Overview of thyroid disease and pregnancy

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Literature review current through: **Sep 2023.**
This topic last updated: **Mar 23, 2023.**

INTRODUCTION

The evaluation and treatment of pregnant women with thyroid disease parallel that of nonpregnant individuals but present some unique problems. An overview of thyroid physiology and disease during pregnancy is presented here. Some of the disorders reviewed below are discussed separately in individual topic reviews:

- (See "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment".)
- (See "Hyperthyroidism during pregnancy: Clinical manifestations, diagnosis, and causes".)
- (See "Hyperthyroidism during pregnancy: Treatment".)
- (See "Postpartum thyroiditis".)

THYROID ADAPTATION DURING NORMAL PREGNANCY

The diagnosis of thyroid disease during pregnancy requires an understanding of the changes in thyroid physiology and thyroid function tests that accompany normal pregnancy.

Thyroid physiology — To meet the increased metabolic needs during a normal pregnancy, there are changes in thyroid physiology that are reflected in altered thyroid function tests [1]. The major changes in thyroid function during pregnancy are:

- An increase in serum thyroxine-binding globulin (TBG)
- Stimulation of the thyrotropin (thyroid-stimulating hormone [TSH]) receptor by human chorionic gonadotropin (hCG)

Thyroxine-binding globulin — During pregnancy, serum TBG concentrations rise almost twofold because estrogen increases TBG production and TBG sialylation, which results in decreased clearance of TBG [2]. To maintain adequate free thyroid hormone concentrations during this period, thyroxine (T4) and triiodothyronine (T3) production by the thyroid gland must increase. The TBG excess leads to an increase in both serum total, but not free, T4 and T3 concentrations. Levels of total T4 and T3 rise by approximately 50 percent during the first half of pregnancy, plateauing at approximately 20 weeks of gestation, at which time a new steady state is reached and the overall production rate of thyroid hormones returns to prepregnancy rates. (See "Euthyroid hyperthyroxinemia and hypothyroxinemia".)

hCG and thyroid function — Human chorionic gonadotropin (hCG) is one of a family of glycoprotein hormones, including TSH, with a common alpha subunit and a unique beta subunit. However, there is considerable homology between the beta subunits of hCG and TSH. As a result, hCG has weak thyroid-stimulating activity [3]. In a human thyroid cell culture assay, as an example, 1 microU of hCG was equivalent to 0.0013 microU of TSH [4].

Serum hCG concentrations increase soon after fertilization and peak at 10 to 12 weeks. During this peak, total serum T4 and T3 concentrations increase. Serum free T4 and T3 concentrations increase slightly, usually within the normal range, and serum TSH concentrations are appropriately reduced [3]. However, in 10 to 20 percent of normal women, serum TSH concentrations are transiently low or undetectable [5-7]. In a report of 63 women with extremely high hCG concentrations (>200,000 international units/L), TSH was <0.2 microU/mL in 67 percent of samples, and free T4 was above 1.8 ng/dL in 32 percent of samples. All women whose hCG was greater than 400,000 international units/L had a suppressed TSH concentration [8]. Very high levels of hCG can be seen in multiple pregnancies (ie, twins, triplets, etc) and in hyperemesis gravidarum. (See "Hyperthyroidism during pregnancy: Clinical manifestations, diagnosis, and causes", section on 'hCG-mediated hyperthyroidism'.)

This transient, usually subclinical, hyperthyroidism should be considered a normal physiologic finding. It is not known if this action of hCG benefits the mother or fetus. Later in pregnancy, as hCG secretion declines, serum free T4 and T3 concentrations decline and serum TSH concentrations rise slightly to or within the normal range.

Trimester-specific reference ranges — Because of the changes in thyroid physiology during pregnancy, the Guidelines of the American Thyroid Association (ATA) for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum recommend using population-based, trimester-specific reference ranges for TSH and assay method and trimester-specific reference ranges for serum free T4 [9]. Unfortunately, many commercial laboratories currently do not provide these reference ranges. When trimester-specific reference ranges for free T4 are not available and free T4 levels appear discordant with TSH,

measurement of total T4 may be superior to free T4. (See 'Assessment of thyroid function' below.)

In the absence of population and trimester-specific normal ranges, ATA guidelines suggest the following for interpretation of thyroid function tests [9]:

- Weeks 7 to 12 – Reduce the lower limit of the reference range of TSH by approximately 0.4 mU/L and the upper limit by 0.5 mU/L (corresponding to a TSH reference range of approximately 0.1 to 4 mU/L).
- Second and third trimester – There should be a gradual return of TSH towards the nonpregnant normal range.
- The upper reference range for total T4 increases by approximately 5 percent per week, beginning at week 7. At approximately 16 weeks, total T4 (and T3) levels during pregnancy are 1.5-fold higher than in nonpregnant women (due to TBG excess).

The extent of the downward shift in the reference range for TSH during pregnancy varies with different racial and ethnic groups [9,10]. In one of the largest population-based studies (over 13,000 pregnant women), the reference range (2.5^{th} to 97.5^{th} percentile) for TSH in the first trimester was 0.08 to 2.99 mU/L [11,12]. However, other studies in different populations suggest a more modest reduction in the upper limit of normal of TSH of only 0.5 to 1.0 mU/L [13,14]. In several population studies, the lower limit of the reference range for TSH in healthy pregnant women during the first trimester ranged from 0.03 to 0.1 mU/L [11,12,15-17].

