Thyroid Diseases in Pregnancy Part I: Hypothyroidism

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In the management of thyroid disease in pregnancy, it is important to be familiar with the effect of pregnancy and pregnancy-related diseases on maternal thyroid function, the dynamic changes in pregnancy that necessitate frequent review and sometimes adjustment of treatment, and the possibility of inadequately treated and subclinical thyroid disorders that result in pregnancy complications.

THE THYROID HORMONES

The thyroid hormones present in the circulation are thyroxine (T4) and triiodothyronine (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, only 20% of which is released from the thyroid gland. T3 is bound less strongly to plasma proteins, and the free T3 (FT3) level is ten times higher than that of FT4. The synthesis and release of thyroid hormones is 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 of circulating thyroid hormones.

THYROID FUNCTION IN NORMAL PREGNANCY

During pregnancy, serum total T4 (TT4) level increases markedly after the first trimester due to increased protein binding. Serum total T3 (TT3) level is also higher but remains within the normal range. Serum FT4 level is significantly decreased but remains in the normal range, while serum FT3 level is significantly higher. However, serum TSH level is significantly decreased in the first trimester due to the thyrotropin-like activity of human chorionic gonadotropin (hCG). The TSH response to thyrotropin releasing hormone (TRH) is also suppressed.[1,2] The TSH level gradually returns to the nonpregnant value towards the end of pregnancy.[2] The circadian rhythm of TSH secretion is however maintained with a normal nocturnal surge.[3]

THE EFFECT OF PREGNANCY ON THE THYROID GLAND

Pregnancy also has a goitrogenic effect. The thyroid volume increases in size with advancing gestation, from a mean of 20.2 ml at 18 weeks to 24.1 ml at 36 weeks.[4] This is not related to the alterations in the levels of thyroid hormones. A bruit can sometimes be detected over the thyroid as well. Thus a goitre and bruit are by no means features of hyperthyroidism in pregnancy.

HYPOTHYROIDISM AND PREGNANCY

Women with overt hypothyroidism seldom conceive. Most hypothyroid pregnant women have been previously diagnosed and treated. Hypothyroidism diagnosed for the first time during

pregnancy occurs either incidentally or in relation to complications of pregnancy such as preeclampsia (see table).[5] Symptoms of hypothyroidism include excessive fatigue, dry skin, severe constipation, cold intolerance, fluid retention, irritability and paraesthesia. While the majority of patients will have had a thyroidectomy or medical treatment for Graves' disease, or thyroiditis, in a small proportion of cases the cause is uncertain. Some are due to previously undiagnosed Hashimoto's thyroiditis. It has also been reported to occur in pregnancies complicated by insulin dependent diabetes mellitus.[6]

Untreated hypothyroidism increases pregnancy wastage. Inadequate treatment or subclinical hypothyroidism can also be associated with adverse outcome, including pre-eclampsia, anaemia, foetal growth restriction, placental abruption, and neonatal morbidity. With adequate replacement therapy, however, the outcome of pregnancy is similar to that of unaffected women.[7-12]

Pregnancy in untreated hypothyroid women can apparently improve the maternal thyroid status and this has been attributed to transplacental transfer of foetal thyroxine.[13,14] Nevertheless, women at increased risk of hypothyroidism, even though subclinical, should be assessed and treated if indicated.

Management of Hypothyroidism in Pregnancy

Assessment and Monitoring

The presentation of hypothyroidism in pregnancy is often subtle. Features such as constipation, fatigue, and fluid retention may also be due to pregnancy. The possibility of hypothyroidism should be considered if the woman develops excessive fluid retention early in pregnancy, has a slow pulse, complains of cold intolerance instead of the usual heat intolerance, and is found to have a low body temperature.[5] If a woman presents with proteinuric pre-eclampsia and a slow or even biphasic tendon reflex, hypothyroidism must be excluded, since the effect of thyroxine replacement can be dramatic.[5] However, 30% of proteinuric pre-eclamptic patients have the Euthyroid Sick Syndrome, with decreased TT4, TT3, FT4 and FT3 levels.[15] Furthermore, the significantly increased TSH level is correlated with the severity of pre-eclampsia.[16] The euthyroid sick syndrome can be differentiated from pre-existing hypothyroidism by the less markedly elevated TSH level (<10 mIU/L) and FT4 and FT3 levels which are mildly decreased, together with the absence of other clinical features of hypothyroidism. As with non-pregnant patients who develop euthyroid sick syndrome following other severe illnesses, thyroxine replacement is not beneficial and should not therefore be given. The disturbance in thyroid function should recover spontaneously with recovery of the patient. Where there is doubt about recovery of function, the thyroid function test can be repeated. Any persistent or further increase in TSH level despite clinical recovery after delivery calls for further monitoring and the exclusion of hypothyroidism.

Table. Clinical Presentation of Hypothyroidism in Pregnancy

- Clinical features of hypothyroidism such as excessive fatigue, dry skin, severe constipation, cold intolerance, fluid retention, irritability and paraesthesia
- Spontaneous abortion
- Preterm labour
- Pre-eclampsia
- Foetal growth restriction
- Asymptomatic

Thyroxine Replacement

For patients receiving thyroxine replacement prior to conception, the dose may need to be increased with advancing gestation. For those diagnosed during pregnancy, replacement can commence with 0.05 to 0.1 mg daily and the dose adjusted to keep the serum TSH at < 3 mIU/L. Monitoring by TSH measurement allows fine adjustment of the dose of thyroxine.[17] The usual dose required is between 0.1 to 0.2 mg daily.

This is a two-part paper, Part II will discuss hyperthyroidism in pregnancy.

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• INTERNATIONAL ABSTRACTS •

Preventing Osteoporosis: Alendronate vs HRT

Alendronate is almost as effective as HRT for preventing bone loss in postmenopausal women under 60 years of age, according to the results of a trial from the US.

The researchers studied the effect on bone mineral density in 1,174 postmenopausal women taking 2.5 mg or 5 mg per day of alendronate, or placebo. In addition, 435 women were randomised to receive one the above regimens or conjugated oestrogens, 0.625 mg per day, plus medroxyprogesterone acetate, 5 mg per day.

Follow-up at two years showed that women who received 5 mg per day of alendronate had an average increase in bone mineral density of 1.9% at the hip, 3.5% at the lumbar spine, and 0.7% for the total body. Smaller increases were seen in the women who received 2.5 mg per day. Bone mineral density was not increased at the forearm by alendronate, but the rate of loss was slowed.

Bone mineral density increases were one to two percentage points higher with oestrogenprogestogen therapy than with the 5 mg per day dose of alendronate. Women who received placebo lost bone mineral density at all measured sites.

The researchers concluded that alendronate provides an alternative to HRT for maintaining bone mass, and thus reducing the risk of fractures, in postmenopausal women.

Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. N Engl J Med 1998;338:485-492.