PEER REVIEWED

Investigating thyroid function in pregnancy

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This section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

The scope of thyroid disease during pregnancy is similar to that in the normal female population (see Box 1);[1] however, it is considerably more common with 2 to 3% of pregnant women affected.[2] Prompt diagnosis and evidence-based management of thyroid disease is essential to reduce the associated risk of maternal and fetal complications (Table 1).[3] In most situations diagnosis depends on the judicious use of biochemical tests of thyroid function. To meet the increased demand for thyroid hormone during pregnancy significant adaptation to thyroid physiology occurs (see Figure 1). This is reflected in changes to the reference ranges for thyroid function tests (TFTs), such that 'normal' values in each trimester differ significantly from those in nonpregnant women (Table 2).[4-7] It is therefore important that these trimester-specific reference ranges are used to correctly classify thyroid disease in pregnancy. Thyroid-stimulating hormone (TSH) immunoassays are methodologically reliable in pregnancy but commercially available free thyroxine (T4) and free triiodothyronine (T3) assays are not because various physiological changes in pregnancy, including changes in the levels of thyroxine-binding globulin, albumin and free fatty acids, invalidate the assumptions made in these assays (Figure 1). More reliance should therefore be placed on TSH than free T4 or free T3 in the assessment of thyroid status in pregnancy.

The following two cases illustrate an approach to the diagnosis and management of thyroid disease in pregnancy.

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Case 1.

A 32-year-old woman presents to her GP 11 weeks pregnant. This is her second pregnancy after a previous miscarriage. She has no significant medical history but does have a family history of hyperthyroidism in her father and hypothyroidism in her paternal aunt. She is asymptomatic and her examination is unremarkable.

Should TFTs be performed for this patient?

Universal screening is not yet recommended by major guidelines but this remains a matter of active discussion.[6,8] Current guidelines recommend a case-finding approach, which we adhere to. This means only women at high risk are tested, given universal screening has not yet been shown to reduce adverse outcomes.[9] We note that some individual clinics may develop their own institutional

1. Classification of thyroid disease in pregnancy[1]

Hyperthyroidism

Common

- Graves' disease: most commonly detected in 1st trimester and requires treatment (propylthiouracil in 1st trimester, carbimazole in 2nd and 3rd trimesters); beware of postpartum flare; prompt endocrinology referral recommended
- Subacute (painful) thyroiditis
- Lymphocytic (painless) thyroiditis
- Toxic adenoma or 'hot' nodule
- Toxic multinodular goitre
- Gestational thyrotoxicosis (sometimes presenting as hyperemesis gravidarum): common during pregnancy when human chorionic gonadotropin level is high; treatment rarely necessary

Rare

- Iodine-induced thyrotoxicosis
- Thyrotoxicosis factitia
- Gestational trophoblastic neoplasia-associated hyperthyroidism
- Inappropriate thyroid-stimulating hormone secretion
- Metastatic follicular carcinoma

Hypothyroidism

Common

- Chronic autoimmune thyroid disease (also known as Hashimoto's thyroiditis)
- Postablative hypothyroidism
- Surgical hypothyroidism

Rare

- Pituitary dysfunction (central hypothyroidism)

Post-partum thyroiditis

Common

- Thyrotoxicosis: consider differential diagnosis of postpartum Graves' hyperthyroidism
- Hypothyroidism

Goitre and thyroid nodules

Common

- Simple (nontoxic) goitre
- Solitary thyroid nodule
- Multinodular goitre
- Papillary carcinoma

Table 1. Complications of thyroid disease in pregnancy[3]

Condition	Preconception	Pregnancy	Postpartum
Hyperthyroidism, overt	Congenital malformations	Maternal: heart failure, placental abruption, pre-eclampsia, preterm delivery Fetal: congenital malformations, tachycardia, hydrops fetalis, advanced bone age, goitre, intrauterine growth restriction, small for gestational age, stillbirth, thyroid dysfunction	–
Hyperthyroidism, subclinical	–	None	–
Hypothyroidism, overt	Decreased fertility, increased miscarriage	Maternal: anaemia, gestational hypertension, miscarriage, placental abruption, pre-eclampsia, preterm birth Fetal: neurocognitive deficits, low birth weight	Maternal thyroid dysfunction, haemorrhage
Hypothyroidism, subclinical	Effects similar to overt hypothyroidism, but less evidence exists		

protocols adopting universal screening.

