Thyroid Diseases in Pregnancy Part II: Hyperthyroidism and Pregnancy

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Patients with hyperthyroidism present to the obstetrician in several ways, some of which may not be clinically obvious at the time (see box). Hyperthyroidism may be due to a relapse of Graves' disease, or present for the first time in pregnancy as a result of Graves' disease, thyroiditis, or hyperemesis gravidarum.[1,2] In hyperemesis gravidarum, the thyroid function should spontaneously return to normal by the last trimester.[3] Nevertheless, the clinical features may be indistinguishable from those of Grave's disease, apart from eye signs; the thyroid function test is also of little help. A parameter of the tissue effects of hyperthyroidism, such as the measurement of erythrocyte zinc concentration which is reduced significantly in pre-existing hyperthyroidism, can be utilised to differentiate between these two conditions.[4] In severe cases of hyperthyroidism complicating hyperemesis gravidarum, a short course of antithyroid treatment may be required, usually resulting in a rapid and dramatic response,[2,5] but there have been no randomised studies that have proven the efficacy of antithyroid treatment in the management of hyperemesis gravidarum, and the management of these cases must be individualised.

Uncontrolled hyperthyroidism can lead to congestive heart failure, thyroid storm, preterm labour, pre-eclampsia, foetal growth restriction, and increased perinatal mortality. Even when hyperthyroidism is controlled during pregnancy, the risk of a low birthweight infant is still increased compared with patients in whom hyperthyroidism was controlled before pregnancy.[6,7] Erythrocyte zinc concentration at 24 to 28 weeks of gestation, an indicator of the tissue effect of hyperthyroidism in early pregnancy, has been shown to be significantly correlated with gestational age and birthweight.[8] Hyperthyroidism should be controlled before conception to ensure optimal pregnancy outcome.

The more common and important causes of hyperthyroidism (see also table) are described below.

Clinical Presentation of Hyperthyroidism in Pregnancy

- Clinical features of hyperthyroidism including nervousness, emotional lability, inability to sleep, tremors, weight loss, excessive sweating, heat intolerance.
- Hyperemesis gravidarum
- Spontaneous abortion
- Preterm labour
- Pre-eclampsia
- Foetal growth restriction
- Asymptomatic

GRAVES' DISEASE

This is the commonest cause of hyperthyroidism in pregnancy. Instead of the classical features of Graves' disease, features which are common to pregnancy, such as tachycardia, palpitation, systolic

hypertension, cardiac murmur, tremour, excessive sweating, heat intolerance, nervousness, insomnia and emotional lability, are more likely to be found. A relapse or deterioration can present with failure to gain weight or weight loss despite good appetite, tachycardia, excessive sweating, and frequent bowel motion in contrast to the tendency towards constipation. Some cases of Graves' disease can also present as hyperemesis gravidarum,[9,10] and thyroid storm can present as eclampsia.[11] Because of the increased incidence of HLA B8, DR5 and DR3 in patients with Graves' disease,[12] any mothers with a positive family history should have their thyroid function tested even if only mild features are found.

Table. Summary of Disturbances of Thyroid Function During Pregnancy

	Hyperthyroid	Hypothyroid	Euthyroid Sick Syndrome
Unrelated to pregnancy	Graves' Disease	Post-treatment of Graves' Disease	—
	Hashimoto's Thyroiditis	Thyroiditis	
	Adenoma (toxic nodule)	Iodine deficiency	
	Iodine induced		
Related to pregnancy	Hyperemesis gravidarum	—	Pre-eclampsia
	Molar pregnancy		

Management of Graves' Disease in Pregnancy

Assessment and Monitoring

Patients taking antithyroid medication should have their clinical progress closely monitored ie. weight gain and foetal growth, and maternal serum TSH and FT4 measured every 4 to 8 weeks. Provided foetal growth and maternal symptomatic control are satisfactory, the patient should be maintained at a slightly hyperthyroid state. The dose of antithyroid medication may need to be adjusted in each trimester. The addition of thyroxine may help the mother but will not benefit the foetus who will be rendered hypothyroid by excessive maternal medication. Treatment can be stopped at 36 to 37 weeks if maternal and foetal conditions are satisfactory. If euthyroidism has not been achieved by delivery, such as may be the case with preterm labour, antithyroid medication should be continued, perhaps at a reduced or minimal effective dose, rather than stopped abruptly. For mothers with a relatively short duration of treatment, the dose should not be reduced too rapidly, as relapse may occur in the last trimester even before cessation of treatment.

