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Thyroid Autoimmunity and Hypothyroidism in Pregnancy

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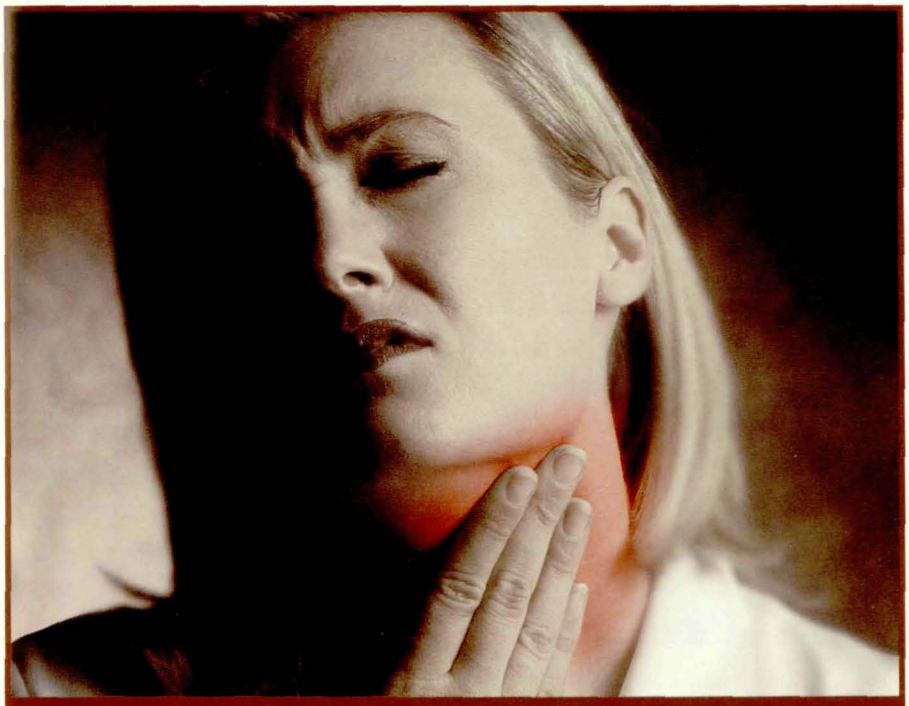

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INTRODUCTION

The incidence of overt thyroid dysfunction in pregnant women is 1% to 2%, but it has been suggested that milder, subclinical forms of hypothyroidism are probably more prevalent yet remain unrecognized.[1] In managing patients with hypothyroidism, it is important to be familiar with the effects of pregnancy and pregnancy-related diseases on maternal thyroid function, the dynamic changes in pregnancy that necessitates frequent review and sometimes adjustments in thyroxine replacement, and the possible impact of inadequately treated and subclinical hypothyroidism on pregnancy outcome and the long-term development of the offspring. Clinicians should also be aware of the effect of maternal thyroid autoimmunity on pregnancy outcome.

EFFECT OF PREGNANCY ON THYROID FUNCTION AND SIZE

Pregnancy has a significant effect on thyroid function and size. The thyroid hormones present in the circulation are thyroxine (T4) and tri-iodothyronine (T3). Circulating T4 is mostly bound to proteins, with a small unbound fraction measured as the free T4 (fT4). T4 provides a circulating reserve, ready for deiodination to the active hormone T3, of which only 20% is released from the thyroid gland. T3 is bound less strongly to plasma proteins, and the free T3 (fT3) concentration is 10 times higher than fT4. The synthesis and release of thyroid hormones are controlled by the pituitary secretion of thyroid-stimulating hormone (TSH), which is in turn controlled by the hypothalamic secretion of thyrotropin-releasing hormone (TRH); both are regulated by the negative feedback from circulating thyroid hormones.