Screening is conducted with serum TSH measurement.[6,8] A value within the trimester-specific reference range practically excludes thyroid dysfunction in the absence of strong clinical suspicion or known thyroid disease (Table 2).[10]

This patient has multiple risk factors for thyroid disease in pregnancy by way of her age, prior history of miscarriage and possible family history of autoimmune thyroid disease (Box 2) and hence TFTs are performed. Screening reveals a serum TSH level of 3.43 mU/L (first trimester reference range, 0.1–2.5 mU/L).

What does this test result tell you and what further investigations should be performed?

Although this patient's TSH level is within the nonpregnant reference range it is above the first-trimester reference range (Table 2). Further investigations that should be performed are measurement of serum free T4 levels and anti-thyroid peroxidase antibodies (TPOAb). It is generally unnecessary to measure anti-thyroglobulin antibodies (TgAb) if TPOAb is measured, as TPOAb is more sensitive and the isolated presence of TgAb, usually in low titre, is not associated with thyroid dysfunction.[11]

The results show a serum free T4 level of 13.4 pmol/L (nonpregnant reference range, 9.1–19.6 pmol/L) and TPOAb value of 130 IU/mL (reference range, <34 IU/mL).

What is this patient's diagnosis?

When TSH level is elevated, measurement of serum free T4 levels enable further characterisation of hypothyroidism as either overt or subclinical (Figure 2). Additionally, pregnant women with very high TSH levels (>10.0 mU/L)

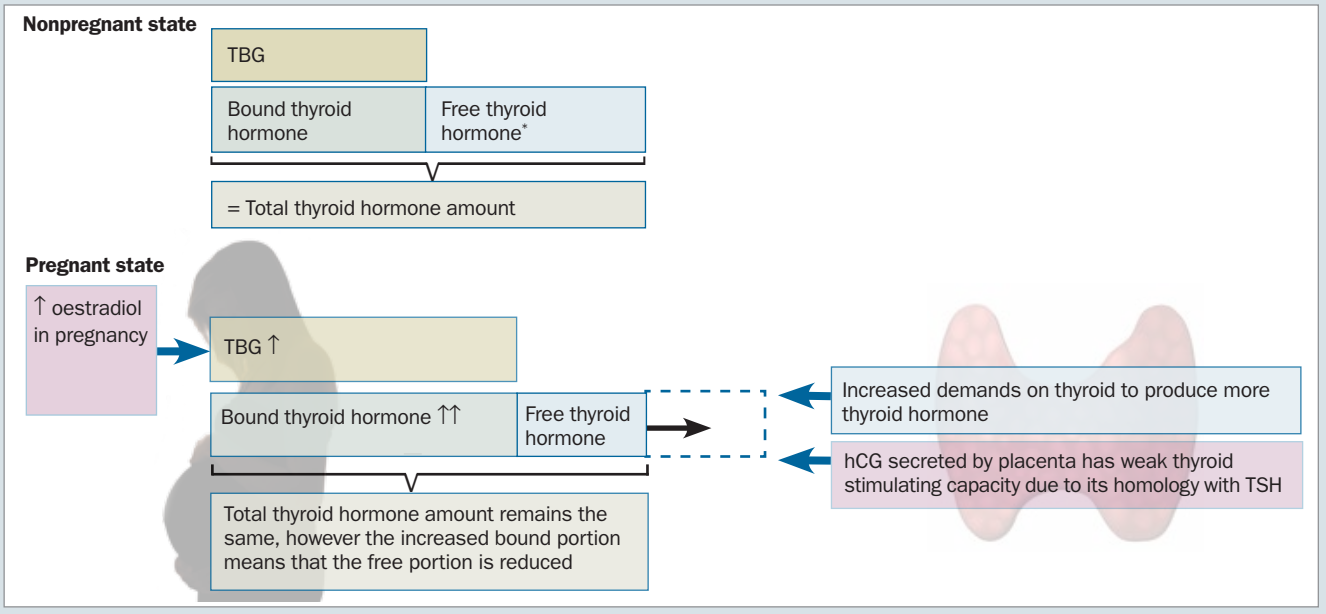

Figure 1. Changes in thyroid physiology occurring in pregnancy.

Abbreviations: hCG = human chorionic gonadotropin; TBG = thyroxine-binding globulin; TSH = thyroid-stimulating hormone.

