CASE REPORT

The interplay of Graves' disease and twin molar pregnancy

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SUMMARY

Twin molar pregnancy with coexistent viable fetus in a patient with Graves' disease is a rare entity. The patient is a 37-year-old woman who was hospitalised owing to persistent vomiting and vaginal bleeding. The pregnancy test was positive and the pelvic ultrasound disclosed twin gestation of complete mole and a coexistent viable 12-week fetus. β -Human chorionic gonadotropin (β -HCG) and free thyroid hormones were both elevated. The patient was also a diagnosed case of Graves' disease prior to this pregnancy. Given the risks for perinatal complications, the patient was offered early termination of pregnancy. She, however, decided to continue her pregnancy and control the hyperthyroidism with an antithyroid drug (ATD). A week after her discharge from the hospital, she had spontaneous abortion and the histopathology of the abortus revealed complete hydatidiform mole and a 13-week fetus.

BACKGROUND

The incidence of hyperthyroidism in pregnant women has been estimated to range between 0.1% and 0.4%, with Graves' disease as the most common cause.¹ Pregnancy-specific conditions like hyperemesis gravidarum, especially in twin pregnancy, and gestational trophoblastic disease can also lead to clinical hyperthyroidism.¹ Twin pregnancy with hydatidiform mole and coexistent fetus is a rare entity.² In most cases, treatment of pregnancy-specific hyperthyroidism with ATD is not necessary since foetal thyroid tissue is not stimulated by the large amount of β -HCG in the maternal serum and, therefore, treatment of the mother with ATD would result in foetal hypothyroidism.³ Furthermore, evacuation of the hydatidiform mole usually resolves the thyrotoxicosis without medical treatment.³ Coexistence of Graves' disease with this type of condition poses challenges and difficulties in the diagnosis and treatment of both the mother and the live fetus.

CASE PRESENTATION

A 37-year-old Filipina, G3P2 (2002), was hospitalised because of persistent vomiting and vaginal bleeding. She has been amenorrhoeic for 2 months before she started experiencing abdominal pain, vomiting and vaginal spotting. Urine pregnancy test was positive a month prior to her admission. She had been experiencing episodes of palpitations, tremors and heat intolerance which she attributed to her Graves' disease. Thinking that her ATD, methimazole, is contraindicated to her current

pregnancy, she decided to stop the medication without consulting her endocrinologist. Although she had no worsening of hyperthyroid symptoms, she had frequent vomiting and more profuse vaginal bleeding.

She had been diagnosed with Graves' disease with orbitopathy for 5 years. She was, most of the time, euthyroid at 10 mg methimazole once a day except lately when she had episodes of palpitations, tremors and heat intolerance. She was offered radioactive iodine ablation or surgery 3 years prior to this admission but she opted to simply continue her medical treatment alone. She had two previous normal pregnancies, no previous history of abortion, ectopic pregnancy, molar pregnancy or gestational trophoblastic diseases.

Upon physical examination, she was awake, hypertensive at 140/90 mm Hg, tachycardic at 110 bpm, afebrile, with pinkish conjunctivae and exophthalmos. She had diffuse thyromegaly (8×8 cm per lobe), loud first heart sound with regular rhythm, moist warm skin, fine tremors and with heightened deep tendon reflexes. Her abdomen was slightly globular and on internal gynaecological examination, her cervix was closed with blood on examining finger.

INVESTIGATIONS

Pregnancy test was positive. Her pelvic ultrasound revealed a heterogenous mass measuring 13.7×13.0×7.9 cm with multiple cysts, suggestive of complete hydatidiform mole, and a coexistent 12-week live fetus. Human chorionic gonadotropin (β -HCG) was elevated at 1 000 000 IU/l (27 832–210 612) with thyroid stimulating hormone (TSH) of 0.005 mIU/l (0.3–3.8) and free thyroxine (FT4) of 70.4 pmol/l (11–24). We considered hyperthyroidism secondary to the following conditions: (1) Graves' disease and (2) twin molar pregnancy.

