ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 223   *(Replaces Practice Bulletin Number 148, April 2015)*

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Thyroid Disease in Pregnancy

Both thyrotoxicosis and hypothyroidism are associated with adverse pregnancy outcomes. There also is concern about the effect of overt maternal thyroid disease on fetal development. In addition, medications that affect the maternal thyroid gland can cross the placenta and affect the fetal thyroid gland. This document reviews the thyroid-related pathophysiologic changes that occur during pregnancy and the effects of overt and subclinical maternal thyroid disease on maternal and fetal outcomes. This Practice Bulletin has been updated with information on the diagnosis and the management of thyroid disease in pregnant women and includes a new clinical algorithm on management of thyroid disease in pregnancy.

Background

Changes in Thyroid Function During Pregnancy

Physiologic thyroid changes during pregnancy are considerable and can be confused with maternal thyroid abnormalities. Maternal thyroid volume increases anywhere from 10% to 30% during the third trimester and is attributable to increases in extracellular fluid and blood volume during pregnancy (1). In addition, there are changes to thyroid hormone levels and thyroid function throughout pregnancy. Table 1 depicts how thyroid function test results change in normal pregnancy and in overt and subclinical thyroid disease. First, maternal total or bound thyroid hormone levels increase with serum concentration of thyroid-binding globulin. Second, the level of thyrotropin (also known as thyroid-stimulating hormone [TSH]), which plays a central role in screening for and diagnosis of many thyroid disorders, decreases in early pregnancy because of weak stimulation of TSH receptors caused by substantial quantities of human chorionic gonadotropin (hCG) during the first 12 weeks of gestation. Thyroid hormone secretion is thus stimulated, and the resulting increased serum free thyroxine (T_4) levels suppress hypothalamic thyrotropin-releasing

hormone, which in turn limits pituitary TSH secretion. After the first trimester, TSH levels return to baseline values and progressively increase in the third trimester related to placental growth and production of placental deiodinase (2). These physiologic changes should be considered when interpreting thyroid function test results (Table 1) during pregnancy.

Thyroid Function Tests in Pregnancy

Ideally, reference ranges for thyroid function in pregnancy are established locally at the population level in pregnant women without thyroid disease. The American Thyroid Association recommends that when local reference ranges are not available, the lower reference range for TSH can be reduced by 0.4 milliunits/L and the upper reference range for TSH can be reduced by 0.5 milliunits/L in the late first trimester of pregnancy (3). Beyond the first trimester, TSH normalizes towards the nonpregnant reference ranges (3), and nonpregnant reference ranges can be used. Reference ranges for total T_4 and total T_3 also should be adjusted for pregnancy. The upper reference range limits for total T_4 and total T_3 can be increased by approximately 50% after 16 weeks of gestation (3, 4). Before 16 weeks of gestation, there is a gradual increase in total T_4 and total T_3 compared with

Table 1. Changes in Thyroid Function Test Results in Thyroid Disease

Maternal Status	TSH*	Free T$_4$
Overt hyperthyroidism	Decrease	Increase
Subclinical hyperthyroidism	Decrease	No change
Overt hypothyroidism	Increase	Decrease
Subclinical hypothyroidism	Increase	No change

Abbreviations: T$_4$, thyroxine; TSH, thyroid-stimulating hormone.

*The level of TSH decreases in early pregnancy because of weak TSH receptor stimulation due to substantial quantities of human chorionic gonadotropin during the first 12 weeks of gestation. After the first trimester, TSH levels return to baseline values.

nonpregnant adults. These adjustments to total T$_4$ and total T$_3$ reference ranges are necessary to account for the increase in thyroid-binding globulin in pregnancy (3).

Fetal Thyroid Function

The fetal thyroid gland begins concentrating iodine and synthesizing thyroid hormone by approximately 12 weeks of gestation (5, 6). That said, maternal T$_4$ is transferred to the fetus throughout the entire pregnancy and is important for normal fetal brain development, especially before the fetal thyroid gland begins functioning (7). Approximately 30% of T$_4$ in umbilical cord serum at delivery is maternal in origin (8). A history of maternal thyroid disorder, and in particular the use of propylthiouracil or methimazole during pregnancy, or a history of known maternal thyroid receptor antibodies should be communicated to the neonatologist or pediatrician who will care for the infant after birth because these medications and antibodies can affect neonatal thyroid function.