For patients in whom previous antithyroid treatment has been stopped, there is still a high frequency of relapse within 24 months of completing a course of treatment.[13] Thyroid function tests should be performed at booking, and repeated as indicated. Treatment should be recommenced if necessary.

For patients with previous ablation of their thyroid gland, or who have been in remission for many years, there may be subclinical hypothyroidism. Maternal TSH level should be assessed at each trimester, and thyroxine replacement considered if there is a progressive increase in the TSH level above the normal range.

Antithyroid Medications

• *Thionamides.* These include propylthiouracil (PTU), methimazole and carbimazole. By preventing organification of iodide and coupling of iodotyrosines to form T4 and T3, they inhibit thyroid hormone biosynthesis. There is also a significant immunosuppressive effect.[14] In addition, PTU

blocks the peripheral conversion of T4 to T3 and lowers T3 levels faster, thus making it the drug of choice for women who need to start treatment during pregnancy. The starting dose of PTU is 200 to 450 mg per day, with a daily maintenance of 50 to 300 mg. The commencing dose of methimazole and carbimazole varies from 10 to 45 mg per day. Since a higher dose is associated with an increased rate of side effects, such as allergic reactions and skin rash, it may be safer to begin with a lower dose eg. methimazole 10 mg or carbimazole 15 mg daily. The most serious side effect is agranulocytosis, therefore a baseline complete blood count should be recorded. In areas of borderline iodine supply, patients may be more sensitive to treatment and their thyroid function must be closely monitored. Once euthyroidism is achieved, the doses can be adjusted to the minimal effective dose for maintenance.

• *Beta-blockers.* Beta-blockers such as propranolol are a useful adjunct to the thionamides and control the sympathetic-like symptoms of hyperthyroidism, while waiting for the effect of thionamides to be established. Propranolol also inhibits the peripheral conversion of T4 to T3,[15] and is complementary to the effect of the thionamides. A therapeutic effect can be seen with daily doses of 30 mg orally, but up to 160 mg may be necessary. Once control is established, propranolol can be discontinued and foetal complications like intrauterine growth restriction and neonatal hypoglycaemia that occur with prolonged use can be avoided.

• *Iodides.* Iodides inhibit the release of synthesised thyroid hormones and the effect is additive to that of the thionamides. However, long term use will cause foetal goitre, while the mother will become refractory to the action of iodides within 14 days. Therefore intravenous sodium iodide 1 g daily, or potassium iodide solution orally, is used as adjunctive therapy for 7 to 10 days as the initial treatment for severe relapse or thyroid storm.

• *Radioactive Iodine.* This is contraindicated in pregnancy because of the risk of foetal thyroid ablation. However, as the foetal thyroid does not begin to concentrate iodine until 10 to 12 weeks of gestation, radioactive iodine given even in the early first trimester should not affect the foetus.

Subtotal Thyroidectomy

Subtotal thyroidectomy is rarely performed when medical treament has failed to achieve control by the second trimester. Postoperative hypocalcaemia may be a problem and the maternal serum calcium level must be monitored and appropriate treatment instigated.

The Foetus and Neonate

The thyrotropin stimulating antibodies (TSAb) in the mother cross the placenta and stimulate the foetal thyroid as well, resulting in foetal and neonatal thyrotoxicosis even in infants born to euthyroid or hypothyroid mothers who have undergone partial thyroidectomy. The TSAb levels in maternal and cord blood are similar,[16] and the titre is predictive of neonatal thyrotoxicosis and hypothyroidism in infants born to both treated and untreated mothers.[16,17] The commonest clinical feature of foetal Graves' disease is a persistent foetal tachycardia. Other features include foetal goitre and frontal bossing, premature craniosynostosis, growth restriction and heart failure. If there is doubt about the diagnosis, confirmation can be achieved by cordocentesis and direct assessment of foetal thyroid function.[18]

Untreated foetal thyrotoxicosis is associated with increased perinatal mortality, preterm labour and foetal growth restriction,[19] so in utero treatment is necessary, using thionamides which also cross the placenta and are taken up by the foetal thyroid as early as the second trimester. Starting doses of 50 to 200 mg daily of PTU can be given and the dose assessed frequently and titrated against the foetal heart rate. This can reverse the features of foetal thyrotoxicosis and enable the pregnancy to continue with an improved out-

come.[19] If large doses, eg. PTU 300 mg or more per day, are given or maintained towards the end of pregnancy, the neonate may have hypothyroidism. All infants born to mothers with a history of Graves' disease, regardless of status, should undergo thyroid assessment after birth. Methimazole and carbimazole have also both been associated with aplasia cutis in the foetus, and the neonate should be examined carefully after birth.

