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Improving Maternal and Fetal Health: A Look at Thyroid Function During Pregnancy

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Abstract

Maintenance of thyroid function during pregnancy is critical for both maternal and fetal health and development; therefore, knowledge regarding the relationship between thyroid hormones and pregnancy is essential. The American Thyroid Association task force has developed clinical guidelines on the diagnosis and treatment of thyroid disease during pregnancy. Gestational thyroid diseases are divided into two classifications, hypothyroidism and hyperthyroidism, which are further divided into more specific classifications based on clinical presentation. Differentiation, diagnosis, and monitoring of thyroid diseases throughout pregnancy require assessing symptoms, as well as obtaining levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) concentration by a simple serum test. Treatment goals are based on trimester-specific normal ranges of these hormone levels. Uncontrolled hypothyroidism and hyperthyroidism during pregnancy can lead to adverse pregnancy complications and have negative effects on fetal development. However, debate still exists as to the benefit of thyroid hormone level screening in all pregnant patients versus only those with higher risk.

Introduction

Pregnancy has a significant impact on the thyroid gland and thyroid function. Knowledge regarding the relationship between thyroid hormones and pregnancy is advancing at a rapid pace.[1] Many studies are now focusing on the potential impact of hypothyroidism or hyperthyroidism, as well as treatment outcomes on maternal and fetal health. It is important to recognize that until between 10 and 12 weeks gestation, the fetus is entirely dependent upon placental transfer of maternal thyroid hormone. Although maintenance of maternal thyroid hormone levels is critical throughout the entire pregnancy, avoidance of suboptimal levels is of great importance during this time.[2] By the end of the first trimester, the fetal thyroid begins producing thyroid hormones on its own, but remains dependent on the mother for ingestion of adequate amounts of iodine, an essential component in the production of thyroid hormones. During pregnancy, the maternal thyroid gland increases in size by 10 to 40 percent. Along with a 50 percent increase in maternal daily iodine requirement, production of thyroxine (T_4) and triiodothyronine (T_3) also increases by 50 percent during this time. Serum thyroid-stimulating hormone (TSH) levels fall during the first trimester of a normal pregnancy as a physiological response to the stimulating effect of human chorionic gonadotropin (hCG) on the TSH receptor. Normal TSH levels during pregnancy range from 0.03 mIU/mL to 2.5 mIU/mL.[1]

The American Thyroid Association (ATA) task force has developed clinical guidelines for the diagnosis and treatment of thyroid disease during pregnancy. Hypothyroidism during gestation is defined as the presence of an elevated serum TSH concentration. Hypothyroidism is prevalent in 2 percent of pregnancies and can be further classified as either subclinical (SCH) or overt hypothyroidism (OH), dependent upon measurement of serum free thyroxine (FT_4) concentration. Hyperthyroidism is characterized by an overactive thyroid gland and defined by elevated FT_4, as a result of increased serum concentrations of T_4 and T_3, and suppressed or undetectable serum TSH.[1] Thyroid hormone fluctuations associated with hypothyroidism and hyperthyroidism have been shown to impact both maternal and fetal health and development.

Diagnosis and Complications of Hyperthyroidism During Pregnancy

Hyperthyroidism is less common during pregnancy than hypothyroidism. It is estimated that the prevalence falls in the range of 0.1 percent to 0.4 percent, with 85 percent of cases attributed to Graves' disease.[3] Graves' disease is most common in women during the reproductive years and can be associated with infertility. Most pregnant women with hyperthyroidism are diagnosed with Graves' disease prior to conception. In the first trimester, a diagnosis of Graves' disease is based on very low serum TSH (<0.1mIU/L) and elevated FT_4, which must be differentiated from gestational hyperthyroidism.[1] Gestational hyperthyroidism is characterized by low serum TSH and elevated FT_4 during the first half of pregnancy, as well as the absence of serum markers of thyroid autoimmunity. In patients with Graves' disease, TSH receptor antibodies (TRAb) will be present and physical findings may include a goiter or thyroid-associated orbitopathy. Obstetric complications, such as increased risk of stillbirth, miscarriage and premature birth, are similar to the complications seen with hypothyroidism.[3] Patients with uncontrolled hyperthyroidism during pregnancy may experience congestive heart failure, thyroid storm triggered by preeclampsia or maternal TRAb may cross the placenta and stimulate the fetal thyroid. Stimulation of the fetal thyroid can lead to fetal tachycardia, fetal growth retardation, cardiac failure, development of a fetal goiter and, rarely, neonatal hyperthyroidism.

