

Maternal Hypothyroidism

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ABSTRACT

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The occurrence of hypothyroidism in pregnancy can have adverse effects on the mother and the fetus. In addition, recent research has indicated that in the first half of pregnancy, an adequate thyroid hormone level could play an important role in fetal brain development. Clinical signs of hypothyroidism in pregnancy are not very specific and sensitive. Therefore, serum TSH estimation is the best way to make a diagnosis. Hypothyroidism in pregnancy, whether overt or subclinical, requires therapy with levothyroxine. Frequent monitoring and precise dose titration are required. The aim of therapy is to achieve a TSH value <2.5 mu/L. This is important to ensure a successful pregnancy outcome.

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MATERNAL HYPOTHYROIDISM: AN INTRODUCTION

The occurrence of hypothyroidism during pregnancy poses a challenge to the treating clinician. The diagnosis is made by a TSH that is greater than normal, and during pregnancy, this situation deserves therapy. Research over the years has shown that maternal thyroid hormones are very important in pregnancy.¹⁻³ Importantly, emerging data seems to suggest that thyroid hormones are important for fetal brain development, especially during early pregnancy.⁴ This article will focus on the clinical approach to hypothyroidism in a pregnant woman.

Pregnancy and alterations in thyroid physiology

Pregnancy can cause several physiological changes in thyroid function tests (Table 1).⁵⁻⁹ The requirement for thyroid hormones is increased during pregnancy, and this is achieved by an increased thyroid gland function. The thyroid gland of subjects with pre-existing hypothyroidism lacks the functional reserve to increase thyroxine secretion appropriately. This results in a 25-47% increase in levothyroxine dose requirement during pregnancy.⁵

Lack of adequate iodine intake is another factor that can compromise thyroid function in pregnancy, especially in iodine-deficient zones.^{6,7} HCG too is an important factor confounding thyroid function tests. HCG has a structure that is similar to TSH thus HCG too can stimulate the thyroid gland. This causes transient

suppression of TSH in the first trimester.⁸ Finally, the estrogenic milieu of pregnancy results in increased sialic acid content of thyroid binding globulin (TBG); this reduces the clearance of TBG and prolongs its circulation time.⁹ 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 is 1.5 times the upper limit in non-pregnant adults. Postpartum thyroiditis is an important pregnancy-related thyroid disease. Autoimmune thyroid

Table 1. Important Physiological thyroid alterations in pregnancy

Phenomenon	Explanation
High thyroxine-binding globulin (TBG)	Increased serum estrogen
First trimester TSH suppression	HCG
Slight increase in FT4	HCG
Goiter in iodine deficiency areas	Increased iodide clearance
Goiter in iodine sufficient areas	Increased demand
Increased T4 and T3 demand	High type III deiodinases
High total T4 and T3	Increase in TBG
Increased thyroglobulin	Increased demand for thyroid hormones

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disorders remit during pregnancy as a part of the immunosuppressive effects of pregnancy. Classically, there is a post-partum period of exacerbation. A key finding associated with thyroid autoimmunity is that patients who are euthyroid but positive for antibody have an increased rate of miscarriage.¹⁰ The reason for this is not well understood.

The clinical importance

Hypothyroidism, as defined by a raised TSH level, affects 2.5% of all pregnancies.¹¹ Thus, about 40 patients need to be screened to detect one case. In iodine-sufficient areas, the most common cause is Hashimoto's thyroiditis. The issue of universal screening during pregnancy for this common, serious and easily treatable disease definitely merits consideration, but is a hotly debated controversy.

The diagnosis of maternal hypothyroidism is important because of its implications on both maternal and fetal outcomes (Table 2).^{2,12} This is even true with subclinical hypothyroidism.¹³ In addition, it is well known that untreated hypothyroidism can cause infertility.¹⁴

Emerging evidence in the last decade has linked thyroid hormones with fetal brain development. Classic studies on neurological cretinism had earlier shown that iodine deficiency caused fetal brain damage.¹⁵ This occurs presumably by reducing thyroid hormone synthesis, as iodine is an integral component of both T3 and T4. However, in addition to iodine deficiency, any cause of maternal hypothyroidism in early pregnancy can cause fetal brain damage.

Thyroid gland develops in the fetus only after 3 weeks. This thyroid gland can trap iodine and synthesize thyroid hormones only after about 3 months. Till this time, the mother gives thyroid hormones to her fetus through placental diffusion. Even after 3 months, maternal T4 transfer continues.¹² In order to know whether this transfer was significant, Vulsmä et al studied 25 neonates with complete inability to produce thyroid hormones.¹⁶ T4 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 (T4) transfer, and that this indicated substantial maternal-fetal thyroxine transfer during the first trimester. Do these transferred hormones serve any important function? In animal studies, thyroid hormones regulate neuronal proliferation, migration of neurons, synapse formation and myelination.¹⁷⁻¹⁹ It has been hypothesized that T4 gets converted to tri-iodothyronine (T3) in the cerebral cortex, which binds to specific nuclear

receptor isoforms to carry out these functions. Hypothyroidism as a result low maternal T4 may be overt or mild, presenting with very subtle neurological defects, like learning disabilities or a low intelligence quotient.¹⁷⁻¹⁹ However, the evidence linking hypothyroidism with poor obstetrical outcome is much stronger than that linking it to neurological outcomes. To summarize published evidence suggests that maternal hypothyroidism is common, and that it is of crucial significance during both early and late pregnancy.