Postnatal Management

Breast feeding is safe even in mothers who continue with treatment, as drugs such as PTU are excreted in insignificant amounts in the breast milk and neonatal thyroid function is not depressed.[20,21] Nevertheless, for nursing mothers taking high doses of thionamides, infant thyroid function should be assessed as a precaution against undiagnosed neonatal hypothyroidism.

T3 THYROTOXICOSIS

T3 thyrotoxicosis, found in 4% of hyperthyroid patients, is characterised by normal or low T4 level and elevated T3 level. The condition is associated with prolonged hyperthyroidism and long term therapy with PTU, and it has been reported in pregnancy.[22] Serum FT3 level should be checked in mothers with clinical features of hyperthyroidism, suppressed serum TSH level and a normal or low FT4 level.

HASHIMOTO'S THYROIDITIS

Hashimoto's thyroiditis can present with hyperthyroidism before or during pregnancy, and the clue is the elevated titre of antimicrosomal antibody. While the hyperthyroidism should be managed much like that of Graves' disease, the serum TSH level must also be monitored closely as hypothyroidism can develop.

POSTPARTUM HYPERTHYROIDISM AND THYROIDITIS

The reported incidence of postpartum thyroid disorder varies between 4 and 7%, and has possible effects on lactation, postpartum mood changes and depression, and menstrual disturbance. Postpartum hyperthyroidism may be the first presentation or an exacerbation of Hashimoto's thyroiditis and Graves' disease. Hashimoto's thyroiditis may present initially with transient and self-resolving hyperthyroidism occurring 2 to 4 months postpartum, followed by hypothyroidism 3 to 8 months postpartum.[23] The Postpartum Painless Thyroiditis (PPT) syndrome, an atypical form of hyperthyroidism due to thyroiditis and unrelated to such conditions as atypical subacute thyroiditis, occurs shortly after delivery, and is clinically indistinguishable from the non-pregnancy-related form. A phase of transient thyrotoxicosis of abrupt onset is followed by a second phase of transient hypothyroidism, before recovery to euthyroidism. This is associated with positive antimicrosomal antibody titre. In some cases, there is no preceding hyperthyroid phase, while the hypothyroid phase may be absent in up to 60% of the cases, and the typical course of events can develop over a period of 8 to 12 months.[24-26] It can also appear within a few weeks or even days of delivery,[27] and present not only with signs of hyperthyroidism but also severe hypertension.[28] The postpartum administration of 0.1 mg of L-thyroxine can ameliorate the hypothyroid symptoms but does not alter the course, while the use of 0.15 mg iodide daily appears to aggravate the condition.[29] Despite the recovery to euthyroidism, a significant proportion of PPT patients also develop hypothyroidism 2 to 4 years postpartum, the risk factors being high antimicrosomal antibody titre during pregnancy, activity of hypothyroid phase, multiparity, and a previous history of spontaneous abortion.[30] Patients with PPT should therefore receive long term follow-up.

ASSOCIATION WITH OTHER AUTOIMMUNE DISORDERS

Graves' disease and Hashimoto's

thyroiditis can be associated with other autoimmune diseases, such as haemolytic anaemia, immune thrombocytopaenic purpura, myasthenia gravis, pernicious anaemia and systemic lupus erythematosis.[31-33] These conditions can present before or after the clinical manifestation of thyroid disorder, as well as incidentally during the workup for hyperthyroidism, and further investigations will depend on the clinical findings.

CONCLUSION

Thyroid disorders are commonly encountered in women in the reproductive age group, and are a well known cause of poor reproductive performance. Thyroid function should be assessed in women with a history of obstetric problems and certain obstetric complications such as preterm labour and pre-eclampsia. Appropriate and prompt treatment dramatically improves the outcome of pregnancy.

This is a two-part paper, Part I dicussed Hypothyroidsism in Pregnancy.

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