Treatment and Monitoring of Hyperthyroidism

For patients with a diagnosis of Graves' disease, the safest time to conceive is while euthyroid.[1] It is strongly suggested that uncontrolled patients planning on becoming pregnant use adequate contraception until they become euthyroid. A hyperthyroid patient may be treated with ablative therapy or antithyroid drugs (ATD) prior to conception, but after con-

ception the preferred treatment is ATD. The main antithyroid drugs used are propylthiouracil (PTU) and methimazole (MMI).[3] During the first trimester, the current ATD of choice is PTU because more teratogenic effects have been associated with MMI.[1] Women on MMI prior to conception should be switched to treatment with PTU. After the first trimester, patients may consider switching to MMI because there have been reports of hepatotoxicity with prolonged PTU treatment.[1,3] Both PTU and MMI cross the placental barrier; for this reason, the lowest dose of ATD that maintains FT_4 levels at or moderately above the normal reference values should be used.[1] Levels of FT_4 and TSH should be monitored every two to six weeks during pregnancy with a primary goal of keeping FT_4 levels controlled. If maternal FT_4 levels are not under control, fetal heart rate, growth and thyroid size may be evaluated as needed using ultrasound.[4] Lactating mothers should be treated with MMI doses up to 30mg/day given in divided doses immediately following each feeding. PTU is typically avoided during lactation due the hepatotoxicity risks.[1]

Antithyroid drugs are not indicated for the treatment of gestational hyperthyroidism, because FT_4 levels return to normal by 14 to 18 weeks gestation.[1] Gestational hyperthyroidism may cause nausea and vomiting in the form of hyperemesis gravidum. Management should include supportive therapy for symptoms and hospitalization if required.

Diagnosis and Complications of Hypothyroidism During Pregnancy

Hypothyroidism can be difficult to diagnose during pregnancy.[5,6] Typical symptoms of hypothyroidism such as weight gain, muscle cramps, constipation, fatigue and dry skin are common symptoms of pregnancy itself. For this reason, a diagnosis of hypothyroidism is confirmed by an increase in serum TSH.[6] Hypothyroidism during pregnancy is differentiated into overt and subclinical types. The estimated prevalence of each type during pregnancy is 0.2 to 0.3 percent and 2 to 2.5 percent, respectively.[7] Overt hypothyroidism (OH) during pregnancy is defined as an elevated TSH level of greater than 2.5 mIU/L in conjunction with a decreased FT_4 concentration or a TSH level above 10mIU/L regardless of FT_4 levels.[1,8] Subclinical hypothyroidism (SCH) is defined as a TSH level within the range of 2.5mIU/L and 10mIU/L with a normal FT_4 level. OH is symptomatic whereas SCH may be symptomatic or asymptomatic.[5]

When left untreated, OH has been firmly associated with adverse pregnancy complications and negative effects on fetal brain development.[1,9] Depending on when during the pregnancy untreated OH is present, it can lead to infertility, increased risk of preeclampsia, premature birth, low birth weight, miscarriage, increased admission to neonatal intensive care and perinatal morbidity and mortality.[1,4,7] Maternal OH in all trimesters has been associated with the development of fetal neurological deficits, but during the third trimester the fetal thyroid gland is able to provide some thyroid hormone to the fetus lessening the severity of fetal brain damage occurring during the last trimester.[6,10] Untreated SCH is associated with similar adverse pregnancy outcomes, but whether or not it has negative effects on infertility or causes neurocognitive deficits in the developing fetus remains controversial.[1,10]

Treatment and Monitoring of Hypothyroidism

The goal of treatment for both OH and SCH is to normalize serum TSH to the following trimester-specific ranges: first trimester 0.1 mIU/L to 2.5 mIU/L; second trimester 0.2 mIU/L to 3.0 mIU/L; and third trimester 0.3 to 3.0 mIU/L .[1] It is important to note these ranges are lower than the 0.4 mIU/L to 4.0 mIU/L target range for non-pregnant women.[8] The American Thyroid Association recommends using levothyroxine (LT_4) thyroid preparations rather than T_3 or dessicated preparations.[1] Up to 50 to 80 percent of women receiving exogenous levothyroxine prior to pregnancy will require a dosage increase during pregnancy.[8] For patients planning a pregnancy and receiving exogenous levothyroxine for a diagnosis of hypothyroidism, a levothyroxine dosage adjustment should be made as soon as pregnancy is suspected or immediately after a missed menstrual cycle. The American Thyroid Association recommends an approximate 25 to 30 percent increase in dose for euthyroid newly pregnant women receiving levothyroxine.[1] This can be accomplished using a two tablet dosage increase based on a prospective, randomized trial by Yassa et al. The study demonstrated a reduced risk of maternal hypothyroidism during the first trimester when patients had their total weekly T_4 dose increased by two tablets.[11] For example, a woman on seven tablets per week would increase her dose to nine tablets per week.[1] Maternal TSH levels should be monitored every four weeks during the first 20 weeks of pregnancy for patients receiving levothyroxine and patients with untreated SCH because further dosage adjustments are often required to keep TSH in range. Maternal TSH should be checked again at least once between 26 and 32 weeks gestation. Thyroxine (T_4) requirements will likely increase as the pregnancy progresses.[6] Pharmacists can help maximize intestinal absorption of the hormone by counseling patients to take levothyroxine on an empty stomach with a glass of water, either one hour before or two hours after a meal and four hours apart from products containing iron such as prenatal vitamins.[6,12]