Most studies report a progressive decrease in measured free T4 during pregnancy [1,18,19]. However, direct free T4 measurements may be unreliable in some patients due to changes in binding proteins during pregnancy. Measurement of free T4 in the dialysate or ultrafiltrate of serum samples using liquid chromatography/tandem mass spectrometry appears to be the most reliable, and when this method is used, free T4 concentrations were shown to decrease modestly with advancing gestational age, particularly between the first and second trimester [20,21]. This assay is relatively expensive and not universally available. Other free T4 assays (and probably free T3 assays) frequently fail to meet performance standards in pregnant patients, owing to increases in TBG and decreases in albumin concentrations that cause the immunoassay to be unreliable [18]. To compensate, assay kits should provide different free T4 normal ranges for pregnant patients, usually lower than those of nonpregnant patients. (See "Laboratory assessment of thyroid function", section on 'Serum free T4 and T3'.)

Assessment of thyroid function — When evaluating thyroid tests during pregnancy, we typically measure TSH and free T4 (if there is a trimester-specific reference range) and/or total T4. It is not uncommon to find free T4 levels to be at or below the reference range for

nonpregnant adults in association with normal serum TSH levels, a finding related to free T4 assay inaccuracy due to changes in binding proteins. In such settings where free T4 measurements appear discordant with TSH measurements, total T4 should also be measured.

For patients whose initial thyroid tests show **subclinical** thyroid disease or isolated changes in free T4, we repeat the thyroid tests in a couple of weeks to confirm the abnormality, as the findings may vary even when using pregnancy-specific reference ranges [22,23]. In a Danish study of 1466 pregnant women, 89 had a high TSH in the first trimester, but only 44 (49 percent) were elevated approximately two weeks later; 47 had a suppressed TSH, but only 19 (40 percent) were subnormal on repeat testing [22]. Among women with isolated changes in free T4, <20 percent were similarly abnormal in the repeat sample. Confirmation of an abnormal TSH was more likely with a higher initial TSH deviation or when antithyroid antibodies were positive.

Iodine requirements — Iodine requirements are higher in pregnant than in nonpregnant women due both to the increase in maternal T4 production required to maintain maternal euthyroidism and an increase in renal iodine clearance. Severe maternal iodine deficiency during pregnancy results in a reduction in maternal T4 production, inadequate placental transfer of maternal T4, and impairment of fetal neurologic development. However, markedly excessive iodine intake may also be harmful as it can lead to fetal hypothyroidism and goiter.

The World Health Organization (WHO) recommends 250 mcg of iodine daily during pregnancy and lactation. The National Academy of Medicine (formerly the Institute of Medicine) recommends daily iodine intake of 220 mcg during pregnancy and 290 mcg during lactation. For women in the United States to achieve this level of daily intake, the ATA recommends supplementation with 150 mcg of iodine daily during pregnancy and lactation, which is the dose included in the majority of prenatal vitamins marketed in the United States, though pregnant women should verify the iodine content in their own prenatal vitamin [24] (see "Nutrition in pregnancy: Dietary requirements and supplements"). The WHO sets the tolerable upper intake amount for iodine as 500 mcg daily for pregnant women, while the National Academy of Medicine uses 1100 mcg daily for adults and pregnant women >19 years of age.

Iodine requirements and the consequences of inadequate and excess intake are reviewed in detail elsewhere. (See "Iodine deficiency disorders", section on 'Iodine requirements' and "Iodine deficiency disorders", section on 'During pregnancy and lactation' and "Iodine deficiency disorders", section on 'Adverse effects' and "Iodine-induced thyroid dysfunction".)

THYROID FUNCTION IN THE FETUS

During the 10th to 12th week of gestation, fetal TSH appears, and the fetal thyroid is capable of concentrating iodine and synthesizing iodothyronines. However, little hormone synthesis occurs until the 18th to 20th week. Thereafter, fetal thyroid secretion increases gradually [25].

At term, fetal serum T4, T3, and TSH concentrations differ substantially from those in the mothers. Serum TSH concentrations are higher, serum free T4 concentrations are lower, and serum T3 concentrations are one-half those of the mothers. Soon after birth, serum TSH concentrations rapidly increase to 50 to 80 mU/L and then fall to 10 to 15 mU/L within 48 hours. Serum T3 and T4 concentrations rapidly increase to values slightly higher than those in normal adults.

The extent to which maternal thyroid hormones cross the placenta is controversial, but maternal thyroid hormones are critical for growth and development in the first trimester when the fetus has no functional thyroid of its own. In infants with congenital absence of the thyroid, cord serum concentrations range from 20 to 50 percent of the concentrations in normal infants [26]. TSH-receptor antibodies can cross the placenta and cause either fetal hyperthyroidism or hypothyroidism (see 'Fetal and neonatal Graves' disease' below). Little TSH crosses the placenta [27].

HYPERTHYROIDISM COMPLICATING PREGNANCY

Overt hyperthyroidism (low TSH, with free T4 and/or T3 levels that exceed trimester-specific normal reference ranges or total T4 and T3 that exceed 1.5 times the nonpregnant range) is relatively uncommon during pregnancy, occurring in 0.1 to 0.4 percent of all pregnancies [28]. Subclinical hyperthyroidism (low TSH, normal free T4 and T3 using trimester-specific normal reference ranges or total T4 and T3 that are less than 1.5 times the nonpregnant range) is usually transient, and in the first trimester of pregnancy, is considered a normal physiologic finding. In a Chinese study of 42,492 mothers, subclinical hyperthyroidism in early pregnancy was present in 1.3 percent and persisted until the third trimester in only 21 percent of cases [29].

Although hyperthyroidism from any cause can complicate pregnancy, Graves' disease and human chorionic gonadotropin (hCG)-mediated hyperthyroidism are the most common causes of hyperthyroidism. Graves' disease usually becomes less severe during the later stages of pregnancy due to a reduction in TSH-receptor antibody concentrations or, rarely, mediated by a change in the activity of TSH-receptor antibodies from stimulatory to blocking. hCG-mediated hyperthyroidism usually occurs transiently in the first half of gestation and is typically less severe than Graves' disease. (See "Hyperthyroidism during pregnancy: Clinical manifestations, diagnosis, and causes", section on 'Establishing the cause'.)

