During pregnancy the production and metabolism of thyroid hormone change. Appropriate monitoring of thyroid-stimulating hormone levels with trimester-specific reference ranges is essential to avoid adverse effects in the pregnant woman and fetus.

The management of thyroid dysfunction in pregnant women has received much attention since the recent publication of three comprehensive sets of guidelines from the USA and Europe. Debate still continues as to whether all pregnant women, or even all women planning pregnancy, should be screened for thyroid dysfunction with measurement of their thyroid-stimulating hormone (TSH) levels. It is important to identify significant thyroid dysfunction at crucial stages of pregnancy, especially hypothyroidism in the first trimester, which can cause adverse fetal outcomes.4-6

The responsibility of care of pregnant women with thyroid dysfunction often falls between the GP, endocrinologist and obstetrician. There needs to be consensus by the managing team as to who is assuming primary responsibility for organising thyroid function tests (TFTs). The results of these tests can then be forwarded to the endocrinologist, who can offer guidance for the patient and all clinicians involved throughout the pregnancy.

Thyroid dysfunction in pregnancy is most commonly detected incidentally either by TSH screening in asymptomatic women with no...
1. PATIENTS AT HIGH RISK OF HYPOTHYROIDISM WHO SHOULD BE ScreenED PRECONCEPTION1

- Maternal age >30 years
- Thyroid peroxidase antibody (TPOAb) positivity
- Family history of thyroid dysfunction
- History of head and neck irradiation
- Type 1 diabetes
- Other known autoimmune disease
- History of unexplained miscarriage
- History of preterm delivery
- History of childhood malignancy
- History of infertility
- Living in an area of known iodine insufficiency

PHYSIOLOGICAL CHANGES IN NORMAL PREGNANCY AND EFFECTS ON TFF PARAMETERS

The first trimester of pregnancy is associated with a rise in concentration of serum thyroxine-binding globulin (TBG) because oestrogen increases TBG production and sialylation, which results in decreased clearance of TBG, along with stimulation of the TSH receptor by human chorionic gonadotrophin (hCG). hCG has a common α-subunit and a unique β-subunit, which has considerable similarity to the β-subunit of TSH. Therefore, beta hCG acts as a weak stimulus to the TSH receptor.2

Often during pregnancy there is a minor reduction in TSH levels with normal thyroxine (T4) and tri-iodothyronine (T3) levels and negative thyroid antibodies (including negative thyroid receptor antibodies [TRAb]). There are also normal physiological changes that occur during pregnancy that affect thyroid homeostasis, predisposing a woman to thyroid deficiency. These include increased renal excretion of T4, transfer of T4 to the fetus and breakdown of T4 by placental deiodinases.3,10

IODINE INTAKE DURING PREGNANCY

Iodine requirements are greater during pregnancy because of increased maternal T3 production, which is required to maintain maternal euthyroidism, and increased renal iodine clearance. The World Health Organization global recommendations are that pregnant and lactating women should ingest 250 µg/day of iodine from supplements and dietary sources.11 When planning a pregnancy, women will usually need to supplement their diet with an oral iodine supplement of 150 µg/day.12

Large iodine doses (>1000 µg/day) from dietary sources or very high-dose supplements should be avoided due to the risks of fetal hypothyroidism and goitre. Less than 50% of pregnant women have adequate knowledge about the need for iodine supplementation in pregnancy.13

TRIMESTER-SPECIFIC TFF RANGES IN PREGNANCY

Laboratories should quote their own trimester-specific TSH reference ranges for pregnancy. Large population studies, which included more than 13,000 pregnant women, have established the reference range for TSH levels in the first trimester as 0.03 to 2.99 mIU/L.14,15 The ranges given in Table 1 for each trimester are those recommended by the American Thyroid Association (ATA) guidelines.1

Measurements of direct free T4 may be unreliable during pregnancy, especially if certain laboratory methods are not adopted (i.e. online extraction, liquid chromatography and tandem mass spectrometry). The decreased albumin concentrations during pregnancy can cause the immunoassay to be inaccurate.16 Measurement of TSH levels remains more accurate.