During pregnancy, serum total T4 (TT4) concentration increases markedly from the first trimester due to increased protein binding, and serum total T3 (TT3) concentration is also raised but remains within the normal range. Serum fT4 concentration tends to decrease significantly while remaining in the normal range, a phenomenon attributed to problems with laboratory assays, as there is no evidence of any form of pregnancy-induced hypothyroidism. Therefore, a relatively low maternal fT4 concentration found in the routine thyroid function test does not necessarily indicate maternal hypothyroidism. On the other hand, serum fT3 concentration is considerably higher during pregnancy. Serum TSH concentration is significantly decreased

especially in the first trimester due to the thyrotropin-like activity of human chorionic gonadotropin (hCG), and the TSH response to TRH is also suppressed.[2,3] A maternal TSH concentration in the high end of the normal laboratory reference range is therefore contrary to the known physiological effect of pregnancy, and suggests insufficient thyroid hormone at the cellular level. TSH concentration gradually returns to nonpregnant values towards the end of pregnancy.[3] The circadian rhythm of TSH secretion is, however, maintained with a normal nocturnal surge.[4]

In normal euthyroid women, pregnancy has a goitrogenic effect. Thyroid volume increases with advancing gestation, from a mean 20.2 mL at 18 weeks to 24.1 mL at 36 weeks.[5] Furthermore, pregnancy can induce formation of new thyroid nodules, which is associated with higher urinary iodine excretion and features of nodular hyperplasia on fine-needle biopsy.[6] These changes are not related to alterations in thyroid hormone levels. Thus a goitre found in pregnancy is not necessarily a feature of maternal hypothyroidism or iodine deficiency.

In euthyroid women with subtle thyroid abnormalities such as goitre, nodules, autoimmunity or a history of thyroid disorders, pregnancy results in a marked elevation of serum thyroglobulin (TG), an increase in goitre size with evidence of functional stimulation and partial thyroidal autonomy, as well as increases in the number and size of nodules.[6,7] In some cases, the TSH concentration is elevated at delivery, which suggests a diminished thyroid reserve. Nevertheless, thyroid function in the newborn is normal and has no difference from controls.

OBSTETRIC COMPLICATIONS AND TRANSIENT HYPOTHYROIDISM

In an earlier study, 30% of proteinuric pre-eclamptic patients were found to exhibit the euthyroid sick syndrome, with decreased TT4, TT3, fT4 and fT3 concentrations.[8] The significantly increased TSH concentration was shown later to correlate with the severity of pre-eclampsia.[9] These findings have been confirmed by a recent report, which indicated that while mild pre-eclampsia was associated with elevated fT4 and TSH levels, severe pre-eclampsia was associated with an even higher TSH level but significantly lower fT4 and fT3 concentrations compared with healthy controls.[10] As in the case of nonpregnant patients who developed euthyroid sick syndrome following other severe illnesses, thyroxine replacement is not indicated and should not be given, as disturbances in thyroid function would improve spontaneously as the patient recovers. This phenomenon has to be distinguished from pre-eclampsia associated with pre-existing hypothyroidism. In case of doubt, thyroid function test should be repeated serially, and a persistent or further increase in TSH concentration despite clinical recovery after delivery points to underlying hypothyroidism.

SUBCLINICAL THYROID DYSFUNCTION AND PREGNANCY OUTCOME

In all communities, there are a certain number of clinically euthyroid mothers whose thyroid hormone concentrations are borderline or definitely decreased, but there is no reported worldwide incidence of subclinical thyroid dysfunction in pregnancy as no population survey has been performed. This is probably related to the fact that, until recently, the significance of subclinical thyroid dysfunction on pregnancy outcome has remained unknown.

It is now realized that normal maternal thyroid function is critical for fetal brain development and normal cognitive development, and subclinical hypothyroidism is associated with impaired neurological development in the offspring.[1,11-14] However, even when the TSH concentration was within the reference range, mothers with fT4 concentrations below the 10th percentile at 12 weeks of gestation had offspring who, at the age of 1 to 2 years, scored significantly lower in the mental and motor scales of the Bayley Scales of Infant Development.[12] In the subgroup of mothers whose fT4 concentration was increased at 24 and 32 weeks, the scores of their offspring were normalized and similar to those in the controls. In this subgroup, whose fT4 concentration was lowered only at 12 weeks, the risk of fetal breech presentation at >37 weeks gestation was significantly increased (OR 4.7, 95% CI 1.1-19).[15] However, no significant association was found between fT4 concentrations at 24 or 32 weeks and fetal breech presentation at >37 weeks gestation; the underlying mechanism for this association remains unclear.

