CLINICAL OBSTETRICS AND GYNECOLOGY
Volume 62, Number 2, 308–319

Hypothyroidism in Pregnancy

SCOTT A. SULLIVAN, MD, MSCR

Department of Obstetrics/Gynecology, Division of Maternal-Fetal Medicine, Medical University of South Carolina, Charleston, South Carolina

Abstract: Hypothyroidism in pregnancy is defined as the presence of an elevated thyroid stimulating hormone during gestation, affecting 2% to 3% of the population. Overt hypothyroidism is diagnosed by a decreased FT4, while patients with a normal FT4 are considered to have subclinical disease. Poorly controlled disease is associated with both pregnancy complications and developmental delays in the offspring. Treatment consists of replacement with levothyroxine and regular monitoring. Most pregnant women will require an increase in their dosing from 25% to 30%. While treatment for SCH remains controversial, current recommendations do not support universal screening of low-risk women during pregnancy.
Key words: hypothyroidism, pregnancy, hashimoto's thyroiditis, thyroid screening, subclinical hypothyroidism

Hypothyroidism in pregnancy is usually defined as the presence of an elevated thyroid stimulating hormone (TSH) and a decreased serum FT4 concentration during gestation, with both concentrations outside the trimester-specific reference ranges. When iodine intake is adequate, the most frequent cause of hypothyroidism is autoimmune thyroid disease, sometimes referred as Hashimoto's thyroiditis. It is important to exclude other rare causes of abnormal thyroid function such as TSH-secreting pituitary tumors, thyroid hormone resistance, or central hypothyroidism with biologically dysfunctional TSH (Table 1). It is estimated that 2% to 3% of healthy, nonpregnant women of childbearing age have an elevated serum TSH.[1] The prevalence may be higher in areas of relative iodine insufficiency. Thyroid autoantibodies can be detected in ~30% to 60% of pregnant women with an elevated TSH concentration.

Population-based studies demonstrate substantial differences in the TSH upper-reference limit.[2] These differences may be partly attributable to differences in the iodine status between populations, as well as the TSH assays used for analysis. There also seems to be important influences of body mass index, geography, and ethnicity upon TSH concentrations in pregnant women. Substantial variation exists between populations, with recent evidence confirming a more liberal upper TSH reference range in healthy pregnant women with no thyroid disease. Studies have also demonstrated an important additive influence of thyroid peroxidase antibodies (TPOAb) positivity upon maternal thyroid status. There seems to be a greater risk for adverse events in women who

Correspondence: Scott A. Sullivan, MD, MSCR, Department of Obstetrics/Gynecology, Division of Maternal-Fetal Medicine, Medical University of South Carolina, Charleston, SC. E-mail: sullivas@musc.edu

The author declares that there is nothing to disclose.

TABLE 1. Potential Etiologies of Hypothyroidism

Hypothyroidism Causes
Hashimoto's thyroiditis
Iodine deficiency
Post ablative/surgical
Congenital hypothyroidism
Medication—(ex amiodarone)
Suppurative thyroiditis
Lymphocytic hypophysitis
Subacute thyroiditis
Sheehan's syndrome

are TPOAb positive compared with those who are TPOAb negative, even when thyroid function is identical. The reasons for this remain unclear. Other studies suggest that euthyroid, TPOAb-positive women may be at increased risk for adverse clinical outcomes not observed in TPOAb-negative women. As a consequence, it is difficult to precisely define a universal TSH cutoff above which replacement therapy should be initiated for all pregnant women. Rather, decisions about levothyroxine treatment should be based upon measurement of both thyroid function and TPOAb status.

Elevations in serum TSH concentrations during pregnancy should ideally be defined using pregnancy and population-specific reference ranges. Detection of an increased TSH concentration is not always synonymous with decreased FT4 concentrations. Frequently, elevated maternal TSH is detected when FT4 concentrations are normal, this is also known as subclinical hypothyroidism. Conversely, low FT4 concentrations can be detected despite normal TSH concentrations. This finding is referred to as isolated hypothyroxinemia. Excepting unusual scenarios, serum TSH measurement remains the principal determinant of maternal thyroid status and should be used to guide treatment decisions and goals. Since there are substantial differences in the upper-reference limit for TSH among different populations, each practitioner or laboratory should in the ideal situation seek to determine their own population and trimester-specific reference ranges. This is often not easily available or even feasible. In the absence of local population data, pregnancy-specific TSH reference ranges could be obtained from comparable patient populations, performed using similar TSH assays. If internal or transferable pregnancy-specific TSH reference ranges are not available, an upper-reference limit of 4.0 mU/L may be used. For most assays, this represents a reduction in the nonpregnant TSH upper-reference limit of ~0.5 mIU/L.[3]

