

Thyroid disease in pregnancy

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ABSTRACT

Pregnancy is accompanied by metabolic changes associated with the thyroid gland. It is therefore important to understand the underlying physiological alterations and the management of patients with thyroid disorders in pregnancy. This review focuses on the physiology and the management of hyperthyroidism, hypothyroidism and thyroid nodules in the context of pregnancy.

Thyroid physiology

Given endocrinologists' preoccupation with the scientific principles of endocrine and metabolic physiology, we propose a clear comprehension of first principles (Fig 1) which allows for the subsequent understanding of physiological change in pregnancy. Fluctuations in thyroid function tests during pregnancy are not always pathological. Consequently, the diagnosis and management of thyroid disease in pregnancy can be challenging for general physicians.

Maternal physiological adaptations occur in response to foetal physiology and foetal thyroxine requirements. At around 12 weeks, the foetal thyroid is functional; however, it does not produce sufficient thyroxine until 18–20 weeks gestation.¹ Importantly, adequate thyroxine is crucial for the developing foetal brain.

A number of physiological alterations occur in pregnancy that result in an increase in oestrogen, leading to increased production and reduced clearance of thyroid binding globulin (TBG), resulting in an overall net increase in the serum TBG.² There is increased affinity of T4 (thyroxine) / T3 (tri-iodothyronine) to TBG during the first half of pregnancy by 50%.³ This results in an increase in the total T4/T3 concentration by 50%, but consequent reduction in the free T4/T3 levels, which plateaus at 20 weeks of gestation.³

These alterations occur alongside increasing production of human chorionic gonadotropin (HCG) from the placenta. HCG and TSH share a common alpha subunit, with HCG having weak thyroid stimulating activity.⁴ This also accounts for the physiological rise in total T4 and T3 concentrations and occurs in parallel with a reduction in the thyroid stimulation hormone (TSH) concentration. As a consequence, there is consensus for an adapted trimester-specific reference range for the upper limit of

total T4 levels in the second and third trimester to be multiplied by ~1.5 times the normal range.³ There is also a 50% increase in the total daily iodine requirement in pregnancy as a result of greater T4/T3 production.⁵

Women before pregnancy, during pregnancy and while breastfeeding should aim to increase their daily iodine intake to 250 µg.³ To achieve this, it is recommended that once-daily prenatal vitamins containing 150–200 µg iodine are taken, in the form of potassium iodide or iodate, ideally pre-conception.³ Additionally, it is also advised that any iron supplements should be separated from thyroid hormone administration by a minimum of 4 hours.³

If trimester-specific reference ranges for TSH are unavailable in the local laboratory, the recommended reference ranges are available in Table 1.⁵

Key points

Pregnancy results in physiological alterations in thyroid hormones. This includes a rise in the total T4 and T3 levels due to an increase in thyroid binding globulin (TBG) levels and a reduction of TSH levels due to the thyrotrophic effect of human chorionic gonadotrophin (hCG) released from the placenta.

Overt maternal hypothyroidism and subclinical hypothyroidism, regardless of antibody status, requires treatment to avoid adverse clinical outcomes for both mother and baby.

An increase in levothyroxine dose by 30–50% as compared to the pre-pregnancy levels is generally required in pre-existing hypothyroidism.

Maternal subclinical hyperthyroidism usually does not require pharmacological intervention with propylthiouracil (PTU) or carbimazole (CBZ).

Overt maternal hyperthyroidism should be treated with PTU in the first trimester and then switched to CBZ subsequently (first line treatment regime). Routine monitoring of full blood count (for thioamide-induced agranulocytosis) and liver function (for thioamide-induced liver dysfunction/hepatic failure) is required at initiation and at frequent intervals.