Pregnancy complications — Hyperthyroidism can have adverse effects on the mother and child, depending upon the severity of the biochemical abnormalities. This topic is reviewed in detail elsewhere. (See "Hyperthyroidism during pregnancy: Clinical manifestations, diagnosis, and causes", section on 'Pregnancy complications'.)

Diagnosis — The diagnosis of hyperthyroidism during pregnancy should be based primarily upon a finding of a suppressed (<0.1 mU/L) or undetectable (<0.01 mU/L) serum TSH value and elevated thyroid hormone levels that exceed the reference ranges for pregnancy [9]. If a TSH level is <0.1 mU/L, free T4 (or free T4 index) and total T3 (or free T3) should be obtained. In the event that free thyroid hormone levels are discordant with serum TSH and clinical findings, total T4 should be measured. It should be recalled that 10 to 20 percent of normal women have a subnormal or suppressed serum TSH in the first trimester, usually in association with normal free T4 levels.

Most pregnant women with significant overt hyperthyroidism in the first trimester will have a serum TSH below that which is seen in asymptomatic, healthy pregnant women (ie, <0.01 mU/L), associated with an elevated free T4 and/or free T3 (or total T4 and/or total T3) measurement. Establishing the diagnosis and ascertaining the cause of hyperthyroidism during pregnancy are reviewed separately. (See "Hyperthyroidism during pregnancy: Clinical manifestations, diagnosis, and causes", section on 'Diagnosis' and "Hyperthyroidism during pregnancy: Clinical manifestations, diagnosis, and causes", section on 'Establishing the cause'.)

Treatment — hCG-mediated hyperthyroidism is usually transient and does not require treatment. Treatment options for pregnant women with overt hyperthyroidism due to Graves' or nodular thyroid disease are limited because therapy may be harmful to the fetus. However, a good fetal and maternal outcome depends upon controlling the mother's hyperthyroidism. Most women are treated with thionamides. The goal of thionamides is to reduce and maintain the mother's serum free T4 concentration in the high-normal range for nonpregnant women using the lowest dose [9]. This requires assessment of free T4 (and/or total T4) frequently (ie, at four-week intervals) with appropriate adjustment of medication. Treatment recommendations are reviewed in detail separately. (See "Hyperthyroidism during pregnancy: Treatment".)

Fetal and neonatal Graves' disease — One to 5 percent of neonates born to women with Graves' disease have hyperthyroidism due to transplacental transfer of TSH-receptor-stimulating antibodies. The incidence is higher in women with high titers of these antibodies.

High fetal heart rate (>160 beats/minute), fetal goiter, advanced bone age, poor growth, and craniosynostosis are manifestations of fetal hyperthyroidism. Cardiac failure and hydrops may occur with severe disease. All fetuses of women with Graves' disease should be

monitored for signs of fetal thyrotoxicosis by determination of fetal heart rate and assessment of fetal growth [30].

This topic is reviewed in detail separately. (See "Evaluation and management of neonatal Graves disease" and "Hyperthyroidism during pregnancy: Treatment", section on 'Fetal or neonatal hyperthyroidism'.)

HYPOTHYROIDISM DURING PREGNANCY

When iodine nutrition is adequate (as in the United States), the most common cause of hypothyroidism during pregnancy is chronic autoimmune (Hashimoto's) thyroiditis. In iodine-deficient areas, iodine deficiency itself is associated with hypothyroidism and goiter. Other causes of hypothyroidism, such as prior radioiodine ablation, prior surgical removal of the thyroid, or disorders of the pituitary or hypothalamus, can also occur in pregnant women. (See "Disorders that cause hypothyroidism".)

Pregnancy complications — Hypothyroidism can have adverse effects on the mother and child, depending upon the severity of the biochemical abnormalities. This topic is reviewed in detail elsewhere. (See "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Overt hypothyroidism' and "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Subclinical hypothyroidism'.)

Diagnosis — The diagnosis of primary hypothyroidism during pregnancy is based upon the finding of an elevated serum TSH concentration, defined using population and trimester-specific TSH reference ranges for pregnant women [9]. For women with a TSH above the population and trimester-specific upper limit of normal, or above 4.0 mU/L when local reference ranges are not available, we also measure a free T4. (See "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Diagnosis'.)

- **Overt hypothyroidism** – Overt hypothyroidism is defined as an elevated population and trimester-specific TSH concentration in conjunction with a decreased free T4 concentration (below assay normal using reference range for pregnant women).
- **Subclinical hypothyroidism** – Subclinical hypothyroidism is defined as an elevated population and trimester-specific serum TSH concentration and a normal free T4 concentration.

Women with central hypothyroidism from pituitary or hypothalamic disease will not have elevated TSH concentrations during pregnancy. (See "Central hypothyroidism", section on 'Diagnosis'.)

Screening — The universal screening of asymptomatic pregnant women for hypothyroidism during the first trimester of pregnancy is controversial. This topic is reviewed in detail elsewhere. (See "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Screening'.)

Treatment — A good fetal and maternal outcome depends upon treating maternal hypothyroidism with thyroid hormone (T4). The goal of treatment is to maintain the mother's serum TSH in the population and trimester-specific reference range (approximately 0.1 to 4.0 mU/L if local reference ranges are not available). Women with preexisting hypothyroidism who become pregnant need more T4 during pregnancy. Dose requirements increase, on average, 30 percent during pregnancy and may increase by as much as 50 percent, and the increase occurs as early as the fifth week of gestation. The treatment of newly diagnosed and preexisting hypothyroidism is reviewed in detail elsewhere. (See "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Treatment'.)