Overt maternal hypothyroidism has consistently been shown to be associated with an increased risk of adverse pregnancy complications as well as detrimental effects upon fetal neurocognitive development. Specific adverse outcomes associated with overt maternal hypothyroidism include increased risks of premature birth, low birth weight, pregnancy loss, and lower offspring intelligence quotient (IQ). Abalovich et al[4] demonstrated that women with overt hypothyroidism carry an estimated 60% risk of fetal loss when not adequately controlled. Separately, Leung demonstrated an increased risk of gestational hypertension in pregnant women with overt maternal hypothyroidism. Allan similarly described an increased risk of fetal death among pregnant women with overt disease.[1] Together, these data demonstrate a clear association between overt maternal hypothyroidism and risk to the maternal-fetal unit. Numerous retrospective and case-control studies confirm the detrimental effects of overt hypothyroidism on both pregnancy and fetal health. There are no known safety concerns with adequate thyroid replacement therapy in pregnancy. A recent retrospective study of >1000 pregnant women on chronic levothyroxine replacement, showed that the risk of pregnancy loss increased proportionally to the degree of TSH elevation, with no increased risk associated with TSH normalization.[5] Nonetheless, available data confirm the benefits of treating overt hypothyroidism during pregnancy.

Subclinical hypothyroidism, or elevated TSH with normal FT4, is associated with an increased risk of adverse pregnancy outcomes in some, but not all studies. This may be explained in part to the fact that separate studies use differing cutoffs to define an elevated TSH concentration. Also, many studies do not account for TPOAb status, which is likely an independent risk factor for poor outcomes.

Pregnancy loss naturally occurs in ~20% to 30% of pregnancies. Since a significant proportion of pregnancy losses occur even before pregnancy is clinically recognized, pregnancy loss is a challenging study endpoint. Nevertheless, different studies have suggested a relationship between higher levels of maternal TSH and pregnancy loss. Negro reported a significantly higher pregnancy loss rate in TPOAb-negative women with TSH concentrations between 2.5 and 5.0 mIU/L compared with those with TSH concentrations below 2.5 mIU/L (6.1% vs. 3.6%).[6] Benhadi performed a prospective cohort study investigating the risk of pregnancy loss in 2497 Dutch women. In this cohort of pregnant women without overt hypothyroidism, the risk of pregnancy loss increased with higher levels of maternal TSH, although results should be interpreted with caution given the very small number of 27 cases studied, as well as the heterogeneity of the study's endpoint. In an Australian cohort, early pregnancy TSH levels > 95th percentile were associated with an increased risk of pregnancy loss (OR, 3.66) although subclinical and overt hypothyroid cases were considered together. A retrospective study that determined thyroid parameters in early pregnancy samples obtained from 202 pregnancy losses showed higher mean TSH and lower FT4 concentrations, as well as a higher prevalence of TSH concentrations > 97.5th percentile and FT4 concentrations <2.5th percentile compared with 3592 normal pregnancies. Liu et al[7] demonstrated a corresponding increase in loss risk as maternal TSH concentrations increased, particularly in TPOAb-positive women.

Casey investigated the association of maternal hypothyroidism and premature delivery in a cohort of 17,298 pregnant women presenting for prenatal care.[8] Subclinical hypothyroidism was associated with an increased risk of premature delivery <34 weeks (4% vs. 2.5%, $P = 0.01$), but not with premature delivery <32 weeks (2.5% vs. 1%, $P = 0.07$), or <36 weeks (7% vs. 6%, $P = 0.39$). This lack of continuous effect raises questions about the 34-week finding. A later study by Cleary-Goldman showed no association of an elevated TSH with prematurity <37 weeks. Various studies have also investigated this potential adverse relationship, albeit with conflicting results. This variation possibly can be explained by the fact that some studies pooled overt and subclinical hypothyroid cases together, while others used different TSH cutoff values, and yet others enrolled a small number of subjects. A recent study compared the value of using population-based reference range limits (TSH > 4.0 mU/L) versus a fixed TSH cutoff of 2.5 mU/L. While a TSH > 2.5 mU/L was not associated with premature delivery, 1.9× and 2.5× increased risks of prematurity at <37 and <34 weeks, respectively, were observed among women with TSH > 4.0 mU/L. Interestingly, this association no longer persisted after exclusion of TPOAb-positive women or women with medical comorbidities. The association of TPOAb and poor outcome is found in multiple studies. However, in TPOAb-negative women similar adverse risk is not consistently apparent until maternal TSH exceeds 5 to 10 mIU/L.

