Thyroid disease in pregnancy

Thyroid disease is common in the childbearing years. It impairs fertility and, if untreated, greatly increases risks of complications in pregnancy. The physiological changes of pregnancy place stresses on the thyroid axis, but most women adapt to these and remain euthyroid. This article will assist GPs managing patients with thyroid disease during pregnancy and in the postpartum period.

H. DAVID McINTYRE
MB BS, FRACP
KARIN M. LUST
MB BS, FRACP

Dr McIntyre is Director of Endocrinology, Mater Hospital; Dr Lust is Staff Specialist in Internal and Obstetric Medicine, Mater Misericordiae Hospital, South Brisbane, Qld.

Thyroid under- or overactivity is common in young women. If thyroid dysfunction is undetected in pregnancy, adverse outcomes may result for both mother and baby. Most patients initially present to their GP, but specialist assistance is often desirable, especially in the management of thyrotoxic patients.

The physiological adaptations to pregnancy are discussed in the box on page 40.

Hypothyroidism

Hypothyroidism reduces fertility by causing hyperprolactinaemia, anovulation and luteal phase defects. Autoimmune thyroid disease has been associated with increased rates of spontaneous abortion, even in euthyroid patients.

Untreated frank hypothyroidism carries a risk of 20 to 40% for pregnancy complications including anaemia, pre-eclampsia, placental abruption and postpartum haemorrhage. Subclinical hypothyroidism (clinically normal, normal free T4 and mildly elevated TSH) has been detected in around 2% of pregnancies in screened populations, and is associated with complication rates of about one-third of those for overt disease.

A baby with congenital hypothyroidism is shown in Figure 1. Recent data from a large population-based study in the USA have suggested that even mild degrees of maternal thyroid deficiency in early pregnancy are associated with reduced intelligence in the offspring.[1] Screening for thyroid disease in early pregnancy has been advocated but is not generally accepted at present.

IN SUMMARY

- **In pregnant women, thyroid function tests should be checked every six to eight weeks in hypothyroidism and every four to six weeks in hyperthyroidism.**
- **Thyroid stimulating antibodies cross the placenta and may produce fetal and neonatal hyperthyroidism, and should be measured during the first and third trimesters.**
- **Propylthiouracil and carbimazole are safe in pregnancy and in breastfeeding.**
- **Beware of patients with a past history of thyroid ablation for Graves' disease – the fetus may still be affected by maternal antibodies crossing the placenta.**
- **Patients with postpartum thyroid disease are at increased risk of developing permanent hypothyroidism and should have annual thyroid function tests.**

Causes

The common causes of hypothyroidism in pregnancy are:

- immune thyroiditis with goitre (Hashimoto's disease)
- immune thyroiditis without goitre (atrophic thyroiditis)
- surgical or iodine-131 ablation of thyroid prior to pregnancy
- iodine deficiency.

Diagnosis

The diagnosis of hypothyroidism in pregnancy entails measurement of free T4 and TSH. Autoimmune thyroid disease may be confirmed by measurement of thyroid antimicrosomal and antithyroglobulin antibodies. These antibodies cross the placenta and, although they do not produce thyroid disease in the fetus, they are associated with an increased risk of spontaneous abortion, and recent data have suggested an adverse effect on fetal neurological development.

Treatment

In pregnancy, treatment with thyroxine (Oroxine) is tailored to maintain normal T4 and TSH levels. In most women with pre-existing hypothyroidism, this requires an increase in T4 replacement by 30 to 50% (around 50 µg per day).

This increase in T4 requirement is generally seen early in pregnancy. Thyroid function tests should be checked when pregnancy is diagnosed, and every six to eight weeks thereafter.

Hyperthyroidism

Hyperthyroidism occurs in around 0.2% of pregnancies. Fertility is affected by only severe disease, which increases the risk of spontaneous abortion. As with most autoimmune diseases, there is a tendency for spontaneous improvement during pregnancy and for relapse during the postpartum period. Untreated hyperthyroidism severely affects pregnancy outcomes, with increased risks (five- to sixfold) of fetal anomalies, growth retardation, preterm delivery and perinatal mortality.

Causes

The common causes of hyperthyroidism in pregnancy include:

- Graves' disease, the most common cause of hyperthyroidism in women of reproductive age (Figure 2)
- hCG-related thyrotoxicosis
- toxic adenoma
- toxic multinodular goitre
- thyroiditis.

Diagnosis

The diagnosis of Graves' disease during pregnancy may be difficult because symptoms such as heat intolerance, tachycardia and insomnia are common in normal pregnancy. Radionuclide scans are contraindicated, so diagnosis depends on clinical assessment and estimation of thyroid stimulating antibodies which are also known as 'TSH receptor antibodies' or 'thyrotropin binding inhibiting immunoglobulins'. Thyroid stimulating antibodies freely cross the placenta and may cause thyrotoxicosis in the fetus. High titres are associated with postpartum relapse and with fetal and neonatal thyrotoxicosis.