Postpartum, TSH levels and T_4 requirements should return to their pre-pregnancy state allowing patients to resume their pre-pregnancy dosing schedules.[1] TSH should be checked at six weeks postpartum.

Screening for Thyroid Function

There is much discussion as to the benefit of monitoring thyroid hormone levels during pregnancy, and it has been five years since the American Association of Clinical Endocrinologists recommended thyroid function screening in all women during the first trimester of pregnancy.[13] The most recent guidelines set forth by the Endocrine Society recommend screening in high-risk women as opposed to routine screenings in pregnancy.[14] High-risk women should be screened for thyroid function during and/or before pregnancy (Table 1).

Despite these criteria, a single-center cohort study that measured TSH, free T_4 and free T_3 in 1,560 consecutive preg-

nant women during their first visit to the gynecologist at a median of nine weeks gestation, discovered that thyroid function testing of only the high-risk women would miss about one-third of pregnant women with hypothyroidism (Table 1).[15] Thus, it is recommended from the results of this particular trial that all pregnant women receive thyroid function tests.

A 2008 study assessed the cost-effectiveness of screening for thyroid function during pregnancy by using a Markov model. Three strategies including no screening, screening with anti-thyroid peroxidase (TPO) antibodies and screening with TSH were evaluated in women with no known history of thyroid disease.[16] In the first screening, serum was tested for anti-TPO antibodies. If that was positive, the serum was tested for TSH. If TSH was high, FT_4 was tested. Treatment with levothyroxine was administered if necessary. Hypothyroidism costs were generated using the costs of a 10 minute follow-up visit, TSH test, FT_4 test, annual levothyroxine treatment, low IQ level, and gestational hypertension as opposed to no gestational hypertension. The study concluded that screening women with TSH in their first trimester saved $102 and increased maternal life expectancy by 5.84 days. Screening women with anti-TPO antibodies proved to be more cost-effective compared with TSH as maternal age increased. Thus, the cost of screening should not be a factor in determining whether all women should be tested for thyroid function during pregnancy.

Conclusion

Determining and treating thyroid function abnormalities during pregnancy is essential for the health of both the mother and the fetus. Simple serum tests can be done to test thyroid function, especially if the mother has a personal or family history of thyroid disease. Hypothyroidism can be confirmed by an elevated serum TSH level and, when left untreated, can be associated with adverse pregnancy complications and negative effects on fetal brain development. Levothyroxine can be used to treat hypothyroidism. Hyperthyroidism can be confirmed when serum TSH is very low and FT_4 is elevated. Patients with uncontrolled hyperthyroidism during pregnancy may experience maternal congestive heart failure, thyroid storm triggered by preeclampsia, or maternal TRAb may cross the placenta and stimulate the fetal thyroid leading to fetal tachycardia, growth retardation, cardiac failure, development of a fetal goiter, and rarely neonatal hyperthyroidism. Hyperthyroidism can be treated with antithyroid drug therapy, specifically propylthiouracil and methimazole. Although there is much debate as to whether or not thyroid function tests are necessary in pregnant women, studies show that testing is cost-effective and should be recommended to ensure the health of both mother and fetus.

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Table 1. Characteristics of Women at High Risk for Thyroid Disease[14]

Past history of thyroid disease	Goiter
Thyroid lobectomy	TRAbs
Family history of thyroid disease	Type I diabetes
Symptoms or clinical signs of hyperthyroidism	Symptoms or clinical signs of hypothyroidism
Autoimmune disorders	Infertility
Previous therapeutic head and neck irradiation	History of miscarriage and preterm delivery