Pregnancy is associated with physiological changes in thyroid function that can make the diagnosis of hyperthyroidism difficult. Many symptoms of normal pregnancy mimic the symptoms of hyperthyroidism. Graves’ disease represents the commonest cause of maternal hyperthyroidism, but although they are rare, trophoblastic tumours should be included in the differential diagnosis to avoid untoward consequences.

Gestational trophoblastic neoplasia (GTN) includes hydatidiform moles at one end of the spectrum and highly malignant choriocarcinoma at the other. The prognosis of choriocarcinoma has improved dramatically, and what was once one of the most fatal malignancies now has cure rates exceeding 90%. However, delays in diagnosis and misdiagnosis still contribute to morbidity and mortality associated with choriocarcinoma. We present two cases to illustrate the spectrum of GTN.

Case reports

A 29-year-old woman was admitted to Helen Joseph Hospital with a 2-day history of dyspnoea, cough productive of pink, frothy sputum, malaise and anorexia. Further inquiry revealed that she had been bleeding per vagina for a month and that she believed herself to be 4 months pregnant with her second child. Her previous pregnancy, 3 years earlier, had been uneventful. She had no other history of note.

Examination revealed the patient to be in gross congestive cardiac failure with frank pulmonary oedema, a hyper-dynamic circulation and significant tachycardia. She had a 22-week uterus on palpation and a positive urine pregnancy test upon dilution of the specimen. An abdominal ultrasound scan suggested a hydatidiform mole.

Biochemical investigations showed a free thyroid hormone level (fT₄) of 33.3 pmol/l, a thyroid stimulating hormone (TSH) level of <0.01 mIU/l, and a markedly increased human chorionic gonadotrophin (hCG) level of 51 972 mIU/ml. A chest radiograph showed an increased cardiothoracic ratio with features of pulmonary oedema. Echocardiography showed a globally dilated heart with a left ventricular ejection fraction of 30%, mild mitral regurgitation, and a small pericardial effusion.

Management of the patient included diuresis, afterload reduction, anticoagulation, beta-blockade, pre-emptive management for thyrotoxic storm pre- and peri-operatively, and early evacuation of the uterus under general anaesthesia. Pathology confirmed a hydatidiform mole with no features of invasive choriocarcinoma. The patient’s general condition improved rapidly after evacuation. Cardiac function and echocardiography findings normalised by postoperative day 7, thyroid symptoms and biochemical values returned to normal, allowing for rapid weaning of medications, and hCG returned to normal over several weeks.

The second case was that of a 27-year-old woman admitted to Johannesburg Hospital with a 2-month history of severe shortness of breath and non-productive cough. Her past gynaecological history included a miscarriage 3 months before admission and birth of a healthy child 5 years previously, but she had no other significant past medical or surgical history. She had been well before the miscarriage. During the previous 2 months the patient had been admitted twice to another hospital with shortness of breath and, in view of an inadequate response to antibiotics, a provisional diagnosis of non-resolving pneumonia was made. Clinical examination revealed central cyanosis, spider naevi, palmar erythema.
and a clinically palpable 16-week uterus. The patient was initially treated with intravenous broad-spectrum antibiotics and steroids. In view of the central cyanosis and marked respiratory distress an urgent computed tomography scan of the chest was requested but revealed no pulmonary embolus. However, a diffuse bilateral fine nodular infiltrate with pleural-based lesions called for provisional review of the initial diagnosis from non-resolving pneumonia to probable autoimmune interstitial lung disease. The autoimmune markers were negative. In view of a history of a recent miscarriage and clinical evidence of a palpable uterus as well as spider naevi and palmar erythema, blood tests for hCG and thyroid function were requested by the Division of Endocrinology upon consultation.

Blood results revealed an hCG >1 000 mIU/ml, progesterone 107.7 pmol/l, oestrogen 3 670 pmol/l, fT₄ 67.6 pmol/l and TSH <0.001 mIU/l. An ultrasound scan of the abdomen confirmed a suprapubic mass. A provisional diagnosis of interstitial lung disease was changed to that of a probable choriocarcinoma with lung metastasis. There was no evidence of thyroid storm, and treatment with anti-thyroid medication was initiated. Clinical improvement was noted but the patient developed vaginal bleeding 4 days after admission, which subsided. She died unexpectedly 5 days after admission. The family declined the request for an autopsy.

**Discussion**

Normal pregnancy is accompanied by a series of hormonal and metabolic events that provide a favourable environment for the developing fetus. These physiological alterations make the diagnosis of thyroid dysfunction in pregnant women very difficult as the clinical signs and symptoms may be mimicked by the hyper-metabolic state of normal pregnancy. The most common cause of maternal hyperthyroidism is Graves’ disease. Other causes such as single toxic adenoma, multinodular toxic goitre and thyroiditis account for most of the remaining cases. Gestational trophoblastic disease is a much rarer cause of gestational thyrotoxicosis. Changes in thyroid function are normal in healthy pregnancy and are secondary to the weak thyroid-stimulating activity of hCG, which peaks at approximately 10 - 12 weeks, but despite a secondary increase in serum free thyroid hormone (fT₄ and fT₃) concentrations the latter hormones usually remain within the normal range. Transient gestational thyrotoxicosis represents exaggeration of the physiological increase in thyroid stimulation during the first trimester and may be associated with hyperemesis. This response may be further exaggerated in gestational trophoblastic disease resulting in significant hyperthyroidism.

