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CASE REPORT

Biochemical Derangement in Twin Pregnancy: Complete Hydatidiform Mole and Viable Foetus

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ABSTRAK

Kes kehamilan kembar molar bersama dengan kehamilan intrauterin yang normal adalah sangat jarang berlaku. Insiden kehamilan tersebut adalah sangat rendah dengan kadar satu kes di dalam 20,000 – 100,000 kelahiran. Kehamilan tersebut dikaitkan dengan risiko keguguran, kelahiran pramatang, kematian janin didalam rahim, pendarahan, pre-eklampsia, dan persistence trophoblastic disease (PTD). Kehamilan ini juga boleh mengakibatkan perubahan paras ujian biokimia di dalam ibu hamil dan mengakibatkan manifestasi gejala kepada ibu. Terdapat beberapa kes yang sama telah dilaporkan di kalangan penduduk Asia dengan dilema pengurusan klinikal yang signifikan kepada ibu dan janin. Di sini, kami laporkan kes seorang wanita muda dengan sejarah obstetrik yang kompleks hadir dengan masalah pendarahan per vagina di awal kehamilan. Beliau mempunyai kehamilan kembar molar hydatidiform lengkap dengan janin yang normal. Keadaan ini mengakibatkan paras ujian biokimia human chorionic gonadotrophin (hCG) yang sangat tinggi. Beliau juga mengalami hipertiroid. Selepas proses kelahiran, nilai hCG masih tinggi dan beliau didiagnosakan sebagai 'Gestational Trophoblastic Neoplasm'.

Kata kunci: hipertiroid, human chorionic gonadotrophin, kehamilan kembar, molar hydatidiform

ABSTRACT

Case of co-existence of twin pregnancy of complete hydatidiform molar with viable intrauterine pregnancy is extremely rare with low incidence of 1 case for 20,000 – 100,000. It is associated with high risk of spontaneous abortion, preterm delivery, intrauterine death, bleeding, pre-eclampsia, and persistence trophoblastic disease (PTD). It may associate with biochemical derangement that may induce

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symptomatic manifestation to the mother. There are few cases reported in Asia population with significant clinical dilemma and management to the maternal and foetus. Here, we report a case of a young woman with previous bad obstetric history who presented with antepartum per-vaginal bleeding and was noted to have a twin pregnancy with complete hydatidiform molar and viable foetus. It was complicated with markedly elevated human chorionic gonadotropin (hCG) and hyperthyroidism. Postpartumly, her hCG level was persistently high and her condition progressed into gestational trophoblastic neoplasm.

Keywords: complete hydatidiform molar, human chorionic gonadotrophin, hyperthyroid, twin pregnancy

INTRODUCTION

Twin pregnancy with complete mole co-existing with healthy live foetus is extremely rare with an estimated incidence of 1:20,000 – 100,000 (Vimercati et al. 2013; Lin et al. 2017). These pregnancies are associated with significant maternal and foetal complications that range from pre-eclampsia, thyrotoxicosis, antepartum haemorrhage, persistent trophoblastic disease, foetal malformation, prematurity and intrauterine death (Sharma et al. 2013). Patients with complete hydatidiform mole co-existing with normal foetus may have high risk of developing persistent trophoblastic disease, although others identify the risk as similar to that after a singleton molar pregnancy (Aguilera et al. 2012). The management of these pregnancies are difficult and involve other medical disciplines to minimise the complications that may arise. We report a case of abnormal twin pregnancy with complete hydatidiform molar co-existing with healthy live foetus accompanied with symptomatic biochemical derangement that progressed to persistent trophoblastic disease.

CASE REPORT

A 35-year-old woman of Gravida 7, Para 3+3 (3 live births and 3 abortions) presented to the Patient Admission Centre (PAC) of Obstetric Department in a general hospital at 22 weeks of gestation due to painless per-vaginal (PV) bleeding. It was the second episode of PV bleeding and was associated with lower abdominal pain. This was a planned pregnancy and she was sure of her dates. The dating scan was done at 6 weeks gestation at a private hospital. She was informed that she has twin pregnancy of one viable foetus with molar. A detailed scan was done and foetal parameters were corresponding to the gestational age. There was no subsequent follow-up as the patient opted for general public hospital for continuation of her management. She had a poor obstetric and gynaecological history of poor spacing, 2 miscarriages, and 1 ectopic

pregnancy that required salpingectomy and ovarian cyst requiring surgical removal. She did not have any other medical problem.

