Review Thyroid disease in pregnancy

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Key content:

- Trimester-specific reference ranges should be used to interpret thyroid function during pregnancy.
- The fetus requires maternal thyroxine in the first trimester.
- Optimal management of hypothyroidism should be achieved prior to conception; pregnant women may need to alter their dose of thyroxine in early pregnancy.
- Treatment for hyperthyroidism can often be reduced in the third trimester, to minimise the risk of fetal hyperthyroidism, and then restored postnatally.
- Human chorionic gonadotrophin-driven hyperthyroidism in hyperemesis gravidarum usually resolves by 20 weeks and does not require antithyroid medication, although thyrotoxicosis must be excluded.

Learning objectives:

- To understand the basis of and treatment options for hypothyroidism in pregnancy.
- To appreciate the fetal and neonatal implications of maternal thyrotoxicosis.

Ethical issues:

- Worldwide, iodine deficiency has devastating neurological effects on the fetus, many of which can be prevented by supplementation.

Keywords hyperemesis gravidarum / hyperthyroidism / hypothyroidism / iodine deficiency

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Introduction

Thyroid disease is common in women of childbearing age. It is essential that obstetricians understand the physiological changes brought about by pregnancy and the pathophysiology of thyroid disorders, to be able to treat women safely and optimise outcome without inappropriate medicalisation of the pregnancy.

Physiology

The circulating thyroid hormones are thyroxine (T_4) and triiodothyronine (T_3), of which only the free portions (f), fT_4 and fT_3, are active. The biologically more important fT_3 is formed mainly peripherally in the liver, kidneys and muscle, where it is converted from fT_4 by deiodinase enzymes.[1] Most tissues, including heart, brain and muscle, have specific nuclear receptors for fT_3 by which metabolic and cellular activities can be influenced. In normal circumstances, the anterior pituitary gland produces thyroid stimulating hormone (TSH) as part of a negative feedback loop controlled by fT_3 concentration. Dietary iodine is essential for thyroid hormone synthesis.

In the fetus, the pituitary–thyroid axis is controlled in a very similar way, with iodine supplied transplacentally. Prior to 12 weeks' gestation, maternal thyroxine (but not fT_3) crosses the placenta. Following binding to receptors in fetal brain cells, thyroxine is converted intracellularly to fT_3, a process thought to be important for normal fetal brain development. From 12 weeks onwards, placental changes prevent significant passage of maternal thyroxine and fetal thyroid function is controlled independently of the mother, provided that her iodine intake is adequate. When the fetus is athyrotic, however, deiodinase III on the fetal side of the placenta is suppressed such that fetal levels of T_4 can still reach one-third of that expected in a normal pregnancy. Well-designed, isolated, term placental studies show passage to the fetal side of only 0.008% of maternal thyroxine in normal circumstances; this is increased 2700-fold by the addition of a deiodinase inhibitor.[1]

Four important pregnancy-specific changes occur:

1 The half-life of thyroxine binding globulin extends from 15 minutes to 3 days and its concentration triples by 20 weeks of gestation, as the result of estrogen-driven glycosylation. Total thyroid hormone levels increase and, therefore, measurements of total T_4 and total T_3 are not reliable in pregnancy. fT_4 and fT_3 remain relatively constant and are the tests of choice in pregnancy: they should be interpreted in relation to pregnancy-specific reference ranges.
2 Human chorionic gonadotrophin (hCG) and thyroid stimulating hormone (TSH) have similar alpha subunits and receptors. In the first trimester a hormone spillover syndrome can occur in which hCG stimulates the TSH receptor and gives a biochemical picture of hyperthyroidism. This is particularly common in multiple pregnancy, trophoblastic disease and hyperemesis gravidarum, where concentrations of both total hCG and thyrotropic subtypes can be greater (see below). Thyroid function tests should be interpreted with great caution in these circumstances.
3 Increased glomerular filtration and greater uptake of iodine into the thyroid gland driven by increased total thyroxine concentration can deplete iodine and cause or worsen iodine deficiency. Transplacental transfer can also exacerbate this but when there is severe maternal iodine deficiency, maternal iodine trapping overrides fetal needs, resulting in cretinism.
4 Three deiodinase hormones control metabolism of T_4 to the more active T_3 and their breakdown to inactive compounds. The concentration of deiodinase III increases in the placenta with gestation, releasing iodine where it is required for transport to the fetus and, possibly, contributing to reduced thyroxine transfer.

