Thyroid disease in pregnancy

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Some interesting recent developments have influenced the modern management of thyroid disease in pregnancy and enhanced our understanding of the interaction between maternal and fetal thyroid function, including the complex role of the placenta. This article will review the latest ideas in this area.

Thyroid disease is the commonest endocrine condition in women of childbearing age, and affects approximately 12 per 1000 pregnant women. There are a number of important differences in management during pregnancy, which will be discussed in this article. In particular, this article will consider physiological changes which occur in pregnancy, fetal thyroid function and its dependence upon and interaction with the maternal thyroid status, and the management of thyroid diseases in pregnancy.

CHANGES IN THYROID PHYSIOLOGY IN PREGNANCY

Four important physiological changes occur during pregnancy, which influence thyroid activity.

Altered metabolism of thyroxine-binding globulin

Less than 1% of thyroxine (T_4) and triiodothyronine (T_3) is unbound and active; the remainder is bound predominantly to thyroxine-binding globulin (TBG). From early in pregnancy, increased concentrations of oestrogen result in greater sialylation of the carbohydrate moieties on TBG, thus extending its half-life from 15 minutes to 3 days (Brent, 1997). This results in increased total T_4 and total T_3, although free T_4 (fT_4) and free T_3 (fT_3) remain largely unchanged (see below).

Iodine deficiency

As the extrathyroidal iodine pool is in dynamic equilibrium with the thyroid and kidneys, the enhanced renal function of pregnancy results in increased clearance of iodine. In iodine-deficient areas of the world, this may result in reduced circulating concentrations of iodine, uptake of an increased proportion of iodine from the circulation and possibly goitre formation (Dillon and Milliez, 2000). This iodine deficiency is exaggerated by transport of iodine to the fetus from early in the second trimester, although where iodine is in short supply, maternal thyroid trapping mechanisms over-ride demands of the fetus, who may consequently be afflicted by cretinism.

Human chorionic gonadotrophin

Human chorionic gonadotrophin (hCG) and thyroid-stimulating hormone (TSH) share an identical alpha subunit, and have similar beta subunits and receptors. High hCG in the first trimester may result in a hormone 'spillover' syndrome in which hCG stimulates the TSH receptor, especially in pregnancies complicated by exceedingly high hCG or where there is an increased proportion of aberrant hCG (with increased thyrotropic activity), for example molar pregnancies or those complicated by hyperemesis gravidarum (HG). This may transiently give a biochemical picture similar to hyperthyroidism during the first trimester (see later).

Deiodination of thyroid hormones

T_3 has greater activity and a shorter half-life than T_4, and biologically is the more important hormone, especially for intracellular functions. Three deiodinase enzymes are recognized which control the activation and inactivation of T_4 and T_3 in target tissues, in order to ensure stable supply of T_3 to critical areas. Deiodinase type II activates T_4 to T_3, especially intracellularly and when there is reduced availability of thyroid hormones. It is found in the placenta.

Type III deiodinase also occurs in the placenta. It inactivates T_4 and T_3 (by removing iodine

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molecules), and increases in concentration with advancing gestation (Koopdonk-Kool et al, 1996); this accounts for the fall in circulating hormones seen in later pregnancy and the decreased transfer of T_4 to the fetus. It also enhances the availability of iodine in the placenta for transfer to the fetus.

BIOCHEMICAL ASSESSMENT OF THYROID FUNCTION IN PREGNANT WOMEN

Free T_4, fT_3 and TSH should be analysed when assessing maternal thyroid function; total T_4 and T_3 measurements should not be used in pregnancy. When deciding whether to change the dose of treatment, more weight should be placed upon fT_4 and fT_3 concentrations, as these reflect the actual thyroid status more accurately, rather than TSH levels. In cases of hypothyroidism, the latter may remain elevated despite normal fT_4 and fT_3 for sometime after the correct dose of T_4 is initiated or because of poor compliance with therapy. Conversely, TSH may remain suppressed once fT_4 and fT_3 return to normal in hyperthyroidism.