On examination, she had mild elevation of blood pressure (131/70 mmHg) compared to her booking blood pressure (106/72 mmHg) and was tachycardic (103 beats/ minute) with normal respiratory rate. Abdominal examination showed soft non-tender abdomen with gravid uterus of 28 weeks size. Left vulva varicose vein was noted with normal healthy cervix and minimal stale blood per speculum examination. Other systems were unremarkable. An urgent ultrasound scan was done and the results were consistent with the previous ultrasound done at the private hospital. The foetal parameters were corresponded with gestational age. Routine blood investigations showed hypochromic microcytic anaemia secondary to pregnancy with normal coagulation function and biochemical results.

The couple were counselled and agreed to continue with the pregnancy. The patient was advised for admission until delivery for her safety. Amniocentesis and assessment for gestational trophoblastic disease were performed. The karyotyping showed normal XY of the viable foetus. Further investigation showed that there was no evidence of malignant change in the patient.

However, at the 5th week of admission, she complained of palpitation. According to her, it was persistent since admission. Retrospectively, thyroid function test (TFT) was taken on admission which showed hyperthyroidism (Free T4: 21.8 pmol/L and TSH: <0.01 um/L). Unfortunately, the result was only reviewed at the time of complaint addressed by the patient. There was no other hyperthyroidism symptoms and no family history of thyroid disease. Physical examination for thyroid gland

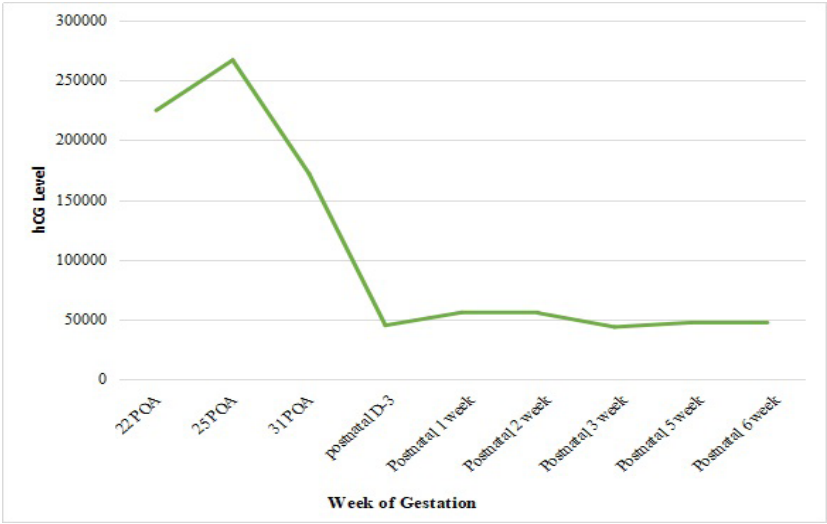

Figure 1: Serial hCG Level

Table 1: Serial Thyroid function test

	22 weeks POA	24 weeks POA	25 weeks POA	28 weeks POA	31 weeks POA	32 weeks POA	Post-natal Day 3	Post-natal Day 4	Post-natal 2 weeks	Reference Range
Free T4	21.8	30.3	24.9	15.8	10.9	9.0	7.0	7.4	12.0	12.0 – 22.0 pmol/L
TSH	< 0.01	<0.01	< 0.01	<0.01	< 0.01	<0.01	0.04	0.76	0.24	0.27 – 4.20 mu/L
Free T3	-	-	-	5.1	4.0	-	-	-	-	

was unremarkable.

It was also noted that her serum hCG was markedly elevated since admission which was reported as >225,000.00 mIU/ml. In view of symptomatic biochemical derangement, she was referred to the Endocrine Team for further management. Her thyroid antibodies results were negative suggestive of no underlying autoimmune pathology. She was treated with Carbimazole 15 mg tablet daily and Propanolol 20 mg tablet twice daily. Her serial TFT and hCG results were monitored biweekly. (Table 1, 2 and Figure 1). Her condition improved after commencement of medication.

At 29 weeks of gestation, the patient had another episode of painless PV bleeding and it was stable. She was planned for an emergency Caesarian section if her condition worsens. However, at 34 weeks of gestation, she had spontaneous vaginal delivery and a baby boy was safely delivered. The complete placenta was successfully removed. There was an area of abnormality seen on the placenta and histopathological examination showed that it was consistent with a complete mole in a twin gestation.

At 2 weeks postpartum, there was an improvement of the TFT results. However, the hCG level remain persistently high up to 6 weeks postpartum (Table 1 and Figure 1). In view of the persistently high level of hCG level, a malignant change of trophoblastic disease was suspected. This would necessitate urgent intervention to prevent complication from arising.

