Thyroid disease in the perinatal period

Background
Thyroid hormone plays a critical role in fetal development. In pregnancy, increased thyroid hormone synthesis is required to meet fetal needs, resulting in increased iodine requirements.

Objective
This article outlines changes to thyroid physiology and iodine requirements in pregnancy, pregnancy specific reference ranges for thyroid function tests and detection and management of thyroid conditions in pregnancy.

Discussion
Thyroid dysfunction affects 2–3% of pregnant women. Pregnancy specific reference ranges are required to define thyroid conditions in pregnancy and to guide treatment. Overt maternal hypothyroidism is associated with adverse pregnancy outcomes; thyroxine treatment should be commenced immediately in this condition. Thyroxine treatment has also been shown to be effective for pregnant women with subclinical hypothyroidism who are thyroid peroxidase antibody positive. Gestational thyrotoxicosis needs to be differentiated from Graves disease and rarely requires thionamide treatment. Postpartum thyroiditis most commonly presents with isolated hypothyroidism but a biphasic presentation and isolated hyperthyroidism can occur: a high index of suspicion is warranted for diagnosis.

Keywords
thyroid diseases; postnatal care; pregnancy; prenatal care; perinatal care

Thyroid physiology and pregnancy
The fetus is dependent on transplacental transfer of maternal thyroxine (T4). Deiodination of maternal T4 by the fetus results in local fetal production of liothyronine (T3), which is particularly important for neurological development. Maternal T3 does not cross the placenta and appears to have little, if any, role in development. Other changes in pregnancy include an increase in thyroid binding globulin (TBG), resulting in a larger volume of distribution for thyroid hormone, an increase in urinary iodine excretion and deiodinase activity of the placenta, which increases thyroid hormone metabolism. Pregnancy is therefore a state of increased thyroid hormone demand necessitating an increase in thyroid hormone synthesis by as much as 50%.

Human chorionic gonadotropin (hCG) and thyroid stimulating hormone (TSH) are glycoprotein hormones and share a common alpha subunit; their beta subunits also have significant homology. As a result, hCG has thyrotropic activity and as levels increase in pregnancy, there is an appropriate reciprocal decline in TSH.

Thyroid function tests in pregnancy
Several population studies have demonstrated that it is normal for TSH in pregnancy to be below the classic lower limit of normal. Therefore, use of nonpregnant reference ranges result in the overdiagnosis of hypothyroid states and under-recognition of hypothyroid states. Laboratories should provide trimester specific reference ranges but if these are not available the trimester specific TSH ranges indicated in Table 1 are recommended.

Free T4 levels tend to increase in the first trimester and then progressively decrease later in pregnancy. Free T4 immunoassays generally perform well although should be interpreted with caution as there is significant inter-assay variation and may be influenced by alterations in protein binding kinetics due to pregnancy.
Thyroid stimulating hormone and free T4 are useful to guide diagnosis and monitoring of thyroid conditions in pregnancy. As free T3 does not cross the placenta, ordering of free T3 levels is usually limited to specific circumstances such as T3 predominant thyrotoxicosis (discussed below).

**Iodine requirements**

Iodine requirements are increased in pregnancy due to increased thyroid hormone production to maintain maternal euthyroidism and increased urinary iodine excretion. In Australia, Travers et al demonstrated moderate to severe iodine deficiency as indicated by urinary iodine excretion <50 mcg/L in 16.6% of pregnant women. The World Health Organization recommends 250 µg daily of iodine in pregnancy and lactation to meet the increased demands. The National Health and Medical Research Council recommends women who are pregnant have a daily intake of 220 µg iodine and women who are breastfeeding have a daily intake of 270 µg per day. Women can obtain some iodine from fortified bread, dairy and seafood; however, an iodine supplement of 150 µg per day is recommended for pregnant women while breastfeeding and for those planning pregnancy to achieve the recommended daily intakes.

While the importance of iodine cannot be understated, excessive iodine can paradoxically cause fetal hypothyroidism and very high doses of iodine should be avoided (eg. Kelp tablets, Lugol’s iodine solution).

**Overt hypothyroidism**

Overt hypothyroidism is defined as an elevated TSH associated with a low free T4 and is clearly associated with adverse pregnancy outcomes. Most notably, Haddow et al demonstrated children born to mothers with untreated overt hypothyroidism had an intelligence quotient (IQ) seven points lower at age 7–9 years compared to children born to euthyroid mothers. Obstetric complications of spontaneous miscarriage, premature birth, stillbirth and low birthweight are also described.