Hyperthyroidism

Overt hyperthyroidism is characterized by a decreased TSH level and an increased free T$_4$ level (Table 1). Hyperthyroidism occurs in 0.2–0.7% of pregnancies, and Graves disease accounts for 95% of these cases (9, 10). The signs and symptoms of hyperthyroidism include nervousness, tremors, tachycardia, frequent stools, excessive sweating, heat intolerance, weight loss, goiter, insomnia, palpitations, and hypertension. Distinctive features of Graves disease are ophthalmopathy (signs include lid lag and lid retraction) and dermopathy (signs include localized or pretibial myxedema). Although some symptoms of hyperthyroidism are similar to normal symptoms of pregnancy or some nonthyroid-associated diseases, the results of serum thyroid function tests differentiate thyroid disease from these other possibilities. Inadequately treated maternal thyrotoxicosis is associated

with a greater risk of preeclampsia with severe features, maternal heart failure, and thyroid storm than treated, controlled maternal thyrotoxicosis (11–14).

Fetal and Neonatal Effects

Pregnancy outcomes generally depend on whether metabolic control is achieved before and during pregnancy (15). Inadequately treated hyperthyroidism is associated with an increase in medically indicated preterm deliveries, low birth weight, miscarriage, and stillbirth (11, 12, 16, 17). Fetal and neonatal risks associated with Graves disease are related either to the disease itself or to thioamide (propylthiouracil or methimazole) treatment of the disease. Because of the persistence of maternal antibodies, the possibility of fetal thyrotoxicosis should be considered in all women with a history of Graves disease (9). Fetal thyrotoxicosis typically manifests as fetal tachycardia and poor fetal growth. If fetal thyrotoxicosis is suspected, consultation with a clinician with expertise in such conditions is warranted.

Because a large proportion of thyroid disease in women is mediated by antibodies that cross the placenta, there is a concern about the risk of development of immune-mediated hypothyroidism and hyperthyroidism in the neonate. Pregnant women with Graves disease can have thyroid-stimulating immunoglobulin and TSH-binding inhibitory immunoglobulins (also known as thyrotropin-binding inhibitory immunoglobulins) that can stimulate or inhibit the fetal thyroid, respectively. In some cases, maternal TSH-binding inhibitory immunoglobulins may cause transient hypothyroidism in neonates of women with Graves disease (18, 19). Also, 1–5% of these neonates have hyperthyroidism or neonatal Graves disease caused by the transplacental passage of maternal thyroid-stimulating immunoglobulin (20, 21). In neonates, maternal antibodies are cleared less rapidly than thioamides, which sometimes results in delayed presentation of neonatal Graves disease (21). Therefore, the pediatrician should be notified of maternal Graves disease at the time of delivery, and the neonate should be followed for potential development of Graves disease (21). The incidence of neonatal Graves disease is unrelated to current maternal thyroid function. The neonates of women with Graves disease who have been treated surgically or with radioactive iodine-131 before pregnancy, and whose mothers required no thioamide treatment, still may have circulating antibodies, and therefore remain at risk of neonatal Graves disease and should be monitored accordingly (3).

Subclinical Hyperthyroidism

Subclinical hyperthyroidism, reported in 0.8–1.7% of pregnant women (22, 23), is characterized by an abnormally low serum TSH concentration with free T$_4$ levels

within the normal reference range (24) (Table 1). Importantly, it has not been associated with adverse pregnancy outcomes (22, 25, 26). Treatment of pregnant women with subclinical hyperthyroidism is not recommended because there is no demonstrated benefit to the mother or fetus. In addition, there are theoretical risks to the fetus because antithyroid medications cross the placenta and may adversely affect fetal thyroid function.

Hypothyroidism

Overt hypothyroidism complicates 2–10 per 1,000 pregnancies (10). Hypothyroidism is diagnosed based on laboratory values with a TSH above the upper limit of normal and a free T_4 below the lower limit of normal (Table 1). Hypothyroidism can present with nonspecific clinical findings that may be indistinguishable from common signs or symptoms of pregnancy, such as fatigue, constipation, cold intolerance, muscle cramps, and weight gain. Other clinical findings include edema, dry skin, hair loss, and a prolonged relaxation phase of deep tendon reflexes. Goiter may or may not be present and is more likely to occur in women who have Hashimoto thyroiditis (also known as Hashimoto disease) or who live in areas of endemic iodine deficiency. Hashimoto thyroiditis is the most common cause of hypothyroidism in pregnancy and is characterized by glandular destruction by autoantibodies, particularly antithyroid peroxidase antibodies.

Adequate maternal iodine intake is needed for maternal and fetal synthesis of T_4. The majority of women living in the United States have sufficient iodine intake (3). However, women of reproductive age are at higher risk than other women of low iodine levels. The recommended daily dietary intake of iodine is 220 micrograms for pregnant women and 290 micrograms for lactating women (27). The benefits of routine iodine supplementation during pregnancy, especially in women living in areas of mild iodine deficiency, have not been clearly established (28, 29). It should be noted that iodine is not always included in supplemental multivitamins, including prenatal vitamins. In addition, not all salts on the market are iodized.

