OBG MANAGEMENT

FIRST OF 2 PARTS

How to manage hypothyroid disease in pregnancy

Pregnancy complicated by hypothyroidism puts mother and fetus at risk—symptoms or otherwise

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A pregnant woman whose thyroid gland isn't doing its job presents a serious management problem for her obstetrician. If she has overt hypothyroidism, seen in between 0.3% and 2.5% of pregnancies, active intervention is required to prevent serious damage to the fetus.[1,2] Even if she has subclinical disease, seen in 2% to 3% of pregnancies, current research indicates that intervention may be indicated.

Fetal thyroxine requirements increase as early as 5 weeks of gestation, when the fetus is still dependent on maternal thyroxine. A deficiency of maternal thyroxine can have severe adverse outcomes, affecting the course of the pregnancy and the neurologic development of the fetus. To prevent such sequelae, patients who were on thyroid medication before pregnancy should increase the dosage by 30% once pregnancy is confirmed, and hypothyroidism that develops in pregnancy should be managed aggressively and meticulously.

Here, we'll examine the published research to advise you on evidence-based approaches for diagnosis and management of this complex condition.

Maternal thyroid function

An elaborate negative-feedback loop prevails before pregnancy

In a nonpregnant woman, thyroid function is controlled by a negative-feedback loop that works like this:

- The hypothalamus releases thyroid-releasing hormone (TRH)
- TRH acts on the pituitary gland to release thyroid-stimulating hormone (TSH)
- TSH, in turn, acts on the thyroid gland to release the thyroid hormones iodothyronine (T_3) and thyroxine (T_4) that regulate metabolism
- TRH and TSH concentrations are inversely related to T_3 and T_4 concentrations. That is, the more TRH and TSH circulating in the blood stream, the less T_3 and T_4 will be produced by the thyroid gland[3]
- Almost all (approximately 99%) circulating T_3 and T_4 is bound to a protein called thyroxine-binding globulin (TBG). Only 1% of these hormones circulate in the free form, and only the free forms are biologically active.[3]

This relationship is illustrated in **FIGURE 1** (page 30).

Pregnancy reduces free forms of T_3 and T_4, and increases TSH slightly

Pregnancy alters thyroid function in significant ways:

- Increases in circulating estrogen lead to the production of more TBG
- When TBG increases, more T_3 and T_4 are bound and fewer free forms of these hormones are available

IN THIS ARTICLE

Coming in FEBRUARY

In Part 2 of this series, Dr. Bombrys, Dr. Habli, and Dr. Sibai review hyperthyroidism in pregnancy

FIGURE 1

Thyroid physiology and the impact of pregnancy

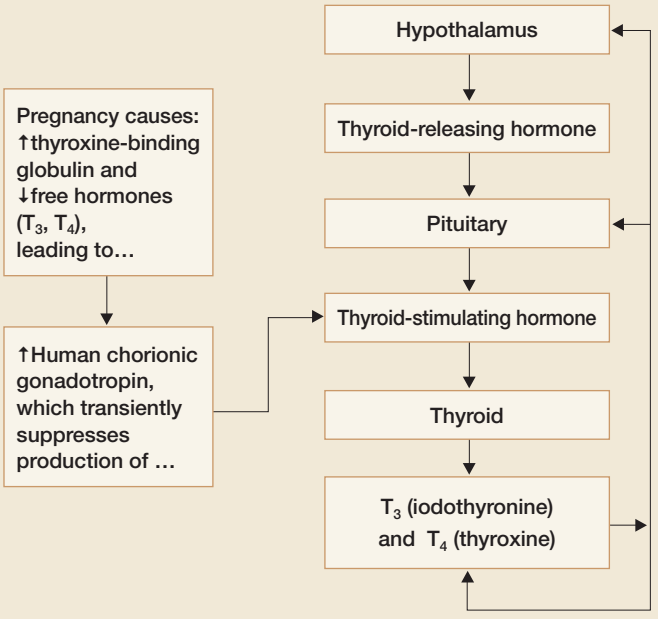

TABLE 1

Distinguishing hypothyroidism from a normal gestation can be challenging

SYMPTOM	HYPOTHYROIDISM	PREGNANCY
Fatigue	•	•
Constipation	•	•
Hair loss	•	
Dry skin	•	
Brittle nails	•	
Weight gain	•	•
Fluid retention	•	•
Bradycardia	•	•
Goiter	•	
Carpal tunnel syndrome	•	•

- Because the total T_3 (TT_3) and total free T_4 (TT_4) are decreased in pregnancy, they are not good measures of thyroid function. Maternal thyroid function in pregnancy should be monitored using free T_4 (FT_4) and TSH levels
- Increased TBG also leads to a slight increase in TSH between the first trimester and term
- Human chorionic gonadotropin (hCG) concentrations also increase in pregnancy. Because hCG has thyrotropin-like activity, these higher levels cause a transient decrease in TSH by suppression of TSH production between approximately 8 and 14 weeks of gestation.

