

THYROID DISEASE DURING PREGNANCY

Part 2: Hyperthyroidism

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Thyroid disease is one of the most common conditions the clinician may encounter in pregnant patients.

This is the second of a 2-part series about thyroid disease during pregnancy, focusing on hyperthyroidism.

Clinical hyperthyroidism is diagnosed by a suppressed thyroid-stimulating hormone (TSH) and elevated serum free thyroxine (FT₄). Subclinical hyperthyroidism, defined by a suppressed TSH and normal FT₄, affects 1.7% of pregnant women. The incidence of overt hyperthyroidism in pregnancy is approximately 2 per 1,000.

The majority of cases (95%) are due to Graves disease, an autoimmune process characterized by the presence of autoantibodies (thyroid-stimulating immunoglobulin, or TSI) that directly stimulate the thyroid gland by binding to TSH receptors.¹ Other less common causes of hyperthyroidism include a functioning adenoma, toxic nodular goiter, and subacute thyroiditis.

SIGNS AND SYMPTOMS OF HYPERTHYROIDISM

The hypermetabolic state of pregnancy can mimic the symptoms seen in hyperthyroidism. This includes an increase in heart rate,

fatigue, and heat intolerance. Physical examination may reveal hypertension, goiter, tachycardia, and weight loss. Symptoms specific to Graves disease include dermatopathy (localized, pretibial myxedema) and ophthalmopathy (lid lag and retraction). A list of signs and symptoms for hyperthyroidism and hypothyroidism is included in Table 1.

MATERNAL AND FETAL RISKS OF HYPERTHYROIDISM

Hyperthyroidism during pregnancy is associated with increased perinatal morbidity and mortality.² Risks include spontaneous pregnancy loss, preterm birth, fetal growth restriction, preeclampsia, congestive heart failure, and thyroid storm. TSIs can cause fetal or neonatal Graves disease, and transfer of antithyroid drugs across the placenta may lead to fetal hypothyroidism.

When hyperthyroidism is uncontrolled, excessive thyroxine can lead to congestive heart failure, which has been reported to occur more commonly during pregnancy.³ Thyroid storm is the most serious complication of thyrotoxicosis, a life-threatening medical emergency that carries a risk of heart failure. Thyroid storm is rare during pregnancy, occurring in 1% of women with hyperthyroidism. Treatment of both thyroid storm and thyrotoxic heart failure is similar, as both require management in an intensive care unit setting. Precipitating factors for thyroid storm include infection, preeclampsia, labor and delivery, and surgery.

Both hyperthyroidism and hypothyroidism are potential fetal complications in patients with hyperthyroidism. In patients with Graves disease, transplacental passage

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of maternal TSI (immunoglobulin G antibodies) can stimulate the fetal thyroid gland, resulting in fetal hyperthyroidism.

The risk of fetal hyperthyroidism is increased in women with high TSI levels; however, maternal disease status does not correlate with fetal effects. Of note, some patients with Graves disease may produce TSH-binding inhibitory immunoglobulin (TBII) that may inhibit the fetal thyroid gland, resulting in fetal or neonatal hypothyroidism, which is usually transient.⁴

Both TSI and TBII may coexist in 30% of patients with Graves disease.⁵ Fetal hypothyroidism can also result from transplacental passage of antithyroid medication used to treat the mother. Fetal goiter can be seen in both fetal hyperthyroidism and hypothyroidism, and umbilical cord sampling is required to determine the exact etiology. Fetal hyperthyroidism can be suspected in the presence of a fetal neck mass, fetal tachycardia, or growth restriction.

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Both PTU and MMZ are acceptable choices to treat hyperthyroidism during pregnancy.

MANAGEMENT OF HYPERTHYROIDISM

The treatment of hyperthyroidism during pregnancy can reduce the risk of maternal, fetal, and neonatal complications.⁶ The goal is to achieve and maintain a euthyroid state, using the minimum amount of antithyroid medication. Treatment is warranted for a FT₄ level greater than 1.8 ng/dL.

