Thyroid and other endocrine disorders in pregnancy

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Abstract

Thyroid disorders are common endocrine problems encountered in pregnancy. To optimize pregnancy outcomes it is essential to understand the effects and treatments of both hyper- and hypo-thyroidism. Pituitary disease is not uncommon in pregnancy. Other endocrine pathologies are much rarer in pregnancy, often because of high levels of subfertility; they are often associated with significant maternal or fetal morbidity and even mortality if not recognized or treated adequately. This review summarizes the important consequences of thyroid and other endocrine diseases in pregnancy.

Keywords Addison's disease; congenital adrenal hyperplasia; conn syndrome; cushing syndrome; diabetes insipidus; hypopituitarism; phaeochromocytoma; pituitary adenomas; thyroid disease

Thyroid disorders in pregnancy

Thyroid problems are common in pregnant women and have, together with their treatments, the potential to influence maternal well-being and the outcome of the pregnancy. It is therefore important that they are well understood.

Thyroid physiology in pregnancy

The half-life of thyroxine binding globulin [TBG; the main binding protein for thyroxine (T4) and tri iodothyronine (T3)] is prolonged by oestrogen-driven sialylation, which results in an increased circulating concentration of both TBG and therefore of total T4 and T3. It is for this reason that these hormones are not measured in pregnancy. Instead, freeT4 and freeT3, the biologically active hormones, are measured: these are not greatly changed in normal pregnancy, although the lower limit of normal is reduced slightly in the third trimester. Normal values for thyroid stimulating hormone (TSH) rise slightly in the third trimester, but otherwise are unchanged compared with non-pregnant ranges.

TSH and T3 do not cross the placenta. In the first trimester, T4 does cross the placenta and is believed to play a role in fetal brain development prior to the onset of fetal thyroid activity, which occurs late in the first trimester. Changes in placental iodinase enzymes at the end of the first trimester prevent the transfer of maternal T4 to the fetal circulation beyond this gestation: 0.008% of maternal T4 passes across at term. This applies to both endogenous T4 and pharmaceutical T4, and should be remembered when considering the management of pregnant women with hypothyroidism. In pregnancies where the fetus is athyrotic (i.e. is unable to produce thyroid hormones due to, for example, enzyme deficiency, failure of gland formation or profound iodine deficiency), alteration in placental iodinase enzymes – believed to be driven by changes on the fetal side of the circulation – allow transfer of T4 from the mother to the fetus to achieve levels one third of those expected.

In the first trimester, human chorionic gonadotrophin (hCG) may influence thyroid function because the alpha subunits of hCG and TSH are identical, and therefore HCG has some thyrotropin-like effect. Beta subunits of TSH show considerable heterogeneity and in some pregnancies have greater TSH-like effect than others; this is particularly evident in multiple pregnancies, where the titre may be higher, and in hyperemesis gravidarum, and may result in a biochemical picture of thyrotoxicosis, with raised T4 and suppressed TSH: this is self-limiting and does not need treatment with antithyroid medication. True thyrotoxicosis, rarely, may present de novo in the first[t] trimester and a careful history, including the time course of any symptoms and follow-up to ensure return to biochemical euthyroidism in the second trimester, is required.

Hypothyroidism

Around 1% of pregnant women have hypothyroidism, so this condition will be seen frequently in most units. A few women – those who have had surgery for thyroid cancer – will be on suppressive doses of thyroxine to render the TSH undetectable and so reduce the risk of recurrence. The majority of women with hypothyroidism will be on life-long thyroxine replacement therapy, usually because of: autoimmune hypothyroidism – Hashimoto disease, the consequences of thyroid surgery for benign nodules or goitre, or following treatment for autoimmune hyperthyroidism – Graves disease (both surgical and radioactive iodine treatment frequently result in hypothyroidism), with the aim being to maintain biochemical and clinical euthyroidism. These women usually have an annual thyroid function measurement and review of their thyroxine requirements.

There is an unresolved debate in non-pregnant women regarding the best target for thyroid function tests (TFTs) (i.e. normal range TSH or low TSH) and whether dose changes should be based on TSH or fT4 concentrations, or both. In pregnancy these issues are no clearer.

Although it has been suggested that women with treated hypothyroidism are more likely to have miscarriage, pre-eclampsia, prematurity and other adverse outcomes, there are no data to support this and these women do not need increased antenatal surveillance in respect of these complications. There are some data suggesting that the neonatal outcome of women who have under-treated hypothyroidism or untreated subclinical (i.e. asymptomatic) hypothyroidism in pregnancy may be less good than those women without hypothyroidism: one study suggested a maximum IQ deficit of 7 points compared with that in a control

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group. Unfortunately, neurological and psychomotor development in children has so many diverse influences that it is not easy to distinguish the role of the in utero thyroid environment and ex utero factors, including of course the possibility that a woman with untreated hypothyroidism may be subtly less able to carry out the role of motherhood. For example, multiple logistic regression analyses point to smoking, alcohol intake and maternal depression as being factors influencing the child's development, as well as the mother's thyroid status.