THYROID PEROXIDASE ANTIBODIES IN EUTHYROID WOMEN

An increased risk of adverse pregnancy outcomes has been reported in euthyroid women with elevated thyroid peroxidase (TPO) antibody concentrations. In addition, euthyroid women with TPO antibodies are at high risk for developing subclinical hypothyroidism in the first trimester and thyroiditis in the postpartum period. In one study, approximately 20 percent of TPO-positive women subsequently developed subclinical hypothyroidism by term if left untreated [31]. Women with TPO antibodies are less likely to have human chorionic gonadotropin (hCG)-mediated reductions in TSH and increases in free T4 during the first trimester [32]; impaired response to hCG has been associated with reduced crown-rump length measurements on ultrasound [33].

Pregnancy outcomes — An increased risk of fetal loss, preterm delivery, perinatal mortality, and large for gestational age infants has been reported in euthyroid women with high serum TPO antibody concentrations [34-37]. In meta-analyses of case-control and cohort studies, the presence of thyroid autoantibodies in euthyroid women was associated with an increased risk of spontaneous miscarriage that is two to three times higher than in women without antibodies [38,39]. In addition, the risk of preterm birth was approximately doubled [13,39,40].

Euthyroid women with positive TPO antibodies undergoing in vitro fertilization (IVF) also have higher pregnancy loss rates. In a meta-analysis of 21 observational studies (7606 women undergoing IVF), the risk of pregnancy loss was higher in euthyroid women with than without positive TPO antibodies (relative risk [RR] 1.52, 95% CI 1.14-2.01) [41]. However, in a retrospective study of 449 antibody-positive and 2945 antibody-negative Chinese women undergoing IVF or intracytoplasmic sperm injection (ICSI), there was no difference in

the high-quality cleavage embryo rate, oocyte retrieval, fertilization, embryo utilization, blastocyte formation, pregnancy rate, or live birth rate [42].

Cognitive outcomes — It is unclear if the presence of TPO antibodies in euthyroid pregnant women correlates with the cognitive or behavioral development of their children. In a population-based cohort study from the Netherlands, 4770 pregnant women had blood collected at 13.5 weeks of gestation, and cord blood was obtained immediately after birth in 2121 of the neonates [43]. All samples were analyzed immediately postdelivery for TSH, free T4, and TPO antibodies. TPO antibodies were elevated in 4.7 percent. TSH levels were higher in TPO-positive than TPO-negative women (3.8 versus 1.5 mU/L), but TSH levels in the cord blood did not differ between positive and negative women. Elevated titers of TPO antibodies during pregnancy did not predict the verbal and nonverbal cognitive function of the children when tested at 2.5 years. However, children of euthyroid mothers with positive TPO antibodies were at higher risk of attention deficit/hyperactivity problems (odds ratio [OR] 1.77, 95% CI 1.15-2.72). When the analysis was adjusted for maternal TSH level, the association was attenuated but remained significant (OR 1.56).

Effect of T4 treatment — For women with TPO antibodies who remain **euthyroid**, thyroid hormone treatment is controversial. (See 'Our approach' below.)

Meta-analyses of trials evaluating the effect of levothyroxine on pregnancy outcomes in TPO-positive women are often limited by significant heterogeneity, due to the inclusion of both euthyroid and subclinically hypothyroid women with TPO antibodies [44-46]. Interpretation of the data is further complicated by the evolving definition of subclinical hypothyroidism in pregnancy (and in women with infertility seeking pregnancy). TSH values should be interpreted using population-based, trimester-specific reference ranges. (See 'Trimester-specific reference ranges' above.)

A meta-analysis of trials comparing TPO antibody-positive women without overt hypothyroidism who were treated with levothyroxine during or prior to pregnancy with women who were not treated found no difference in rates of achieved pregnancy, miscarriage, preterm delivery, or live births [46].

Subclinical hypothyroidism in pregnant women and in women with ovulatory dysfunction or infertility who are trying to conceive is reviewed in separate topics. (See "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Subclinical hypothyroidism' and "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Indications for treatment' and "Subclinical hypothyroidism in nonpregnant adults", section on 'Fertility' and "Subclinical hypothyroidism in nonpregnant adults", section on 'Candidates for T4 replacement'.)

- **During pregnancy** – In some [31,47,48], but not all [49], studies, treatment of TPO antibody-positive pregnant **euthyroid** women with levothyroxine (T4) improved miscarriage rates. In a meta-analysis of euthyroid women with TPO antibodies that included three studies of levothyroxine treatment beginning in the first trimester of pregnancy, there was no effect of levothyroxine on miscarriage, but there was a significant reduction in the preterm birth rate (6.2 versus 11.7 percent, RR 0.54, 95% CI 0.31-0.92) [50]. The two larger studies are described below:

  - In a prospective study of 115 euthyroid, TPO antibody-positive patients, half were randomly assigned to T4 (median dose 50 mcg daily) and half were not treated; comparison was made with 869 euthyroid, TPO antibody-negative patients. Mean baseline TSH was slightly higher in the TPO antibody-positive women (1.65 versus 1.1 mU/L in TPO antibody-negative women) and was significantly higher during the pregnancy in the untreated TPO antibody-positive women compared with the T4-treated, TPO antibody-positive women (eg, 2.5 versus 1.1 mU/L at 20 weeks). Miscarriage rates were 3.5 percent in TPO antibody-positive, treated patients; 13.8 percent in TPO antibody-positive, untreated patients; and 2.4 percent in the TPO antibody-negative patients. Premature delivery rates were 7, 22.4, and 8.2 percent, respectively [31].