DIFFERENTIAL DIAGNOSIS

Two causes of hyperthyroidism were considered in this case. Graves' disease was favoured over transient gestational hyperthyroidism by the presence of diffuse thyromegaly, thyroid-related ophthalmopathy and thyrotoxicosis prior to pregnancy. Hyperthyroidism, however, was further aggravated by the presence of severely elevated β -HCG from the complete molar pregnancy.

TREATMENT

Upon confirmation of twin molar pregnancy with viable fetus, our team (endocrinologists and

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obstetrician-gynaecologists) planned for the strategies to continue the pregnancy without risking the health of both the mother and viable fetus. However, knowing the risks for miscarriage and persistent trophoblastic disease, early termination of pregnancy was offered to the couple. When the couple opted to keep the pregnancy, medical management which includes careful surveillance of fetus' viability, foetomaternal haemorrhage and gestational trophoblastic disease, was instituted.

The patient was also started on propylthiouracil (PTU) at 150 mg/day in three divided doses to target FT4 at the upper limit of normal values. Vomiting, tremors and vaginal bleeding, as well as hypertension and tachycardia subsequently resolved.

However, 1 week after the hospital discharge, the patient had spontaneous abortion from foetomaternal haemorrhage. Completion curettage was done and histopathology of the abortion revealed a 13-week fetus with grape-like soft tissue fragments admixed with blood clots and meaty tissue fragments read as complete hydatidiform mole (see figure 1). Repeat β -HCG went down to 32 610 IU/l (from 1 000 000) with TSH of 0.005 mIU/l (0.3–3.8) and FT4 of 21.5 pmol/l (11–24). PTU was shifted to methimazole 10 mg once a day. Methotrexate with folinic acid was also given as chemoprophylaxis for persistent trophoblastic disease.

OUTCOME AND FOLLOW-UP

A month after the termination of pregnancy and chemoprophylaxis with methotrexate, the patient was clinically euthyroid with normal FT4 (18.1 pmol/l) and slightly decreased TSH (0.2 mIU/l). She is currently on serial β -HCG monitoring.

DISCUSSION

Molar pregnancy, which is relatively common among Asians with an incidence rate of 1 per 120–400 pregnancies⁴ is the result of an aberrant fertilisation of the ovum with imbalanced genetic inputs.⁵ It is classified as gestational trophoblastic neoplasia, partial hydatidiform mole and complete hydatidiform mole.⁵ Hyperthyroidism arising from a molar pregnancy occurs at 2%⁶ but some reports showed as high as 25–64%.⁷ This hyperthyroid state in molar pregnancy is secondary to the thyrotropic action of HCG, a glycoprotein molecule secreted by trophoblastic tissues.⁸ Although with lower potency to stimulate TSH receptor compared with TSH, HCG at >100 000 IU/l will usually result in clinical hyperthyroidism.⁹

Figure 1 A 13-week fetus with grape-like soft tissue fragments admixed with blood clots and meaty tissue fragments read as partial hydatidiform mole.

Surgical removal of the hydatidiform mole is the definite treatment of choice in molar pregnancy and should be performed as soon as possible to attain euthyroidism and to prevent persistent trophoblastic disease.⁸ ATD like thionamides are not usually indicated in the treatment of hyperthyroidism in molar pregnancy unless the patient is moderately to severely symptomatic.⁸

