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Controversies in the Management of Hypothyroidism During Pregnancy

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Importance: In the last 3 years, we have witnessed the publication of multiple but conflicting guidelines on the management of hypothyroidism during pregnancy. Hypothyroidism is one of the most common endocrinopathies in reproductive-age and pregnant women. Given the prevalence of thyroid disease, it is highly likely that obstetricians will encounter and provide care for pregnant women with thyroid disease. Therefore, a review of current guidelines and management options is clinically relevant.

Objectives: Our goals are to review the changes in thyroid function during pregnancy, the options for testing for thyroid disease, the different categories of thyroid dysfunction and surveillance strategies among subspecialty societies, and the obstetric hazards associated with thyroid dysfunction and review the evidence for benefit of treatment options for thyroid disease.

Evidence Acquisition: We reviewed key subspecialty guidelines, as well as current and ongoing studies focused on the treatment of hypothyroidism during pregnancy.

Results: There are significant differences in the identification and management of thyroid disease during pregnancy among subspecialists. We present our recommendations based on the available evidence.

Relevance: Evidence exists that obstetricians struggle with the diagnosis and treatment of hypothyroidism. According to recent surveys, the management of hypothyroidism during pregnancy is the number 1 endocrine topic of interest for obstetricians. A synopsis of recently published subspecialty guidelines is timely.

Conclusions: Recent, evidence-based findings indicate that obstetricians should consider modifying their approach to the identification and treatment of thyroid disease during pregnancy.

Target Audience: Obstetricians and gynecologists, family physicians

Learning Objectives: After completing this CME activity, physicians should be better able to identify the changes in thyroid function testing during pregnancy; choose the appropriate methods of testing thyroid function during the first, second, and third trimesters; and compare treatment options of the various forms of thyroid dysfunction and the evidence behind treatment recommendations.

Hypothyroidism is one of the most common endocrinopathies in reproductive-age women. According to the National Health and Nutrition Examination Survey III, roughly 5% of women in the United States have unrecognized thyroid disease composed of either overt hypothyroidism (high thyroid-stimulating hormone [TSH] and low free thyroxine [FT4]) or subclinical hypothyroidism (elevated TSH but normal FT4).[1] Similar findings were reported in the Colorado Thyroid Disease prevalence study, which found that 4% to 6% of reproductive-age women have an elevated TSH level.[2] Another 10% of euthyroid women have antibodies directed against thyroid tissue (broadly termed thyroid autoimmunity or autoimmune thyroid disease). Isolated hypothyroxinemia (normal TSH but low FT4) occurs in

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a much smaller percentage of women (1%–2%).[3,4] During pregnancy, the incidence of hypothyroidism ranges from 0.4% to 11% worldwide, with a mean of 2.4%. The majority of cases (roughly two thirds) represent subclinical hypothyroidism.[5]

Given the prevalence of thyroid disease, most obstetricians will encounter and provide care for pregnant women with thyroid disease. Nevertheless, evidence exists that nonspecialist providers struggle with management of thyroid disease[6] and are unfamiliar with subspecialty recommendations.[7] Even care provided by experienced providers may be suboptimal, and roughly 30% to 50% of hypothyroid women on levothyroxine (L-T4) exhibit elevated TSH levels in the first trimester and 33% in the second trimester.[8,9]

Over the last 2 decades, research findings on maternal and/or fetal risks associated with thyroid disease have proliferated. In 2012, the Endocrine Society (ES) published a revised guideline on the management of thyroid dysfunction during pregnancy including a total of 27 new articles from the previous 2007 document.[10] Similar, but separate, guidelines were published by the American Thyroid Association (ATA) in 2011,[11] and a joint guideline was published by the ATA and American Association of Clinical Endocrinologists (AACE) in 2012.[12] In the preparation of the guidelines, the extensive and exhaustive analytical efforts by proven investigators in the field are noteworthy. However, the submitted recommendations are at times inconsistent and potentially confusing. Despite these limitations, we believe that subspecialty guidelines (ES, ATA, and ATA + AACE) offer more comprehensive and contemporary strategies for preconceptual, antepartum, and postpartum care when compared with other specialty organizations, including the American Congress of Obstetrics and Gynecology (ACOG) (Table 1).