In the United States, the 2 thioamide drugs available for treatment are propylthiouracil (PTU) and methimazole (MMZ). These medications decrease the synthesis of thyroid hormone by blocking the organification of iodide. PTU also inhibits peripheral conversion of T₄ to triiodothyronine (T₃). The data suggest these medications are equally effective in achieving euthyroidism without any difference in neonatal outcomes.^{7,8}

PTU tends to be the preferred drug, due to a possible association between MMZ and aplasia cutis, a congenital skin defect of the scalp at the parietal hair whorl. In addition, PTU has been thought to cross the placenta less readily. However, data comparing PTU to MMZ did not demonstrate any differences in placental transfer or the incidence of aplasia cutis.^{8,9}

An embryopathy specific to MMZ has been reported in mothers who used this medication during the first trimester of

TABLE 1. Signs/Symptoms of Thyroid Disease

Hypothyroidism	Hyperthyroidism
• Fatigue	• Heat intolerance
• Constipation	• Nervousness
• Somnolence	• Weight loss
• Cold intolerance	• Resting tremor
• Hair loss	• Palpitations
• Dry skin	• Diaphoresis
• Depression	• Warm, moist skin
• Decreased libido	• Tachycardia
• Weight gain despite poor appetite	• Increased appetite
• Periorbital puffiness	• Exophthalmia
• Hoarseness	

pregnancy. It consists of choanal and esophageal atresia, developmental delay, and minor dysmorphic features. As these anomalies have not been seen with maternal use of PTU, many recommend PTU as the preferred thioamide. According to the American Academy of Pediatrics, both medications are compatible with breastfeeding.¹⁰

The usual starting dose for PTU is 100 mg 3 times a day (range of 50-150 mg 3 times a day). On occasion, a dose as large as 600 mg/d may be necessary. MMZ has a longer half-life and can be administered less frequently. A typical dose for MMZ is 10 to 20 mg twice a day. As previously noted, thioamides can suppress fetal thyroid function, which can lead to fetal and neonatal hypothyroidism, and possibly fetal goiter. To minimize this risk, the FT₄ or FT₄ index should be maintained in the high normal (upper third) range using the lowest thioamide dose possible.

Once treatment is initiated, thyroid function tests (TSH and FT₄) should be measured every 2 to 4 weeks. Once a consistent euthyroid state is achieved, the dose of thioamide can be decreased. Improvement in the FT₄ level is usually seen within 4 weeks. Although normalization of TSH levels occurs in 6 to 8 weeks, TSH should not be used to assess therapy, as suppression may persist for months. Most women will need less PTU

in the third trimester, and some are able to discontinue treatment and remain euthyroid.

Minor maternal side effects of thioamide treatment occurring in 5% of patients include rash, nausea, anorexia, fever, and loss of taste or smell.¹¹ More serious side effects in 1% of patients include hepatitis, thrombocytopenia, and vasculitis. The most serious side effect is agranulocytosis, noted in 0.1% to 0.4% of women. Signs and symptoms appear acutely and include fever, sore throat, general malaise, and gingivitis. This complication is not dose-related, and serial leukocyte counts are not helpful. Discontinuation of therapy and checking a complete blood count are warranted if a patient with hyperthyroidism receiving thioamide treatment presents with a sore throat and/or fever. Baseline white blood cell and liver function tests are reasonable prior to the initiation of antithyroid therapy.

Beta-blockers can be used to treat symptoms of thyrotoxicosis until thioamides decrease thyroid hormone levels. The patient should be without palpitations, with a heart rate maintained at 80 to 90 bpm. Propranolol at a dose of 20 to 40 mg every 8 to 12 hours and atenolol 50 to 100 mg orally once a day

are 2 options. Thyroidectomy is rarely performed during pregnancy. It is usually reserved for patients unable to tolerate thioamide therapy, those with an allergy to both thioamides, large goiters, patient preference, and the rare case of drug resistance.