The patient was referred with the Gynae-Oncology team for further management. CT-scan was done at a private hospital showed presence of metastases lesion of undetermined site. The patient then defaulted treatment and was lost to follow up.

DISCUSSION

Twin pregnancy of complete

Table 2: Serial serum hCG level

	22 weeks POA	25 weeks POA	31 weeks POA	Post-natal Day 3	Post-natal 1 week	Post-natal 2 weeks	Post-natal 3 weeks	Post-natal 5 weeks	Post-natal 6 weeks	Reference Range
hCG	>225000	267057	172024	44973	55801	55325	43637	47308	47454	< 5 mIU/ml

hydatidiform molar with co-existing live twin is an extremely rare entity. The incidence reported in literature varies from 1 in 20,000 to 1 in 100,000 pregnancies (Vimercati et al. 2013; Lin et al. 2017). The diagnosis in such cases can be simply made by obstetric ultrasound examination but the management of subsequent complication is challenging. Traditionally, termination of pregnancy is executed to avoid the unacceptable risk of complications of complete hydatidiform molar pregnancy such as early onset pre-eclampsia, thyrotoxicosis, antepartum haemorrhage and increased risk of persistent trophoblastic disease (Shazly et al. 2012).

There is a paucity of study on the multiple gestations with complete hydatidiform mole. The largest report concerning complete mole and normal co-twin is from the Charing Cross and Weston Park Gestational Trophoblastic Disease Centers in the United Kingdom. Based on the report, between 1998 and 2011, 90 patients with complete mole and normal co-existing twin were managed. Among 51 patients deciding to continue pregnancy, 29 (57%) delivered a live baby at a median age of 34 weeks. Gestational trophoblastic neoplasia developed in 24 of 90 (27%) pregnancies, and there was no maternal death (Berkowitz et al. 2018).

A national study from Japan of 18 patients with proven androgenetic complete mole co-existent with twin live foetus found that persistent tumour developed in 50% of patients, and metastases were detected in six patients. Among the 13 patients who intended to continue the pregnancy, the pregnancy was terminated in 10 patients due to maternal complications, including preeclampsia, haemorrhage, or intrauterine fetal demise (Berkowitz et al. 2018).

Complete hydatidiform molar may have association with advanced maternal age and the use of assisted reproductive techniques. Thus, decision to terminate pregnancy would be difficult for the couple (Montes-De-Oca-Valero et al. 1999). Our patient had bad obstetric history prior to the current pregnancy with advanced maternal age. It was spontaneous non assisted pregnancy. The diagnosis of twin pregnancy of molar pregnancy co-existing with viable intrauterine foetus was made by ultrasonography at the private setting with regular follow-up to monitor the progress. Subsequently, she developed multiple episodes of anterpartum haemorrhage throughout her pregnancy which was further complicated by hyperthyroidism. Both patient and her spouse decided to continue with the pregnancy after being counsel regarding the possible complication of her pregnancy journey.

Her serum hCG and serum free T4 were elevated throughout the pregnancy that was only noted at 5th week of admission as she complaint of palpitation without other accompanying thyroid related symptoms. Her palpitation was controlled with anti-thyroid medication and her subsequent TFT showed subclinical trend and normalized post-delivery. Hyperthyroidism occurred in the patient as extremely high

level hCG had thyrotrophic activity because of structural similarity to thyroid stimulating hormone (TSH) (Swaminathan et al. 2017). A hCG level greater than 200,000 mIU/ml has been found to suppress TSH (Virmani et al. 2017). In our patient, the hCG level was >225000 mIU/ml and it explained the symptomatic hyperthyroidism in the patient.

At this point of time, she was treated as gestational trophoblastic disease (GTD) and received supportive treatment. She was prepared for possible emergency intervention that may occurred. GTD forms a group of disorders which comprises the conditions of complete and partial molar pregnancies, and the malignant conditions of invasive mole, choriocarcinoma and placental site trophoblastic disease (Gestational Trophoblastic Disease Guideline 2010 by Royal College of Obstetrics and Gynaecology). Gestational trophoblastic neoplasma (GTN) is defined as persistent GTD characterised by persistent elevation of serum hCG. Hydatidiform mole is the most common form of GTD representing 80% of cases. Moles may be complete, partial, or invasive. Complete and partial hydatidiform moles are differentiated by their karyotype, gross morphology, histologic appearance, and clinical features. Invasive moles act in an aggressive manner and are often treated similarly to choriocarcinomas.

