

DOI: 10.4172/2471-9803.1000136

## A Case of Hook Effect in Molar Pregnancy

Ka Hee Chua<sup>a\*</sup>, Sze Ching Hong<sup>b</sup>, Bernard Su Min Chern<sup>a</sup>, Cynthia Chia Yng Kew<sup>c</sup><sup>a</sup> Department of Obstetrics & Gynecology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899<sup>b</sup> Mount Alvernia Medical Centre, Singapore 574623<sup>c</sup> Mount Elizabeth Novena Specialist Centre, Singapore 329563.

\*Corresponding author: Ka Hee Chua, Department of Obstetrics & Gynecology, KK Women's and Children's Hospital, Singapore, Tel: +65 6225 5554; E-mail: ka-hee.chua@mohh.com.sg

Received date: October 23, 2016; Accepted date: November 14, 2016; Published date: November 21, 2016

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Citation: Chua KH, Min S, Chern B, et al. A case of hook effect in molar pregnancy. Crit Care Obst&Gyne. 2016, 2:5.

### Abstract

Molar pregnancies are associated with extremely high levels of BhCG, out of proportion to the stage of pregnancy. However, urine and serum BhCG assays can paradoxically be negative, despite the high BhCG levels, leading to misdiagnosis and delayed treatment. This is due to saturation of the assay by the BhCG molecules. We present such a case where the initial urine pregnancy test was negative in an advanced complete molar pregnancy. Primary care and emergency department physicians should be mindful of this possibility and go on to do serum BhCG with sample dilution in cases where pregnancy is strongly suspected.

**Keywords:** Molar pregnancy; Hook effect; BhCG

### Introduction

Molar pregnancy is an abnormal pregnancy event. There is abnormal proliferation of trophoblastic cells, with potential for malignancy and metastasis. The incidence appears to vary in different regions, with increased incidence in Asia [1]. They present with exaggerated symptoms of pregnancy: severe nausea and vomiting, bleeding per vagina, abdominal pain or mass [2]. They may also present with thyrotoxicosis or pre-eclampsia. These symptoms are thought to be due to grossly elevated levels of BhCG. BhCG is produced by trophoblastic tissue; the excessive proliferation of trophoblast in hydatidiform mole produces extremely high levels of BhCG. Very occasionally, a falsely low serum BhCG may occur in molar pregnancy. This phenomenon is known as the hook effect.

### Case Presentation

A 26 year old Vietnamese lady, gravida 4 para 2 (2 vaginal deliveries, 2 terminations) presented at 4 weeks and 2 days amenorrhoea to the primary health physician for main complaint of enlarging pelvi-abdominal mass. She also had pedal edema, fatigue and orthopnea of a few days' duration. She had

no significant past medical history and was well before the onset of her symptoms.

She had a regular 30 day menstrual cycle; however the last menstrual period was different and consisted of spotting only. She had a normal sexual relationship with her husband and was not using any contraception. On examination, she was tachycardic at 128 beats per minute and had bibasal crepitations on auscultation of her lungs. Temperature, blood pressure and oxygen saturations were within normal limits. A non-tender mass was felt arising from the pelvis extending to the umbilicus. Cervix was posterior and not well visualized, possibly due to compression from the pelvic mass. Blood stains were seen in the vagina. Bilateral pitting edema was present up to the ankle. Urine pregnancy test was negative.

She was admitted to the intensive care unit. CXR showed small bilateral pleural effusions and a mildly enlarged heart. She was seen by a cardiologist and was started on bisoprolol, digoxin and frusemide. Haemoglobin was mildly reduced at 11.6 g/dl. Abdominal and pelvic ultrasound showed a uterine cavity distended to 14.3x7.1x13.9 cm by solid echogenic material interspersed with numerous cystic spaces of varying sizes. Myometrium appears stretched but intact. No fetal pole was seen, and both ovaries contained anechoic cysts up to 4 cm in diameter. The right pelvi-calyceal junction appeared mildly distended, possibly secondary to external compression by the uterine mass.

In view of the ultrasound findings, a urine pregnancy test was repeated. This time it was positive. Serum BhCG level was measured at 850 mIU/ml. This level did not correlate with the ultrasound findings; hook effect was suspected. The biochemistry laboratory was notified and proceeded to do dilutions of the same serum sample; the BhCG returned as 1912112 mIU/ml. A thyroid function test was ordered and it showed raised free thyroxine of 28.5 pmol/L with markedly suppressed thyroid-stimulating hormone of 0.01 mIU/L. Carbimazole was started by an endocrinologist. Impression was that of a complete molar pregnancy causing thyrotoxicosis and cardiac failure. She was stabilized in the intensive care unit and

was transferred the next day to a tertiary hospital with a gynaecology service.