Thyroid ablation with radioactive ¹³¹Iodine is contraindicated during pregnancy, since it can destroy fetal thyroid tissue. At approximately 10 to 12 weeks' gestation, the fetal thyroid gland begins concentrating iodine. If exposure occurs after 10 weeks' gestation, termination of the pregnancy should be discussed, as fetal thyroid tissue will be ablated, leading to congenital hypothyroidism. Exposure prior to 10 weeks' should not affect the fetal thyroid gland.

Treatment with ¹³¹Iodine is a viable option for nonpregnant patients; however, a pregnancy test should always be performed prior to this procedure. Breastfeeding should be discontinued for 4 months after treatment. Pregnancy should be avoided for 4 to 6 months after radioablative therapy.

After a radioablation procedure, some patients remain euthyroid without the need for thyroid replacement, while others exhibit overt hypothyroidism and require medication. Importantly, neonates of women who

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When treating hyperthyroidism during pregnancy, the FT₄ level should be maintained at the upper limits of normal.

Coding for Hyperthyroidism

Philip N. Eskew Jr, MD

This article discusses another complication of pregnancy, hyperthyroidism, which requires the use of 2 different types of ICD-9 codes.

The first are those codes related to a complication of pregnancy:

- 648** Other current conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium
Use additional code(s) to identify the condition
Requires fifth digit

So, you would use the following and then add the appropriate fifth digit.

- 648.1** Thyroid dysfunction
[0-4] **0** unspecified as to episode of care or not applicable
1 delivered, with or without mention of antepartum condition
2 delivered, with mention of postpartum complication
3 antepartum condition or complication
4 postpartum condition or complication

Then you would use the appropriate code for the clinical condition, in this article, hyperthyroidism.

- 242.0** Toxic diffuse goiter (Basedow disease, Exophthalmic or toxic goiter, Graves disease)
242.3 Toxic nodular goiter, unspecified (Adenomatous or Nodular goiter, toxic or with hyperthyroidism)
245.1 Subacute thyroiditis

The ICD-9 code for thyroid storm is:

- 242.9** Thyrotoxicosis (Thyroid Storm) without mention of goiter or other cause

As mentioned in this article:

"Antepartum surveillance in the pregnant patient with hyperthyroidism includes an increased frequency of visits and watching for signs and symptoms of thyrotoxicosis."

Therefore, you should use the appropriate E & M code for each extra prenatal visit and use the appropriate ICD-9 codes to document the clinical condition that you are monitoring.

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TABLE 2. Treatment of Thyroid Storm During Pregnancy¹²

1. Admission to the intensive care unit for supportive therapy including fluids, correction of electrolyte abnormalities, oxygen as needed, and control of hyperpyrexia (acetaminophen).
2. Start propylthiouracil (PTU) immediately (even before any laboratory results are available), 600-800 mg, orally, followed by 150-200 mg orally every 4-6 hours. Use methimazole rectal suppositories if oral administration is not possible.
3. Start iodides 1-2 hours after PTU administration: saturated solution of potassium iodide, 2-5 drops orally every 8 hours, or sodium iodide, 0.5-1 g intravenously every 8 hours, or Lugol solution, 8 drops every 6 hours, or lithium carbonate, 300 mg orally every 6 hours.
4. Dexamethasone, 2 mg intravenously or intramuscularly every 6 hours for 4 doses.
5. Propranolol, 20-80 mg orally every 4-6 hours, or propranolol, 1-2 mg intravenously every 5 minutes for a total of 6 mg, then 1-10 mg intravenously every 4 hours. If the patient has a history of severe bronchospasm, use:
 - a. Reserpine, 1-5 mg intramuscularly every 4-6 hours
 - b. Guanethidine, 1 mg/kg orally every 12 hours
 - c. Diltiazem, 60 mg orally every 6-8 hours.
6. Phenobarbital, 30-60 mg every 6-8 hours as needed to control restlessness.
7. Once clinical improvement noted, may discontinue iodides and steroids.
8. Plasmapheresis or peritoneal dialysis to remove circulating thyroid hormone are extreme measures reserved for patients who do not respond to conventional therapy.