Table 2. Negative outcomes associated with maternal hypothyroidism

Maternal disorders
Abortion
Gestational hypertension
Increased use of cesarean section
Anemia
Placental abruption
Preterm labor
Postpartum hemorrhage
Fetal disorders
Premature birth
Fetal and perinatal death
Disorders of brain development
Low IQ scores
Fetal respiratory distress
Low birth weight
Cretinism

Making the diagnosis of maternal hypothyroidism

It is difficult to detect hypothyroidism during pregnancy based on symptoms and signs alone. Thus, the diagnosis is made by serum TSH estimation. Trimester-specific normative TSH data are important in this regard, but need to be validated.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 either a total or free T4 must also be simultaneously tested during screening.²¹ This is because a low T4, even with a normal TSH, is now considered abnormal (especially in iodine deficient zones), and this deserves therapy.²¹ Thus, the focus seems to be shifting towards maternal hypothyroxinemia rather than hypothyroidism.²¹

In general, free T4 estimation is important in pregnancy. However, the total T4 is increasingly being used nowadays, given fallibilities in the free T4 assay. Normal levels of total T4 in pregnancy can be decided by multiplying non-pregnant levels by a factor of 1.5 for pregnant women.⁵ Antithyroid antibody testing is not mandatory, but may can be useful because it identifies an underlying autoimmune basis. Also, high antithyroid antibody titers are associated with infertility and pregnancy losses.²²

Management of maternal hypothyroidism

Levothyroxine (LT4) is the treatment of choice. In subjects with florid, overt hypothyroidism, the dose required is 2 ug/kg/day.⁵ This higher dose is important to cover for higher thyroxine demand during pregnancy. In subjects with subclinical hypothyroidism and in subjects with a TSH <10 mU/L, the starting dose of LT4 is usually 50-100ug/day. Considerations are different in subjects with "pregestational" hypothyroidism i.e. in subjects who have become pregnant while already taking LT4 for hypothyroidism. These subjects require a 25-47% increase in dosage. This excess need is because of excess TBG, increased distribution of T4 as well as the placental transport of thyroid hormones. It has been recommended that when a hypothyroid woman taking LT4 becomes pregnant, the dose should be increased by about 25-50 ug as soon as pregnancy is diagnosed.²³ Usually, the dosage required is stable and plateaus beyond the 20th week. Thus, after this time, very frequent monitoring is not needed.^{23,24} Women taking iron or calcium tablets should not take them simultaneously with LT4. These tablets may be taken about 4 hours after taking LT4. Iodine intake is important in pregnancy.²⁵

Monitoring and therapeutic targets

In the first half of pregnancy, it is best to monitor with free T4 and TSH every 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 50ug at a time. However, in cases where the TSH is high (>10 mU/L), the dosage may need to be increased by 50-75 ug at a time. Where TSH is > 20 mU/L the dose may need to be increased by 75-100 ug at a time. Post-delivery, the dose must be reduced to the pre-pregnancy dosage. Thyroid functions may be re-checked when 6 weeks have elapsed following delivery.

Isolated anti-thyroid antibody positivity

Pregnancy loss has been linked to thyroid autoimmunity.²⁶ The reasons are hypothetical: firstly, antithyroid antibodies may only be a marker of generalized autoimmunity, which could explain the high occurrence of miscarriages.²² It is also possible that 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 pregnancy.²² The third hypothesis suggests that both anti-TPO positivity as well as miscarriages are common in older women: thus the link between thyroid autoimmunity and pregnancy loss is a statistical aberration that is due to the confounding effect of age.²² None of these hypotheses have been proved or disproved, despite several studies on the issue. In a recent study, the authors reported that LT4 therapy in euthyroid TPO+ve pregnancies could improve miscarriage rate by 75% and premature deliveries by 69%.²⁷ This study implies, but cannot conclude with certainty, that the judicious use of levothyroxine could improve outcomes, especially in pregnant, anti-TPO positive subjects with a high-normal TSH. Future studies looking into this emerging area are needed before clinical recommendations can be made.

SUMMARY

The presence of hypothyroidism during pregnancy is common, and can have serious consequences on obstetrical and fetal outcomes. Diagnosis is based on serum TSH estimation. Levothyroxine is the therapy of choice. Frequent monitoring every 4-6 weeks and dose titration are important. Indeed, a recent guideline suggests that thyroid functions (T4 and TSH) should be normalized "as rapidly as possible" when hypothyroidism complicates pregnancy.²⁸ These guidelines recommend target TSH values that are <2.5 mu/L in the first trimester, and < 3 mu/L in the 2nd and 3rd trimesters.²⁸ When T4 measurements are used, the guidelines suggest that total T4 could be a very reliable test, and advise caution while interpreting free T4 measurements.²⁸ It seems likely that the focused treatment of hypothyroidism during pregnancy will become more important in the years to come.

END NOTE

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