INTRODUCTION

Maternal hypothyroidism, in simple terms, refers to low thyroid hormone levels during pregnancy. The diagnosis is made by a TSH that is greater than normal, and this situation deserves therapy. Many studies have shown that maternal thyroid hormones are very important in pregnancy. Most importantly, emerging data seems to suggest that thyroid hormones are especially important for fetal brain development, especially during early pregnancy. This article will discuss the importance, diagnosis and management of maternal hypothyroidism, from a clinician’s perspective.

Thyroid Physiology in Pregnancy

Pregnancy may be associated with several physiological changes in laboratory tests of thyroid function. Table 1. During pregnancy, there is an increased requirement of thyroid hormones, and this is achieved by an increased thyroid gland function. However, in subjects with pre-existing hypothyroidism, where the gland lacks the functional reserve to increase thyroxine secretion appropriately, there is an approximately 25-47% increase in dosage requirement during pregnancy. Also, iodine deficiency can compromise thyroid function in pregnancy. In addition, as HCG levels increase in pregnancy, there is a transient suppression of TSH in the first trimester. Finally, the estrogenic milieu of pregnancy results in increased sialic acid content of thyroxine-binding globulin (TBG); this reduces the clearance of TBG and prolongs its circulation time. This increase in TBG (which binds to thyroid hormones) can result in a falsely high thyroid hormone (especially T4) levels during pregnancy; however, adaptation mechanisms ensure that the free or active thyroid hormone levels are kept normal. Though these changes affect both the thyroid hormones (T3 and T4), T4 is the more appropriate hormone to measure, and it has been suggested that free T4 hormones be measured in pregnancy. In case total T4 is being used as a measuring tool, recent reports suggest that a different cut-off be used: It has been reported that the normal upper limit of total T4 level in pregnancy is 1.5 times the upper limit in non-pregnant adults. Also, autoimmune thyroid disorders remit during pregnancy as a part of the immunosuppressive effects of pregnancy. Classically, there is a post-partum period of exacerbation. Patients who are euthyroid but positive for antithyroid antibodies have an increased rate of miscarriage. The reason for this is not well understood.

Maternal Hypothyroidism: Clinical Importance

The prevalence of maternal hypothyroidism, as defined by a raised TSH level, is about 2.5% of all pregnancies. This means that about 40 patients need to be screened to detect one case. In iodine-sufficient areas, the most common cause is Hashimoto’s thyroiditis.
The diagnosis of maternal hypothyroidism is important because of its implications on both maternal and fetal outcomes (Table 2)\textsuperscript{2,12}. This is even true with subclinical hypothyroidism\textsuperscript{13}. In addition to these issues is the important etiologic association between hypothyroidism and infertility\textsuperscript{14}.

In the last few decades, emerging evidence has linked thyroid hormones with fetal brain development. This issue of recent interest deserves a special focus. Classic studies on neurological cretinism had earlier shown that iodine deficiency caused fetal brain damage\textsuperscript{15}. This occurs presumably by reducing thyroid hormone synthesis, as iodine is an integral component of both T\textsubscript{3} and T\textsubscript{4}. However, in addition to iodine deficiency, any cause of maternal hypothyroidism in early pregnancy can cause fetal brain damage.

The fetus develops a thyroid gland only after 3 weeks, and this thyroid gland can trap iodine and synthesize thyroid hormones only after about 3 months. Till this time, it is the mother who gives thyroid hormones to her fetus through placental diffusion. Even after 3 months, maternal T\textsubscript{4} transfer continues to occur\textsuperscript{12}. Is the quantity of thyroxine transferred substantial? In order to answer this question, Vulsma et al studied 25 neonates with complete inability to produce thyroid hormones\textsuperscript{16}. T\textsubscript{4} levels in the cord serum of affected neonates ranged from 35 to 70 nmol per liter. The authors concluded that this level purely accrued from maternal thyroxine (T\textsubscript{4}) transfer, and that this indicated substantial maternal-fetal thyroxine transfer during the first trimester. What could these thyroid hormones do in this period? In animal studies, thyroid hormones regulate neuronal proliferation, migration of neurons, synapse formation and myelination\textsuperscript{17-19}. It has been hypothesized that T\textsubscript{4} gets converted to tri-iodothyronine (T\textsubscript{3}) in the cerebral cortex, which binds to specific nuclear receptor isoforms to serve these functions. Hypothyroidism as a result low maternal T\textsubscript{4} may be overt, or can even present with very subtle neurological defects, like learning disabilities or a low intelligence quotient\textsuperscript{17-19}.

Overall data seems to suggest that maternal hypothyroidism is of crucial significance during both early and late phases of pregnancy. Thus, maternal hypothyroidism is a common and serious problem, which needs early diagnosis and therapy. The issue of universal screening during pregnancy for this common, serious and easily treatable disease definitely merits consideration, but is a hotly debated controversy.