T_4 concentration falls in the second half of pregnancy; the lower limit of normal is below the non-pregnant reference range in the third trimester. TSH levels often increase at the same time. This does not usually indicate the onset of hypothyroidism nor the need to increase the dose of T_4 in established cases of hypothyroidism. Increasing concentrations of type II deiodinase enhance the intracellular conversion of T_4 to T_3, thereby raising at the cellular level the thyroid activity for a given concentration of fT_4. In an evolutionary sense, this economy of maternal metabolism before the exertions of labour and lactation may enhance self-preservation.

In pregnancy, thyroid function results should be interpreted against pregnancy-specific reference ranges (*Table 1*). The absolute values provided in the table should not automatically be used; rather the equivalent adjustment must be made to the non-pregnant ranges used in an individual hospital.

INFLUENCE OF MATERNAL THYROID FUNCTION ON FETAL THYROID FUNCTION

The fetal thyroid gland functions from 10 weeks gestation. Before then fetal brain development is dependent upon maternally-derived T_4, which undergoes intracellular conversion to T_3. Maternal hypothyroxinaemia in the first trimester may have adverse consequences on fetal neurological development (Haddow et al, 1999; Pop et al, 1999) (see later), particularly in iodine deplete areas where pregnant women are both T_4 and iodine deficient.

After the first trimester, in fetuses with normal thyroid function little if any maternal T_4 crosses the placenta, as a result of poor permeability of fetal membranes to iodothyronines (Roti et al, 1983) and the action of placental deiodinases. Placental perfusion studies show that only 0.008% of maternal T_4 reaches the fetus (Mortimer et al, 1996). Inhibition of placental deiodination enhances transfer by 2700 times, so that fetal levels reach 30% of maternal concentrations. This may explain Vulsma's findings of umbilical cord T_4 levels up to 50% of normal in neonates unable to produce their own thyroid hormones (Vulsma et al, 1989); these data should not be incorrectly extrapolated to normal fetuses.

Studies in normal fetuses undergoing cordocentesis or cardiocentesis show that fetal T_4, T_3, TSH and TBG are produced from the end of the first trimester, and increase with advancing gestation. Fetal TSH is greater than maternal TSH, fT_4 and total T_4 reach adult levels by 36 weeks' gestation, but circulating fetal T_3 remains low (Thorpe-Beeston et al, 1991). The low T_3 is the result of ineffective peripheral conversion of T_4 to T_3 (which is the main source of T_3 in adults) and placental deiodination of T_3.

HYPEREMESIS GRAVIDARUM

In 40% of cases of HG, thyroid function tests are abnormal, with either an elevated fT_4 (sometimes up to 80 pmol/litre) or a suppressed TSH or both. This occurs in the more severe cases of HG, and returns to normal as the vomiting set-

TABLE 1.
Pregnancy-specific reference ranges for thyroid function tests

		Trimester		
	Not pregnant	First	Second	Third
Free thyroxine (pmol/litre)	11–23	11–22	11–19	7–15
Free triiodothyronine (pmol/litre)	4–9	4–8	4–7	3–5
Thyroid-stimulating hormone (mu/litre)	0–4	0–1.6	1–1.8	7–7.3

Data from Parker (1985); Chan and Swaminathan (1988); Kotarba et al (1995)

tles. It is caused by stimulation of the TSH receptor by hCG moieties with increased thyrotropic activity (Kimura et al, 1993). Therefore, although the total hCG concentration as measured by routine laboratory assays may not be elevated, increased proportions of pro-thyrotropic hCG portions result in increased TSH-like activity, and therefore a situation of temporary biochemical thyrotoxicosis.

Treatment is centred on correcting the metabolic insults of prolonged vomiting, and on minimizing further vomiting. There is no place for the use of antithyroid medication, since the thyroid abnormality is not of intrinsic thyroid overactivity, and is short-lived and self-limiting. If antithyroid medication is used for hCG-induced hyperthyroidism, it is either ineffective or extremely high doses are required to achieve biochemical euthyroidism (Chowdhury et al, 2000). As these agents cross the placenta (see hyperthyroidism), they could make the fetus hypothyroid.