Hypothyroidism

Hypothyroidism occurs in around 1% of pregnant women. Its management in pregnancy remains surprisingly contentious and complicated.[2,3] Some state that all women must increase their thyroxine dose at conception and have their thyroid function tested regularly throughout the whole pregnancy;[4] others feel that testing once per trimester is adequate, with dose changes made in response to biochemical tests, if required.[5] As there is some evidence that excess thyroxine can be harmful,[6] routine increases in thyroxine must not be advised.

Reasons for lack of uniformity in treatment

1 There can be confusion between women with:

- **untreated hypothyroidism** (low fT4, high TSH, often symptomatic) who require urgent initiation of treatment with thyroxine
- **previously diagnosed hypothyroidism** who may be on optimal therapy (normal fT4 and TSH) at conception or who may not (low fT4, high TSH): in the latter, rapid achievement of euthyroidism is important, particularly in the first trimester
- **subclinical hypothyroidism** (normal fT4, raised TSH, asymptomatic) in whom the place of thyroxine therapy is debatable
- **hypothyroxinaemia** (low T4, normal TSH).

2 It is important to decide the targets of treatment in pregnancy. From a fetal perspective, maternal thyroxine concentrations do not have a major impact on fetal thyroid function beyond the

first trimester. The consequences of suboptimal replacement therapy in the first 3 months of pregnancy have been examined by a number of groups. Most have used tests of neuropsychological development of the offspring at ages ranging from 3 weeks to 9 years[7–10] but inherent problems with these types of tests and the very large number of factors that influence a child's development mean that it is difficult to be certain what impact hypothyroidism has on the fetal brain.

Haddow *et al.*,[7] using second trimester TSH as a surrogate marker for first trimester thyroid function in 62 women with values above the 98th percentile and 124 poorly-matched controls (not excluding women with a diagnosis of treated hypothyroidism), suggested a loss of 4–7 IQ points. Pop *et al.*,[8,9] using fT_4 levels at 12 and/or 32 weeks of gestation, reported that babies born to mothers with the lowest values at 12 weeks may have the poorest development and that this was[9] or was not[8] sustained only if the fT_4 remained low in the third trimester. Multiple logistic regression analysis identified alcohol intake, gestational depression, low educational achievement and negative life events during pregnancy as strongly related to low scores in these babies. There are no data to inform us as to whether correcting the biochemical picture by administering thyroxine improves outcome. Other studies have suggested that neonatal encephalopathy may be associated with thyroxine replacement therapy, or lack of it. The two papers examine only 13 women in total, some of whom were not taking thyroxine while others were taking antithyroid medication or nothing; many had other reasons for encephalopathy. A subsequent re-analysis of the data showed no association between thyroxine use and encephalopathy.

From a maternal perspective, biochemical euthyroidism remains the goal, as it is outside of pregnancy. Adjustment of thyroxine dose on the basis of clinical signs and symptoms is particularly challenging in pregnancy. Both excess and deficient thyroid hormone levels cause problems that are difficult to distinguish from those of normal pregnancy (**Box 1**). This results in an increased dependence upon biochemical results and pregnancy-specific reference ranges. Some data[5] suggest an association between treated hypothyroidism and adverse pregnancy outcomes, including miscarriage, pre-eclampsia, placental abruption and prematurity.

These data are, however, conflicting: stratification of important demographic (e.g. age or smoking status) and obstetric confounding factors (e.g. obstetric history or pre-existing medical disorders) is poor, many of the studies are based on small numbers of events that are often not properly defined and none show causality.[4] It is not appropriate, therefore, to base clinical decisions regarding the management of hypothyroidism on the premise that this will influence the risk of obstetric complications.

Excess thyroid hormone levels	Deficient thyroid hormone levels
Heat intolerance	Constipation
Increased appetite	Tiredness
Sweating	Weight gain
Palpitations	Hair thinning
Tachycardia	

Box 1
Symptoms of thyroid disease resembling common features of normal pregnancy

3 Factors that could influence thyroxine dosage during pregnancy must be considered (**Box 2**).

4 Finally, the therapeutic window of thyroxine is broad, with dose adjustments usually of 25 or 50 micrograms, i.e. by approximately 25%. Few individuals are on a tightrope of therapeutic control. Although in pregnancy increased concentrations of thyroxine binding proteins occur that result in an increased total thyroid hormone pool, it is likely that, for many women, this will not in itself necessitate dose adjustment. In addition, deiodinase II, the enzyme responsible for peripheral activation of T4 to T3 in the brain, increases in concentration with advancing gestation (when fT4 is low). This may help to explain why thyroxine increases are not routinely required, despite the physiological changes explained above.