If the TSH level is abnormal then free T4 and free T3 levels should be measured, along with TRAb (for Graves’ disease), thyroid peroxidase antibody (TPOAb; also known as thyroid microsomal antibody [TMAb]) and thyroglobulin antibody (TgAb; levels for Hashimoto’s disease). This is to clarify if there is autoimmune thyroid disease and, if present, to assess the severity. Total T4 measurements are not routinely performed in Australia.

HYPOTHYROIDISM IN PREGNANCY

Iodine deficiency can cause hypothyroidism. With the availability of trimester-specific reference ranges in routine clinical practice, milder forms of thyroid dysfunction (such as subclinical hypothyroidism and maternal isolated hypothyroxinaemia) are being diagnosed in about 15% of pregnant women.10 The most common cause of overt hypothyroidism in pregnancy is chronic autoimmune thyroiditis, known as Hashimoto’s disease. This and other less common causes are listed in Box 2.
2. CAUSES OF PREGNANCY-RELATED HYPOTHYROIDISM

Common
• Hashimoto’s disease – autoimmune thyroid disease
• Iodine deficiency (although uncommon in Australia)

Less common
• Post-thyroid surgery hypothyroidism
• Central hypothyroidism/hypopituitarism

Profound hypothyroidism (elevated TSH and reduced free T4 levels) is unusual in pregnancy due to the reduced fertility rate and high rate of first trimester spontaneous abortion in affected women.17 Adverse associations with hypothyroidism in pregnancy are listed in Box 3.16,19

Overt hypothyroidism, subclinical hypothyroidism and maternal isolated hypothyroxinaemia

All pregnant women with a TSH level of more than 10 mIU/L should be treated for overt hypothyroidism with thyroxine replacement, regardless of the free T4 level. Pregnant women with TSH levels between 2.5 and 10 mIU/L should also be treated. However, those with isolated low free T4 levels need no treatment if the TSH levels are normal, as this is maternal isolated hypothyroxinaemia.1,2 Treatment with thyroxine replacement is also required for pregnant women with positive TPOAb or TgAb results and subclinical hypothyroidism (i.e. TSH level between 2.5 and 10 mIU/L with normal free T4 level; Table 2).2,20

Subclinical hypothyroidism is associated with adverse fetal outcomes.19,21 The guidelines from the American Endocrine Society recommend treatment of affected women as there is evidence that thyroxine replacement in such circumstances may reduce obstetric complications.1 The most recent European guidelines recommend thyroxine therapy for maternal subclinical hypothyroidism.3 The decision to treat euthyroid women with elevated TPOAb or TgAb levels and monitor for the development of hypothyroidism is subject to debate. The American Thyroid Association has not recommended against therapy.1,2

Treatment should be with conventional thyroxine rather than with alternative preparations (such as T3 or thyroid extract) and trimester-specific TSH targets are the goal of therapy. TSH level cut-offs are lower in pregnant women than in nonpregnant women. Patients taking T3 should stop taking it when they become pregnant and change to thyroxine during pregnancy because T3 is not thought to cross the placenta. Maternal transfer of thyroxine during the first trimester is required until the fetus makes its own thyroid hormones during the second and third trimesters. If patients have been stabilised on a dose of thyroxine, most will need a 30 to 50% increase in dose by four to six weeks of gestation. If dose adjustments are being made, more frequent biochemical testing will be necessary until target levels are reached.

If treatment is not required initially, such as in cases of subclinical hypothyroidism, the patient should have monthly monitoring for overt hypothyroidism until 20 weeks of gestation and at least once between 26 and 32 weeks of gestation.