  - In a similarly designed study (which included 198 euthyroid, TPO antibody-positive women treated with T4; 195 untreated, euthyroid, TPO antibody-positive women; and 197 untreated, TPO antibody-negative women), the rate of miscarriage did not significantly differ between the three groups (11.6, 14.9, and 8.1 percent, respectively) [49]. Although the rate of preterm delivery was lower in TPO antibody-negative women compared with untreated, TPO-positive women (2.8 versus 10.8 percent), the difference between treated and untreated TPO-positive women was not significant (6.9 versus 10.8 percent). Mean baseline TSH levels were 1.42, 1.37, and 1.27 mU/L in the three groups, respectively. As in the prior study, serum TSH levels were significantly higher in the second and third trimesters in the untreated versus the treated TPO antibody-positive women.

- **Prior to pregnancy** – In trials and meta-analyses of **euthyroid** women with TPO antibodies, levothyroxine treatment beginning prior to pregnancy did not reduce the risk of miscarriage or preterm birth, nor did it improve live birth rates [50-56]. In all of these trials [51-56], women who were enrolled were undergoing treatment for infertility and/or had a history of recurrent pregnancy loss.

  As examples:

  - In a trial evaluating levothyroxine or no treatment in 600 Chinese women with TPO antibodies and normal thyroid function (mean baseline TSH levels 2.94 and 2.12

mU/L, respectively) who were undergoing IVF with embryo transfer, there was no difference in the pregnancy loss rate (10.3 and 10.6 percent, respectively) or in the live birth rate (31.7 and 32.3 percent) [52]. However, these results may be confounded by the presence of additional infertility factors in women undergoing ART.

- In a subsequent trial evaluating levothyroxine (50 mcg daily) or placebo in 952 TPO-positive euthyroid women with a history of pregnancy loss or receiving treatment for infertility, there was no difference in the live birth rate (37.4 versus 37.9 percent [RR 0.97, 95% CI, 0.83-1.14]) [54]. There was also no difference in any of the secondary outcomes, including pregnancy loss at <24 weeks (28.2 versus 29.6 percent in the placebo group) and preterm delivery (3.8 versus 3.6 percent). The outcomes were similar in women who did or did not have previous pregnancy loss and in women with or without infertility. As expected, serum TSH was slightly lower in the treated group at all time points (eg, three months 1.33 versus 2.11 mU/L). The live birth rates were only 37.4 and 37.9 percent in the levothyroxine group and placebo group, respectively, emphasizing that the study group was not necessarily representative of the general population without prior miscarriage or infertility. In a subsequent analysis, the levothyroxine group was found to have a higher failure to conceive rate [55].

- In a multicenter, double-blinded, placebo-controlled trial in 187 patients with history of two or more pregnancy losses, TPO antibodies, and normal TSH, there was no difference in live birth rates among those treated with levothyroxine versus placebo [56].

Our approach — The decision to treat euthyroid women with elevated TPO antibodies with T4 or to monitor for the development of hypothyroidism during pregnancy is controversial. Most pregnant women are unlikely to know their antithyroid antibody status because universal screening is not routinely done.

In view of conflicting data regarding the efficacy of levothyroxine (T4) for reducing the risk of miscarriage, the approach to management varies (see 'Effect of T4 treatment' above). Some experts, including one editor of this topic, do not treat euthyroid (TSH ≤4.0 mU/L), TPO-positive pregnant women. Since carefully monitored thyroid hormone treatment is safe, however, other experts individualize the decision to treat based upon patient characteristics, values, and preferences.

- Some experts, including the author and one editor of this topic, offer T4 treatment (50 mcg daily) to TPO-positive pregnant women who have a history of pregnancy loss and who prefer this intervention, if their TSH is >2.5 mU/L. (See "Recurrent pregnancy loss: Management", section on 'Thyroid dysfunction and diabetes mellitus'.)

- Some experts, including one editor of this topic, will offer T4 treatment (50 mcg daily) to TPO-positive pregnant women who prefer this intervention if their TSH is >2.5 mU/L, regardless of prior history of pregnancy loss.

In TPO antibody-positive, euthyroid pregnant women who are not treated with thyroid hormone, TSH should be measured every four weeks during the first trimester and, if stable, once during the second and third trimesters to monitor for the development of hypothyroidism. If TSH rises above the population and trimester-specific upper limit of normal (approximately 4 mU/L), we begin treatment with T4. (See "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Indications for treatment'.)

TSH should also be measured at three and six months postpartum to monitor for the development of postpartum thyroiditis. (See "Postpartum thyroiditis", section on 'Screening'.)

The American Thyroid Association (ATA) found there was insufficient evidence to recommend for or against T4 therapy in euthyroid, TPO antibody-positive pregnant women; however, monitoring for the development of hypothyroidism was recommended [9]. In women with a prior history of pregnancy loss, treatment with T4 may be considered. (See "Recurrent pregnancy loss: Evaluation" and "Recurrent pregnancy loss: Management", section on 'Thyroid dysfunction and diabetes mellitus'.)

GOITER

Goiter during pregnancy is common in regions where iodine intake is low, occurring in 16 to 70 percent of women in iodine-deficient regions of Western Europe. Increased urinary iodine excretion during pregnancy may further deplete thyroidal iodine stores by as much as 40 percent [57]. Plasma iodide concentrations may decrease during pregnancy due to increased maternal renal clearance and fetal utilization of iodide [25]. Studies from Europe show that iodine deficiency relative to the nonpregnant state leads to mild thyroid enlargement detectable sonographically (mean increase in volume 18 percent), a change that is clinically detectable in some women [1,58]. In areas of moderate iodine deficiency, thyroid volume in women correlates with the number of previous pregnancies [59]. (See 'Iodine requirements' above.)