* In reality, the free thyroid hormone component is less than 1% of the total thyroid hormone amount; the proportions shown here are not to scale.

may be considered to have overt hypothyroidism regardless of their serum free T4 levels.[6]

This patient's serum free T4 level is near the mean trimester-specific free T4 value. An elevated TSH level and normal free T4 level in this asymptomatic patient, with higher-risk criteria justifying case-finding, are consistent with subclinical hypothyroidism (SCH). SCH accounts for the vast majority of cases of thyroid disease in pregnancy.[12]

This patient's TPOAb positive status is consistent with chronic autoimmune thyroid disease (also known as Hashimoto's thyroiditis). It is the main cause of SCH during pregnancy in Australia. Women who are TPOAb positive are at increased risk of both overt and SCH during the stress of pregnancy as the thyroid fails to increase production to meet increasing demand. This patient's TPOAb positivity also increases her chance of miscarriage over and above that from SCH alone, and increases her chance of post-partum thyroiditis.

How should this patient be managed?

A TSH level over the trimester-specific reference range may be associated with adverse pregnancy outcomes. Interventional studies have demonstrated thyroxine treatment reduces pregnancy complications in women with SCH who are also TPOAb positive.[9] Although the majority of evidence suggests that women with SCH who are TPOAb negative also suffer a significantly higher rate of miscarriages, to date no interventional studies have been conducted in this cohort.[6] An association between SCH and adverse fetal neurocognitive development is possible,[13] but has not been definitively demonstrated and treatment with thyroxine has not been shown to improve cognitive outcome.[14] It is our practice to offer thyroxine treatment to all women with SCH regardless of their TPOAb status because we feel the risk is minimal and there is potential for good in at least some cases. We however acknowledge that there is no clear consensus among current guidelines.[6,8]

This patient is commenced on thyroxine at a dose of 50 µg daily. We usually find that this dose is sufficient to bring a serum TSH level of between 2.5 and 10 mU/L into the trimester-specific reference range.

Table 2. Nonpregnant and trimester-specific reference ranges for TSH and estimates of mean free T4 levels[6,7]

	Serum TSH (mU/L)	Serum free T4* (pmol/L)
Nonpregnant	0.3–4.3	9.1–19.6 (reference range)
1st trimester	0.1–2.5	13.5 ± 2.8†
2nd trimester	0.2–3.0	11.3 ± 2.2†
3rd trimester	0.3–3.0	11.4 ± 2.2†

Abbreviations: TSH = thyroid-stimulating hormone; T4 = thyroxine.
* The trimester-specific serum free T4 reference range is highly assay-dependent and all commercially available free T4 assays are unreliable in pregnancy. Ideally each laboratory should establish an indicative range for its own assays.
† Pregnancy-related values for free T4 cited here are the mean ± standard error of the mean immunoassay value, not a reference range.