Hashimoto’s disease

Hashimoto’s disease is the most common cause of overt hypothyroidism in pregnant

3. ADVERSE ASSOCIATIONS WITH HYPOTHYROIDISM IN PREGNANCY16,19

- Spontaneous abortion
- Premature labour
- Low birthweight
- Placental abruption
- Pre-eclampsia
- Cognitive impairment in the offspring
- Postpartum haemorrhage

---

TABLE 2. HYPOTHYROIDISM: ASSOCIATED BIOCHEMISTRY AND TREATMENT RECOMMENDATIONS1,3,20,21

<table>
<thead>
<tr>
<th>Thyroid status and disease</th>
<th>TSH level</th>
<th>T4 level</th>
<th>TPOAb or TgAb status</th>
<th>Treatment recommended (thyroxine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid, positive TPOAb</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
<td>Insufficient evidence – no</td>
</tr>
<tr>
<td>Maternal isolated hypothyroidism</td>
<td>Normal</td>
<td>Low</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Low</td>
<td>No</td>
</tr>
</tbody>
</table>

ABBREVIATIONS: T4 = thyroxine; TgAb = thyroglobulin antibody; TPOAb = thyroid peroxidase antibody; TSH = thyroid-stimulating hormone.
women and is characterised biochemically by an elevated TSH level, reduced free T₄ level and positive TPOAb and/or TgAb. Patients already taking thyroxine for autoimmune hyperthyroid disease may have changes in TFTs after conception, and may require an early increase in the thyroxine dose. An automatic increase of 20 to 30% in the dose is usually recommended when pregnancy is confirmed. However, some patients on low doses require no change as the thyroid gland seems to adjust, whereas others require large increases. Regular testing is needed, starting with monthly monitoring in the first trimester to 20 weeks of gestation and at least one TSH measurement between 26 and 32 weeks of gestation.

**HYPERTHYROIDISM IN PREGNANCY**

Hyperthyroidism is characterised biochemically by a suppressed TSH level and elevated free T₄ and/or T₃ level. It is relatively uncommon, affecting 0.1 to 1.0% of all pregnancies.¹⁴

The most common causes of hyperthyroidism are gestational transient thyrotoxicosis (GTT; or hCG-mediated hyperthyroidism) and Graves’ disease (autoimmune hyperstimulation of the thyroid gland by TRAb).²² These and other less common causes of hyperthyroid states are listed in Box 4. Overt hyperthyroidism (most often Graves’ disease) is associated with maternal and fetal adverse outcomes (Box 5).²¹ Rare cases of thyroid storm precipitated by infection, pre-eclampsia, caesarean section or parturition have been reported. Subclinical hyperthyroidism is not associated with adverse pregnancy outcomes.²⁴

The usual investigations to elucidate the cause of hyperthyroidism involve measurement of TSH, T₄, T₃ and TRAb levels. A nuclear medicine radioidine uptake scan is sometimes required but is contraindicated during pregnancy.

The goal of therapy is to reduce and maintain the maternal serum free T₄ concentration in the high–normal range using the lowest drug dose. This requires TFTs every four weeks with dose adjustment if needed.¹ ² Table 3 summarises the biochemical features and recommendations in hyperthyroidism.

**Gestational transient thyrotoxicosis**

Patients may develop elevated free T₄ and/or free T₃ levels in association with a low TSH level, and negative thyroid antibodies in the first trimester. GTT is seen particularly in women with high levels of beta hCG, associated with twin pregnancies and hyperemesis. Thyrotoxic symptoms are difficult to assess in the presence of tachycardia and fatigue, which are common in normal pregnancy.

Patients with hyperemesis and GTT may require hospitalisation for supportive therapy, such as intravenous fluids; low-dose antithyroid drugs are only rarely given for very short periods in overt cases and generally not used in patients with mild GTT. The condition resolves after the first trimester when the beta hCG levels decline. A transient, usually subclinical hyperthyroidism can therefore be considered a normal physiological finding.⁴

**Graves’ disease**

Graves’ disease tends to improve during pregnancy due to a reduction in TRAb or, rarely, when the antibodies become blocking in nature rather than stimulatory. A relapse in the condition often occurs in the postpartum period, but there are exceptions to this rule. Patients with Graves’ disease are advised not to embark on pregnancy unless their disease is in remission or well controlled with very low doses of antithyroid drugs (or their thyroid has been ablated by surgery or radioactive iodine).