Adverse perinatal outcomes such as spontaneous abortion, preeclampsia, preterm birth, abruptio placentae, and stillbirth are associated with untreated overt hypothyroidism (30, 31). Adequate thyroid hormone replacement therapy during pregnancy in women with overt hypothyroidism minimizes the risk of adverse outcomes (32, 33).

Fetal and Neonatal Effects

Overt, untreated maternal hypothyroidism has been associated with an increased risk of low birth weight and impaired neuropsychologic development of the offspring (25, 31). However, it is rare for maternal thyroid inhibitory antibodies to cross the placenta and cause fetal hypothyroidism. The prevalence of fetal hypothyroidism in the offspring of women with Hashimoto thyroiditis is estimated to be only 1 in 180,000 neonates (34).

Subclinical Hypothyroidism

Subclinical hypothyroidism is defined as an elevated serum TSH level in the presence of a normal free T_4 level (24) (Table 1). The prevalence of subclinical hypothyroidism in pregnancy has been estimated to be 2–5% (10, 35–37). Subclinical hypothyroidism is unlikely to progress to overt hypothyroidism during pregnancy in otherwise healthy women.

Interest in subclinical hypothyroidism in pregnancy was heightened by two observational studies suggesting that undiagnosed maternal thyroid hypofunction might be associated with impaired neurodevelopment in offspring (38, 39). However, a large randomized controlled trial published in 2012, the Controlled Antenatal Thyroid Screening (known as CATS) trial, and the Maternal–Fetal Medicine Units Network's Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy published in 2017 demonstrated no difference in neurocognitive development in offspring through age 5 years who were born to women screened and treated for subclinical hypothyroidism (40, 41). Moreover, follow-up of children from the CATS study through age 9 years confirmed that there was no neurodevelopmental improvement in offspring of treated women (42). In some studies, maternal subclinical hypothyroidism has been shown to be associated with higher incidences of preterm birth, abruptio placentae, admission of infants to the intensive care nursery, preeclampsia with severe features, and gestational diabetes (25, 26, 35, 43). However, other studies have not identified a link between maternal subclinical hypothyroidism and these adverse obstetric outcomes (17, 36, 44). Currently, there is no evidence that identification and treatment of subclinical hypothyroidism during pregnancy improves these outcomes (40–42, 45).

Clinical Considerations and Recommendations

▶ *Which pregnant patients should be screened for thyroid disease?*

Universal screening for thyroid disease in pregnancy is not recommended because identification and treatment of

maternal subclinical hypothyroidism has not been shown to result in improved pregnancy outcomes and neurocognitive function in offspring. Indicated testing of thyroid function should be performed in women with a personal or family history of thyroid disease, type 1 diabetes mellitus, or clinical suspicion of thyroid disease. The performance of thyroid function studies in asymptomatic pregnant women who have a mildly enlarged thyroid is not warranted because up to a 30% enlargement of the thyroid gland is typical during pregnancy (46). In a pregnant woman with a significant goiter or with distinct thyroid nodules, thyroid function studies are appropriate, because these physical examination findings would be considered outside the acceptable range of normal for pregnancy.

The results of the CATS study and the 2017 Maternal–Fetal Medicine Units Network's Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy trial demonstrate that screening and treatment of women with subclinical hypothyroidism during pregnancy does not improve the cognitive function of their children at age 3 years and 5 years, respectively (40, 41). Therefore, the American College of Obstetricians and Gynecologists, the Endocrine Society, and the American Association of Clinical Endocrinologists recommend against universal screening for thyroid disease in pregnancy and recommend testing during pregnancy only for women who are at increased risk of overt hypothyroidism (47, 48). The American Thyroid Association currently finds that there are insufficient data to recommend for or against universal thyroid screening (3).

▶ *What laboratory tests are used to diagnose thyroid disease during pregnancy?*

Levels of TSH and thyroid hormone are both used to diagnose thyroid disease in pregnancy (Fig. 1). If indicated, the first-line screening test to assess thyroid status should be measurement of the TSH level. Assuming normal hypothalamic–pituitary function, an inverse log-linear relationship exists between serum TSH and serum thyroid hormone, such that small alterations in circulating hormone levels will produce large changes in TSH. Furthermore, because the free hormone assays used by most clinical laboratories do not use physical separation techniques, such as equilibrium dialysis, test results depend on individual binding protein levels and represent only estimates of actual circulating free T_4 concentrations. Therefore, TSH is the most reliable indicator of thyroid status because it indirectly reflects thyroid hormone levels as sensed by the pituitary gland. When the TSH level is abnormally high or low, a follow-up study

to measure the free T_4 level should be performed to determine if there is overt thyroid dysfunction. In cases of suspected hyperthyroidism, total T_3 also is measured (Fig. 1). Total T_3 is used preferentially over free T_3 because assays for estimating free T_3 are less robust than those measuring free T_4 (4). The level of free T_4 should be monitored in pregnant women being treated for hyperthyroidism, and the dose of antithyroid drug (thioamide) should be adjusted accordingly to achieve a free T_4 at the upper end of the normal pregnancy range. Among women who also have T_3 thyrotoxicosis, total T_3 should be monitored with a goal level at the upper end of normal pregnancy range.