Coexistence of viable fetus with molar pregnancy is a rare entity. The incidence ranges from 1 in 22 000 to 100 000 pregnancies and this may be increasing with greater use of assisted reproductive techniques.² The association of complete hydatidiform mole and live fetus in the same pregnancy, as in this case, generally represents dizygotic twin pregnancies in which one fertilisation results in a complete mole and the other in a normal cotwin.¹⁰ Hyperthyroidism in this type of pregnancy is more pronounced compared with molar pregnancy alone. Grun *et al*¹¹ has reported suppressed TSH levels in 60% of twin gestations compared with 21% matched controls. This finding corresponded to the much higher and more sustained peak of HCG in twins.⁸ As in molar pregnancy alone, ATD-like thionamides are not usually indicated in the treatment of hyperthyroidism. The large amount of HCG circulated in the maternal serum in twin molar pregnancy does not significantly cross the placental barrier and, therefore, does not stimulate the foetal thyroid. Thus treatment of thionamides will only result to foetal hypothyroidism.¹²

Coexistence of Graves' disease with this type of pregnancy further complicates the condition as both hyperthyroidism and therapy of the disease may affect the course and outcome of the pregnancy. Hyperthyroidism in this case may have resulted from the interplay of autoimmune process of Graves' disease and HCG-induced thyrotoxicosis of molar pregnancy. Graves' hyperthyroidism tends to worsen during the first trimester of pregnancy owing to elevation of thyroid receptor autoantibodies (TRAb) and improve with progression of pregnancy.¹³ Unlike HCG, TRAb readily crosses placental barrier, stimulates foetal thyroid and therefore causes foetal hyperthyroidism.¹³ This uncontrolled hyperthyroidism is associated with numerous adverse foetal outcomes and maternal risks such as increase in neonatal mortality rate, delivery of low-birth weight infants, risk of premature labour and frequency of pre-eclampsia.^{14 15} ATD therapy, therefore, should be used for hyperthyroidism owing to Graves' disease during pregnancy. Although anti-thyroid therapy is not routinely indicated in the management of molar pregnancy, the coexistence of Graves' disease and severely elevated HCG in our patient (1 000 000 IU/l) justified the use of this drug. PTU is the ATD therapy of choice during the first trimester and the dose, however, should be kept as low as possible to avoid foetal hypothyroidism.¹⁶

The decision to keep the fetus in this complicated pregnancy was not tempered by the cumulative risks from Graves' disease and molar pregnancy. Foetal loss rate and maternal complications is high in molar pregnancy particularly in complete mole (~60% and 10%, respectively¹⁷) despite adequate foetomaternal surveillance. Successful delivery of normal fetuses were, however, reported in some cases.^{18 19}

Apart from previously mentioned maternal and foetal outcomes of hyperthyroidism which can be prevented with adequate treatment, there were few reports of molar pregnancy-induced thyroid storm.^{20 21} These crises resulted from severely elevated HCG level during the pregnancy. As in the case of singleton molar pregnancy, patients with twin molar pregnancy have risks of developing persistent trophoblastic disease. The estimated risks based on available case reports and case series has been reported at around 19%²²

and as high as 50%.²³ This is higher compared to the reported risks from partial molar pregnancy.¹⁷ It is not yet known, however, whether this higher risk seen among patients with complete molar pregnancy was owing to delay of termination of pregnancy or rather owing to more aggressive behaviour of trophoblastic tissues.²⁴

Approach to Twin Molar Pregnancy in a background of Graves' disease should be individualised as there are no known protocols or consensus to follow. Management should be directed to prevent foetal loss and morbidity at the same time ensuring adequate treatment to avoid maternal complications both from the hyperthyroidism and the trophoblastic diseases.

Learning points

- ▶ Diagnosis and management of hyperthyroidism in pregnancy entails understanding of the different aetiologies.
- ▶ Whatever is the cause of hyperthyroidism, management should be tailored to prevent maternal and foetal morbidity from undertreatment and overtreatment.
- ▶ Coexistence of more than one cause of hyperthyroidism interplaying during pregnancy poses more challenges as it usually carries poorer outcomes.
- ▶ A multidisciplinary approach to the treatment of twin molar pregnancy in a background of Graves' disease should be instituted.

Competing interests None.

Patient consent Obtained.

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