The majority of studies did not find association between preeclampsia and hypertensive disorders and elevated TSH. Mannisto evaluated the relationship between pregnancy outcomes and thyroid function tests obtained at 12 weeks gestation in 5805 women. No adverse association between thyroid function and perinatal mortality was noted.[9] A separate large study investigating the relationship between subclinical hypothyroidism and birth weight showed no effect on low (< 2500 g) or high

(> 4000 g) birth weights. A meta-analysis broadly analyzed pregnancy outcomes in relation to maternal thyroid status. The authors found an increasing risk of pregnancy complications (pregnancy loss, preterm delivery, and placental abruption) in relation to maternal subclinical hypothyroidism during early pregnancy, although subclinical hypothyroidism was variably defined across studies.[10]

Together, despite some differences in study design, biochemical cutoffs applied, and slightly differing endpoints, the above studies overall convey an increasing risk of pregnancy-specific complications, most notably pregnancy loss and preterm delivery, in relation to elevated maternal TSH concentration. Importantly, however, this effect is exacerbated by the presence of elevated TPOAb, such that any additive risk is apparent in TPOAb-positive women when TSH exceeds 2.5 mIU/L.

Negro et al[11] published data suggesting that subclinical hypothyroidism increases the risk of pregnancy complications in TPOAb-positive women. In this prospective trial of > 4600 subjects, women were randomized to universal screening versus high-risk case finding during pregnancy, with subsequent levothyroxine treatment of anti-TPO–positive women with TSH > 2.5 mIU/L. Low-risk women in the unscreened group had serum collected and stored for analysis postpartum. Within the subset of women classified as low risk for hypothyroidism, treatment of TPOAb-positive women with TSH > 2.5 mU/L resulted in a significant reduction in a composite endpoint of pregnancy complications when compared with no treatment. The composite endpoint remains a significant study limitation, as some variables were subjective in nature. The primary study endpoint was nonsuperior, showing no benefit of universal screening and treatment when compared with screening of high-risk women only. This is because the primary, predefined endpoint analyzed the effects of LT4 treatment on both low-risk and high-risk subjects together. Importantly, all high-risk women in the study were tested and treated for elevated TSH values. Therefore, when combining both groups, the treatment effect on the low-risk group was diluted leading to the conclusion of no superiority of universal screening.

The detrimental effects of maternal thyroid hypofunction on fetal neurocognitive development are less clear. In support of an adverse impact attributable to maternal hypothyroidism, data from a large case-control study demonstrated a 7-point reduction in IQ among children born to untreated overtly hypothyroid women when compared with euthyroid controls.[12] Findings also supported a delay in motor skill development, language development, and attention at 7 to 9 years of age. Subsequent studies have shown similar results for children born to women with isolated hypothyroxinemia.[13] Three small studies analyzing only TPOAb positivity seem to similarly show an effect on neurocognitive outcome in the offspring but need to be confirmed in larger samples.[14] In contrast, the Controlled Antenatal Thyroid Screening (CATS) study was a large prospective, randomized controlled trial investigating the benefit of population screening for elevated TSH concentrations and low FT4 concentrations in pregnant women.[15] In this cohort, detection of either an elevated TSH or low FT4 triggered initiation of 150 mcg/day LT4 therapy, at a mean of 13 weeks gestation. There were 390 women in the screening group and 404 in the control group. This study demonstrated no improvement in cognitive function when children of treated overt or subclinical hypothyroid mothers were evaluated at 3 years of age. There was no difference in either mean IQ or in IQ < 85.

Another large multicenter, randomized, controlled trial by Casey and colleagues, the "Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy," reported similar results. This study screened and treated 677 women with subclinical hypothyroidism and 526

hypothyroxinemic women at a mean time point of 17 weeks (range, 8 to 20 wk). Similarly, this study demonstrated no significant effect of treatment on offspring IQ at the age of 5 years.[16] There were also no differences seen in preeclampsia, abruption, pregnancy loss, or preterm labor between groups.

Taken together, these prospective results provide evidence to conclude that treatment of subclinical hypothyroidism after 13 weeks of gestation is not associated with improved neurocognitive outcomes in offspring. The timing of levothyroxine intervention during gestation likely plays an important role in the effect of any intervention. The 2 randomized controlled studies described above initiated levothyroxine treatment only at the completion of the first trimester or later—which may be too late to significantly impact neurodevelopment. Animal studies have suggested any window of opportunity is likely earlier in gestation. Similarly, the duration and severity of maternal hypothyroidism are likely important, yet rarely controlled for, as all studies include only a single baseline measurement of TSH concentration during pregnancy. It therefore must again be emphasized that overt maternal hypothyroidism during pregnancy should be considered dangerous, and logic dictates that moderate or mild maternal hypothyroidism may similarly impart a risk. What remains uncertain is the nuanced understanding of how this risk is reduced or abated as the extent of maternal hypothyroidism is normalized, or other variables are modified. This point should be emphasized as we consider that the most common cause of maternal hypothyroidism has dramatically changed over the last century. Formerly, severe iodine deficiency was common, while more recently, the principal cause of maternal hypothyroidism is mild maternal Hashimoto's disease. These disorders are physiologically different, though both may impart a similar phenotype demonstrating elevated maternal TSH concentrations.