In all patients with Graves’ disease regardless of previous therapy the stimulating antibody TRAb can cross the placenta and cause neonatal thyrotoxicosis or hypothyroidism. It is important to measure affected women’s TRAb levels through pregnancy to assess fetal risk. About 5% of neonates born to women with Graves’ disease have hyperthyroidism due to transplacental transfer of TRAb, and the incidence increases proportionally with the TRAb titre. All women with Graves’ disease should therefore be monitored for signs of fetal thyrotoxicosis with measurement of fetal heart rate and assessment of fetal growth with ultrasound.

Patients on very low doses of antithyroid drugs can usually cease their medication in the first trimester if they are TRAb negative. Some patients require ongoing therapy, and in such cases it is best to switch treatment to propylthiouracil in the first trimester, with a dose of carbimazole 5 mg being equivalent to propylthiouracil 50 mg. Studies have suggested a lower rate of congenital malformations in pregnant women taking propylthiouracil versus carbimazole in the first trimester. The guidelines then suggest switching back to carbimazole in the second trimester.¹ ² However, a recent
Danish study reported a similar prevalence of birth defects with both propylthiouracil and carbimazole use.

Carbimazole and propylthiouracil are associated with urinary system malformation, and propylthiouracil with malformations of the face, head and neck. Choanal atresia, oesophageal atresia, omphalocele, omphalomesenteric duct anomalies and aplastic cutis are reported in children exposed to carbimazole. Carbimazole is otherwise reserved for insulin-dependent diabetes and autoimmune thyroid diseases.

Thyroidectomy is rarely necessary in pregnancy but may be considered in the second trimester. Thyroid function should be tested in the cord blood of the baby on delivery. Graves’ disease symptoms will often flare during pregnancy. Patients referred for minor aberrations in TSH levels with normal T4 levels should be monitored every four to six weeks in woman taking antithyroid drugs.

**TABLE 3. HYPERTHYROIDISM: ASSOCIATED BIOCHEMISTRY AND TREATMENT RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Thyroid status and disease</th>
<th>TSH level</th>
<th>T4 level</th>
<th>TRAb status</th>
<th>Treatment recommended (antithyroid drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational transient thyrotoxicosis</td>
<td>Normal or suppressed</td>
<td>Normal or elevated</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>Suppressed (&lt;0.1) or undetectable (&lt;0.01)</td>
<td>Normal</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>Suppressed (&lt;0.1) or undetectable (&lt;0.01)</td>
<td>Elevated</td>
<td>Negative</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Suppressed (&lt;0.1) or undetectable (&lt;0.01)</td>
<td>Elevated</td>
<td>Positive (Graves’ disease)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** T4 = thyroxine; TRAb = thyroid receptor antibodies; TSH = thyroid-stimulating hormone.

**THYROXINE REPLACEMENT IN PREGNANCY AND POSTPARTUM**

Patients who have undergone total thyroidectomy will require an increase in their thyroxine dose of at least 30% in early pregnancy. They should be advised to increase their dose automatically at the time of conception and have regular TFT testing, at least monthly in the first trimester. A useful initial rule is to instruct the patient to take the equivalent of two extra daily doses per week once pregnancy is confirmed.

Patients with an intact thyroid are usually advised to increase their dose of thyroxine but some will become over-replaced. There is insufficient evidence to recommend routine screening of all pregnant women for thyroid antibodies in the first trimester. Indeed, if patients are euthyroid but thyroid antibody positive, there is little evidence to recommend treatment with thyroxine, even if they are undergoing IVF or have a history of recurrent spontaneous abortion or preterm delivery.

**CONTROVERSIES IN MANAGING EUTHYROID ANTIBODY POSITIVITY**

There is insufficient evidence to recommend routine screening of all pregnant women for thyroid antibodies in the first trimester. Indeed, if patients are euthyroid but thyroid antibody positive, there is insufficient evidence to recommend treatment with thyroxine, even if they are undergoing IVF or have a history of recurrent spontaneous abortion or preterm delivery.

**POSTPARTUM THYROID DYSFUNCTION**

Patients with ongoing Graves’ disease may breastfeed while taking antithyroid drugs; carbimazole in doses of up to 20 to
30 mg is safe during lactation. It is best given in divided doses and administered after breastfeeding. Propylthiouracil is second-line therapy and high doses (>300 mg/day) should be avoided due to concerns about hepatotoxicity.