This is reflected in the reference ranges for thyroid function, which are broad. Some state that thyroxine doses should be increased such that TSH falls into the lower half of the range;[2] some feel this would be detrimental.[14] Others feel that individuals have their own narrow normal range, outside which they may develop symptoms or be at increased risk of the long-term consequences of hypothyroidism (cardiac failure) or hyperthyroidism (atrial fibrillation or osteoporosis).[15] In pregnancy these questions remain unanswered, as does whether it is the circulating fT_4 or TSH that is a better marker of euthyroidism from the mother's or baby's perspective.

The situation is further complicated by the following issues:

- Thyroid function can be influenced by hyperemesis gravidarum in the first trimester.
- Reference ranges for thyroid hormones are different in pregnancy (especially in the third trimester, when there is a move towards the hypothyroid end of the spectrum):[16] trimester-specific reference ranges should be used in the management of thyroid disease in pregnancy.

Box 2
Factors with the potential to influence thyroxine dosage during pregnancy[11–13]

- Reduced absorption in the first trimester related to nausea and vomiting
- Malabsorption resulting from binding of thyroxine to newly-commenced iron and calcium supplements
- Suboptimal control prior to conception
- Altered compliance, with either an improvement, resulting in an apparent need to reduce the dosage, or a deterioration (perhaps from false concerns of safety), resulting in apparent need to increase the dosage
- Normal variation in thyroxine dosage

Overall, for women with under- or untreated hypothyroidism, optimal replacement doses should, ideally, be reached prior to conception or early in the first trimester. Some women with established hypothyroidism need to increase their dose of thyroxine during pregnancy to maintain euthyroidism according to trimester-specific ranges but only first trimester control influences fetal wellbeing. Hypothyroidism itself does not influence pregnancy outcome or complications. For women with hypothyroidism who intend to become pregnant and who are on the correct dose of thyroxine, thyroid testing is needed only prepregnancy, early in the first trimester and again later in the second or third trimester. The majority of their antenatal care can be midwifery-led unless risk factors dictate otherwise.

Hyperthyroidism

Autoimmune thyrotoxicosis or Graves' disease affects around 2 per 1000 pregnancies. Management is more complex but less controversial than that of hypothyroidism. The main tenet is to ensure euthyroidism is achieved as early as possible in pregnancy, preferably prior to conception, as this minimises the likelihood of maternal or fetal complications (**Box 3**). Beta blockade, usually with propranolol hydrochloride, should be used in pregnancy, if required, to control tachycardia, tremor or anxiety. In this context, any concerns there may be about fetal growth restriction are vastly outweighed by the maternal and fetal benefits. Euthyroidism is achieved using the antithyroid agents carbimazole or propylthiouracil. These block thyroid hormone synthesis and have an immunosuppressive effect, reducing the titre of TSH receptor stimulating antibodies and, thereby, directly influencing the course of the disease. As both of these drugs cross the placenta in similar amounts, it is important that the lowest effective dose is used to minimise the risk of fetal hypothyroidism. In practice, it can be difficult to distinguish clinically between the signs and symptoms of hyperthyroidism and pregnancy and so, again, reliance is placed on serial biochemical measurements, which must be assessed in relation to trimester-specific reference ranges. Failure to gain weight, despite a good appetite, and tachycardia greater than 100 beats per minute that fails to slow with the Valsalva manoeuvre, are good indicators of thyrotoxicosis, as is the rare finding of onycholysis (elevation of the distal nail bed). Eye signs and pretibial myxoedema do not reflect disease activity.

Box 3
Complications of poorly controlled hyperthyroidism in pregnancy

Maternal	Fetal
Thyroid storm	Fetal growth restriction
Congestive cardiac failure	Prematurity
Pre-eclampsia	Stillbirth

Clinical disease activity follows the titre of TSH receptor stimulating antibodies, which rises in the first trimester and puerperium and falls in the second and third trimesters. Thyroid function should be measured monthly when control is good and more frequently when the diagnosis is new or there is a relapse: antithyroid medication is titrated against the results. Most women can, therefore, reduce their dose and almost one-third of women can stop treatment during pregnancy, which helps prevent fetal hypothyroidism. Most women will need to restart or increase their dose in the puerperium to avoid a relapse.

Propylthiouracil or carbimazole?