Increased responsiveness of abnormal TSH receptors to hCG represents a rare genetic variant of gestational thyrotoxicosis.

Gestational trophoblastic neoplasia (GTN) includes a clinical spectrum of diseases that derive from fetal trophoblastic tissues and have characteristic geographical variation. At one end of the spectrum are the benign partial and complete hydatidiform moles and at the other end the malignant group, which includes persistent hydatidiform mole, invasive hydatidiform mole and choriocarcinoma. Together they represent a spectrum of histopathological conditions.

Risk factors include maternal age (higher risk for women under 20 years and older than 40 years), history of previous hydatidiform mole, reproductive history (increased risk for parous women), parental blood groups (increased risk for hydatidiform mole in women with blood group A and men with blood group O or A), use of oral contraceptives, infections, and environmental and lifestyle factors such as diet and smoking.

hCG is a glycoprotein hormone that consists of two dissimilar subunits, α and β, joined non-covalently. The primary role of hCG in a normal pregnancy is to serve as a signal to the ovary to maintain the corpus luteum. Malignant trophoblastic tissue retains its ability to produce differentially glycosylated hCG molecules as well as human placental lactogen and sex steroids. With the exception of placental site trophoblastic tumours almost all forms of GTN produce hCG in proportion to the amount of trophoblastic tissue present. Serum hCG is used not only to diagnose but also to monitor therapy of gestational trophoblastic disease.

hCG has thyrotropic activity due to its structural homology with TSH and there is direct correlation between hCG and fT₄ levels. As a result of the stimulation of TSH receptors by hCG, as well as an increase in thyroxine-binding globulin, sub-clinical hyperthyroidism is a common manifestation of early pregnancy. This phenomenon also contributes to hyperemesis gravidarum. The high circulating levels of hCG, and the presence of isoforms with increased activity, make hyperthyroidism a common complication of GTN with a spectrum ranging from mild hyperthyroidism to severe thyrotoxicosis. Molar pregnancies also have higher progesterone levels than normal pregnancies. Oestrogen levels are generally higher than in the non-pregnant state but in complete moles tend to be lower than in normal pregnancy owing to the lack of fetal adrenal tissue.

Patients with hydatidiform mole may present with vaginal bleeding, uterine enlargement greater than expected for gestational age, unilateral or bilateral ovarian enlargement, hyperemesis, pre-eclampsia,
pregnancy-induced hypertension or hyperthyroidism. Diagnosis is confirmed with pelvic ultrasound and the patient should be optimised for evacuation. Postmolar GTN may complicate as many as 15 - 20% of all patients and careful follow-up with regular hCG measurements is therefore recommended. Baseline hCG should be obtained 48 hours after evacuation followed by weekly measurements until values normalise. Thereafter levels should be monitored at 1- or 2-monthly intervals to ensure a sustained remission beyond 12 months.

Malignant trophoblastic diseases often pose a diagnostic difficulty, and as a result delays in diagnosis are a common problem. The diagnosis often requires a high index of suspicion and prolonged, irregular bleeding after delivery or miscarriage should prompt the diagnosis. Metastatic disease is commonly present at presentation mostly due to delays in diagnosis. Clinically, malignant GTN can be classified as metastatic and non-metastatic. Metastatic disease can be further subdivided into GTN with good and poor prognosis. Poor prognosis is indicated by any of the following: long duration (>4 months since last presentation), pre-treatment hCG >40 000 mIU/ml, brain or liver metastases, antecedent term pregnancy and prior chemotherapy. Patients with non-metastatic and good prognosis metastatic disease have better outcomes and the initial therapy is usually with a single agent, whereas the metastatic poor prognosis group should have multi-agent therapy as the primary treatment. Methotrexate or dactinomycin are often used as primary agents in the non-metastatic and good prognosis metastatic disease groups. Patients treated with chemotherapy for malignant GTN benefit from weekly hCG measurements and therapy should be considered beyond the first normal value. Of note, respiratory failure from pulmonary metastases is rare but if the patient is breathless at rest before treatment initiation, as was our second patient, their respiratory function is likely to deteriorate further with initiation of chemotherapy.

Conclusion

Thyroid hormone physiology is naturally altered in pregnancy. Compounding the problem is the hyperdynamic state of pregnancy that may mimic the signs and symptoms of hyperthyroidism, making the diagnosis of hyperthyroidism difficult. Graves’ disease is the commonest cause of thyrotoxicosis in pregnancy, but rare causes such as trophoblastic disease should be included in the differential diagnosis. Malignant trophoblastic diseases have been associated with a much better prognosis with the advent of effective chemotherapy, but delays in diagnosis and metastatic diseases that are refractory to conventional chemotherapy still contribute to morbidity and mortality associated with GTN.10,11

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