Thyroid function returns to normal once HG settles; this should be confirmed, to ensure that the rare case of true hyperthyroidism is not overlooked, since vomiting may occasionally be the sole presenting complaint in thyrotoxicosis. However, the clinical picture of HG is otherwise quite different from that of thyrotoxicosis. The typical patient with HG is washed out, tired, lacking in energy and deflated; there is no goitre, tremor or eye signs; if present, tachycardia is secondary to dehydration, weight loss to poor nutritional intake and warm peripheries to the vasodilatation of pregnancy; the symptoms are clearly of recent onset and do not antedate the pregnancy. If there is clinical doubt concerning the differential diagnosis of the thyroid dysfunction, the absence of thyroid antiperoxidase, antithyroglobulin and TSH receptor autoantibodies supports the diagnosis of HG.

A genetic mutation of the TSH receptor making it unusually sensitive to hCG has been described in a mother–daughter pair who both had recurrent severe HG (Rodien et al, 1998). The old wives tale that HG 'runs in families' may therefore have some truth in it in some cases; it is likely that further similar mutations will be detected in the future.

HYPERTHYROIDISM

Conception is unusual with acute untreated thyrotoxicosis (*Figure 1*). However, as the condition improves, libido and fertility return. The incidence of thyrotoxicosis is 2 per 1000 pregnancies (Burrow, 1985), 95% cases being the result of Graves' disease. If a new diagnosis of thyrotoxicosis is suspected in the first trimester of pregnancy, HG and molar pregnancy are the most likely causes (see above).

Typically, Graves' disease flares in the first trimester and puerperium and remits in between; there is a reduced requirement for antithyroid medication and 30% of women can discontinue treatment during the second and third trimester. After delivery the majority need to increase the dose and/or recommence therapy in order to avoid a relapse. These changes reflect alterations in titre of thyroid receptor-stimulating antibodies and a change from stimulating to inhibitory antibodies as pregnancy advances (Kung and Jones, 1998).

Clinical assessment of disease activity

The clinical assessment of thyroid disease activity is difficult in pregnancy because of overlap between the symptoms of pregnancy and those of hyperthyroidism (*Table 2*). Failure to gain weight despite a good appetite and maternal tachycardia which does not slow with Valsalva manoeuvre may be helpful indicators of hyperthyroidism; eye signs and pretibial myxoedema do not reflect disease activity, although onycholysis does.

Pregnancy outcome

If thyrotoxicosis is well controlled, the outcome for mother and baby is good. However, when

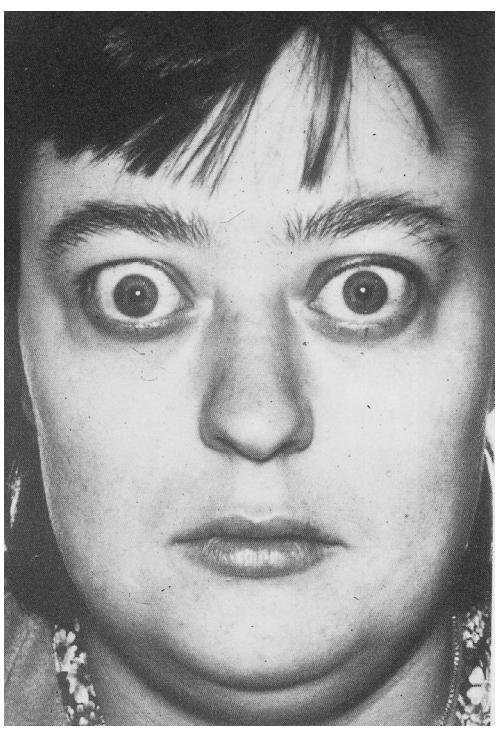

Figure 1. Typical facial appearance in thyrotoxicosis.

control is inadequate, maternal and fetal complications (such as thyroid storm, cardiac failure, hypertensive disease of pregnancy, small for gestational age infants, preterm labour and stillbirth) are increased. Outcome is worst for those pregnancies in which control is never achieved, intermediate when euthyroidism occurs during the pregnancy and best when thyrotoxicosis is controlled before conception (Wing et al, 1994).

Treatment of thyrotoxicosis in pregnancy

Radioactive iodine: Use of radioactive iodine is totally contraindicated during pregnancy and lactation, or in women contemplating pregnancy in the near future. It crosses the placenta freely throughout pregnancy and irreversibly destroys the fetal thyroid gland (Lazarus, 1995).