Fetal thyroid function

During early gestation, the fetus receives thyroid hormone from the mother.[1] Maternal T_4 crosses the placenta actively—the only hormone that does so.[4] The fetus's need for thyroxine starts to increase as early as 5 weeks of gestation.[5]

Fetal thyroid development does not begin until 10 to 12 weeks of gestation, and then continues until term. The fetus relies on maternal T_4 exclusively before 12 weeks and partially thereafter for normal fetal neurologic development. It follows that maternal hypothyroidism could be detrimental to fetal development if not detected and corrected very early in gestation.

How (and whom) to screen for maternal hypothyroidism

Routine screening has been recommended for women who have infertility, menstrual disorders, or type 1 diabetes mellitus, and for pregnant women who have signs and symptoms of deficient thyroid function.[6] In recent years, some authors have recommended screening all pregnant women for thyroid dysfunction, but such recommendations remain controversial.[3,7,8] Routine screening is not endorsed by the American College of Obstetricians and Gynecologists.[6]

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Symptoms overlap typical conditions of pregnancy

The difficulty here is that the characteristic signs and symptoms of hypothyroidism are very similar to physiologic conditions seen in most pregnancies. They include fatigue, constipation, cold intolerance, muscle cramps, hair loss, dry skin, brittle nails, weight gain, intellectual slowness, bradycardia, depression, insomnia, periorbital edema, myxedema, and myxedema coma.[6] A side-by-side comparison of pregnancy conditions and hypothyroidism symptoms is provided in **TABLE 1** (page 30).

Which laboratory tests are informative?

Because screening is controversial and symptomatology does not reliably distinguish hypothyroidism from normal pregnancy, laboratory tests are the standard for diagnosis. Overt hypothyroidism is diagnosed in a symptomatic patient by elevated TSH level and low levels of FT_4 and free T_3 (FT_3). Subclinical hypothyroidism is defined as elevated TSH with normal FT_4 and FT_3 in an asymptomatic patient. Level changes characteristic of normal pregnancy, overt hypothyroidism, and subclinical hypothyroidism are given in **TABLE 2.**[6]

TABLE 2

Laboratory diagnosis of hypothyroidism

MATERNAL CONDITION	TSH	FREE T_3	FREE T_4	TOTAL T_3	TOTAL T_4
Normal pregnancy	No change	No change	↑	↑	↑
Hypothyroidism	↑	↓	↓	↓	↓
Subclinical hypothyroidism	↑	No change	No change	↓	↓

Adapted from American College of Obstetricians and Gynecologists[6]

TABLE 3

Causes of hypothyroidism

- Iodine deficiency
- Hashimoto's thyroiditis
- Radioactive iodine therapy
- Thyroidectomy
- Viral thyroiditis
- Sheehan's syndrome
- Medications
  - Thionamides
  - Lithium
  - Drugs that inhibit absorption of thyroid medication
    - Ferrous sulfate
    - Sucrafate
    - Cholestyramine
    - Antacids (aluminum hydroxide)

What causes hypothyroidism?

The most common cause of hypothyroidism in most of the world is iodine deficiency. In developed countries, however, where lack of iodine in the diet is not a problem, Hashimoto's thyroiditis, also known as chronic autoimmune thyroiditis, is the most common cause. Hashimoto's thyroiditis is characterized by the presence of antithyroid antibodies, including both thyroid antimicrosomial and antithyroglobulin antibodies. Both iodine deficiency and Hashimoto's thyroiditis are associated with goiter.[5] Other causes of hypothyroidism include radioactive iodine therapy for Graves' disease, a condition we will discuss in Part 2 of this series in February; thyroidectomy; viral thyroiditis; pituitary tumors; Sheehan's syndrome; and a number of medications.