Other asymptomatic thyroid abnormalities, mainly in the form of abnormal echostructure in the thyroid, were also reported to be associated with an increased risk of pregnancy-induced hypertension.[16]

THYROID AUTOIMMUNITY AND PREGNANCY OUTCOME

Some euthyroid women show evidence of thyroid autoimmunity on investigation, and there is accumulating evidence that maternal thyroid autoimmunity is an independent risk factor for adverse pregnancy outcome. Increased incidence of spontaneous miscarriage (13.3% vs. 3.3%) has been found in association with maternal thyroid autoimmunity.[7] In a cohort of 552 women who were screened in the first trimester for TG and thyroperoxidase antibodies, antibody-positive mothers had twice the miscarriage rate compared with antibody-negative mothers (17% vs. 8.4%), a difference not related to other factors such as thyroid hormone levels, cardiolipin antibodies or demographic risk factors.[17] Subsequent studies confirmed the association between the presence of TG and thyroperoxidase antibodies with increased risk of miscarriage in subsequent or index pregnancies, in both nonpregnant women with history of recurrent miscarriages and in pregnant women in the first trimester.[13,16,18,19] For mothers with evidence of thyroid autoimmunity, 40% of their offspring had elevated serum thyroperoxidase antibody titre at birth, which was significantly correlated with maternal antibody titres.[7] The latest meta-analysis has confirmed the association between thyroid autoimmunity and miscarriage.[20] It is likely that these women are in a heightened autoimmune state, which affects the fetal allograft with consequent miscarriage, while the thyroid antibodies serve mainly as a marker. However, mild subclinical thyroid failure, as suggested by a higher TSH concentration, could also have played a significant role in this situation.

HYPOTHYROIDISM AND PREGNANCY OUTCOME

Hypothyroidism is a common and often unrecognized condition that is particularly prevalent in older women due to autoimmune thyroiditis, while iodine deficiency is an important cause worldwide.[21] The use of iodized salt and multivitamin supplements containing iodine would correct the hypothyroxinaemia associated with insufficient iodine intake and this will not be further discussed here. There are as yet no large-scale studies to examine the cost-benefit of routine screening or treatment for subclinical hypothyroidism (as indicated by serum TSH concentration above the reference range despite normal fT4 and fT3 concentrations within the reference range). Nevertheless, it has been proposed recently that subclinical hypothyroid disease in pregnant women represents a special category for which aggressive case finding and treatment are justified.[22]

In clinical practice, the majority of reproductive-age women who were found to have hypothyroidism had a history of treatment for thyrotoxicosis, especially with thyroid ablation by surgery or radioactive iodine (RAI), or a history of treatment for thyroiditis. Many of these women do not have regular thyroid function assessment after they have become euthyroid for some time, and the gradual decline in their thyroid function may have escaped notice. Among those diagnosed subsequently with hypothyroidism, only a proportion received thyroxine therapy before the index pregnancy. However, suboptimal thyroxine replacement dosing is common in this group, and inadequate treatment can also result from patient noncompliance or drug interactions.[21] In a small proportion of hypothyroid women the cause remains uncertain, and most of these cases are thought to be due to previously undiagnosed thyroiditis. With increasing awareness, it has now been reported that asymptomatic gestational hypothyroidism may occur in up to 2.5% of women.[23] Hypothyroidism may also develop in women with insulin-dependent diabetes mellitus,[24] and it is worthwhile to screen the thyroid function in all women with pre-existing diabetes mellitus at the time of antenatal booking.

The presentations and features or complications of hypothyroidism during pregnancy are summarized in Table 1. The patients may complain of nonspecific constitutional and neuropsychiatric features that antedated the pregnancy, such as cold intolerance, constipation, fluid retention, decreased alertness and fatigability. They may also present with hyperprolactinaemia and hyperhomocysteinaemia, which can affect fertility. For those patients who managed to conceive despite untreated or subclinical hypothyroidism, there is increased pregnancy wastage.[1,13] In yet undiagnosed patients, the presentations of hypothyroidism in pregnancy are often subtle. Features such as constipation, fatigue and fluid retention could be caused by the pregnancy itself. Other symptoms include