Many prospective and retrospective studies have demonstrated an increased risk of pregnancy complications associated with mildly elevated maternal TSH concentrations, especially in TPOAb-positive women. However, only a small number of studies have investigated the impact of LT4 treatment on pregnancy complications in such women. A single randomized controlled trial has demonstrated a potential benefit of levothyroxine intervention at 9 weeks gestation. Importantly, this study documented a reduction in the adverse pregnancy composite outcome only in TPOAb-positive women with mild hypothyroidism (defined as a TSH > 2.5 mIU/L). It should again be noted that the majority of women with subclinical hypothyroidism detected in this investigation were TPOAb negative, for whom no intervention or treatment was provided. This study also used a composite endpoint which included endpoints such as Cesarean section rates and postdelivery admission to the NICU that are often guided by provider judgment, and therefore subjective. Importantly, the authors' conclusion for their primary endpoint stated that universal screening for elevated TSH concentration in a broad spectrum of pregnant women did not improve outcomes when compared with a high-risk screening strategy. Outcomes of universal screening compared with no screening were not assessed. A separate randomized controlled trial demonstrated a decrease in preterm delivery and pregnancy loss in euthyroid (defined as TSH < 4.2 mIU/L) TPOAb-positive women who were treated with levothyroxine beginning in the first trimester of pregnancy. However, the majority of pregnancy losses in the control group occurred before the average start of LT4 therapy.

Many studies have stratified the risk imparted by hypothyroidism according to TPOAb status, and consistently show that this risk is higher in TPOAb-positive women. These data also suggest that the adverse impact associated with maternal TSH levels is apparent at lower TSH elevations in women known to be TPOAb positive compared with women who are TPOAb negative. Furthermore, 2 studies suggest a reduction in

pregnancy loss when TPOAb-positive women are treated with levothyroxine, even when biochemically euthyroid. Intervention trials have not been performed in TPOAb-negative women.

Two large prospective trials did not show benefit for treatment of subclinical hypothyroidism. Another small prospective trial was positive for reducing pregnancy loss in TPOAb-positive women. While all the trials have limitations, it is difficult to recommend universal treatment for subclinical hypothyroidism at the present time. It seems reasonable that providers could consider levothyroxine treatment for specific individuals or subgroups of pregnant women with subclinical hypothyroidism. These might include TPOAb-positive women, or those with a TSH > 10 mIU/L. The strength of such recommendations, however, should differ depending on TPOAb status, as will the strength of evidence supporting treatment for each subgroup. This approach would require that any pregnant women with an elevated TSH concentration be evaluated for TPOAb status.

Isolated hypothyroxinemia is typically defined as a free thyroxine concentration in the lower 2.5th to 5th percentile of a given population, in conjunction with a normal maternal TSH concentration. Pop and colleagues initially reported a decrease in psychomotor test scores among offspring born to women with FT4 indices in the lowest 10th percentile, despite having normal serum TSH concentrations. Similarly, Li et al[17] observed a reduction in IQ among offspring of mothers suffering from either overt hypothyroidism or isolated hypothyroxinemia during the first trimester. In recent years, additional prospective, nonrandomized studies have similarly reported adverse child outcomes in children born to mothers with isolated hypothyroxinemia. Adverse outcomes include lower IQ, language delay, worsened motor function, smaller head circumference, and an increased risk of autism. These data are derived from different populations across the world (China, Belgium, The Netherlands, Spain) with known differences in iodine nutrition. In contrast to those studies investigating the association of elevated TSH concentrations with adverse pregnancy outcome, however, there are very few studies investigating isolated hypothyroxinemia and adverse pregnancy outcomes, excepting birth weight and premature delivery. Available data suggest an association with higher birth weight and higher risk of premature delivery. Interestingly, many large-scale studies demonstrate that the populations of women with elevated TSH concentrations are generally exclusive from those identified with low-free T4 concentrations. For example, in the CATS study, approximately the same proportion of screened mothers were identified in the hypothyroxinemic and subclinical hypothyroid groups, with little overlap.