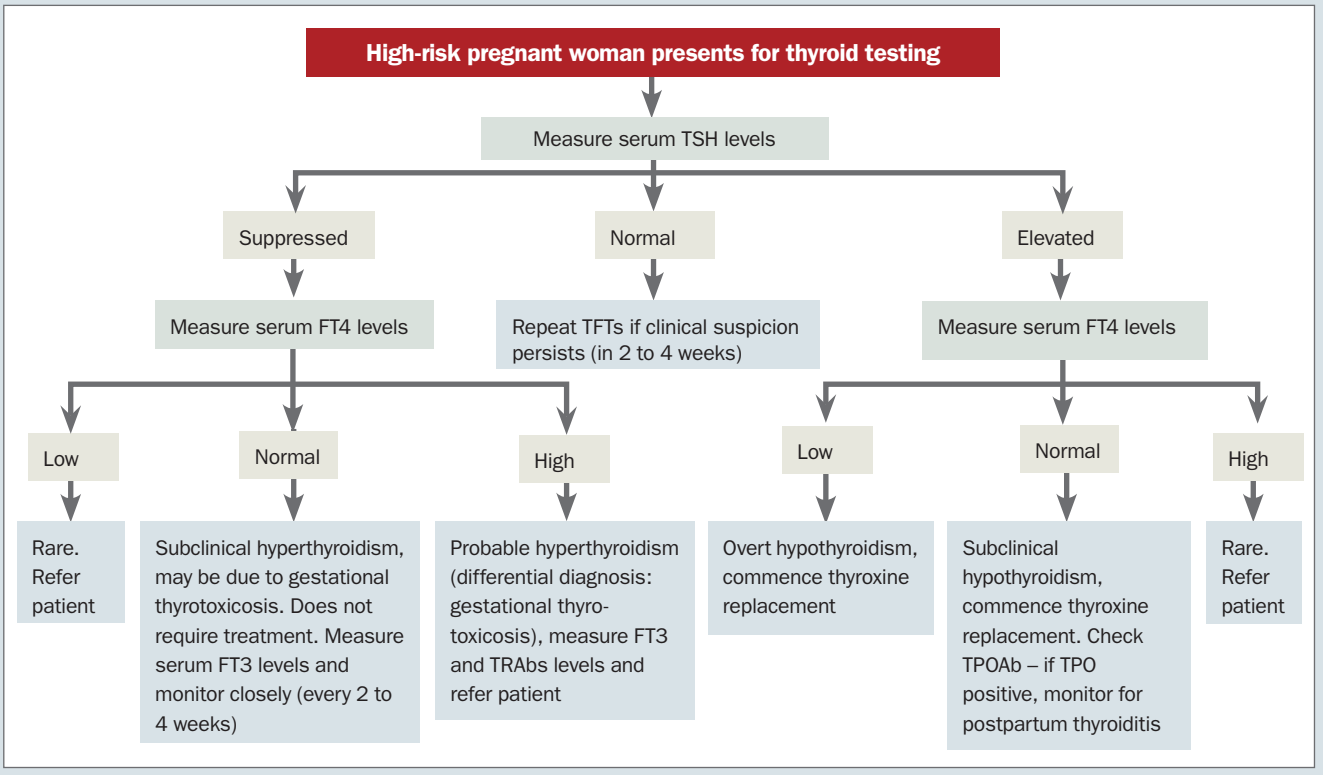

Figure 2. Suggested algorithm for diagnosis and management of women with thyroid disease in pregnancy who fulfil case-finding criteria.
Abbreviations: FT4 = free thyroxine; FT3 = free tri-iodothyronine; TFT = thyroid function tests; TPO = thyroid peroxidase; TPOAb = thyroid peroxidase autoantibodies; TRAbs = thyroid-stimulating hormone receptor antibodies; TSH = thyroid-stimulating hormone.

2. Women at high risk of thyroid disease in pregnancy[8]

Women who are at high risk of thyroid disease during pregnancy and therefore should have thyroid function tests performed when planning pregnancy or when newly pregnant include those:

- over age 30 years
- with a family history of autoimmune thyroid disease or hypothyroidism
- with a goitre
- with thyroid antibodies, primarily antithyroid peroxidase antibodies
- with symptoms or clinical signs suggestive of thyroid hypofunction
- with type 1 diabetes mellitus or other autoimmune disorders
- with infertility
- with a prior history of miscarriage or preterm delivery
- with prior therapeutic head or neck irradiation or prior thyroid surgery
- currently receiving thyroxine replacement
- living in a region with presumed iodine deficiency

What is important to counsel the patient about when commencing thyroxine?

It is important to advise patients to take thyroxine in the morning when fasting, separately to other vitamins (e.g. calcium and iron) and to wait half an hour before eating to ensure adequate absorption. In addition all pregnant and lactating women should take 150 µg of iodine daily regardless of thyroid status.

How should this patient be monitored?

Thyroxine requirements during pregnancy vary and may be related to the underlying aetiology, preconception TSH levels and variations in maternal oestrogen levels. Hence, TFTs should be carefully monitored and the thyroxine dose titrated to keep TSH within the trimester-specific reference range. We advocate checking TFTs every four to six weeks throughout pregnancy, as noted in recent guidelines.[8]

Four weeks later at 15 weeks gestation, monitoring reveals a serum free TSH level of 1.26 mU/L (second trimester reference range, 0.2–3.0 mU/L). What do you advise next?

As this patient's TSH is now within the trimester-specific reference range the current thyroxine dose is continued. If TSH is over target, suggesting inadequate replacement, we find that a simple dose increment such as doubling the dose on one day (14% dose increase) is usually sufficient to normalise TSH.

This patient's TSH level remained within the trimester-specific reference range throughout pregnancy suggesting adequate thyroxine replacement, hence no further dose adjustment was required. Normal vaginal delivery eventuated without complication.

How should this patient be managed after delivery?

At the antenatal visit, the patient's plans regarding further pregnancies and contraception are discussed. Continuing thyroxine until childbearing is complete is reasonable. If thyroxine is ceased upon delivery (no need to wean), contraception should be used. We generally check TFTs six weeks postpartum.

Given TPO antibody positivity, what long-term advice should this patient be given?

During the postpartum period, TFTs should be performed for postpartum thyroiditis six months following delivery or as clinically indicated. Regarding future pregnancies, she should be advised she is at increased risk of developing autoimmune thyroid disease in the future and therefore should have TFTs measured every one to two years. She is at increased risk of SCH in future pregnancies due to her SCH this pregnancy in addition to her TPOAb positive status. She should therefore be screened for hypothyroidism, overt and subclinical, prior to conception. If TSH level is above 2.5 mU/L, thyroxine should be commenced or increased.