Table 1. Clinical features and complications of hypothyroidism in pregnancy

Clinical presentation	Features/complications
Asymptomatic finding at screening	• Incidental finding at screening
Features in common with pregnancy effect	• Constipation • Fatigability • Fluid retention
Features not explained by pregnancy effect	• Cold intolerance • Dry skin • Irritability or decreased alertness • Paraesthesia
Past history and conditions found during pregnancy	• Hyperprolactinaemia • Hyperhomocysteinaemia
Pregnancy-related complications	• Spontaneous miscarriage • Anaemia • Preterm labour • Pre-eclampsia • Placental abruption • Fetal growth restriction • Neonatal morbidity

dry skin, cold intolerance, irritability and paraesthesia are more unusual and tend to alert the obstetrician to screen for hypothyroidism. Hypothyroidism may be diagnosed for the first time during pregnancy incidentally or in relation to some obstetric complications such as pre-eclampsia, where the paradoxical feature of a slow or biphasic tendon reflex is prominent.[25] Other features include excessive fluid retention early in pregnancy, heavy proteinuria out of proportion to the severity of hypertension, bradycardia, cold intolerance instead of the usual heat intolerance and a low body temperature.

In addition to miscarriage, other obstetric complications such as pre-eclampsia, anaemia, fetal growth restriction, placental abruption and neonatal morbidity are associated with undiagnosed or subclinical hypothyroidism or inadequate thyroxine treatment.[26-31] It has been reported that, even in mothers who appeared adequately treated, their newborns had reduced birthweight and head circumference, while the cord serum TSH and fT4 concentrations were higher than healthy controls.[32] Therefore, thyroid function in women on replacement therapy needs to be closely monitored to ensure an adequate dosage on the one hand, and to avoid over-treatment on the other, because it has been reported that thyroid function can sometimes improve in untreated hypothyroid women due to transplacental transfer of fetal thyroxine.[33]

MANAGEMENT OF HYPOTHYROIDISM IN PREGNANCY

The most reliable means of monitoring thyroid function is by serial measurements of serum TSH concentration, the changes of which represent amplifications of minor alterations in T4 and T3 concentrations.[1,11] However, a TSH level within the normal range does not necessarily exclude slightly abnormal thyroid function, especially in pregnancy, and consistently raised TSH concentrations indicate inadequate T4 and T3 even if thyroid hormone concentrations are within the laboratory reference range.

It is now well established that maternal thyroid hormone requirement is increased during pregnancy. Patients already on thyroxine replacement before pregnancy usually require dose increment from the first trimester,[13] as it has been shown that the requirement may increase by as much as 47% during the first half of pregnancy, and from as early as the 5th week of gestation.[14] The latest recommendation is to increase the dose by about 30% as soon as pregnancy is confirmed, and the dose is adjusted subsequently through monitoring of TSH concentrations. It has been found, however, that the dose of thyroxine does not always change systematically in all hypothyroid mothers during pregnancy, and it was those with thyroidectomy who had significant increases in serum TSH concentration during pregnancy who required a modest increase in dose.[34] It has also been suggested that diminished absorption of thyroxine due to concomitant or recent ingestion of absorption-inhibiting agents, e.g. iron and calcium, may have accounted for the need for substantial dose increment in some.

Patients diagnosed with hypothyroidism for the first time during pregnancy

should start treatment with at least 0.05 to 0.1 mg thyroxine daily, depending on the initial TSH concentration. It should be remembered that in order to promptly normalize the thyroid hormone concentration at the cellular level, a higher starting dose is necessary due to increased protein binding and metabolism of thyroxine. The subsequent dose should be adjusted to maintain a serum TSH concentration of <3 mIU/L. Monitoring TSH concentration is superior to monitoring fT4 concentration, as the former allows fine adjustment of thyroxine replacement dosage.[35] The usual dose required during pregnancy is between 0.1 and 0.2 mg daily. After delivery, the dose can usually be reduced gradually, but for most women with hypothyroidism first diagnosed during pregnancy, life-long replacement therapy may be necessary.

CONCLUSIONS

Hypothyroidism is not uncommon in women of reproductive age, and it represents a well-known cause of poor reproductive performance. In women with a poor reproductive history, and in mothers with unusual pregnancy complications both in terms of the timing in pregnancy and features that are incompatible with the apparent clinical severity, thyroid function should be assessed. In high-risk women, screening for thyroid dysfunction and autoimmunity should be performed early in pregnancy to identify subtle abnormalities, for which prompt treatment not only improves pregnancy outcome but also has long-term implications in the offspring.

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