Overall, available evidence seems to show an association between hypothyroxinemia and cognitive development of the offspring, with uncertain effects on prematurity and low birth weight. However, there exist no studies in which levothyroxine administration has been shown to ameliorate such harmful effects. In neither the CATS nor Casey trial, women identified with low free T4 concentrations, and randomized to treatment with levothyroxine did not demonstrate any improvement in pregnancy or neurocognitive outcomes in the offspring. Although several studies have reported adverse outcomes in children born to mothers with isolated hypothyroxinemia, no interventional data have yet been published that demonstrate beneficial effects of levothyroxine therapy. One observational study analyzing women at 12, 24, and 32 weeks of pregnancy demonstrated delayed infant neurodevelopment in women with persistent hypothyroxinemia. However, when FT4 concentrations increased during pregnancy, infant development was not adversely affected. Nevertheless, at present there are only 2 randomized, prospective, intervention trials in which women with a low FT4 were treated with levothyroxine, at 13 and 17

weeks gestation, respectively. Both investigations failed to show any beneficial effect on cognitive development following levothyroxine administration, though a limitation of the studies was the timing of the intervention, after completion of the first trimester. Nevertheless, given the existing interventional data, treatment of isolated hypothyroxinemia cannot be currently recommended.

The recommended treatment of maternal hypothyroidism is administration of oral levothyroxine. Delivery of T4 is crucial for the developing fetal brain. The ratio of T4 to T3 in desiccated thyroid preparations is 4.2:1, which is significantly lower than the 14:1 ratio of secretion by the human thyroid gland. This relative excess of T3 leads to supraphysiologic maternal levels of T3 and relatively low levels of T4. Patients using either desiccated thyroid or a treatment regimen combining T3 and T4 are likely at risk for having insufficient transfer of maternal T4 to the fetal brain. It is notable that the majority of fetal T3 present in the central nervous system during pregnancy is derived from maternal T4 actively transported into this space. The fetal CNS is relatively impermeable to T3, which therefore argues against using triiodothyronine (T3) or desiccated thyroid during pregnancy. In parallel to the treatment of hypothyroidism in a general population, it is reasonable to target a TSH in the lower half of the trimester-specific reference range. When this is not available, as is commonplace, a target maternal TSH concentrations below 2.5 mIU/L is desirable. To ensure this goal is consistently met during gestation, increased surveillance is recommended. On the basis of findings extrapolated from investigations of treated hypothyroid women from early pregnancy onwards it is reasonable to evaluate these women for TSH elevation approximately every 4 to 6 weeks during pregnancy. Serial testing is preferably continued through mid-pregnancy, as the increased thyroxine demand continues throughout the first half of gestation. A study by Yassa and colleagues investigated the optimal timing of subsequent assessment of thyroid function following dose modification though this was in patients consuming levothyroxine prenatally, and may not be generalizable to patients not taking levothyroxine but at risk for hypothyroidism.

Glinoer performed a prospective study in 87 euthyroid, TPOAb-positive women evaluated before and during early pregnancy. Twenty percent of women in the study developed a TSH > 4 mIU/L during gestation despite a normal TSH and no requirement for levothyroxine prenatally. This occurred despite the expected decrease in TPOAb titers during pregnancy.[18] Negro and colleagues demonstrated similar results in a prospective study. The authors found that in TPOAb-positive euthyroid women, TSH levels increased progressively as gestation progressed, from a mean of 1.7 mIU/L (12th week) to 3.5 mIU/L (term), with 19% of women having a supranormal TSH concentration at delivery. These findings confirm that an increased requirement for thyroid hormone occurs during gestation. In women who are TPOAb positive, both overt and subclinical hypothyroidism may occur due to a lack of ability of the thyroid to augment production when needed during pregnancy. Similarly, patients who undergo hemithyroidectomy or receive radioactive iodine and are euthyroid before pregnancy are at risk for developing elevated serum TSH during gestation. Euthyroid patients who are antithyroid Ab positive, posthemithyroidectomy or treated with radioactive iodine, have an increased propensity for the development of hypothyroidism in gestation, and should be monitored regularly.

There are major physiologic thyroid changes during pregnancy that impact thyroid replacement therapy. Total body thyroxine requirements are not static throughout gestation. Data demonstrate that total body thyroxine pool must increase by ~40% to 50% to maintain a euthyroid state. In a healthy woman who becomes pregnant, the pregnancy hormone hCG plays a major role as a stimulus of maternal thyroid hormone production, especially throughout the

first half of pregnancy. Together with pituitary TSH, placental hCG stimulates endogenous thyroid hormone production when an intact thyroid is present, and helps to maintain a euthyroid state during gestation.

In women with overt hypothyroidism, serum hCG and TSH cannot stimulate adequate thyroxine production. If exogenous levothyroxine is not adjusted, the increased demand of pregnancy will outstrip supply. Clinical studies have confirmed that the increased requirement for thyroxine, or exogenous levothyroxine, occurs as early as 4 to 6 weeks of pregnancy. Such requirements gradually increase through 16 to 20 weeks of pregnancy, and thereafter plateau until the time of delivery. These data provide the basis for recommending adjustments of LT4 dosage when affected women become pregnant and also for the timing of follow-up intervals for TSH in treated patients.