Surgery: Surgery may be used for failed medical therapy, compressive symptoms caused by goitre and suspicion of or definite diagnosis of thyroid cancer. It is usually carried out in the second trimester.

Medical therapy: Propylthiouracil (PTU) and carbimazole are the usual first-line choices for treatment of thyrotoxicosis in pregnancy. Contrary to earlier beliefs, both drugs cross the placenta in similar amounts (Mortimer et al, 1997), and they are equally effective at achieving euthyroidism (Wing et al, 1994). The dose should be titrated against maternal wellbeing and biochemistry, aiming for fT_4 at the upper limit of normal for pregnancy, in order to minimize the dose required. Propranolol may be used safely in pregnancy if required to control tremor, anxiety or tachycardia.

Teratogenesis: PTU and carbimazole are safe in pregnancy. Early reports suggested that PTU caused aplasia cutis of the fetal scalp, but this association is now thought to be spurious or at worst extremely weak (van Dijke et al, 1987). Pregnancies where thyrotoxicosis is controlled by antithyroid drugs have less congenital abnormality than those where thyrotoxicosis is untreated or partially treated, suggesting that not only are they not teratogenic but also that they can reduce the risk of abnormality which thyrotoxicosis itself causes (Momotani et al, 1984).

Fetal and neonatal effects of medical therapy: Both drugs cross the placenta. Carbimazole and PTU have an equal chance of causing fetal hypothyroidism, although the risk does not correlate well with the dose of the drug (Momotani et al, 1997). As they do not inhibit deiodinases II or III, normal intracellular T_3 levels are maintained in the developing brain, provided that there is sufficient iodine available. Between 10 and 20% of babies whose mothers are taking antithyroid drugs at delivery have transient asymptomatic hypothyroidism that resolves by day 5. It may mask neonatal hyperthyroidism, a potentially dangerous condition, which usually presents at 7–10 days. Between 1–2% of babies have small goitres, which resolve quickly.

TABLE 2.
Overlap between clinical symptoms of thyroid disease and pregnancy

Pregnancy	Hyperthyroidism	Hypothyroidism
Heat intolerance	√	
Increased appetite	√	
Nausea	√	
Palpitations	√	
Tachycardia	√	
Tremor	√	
Sweating	√	
Warm palms	√	
Goitre	√	√
Amenorrhoea	√	
Weight gain		√
Carpal tunnel syndrome		√
Fluid retention		√
Constipation		√
Loss concentration	√	√
Tiredness	√	√

Long-term effects on offspring: Four small studies of 101 children have demonstrated comparable physical and psychological development, thyroid size and function in children exposed to antithyroid drugs in utero when compared with children whose mothers had thyroidectomy to control hyperthyroidism (Mandel et al, 1994).

Lactation: Small amounts of both PTU (0.025–0.077%) and carbimazole (0.47%) cross into breast milk. However, at normal doses this does not cause hypothyroidism nor prevent the recovery from neonatal hypothyroidism caused by in-utero transfer of PTU (Lamberg et al, 1984; Momotani et al, 1989). If doses above carbimazole 15 mg or PTU 150 mg are needed, the dose should be split, and neonatal wellbeing monitored clinically and biochemically.

Blocking replacement regimen in pregnancy: This should not be used in pregnant women as the high dose of antithyroid drug crosses the placenta, but the additional T_4 does not (see above). Of 20 cases recorded in pregnancy, cord TSH was increased, and one baby had a goitre (Ramsay et al, 1983). In addition, outside pregnancy McIver has shown that it is not more effective than 'traditional' therapy (McIver et al, 1996).

Neonatal Graves' disease

Transplacental passage of maternal TSH receptor stimulating antibodies (half-life 21 days) in women with active Graves' disease may occasionally cause fetal or neonatal Graves' disease (*Figure 2*). The literature describes a 2–10% risk of neonatal Graves' disease (Laurberg et al, 1998), although in clinical practice it seems lower. Presentation is usually at 7–10 days of age, when the effect of transplacental antithyroid drugs has waned. Cord thyroid function tests should be recorded to provide a baseline, and parents should be aware of the symptoms of neonatal thyrotoxicosis.

