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HYPOTHYROIDISM IN PREGNANCY

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CLINICAL RECOGNITION

The prevalence of overt and subclinical hypothyroidism in pregnancy is 0.3-0.5% and 2-3% respectively. Overt hypothyroidism in pregnancy may present classically but is often subtle and difficult to distinguish from the symptoms of normal pregnancy. A high index of suspicion is therefore required, especially in women with a predisposition to thyroid disease such as a personal or family history of thyroid disease, the presence of goiter or the co-existence of other autoimmune disorders like type 1 diabetes. Subclinical hypothyroidism (high TSH with normal FT4) accounts for the majority of cases. Isolated hypo-thyroxinemia (FT4 below the trimester specific reference range without elevation of TSH) occurs in about an equal number of cases.

PATHOPHYSIOLOGY

Although endemic iodine deficiency (areas where the ambient urinary iodine concentration is less than 50µg/liter) is the most common cause of hypothyroidism worldwide, the main cause in iodine-replete populations is chronic autoimmune thyroiditis. Other causes include post-surgical or post-radioiodine ablation. Adverse effects on mother and child range from anemia in pregnancy to miscarriage, or if pregnancy is continued, preterm birth with its consequences (table 1). Even in an iodine sufficient area maternal thyroid dysfunction (hypothyroidism, subclinical hypothyroidism or hypothyroxinemia) during pregnancy results in neuro-intellectual impairment of the child; hence maternal thyroid hormones are required through gestation for proper fetal brain development. Specific effects will depend on when maternal hormone deficiency occurs during pregnancy. Low maternal thyroid hormone concentrations in early gestation can be associated with significant decrements of IQ of young children. A significant decrement in IQ has also been reported in children born to euthyroid mothers with circulating anti TPO antibodies, but this is not an established association as yet.

Table 1. Adverse Outcomes of Pregnancy with Maternal Hypothyroidism
Infertility
Miscarriage
Increased fetal death rate

Anemia in pregnancy Preeclampsia Abruptio placenta Postpartum hemorrhage Preterm birth Low birth weight Increased neonatal respiratory distress Impaired neurointellectual child development

DIAGNOSIS AND DIFFERENTIAL

Hypothyroidism is diagnosed on the basis of a low FT4 or TT4 and high TSH. In pregnancy there are changes in the ranges of both these hormones requiring the use of gestational trimester-specific reference ranges. Thyroid antibody testing (thyroid peroxidase antibody) confirms the autoimmune nature of hypothyroidism and may also identify antibody positive women who are at risk of postpartum thyroiditis. Subclinical hypothyroidism is diagnosed when TSH is above the reference range while the T4 level is normal. The TSH level is difficult to interpret during the 1st trimester due to the weak thyromimetic action of hCG. Isolated hypothyroxinemia occurs most frequently in the 3rd trimester. The clinical significance is not clear as it may arise due to hemodilution.

Table 2. Etiology and Diagnosis of Hypothyroidism During Pregnancy
Autoimmune thyroiditis: Positive thyroid antibody test (TPOAb)
Iodine deficiency: Low urinary iodine, Goiter
Post-surgical: History of Graves' disease, toxic nodular goiter, thyroid cancer, benign goiter

Table 3. Patients at Risk of Thyroid Dysfunction (American Thyroid Association Case Finding Criteria)	
1.	Age >30 years
2.	History of thyroid dysfunction or positive thyroid antibodies
3.	Type 1 diabetes or other autoimmune disorders
4.	Head or neck radiation
5.	Use of drugs that affect thyroid function
6.	Administration of iodinated contrast materials
7.	Goiter or symptoms or signs of thyroid dysfunction
8.	Residents in areas of moderate to severe iodine deficiency
9.	Multiple prior pregnancies (> 2)
10.	Previous pregnancy loss, preterm delivery, or infertility
11.	Family history of thyroid disease
12.	Morbid obesity (BMI > 40 kg/m2)

THERAPY

Women with overt hypothyroidism in pregnancy should be treated with levothyroxine, but there is no consensus regarding treatment for women with subclinical hypothyroidism or isolated hypothyroxinemia. Treatment should be considered in women with subclinical hypothyroidism if they have TSH concentrations above 10 mU/L, positive thyroid antibodies,

or other risk factors for thyroid disease such as goiter, personal or family history of thyroid autoimmunity, or type 1 diabetes (table 3). Women with infertility or recurrent pregnancy loss could also be treated on the basis that treatment could potentially improve live delivery rates. Treatment of isolated hypothyroxinemia is controversial and is probably not indicated in the 3rd trimester.

In women not receiving T4 who may have risk factors for thyroid disease (e.g. personal or family history of an autoimmune disorder, positive thyroid antibodies, Type 1 DM, prior pre-term delivery, possible iodine deficiency, or neck irradiation) thyroid function should be measured pre-conception. If the TSH is above the laboratory reference range, the test should be confirmed, and supplemental thyroxine therapy should be considered, especially if thyroid antibodies or other risk factors for thyroid disease are present (table 3). Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored for elevation of TSH above the normal range for pregnancy.

Women receiving T4 for hypothyroidism before pregnancy should have thyroid function checked to maintain TSH levels not higher than 2.5mIU/L in the first trimester and not higher than 3.0mIU/L in subsequent trimesters. As soon as pregnancy is confirmed T4 dose should be increased by 30-50% and TFTs checked every 4 weeks. Note that TSH level is difficult to interpret in the 1st trimester due to HCG action. Not all women require an increase in T4 dosage in pregnancy. Women who are newly diagnosed to be hypothyroid in pregnancy should receive 100µg T4 daily and the dose adjusted after 4 weeks to the optimal level. In summary, women with overt hypothyroidism or with subclinical hypothyroidism who are TPO antibody positive should be treated with oral levothyroxine.

Screening

Because of the proven adverse effects of hypothyroidism on pregnancy, and the failure of testing only women at “high risk” of hypothyroidism (defined above) to detect more than 50% of thyroid problems, a case can be made for screening all women for thyroid function in early pregnancy with administration of levothyroxine in women with subnormal thyroid function. Another recommended approach is to screen only women at “high risk”. However, the issue remains unsettled.

FOLLOW-UP

In women with previously treated Graves’ hyperthyroidism who are receiving thyroxine for post ablative hypothyroidism the Thyroid Stimulating Hormone Receptor Antibodies (TRAbs) assay may be positive even many years later. The woman should be counselled if another pregnancy is planned to guard against fetal or neonatal hyperthyroidism due to transplacental passage of maternal TRAb. Before a further pregnancy thyroid function should be checked in order to keep the TSH less than 2.5mIU/l. When first pregnant the woman should increase T4 dose by 25-50% (usually by 50 micrograms per day) and then have a further thyroid function test 4 weeks later and at least in every trimester thereafter. About 25% do not require an increase in T4 dose.

GUIDELINE

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