Goiter during pregnancy is rare in the United States (an iodine-sufficient region). In the United States, any thyroid growth during pregnancy should be considered potentially abnormal, requiring further investigation with thyroid function testing and possibly thyroid sonography [60].

THYROID NODULES

A pregnant woman found to have a thyroid nodule should be evaluated in the same way as if she were not pregnant. TSH and ultrasound should be performed. Thyroid radionuclide scanning is contraindicated during pregnancy. The indications for fine-needle aspiration (FNA) biopsy of the nodule are the same as in nonpregnant patients [9,61,62]. (See "Diagnostic approach to and treatment of thyroid nodules", section on 'Sonographic criteria for FNA'.)

FNA is safe to perform during pregnancy. However, if there is no evidence of nodular growth, concerning ultrasound features (eg, extension beyond the thyroid or extension adjacent to the trachea or recurrent laryngeal nerve), or development of cervical lymph nodes during the period of observation, many endocrinologists defer FNA until after pregnancy [63]. If surgery is required during pregnancy, the optimal timing is the second trimester. Therefore, the timing of a follow-up ultrasound to assess growth of the nodule should be mid-second trimester if the nodule was first noted in early pregnancy. If the nodule was first noted in later pregnancy, follow-up ultrasound can be deferred to the postpartum period.

If FNA is performed, subsequent management varies according to the biopsy results. Rarely, benign nodules require surgery during the second trimester due to rapid growth and/or the development of compressive symptoms. When FNA shows indeterminate cytology (follicular neoplasm, atypia of undetermined significance, or follicular lesion of undetermined significance), molecular testing can either be done during pregnancy or, frequently, patients are followed and further evaluation (molecular testing, thyroid scan when indicated, surgery) is delayed until after delivery as most of these nodules are benign, although reported malignancy rates vary from 6 to 52 percent [9]. Rarely, second trimester surgery is indicated due to rapid growth or the emergence of lymphadenopathy associated with a suspicious indeterminate nodule. (See "Diagnostic approach to and treatment of thyroid nodules", section on 'FNA cytology' and "Evaluation and management of thyroid nodules with indeterminate cytology".)

In areas of mild to moderate iodine deficiency, the prevalence of thyroid nodules during pregnancy varies between 3 and 21 percent [64-66]. In retrospective studies, the frequency of thyroid cancer in pregnant women with thyroid nodules ranges from 12 to 43 percent [67-70]. In one prospective study, there were no malignancies among the 15 percent of women with newly detected thyroid nodules (detected via ultrasonography) [64]. The wide range of thyroid cancer prevalence is likely due to differences in patient population and study design.

THYROID CANCER

Diagnosed during pregnancy — In most observational studies, thyroid cancer discovered during pregnancy does not significantly impact the prognosis [71-75]. As an example, a California cancer registry identified 129 antepartum and 466 postpartum thyroid cancers and found no difference in overall prognosis compared with women with thyroid cancer not associated with pregnancy [72]. In contrast, an Italian study found a recurrence rate of 10 percent for women with thyroid cancer diagnosed during pregnancy versus 4.3 percent for nonpregnant women [76].

- **Timing of surgery** – Women with differentiated thyroid cancer require surgery. However, given the typically indolent nature of thyroid cancer, thyroidectomy is usually delayed until the postpartum period to minimize maternal and fetal complications [71,77]. This approach does not appear to have a negative impact on prognosis, as illustrated by the results of a retrospective study of 61 pregnant women with thyroid cancer, of whom 77 percent delayed surgery until after delivery [71]. There was no difference in the outcome after 20 years (recurrence or distant metastases) as compared with those women having surgery in the second trimester or nonpregnant women.

  Surgery during pregnancy is sometimes indicated for rare patients with larger, more aggressive or rapidly growing cancers, or in the presence of extensive nodal or distant metastasis. The safest time for any type of surgery during pregnancy is the second trimester [9,67,78]. However, in one retrospective study of 201 pregnant women undergoing thyroid or parathyroid surgery (92 women underwent thyroidectomy for thyroid cancer), pregnant women had significantly higher rates of surgical complications (11 versus 4 percent) and endocrine-specific complications (16 versus 8 percent) than nonpregnant women [79]. Endocrine-specific complications were defined as maternal hypoparathyroidism, hypocalcemia, or recurrent laryngeal nerve injury. In this study, 50 of the 201 procedures were considered to be urgent [79]. Higher surgeon volume (ie, surgical expertise) was a predictor of lower complication rates.

  Thus, when surgery is required during the second trimester, it should be performed only by expert thyroid surgeons. The risks of nonobstetric surgery during pregnancy are discussed in detail separately. (See "Anesthesia for nonobstetric surgery during pregnancy".)

- **Monitoring of women not undergoing surgery** – When surgery for biopsy-proven thyroid cancer is deferred, the patient should be monitored during pregnancy with thyroid ultrasound performed during each trimester. In a study of 19 women with biopsy-proven papillary thyroid cancer who were monitored with ultrasound during gestation, there were no clinically significant increases in the size of the cancer and no patient developed cervical nodal metastases [80].

If, by 24 weeks, there is a significant increase in thyroid cancer size (50 percent in volume or 20 percent in diameter in two dimensions), surgery might be considered during the second trimester [9,62]. The development of nodal metastases is a clear indication for surgical intervention. However, if the lesion remains stable or increases minimally in size or if the cancer is diagnosed in the second half of pregnancy, surgery may be performed after delivery. In such cases where thyroid surgery is deferred, we suggest thyroid hormone suppressive therapy with a goal of maintaining the TSH in the range of 0.3 to 2.0 mU/L.