Between 50% and 85% of LT4-treated hypothyroid women need to increase exogenous levothyroxine dosing during pregnancy.[19] The incremental increase largely depends on the underlying etiology of the hypothyroidism. There is a greater likelihood that dose increases will be required in those patients without functional thyroid tissue (eg, due to radioablation or surgery) in comparison to patients with Hashimoto's thyroiditis. The preconception level of TSH as well as other factors can also influence the rapidity and extent of LT4 augmentation necessary to maintain a euthyroid state during pregnancy. For example, variation and changes in maternal estrogen levels during pregnancy correlate with variations in the gestational requirements for LT4.

The levothyroxine adjustment should be made as soon as possible after pregnancy is confirmed to reduce the impact of poorly controlled hypothyroidism. Treated hypothyroid women of reproductive age should be counseled regarding the likelihood of increased demand for levothyroxine during pregnancy. Such women should also be counseled to contact their provider immediately upon a confirmed or suspected pregnancy. Normalization of TSH concentrations throughout gestation is the goal. For women receiving LT4 preconception, a prospective, randomized study has provided evidence that supports a single dose–adjustment strategy rather than a stepwise approach for LT4 dosage–adjustment postconception.[20] Euthyroid women receiving once-daily dosing of LT4, regardless of the dose, a recommendation to increase by 2 additional tablets weekly (9 tablets per week instead of 7 tablets per week, giving a 29% increase) can effectively mimic gestational physiology and thus prevent maternal hypothyroidism during the first trimester. Another option is to increase the dosage of daily levothyroxine by ~25% to 30%. Dosage augmentation should occur as soon as possible when a suspected pregnancy occurs, and this should be discussed with every patient in the prepregnancy setting. Unfortunately it is well known that the minority of patients seek or receive preconception counseling regarding their medical comorbidities. Although untreated (or incompletely treated) hypothyroidism can adversely affect pregnancy, there are no data to suggest that women with adequately treated subclinical or overt hypothyroidism have an increased risk of any obstetrical complication. Consequently, there is no indication for any additional obstetric testing or surveillance (such as serial fetal ultrasounds, antenatal testing, and/or umbilical blood sampling) in pregnancies of women with either subclinical or overt hypothyroidism who are being monitored and treated appropriately. An exception to this is women with Graves' disease effectively treated with ^{131}I ablation or surgical resection, who require TRAb monitoring. Maternal thyroid function should be monitored throughout pregnancy, as previously mentioned. The difficulties inherent to achieving rapid, postconceptional TSH normalization have also focused attention upon preconception TSH control. Different cutoff values for preconception TSH, ranging from <1.2 to

<2.5 mIU/L have been advocated. In 1 study, only 17% of women with TSH < 1.2 mIU/L had to increase LT4 dose later during pregnancy.

Given this, it is recommended that all treated hypothyroid women who are currently receiving levothyroxine optimize thyroid parameters preconception. A maternal serum TSH concentration <2.5 mIU/L is a reasonable goal for such women. Even lower preconception TSH values (< 1.5 mIU/L) could reduce the risk of TSH elevation during the first trimester, but a lower treatment target may not improve outcomes as the LT4 dose can be increased upon a pregnancy confirmation. Following delivery, maternal LT4 dosing should usually be reduced to prepregnancy levels, and a serum TSH assessed 4 to 6 weeks thereafter. However, a study demonstrated that > 50% of women with Hashimoto's thyroiditis required an increase in the pregestational thyroid hormone dose in the postpartum period, presumably due an exacerbation of autoimmune thyroid dysfunction postpartum. Some women in whom LT4 is initiated during pregnancy may not require LT4 postpartum. Such women are candidates for discontinuing LT4, especially when the LT4 dose is low, such as 50 mcg daily. The decision to discontinue LT4, if desired, should be made by the patient and their caregiver. If LT4 is discontinued, serum TSH should be evaluated in 4 to 6 weeks as a precaution.

Despite the potential obstetric and pediatric complications from maternal thyroid dysfunction reported in the past 50 years, the consistency of reports on the incidence of maternal subclinical and clinical hypothyroidism in the first trimester, and our recognized difficulty in diagnosing the disease both by medical history and physical examination, when and how to screen for thyroid disease in pregnant and nonpregnant individuals remains a very controversial issue, and different positions have been adopted by several medical organizations.