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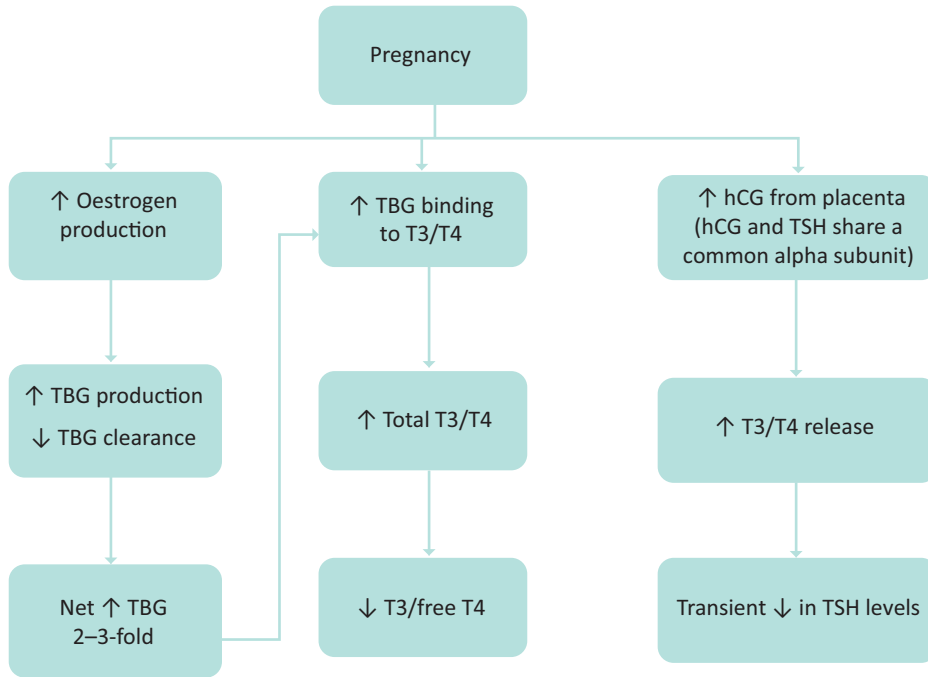


Fig 1. Physiological alterations of thyroid hormones in pregnancy. hCG = human chorionic gonadotrophin; TBG = thyroid binding globulin; TSH = thyroid stimulation hormone.

Hypothyroidism

Overt maternal hypothyroidism has serious deleterious effects on the foetus, and as such should be entirely avoided.^{6,7} Subclinical maternal hypothyroidism, regardless of antibody status, should also be treated given its association with an adverse outcome for both mother and baby^{6,7} which includes premature birth, low birth weight, miscarriage, gestational hypertension and impaired foetal neurocognitive development.^{5,8}

Hypothyroidism diagnosed during pregnancy can be treated according to TSH levels.⁹ Levothyroxine should be titrated to achieve a target TSH in the lower half of the trimester specific reference range and if these are not available locally, then maternal TSH concentrations should be maintained at ≤ 2.5 mIU/l in the first trimester and ≤ 3.0 mIU/l in the second and third trimester.⁵ Typical dosing in levothyroxine-naïve patients is demonstrated in Table 2. Levothyroxine is typically increased by approximately 30% to 50%, compared to the pre-pregnancy dose.¹⁰ Thyroid function tests (TFTs) should be performed every 4–6 weeks to ensure adequate dosing in response to the TSH levels.¹⁰ However, it should be noted that there are substantial population differences in the ‘normal’ TSH upper reference limit.

Additionally, there are greater risks of adverse events in women who are thyroid peroxidase antibody (TPOAb)-positive compared to those

who are TPOAb-negative. Therefore, pregnant women with a TSH >2.5 mu/l should be assessed for their TPOAb status. Levothyroxine typically may need to be increased incrementally every 4–6 weeks during gestation. TFTs are required every 4–6 weeks to ensure adequate dosing in response to the TSH levels.¹⁰

TPOAb-positive women who are euthyroid require TFT monitoring every 3–6 weeks to detect TSH rise above the normal pregnancy-specific ranges.¹⁰ With a TSH of >2.5 mU/L, but below the upper limit of the pregnancy-specific reference range, Levothyroxine replacement should be considered.⁵ Postpartum, most women will revert to their pre-pregnancy levothyroxine dose. Thyroid function tests should be evaluated 6 weeks post-partum.⁵