▶ *What medications should be used to treat overt hyperthyroidism in pregnancy, and how should they be administered and adjusted during pregnancy?*

Pregnant women with overt hyperthyroidism should be treated with antithyroid drugs (thioamides). Either propylthiouracil or methimazole, both thioamides, can be used to treat pregnant women with overt hyperthyroidism. The choice of medication is dependent on trimester of pregnancy, response to prior therapy, and whether the thyrotoxicosis is predominantly T_4 or T_3. Women should be counseled about the risks and benefits of the two thioamides described below using shared decision making to develop an appropriate treatment plan.

Methimazole typically is avoided in the first trimester because it has been associated with a rare embryopathy characterized by esophageal or choanal atresia as well as aplasia cutis, a congenital skin defect (49). In a 2012 review of 5,967 live births to women with known Graves disease, there was a twofold increased risk of major fetal malformations reported in those who were exposed to methimazole compared with those exposed to propylthiouracil (49). Specifically, seven of nine cases of aplasia cutis, and the only case of esophageal atresia, occurred in methimazole-exposed infants. Therefore, propylthiouracil generally is prescribed for control of hyperthyroidism in the first trimester.

After the first trimester, either methimazole or propylthiouracil can be used for treatment of hyperthyroidism. In rare cases, propylthiouracil results in clinically significant hepatotoxicity (4), which has prompted some health care professionals to transition to methimazole after the first trimester. However, a transition from propylthiouracil to methimazole may result in a period of poor control of hyperthyroidism. Both medications have known adverse effects that must be weighed against each other and discussed with the patient (4). As such, some women are maintained on propylthiouracil throughout the
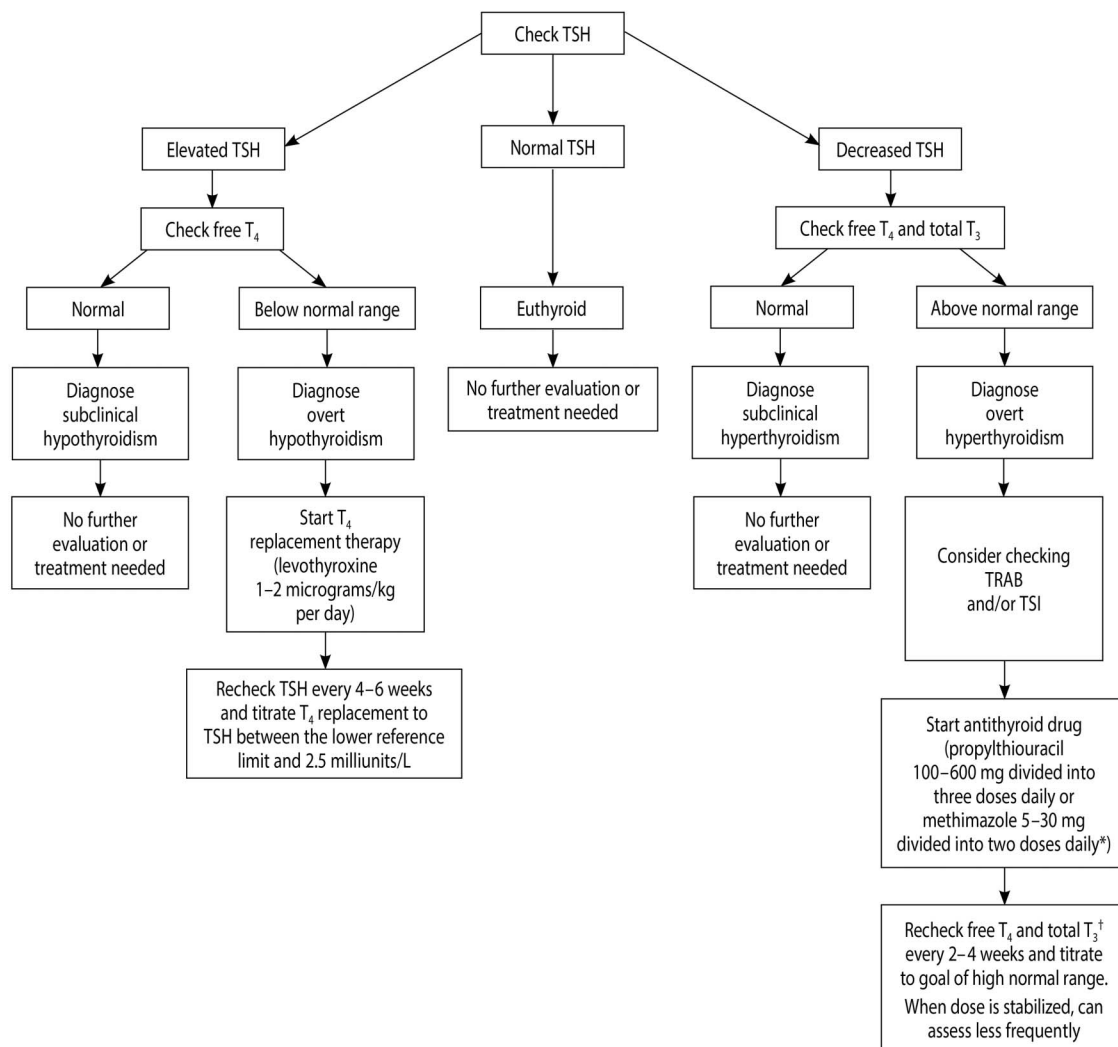
Figure 1. Clinical Algorithm for Management of Thyroid Disease in Pregnancy. Abbreviations: T_3, triiodothyronine; T_4, thyroxine; TRAB, thyroid receptor antibodies; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin. *Propylthiouracil should be used in the first trimester because methimazole has been associated with birth defects. Propranolol can be started at 10–40 mg every 6–8 hours for women with symptomatic palpitations or other hypermetabolic symptoms. †Total T_3 normal range in pregnancy is 1.5 times the nonpregnant normal range.