Patients with positive antithyroid antibodies in early pregnancy have about a 30% risk of developing postpartum thyroiditis. This is a self-limiting condition that presents in the first six to 12 months’ postpartum. It manifests with transient thyrotoxicosis, transient hypothyroidism or both, and patients often have a full recovery. Some 20 to 40% of patients may develop permanent hypothyroidism and thus monitoring for this is required.26 Patients who present with postnatal depression must also be assessed for postpartum thyroiditis.

It can sometimes be difficult to distinguish postpartum thyroiditis from Graves’ disease; however, patients with Graves’ disease will usually present with more marked TFT disturbance, positive TRAb, more pronounced symptoms and other features including larger thyroid size and thyroid eye disease. The two conditions can be distinguished on technetium-99 nuclear uptake scan (low uptake versus diffuse increased uptake) but these scans are usually not needed and are unsuitable for women who are breastfeeding.

During the thyrotoxic phase, symptomatic patients are treated with propranolol. Antithyroid drugs are not used, but thyroxine may be needed in the hypothyroid phase in some patients who are asymptomatic. Patients with asymptomatic hypothyroidism may not require treatment but TSH monitoring is important to document recovery and exclude ongoing Hashimoto’s disease, especially if they are considering another pregnancy. Similarly, patients treated with thyroxine should try tapering (and ceasing) their therapy after three to six months unless they are planning to conceive again in the near future.

Women with a prior history of postpartum thyroiditis should have ongoing annual TSH level measurement to monitor for the onset of permanent hypothyroidism.

MANAGEMENT OF THYROID NODULES AND THYROID CANCER DURING PREGNANCY

Mild diffuse thyroid swelling is common in normal pregnancy and nodules may be detected clinically or on imaging. Thyroid nodules should be assessed with neck ultrasound and TSH level measurement. If there is concern about the size or behaviour of a nodule or its appearance on ultrasound, they may be biopsied under ultrasound guidance with fine-needle aspiration biopsy (FNAB) in the same way as if the woman were not pregnant.1,2 Otherwise FNAB can be deferred to the postpartum period. Any patient with atypical or malignant thyroid cytology during pregnancy should be referred to a specialist.

If surgery is deemed to be appropriate during pregnancy, it is usually deferred until the second trimester, where it carries no greater risk to the fetus or woman than it would during the postpartum period. Some patients with small well-differentiated thyroid cancers can have surgery deferred to the postpartum period but they need regular neck ultrasound during pregnancy to monitor the growth of the malignant nodule. More detail is given in both the American and European Thyroid Associations guidelines.1,3 Imaging or therapy with radioactive iodine or other isotopes is not advised in pregnancy. Previous therapy with radioactive iodine for thyroid cancer or Graves’ disease given at least six months before pregnancy will not adversely affect the outcome of the pregnancy or the fetus.

Patients with thyroid cancer diagnosed during pregnancy will need to be counselled about whether breastfeeding is feasible and for how long, noting that radioactive iodine ablation will have to be postponed for several months after cessation of breastfeeding. These decisions are made on an individual basis, based on the histopathology, staging and risk assessment of the cancer. The patient should be referred to a thyroid unit with multidisciplinary input.

CONCLUSION

It is important to detect significant thyroid dysfunction at the time of conception or as early as possible in the first trimester so that appropriate therapy can be promptly instituted to optimise maternal and fetal outcomes. Appropriate therapy and monitoring of both the mother and fetus during pregnancy and into the postpartum period is guided by the clinical scenario, past and family history, degree of TFT derangement and autoimmune status. Universal screening for thyroid dysfunction in pregnancy during the first trimester with measurement of TSH levels is generally recommended.

REFERENCES

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

Online CPD Journal Program

The World Health Organization recommends that pregnant women take an iodine supplement of 150 µg/day. True or false?

Review your knowledge of this topic and earn CPD/PDP points by taking part in Medicine Today’s Online CPD Journal Program.


REFERENCES