### Diagnosing Maternal Hypothyroidism

It is difficult to make a diagnosis of hypothyroidism based on symptoms and signs alone. Even when there are subtle symptoms, like weight gain and constipation, they may be attributed to pregnancy itself. Thus the diagnosis is made by serum TSH estimation. Ideally, trimester-specific normative TSH data is essential, though not available. There is an urgent need for developing normative trimester specific TSH levels from longitudinal studies\textsuperscript{20}. A TSH value that is more than the upper limit of normal (i.e. > 4mU/L) should alert the clinician to the diagnosis. Recent studies have suggested that free T\textsubscript{4} must also be simultaneously tested during screening\textsuperscript{21}. This is because a low free T\textsubscript{4}, even with a normal TSH, is now considered abnormal (especially in iodine deficient zones), and this deserves therapy. Thus the focus seems to be shifting towards maternal hypothyroxinemia rather than hypothyroidism\textsuperscript{21}.

Wherever free T\textsubscript{4} testing is not available or cannot be relied upon, the total T\textsubscript{4} may be used: normal levels of total T\textsubscript{4} in pregnancy may be decided by multiplying non-pregnant levels by a factor of 1.5 for pregnant women\textsuperscript{5}. Antithyroid antibody testing is not mandatory, but may serve two purposes: firstly, it identifies underlying autoimmunity and secondly, high antibody titers are associated with pregnancy losses\textsuperscript{22}.

### Treatment

The drug of choice is levothyroxine (LT\textsubscript{4}). In subjects with florid, overt hypothyroidism, the dose required is 2 µg/kg/day\textsuperscript{3}. The increased dose is important to cover for higher thyroxine demand during pregnancy.
subjects with subclinical hypothyroidism/in subjects with a slightly high TSH (4-10 mU/L), the dose of LT4 is 100 µg/day.

Considerations are slightly different in subjects with pre-gestational hypothyroidism i.e. in subjects who have become pregnant while already taking LT4 for hypothyroidism. These subjects require a 25-47% increase in dosage. Indeed, it has been recommended that when a hypothyroid woman taking LT4 becomes pregnant, the dose should be increased by about 25-50 µg as soon as pregnancy is diagnosed23. Usually, the dosage required is stable and plateaus beyond the 20th week; after this time, very frequent monitoring is not needed23,24. Women taking iron or calcium tablets should not take them with LT4. These tablets may be taken about 4 hours after taking LT4. Iodine intake is important in pregnancy, an important consideration in iodine-deficient zones25.

Follow-up and Targets of Therapy

During the first half of pregnancy, it is best to do monitoring with free T4 and TSH every 3-4 weeks. But later on, the monitoring may be done every 6 weeks. The target TSH level in pregnancy is <2.5 mU/L.5. In subclinical hypothyroidism, the dose may be increased by about 50 µg at a time. However, in cases where the TSH is still very high (>10 mU/L), the dosage may need to be increased by 75 to 100 µg.5. Soon after delivery, the dose must be reduced to the pre-pregnancy dosage, and then thyroid functions checked after 6 weeks.

Controversy: Levothyroxine in Euthyroid Antibody-Positive Subjects

Thyroid autoimmunity is a risk factor for pregnancy loss26. Three explanations have been proposed: firstly, antithyroid antibodies may only be a marker of generalized autoimmunity, which could explain the high occurrence of miscarriages22. Secondly anti-TPO (anti-thyroid peroxidase) antibodies, a marker of autoimmune thyroid disease (AITD) could pick out groups of subjects with subtle damage to the thyroid gland. These subjects might be at risk of developing hypothyroidism because the thyroid gland that is damaged via autoimmune mechanisms is unable to adjust to the physiological loads that are imposed on it during pregnancy22. The third hypotheses questions the role of these antibodies, suggesting that both anti-TPO positivity as well as miscarriages are common in older women: Thus this hypothesis suggests that the link between thyroid autoimmunity and pregnancy loss is a statistical aberration that is borne out of the confounding effect of age22. None of these hypotheses have been proved or disproved, despite several studies on the issue.

A recent study attempted to answer this fascinating question27. In a prospective study of euthyroid pregnant women, subjects with anti-TPO positivity were either treated with LT4 (n = 57) or not treated (n = 58). The authors reported that LT4 therapy in euthyroid TPO+ve pregnancies could improve miscarriage rate by 75% and premature deliveries by 69%27. Antibody positive subjects had a higher TSH at baseline (though within the euthyroid range) as compared with antibody negative group. The results of this study suggest that subjects with the autoimmune thyroid disease may have a subtle deficiency of thyroid hormones due to impaired adaptability, and also implies that the judicious use of levothyroxine, at least in subjects with a high-normal TSH, could improve outcomes. More studies are needed before these findings can change clinical practice.

REFERENCES