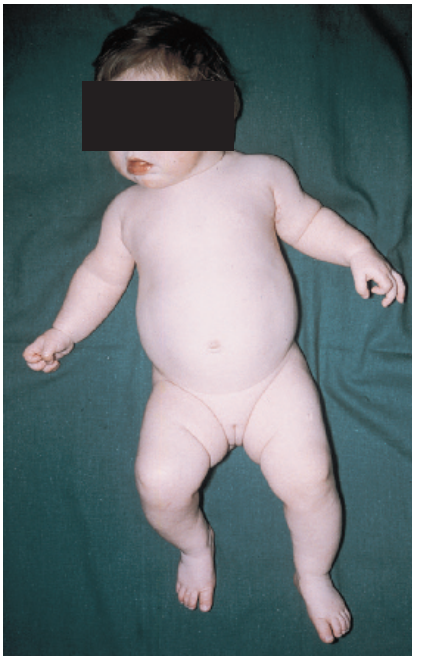

Figure 1. Congenital hypothyroidism.

Management

Thionamides (propylthiouracil [Propylthiouracil] and carbimazole [Neo-Mercazole]) are the mainstays of treatment for thyrotoxicosis in pregnancy. These drugs act by inhibiting the synthesis of thyroid hormone, so the onset of action is relatively slow. Propylthiouracil also has some effect on the peripheral conversion of T4 to T3 and may have a more rapid onset of action than carbimazole.

Up to 40% of women taking thionamides in early pregnancy are able to cease treatment entirely by the third trimester; dose reduction is possible in most other cases. Thyroid function tests should be checked every four to six weeks during pregnancy, and the thionamide dose should be tailored to maintain free T4 and free T3 levels in the upper-third of the normal reference range.

Women with Graves' disease previously

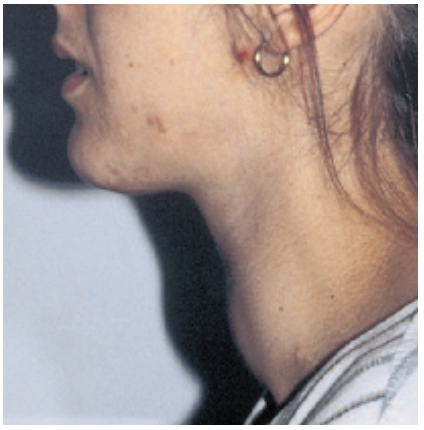

Figure 2. A pregnant woman with Graves' disease.

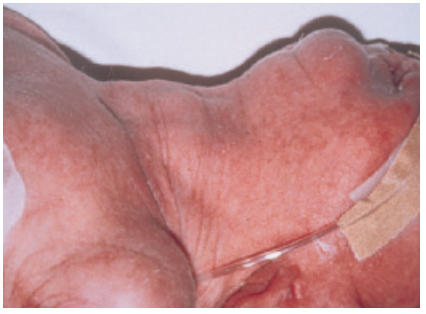

Figure 3. Thyrotoxicosis (goitre) caused by maternal Graves' disease. The neonate's mother is shown in Figure 2.

treated with surgical or iodine-131 ablation sometimes escape detection during pregnancy, with potentially severe consequences for the fetus. In these women, thyroid stimulating antibodies may persist, without any detectable maternal effects. However, thyroid stimulating antibodies readily cross the placenta and may still cause fetal thyrotoxicosis. The fetal disease may be missed or diagnosis may be delayed because of the absence of any obvious disease in the mother.

Fetal thyrotoxicosis may present with fetal tachycardia (more than 160 beats per minute), growth retardation, goitre (Figure 3), cardiomegaly and premature fusion of the cranial sutures. To detect babies at risk of this problem, all women with past or current Graves' disease should have titres of thyroid stimulating antibodies measured early in pregnancy and again at 26 to 30 weeks' gestation. Fetal thyrotoxicosis is treated by administration of thionamides to the mother. In this situation, the mother is usually also thyrotoxic, and will benefit from the treatment. In the rare case of a mother who is euthyroid or hypothyroid due to previous thyroid ablation, supplemental thyroxine may be needed.

Rarely, severe cases of thyrotoxicosis present during pregnancy with tachyarrythmias, cardiac decompensation or thyroid storm. In these situations, rapid reduction in thyroid hormone levels may be achieved with glucocorticoid therapy or short term use of Lugol's iodine in association with thionamide therapy. Beta blockers may also be used in the short term for control of adrenergic symptoms but are best avoided late in pregnancy because of the risk of fetal growth retardation, bradycardia and hypoglycaemia.