A multi-disciplinary team consisting of cardiologists, endocrinologists, anaesthetists, interventional radiologists and gynaecologists was involved in her care. She was planned for an evacuation of uterus after optimization of her medical condition. A repeat CXR showed improvement in the pleural effusion and no lesions suggestive of metastases. An echocardiogram showed normal ejection fraction of 60%. Repeat thyroid panel showed a decrease in free thyroxine after initiation of carbimazole. The blood bank was notified to reserve blood products for her operation.

Gemeprost pessary was inserted 4 hours before her operation for cervical priming. Prophylactic internal iliac artery balloons were placed, ready to be inflated in case of massive vaginal bleeding. She underwent uneventful suction curettage of the uterine cavity under general anaesthesia. Transabdominal ultrasound was used to guide the operation. Uterine size went from 24 week's size pre-procedure to 12 week's size post-procedure. 1.1 litres of products were evacuated. IV syntocinon infusion was started once the cavity was clear of its contents, as seen by a thin endometrial stripe on ultrasound. Per vaginal bleeding was minimal and the internal iliac artery balloons were not inflated.

She was monitored in the intensive care unit post-operatively. Internal iliac artery balloons were removed 4 hour post operation once we were satisfied that there was no further heavy vaginal loss. The patient recovered well post-operatively and was discharged on post-operative day 4. Serum BhCG trended downwards, from more than 225000 mIU/ml on days 1 and 2 post-operatively, to 70523 mIU/ml on day 4. Her thyroid function test was normal by day 8. Histology returned as complete hydatidiform mole. Unfortunately, she defaulted subsequent appointments to the molar pregnancy clinic despite numerous reminders.

## Discussion

Gestational trophoblastic disease exhibits marked geographical variation. Incidence appears to be higher in some parts of Asia, Middle East and Africa. In Singapore, a previous study estimated the rate to be 1 in 814 pregnancies [3]. Extremes of maternal age is a risk factor for development of this condition. Symptoms include nausea and vomiting, abnormal vaginal bleeding or uterus larger than dates. Any reproductive aged woman with a missed menstrual period and the above symptoms would have a pregnancy test at first presentation. If positive, they will be referred on to a gynaecologist for review, and will likely receive an ultrasound examination for early pregnancy assessment. In this case, her urine pregnancy test was negative, and an ultrasound was arranged only because of the large pelvic mass. In cases presenting without a pelvic mass, the diagnosis may be missed, thereby delaying treatment for this condition.

Hydatidiform moles are suspected based on greatly raised BhCG levels or ultrasound features. A BhCG level in excess of 100000 is suggestive of this condition [4]. Final confirmation is

dependent on histology. A complete mole appears as a "snowstorm" on ultrasound; endometrial mass with multiple anechoic spaces, no fetus, and no amniotic fluid. It is an obviously abnormal scan and unlikely to be missed. A partial mole has more subtle signs. A fetus and amniotic fluid may be present, and the placenta may appear to be enlarged and cystic. The transverse diameter of the gestational sac may also be larger than the anteroposterior diameter. As a result, they are often diagnosed as missed or incomplete miscarriage [5], and the diagnosis is only discovered later on pathological examination of the abortus.

The mechanism of BhCG testing is based on two antibodies attaching to the beta subunit of the hCG molecule. The 2 antibodies attach at 2 distinct sites, forming an antibody - hCG - antibody "sandwich". One antibody fixes the hCG molecule, and the other is the signal antibody. Excess antibodies are washed away. The amount of fixed signal antibodies is measured as the BhCG level.

In hydatidiform moles, the large amount of hCG molecules saturate the antibodies, preventing the formation of the antibody sandwich. Thus a falsely low BhCG result is read. This hook effect occurs at serum levels of more than 500000 mIU/ml [6]. Laboratories need to do dilutions of 1:1000 to obtain the correct result. This is known to affect immunoassays for prolactin, prostate-specific antigen, thyrotropin, Ca 125 and ferritin as well.

Interventional radiology procedures are becoming more widely used in obstetrics and gynaecology practice. Under fluoroscopic guidance, a catheter is passed from the femoral artery to the internal iliac or uterine artery, and occlusion of the artery is achieved temporarily by balloon occlusion, or permanently by particles or gels. Common indications are management of obstetric haemorrhage and uterine artery embolization of fibroids. It is especially useful in perioperative management of placenta previa accreta to reduce bleeding. In our hospital, the interventional radiology service is well established and is a valuable adjunct to control bleeding in potentially difficult surgeries, such as this case.

In conclusion, the hook effect is a rare occurrence in molar pregnancy. However, it can lead to misdiagnosis and delayed treatment. Clinicians need to be mindful of this possibility, and if suspicion is high, dilutions of the sample should be carried out. In cases with secondary complications, a multidisciplinary approach is ideal. Prompt evacuation of uterine contents is the mainstay of treatment.

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