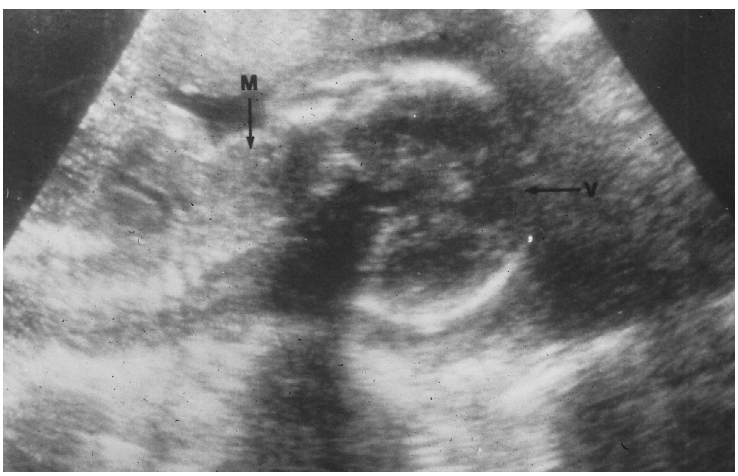

Figure 2. Fetal goitre. M = goitre.

HYPOTHYROIDISM

Hypothyroidism (*Figure 3*) affects 9 per 1000 pregnancies (Niswander and Gordon, 1972), and is usually the result of Hashimoto's thyroiditis or following hyperthyroidism.

Clinical assessment of hypothyroidism

As with hyperthyroidism, it is difficult to differentiate clinically between the symptoms of pregnancy and those of hypothyroidism (*Table 2*). Biochemical assessment, with interpretation of results against pregnancy-specific ranges, is required.

Management of hypothyroidism in pregnancy

T_4 therapy is the mainstay of medical treatment of hypothyroidism in pregnancy. T_4 is safe in pregnancy and lactation; there is no evidence of teratogenicity, or that significant amounts pass into breast milk. The dose of T_4 should be titrated against the biochemical results. Thyroid function tests should be performed at 8–12-week intervals when the thyroid dose is stable and the woman clinically and biochemically euthyroid, the first assessment being made as early in pregnancy as possible (and ideally just before conception as well) (see below). Testing is required more frequently if the dose is being adjusted, usually

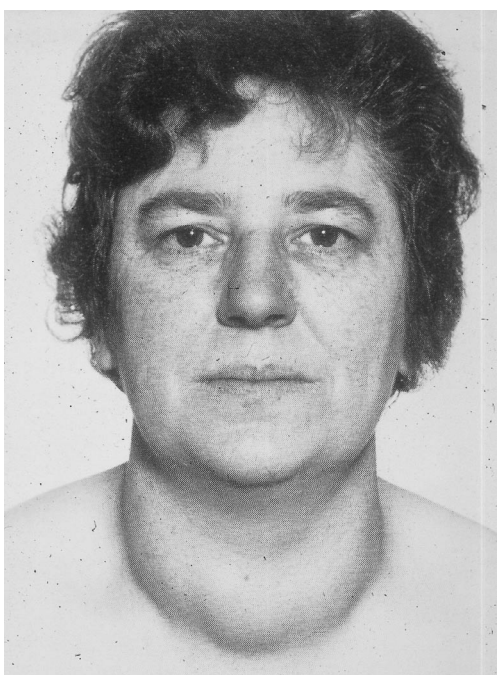

Figure 3. Typical facial appearance in hypothyroidism.

every 4–6 weeks, especially if undertreatment is present in the first trimester when testing at 2-weekly intervals is required.

Some authorities have recommended a blanket increase in T_4 to 200 μg daily in pregnancy, although the logic for this is unclear (Hall et al, 1993). Others have found that the majority of patients need an increase in T_4 dose: Mandel and colleagues studied 12 women with hypothyroidism, and found that 9 needed an increased dose during pregnancy, which was reduced again after delivery (Mandel et al, 1990). In the author's experience, of 36 pregnancies only 20% of women with hypothyroidism needed to increase their T_4 dosage; invariably they had been undertreated before conception and continued on the same increased dose postnatally. The remaining 80% of women were euthyroid at booking and remained so throughout pregnancy without a change in dose (Girling and de Swiet, 1992).