Our patient was admitted to hospital due to possible foeto-maternal complications. She had few episodes of minimal antepartum haemorrhage while in the ward not requiring active intervention. Foetal growth was according with gestational age. Her molar pregnancy was monitored by serial serum hCG which showed down going trend with increasing gestational age although still in the high range. She had spontaneous vaginal delivery of a healthy baby boy at 34 weeks of gestation. Manual evacuation of her molar pregnancy was then successfully done. Histopathological examination confirmed that the molar tissue sample was complete hydatidiform mole. Serial hCG was done to monitor her postpartum progress.

Post evacuation of molar pregnancy, trophoblastic tissue was found to be persistent in about 20% of patient overall, but in a greater proportion of high risk patients. Higher risk is associated with advance maternal age, longer interval from previous pregnancy, and higher hCG. Surveillance is important after evacuation of molar pregnancy to exclude presence of persistent disease. The diagnosis is usually based upon the finding of stable or serially rising serum hCG concentration rather than by examination of tissues. To note, GTN may occur many years after the antecedent pregnancy and may even occur during menopause. Molar pregnancy with a persistent hCG elevation is considered to be persistent or recurrent GTN. The risk of choriocarcinoma is increased after a complete mole and only rarely been reported after a partial mole (Niemann et al. 2007).

The follow-up of after GTD is increasingly individualized according to Royal College of Obstetricians and Gynaecologists Guideline 2010. In those patients where hCG has

reverted to normal within 56 days of the pregnancy event, the follow-up will be for 6 months from the date of uterine evacuation. Those cases in which hCG has not reverted to normal within 56 days of the pregnancy event, the follow-up will be for 6 months from normalization of the hCG level. There are two large case series which showed that once hCG has normalised, the possibility of developing GTN is very low (Pisal et al. 2004; Sebire et al. 2007).

In this case, the patient GTD status was monitored by serial postpartum hCG for 6 weeks. It was noted that her serum hCG level remained high despite evacuation of molar tissue. Computed tomography (CT) scan was done for her at private setting and revealed that the disease has evidence of metastases but was not made available to treating hospital. She was diagnosed to have gestational trophoblastic neoplasia (GTN) and was scheduled for chemotherapy. However, the patient refused to continue follow-up in the government hospital. She opted for private facilities to manage her disease complication.

The use of serum hCG is important in the patient case as it help with the initial diagnosis of molar pregnancy as well as to monitor the progression. The serum hCG level also being one of the criteria in International Federation of Obstetrics and Gynaecology (FIGO) scoring for GTN. Thus, it is important to know the analytical requirement of the test in order to ensure the reliability of the available result to avoid confusion and misinterpretation by the Obstetrician and Gynaecologist.

Women with GTN can be treated either with single-agent or multi-agent chemotherapy. The treatment used is according to the FIGO 2000 scoring system for GTN following assessment at the treatment centre. The need for chemotherapy following a complete mole or partial mole is 15% and 0.5%, respectively. According to Newland (2003), the development of postpartum GTN requiring chemotherapy occurs at a rate of 1/50000 births.

Based on the FIGO 2000 scoring system, women with scores ≤ 6 are at low risk and are treated with single-agent chemotherapy. Those with score < 6 has cure rate almost 100%. For women with scores ≥ 7 are at high risk and are treated with intravenous multi-agent chemotherapy. The treatment is commences in all cases until the hCG level normalized for further 6 consecutive weeks. The cure rate is 95% for women with FIGO scores ≥ 7. For women who undergo chemotherapy are advised not to conceive for 1 year after completion of treatment as to avoid recurrent of molar, risk of miscarriage, termination of pregnancy, congenital abnormality and stillbirth.

Since our patient was lost to follow-up, the details regarding her metastases status was unavailable to us. Therefore, it is difficult to categorise patients according to FIGO score. It is expected that the patient has a score less than 6 and considered as low risk.

CONCLUSION

Twin pregnancy with complete hydatidiform molar and viable foetus is

a very rare condition seen worldwide. Even though the diagnosis is based on sonography and non-invasive, the complication that may arise can be disastrous to the mother and fetus. Thorough follow-up and management of the patient is a must to ensure a good outcome for both mother and baby. The knowledge on hCG and its clinical utility is important as it is essential in the diagnosis of complete hydatidiform mole as well as managing the complications that may arise. Once diagnosed, proper management must be commenced in order to reduce the risk of related complications.

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