Nonetheless, it seems logical, even if the evidence base regarding outcome is weak, to aim for the pregnant woman to be euthyroid, both for her sense of well-being and to ensure optimal transfer of T4 to the fetus in the first trimester. However, it is important to remember that after this period it is unlikely that adjustments to the maternal dose will have any influence on the fetal thyroid status or development. Blanket increase in thyroxine dose is not advised, not least because there is evidence from both thyrotoxic and thyroid hormone resistant pregnancy that excess thyroxine is associated with increased miscarriage and low birth weight.

There is some debate about whether pregnant women with hypothyroidism should increase their dose of thyroxine with some recommending that they all should, and others advising that changes are made only on the basis of thyroid function tests. It is important when considering this to bear in mind the possible aims of dose changes, which might be to achieve biochemical euthyroidism, to improve maternal well-being or to influence the fetal environment. From the previous discussion it should be clear that the latter is unlikely to be possible after the first trimester. Those women with hypothyroidism who conceive when their thyroid function is well-controlled and their thyroxine dose is stable are relatively unlikely to need to increase their dose of thyroxine while they are pregnant. If they do, it is generally because of reduced absorption in the first trimester due to vomiting; reduced compliance due to unfounded concerns about teratogenicity; introduction of iron or calcium supplements (both of which reduce absorption and so should be taken separately from thyroxine); or, in the first trimester, transfer of small amounts of thyroxine to the fetus. In iodine replete areas, such as the UK, increased renal iodine loss does not influence maternal thyroid function. However, the natural fluctuations in a long term condition may necessitate a dose change, and women who conceive when their hypothyroidism is not well-controlled may need to increase thyroxine dose to 'catch up'.

Pragmatically, women should check their thyroid function prior to conception, and make any required thyroxine dose adjustments before they are pregnant. Further tests can be done early in pregnancy and again in the last trimester in women whose results are normal and whose condition is stable. Other women may need more frequent tests, but beyond the first trimester these would not be anticipated directly to influence the fetus.

A common difficulty in interpretation of TFTs in hypothyroid pregnant women occurs when the TSH is high and the fT4 normal: this may reflect recently improved or fluctuating compliance, as TSH returns to normal more slowly than fT4 – the patient should be questioned regarding how long she has been taking the tablets regularly.

Thyroxine is safe to take during lactation. Babies born to women with primary autoimmune hypothyroidism are not at increased risk of neonatal hypo- or hyper-thyroidism, but do have a small lifetime increased risk of hypothyroidism in adult life. Babies whose mothers are hypothyroid following treatment of hyperthyroidism do have an increased risk of both fetal and neonatal hyperthyroidism, as discussed below.

Hyperthyroidism

Hyperthyroidism affects around 2 in 1000 pregnancies. The majority is due to Graves disease, an autoimmune disorder in which clinical disease activity reflects the titre of TSH receptor stimulating antibodies.

Pregnancy does not affect the long term course of hyperthyroidism. In the first trimester there may be deterioration in control, due to reduced absorption of medication secondary to vomiting or to hCG-driven stimulation of TSH receptors (see above). In the second and third trimesters, typically, treatment doses can be reduced as the immune effects of pregnancy result in an increase in TSH receptor inhibitory antibodies and a fall in the stimulatory ones: one third of women will be able temporarily to discontinue treatment at this time. The majority need to return to their pre-pregnant doses in the puerperium to prevent a disease flare.

The drugs usually used in the treatment of hyperthyroidism, propylthiouracil (PTU) and carbimazole, are safe in pregnancy and should not be stopped because of concerns about teratogenicity. Indeed, a number of studies have shown that neonatal outcome is better, with fewer anomalies and lower chance of delivering prematurely, if euthyroidism is achieved prior to conception, when compared with those women in whom either control is achieved in early pregnancy or later pregnancy, in a stepwise manner. Older studies have linked carbimazole with aplasia cutis – a very rare condition resulting in deficits in the scalp and hair growth, but larger more recent studies show that either this link is spurious or at worst that the risk of the fetus developing this condition is extremely small. Both agents cross the placenta in similar amounts and, rarely, can cause fetal hypothyroidism: this risk can be minimized by ensuring that the patient takes the lowest doses of treatment to keep her clinically euthyroid and biochemically at the upper limit of the normal range. Fetal hypothyroidism rarely manifests clinically, in part because of the opposing stimulatory effect of transplacental TSH receptor antibodies.

Fetal and neonatal hyperthyroidism are also rare, but should be looked for in women at risk, chiefly those with active Graves disease or previous Graves' disease treated by surgery or radioactive iodine and in whom TSH receptor stimulating antibodies are present. This test should be requested early in the pregnancy of women who fall in these categories. The fetal thyroid can be stimulated by these antibodies beyond 24 weeks' gestation and so women should be aware of the symptoms of fetal thyrotoxicosis (such as excessive fetal movements), have the fetal heart rate auscultated regularly to check for fetal tachycardia, and be serially scanned to exclude growth restriction or fetal goitre. If fetal thyrotoxicosis is suspected, delivery should be considered if the gestation is close to term. If not, the diagnosis should be confirmed by fetal blood sampling and then doses of maternal antithyroid medication should be increased, if necessary with the addition of thyroxine, which does not cross the placenta, to prevent hypothyroidism in the mother. Neonatal thyrotoxicosis typically presents after the first week of life, when the 'protective' effects of maternally derived antithyroid medication are no