Overt maternal hypothyroidism requires urgent treatment with thyroxine. Consideration should be given to loading with thyroxine 150–200 µg daily for 3–4 days in severe cases. Lithotriphrine replacement either alone or in combination should be avoided as overreplacement with T3 may result in maternal hypothyroxinaemia and thus fetal hypothyroidism. Commonly used calcium and iron supplements can reduce thyroxine absorption and should be taken separately.

Women with pre-existing hypothyroidism need to increase their thyroxine dose by approximately 30% in pregnancy – this is best achieved by taking two additional doses per week (in most cases increasing from seven to nine doses per week) on suspicion or confirmation of pregnancy. Thyroid stimulating hormone and free T4 should be rechecked in 4 weeks and monitored every 4–6 weeks in the first half of pregnancy and at least once between 26 and 32 weeks gestation, aiming to keep TSH within trimester specific ranges. After delivery, the thyroxine dose can be reduced to prepregnancy levels. With adequate treatment during pregnancy, neonatal thyroid function testing is not necessary.

**Subclinical hypothyroidism**

Subclinical hypothyroidism (SCH) is associated with adverse pregnancy outcomes, particularly miscarriage but not impaired cognitive function. Benefit of thyroxine treatment has been demonstrated for thyroid peroxidase antibody (TPOab) positive women with SCH, but there is little prospective data on intervention in TPOab negative women. Until prospective data are available to guide management, some clinicians may choose to consider low dose thyroxine replacement, which is safe in pregnancy, aiming for TSH values within the trimester specific reference ranges in all women with SCH.

**Universal screening versus case finding**

Regarding overt hypothyroidism and subclinical hypothyroidism, it is controversial whether universal screening or case finding should be adopted. A recently published study failed to demonstrate neurocognitive benefit of universal screening and intervention compared to selected screening as measured by IQ at 3 years of age. It is worth noting that in this trial, thyroxine replacement was commenced on average at 13 weeks 3 days gestation, which is after the critical time for neurodevelopment. There remains no prospective data to support universal screening and as such this is not supported by either Royal Australian and New Zealand College of Obstetricians and Gynaecologists or the National Institute for Health and Clinical Excellence guidelines.

Proponents of universal screening argue that screening at the first antenatal visit is commonly practised in some areas, appears cost effective and that case finding misses 30% of cases of thyroid dysfunction.

The American Thyroid Association guidelines do not support universal screening, but recommend ordering TSH at the first antenatal visit for women with high risk attributes for thyroid dysfunction (Table 2), with a reflex free T4 if TSH is abnormal. If TSH is elevated the author advocates TPOab testing. In practical terms the American Thyroid Association definition of ‘high risk’ is broad and likely to capture a large proportion of women. Similarly, consideration should be given to preconception TSH screening in high risk women although this has not been extensively evaluated.

**The thyroid antibody positive euthyroid woman**

Thyroid antibodies are found in approximately 10% of women, but antenatal antibody screening is not routine. Screening for TPOab and TSH is advisable in women with recurrent miscarriage.

<table>
<thead>
<tr>
<th>Trimester</th>
<th>TSH range</th>
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<tbody>
<tr>
<td>First</td>
<td>0.1–2.5 mIU/L</td>
</tr>
<tr>
<td>Second</td>
<td>0.2–3.0 mIU/L</td>
</tr>
<tr>
<td>Third</td>
<td>0.3–3.0 mIU/L</td>
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Table 1. Recommended trimester specific reference ranges for TSH

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Euthyroid antibody positive women have a two- to threefold increased risk of spontaneous miscarriage and the risk of preterm birth is approximately doubled. Thyroid antibody positivity has also been shown to be a risk factor for perinatal death. However, prospective intervention data are limited and the decision to treat with thyroxine or monitor for overt or subclinical hypothyroidism is controversial. In these cases, monitoring of thyroid function every 4 weeks during the first half of pregnancy and once between 26 and 32 weeks gestation has been suggested. In the case of recurrent miscarriage, it is acceptable to treat with low dose thyroxine with judicious monitoring of thyroid function as there is potential benefit from this safe treatment.

