Thyroid disorders and other endocrine disorders in pregnancy

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Abstract

The number of women with endocrine conditions embarking on pregnancy is growing as more choose to delay conception or require assisted reproduction techniques. It is therefore increasingly important for clinicians to have an understanding of common endocrine disorders and how these may impact on pregnancy and fetal development. Over-investigation and subsequent medicalization and treatment of sub-clinical endocrine conditions, which have uncertain clinical impact for the fetus or mother, is a cause for concern and debate surrounding this practice is ongoing. Vitamin D deficiency is increasing in prominence due to the rise in childhood rickets; this startling re-emergence has led to more work on the prevalence of vitamin D deficiency and identified a higher than expected percentage of women affected. For this reason, national advice has called for routine vitamin D supplementation in pregnancy, and diagnosis and treatment of those most at risk. This review also briefly discusses the management of other rarer endocrine conditions, which can lead to significant maternal and fetal morbidity if the diagnosis is delayed or overlooked.

Keywords Addison's disease; congenital adrenal hyperplasia; Conn's syndrome; diabetes insipidus; hypopituitarism; parathyroid; phaeochromocytoma; pituitary adenoma; thyroid disease; vitamin D

Thyroid disease

The maternal thyroid gland is responsible for both fetal and maternal production of thyroxine (T4) and tri-iodiothyronine (T3) until the fetal thyroid starts functioning at the end of the first trimester. Until then, there is good evidence that inadequate or excessive maternal T4 can have serious long term effects on fetal development, which can translate into cognitive neurodevelopmental problems for the child.

As thyroid disorders are common, the incidence being up to 3% of women of child-bearing age, many pregnancies will be complicated by thyroid dysfunction. The vast majority of these women will have a formal diagnosis prior to pregnancy, and should be taking appropriate treatment to ensure they are euthyroid before embarking on pregnancy. In some, inability to conceive or maintain pregnancy leads to the diagnosis as anovulation and, potentially, miscarriage can be a symptom of thyroid disease. However, if thyroid dysfunction has not been recognised prior to conception, establishing the diagnosis during pregnancy can be problematic as many of the symptoms of thyroid dysfunction are comparable to those of normal pregnancy. It is therefore important to have an overview of the physiology of the thyroid, its impact on reproductive health and how it changes in pregnancy.

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Thyroid physiology

The thyroid gland is controlled from the hypothalamus, which produces thyrotropin-releasing hormone (TRH). This polypeptide stimulates thyrotroph cells in the anterior pituitary gland to produce thyroid stimulating hormone (TSH). This glycoprotein hormone, consisting of two alpha and two beta subunits, is released into the blood to bind to the TSH receptor on the thyroid gland, stimulating the production of T3 and T4 from thyroglobulin and iodine. T3 and T4 use a negative feedback loop to balance production of TRH and TSH, and this stepwise production of hormones is modulated by somatostatin, glucocorticoids as well as excess iodine. In early pregnancy, there is conflict between TSH and the homologous human chorionic gonadotrophin (HCG) produced by the developing placental tissue, as the alpha sub-units are identical. HCG can stimulate TSH receptors, (much less potently than TSH) on the thyroid gland, leading to a decline in the production of TSH in some women, and in a smaller subset to a biochemical picture of hyperthyroidism with elevated T4 of women [see later, gestational thyrotoxicosis].

Normative reference ranges in cohorts of healthy pregnant women without thyroid disease indicate that the upper limit of normal for TSH in uncomplicated pregnancy may be higher than outside pregnancy, and these limits may vary according to the laboratory technique or the demographics of the population: ideally local gestation-specific reference ranges should be used. These changes are of importance when interpreting blood results of pregnant women, as the reference range throughout pregnancy differs from non-pregnant women (see Table 1). Table 1 also shows a typical reference range in a multiethnic UK population.

Maternal iodine requirements increase (by as much as 50%) as iodine is actively transported to the developing fetus and the maternal thyroid upregulates to absorb more iodine to allow the total T3 and T4 production to rise. High oestrogen concentrations extend the half-life of plasma proteins including thyroxine binding globulin (TBG), such that the concentration increases at least 1.5 fold by week 8 of pregnancy, and remains at this higher level until delivery. Thus where women have a good supply of iodine, total T4 and T3 concentrations are increased, but the biologically-active free T3 and free T4 stay relatively stable throughout pregnancy. In areas where women have mild iodine deficiency, pregnancy-induced goitre can occur, together with relative hypothyroidism due to the limitation of T4/T3 production; this can impact upon the development of the fetus.

