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NEGATIVE URINE PREGNANCY TEST IN A CASE OF MOLAR PREGNANCY : A DIAGNOSTIC DILEMMA

Obstetrics & Gynaecology

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ABSTRACT

Urine pregnancy tests (UPTs) are highly accurate in detecting pregnancy, with nearly perfect sensitivity and specificity. These tests identify pregnancy by detecting a specific hormone (β-hCG) in the urine. While exceptionally reliable, UPTs can produce false negative results in certain circumstances. One common reason for a false negative is testing too early in pregnancy when serum β-hCG levels are low. Less known is the "hook effect," where extremely high β-hCG levels can also lead to a false negative. We report a case of P3L3, a 46 year old woman, with excessive bleeding per vaginum with abdomino-pelvic mass who was initially diagnosed as Uterine myoma due to false negative urine pregnancy test. USG examination and high serum β-hCG clinched the diagnosis of complete hydatidiform mole. Healthcare providers should be aware of this potential limitation, especially when strongly suspecting gestational trophoblastic disease, to ensure appropriate patient care.

KEYWORDS

UPT – Urine Pregnancy Test. GTD – Gestational Trophoblastic Disease. β-hCG – Beta-Human Chorionic Gonadotropin, GTN - Gestational Trophoblastic Neoplasia

INTRODUCTION

Gestational trophoblastic disease (GTD) refers to a group of tumours characterized by abnormal trophoblast proliferation in the absence of fetal tissue. The trophoblast is responsible for producing human chorionic gonadotropin (hCG). β-hCG is utilized for early diagnosis of pregnancy. Highly raised level of β-hCG is found in GTD as there is abnormal trophoblastic proliferation..[1]

Hydatidiform moles are excessively edematous immature placentas.[2]

Grossly, complete moles have abnormal chorionic villi that appear as a mass of clear vesicles. These vary in size and often hang in clusters from thin pedicles.[1]

Classic histological findings of molar pregnancy include trophoblast proliferation and villi with stromal edema.[1]

The classification of complete or partial hydatidiform moles is based on the extent of histological changes, karyotype and immunostaining differences, and the presence or absence of embryonic elements.

Of these, complete hydatidiform moles have a higher risk of progressing to Gestational Trophoblastic Neoplasia (GTN) compared to partial hydatidiform moles.[1]

Prevalence is higher among Asians, Hispanics, and American Indians. Women at the extremes of reproductive age are at the greatest risk.[3]

Diagnosis should be considered in patients presenting early in pregnancy with inappropriately high levels of β-hCG and no identifiable fetal poles on ultrasound examination. However, in some urinary β-hCG immunoassays (card pregnancy tests), the result may be negative despite very high β-hCG levels in the serum.

We present a case illustrating this phenomenon. A 46-year-old woman was initially diagnosed with a large uterine fibroid after her urine pregnancy test yielded a negative result, but was later diagnosed to have a complete hydatidiform mole.

Case Report

A 46-year-old multiparous(P3L3) woman presented to a tertiary care centre in Gurgaon, Haryana with complaints of heavy menstrual bleeding since 20 days, soaking 4-5 pads a day, associated with clots and dysmenorrhea. She also reported experiencing abdominal bloating, weakness, fatigue, and dizziness for the past 15 days. There was no history of amenorrhea. She had no significant past medical or surgical history and had been well prior to the onset of her symptoms.

The patient had a regular 30-day menstrual pattern and her last normal menstrual bleeding was one month ago. She denied recent sexual activity. She had previous 3 vaginal deliveries(P3L3). Her last child birth was 17 years back. There was no history of tubectomy and she was not using any form of contraception.

On examination, she was significantly pale with a heart rate of 114 bpm and a blood pressure of 116/74 mmHg. Evaluation of her heart and lungs revealed no abnormalities. She had a large, non-tender, mobile abdomino-pelvic mass corresponding to 28 weeks of gestation.

Speculum examination showed a parous cervix with no obvious lesions. Moderate per vaginal bleeding was present at the time of examination.

The patient stated that she had not observed the abdominal mass prior to the examination but had experienced increased bloating of the abdomen, especially after meals. The urine β-hCG pregnancy test yielded a negative result.

Given the clinical presentation of prolonged menses and an abdominal mass in a 46-year-old woman, the initial diagnosis was uterine myoma. The patient was admitted. Comprehensive blood investigations and ultrasonography was done.

