeated with 1:5 dilution and was significantly positive. The histopathology result was reported as molar pregnancy, without malignancy. In view of high serum  $\beta$ -hcg prophylactic Methotrexate (1mg/kg on day 1,3,5,7) leucovorin(0.1mg/kg on day 2,4,6,8) was given. Follow up was done with weekly urine pregnancy test and fortnightly serum  $\beta$ -hcg due to economic constraints. The urine pregnancy test continued to be positive with 1:5 dilution for a duration of 1month after evacuation. After 1month after evacuation serum  $\beta$ -hcg was 4325miu/ml and urine pregnancy test was positive without dilution for 1month duration. Later 2months after the evacuation serum  $\beta$ -hcg raised to 30.325miu/ml. Due to the raising level of serum  $\beta$ -hcg combination chemotherapy with EMA-CO was advised and patient was referred to Regional Cancer Centre, where patient received 2cycles of chemotherapy and the serum  $\beta$  levels declined thereafter and patient recorded normal levels in 1 year. The patient underwent sterilization at a later date.

## 3. Discussion

Molar pregnancy is an uncommon, yet serious condition which may cause significant morbidity. The incidence of molar pregnancy demonstrate marked geographic and ethnic differences ranging from highest incidence of 1 in 120-400 pregnancies in Asian countries to lowest incidence of 1 in 1000-2000 pregnancies in Europe and United States.<sup>1</sup> The disorder is more common in young women and women nearing the end of their reproductive years.<sup>1,2</sup>

Hydatidiform mole have abnormal growth of trophoblastic tissue, categorized as complete or partial mole. Complete mole have diploid karyotype of solely paternal origin and complete absence of fetal tissue. Partial mole have triploid karyotype of maternal and paternal origin and presence of fetal/embryonic tissue.<sup>3-5</sup> Hydatidiform mole changes to invasive mole in 7-17% and metastasis occurs in 4% of cases. The invasive mole and choriocarcinoma comprises the term malignant trophoblastic disease.<sup>2</sup> High risk cases have hcg>100000mIU/ml, excessive uterine enlargement and theca luteal cyst >6cm size. Suction and evacuation is done in patient who desire to preserve fertility hysterectomy is done if patient desires surgical

Sterilization hysterectomy does not prevent metastasis therefore, patient still require follow up with assessment of hcg levels.<sup>4-6</sup> After molar evacuation, patient is advised weekly determination of serum hcg level. Until 3 consecutive weeks sample are normal, followed by monthly determination till the values are normal for 6 consecutive months. Prophylactic chemotherapy may be useful in the management of high risk complete molar pregnancy, especially when hormonal follow up is unavailable/unreliable. 1 in 5 women need chemotherapy after a molar pregnancy.<sup>3</sup> Chemotherapy is given if hcg level begins to rise/is detectable after a 4-6 months/if choriocarcinoma is found in tissue sample.

Methotrexate-leucovorin is given as first line chemotherapy. In high risk and persistent cases combination chemotherapy with EMO-CO is given.<sup>3,6</sup> According to the manufacturer information of Beckman Access 2 analyser, The Hook effect will occur when serum  $\beta$ hcg >1000000IU/L. The hook effect occurs in qualitative urine and qualitative serum  $\beta$  hcg assay. This can be resolved by serum quantification of  $\beta$  hcg by DPC immulite assay to detect serum  $\beta$  hcg and urine sample with 1:10 dilution for the pregnancy test.<sup>4</sup>

Thus when suspicion of molar pregnancy arises USG and quantitative  $\beta$ hcg level are necessary for the work up. The knowledge of high dose hooking effect may be useful to clinicians and clinical laboratory specialist to avoid delay in the diagnosis and therapy.<sup>7-10</sup>

Illustration of hook effect adapted from Schiettecatte et al.<sup>5</sup>

## 4. Conclusion

The Hook effect or the prozone effect is immunologic phenomena whereby the effectiveness of antibody to form immune complex is sometimes impaired when the concentration of an antibody or an antigen is very high. The formation of immune complexes stops increasing with greater concentration and then decreases with extremely high concentration, producing a hook shape on the graph of measurements. The practical relevance is the false negative results which can affect the diagnosis and management.

## 5. Source of Funding

None.

## 6. Conflict of Interest

None.

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