Previously treated — In women previously treated with radioiodine for thyroid cancer, pregnancy should be delayed for at least six months to ensure that thyroid hormone levels have normalized (if they had been withdrawn from thyroid hormone) and that additional radiation treatment is not required. Fertility and pregnancy outcomes after radioiodine therapy are reviewed in detail separately. (See "Differentiated thyroid cancer: Radioiodine treatment", section on 'Gonadal function and fertility' and "Differentiated thyroid cancer: Radioiodine treatment", section on 'Future pregnancy'.)

For women without ultrasound or biochemical (thyroglobulin) evidence of persistent disease, pregnancy itself has not been shown to increase the risk of recurrence [81-83]. In women with persistent disease (structural or biochemical), disease progression may occur during pregnancy [81,83]. However, in a study of 37 women who became pregnant versus 87 women who did not become pregnant following surgery and radioiodine for lung metastases, the 5- and 10-year progression-free survival rates were similar: 94.5 and 63.2 percent in the pregnancy group and 89.8 and 58.1 percent in the nonpregnancy group, respectively [84]. In women who have persistently elevated thyroglobulin levels or evidence of persistent disease on ultrasound prior to pregnancy, periodic ultrasound and thyroglobulin (once each trimester) monitoring is recommended [9].

In women with persistent disease, thyroid hormone suppression therapy should continue, and preconception TSH goals should remain the same. To maintain the same degree of TSH suppression, most women will require an increase in levothyroxine dose. Thus, TSH should be measured as soon as pregnancy is confirmed, every four weeks until 16 to 20 weeks of gestation, and then at least once between 26 and 32 weeks of gestation [9]. The dose of levothyroxine (T4) should be increased to maintain TSH in the desired range. (See "Differentiated thyroid cancer: Overview of management", section on 'Thyroid hormone suppression'.)

POSTPARTUM THYROID DYSFUNCTION

The prevalence of both painless thyroiditis (postpartum thyroiditis) and Graves' disease is increased postpartum. In one Japanese study, 86 percent of patients developing

thyrotoxicosis in the first three months had postpartum thyroiditis, while after 6.5 months, all the patients had Graves' disease [85].

Postpartum thyroiditis — The reported prevalence of postpartum thyroiditis varies globally and ranges from 1 to 17 percent [61,86,87]. Higher rates, up to 25 percent, have been reported in women with type 1 diabetes mellitus [86], and the highest rates occur among women with a prior history of postpartum thyroiditis (pooled prevalence 42 percent) and in women with positive antithyroid peroxidase (TPO) antibodies who had normal thyroid function during pregnancy (40 to 68 percent, compared with 18 percent of women with positive anti-TPO antibodies and hypothyroidism prior to pregnancy and 0 to 5 percent of women without antibodies) [86,88]. (See "Postpartum thyroiditis", section on 'Prevalence and natural history'.)

Two patterns of postpartum dysfunction can be defined: postpartum thyroiditis and a postpartum exacerbation of chronic lymphocytic (Hashimoto's) thyroiditis. Postpartum thyroiditis is characterized by transient hyperthyroidism or transient hyperthyroidism followed by transient or, not infrequently, permanent hypothyroidism. Postpartum exacerbation of Hashimoto's thyroiditis is characterized by postpartum progression of autoimmune destruction. It may cause a transient or permanent increase in thyroid hormone requirements. In one study, for example, more than 50 percent of women with Hashimoto's thyroiditis required an increase in their pregestational T4 dose in the postpartum period [89].

The diagnosis and treatment of postpartum thyroiditis are reviewed in detail separately. (See "Postpartum thyroiditis".)

Graves' disease — Women may develop Graves' disease postpartum or experience an exacerbation. In addition, women in remission after antithyroid drug therapy have a higher incidence of relapse during the postpartum period than at times unrelated to pregnancy. (See "Hyperthyroidism during pregnancy: Treatment", section on 'Postpartum issues'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Thyroid disease and pregnancy".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th

grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Hyperthyroidism (overactive thyroid) (The Basics)" and "Patient education: Hypothyroidism (underactive thyroid) (The Basics)" and "Patient education: Thyroiditis after pregnancy (The Basics)" and "Patient education: Hyperthyroidism (overactive thyroid) and pregnancy (The Basics)")

- Beyond the Basics topics (see "Patient education: Hyperthyroidism (overactive thyroid) (Beyond the Basics)" and "Patient education: Hypothyroidism (underactive thyroid) (Beyond the Basics)" and "Patient education: Antithyroid drugs (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Thyroid adaptation during normal pregnancy –** The diagnosis of thyroid disease during pregnancy requires an understanding of the changes in thyroid physiology and thyroid function tests that accompany normal pregnancy.

  - **Thyroid physiology –** To meet the increased metabolic needs during a normal pregnancy, there are changes in thyroid physiology that are reflected in altered thyroid function tests. The major changes in thyroid function during pregnancy are an increase in serum thyroxine-binding globulin (TBG) concentrations and stimulation of the thyrotropin (thyroid-stimulating hormone [TSH]) receptor by human chorionic gonadotropin (hCG). Together, these changes lead to an increase in both serum total thyroxine (T4) and triiodothyronine (T3) concentrations and a reduction in serum TSH. (See 'Thyroid physiology' above.)

  - **Trimester-specific reference ranges –** Because of the changes in thyroid physiology during normal pregnancy, thyroid function tests should, whenever possible, be interpreted using population and trimester-specific TSH and T4 reference ranges for pregnant women. If the laboratory does not provide trimester-specific reference ranges for TSH (mU/L), a TSH reference range of approximately 0.1 to 4 mU/L can be used. Total T4 and total T3 levels during pregnancy are 1.5-fold

higher than in nonpregnant women. Reference ranges for free T4 are assay method-specific, and trimester-specific reference ranges should be provided with the assay kits. (See 'Trimester-specific reference ranges' above.)