Hyperthyroidism

Overt maternal hyperthyroidism is an important differential in the context of a low TSH, particularly in early pregnancy, even though normal physiology in pregnancy may result in low TSH levels. Additionally, gestational transient thyrotoxicosis that typically resolves by 18–19 weeks is associated with persistent vomiting of hyperemesis gravidarum with a lack of typical symptoms of

Table 1. Trimester-specific reference ranges for TSH in pregnancy^{3,5}

Trimester	TSH range
First trimester	0.1–2.5 mIU/L
Second trimester	0.2–3.0 mIU/L
Third trimester	0.3–3.0 mIU/L

TSH = thyroid stimulating hormone.

Table 2. Dosing in levothyroxine-naïve hypothyroidism patients diagnosed during pregnancy⁹

Initial TSH levels discovered during pregnancy	Levothyroxine dose required
<4.2 mIU/L	1.2 mcg/kg/day
4.2–10 mIU/L	1.42 mcg/kg/day
>10 mIU/L	2.33 mcg/kg/day

Mcg = micrograms, mIU/L = milli-international units per litre, TSH = Thyroid Stimulating Hormone.

thyrotoxicosis. Gestational transient thyrotoxicosis is *not* treated with anti-thyroid medication. A suppressed or undetectable TSH level (<0.01 mU/l) with elevated free T4 and free T3 levels, with positive TSH receptor antibodies (TRAb), together with clinical evidence of autoimmunity and a goitre differentiates between Grave's disease and gestational transient thyrotoxicosis.¹¹ Antibody status (primarily TSH receptor antibodies; TRAb) should be ascertained if there are concerns regarding the diagnosis of gestational transient thyrotoxicosis. Anti-thyroid medications should be initiated and titrated to maintain the free T4 in the upper limit of the non-pregnant reference range.¹²

For subclinical maternal hyperthyroidism, there is a lack of evidence that intervention with anti-thyroid medication (thioamides: PTU and CBZ) improves pregnancy outcomes.³ Thus, treatment is not routinely advocated as adverse foetal outcomes may occur if patients are rendered hypothyroid as a result of treatment.^{10,13} If the maternal hypothyroidism occurs, this can result in preterm birth, low birth weight, respiratory distress in the short term and impaired neuropsychological development in the foetus in the longer term.¹⁴

In patients with overt hyperthyroidism, PTU is the treatment of choice in the first trimester of pregnancy as CBZ is associated with congenital abnormalities, including choanal and oesophageal atresia, aplasia cutis congenital and minor facial anomalies (Table 3).¹⁵ Monitoring of liver function tests every 3–4 weeks is required in patients on PTU due possible hepatotoxic adverse events which can be accentuated by 'disease'–drug (pregnancy–drug) interaction.³ CBZ is recommended from the second trimester given the rare but severe liver toxicity adverse events associated with PTU.³ Patients switching from PTU to CBZ should have their TFT reviewed after 2 weeks and then at 2–4 weekly intervals, at a conversion of 100 mg PTU to 10 mg of CBZ.³

Radioactive iodine treatment is contra-indicated in pregnancy (or within 6 months of conception). Subtotal thyroidectomy may be indicated during the second trimester of pregnancy for maternal Graves' disease.¹⁶ Indications for a subtotal thyroidectomy includes:

- > severe adverse reaction to anti-thyroid drugs
- > a requirement for persistently high doses of anti-thyroid medication
- > non-adherence to anti-thyroid medication therapy
- > uncontrolled thyrotoxicosis.¹⁷

Iodine treatment should not be used in pregnancy or during breastfeeding.¹⁶

Table 3. Adverse events of thioamide medication in pregnancy^{3,5}

Medication	Trimester to be used	Side effects
Propylthiouracil (PTU)	1st trimester	Hepatotoxicity
Carbimazole (CBZ)	2nd and 3rd trimester	Choanal and esophageal atresia, aplasia cutis congenita, minor facial anomalies and psychomotor delay during 1st trimester organogenesis, hepatotoxicity