**Hyperthyroidism**

Overt hyperthyroidism occurs in up to 0.4% of pregnancies, most commonly due to Graves disease and gestational thyrotoxicosis.

Propylthiouracil (PTU) is the treatment of choice in any woman with Graves disease planning pregnancy or in the first trimester as carbimazole is associated with a rare embryopathy. In the second and third trimesters, switching to carbimazole has been suggested due to the risk of fulminant hepatitis with PTU. However, changing from PTU to carbimazole has the potential to cause fluctuation in thyroid function and the transition can be all the more difficult as the thionamide dose requirement is often decreased from the second trimester. Particularly at the time of transition, TSH and free T4 should be monitored every 2–6 weeks and antithyroid medication adjusted accordingly.

Predominant T3 thyrotoxicosis, commonly seen in patients with toxic nodules and some patients with Graves disease, is a management dilemma. Treatment to normalise T3 may result in hypothyroxinaemia and potentially compromise the fetus. Titration of treatment should be guided by TSH and free T4 and may require an acceptance of some degree of T3 elevation.

In Graves disease, TSH receptor antibodies (TRab) may cross the placenta and cause fetal/neonatal thyrotoxicosis and should be checked at 28–32 weeks gestation. This includes women with a history of Graves disease who have been rendered hypothyroid by either radioiodine or surgery, as TRab may remain elevated in these women. Neonates born to mothers with Graves disease, particularly those with high TRab levels, need to have their thyroid function checked. Regular maternal monitoring postpartum is required as Graves thyrotoxicosis may flare with immune reconstitution. Moderate doses of antithyroid medications (ie. carbimazole 25–30 mg/d or PTU less than 300 mg/d) appear to be safe for the breastfed infant. As far as is practical, medication should be taken after breastfeeding. Monitoring of thyroid function in breastfeeding infants of mothers taking antithyroid medications (particularly those taking high doses) should be considered.

Gestational or hCG mediated thyrotoxicosis is usually less severe than Graves thyrotoxicosis. It usually runs a self limited course and rarely requires antithyroid drug treatment.

**Postpartum thyroiditis**

Postpartum thyroiditis (PPT) affects one in 20 women. The majority of women present with isolated hypothyroidism (48%), but a biphasic presentation with hyperthyroidism followed by hypothyroidism (22%) and isolated hyperthyroidism (30%) are also common. The nonspecific nature of symptoms warrants a high index of suspicion.

Thyroid antibody positive women are at highest risk (33–50%) of developing PPT. Previous PPT and coincident autoimmune conditions confer higher risk. Permanent hypothyroidism develops in 20–40% of women following PPT and is more likely with higher TSH and/or thyroid antibody levels.

If hyperthyroidism occurs, onset is usually about 3–6 months postpartum. This needs to be differentiated from Graves disease. The thyrotoxic phase is self limiting – beta blockers can be used for symptomatic thyrotoxicosis but thionamides are not indicated.

If hypothyroidism occurs, onset is usually between six and 12 months postpartum. Thyroxine is initiated for symptomatic hypothyroid women or those trying to conceive. Continuation of thyroxine treatment throughout subsequent pregnancies reduces the risk of inadvertent hypothyroidism but, as a high proportion of women will ultimately recover normal thyroid function, an attempt should be made to wean thyroxine 6–12 months after the final pregnancy. Long term follow up with annual TFT is recommended.

**Key points**

- Pregnancy specific reference ranges should be used to guide diagnosis and monitoring of thyroid conditions in pregnancy.
- The World Health Organization recommends a daily intake of iodine 250 μg during pregnancy and lactation.
- Hypothyroid states should be treated with thyroxine aiming for a TSH <2.5 prior to conception and in the first trimester and TSH <3.0 for the second and third trimesters.
- Thyroxine should be increased by two additional doses per week (or 30%) on suspicion or confirmation of pregnancy in women already taking thyroxine.
• It is important to separate thyroxine intake from preparations that may reduce absorption.
• Women with high risk attributes for thyroid dysfunction are appropriate for antenatal screening with TSH.
• Gestational thyrotoxicosis needs to be differentiated from Graves disease and rarely requires thiouamide treatment.
• It is important to maintain a high index of suspicion for postpartum thyroiditis, especially in those with known thyroid antibodies or autoimmune conditions.

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References