- **Assessment of thyroid function** – When evaluating thyroid tests during pregnancy, we typically measure TSH and free T4 (if there is a trimester-specific reference range) and/or total T4. In such settings where free T4 measurements appear discordant with TSH measurements, total T4 should also be measured. For patients whose initial thyroid tests show **subclinical** thyroid disease or isolated changes in free T4, we repeat the thyroid tests in a couple of weeks to confirm the abnormality as the findings may vary even when using pregnancy-specific reference ranges. (See 'Assessment of thyroid function' above.)

- **Hyperthyroidism**

  - **Causes** – Hyperthyroidism from any cause can complicate pregnancy, but Graves' hyperthyroidism is the most common cause of overt hyperthyroidism. hCG-mediated hyperthyroidism is a common cause of subclinical hyperthyroidism. It may occur transiently in the first half of gestation and is typically less severe than Graves' disease. (See 'Hyperthyroidism complicating pregnancy' above and "Hyperthyroidism during pregnancy: Clinical manifestations, diagnosis, and causes", section on 'Establishing the cause'.)

  - **Diagnosis** – The diagnosis of hyperthyroidism during pregnancy should be based primarily upon a suppressed (<0.1 mU/L) or undetectable (<0.01 mU/L) serum TSH value and also a serum free T4 and/or free T3 (or total T4 and/or total T3) measurement that exceeds the normal range during pregnancy. (See 'Diagnosis' above.)

  - **Treatment** – Treatment options for pregnant women with hyperthyroidism are reviewed in detail separately. (See "Hyperthyroidism during pregnancy: Treatment".)

- **Hypothyroidism**

  - **Causes** – When iodine nutrition is adequate (as in the United States), the most common cause of hypothyroidism during pregnancy is chronic autoimmune (Hashimoto's) thyroiditis. In iodine-deficient areas, iodine deficiency itself is associated with hypothyroidism and goiter. (See 'Hypothyroidism during pregnancy' above and "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment".)

  - **Diagnosis** – The diagnosis of overt primary hypothyroidism during pregnancy is based upon the finding of a decreased free T4 concentration (below assay normal

using reference range for pregnant women) and an elevated population and trimester-specific serum TSH. Subclinical hypothyroidism is defined as an elevated population and trimester-specific serum TSH concentration with a normal free T4 concentration. (See 'Diagnosis' above and "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Diagnosis'.)

- **Treatment** – The treatment of newly diagnosed and preexisting hypothyroidism is reviewed in detail elsewhere. (See "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Treatment'.)

- **TPO antibodies in euthyroid women** – An increased rate of fetal loss and premature delivery has been reported in euthyroid women with high serum antithyroid peroxidase (TPO) antibody concentrations. In view of conflicting data regarding the efficacy of levothyroxine (T4) for reducing the risk of miscarriage, there is not a consensus approach to the management of euthyroid (TSH ≤4 mU/L), TPO-positive women. Some experts, including one editor of this topic, do not treat euthyroid, TPO-positive pregnant women. Since carefully monitored thyroid hormone treatment is safe, however, other experts offer T4 treatment (50 mcg) to selected women based on clinical characteristics (eg, history of miscarriage, preference for intervention, TSH >2.5 mU/L). (See 'Thyroid peroxidase antibodies in euthyroid women' above.)

  Euthyroid women with high serum TPO antibody concentrations are at risk for developing hypothyroidism. In antibody-positive, euthyroid pregnant women who are not treated with thyroid hormone, TSH should be measured every four weeks during the first trimester and, if stable, once during the second and third trimesters to monitor for the development of hypothyroidism. (See 'Our approach' above and "Hypothyroidism during pregnancy: Clinical manifestations, diagnosis, and treatment", section on 'Indications for treatment'.)

- **Goiter** – Goiter during pregnancy is rare in the United States. However, goiter during pregnancy is common in regions where iodine intake is low, occurring in 16 to 70 percent of women in iodine-deficient regions of Western Europe. (See 'Goiter' above.)

- **Thyroid nodules** – A pregnant woman found to have a thyroid nodule should be evaluated in the same way as if she were not pregnant, except that thyroid radionuclide scanning is contraindicated. (See 'Thyroid nodules' above.)

- **Thyroid cancer** – Given the typically indolent nature of differentiated thyroid cancer, most women with newly diagnosed differentiated thyroid cancer can delay thyroidectomy until the postpartum period to minimize maternal and fetal complications. Surgery during pregnancy is sometimes indicated for rare patients with larger, more aggressive or rapidly growing cancers, or in the presence of extensive

nodal or distant metastasis. The safest time for any type of surgery during pregnancy is the second trimester. (See 'Diagnosed during pregnancy' above.)

When surgery for thyroid cancer is deferred, the patient should be monitored during pregnancy with thyroid ultrasound performed during each trimester. In such cases where thyroid surgery is deferred, we suggest thyroid hormone suppressive therapy (**Grade 2C**). The goal is to maintain the TSH in the range of 0.3 to 2.0 mU/L. (See 'Diagnosed during pregnancy' above.)

- **Postpartum thyroiditis –** Postpartum thyroiditis occurs in 5 to 10 percent of women in the United States. It may occur after pregnancy loss (miscarriage, abortion, ectopic pregnancy), as well as after normal delivery. (See "Postpartum thyroiditis".)

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Topic 7851 Version 38.0

Contributor Disclosures

Douglas S Ross, MD Consultant/Advisory Boards: Medullary Thyroid Cancer Registry Consortium [Thyroid cancer]. All of the relevant financial relationships listed have been mitigated. **David S Cooper, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Charles J Lockwood, MD, MHCM** No relevant financial relationship(s) with ineligible companies to disclose. **Jean E Mulder, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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