Ultrasonography revealed an enlarged uterus (1,094 ml) with heterogeneous mass measuring 17.3 x 10.8cm with multiple diffusely scattered cystic spaces without any associated fetal parts suggestive of a complete hydatidiform mole and a well defined round to oval heterogeneously hypoechoic lesion measuring 4.9 x 2.9 cm in anterior uterine wall with internal degenerative changes suggestive of a uterine fibroid. Bilateral ovaries could not be visualised separately.

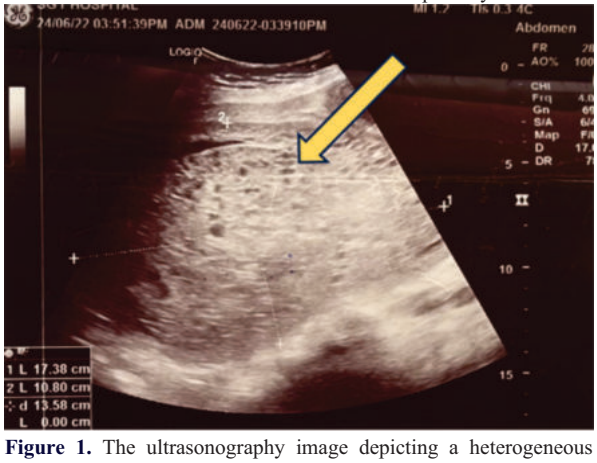

Figure 1. The ultrasonography image depicting a heterogeneous mass(arrow) measuring 17.3 x 10.8 x 13.58 cm, with multiple diffusely scattered cystic spaces.

Her complete hemogram report revealed a hemoglobin level of 4.3 gm/dL. Resuscitative measures were started. An urgent serum β-hCG test was conducted, resulting in a value of > 5,00,000 mIU/ml. Chest X-ray revealed no abnormality. 4 units PRBC and 8 units FFP were arranged. 2 units PRBC were transfused.

Patient had another episode of bleeding amounting to approximately 500 cc and complained of restlessness, vomiting and shortness of breath. Oxygen support was administered as her saturation started falling.

The decision to perform an emergency laparotomy was made due to deteriorating general condition of the patient, presence of high-risk factors for gestational trophoblastic neoplasia (GTN), advanced maternal age, β-hCG levels exceeding 1,00,000 mIU/ml and the patient having completed her family. Subsequently, a total abdominal hysterectomy was performed.

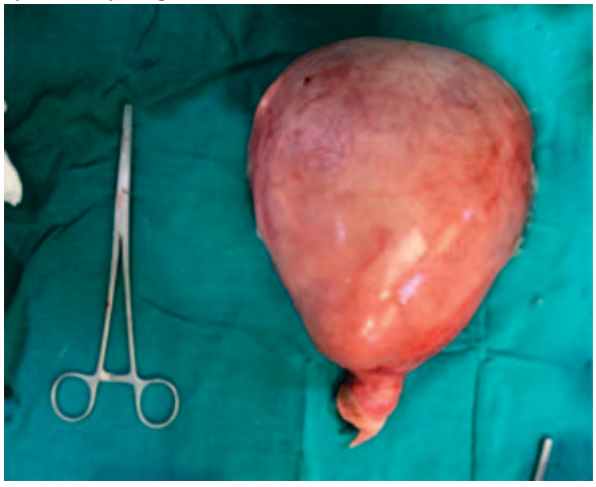

Figure 2. Photograph showing Hysterectomised Uterus with cervix

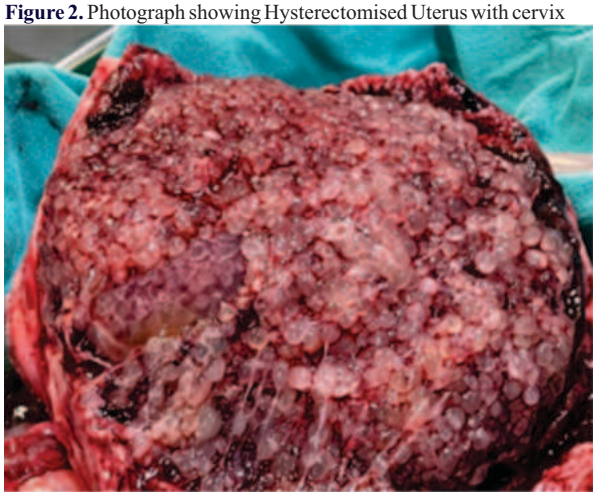

Figure 3. Cut Section of uterus showing molar pregnancy

Post operatively patient was on inotropic support and 3 units PRBC and 4 units FFP were transfused. The post operative β-hCG level was 59,775 mIU/ml. Inj. Methotrexate 60mg intramuscular was given. Patient eventually recovered well and was discharged on post op day 7.