In pregnant women with elevated TRAb (increased two- or three-fold or greater than the upper limit of normal) and treated with anti-thyroid medication, maternal free T4 and potential sonographic signs of foetal thyroid abnormalities should be screened at the foetal anatomy ultrasound undertaken at week 18–22 and repeated every 4–6 weeks.¹⁶ Features suggesting foetal thyroid dysfunction may include growth restriction, hydrops, presence of foetal goitre, tachycardia or foetal cardiac failure. If foetal hyperthyroidism is diagnosed and considered a gestational risk, treatment with PTU in the first trimesters is required with frequent clinical, laboratory, and ultrasound monitoring.¹⁸ After completion of the first trimester, it is recommended that PTU is switched to carbimazole (CBZ) due to the rare association of PTU with severe liver toxicity/hepatic failure.³ The potential adverse effects of PTU and CBZ can be found in Table 3.

Screening for women with high risk of thyroid dysfunction with prenatal measurement of serum TSH is recommended by the ninth week of pregnancy.³ Box 1 demonstrates at risk groups recommended for thyroid screening in pregnancy.

Postpartum thyroid disease

Postpartum thyroiditis is the most common cause of thyrotoxicosis post pregnancy. The prevalence is 4.1% as compared to 0.2% for Graves' disease.⁵ Postpartum thyroiditis typically occurs within 6 months after delivery with an initial hyperthyroid phase and then spontaneous remission thereafter. This may also be followed by a hypothyroid phase before a transition to euthyroidism (by 1 year post-partum) in the majority of patients.⁵ β -blockers are the mainstay of treatment in symptomatic patients in the hyperthyroid phase.¹⁹ Appropriate counselling should be undertaken for β -blocker use in pregnancy (risk of intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia). Women with a previous history of Graves' disease may also relapse, but in this instance requiring anti-thyroid medications.¹⁹

Thyroid nodules

The prevalence of thyroid nodules in pregnancy increases with increasing parity and increasing age. The thyroid nodules tend to

Box 1. At-risk groups of hypo- and hyperthyroidism requiring thyroid function screening: recommended criteria for thyroid function test screening in prenatal women¹

- > Age \geq 30 years old
- > Family history of autoimmune thyroid disease or hypothyroidism
- > Presence of a goitre
- > Thyroid antibodies, primarily thyroid peroxidase antibodies
- > Symptoms or clinical signs suggestive of thyroid hypofunction
- > History of type 1 diabetes or other autoimmune disorders
- > History of infertility
- > Prior history of miscarriage or preterm delivery
- > Previous therapeutic head or neck irradiation or prior thyroid surgery
- > Currently receiving levothyroxine replacement
- > Living in a region with presumed iodine deficiency

increase in size or number during pregnancy. Thyroid ultrasound with or without fine needle aspiration is safe during pregnancy and useful in detecting thyroid nodules and determining their malignancy risk. Slowly growing benign nodules do not require special surveillance or surgery during pregnancy. Indeterminate and malignant nodules should be managed in accordance to American Thyroid Association (ATA) management guidelines with specialist local advice.⁵ For slower growing thyroid cancers, eg papillary thyroid cancer, definitive treatment may wait until after childbirth.

Conclusion

In summary, the management of thyroid disease in pregnancy requires careful consideration for both mother and baby. Overt maternal hypothyroidism or subclinical maternal hypothyroidism, regardless of antibody status, requires treatment to avoid adverse clinical outcomes. Overt maternal hyperthyroidism (and not subclinical maternal hyperthyroidism) requires treatment with PTU in the first trimester and CBZ in the second trimester onwards. Additionally, gestational transient thyrotoxicosis, which is associated with hyperemesis gravidarum and occurs primarily in the first trimester, requires only observation. However, a diagnosis of gestational transient thyrotoxicosis should be carefully evaluated in the presence of pre-existing or past history of Grave's disease or thyrotoxicosis. ■

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