Thyroid dysfunction in pregnancy would seem to meet some of the criteria for population screening; it is prevalent, morbid for mother and fetus, treatment is available and generally effective. However, other criteria are still lacking; clear determination of cost-effectiveness, and RCTs demonstrating population benefit.

In 2015, the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists (ACOG) stated, "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 neurocognitive function in offspring." It is reasonable to perform a determination of serum TSH at the first obstetric visit in those women at higher risk for thyroid dysfunction. In the ATA Clinical Guidelines for Thyroid and Pregnancy, universal screening is not recommended, but it is strongly suggested that health care professionals personally ask during preconception counseling or in the first obstetric visit about risk factors for thyroid disease. The primary barrier to universal screening is the lack of RCTs that demonstrate a reversal of both obstetric and intellectual abnormalities in the offspring after normalization of thyroid deficiency by maternal L-thyroxine replacement therapy.

Several studies have consistently demonstrated the failure to recognize women at risk for thyroid dysfunction when using a case-finding strategy, based on actual thyroid dysfunction symptoms, a personal or family history of thyroid disease, and obstetric history.

Vaidya and coworkers offered thyroid function tests early in pregnancy to 1560 women to evaluate the effectiveness of universal screening versus case finding.[21] They showed that targeted screening would still have missed about one third of all pregnant women with an elevated serum TSH. They divided women early in pregnancy into 2 groups, a low-risk group that included 75% of the women and a high-risk group that comprised the remaining

25%. The high-risk group included those with a personal and family history of thyroid disorders or other autoimmune disease and current and past treatment with ATDs, L-thyroxine, radioiodine, or thyroid surgery. Forty women, 2.6% of the total group, had an elevated serum TSH, and 70% of them were in the high-risk group.

Similar conclusions have been reported in other studies. Wang and coworkers performed thyroid tests in the first trimester of pregnancy and classified 367 women (12.7%) of 2899 as high risk, following the recommendations from the ATA and Endocrine Society. Of the 2899, 294 had thyroid dysfunction: hypothyroidism was reported in 7.5%, most of which was subclinical hypothyroidism; 1% had hyperthyroidism; and 0.9% had hypothyroxinemia. Positive antibodies were detected in 279 (9.6%), and 196 of them were euthyroid. The prevalence of thyroid dysfunction in the high-risk group was higher than in the low-risk group (15% vs. 9.4%; $P = 0.001$). However, of the 217 women with an elevated serum TSH, 171 (78.8%) belonged to the low-risk group. The authors concluded that a case-finding strategy for screening thyroid function in the high-risk group would miss about 81.6% of women with an elevated serum TSH and 80.4% women with hyperthyroidism. In a study from the Czech Republic, Horacek and colleagues concluded that > 55% of pregnant women at risk would be missed if only those with high-risk criteria were examined. The authors stated that a more extensive screening of thyroid autoimmunity and dysfunction seems warranted.

Ong et al[22] performed thyroid tests and evaluated levels of β-hCG and pregnancy-associated plasma protein A (PAPP-A) in 2411 women in Western Australia between 9 and 14 weeks' gestation. Their objective was to determine whether thyroid function tests performed with first-trimester screening predicts adverse pregnancy outcomes. One hundred thirty-three women (5.5%) had serum TSH > 2.15 mIU/L (above the 97.5th percentile for the first trimester), 5 of whom (0.2%) had a serum TSH > 10 mIU/L. On multivariate analysis, neither maternal serum TSH > 2.15 mIU/L nor TSH as a continuous variable predicted primary or secondary outcomes. Their conclusions were that testing TSH as part of first-trimester screening does not predict adverse pregnancy outcomes. The authors question whether screening is justified to detect these cases.

Negro and colleagues reported on a prospective randomized study of 4562 women in southern Italy. Thyroid tests were performed very early in pregnancy. Their conclusion was that universal screening did not affect the rate of adverse events in comparison to targeted high-risk case finding, implying a negative outcome. As discussed in the section on subclinical hypothyroidism, in the same article by Negro and colleagues, a subgroup of low-risk patients detected to be hypothyroid were treated with L-thyroxine and were compared with a nontreated group. The rate of pregnancy-related adverse events was reduced by nearly 40% after detection and treatment.

A cost-effectiveness approach to compare universal screening with case finding was reported in 2 studies, and both concluded that universal screening is cost effective compared with a case-finding strategy.[23] However, Thung and colleagues added in their conclusions that a wide range of circumstances should be considered before universal screening is adopted. The same position was voiced by Stagnaro-Green and Schwartz.