pregnancy. In addition, propylthiouracil decreases T_4 to T_3 conversion and is used preferentially for T_3-predominant thyrotoxicosis (4). Decision making regarding whether and how to transition from one agent to another often occurs in conjunction with endocrinology or maternal–fetal medicine subspecialists. If a switch is deemed appropriate, a dose ratio of 20:1 propylthiouracil to methimazole is recommended (Fig. 1).

Transient leukopenia occurs in up to 10% of pregnant women who take thioamide drugs, but this situation does not require therapy cessation. In less than 1% of patients who take thioamide drugs, however, agranulocytosis develops suddenly and mandates discontinuation of the drugs. The development of agranulocytosis is not related to dosage, and

because of its acute onset, serial leukocyte counts during therapy are not helpful. Thus, if fever or sore throat develops, women are instructed to discontinue use of the medication immediately and report for a complete blood count (50).

The initial thioamide dosing is empirical. If propylthiouracil is selected, an oral dosage of 100–600 mg daily, divided into three doses, may be initiated, depending on clinical severity (3). A typical dose in the average patient is 200-400 mg daily. If methimazole is used, an initial daily dosage of 5–30 mg orally, divided into two doses, is recommended (although the frequency may be reduced to one daily dose as maintenance therapy is established). The goal is treatment with the lowest possible thioamide dose to maintain free T_4 levels

slightly above or in the high-normal range, regardless of TSH levels (3). In women with predominantly T_3 thyrotoxicosis, total T_3 should be monitored.

Beta-blockers can be used as adjunctive therapy for symptomatic palpitations. Propranolol is the preferred agent in pregnancy and is initiated at 10–40 mg taken three to four times daily (4).

▶ *What medications should be used to treat overt hypothyroidism in pregnancy, and how should they be administered and adjusted during pregnancy?*

Pregnant women with overt hypothyroidism should be treated with adequate thyroid hormone replacement to minimize the risk of adverse outcomes. For the treatment of overt hypothyroidism in pregnancy, the American Thyroid Association and the American Association of Clinical Endocrinologists recommend T_4 replacement therapy, beginning with levothyroxine in dosages of 1–2 micrograms/kg daily or approximately 100 micrograms daily (3, 30). Pregnant women who have no thyroid function after thyroidectomy or radioiodine therapy may require higher dosages. T_3-containing preparations (eg, desiccated thyroid extract or synthetic T_3) of thyroid hormone should be avoided in pregnancy as high levels of T_3 compared to T_4 in these preparations leads to supraphysiologic levels of maternal T_3 and low levels of T_4. Maternal T_4 is critical for fetal central nervous system development (3).

Unlike in pregnant women with hyperthyroidism, assessment of therapy in pregnant women with hypothyroidism is guided by measurement of TSH levels rather than free T_4 levels. The TSH level should be monitored in pregnant women being treated for hypothyroidism, and the dose of levothyroxine should be adjusted accordingly with a goal TSH level between the lower limit of the reference range and 2.5 milliunits/L. Thyroid-stimulating hormone typically is evaluated every 4–6 weeks while adjusting medications (3, 46).