Causes of hypothyroidism are summarized in **TABLE 3.**[3]

Effects vary by medication

Medications alter thyroid function in different ways. Iodine and lithium inhibit thyroid function and, along with dopamine antagonists, increase TSH levels. Conversely, thioamides, glucocorticoids, dopamine agonists, and somatostatins decrease TSH levels. Finally, ferrous sulfate, sucrafate, cholestyramine, and aluminum hydroxide antacids all inhibit gastrointestinal

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Characteristic signs and symptoms of hypothyroidism resemble physiologic conditions typically seen in pregnancy

TABLE 4

Fetal and neonatal effects of asymptomatic overt hypothyroidism

STUDY	LABORATORY FINDINGS	OUTCOMES AND RECOMMENDATIONS
Kooistra et al[12]	↓ FT_4	Maternal hypothyroxinemia is a risk for neurodevelopmental abnormalities as early as 3 weeks of age
Casey et al[10]	↑ TSH	Pregnancies with undiagnosed subclinical hypothyroidism were more likely to be complicated by placental abruption and preterm birth. The reduced IQ seen in a prior study (Mitchell and Klein[4]) may be related to effects of prematurity
Mitchell and Klein[4]	↑ TSH	The mean and standard deviation of IQs of the children of treated mothers with hypothyroidism and the control group were significantly higher than those for children of untreated hypothyroid women
Blazer et al[9]	↑ maternal TSH, ↑ fetal FT_4	Impaired intrauterine growth may reflect insufficient levels of hormone replacement therapy in hypothyroid mothers during pregnancy
Pop et al[7]	↓ FT_4	Impaired psychomotor development at 10 months of age in offspring of mothers with low T_4 at ≤12 weeks
Haddow et al[8]	↑ TSH, ↓ FT_4	Elevated TSH levels at <17 weeks' gestation are associated with low IQ scores at 7 to 9 years of age. Routine screening for thyroid deficiency may be warranted
Klein et al[11]	↑ TSH, ↓ FT_4, ↓ TT_4	Inverse correlation between TSH during pregnancy and IQ of offspring

FT_4 = free thyroxine, TSH = thyroid-stimulating hormone, TT_4 = total thyroxine

absorption of thyroid hormone and therefore should not be taken within 4 hours of thyroid medication.[6]

Maternal hypothyroidism: Effects on fetus, newborn

The impact of maternal hypothyroidism on the fetus depends on the severity of the condition.

- **Uncontrolled hypothyroidism.** The consequences of this condition can be dire. The possibilities include intrauterine fetal demise and stillbirth, preterm delivery, low birth weight, preeclampsia, and developmental anomalies including reduced intelligence quotient (IQ).[1,2,4,6] Blazer and colleagues correlated intrauterine growth with maternal TSH and fetal FT_4 and concluded that impaired intrauterine growth is related to abnormal thyroid function and might reflect an insufficient level of hormone production by hypothyroid mothers during pregnancy.[9] Maternal and congenital hypothyroidism resulting from severe iodine deficiency are associated with profound neurologic impairment and mental retardation.[1,3,10] If the condition is left untreated, cretinism can occur. Congenital cretinism is associated with growth failure, mental retardation, and other neuropsychologic deficits including deaf-mutism.[3,4] However, if cretinism is identified and treated in the first 3 months of life, near-normal growth and intelligence can be expected.[6] For this reason, all 50 states and the District of Columbia require newborn screening for congenital hypothyroidism.[6]
- **Asymptomatic overt hypothyroidism.** Several studies have evaluated neonatal outcomes in pregnancy complicated by asymptomatic overt hypothyroidism—that is, women who had previously been diagnosed with hypothyroidism, who have abnormal TSH and FT_4 levels, but who do not have symptoms. Pop and colleagues have shown impaired psychomotor development at 10 months in infants born to mothers who had low T_4 during the first 12 weeks of gestation.[7] Haddow and colleagues correlated elevated maternal TSH levels at less than 17 weeks' gestation with low IQ scores in the offspring at 7 to 9 years of age.[8] Klein and colleagues demonstrated an inverse correlation between a woman's TSH level during pregnancy and the IQ of her offspring.[11] Kooistra and colleagues

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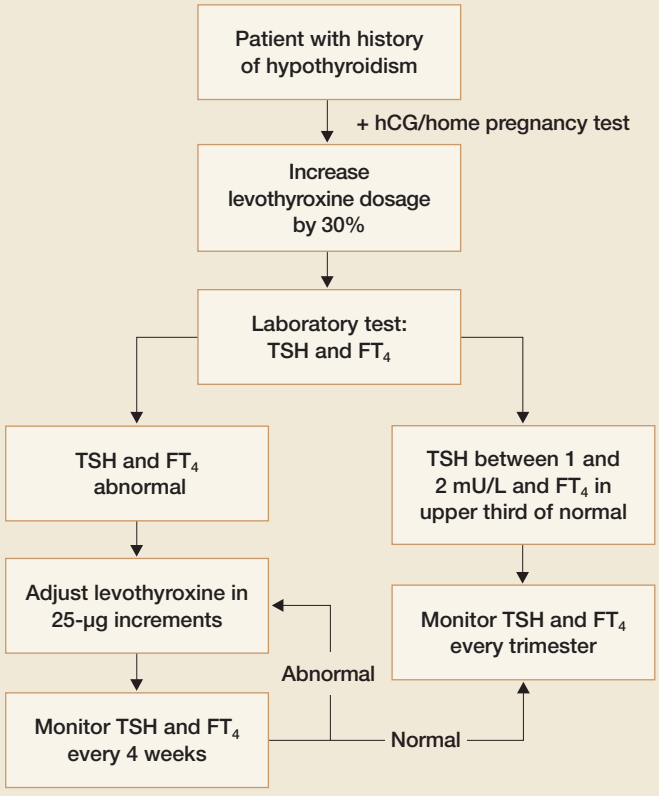
confirmed that maternal hypothyroxinemia is a risk for neurodevelopmental abnormalities that can be identified as early as 3 weeks of age.[12] Studies of this relationship are summarized in **TABLE 4** (page 34).