A number of barriers must be considered before universal routine thyroid function screening can be recommended in pregnancy. They include the selection of thyroid tests to be used (TSH, FT4, TPOAb), the threshold applied to characterize an abnormality, weeks of gestation, appropriate intervention, and monitoring. The second issue still in dispute is the management of hypothyroid women in the preconceptional period. It is accepted that most of these women will need an increase in the L-thyroxine dose soon after conception. It could be argued whether the

target of serum TSH between 0.3 and 2.5 mIU/L before pregnancy is reasonable in anticipation of the increase in T4 requirements. Abalovich and colleagues reported that when the serum TSH is below 1.3 mIU/L before conception, only 17% of women need an increase in L-thyroxine in the first trimester. It has also been recommended that women on L-thyroxine therapy be advised at the time of confirmation of pregnancy to increase their dose empirically by 2 doses a week until the results of the thyroid tests are available.

The Controlled Antenatal Thyroid Screening trial failed to show any benefit of levothyroxine therapy on the cognitive function of children of mothers with hypothyroidism or hypothyroxinemia. An argument about the study is that mothers did not receive thyroxine therapy until a median gestational age of 13.4 weeks. As mentioned above, a small number of children whose hypothyroid mothers started levothyroxine therapy after the first trimester of pregnancy had no neurocognitive deficits when evaluated after 5 years of age. As previously mentioned, the NICHD Maternal-Fetal Medicine Units Network study of universal screening and L-thyroxine treatment for women with subclinical hypothyroidism or euthyroid chronic thyroiditis diagnosed during pregnancy showed no differences in the obstetric outcomes or neurocognitive development of the offspring at 5 years of age.

Despite some of the concerns about existing data, the preponderance of the Level I evidence suggests no benefit for universal screening and treatment for hypothyroidism in pregnancy, consistent with the recommendations from ACOG. Providers should continue to be vigilant in case finding and screening high-risk patients by history, examination and symptoms.

References

1. Allan WC, Haddow JE, Palomaki GE, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen*. 2000;7:127–130.
2. Bestwick JP, John R, Maina A, et al. Thyroid stimulating hormone and free thyroxine in pregnancy: expressing concentrations as multiples of the median (MoMs). *Clin Chim Acta*. 2014;430: 33–37.
3. Alexander E, Pearce E, Brent G, et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum.*Thyroid*. 2017;27:315–389.
4. Abalovich M, Gutierrez S, Alcaraz G, et al. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid*. 2002;12:63–68.
5. Taylor PN, Minassian C, Rehman A, et al. TSH levels and risk of miscarriage in women on long-term levothyroxine: a community-based study. *JCEM*. 2014;99:3895–3902.
6. Negro R, Schwartz A, Gismondi R, et al. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. *J Clin Endocrinol Metab*. 2010;95:E44–E48.
7. Liu H, Shan Z, Li C, et al. Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. *Thyroid*. 2014;24:1642–1649.
8. Casey BM, Dashe JS, Spong CY, et al. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstet Gynecol*. 2007;109:1129–1135.
9. Mannisto T, Vaarasmaki M, Pouta A, et al. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. *J Clin Endocrinol Metab*. 2010;95:1084–1094.
10. Chan S. Boelaert Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. *Clin Endocrinol*. 2015;82:313–326.
11. Negro R, Schwartz A, Gismondi R, et al. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. *J Clin Endocrinol Metab*. 2010;95:E44–E48.
12. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341:549–555.
13. Korevaar TI, Muetzel R, Medici M, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. *Lancet Diabetes Endocrinol*. 2016;4: 35–43.
14. Wasserman EE, Pillion JP, Duggan A, et al. Childhood IQ, hearing loss, and maternal thyroid

autoimmunity in the Baltimore Collaborative Perinatal Project. *Pediatr Res*. 2012;72:525–530.
15. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med*. 2012;366:493–501.
16. Casey B, Thom E. Peaceman treatment of subclinical hypothyroidism or hypothyroxinemia in Pregnancy. *N Engl J Med*. 2017;376:815–825.
17. Li C, Shan A, Mao J, et al. Assessment of thyroid function during first trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? *J Clin Endocr Metab*. 2014;99:73–79.
18. Glinoer D, Riahi M, Grün JP, et al. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab*. 1994;79:197–204.
19. Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med*. 2004;351:241–249.
20. Yassa L, Marqusee E, Fawcett R, et al. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. *J Clin Endocrinol Metab*. 2010;95:3234–3241.
21. Vaidya B, Anthony S, Biklous M, et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab*. 2007;92:203.
22. Ong GS, Hadlow N, Brown S, et al. Does the thyroid-stimulating hormone measured concurrently with first trimester biochemical screening tests predict adverse pregnancy outcomes occuring after 20 weeks gestation? *J Clin Endocrinol Metab*. 2014;99:E2668–E2672.
23. Thung S, Funai EF, Grobman WA. The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. *Am J Obstet Gynecol*. 2009;200:267.