Pregnancy is associated with an increasing T_4 requirement in approximately one third of women receiving thyroid hormone supplementation (51, 52). This increased demand is believed to be related to increased estrogen production (53). Anticipatory 25% increases in T_4 replacement at pregnancy confirmation can be considered for women receiving treatment for known hypothyroidism at the time of presentation to prenatal care.

▶ *Is there a role for screening or testing for thyroid autoantibodies in pregnancy?*

Measurement of antithyroid antibodies in situations of overt and subclinical thyroid dysfunction has been proposed. Autoantibodies to thyroid peroxidase and thyroglobulin have been identified in up to 20% of reproductive-age women (54). Women with thyroid peroxidase antibodies are at increased risk for progression of thyroid disease and development of postpartum thyroiditis (55). However, most who test positive for these antibodies are otherwise euthyroid.

Routine testing for antithyroid peroxidase antibodies in women who are euthyroid (eg, no history of thyroid disease and normal thyroid function tests) is not recommended because thyroid hormone replacement for antithyroid peroxidase antibodies alone has not been found to improve pregnancy outcomes. In an individual patient data systematic analysis including 47,045 pregnant women, thyroid peroxidase antibody status remained significantly associated with preterm birth after adjustment for subclinical hypothyroidism (43). However, in two subsequent trials, levothyroxine therapy, when compared with either no treatment or placebo, did not reduce the rate of preterm birth or improve other outcomes in thyroid peroxidase antibody-positive euthyroid women (56, 57). Similarly, there were no interactions between thyroid peroxidase antibody status and treatment group in the 2017 Maternal–Fetal Medicine Units Network's Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy, which showed no difference in neurocognitive development in offspring or pregnancy outcomes in women treated with levothyroxine (41).

Identification of thyroid antibodies including thyroid receptor antibodies and thyroid stimulating immunoglobulin in women with Graves disease may establish those at an increased risk for fetal or neonatal hyperthyroidism (3). Identification of these antibodies may result in increased fetal surveillance with serial growth assessments by ultrasonography or antenatal fetal surveillance. Some clinicians may use antibody status to guide frequency of assessment of the fetus in women with hyperthyroidism, whereas others may opt to serially assess regardless of antibody status. As such, testing may not influence management and there is not strong evidence for routine assessment for these antibodies. In cases of hyperthyroidism in pregnancy, consultation with maternal–fetal medicine subspecialists may be helpful for creation of a testing and management plan.

▶ *What changes in thyroid function occur with hyperemesis gravidarum, and should thyroid function tests be performed routinely in women with hyperemesis gravidarum?*

Transient biochemical features of hyperthyroidism may be observed in 3–11% of women in early pregnancy (58, 59). Many women with hyperemesis gravidarum have abnormally high serum T_4 levels and low TSH levels. In a 2014

systematic review of markers for hyperemesis gravidarum, two thirds of 34 published studies that analyzed thyroid function revealed a decreased TSH level or an increased free T_4 level in symptomatic women when compared with women without symptoms of hyperemesis (60). These thyroid function abnormalities result from TSH receptor stimulation from high concentrations of hCG.

This physiologic hyperthyroidism, also known as gestational transient hyperthyroidism, may be associated with a multiple gestation or a molar pregnancy. Women with gestational transient hyperthyroidism are rarely symptomatic, and treatment with thioamide drugs has not been shown to be beneficial (30) and, therefore, is not recommended. Furthermore, gestational transient hyperthyroidism has not been associated with poor pregnancy outcomes (59). Expectant management of women with hyperemesis gravidarum and abnormal thyroid function test results usually leads to a decrease in serum free T_4 levels in parallel with a decrease in hCG levels after the first trimester. However, levels of TSH may remain suppressed for several weeks after free T_4 returns to normal levels (37). Therefore, measurements of thyroid function are not recommended in patients with hyperemesis gravidarum unless other signs of overt hyperthyroidism are evident.

▶ *How are thyroid storm and thyrotoxic heart failure diagnosed and treated in pregnancy?*

Thyroid storm and thyrotoxic heart failure are rare, acute, and life-threatening conditions in pregnancy. Thyroid storm in pregnancy carries a high risk of maternal heart failure (61). Thyroid storm is a hypermetabolic state caused by an excess of thyroid hormone. It is a clinical diagnosis in the setting of severe thyrotoxicosis accompanied by systemic decompensation (4). Clinical scoring systems such as the Burch-Wartofsky Point Scale can be used to confirm the diagnosis and evaluate the severity of disease. Thyroid storm typically manifests clinically as a combination of the following signs and symptoms: fever, tachycardia, cardiac dysrhythmia, and central nervous system dysfunction (4).