Neonatal outcome

Substantial but old data suggest that untreated hypothyroidism is associated with stillbirth, prematurity, congenital abnormality and reduced intelligence quotient (IQ) (Jones and Man, 1969; Man and Serunian, 1976). Recent data indicate that untreated hypothyroxinaemia in the first trimester is associated with a loss of 7 IQ points at the age of 7–9 years compared with offspring of euthyroid women, and that maternal treatment with T_4 at this gestation (when T_4 is able to cross the placenta) provides fetal brain protection (Haddow et al, 1999)(see above). Ideally, therefore, maternal T_4 therapy should be optimized before conception or failing that as early as possible in pregnancy.

Antithyroglobulin and thyroid peroxidase antibodies do not cross the placenta, so maternal Hashimoto's thyroiditis does not usually cause fetal or neonatal thyroid dysfunction. TSH receptor blocking antibodies cause transient neonatal hypothyroidism in 1 in 180 000 neonates (Brown et al, 1996).

POSTPARTUM THYROIDITIS

Postpartum thyroiditis (PPT) is a subacute destructive autoimmune condition strongly related to antiperoxidase antibodies, occurring in the first year postpartum. It may present as either hyperthyroidism or hypothyroidism, or most often as a purely biochemical phenomenon: the prevalence in clinical practice is much lower than the 2–17% described in clinical trials. In clinically apparent cases, any or all of the three phases may occur: hyperthyroidism at 1–3 months postpartum, hypothyroidism 3–8 months postpartum and euthyroidism by 1 year. The former occasionally requires treatment with β-blockade (but never with antithyroid drugs as T_4 synthesis is not raised). The hypothyroidism is more likely to need treatment with T_4, although the symptoms may be vague and difficult to distinguish from other postnatal problems; T_4 should be withdrawn when the baby is 1 year old. Follow-up thyroid tests are important as a small proportion of women will have permanent hypothyroidism and 5% per year will develop it subsequently; 70% will get PPT following subsequent pregnancies (Lazarus et al, 1997).

There is insufficient evidence (Ball, 1996) to support calls (Lazarus et al, 1997) for routine screening of pregnant women with thyroid autoantibodies.

KEY POINTS

- Placental deiodinases contribute to changes in maternal thyroid function during pregnancy, and enhance transfer of iodine to the fetus. Biochemical assessment of thyroid function must be with reference to pregnancy-specific ranges.
- Maternal thyroxine does not cross the placenta after the first trimester.
- Forty per cent of cases of hyperemesis gravidarum have a biochemical picture of hyperthyroidism. This does not require treatment with antithyroid medication.
- Thyrotoxicosis may be treated with either propylthiouracil or carbimazole, surgery is generally safe in pregnancy, and radioactive iodine must be avoided.
- Hypothyroidism must be fully controlled before pregnancy whenever possible, to ensure optimal long-term neonatal development.
- Postpartum thyroiditis presents with vague symptoms 1–8 months after delivery, and may be misdiagnosed if not actively considered.
- New thyroid nodules are uncommon in pregnancy. They should be investigated to exclude malignancy, although this is uncommon.

THYROID NODULES AND CANCER

Most reports of thyroid nodules in pregnancy exaggerate the frequency of malignancy, which is likely to be much lower than the 30–50% risk recorded by endocrinologists, otolaryngologists and head and neck surgeons. In an unselected obstetric population, 18 women with thyroid nodules were referred to an obstetric medicine clinic, giving an approximate incidence of 1 in 2500 pregnancies; none were malignant (M de Swiet, personal communication, 2000).

Other than avoiding tests utilizing radioactive iodine, investigation of thyroid nodules is similar in pregnancy, being based on clinical and biochemical assessment, ultrasound and chest X-ray and fine needle aspiration. Surgery may be undertaken if required, and suppressive doses of T_4 used if indicated. Thyroglobulin is elevated in normal pregnancy, and cannot be used to detect recurrence of thyroid cancer. **HM**

Conflict of interest: none.

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