It was previously felt that as propylthiouracil is more heavily protein-bound than carbimazole, it was less likely to be transferred across the placenta and should, therefore, be the agent of choice. Studies[17] using isolated perfused human placental lobules, however, show similar placental transfer kinetics for both drugs. No differences in fetal thyroid function (measured using cord sera) were found in 77 babies whose mothers were taking one or other of the agents.[18]

Similarly, earlier reports[19] suggested that carbimazole causes aplasia cutis congenita of the scalp in the infant, a rare congenital defect affecting 0.03% of the general population. More extensive and recent work[20] indicates, however, that this association is either spurious or, at most, extremely rare and should not influence the choice of drug in pregnancy. No other teratogenesis has been linked with antithyroid drugs. Indeed, pregnancies in which there is poor control in the first trimester are more likely to be complicated by fetal anomaly than those in which drug therapy is successfully used to achieve control.[19,20]

Both drugs cause agranulocytosis and pregnant women should be reminded to report a sore throat immediately. This reaction is unpredictable and is a reason not to change agent routinely during pregnancy.

Lactation is the period when there is some difference between the drugs. Studies of radiolabelled drugs show that 0.077% of propylthiouracil and 0.47% of carbimazole reaches breast milk. Small numbers of babies, however, whose mothers have taken antithyroid medication have had thyroid function monitored in the first weeks of life and adverse

effects have not been found. Nonetheless, there are concerns that high doses, especially of carbimazole, could cause neonatal hypothyroidism. Doses should, therefore, be split through the day, with feeding to occur before a dose where possible, monitoring of neonatal thyroid function and regular consideration given to switching to propylthiouracil.

Thyroid surgery or radioactive iodine?

Thyroid surgery can be carried out in pregnancy if required, most usually in the second trimester. Indications include: compression from a large goitre, suspicion of malignancy and failed antithyroid therapy. Surgery may be more challenging than usual because of the pregnancy-associated increase in the vascularity of the thyroid and so should only be undertaken by an experienced thyroid surgeon and when truly indicated.

Radioactive iodine crosses the placenta and binds to and destroys the fetal thyroid. It is totally contraindicated in pregnancy. Lactation should be stopped (preferably 4 weeks prior to treatment) if it is given in the puerperium.[21]

Fetal and neonatal consequences of thyrotoxicosis

Fetal or neonatal problems relating to well-controlled Graves' disease are rare. However, TSH receptor stimulating antibodies cross the placenta and the risk of fetal Graves' disease after 20 weeks (the gestational age at which the fetal thyroid can respond to these antibodies) is directly proportional to their titre (although even at the highest titres, the risk is very low). It is very important that women who have had Graves' disease in the past treated by surgery or radioactive iodine, as well as those actively being treated for the condition during pregnancy, have this antibody measured. Women with positive results should be monitored for signs of fetal thyrotoxicosis, including tachycardia, excessive movements, fetal growth restriction, oligohydramnios and goitre (**Figure 1**). Fetal Graves' disease can cause premature delivery in untreated women and, in addition to the features above, can be accompanied by any of the following:

- craniosynostosis and associated intellectual impairment
- hydrops fetalis
- intrauterine death
- polyhydramnios related to oesophageal pressure
- obstructed labour from neck extension related to goitre.

Management is usually based on delivery if the gestational age is sufficiently advanced. If this is not appropriate, high doses of propylthiouracil or carbimazole should be given to the mother and the response titrated against the fetal heart rate; the pregnant woman can take thyroxine if she becomes clinically hypothyroid and this will not cross the placenta. Although fetal reference ranges for thyroid function are known, fetal blood sampling is not routinely needed unless the diagnosis is in doubt.

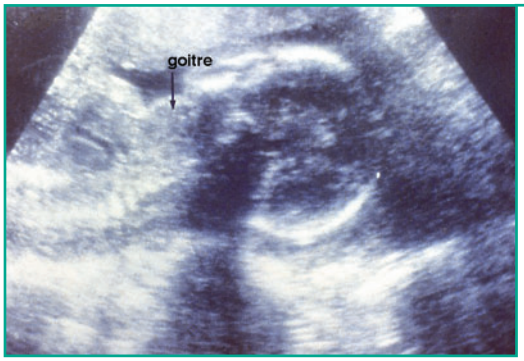

Figure 1
Neck extension caused by fetal goitre

At delivery, thyroid function should be measured using cord blood. Rarely, hypothyroidism is reported secondary to transplacental passage of antithyroid drugs but this is usually self-limiting. Hyperthyroidism is also occasionally detected, although this more typically presents 7–10 days postnatally, since the half-life of maternally-derived antithyroid drugs is shorter than that of TSH receptor antibodies. In practice, parents should be warned to look for changes in their baby, such as weight loss or deteriorating/poor feeding, and local procedures should be followed for paediatric involvement. Neonatal treatment, when required, rarely lasts for more than a few months.