Case 2

A 33-year-old woman has had radioiodine therapy for the treatment of Graves' disease. She takes thyroxine 75 µg daily. She presents to her GP five weeks pregnant. This is her first pregnancy. She is asymptomatic and examination is unremarkable. As she is currently on thyroxine replacement, TFTs should be performed (see Box 2).[8] Investigations show a serum TSH level of 3.15 mU/L (first trimester reference range, 0.1–2.5 mU/L) and serum free T4 level of 15.1 pmol/L (nonpregnant reference range, 9.1–19.6 pmol/L).

What do these tests results suggest?

Her TSH level is above the trimester-specific range (Table 2).[6,7] Thus this patient with pre-existing hypothyroidism is receiving inadequate thyroxine replacement. This is due to the increased metabolic needs of pregnancy which in healthy pregnant women is met by thyroidal adaptation within six to eight weeks of conception, resulting in the production of T4 and T3 increasing by 50% and remaining elevated until delivery (Figure 1).[15,16] In women with pre-existing hypothyroidism, if this increased demand is not met by an appropriate increase in thyroxine dosing, overt hypothyroidism will result, with a significant risk of both maternal and fetal complications (Table 1).[3] Therefore this patient's thyroxine dose should be increased by 30 to 50%.[17,18] We find that this dose increase is most easily accomplished by doubling the dose taken on weekends, such that they take nine doses per week rather than seven (an overall dose increase of 29%).[19] Serum TSH levels should be monitored every four to six weeks as for cases of SCH. Referral of the patient to an endocrinologist is recommended.

What further investigations should be performed?

In patients with Graves' disease, even if treated, TSH receptor antibodies should be measured as they can cross the placenta and cause fetal/neonatal hyperthyroidism. They should be measured by at least the 20th week of gestation.

Investigations show a TSH receptor antibodies value of 29.8 IU/L (reference range less than 1.8 IU/L).

What does this test result suggest?

This patient's elevated level of TSH receptor antibodies increases the risk of fetal hyperthyroidism and it is therefore important that an obstetric ultrasound scan be performed to assess for features associated with this condition.[8,20] TSH receptor antibodies can disappear late after radioiodine therapy, but may not, as in this case. Elevated TSH receptor antibodies also increase the risk of neonatal hyperthyroidism.[21] Hence following delivery the neonate must be screened for this condition by clinical assessment and with formal TFTs.[22] Routine neonatal TSH testing (i.e. via the Guthrie test) is not adequate when TSH receptor antibodies are present as this is optimised to detect very high serum TSH levels as seen in congenital hypothyroidism, not for the suppressed TSH of hyperthyroidism. Neonatal hyperthyroidism requires paediatric endocrinologist consultation and supervision of treatment.

Serum TSH levels remained within the trimester-specific reference range and obstetric ultrasound was unremarkable. Despite this, delivery was premature and the baby was noted to be tachycardic. Neonatal TFTs were consistent with hyperthyroidism necessitating short-term treatment with propranolol and carbimazole. The mother returned to her prepregnancy thyroxine dose and the baby made a complete recovery.

What should this patient be advised regarding future pregnancies?

This patient should be educated on the strong association of hypothyroidism with decreased fertility and miscarriage. Her thyroid function should be tested before she begins to try to conceive and thyroxine dosage adjusted to obtain a preconception TSH level of less than 2.5 mU/L. She should also be advised to independently double her weekend thyroxine dose (total dose increase of 29%) as soon as pregnancy is suspected (providing she is euthyroid on a fixed daily thyroxine dose). This dose should be continued until w is confirmed and subsequent medical review occurs.[6] This is because an increased thyroxine requirement may occur at as early as the fifth week of pregnancy, well before formal antenatal review.[17] Due to this patient's history of Graves' disease, maternal TSH receptor antibodies should again be measured in any subsequent pregnancies.

Summary

Thyroid disease in pregnancy is common and has important implications. TFTs and TPOAb are the principal investigations to be performed. TSH levels within the trimester-specific reference range should be aimed for. This requires doubling the thyroxine dose for two days of the week in women with pre-existing hypothyroidism on confirmation of pregnancy; and commencement of thyroxine when indicated. TPOAb positivity means autoimmune thyroid disease, which puts women at risk of future thyroid dysfunction.

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COMPETING INTERESTS: Dr Cooray and Dr Sztal-Mazer: None. Professor Topliss has served on Advisory Boards on Thyrogen for Genzyme, Nexavar for Bayer, and given talks on thyroid cancer supported by Genzyme.