Heart failure and pulmonary hypertension from cardiomyopathy caused by the myocardial effects of excessive T_4 are more common in pregnancy than thyroid storm and have been identified in 9% of pregnant women with uncontrolled hyperthyroidism (61). Decompensation usually is precipitated by preeclampsia, anemia, sepsis, or a combination of these conditions. Frequently, T_4-induced cardiomyopathy and pulmonary hypertension are reversible (61–63).

If thyroid storm or thyrotoxic heart failure is suspected, serum free T_4, total T_3, and TSH levels should be evaluated to confirm the diagnosis, but therapy should not be withheld pending the results. Treatment is similar for thyroid storm and thyrotoxic heart failure in pregnancy and should be carried out in an intensive care area that may include special-care units within a labor and delivery unit (Box 1).

Coincident with treating thyroid storm, the perceived underlying cause (eg, infection, trauma) also should be treated. It is also important to note that even if fetal status is not reassuring in the acute setting of thyroid storm, that status may improve as maternal status is stabilized. In general, it is prudent to avoid delivery in the presence of thyroid storm.

▶ *How is thyroid function in the fetus evaluated?*

A history of maternal hyperthyroidism can lead to fetal thyrotoxicosis regardless of the current maternal thyroid

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Box 1. Medical Management of Thyroid Storm or Thyrotoxic Heart Failure in Pregnancy

- Inhibit thyroid release of T_3 and T_4

  Propylthiouracil, 1,000 mg load by mouth, then 200 mg by mouth every 6 hours

    Iodine administration 1–2 hours after propylthiouracil by

  – sodium iodide, 500–1,000 mg IV every 8 hours

    or

  – potassium iodide, five drops by mouth every 8 hours

    or

  – Lugol solution, 10 drops by mouth every 8 hours

    or

  – lithium carbonate (if patient has an iodine anaphylaxis history), 300 mg by mouth every 6 hours

- Further block peripheral conversion of T_4 to T_3

  Dexamethasone, 2 mg IV every 6 hours for four doses

    or

  Hydrocortisone, 100 mg IV every 8 hours for three doses

- Propranolol, labetalol, and esmolol have all been used successfully to control tachycardia. However, caution must be exercised if using a β-blocking drug in the presence of heart failure.

- Supportive measures, such as temperature control, as needed

Abbreviations: IV, intravenous; T_3, triiodothyronine; T_4, thyroxine.

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status. Therefore, a diagnosis of fetal thyrotoxicosis should be considered in cases of maternal hyperthyroidism complicated by fetal hydrops, growth restriction, fetal goiter, or persistent fetal tachycardia (64). In cases in which fetal thyrotoxicosis is suspected, consultation with a maternal–fetal medicine subspecialist is recommended (64). Routine evaluation of fetal thyroid function by ultrasonography to assess for goiter or through umbilical cord blood sampling is not recommended (65, 66). Umbilical cord blood sampling should only be used in the rare circumstances when the diagnosis of fetal thyroid disease cannot be reasonably excluded based on noninvasive fetal evaluation with ultrasonography and antenatal surveillance (3, 47).

▶ How should a thyroid nodule or thyroid cancer during pregnancy be assessed?

Thyroid nodules are found in 1–2% of reproductive-aged women and prevalence increases with increasing age (37). Management of a palpable thyroid nodule during pregnancy depends on risk stratification that includes factors such as gestational age and size of the mass. Thus, a pregnant woman with a thyroid nodule should have a complete history and physical examination, serum TSH testing, and ultrasonography of the neck. Ultrasonographic examination reliably detects nodules larger than 0.5 cm. It is estimated that 90–95% of solitary thyroid nodules are benign (67, 68). Ultrasonographic characteristics associated with malignancy include hypoechoic pattern, irregular margins, and microcalcifications (69). When all three characteristics are present, these features correlate with a malignancy risk exceeding 70% (3). If ultrasonographic test results are suspicious for malignancy, fine-needle aspiration can be used for histologic examination, including tumor markers and immunostaining to evaluate for malignancy (67, 70). Radioiodine scanning in pregnancy is not recommended because of the theoretic risk associated with fetal irradiation. However, if there has been inadvertent administration of radioiodine before 12 weeks of gestation, the American Thyroid Association has noted that the fetal thyroid gland, which does not become significantly functionally active until approximately 12 weeks of gestation, does not appear to be at risk of damage (3).