• **Subclinical hypothyroidism.** During the past decade, researchers have focused attention on neonatal neurologic function in infants born to mothers who had subclinical disease. Mitchell and Klein evaluated the prevalence of subclinical hypothyroidism at less than 17 weeks' gestation and subsequently compared the IQs in these children with those of controls.[4] They found the mean and standard-deviation IQs of the children in the control and treated groups to be significantly higher than those of the children whose mothers were not treated. Casey and colleagues evaluated pregnancy outcomes in women who had undiagnosed subclinical hypothyroidism.[10] They found that such pregnancies were more likely to be complicated by placental abruption and preterm birth, and speculated that the reduced IQ demonstrated in the Mitchell and Klein study might have been related to the effects of prematurity.

FIGURE 2

During pregnancy, thyroid function merits regular monitoring, fine-tuning of treatment



Managing hypothyroidism in pregnancy

The treatment of choice for correction of hypothyroidism is synthetic T_4, or levothyroxine (Levothyroid, Levoxyl, Synthroid, and Unithroid). Initial treatment in the nonpregnant patient is 1.7 µg/kg/day or 12.5 to 25 µg/day adjusted by 25 µg/day every 2 to 4 weeks until a euthyroid state is achieved.[13]

Patients who were on thyroxine therapy before pregnancy should increase the dose by 30% once pregnancy is confirmed.[1,5] Serum thyrotropin levels should be monitored every 4 weeks to maintain a TSH level between 1 and 2 mU/L and FT_4 in upper third of normal.[1] Once a euthyroid state has been achieved, thyrotropin levels should be monitored every trimester until delivery. **FIGURE 2** provides an algorithm for management of hypothyroidism in pregnancy.

Postpartum thyroiditis

About 5% of all obstetrical patients develop postpartum thyroiditis. Approximately 45% of these women present with hypothyroidism, with the rest evenly divided between thyrotoxicosis (hyperthyroidism) and thyrotoxicosis followed by hypothyroidism. Unfortunately, the signs and symptoms of hypo- and hyperthyroidism are similar to the postpartum state. Many of these patients are not diagnosed. A high index of suspicion warrants thyroid function testing. Women who have a history of type 1 diabetes mellitus have a 25% chance of developing postpartum thyroid dysfunction.

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The diagnosis is made by documenting abnormal levels of TSH and FT_4. Postpartum hyperthyroidism may be diagnosed by the presence of antimicrosomal or thyroperoxidase antithyroid peroxidase antibodies. Goiter may be present in up to 50% of patients.

Postpartum thyroiditis has two phases

The first phase, also known as the thyrotoxic phase, occurs 1 to 4 months after delivery when transient thyrotoxicosis develops from excessive release of thyroid hormones. The most common symptoms with early postpartum thyroiditis are fatigue and palpitations. Approximately 67% of these women will return to a euthyroid state, and thioamide therapy is generally considered ineffective. Hypothyroidism can develop within 1 month of the onset of thyroiditis.

The second phase occurs between 4 and 8 months postpartum, and these women present with hypothyroidism. Thyromegaly and associated symptoms are common. Unlike the first (thyrotoxic) phase, medical treatment is recommended. Thyroxine treatment should be initiated and maintained for 6 to 12 months. Postpartum thyroiditis carries a 30% risk of recurrence.[14]

Postpartum thyroiditis may be associated with depression or aggravate symptoms of depression, although the data on this association are conflicting. The largest study addressing this issue concluded that there was no difference in the clinical and psychiatric signs and symptoms between postpartum thyroiditis and controls.[15] Nevertheless, it would seem prudent to evaluate thyroid function in postpartum depression if other signs of thyroid dysfunction are present. ■

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Expect to see a goiter in as many as half of patients who have postpartum hyperthyroiditis