Iodine deficiency is the commonest cause of hypothyroidism worldwide. The WHO states that iodine deficiency is the single most important preventable form of brain damage in children, now referred to as neonatal cretinism. Severe iodine deficiency also plays a role in increased perinatal mortality. This has led to

Changes in thyroid function in pregnancy

Thyroid function tests (TFT)	Non pregnant	First trimester	Second trimester	Third trimester
FT4 pmol/l	9–26	10–16	9–15.5	8–14.5
FT3 pmol/l	2.6–5.7	3–7	3–5.5	2.5–5.5
TSH mu/l	0.3–4.2	0–5.5	0.5–3.5	0.5–4
TSH mu/l (Endocrine Ass)		0.1–2.5	0.2–3.0	0.3–3.0
TSH mu/l (European Thyroid Ass)		0.1–2.5	0.1–3.0	0.2–3.5

While the literature is useful in identifying antenatal trends in thyroid parameters, the reference ranges cited are to be used as a guide to clinical practice and not an absolute. Reference ranges may vary depending on the laboratory method used to assay the hormones. FT4 and FT3 (Cotzias C et al. *Eur J Obstet Gynecol Reprod Biol.* 2008 **137(1):**61–6).

Table 1

programmes to administer annual boluses of iodine to susceptible women and to national salt, water and flour iodinisation. The UK population is relatively iodine replete, with dairy and fish being the main dietary sources, and currently there is no official UK Government advice to take an iodine supplement prior to or during pregnancy, although, iodine requirements are 250 micrograms per day for pregnant and lactating women, compared with 150 micrograms for non-pregnant women.

Hypothyroidism

Overt hypothyroidism [high TSH, low fT4] affects approximately 20,000 pregnant women a year in the UK. Most of these women have a diagnosis prior to pregnancy, and should aim to conceive when they are euthyroid taking levothyroxine replacement. Some women will enter pregnancy on an inadequate dose of thyroxine, and these women should have their thyroxine dose adjusted according to pregnancy-specific reference ranges. There is ongoing discussion about whether thyroxine replacement should be increased empirically during pregnancy; the evidence for this appears to depend on the reason underlying the hypothyroid status.

The majority of women have an underlying diagnosis of Hashimoto's thyroiditis, an autoimmune condition where the thyroid gland is damaged by auto-antibodies to thyroid peroxidase or thyroglobulin. This condition often co-exists with other auto-immune diseases, particularly Type I diabetes mellitus, rheumatoid arthritis and systemic lupus erythematosus, which may be of greater importance to the mother and fetus than the thyroid dysfunction itself. Other women are hypothyroid following surgical thyroidectomy for treatment of malignancy, goitre or thyrotoxicosis, or following radio-active iodine treatment. These women with total thyroidectomy have no ability to produce thyroxine and are more likely to need an increasing dose of levothyroxine replacement throughout pregnancy, as they have no residual thyroid to enable any production; this is particularly so when complete TSH suppression is required as part of the management of thyroid cancer.

Fetal brain development relies on maternal supply of thyroxine and iodine [as TSH and fT3 cannot cross the placenta] until the fetal thyroid becomes functional, around 12–16 weeks of gestation. Before this gestation, impairment in neurocognitive development can occur without adequate thyroxine replacement. Some studies have demonstrated a reduction in IQ score in the offspring of women with very high TSH, and others suggest a role in neurocognitive problems such as attention deficit disorder. However, there is no convincing evidence of adverse fetal effects when maternal TSH is within the pregnancy-specific reference range. Therefore, the ideal for hypothyroid women is to ensure adequate thyroxine replacement at least 3 months before conception, to avoid the potential adverse effects of untreated or under-treated hypothyroidism on the conceptus.

Although rarely seen in the UK, overt symptomatic untreated hypothyroidism is also associated with an increase in miscarriage, gestational hypertension, preterm delivery, post-partum haemorrhage together with fetal growth restriction. There has also been a suggestion that hypothyroidism is associated with gestational diabetes mellitus, with almost double the number of women on levothyroxine replacement having this diagnosis compared with background population.

There are several schools of thought regarding the need for women with autoimmune hypothyroidism to increase thyroxine replacement dose during pregnancy. The American Thyroid Association (ATA) has advocated an empirical increase in levothyroxine at the diagnosis of pregnancy by 25% with the aim of an upper limit of TSH at 2.5 mU/L. The British Thyroid Association propose an increase of 25–50 micrograms at the beginning of pregnancy to ensure TSH levels are maintained within the normal range, and free T4 are in the upper range of normal. Neither group provide robust evidence to support these statements. Observational data suggest that women with preconception TSH less than 1.2 mU/L do not require any increase in thyroxine replacement, but no indication that this is required for optimal outcome. Others argue that changes in thyroxine replacement should be guided by pregnancy-specific reference ranges. There are many reasons for these differing opinions, and it is important to recall the gestation at which hypothyroidism could have a direct fetal effect, and that the important end point of neurocognitive function in the offspring is dependent on many different variables; no studies of sufficient size have prospectively addressed the impact of first trimester maternal TSH nor shown whether altering thyroxine dose to achieve a predetermined low TSH is beneficial [or harmful] to the fetus [or mother]. In addition, there is some evidence that, at least theoretically, excess circulating T4, as may result from empirical increases in thyroxine dose, may be associated with miscarriage.