Evaluation of thyroid cancer in pregnancy involves a multidisciplinary approach. Most cases of thyroid carcinoma are well differentiated and follow an indolent course. The possibility that thyroid cancer is part of a hereditary familial cancer syndrome is unlikely but should be considered. When thyroid malignancy is diagnosed during the first or second trimester, thyroidectomy may be performed before the third trimester, but concern regarding inadvertent removal of parathyroid glands often leads to the choice to delay surgery until after delivery. In women without evidence of an aggressive thyroid cancer or women in whom thyroid cancer is diagnosed in the third trimester, surgical treatment can be deferred to the immediate postpartum period (3, 69).

▶ How is postpartum thyroiditis diagnosed and treated?

Postpartum thyroiditis is defined as thyroid dysfunction within 12 months of delivery that can include clinical evidence of hyperthyroidism, hypothyroidism, or both. Transient autoimmune thyroiditis is found in approximately 5–10% of women during the first year after childbirth (55, 71). The propensity for postpartum thyroiditis antedates pregnancy and is directly related to increasing serum levels of thyroid autoantibodies (55). In clinical practice, postpartum thyroiditis is diagnosed infrequently because typically it develops months after delivery and causes vague and nonspecific symptoms (72).

The clinical presentation of postpartum thyroiditis varies. Classically, there are two recognized clinical phases that may develop in succession. New-onset abnormal levels of TSH and free T_4 confirm the diagnosis of either phase. Typically, the first phase is characterized by destruction-induced thyrotoxicosis, with symptoms caused by excessive release of thyroid hormone from glandular disruption. The onset is abrupt, and a small, painless goiter commonly is found. Postpartum thyroiditis may give rise to hyperthyroid symptoms of fatigue, irritability, weight loss, palpitations, or heat intolerance (73). This thyrotoxic phase usually lasts only a few months and affected women often are only mildly symptomatic. Treatment with thioamides generally is ineffective, but if symptoms are severe enough, a β-blocking drug may be helpful. The usual second phase is overt hypothyroidism that occurs between 4 and 8 months postpartum, and thyromegaly as well as hypothyroid symptoms of fatigue, constipation, or depression are common (73). In cases of postpartum depression, as with any new diagnosis of depression, a screening TSH to rule out a diagnosis of thyroid dysfunction is reasonable (74).

In most women with postpartum thyroiditis, the condition will resolve spontaneously. Nevertheless, approximately one third of women with either type of postpartum thyroiditis eventually develop permanent, overt hypothyroidism and the annual progression rate is 3.6% (71, 73, 75–77). These cases should be managed in collaboration with the appropriate specialist, and the American Thyroid Association recommends periodic thyroid testing to evaluate for overt hypothyroidism (3). The risk of postpartum thyroiditis and the risk of developing permanent hypothyroidism are increased in women with thyroid autoantibodies, particularly women with higher antibody titers.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

▶ Universal screening for thyroid disease in pregnancy is not recommended because identification and treatment of maternal subclinical hypothyroidism has not been shown to result in improved pregnancy outcomes and neurocognitive function in offspring.

▶ If indicated, the first-line screening test to assess thyroid status should be measurement of the TSH level.

▶ The TSH level should be monitored in pregnant women being treated for hypothyroidism, and the dose of levothyroxine should be adjusted accordingly with a goal TSH level between the lower limit of the reference range and 2.5 milliunits/L. Thyroid-stimulating hormone typically is evaluated every 4–6 weeks while adjusting medications.

▶ Pregnant women with overt hypothyroidism should be treated with adequate thyroid hormone replacement to minimize the risk of adverse outcomes.

▶ The level of free T_4 should be monitored in pregnant women being treated for hyperthyroidism, and the dose of antithyroid drug (thioamide) should be adjusted accordingly to achieve a free T_4 at the upper end of the normal pregnancy range. Among women who also have T_3 thyrotoxicosis, total T_3 should be monitored with a goal level at the upper end of normal pregnancy range.

▶ Pregnant women with overt hyperthyroidism should be treated with antithyroid drugs (thioamides).

The following recommendation is based on limited or inconsistent scientific evidence (Level B):

▶ Either propylthiouracil or methimazole, both thioamides, can be used to treat pregnant women with overt hyperthyroidism. The choice of medication is dependent on trimester of pregnancy, response to prior therapy, and whether the thyrotoxicosis is predominantly T_4 or T_3.

The following recommendations are based primarily on consensus and expert opinion (Level C):

▶ Indicated testing of thyroid function should be performed in women with a personal or family history of thyroid disease, type 1 diabetes mellitus, or clinical suspicion of thyroid disease.

▶ Measurements of thyroid function are not recommended in patients with hyperemesis gravidarum unless other signs of overt hyperthyroidism are evident.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 – January 2020. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I   Evidence obtained from at least one properly designed randomized controlled trial.
II-1   Evidence obtained from well-designed controlled trials without randomization.
II-2   Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3   Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III   Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.