In this review, we compare some of the key differences between the ACOG guidelines and subspecialty guidelines in the management of hypothyroidism during pregnancy. The objective is to appraise the evidence behind and rationale for many of the key subspecialty recommendations, with the goal to provide a foundation for improving the diagnosis and management of hypothyroidism during pregnancy.

Physiologic Changes in Thyroid Function During Pregnancy

During pregnancy, the thyroid gland undergoes multiple functional adaptations. There is a 1.5–2 fold rise in thyroid-binding globulin (TBG) mediated by estrogen-stimulated hepatic production, differential glycosylation, and decreased renal clearance.[13] Circulating thyroid hormones are either bound to transport proteins (primarily TBG, but also transthyretin, T4-binding prealbumin, and albumin) or exist as free hormones, where only the unbound or free fraction is biologically active. Thyroid-binding globulin rises in a linear fashion in the first trimester, then plateaus and remains stable during the second and third trimesters.[13,14] In response to rising TBG, a compensatory rise in T4 production is necessary to maintain physiologic levels of FT4. Total T4 (TT4) levels during the first trimester are roughly 1.5-fold higher than nonpregnant levels and remain elevated throughout pregnancy. Most but not all studies indicate that FT4 levels are only modestly increased and highest during the first trimester, a finding that is temporally related to rising placental production of human chorionic gonadotropin (hCG).[15]

Human chorionic gonadotropin and TSH are polypeptides composed of a common, identical α subunit chain linked to a unique β subunit. Despite differences in amino acid and oligosaccharide content, the β subunits of both trophic hormones contain some structural homology. Acting as a partial thyrotropic agonist, placental hCG induces a small rise in T4 levels by binding and activating the TSH receptor within thyrotropic cells. Free T4 levels then decrease slightly in the second and third trimesters, but remain within the reference range.[15]

In contrast to thyroid hormones, TSH levels decrease in the first trimester, with the lowest levels corresponding to the peak hCG levels (10–12 weeks' gestation). Thyroid-stimulating hormone is exquisitely sensitive to free thyroid hormone levels, and approximately 20% of pregnant women will have TSH levels below the lower limits of the nonpregnant reference range during the first trimester.[16] Thyroid-stimulating hormone levels usually remain detectable, even if they are below the assay reference range, but a small minority of pregnant women has undetectable TSH levels during early gestation with no evidence of thyroid disease. The degree of TSH suppression during early pregnancy is multifactorial. Thyroid-stimulating hormone levels in the lower quartiles are more suppressible than TSH levels in the higher quartiles, and very high hCG levels, as seen with multiple pregnancy or molar pregnancy, suppress TSH levels more than singleton pregnancies.[17] Thyroid-stimulating hormone levels then rise again during the second and third trimesters, but still remain within the normal nonpregnant reference range throughout gestation.

TABLE 1
Preconception/Pregnancy Thyroid Function Strategies According to Specialty Organizations

Organization	TSH Universal Screening	TSH Targeted Screening	Normative TSH Ranges During Pregnancy	Treat Prenatal TSH >2.5	Euthyroid TPOAbs^{+}	Treatment
ACOG 2007	No, level C—USPSTF	Yes, level C—USPSTF	Not addressed	Not addressed	Not addressed	Overt thyroid disease (hyperthyroidism or hypothyroidism) should be appropriately treated to maintain a euthyroid state throughout pregnancy and during the postpartum period.
AACE + ATA 2012	No, grade B, BEL 1	Yes, grade C, BEL 2	Laboratory-established trimester-specific ranges or if unavailable consider upper limit: 1st trimester 2.5 mIU/L, 2nd trimester 3.0 mIU/L, 3rd trimester 3.5 mIU/L; grade B, BEL 2	*Consider* treatment if TSH between 2.5 and upper limit of normal, grade B, BEL 2; *should* treat if TSH >2.5 and + TPOAbs, grade B, BEL 2	Consider treatment, grade B, BEL 2	Treat overt hypothyroidism and subclinical hypothyroidism. Treatment goal is a TSH: 1st trimester <2.5 mIU/L, grade B, BEL 2; 2nd trimester <3.0 mIU/L and 3rd trimester <3.5 mIU/L, grade C, BEL 2
ATA 2011	No, level I—USPSTF	Yes, level B—USPSTF	Laboratory-established trimester-specific ranges in populations with optimal iodine intake, level B—USPSTF; or if unavailable 1st trimester 0.1-2.5 mIU/L, 2nd trimester 0.2-3.0 mIU/L, 3rd trimester 0.3-3.0 mIU/L, level I—USPSTF	Treat if +TPOAbs, level B—USPSTF; insufficient evidence to recommend for or against treatment of subclinical hypothyroidism and TPOAbs^{-}, level I—USPSTF	No, but monitor TSH, level B—USPSTF	Treatment goal is to maintain TSH within trimester-specific ranges, level A—USPSTF