Both propylthiouracil (neonatal dose is 0.07% of the maternal dose) and carbimazole (0.5% neonatal exposure) may be used safely during breastfeeding.

Complications of treatment

Some older reports have described an increased incidence of a scalp defect called 'aplasia cutis' in babies of mothers treated with carbimazole (see Figure 4), but this has not been confirmed in subsequent studies, and carbimazole and propylthiouracil are considered to

Physiological adaptations to pregnancy

Pregnancy may be considered to be a compensated euthyroid state. Physiological changes which occur in pregnancy and effect thyroid homeostasis include:

- an increase in thyroid-binding globulin
- an increase in urinary iodine excretion
- catabolism of thyroxine (T4) by placental deiodinase
- increasing human chorionic gonadotropin (hCG).

Increased thyroid-binding globulin results in increased binding of T4 and tri-iodothyronine (T3). Total T4 and T3 increase to compensate for this change and maintain the free (active) levels of these hormones. Urinary iodine excretion and increased breakdown of thyroid hormone by the placenta tend to lower free T4 and free T3.

Increased synthesis of T4 and T3, which is driven by placental hCG and by subtle changes in thyroid stimulating hormone (TSH), compensates for these changes. In the high concentrations seen in pregnancy, hCG has TSH-like activity. When hCG peaks in the first trimester, TSH declines reciprocally and becomes transiently low in 18% of women and undetectable in 9% of women. The net result of these adaptive changes is clinical euthyroidism with free T4 and free T3 levels that are still within the normal range, but slightly lower than levels prior to pregnancy.

Increased thyroid activity in pregnancy may lead to goitre. Normally, the volume of the thyroid gland increases by 10 to 20% in pregnancy (ancient Egyptians used the snapping of a reed tied around a woman's neck to diagnose pregnancy). The degree of thyroid enlargement in pregnancy is greatest in iodine-deficient areas; Australia is generally considered to be replete in iodine.

The fetal thyroid begins to function at around 10 weeks of gestation, and comes under control of fetal pituitary TSH by about 20 weeks. Iodine is actively transferred across the placenta.

be safe for use in pregnancy. In contrast to older reports, both agents have recently been shown to have similar transplacental passage. Transfer of thionamides has not been shown to be detrimental to the fetus unless very high doses of carbimazole or propylthiouracil are used in conjunction with maternal T4 supplementation. This 'block–replace' regimen is generally avoided during pregnancy because of the risk of fetal hypothyroidism.

Patients should be warned about the rare but potentially lethal complication of agranulocytosis during thionamide therapy. This is an idiosyncratic reaction, most commonly presenting in the first two months of therapy with high fevers or severe pharyngitis. If these symptoms develop, therapy should be ceased and an urgent neutrophil count should be arranged.

Thyroid function and hCG

During early gestation hCG is produced by the placenta in large quantities – this forms the basis of most routine pregnancy tests. At high concentrations, hCG may bind to the TSH receptor and stimulate thyroid function. Such binding may be enhanced in the presence of variant forms of hCG, or in recently described mutations of the TSH receptor.

Clinically, severe hCG stimulation is associated with molar pregnancy (hydatidiform mole [see Figure 5] or choriocarcinoma) or severe hyperemesis gravidarum. Some of these patients develop thyrotoxicosis that is severe enough to require thionamide therapy. Distinction from Graves' disease may be difficult, although thyroid stimulating antibodies are absent.

Mild biochemical hyperthyroidism (suppressed TSH and mildly elevated T4) is much more common, affecting up to 2.4% of pregnancies. Half of these women with 'gestational thyrotoxicosis' may have some symptoms (e.g. failure to gain weight, fatigue or tachycardia). Most cases resolve spontaneously before 20 weeks' gestation and do not require therapy.

Thyroid nodules

Nodular thyroid disease is shown in Figure 6. There is no evidence that nodular thyroid disease is affected by pregnancy. If a suspicious thyroid nodule is detected during pregnancy, fine needle aspiration biopsy is the investigation of choice and may be performed safely. Even if cytology suggests thyroid malignancy, surgical excision can generally be postponed safely until after delivery.

Postpartum thyroid disease

When specifically sought with biochemical or immunological testing, postpartum thyroid disease appears to be very common. However, it often passes clinically undetected. Graves' disease commonly relapses postpartum. Recurrences may be transient or persistent and are thought to be caused by a rebound in immune surveillance after relative suppression during pregnancy.

Diagnosis

Postpartum thyroiditis occurs with a reported prevalence of 4 to 8% across a range of geographic and ethnic groups. It is classically characterised by a triphasic pattern:

- initial thyrotoxicosis (one to three months postpartum)
- subsequent hypothyroidism (three to six months postdelivery)
- eventual recovery.