Hyperemesis gravidarum

Hyperemesis gravidarum is the term for vomiting in the first half of pregnancy that is sufficiently severe to cause dehydration requiring intravenous fluids, weight loss and/or abnormalities in liver function (secondary to starvation) or thyroid function tests. This, usually transient, hyperthyroidism (suppressed TSH and high or very high fT_4) occurs in over 60% of pregnancies with severe hyperemesis and is caused by the TSH-like effect of the beta subunits of hCG. In some pregnancies, either the total concentration of hCG is increased (for example, in multiple or molar pregnancies) or the beta subunits of hCG have a greater ability to bind to TSH receptors. The resulting biochemical hyperthyroidism must be differentiated from the rare, first trimester presentation of Graves' disease with vomiting, by taking a detailed history and by ensuring a return to biochemical normality as the hyperemesis resolves. By 19 weeks' gestation, one series[22] reported that fT_4 levels had fallen to normal and TSH had escaped full suppression in all women. Typically, in women with hyperemesis gravidarum, the symptoms clearly postdate the pregnancy, the woman is washed out, deflated and tired, there are no eye signs or goitre and tachycardia responds to intravenous rehydration.

If there is clinical doubt, the absence of thyroid autoantibodies is helpful in supporting hyperemesis (but the converse is not true).

The focus of therapy is on correcting the metabolic insults of prolonged vomiting and minimising further vomiting. There is no place for antithyroid medication, as there is no intrinsic increase in thyroid activity, the duration of hyperemesis gravidarum is usually relatively short and the antithyroid medication crosses the placenta and has the potential to make the fetus hypothyroid. When hCG-related thyrotoxicosis is treated, antithyroid medication is either ineffective or very high doses are needed.[23]

Iodine deficiency

The World Health Organization[24] estimates that, worldwide, 2 billion people are iodine deficient and more than 20 million have adverse neurological sequelae secondary to *in utero* iodine deprivation. Worldwide, neurological cretinism is the leading preventable cause of mental handicap. It affects 2–10% of people in iodine deficient areas and causes mild mental handicap in a further 10–50%, such that the IQ distribution curve is moved 10 points to the left with a significant negative impact on the economy of afflicted regions. The developing cochlea, cerebral neocortex and basal ganglia are most sensitive to iodine deficiency, especially in the second trimester, resulting in deaf-mutism, intellectual deficiency and spastic motor disorder. Less severe maternal iodine deprivation spares hearing, speech and motor function but causes mental handicap (myxoedematous cretinism), presumably because the mother is able to transfer enough T_4 and iodine and the fetus is subsequently able to make enough T_3 to protect these functions.

In areas of endemic iodine deficiency, pregnant women usually have low or very low T_4 and normal T_3, with raised TSH levels and a compensatory goitre. This supports the physiological pathways outlined above but that maternal T_3 is not enough to protect the fetal brain, which needs intracellular T_3 (derived from circulating T_4). In these circumstances, there is not enough maternal T_4 to be transferred, even if deiodinase II is suppressed, nor enough iodine to allow fetal production of T_4. Changes in renal clearance of iodine and increased thyroxine binding globulin exacerbate the level of iodine deficiency in susceptible populations.

Iodine administration prior to conception or up to the second trimester can protect the fetal brain and, when given early enough, reduce miscarriage and later pregnancy losses.[25,26] Programmes to deliver annual boluses of iodine to susceptible women are difficult to sustain and, unfortunately, national programmes to iodinate flour, salt or water continue to flounder.[27]

Conclusion

If evidence-based practice is used, including pregnancy-specific reference ranges, management of thyroid disorders in pregnancy should be relatively straightforward. Women with hypothyroidism should achieve euthyroidism prior to conception. Once it is confirmed that this is maintained in the first trimester, further dose adjustments are unlikely to influence pregnancy outcome, which is expected to be good unless other obstetric factors intervene. Women with Graves' disease can usually reduce their doses of propylthiouracil or carbimazole, thereby minimising the risks of fetal hypothyroidism. TSH receptor stimulating antibodies should be measured in women with active Graves' disease or a past history of Graves' disease treated by surgery or radioactive iodine and those with positive results monitored for signs of fetal hyperthyroidism.

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