Adapted from ACOG Practice Bulletin Number 37.¹²

undergo radioactive thyroid ablation prior to pregnancy and don't require antithyroid medication may be at greater risk for neonatal Graves disease due to lack of the suppressive effect of antithyroid medication. After a thyroid ablation, the patient will no longer be at risk for thyroid storm.

Antepartum surveillance in the pregnant patient with hyperthyroidism includes an increased frequency of visits and watching for signs and symptoms of thyrotoxicosis. Serial ultrasounds every 4 weeks to assess fetal growth are appropriate, and weekly nonstress tests should be considered starting at 32 to 34 weeks, especially in the patient with uncontrolled symptoms. If there is evidence of fetal growth restriction, twice-weekly testing is recommended.

Routine ultrasound screening for fetal goiter is not recommended. However, in patients with high TSI ($\geq 200\%$ -500% normal), the risk of fetal goiter is increased, and ultrasound assessment is reasonable. A fetal goiter may result in hyperextension of the fetal neck, creating problems at delivery and possible compromise of the airway.

Ultrasound signs of fetal thyrotoxicosis include hydrops, tachycardia, and cardiomegaly. Maternal-fetal medicine consulta-

tion is recommended if fetal thyrotoxicosis and/or fetal goiter is identified. Due to the risk of neonatal thyroid dysfunction seen in mothers with any type of thyroid disease, the pediatrician should be made aware of the maternal diagnosis.

THYROID STORM

Thyroid storm is a medical emergency that occurs in 1% to 2% of pregnancies complicated by hyperthyroidism.¹² A delay in diagnosis can put the patient at risk for cardiovascular collapse and coma. It is usually seen in patients with poorly controlled disease in the setting of a precipitating factor such as surgery, infection, labor, or preeclampsia. Thyroid functions should be obtained to confirm the diagnosis (suppressed TSH, increased FT₄); however, treatment is based on clinical suspicion. Signs and symptoms include fever (sometimes $>103^{\circ}\text{F}$), palpitations, nausea, vomiting, diarrhea, mental status changes (eg, nervousness, restlessness, confusion, rarely seizures), and cardiac arrhythmia. Tachycardia out of proportion to the fever, with a pulse rate above 140 bpm, is not uncommon.

In the patient with thyroid storm, the goals of treatment are to reduce the synthesis and

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Patients with uncontrolled hyperthyroidism are at risk for thyroid storm.

release of thyroid hormone, remove thyroid hormone from the circulation, and treat the underlying cause. PTU will block synthesis and peripheral conversion of T_4 to T_3 . Iodides and steroids block the release of stored hormone from the thyroid gland (steroids also inhibit peripheral conversion of T_4 to T_3).

Of note, iodides initially increase the production of thyroid hormone, thus it is important to start PTU prior to administering iodides. Beta-blockers are effective in controlling tachycardia. If there is a history of severe bronchospasm, reserpine or guanethidine may be used. Phenobarbital is used to control restlessness and may enhance breakdown of thyroid hormone. Plasmapheresis may be used as an extreme measure to remove circulating thyroid hormone when there is an inadequate response to conventional therapy.

In addition to the above medications, supportive treatments should be started, in-

cluding oxygen, antipyretics (acetaminophen), use of a cooling blanket, and maintenance of adequate intravascular volume and electrolytes. Management in an intensive care unit setting is recommended. Occasionally, invasive central monitoring will be necessary. Depending on the gestational age, fetal well-being should be assessed. Delivery should be avoided unless fetal indications for delivery outweigh maternal risks. Table 2 summarizes the treatment of thyroid storm.

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