The toxic phase may be absent or pass undetected – if noted, it is characterised by an excess of thyroid hormone without thyroid pain (as opposed to subacute thyroiditis). Suggestive symptoms include fatigue, palpitations, emotional lability and goitre. On technetium scanning, isotope uptake is low (as opposed to high uptake in Graves' disease).

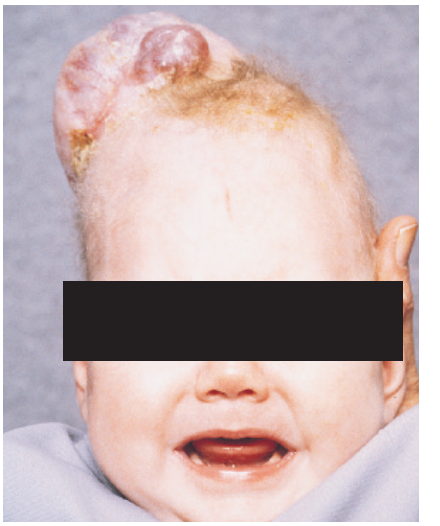

Figure 4. Severe aplasia cutis.

Figure 5. Hydatidiform mole.

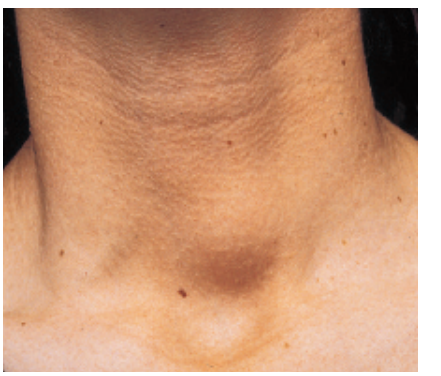

Figure 6. Thyroid nodule.

Management

Thionamides are ineffective because the thyrotoxicosis is caused by release of stored thyroid hormone rather than by increased production. Symptomatic therapy with beta blockers may be useful. The subthyroid phase tends to resolve spontaneously, and only a minority of women require treatment. If symptoms are severe, T4 (50 µg/day) may be used for one to two months.

Although most women return to a euthyroid state, there is an ongoing risk of progression to permanent hypothyroidism (about 23% over 2 to 4 years). This risk is highest (up to 50%) in women who demonstrate high titres of antimicrosomal antibodies at presentation. Follow up thyroid function tests should be checked every six to 12 months.

Screening for thyroid dysfunction

Thyroid abnormalities – including goitre, transient thyrotoxicosis, autoimmune thyroiditis and subclinical hypothyroidism – affect 5 to 15% of pregnant women, and 4 to 8% are affected by postpartum thyroid disorders. Based on this prevalence, some authorities have recommended widespread screening for thyroid dysfunction in early pregnancy. No consensus has yet been reached on this issue, but recent findings of neurological impairment in babies born to mothers with mild hypothyroidism or with positive thyroid antibodies (even if euthyroid) have strengthened the arguments in favour of screening.

Specific high risk groups who merit testing include patients who have:

- a previous history or family history of thyroid disease
- type 1 diabetes
- suffered recurrent abortions.

Initially, TSH should be measured, with thyroid antibodies and other tests added if indicated.

The role of the GP

GPs should maintain a high index of suspicion for thyroid disease in pregnant women and those planning pregnancy. Specific points to be sought in the history and examination are:

- a personal or family history of thyroid disease
- clinical symptoms or signs of thyroid disease
- a history of recurrent spontaneous abortions
- type 1 diabetes
- presence of goitre
- thyroid eye disease.

The arguments in favour of screening for thyroid disease as part of preparation for pregnancy are gaining strength, but have not yet been endorsed by Australian expert bodies.

Shared antenatal care is appropriate for the vast majority of women with known thyroid disease. Thyroid function should be checked at the time of pregnancy confirmation in these women, with therapy modified promptly to achieve a euthyroid state as soon as possible. Specialist assistance is generally desirable in women with thyrotoxicosis, particularly if the disease is suboptimally controlled at any stage of pregnancy.

Summary

General practitioners involved in pregnancy care need to be aware of the range of thyroid problems that present before, during or after pregnancy. Symptoms are often difficult to separate from those of normal pregnancy; therefore, a high index of clinical suspicion is justified. Thyroid function test results change during pregnancy, and reference ranges for free T4, free T3 and TSH are lower. Adverse outcomes can result for both mother and baby, and specialist assistance may be desirable.

Postpartum thyroid dysfunction is also common, and may easily be mistaken for 'baby blues'. Women with postpartum thyroiditis and positive antimicrosomal antibodies carry a high risk for long term hypothyroidism, and should be followed carefully. MT

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Further reading

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