The histological examination revealed a complete hydatidiform mole, without myometrial invasion.

Her repeat β-HCG ten days postoperatively was 10,348 mIU/ml. The patient was subsequently lost to follow up despite multiple reminders.

DISCUSSION

The typical clinical manifestation of complete molar pregnancy involves vaginal bleeding and a large-for-date uterus. It has been found that 7% of women may present with hyperthyroidism. Utilizing high-resolution ultrasonography, the majority of these moles can now be identified in the first trimester, prior to the emergence of traditional signs and symptoms. As this patient was falling into extreme of reproductive age, denied amenorrhoea and any recent sexual activity, with a negative initial urine pregnancy test; suspicion for pregnancy-related complications were very low. This led to a diagnostic dilemma.

Over-the-counter urine pregnancy test kits function by detecting hCG in urine. hCG, a glycoprotein hormone with non-covalently linked α and β subunits, demonstrates immunoreactivity in urine during pregnancy due to the presence of intact hCG molecules (comprising α and β subunits) as well as partially degraded variants present in serum and urine.[5] In these kits, chromatographic sandwich immunoassays are used, where the hCG molecules in the urine sample interact with migratory colloidal gold particles coated with an anti-β-hCG antibody. Subsequently, the resulting product migrates by capillary action to a fixed detection line coated with an anti-α-hCG antibody, resulting in a distinct color change.[6] In cases of complete molar pregnancy, the hCG levels are significantly elevated, leading to the saturation of both the solid migratory phase and the fixed detection antibodies independently.[7] Consequently, the excessive levels of free antigen in the sample allow the anti-β-hCG and anti-α-hCG antibodies to bind subunits of different hCG molecules rather than subunits of the same molecule, thereby hindering the formation of the 'sandwich'. As a result, the unbound gold particle fails to trigger the expected color change, leading to a false-negative test. This is commonly referred to as the "hook effect" or "prozone phenomenon". The hook effect can be effectively managed by diluting the sample, thereby reducing the concentration and allowing the antibodies to properly bind to two portions of the same molecule.[8] It should be noted that the hook effect is not specific to urine and has been documented in serum as well, particularly when the serum β-hCG concentration exceeds 5,00,000 mIU/mL.[9]

It is essential to emphasize the importance of closely monitoring post-molar gestational trophoblastic tumor (GTT), particularly in older women. Studies indicate that in women over 35 years of age, the risk of post-molar GTT following suction evacuation appears to be heightened, with reported rates as high as 56% in women over 50 years of age.[10]

In about 15% of cases of complete molar pregnancies, the abnormal trophoblast cells continue proliferating and invading the uterine wall. This can lead to potential metastasis to other organs, particularly the lungs, with a higher likelihood in older patients.[11] Therefore, for older women diagnosed with a molar pregnancy who have completed their families, it is prudent to consider a hysterectomy to reduce the risk of post-molar GTT and potential invasive disease.[12]

Despite hysterectomy reducing the risk of local invasion, it does not preclude the possibility of disease spread. Therefore, it is essential to continue regular follow-up including serial beta-hCG testing.[13]

CONCLUSION

In cases of molar pregnancy, it is important to be aware that a urine pregnancy test can yield a false negative result due to the high-dose hook effect or variant hook effect. When there is a high suspicion of pregnancy but the urine test result is negative or inconclusive, it is imperative to conduct a serum quantification of β-hCG and appropriate sample dilution for further assessment. Additionally, in instances of molar pregnancy in older patients, heightened vigilance for potential persistent gestational trophoblastic tumors (GTT) is necessary. For individuals who have completed their families or exhibit noncompliance with follow-up, hysterectomy may be considered as a viable option.

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