ES 2012	No consensus for screening all *newly* pregnant women	Some support for aggressive case finding before and during pregnancy, level I—USPSTF	Laboratory trimester-specific ranges, level B—USPSTF; also use upper limit: 1st trimester 2.5 mIU/L, and 3.0 mIU/L for 2nd and 3rd trimesters	Yes, level I	Monitor TSH every 4–6 wk, level A—USPSTF	Treat both overt and subclinical hypothyroidism. Treatment goal is to maintain TSH normalized to trimester-specific range or 1st trimester <2.5 mIU/L, 2nd and 3rd trimesters <3.0, level A—USPSTF
AAFP 2012	Evidence is insufficient to recommend for or against routine screening for thyroid disease in adults, grade I—USPSTF	Yes, grade C	Not addressed	Not addressed	Consider treatment	Treat subclinical hypothyroidism and TSH <10 mIU/L; good level of evidence; subclinical hypothyroidism T4 therapy should target serum TSH 0.35–5.5 mIU/L
ACP 2004	No, grade I—USPSTF	Not addressed	Not addressed	Not addressed	Not addressed	"Few data supporting subclinical hypothyroidism association with adverse outcome or benefits of treatment" 2004
USPSTF 2004	No, grade I—USPSTF	Yes	Not addressed	Not addressed	Not addressed	"Pregnant or planning to become pregnant with elevated TSH should be treated with T4 to restore the serum TSH concentration to the reference range"; subclinical hypothyroidism, TSH 6.5–10 mIU/L, do not treat, poor level of evidence

AAFP indicates American Academy of Family Physicians; ACP, American College of Physicians; USPSTF, US Preventative Services Task Force.

At approximately 8 to 10 weeks of gestation, the fetal thyroid gland acquires the capacity to synthesize thyroid hormone, a functional pituitary-thyroid axis becomes evident by 20 weeks' gestation, and a fully mature axis is not apparent until birth.[14] A small but critical amount of maternal T4 is transferred to the fetal-placental unit during pregnancy, which represents the only source of thyroid hormone for the fetus during early gestation. Thyroid hormone receptors are present in the fetal brain around 8 to 9 weeks' gestation, an embryonic period that reflects rapid neuronal proliferation and growth.[18] The fetal brain is critically dependent on thyroid hormone for normal development.[19] Based on both animal and human studies, it is postulated that neurocognitive development may be compromised under conditions of low maternal thyroid hormone levels (FT4 <10th centile) during early gestation. Numerous observational studies recently reviewed confirm a linkage between impaired neurocognitive testing in children and maternal hypothyroxinemia during pregnancy.[20,21] The concern over impaired fetal neurocognitive development in the setting of maternal hypothyroxinemia is the primary basis for the endorsement by subspecialty organizations for aggressive treatment with L-T4 in women at risk for hypothyroxinemia during pregnancy.

Trimester-Specific TSH Ranges

Thyroid-stimulating hormone is the single best screening test for evaluation and management of primary hypothyroidism in women during pregnancy.[12] Whether all women require screening for thyroid disease during pregnancy is controversial. Selective screening of pregnant women is endorsed by professional societies including ACOG, ATA, AACE, and ES (Table 1). In contrast, many experts advocate universal screening.[22] The debate over screening strategies was recently reviewed.[23,24]

Thyroid-stimulating hormone ranges during pregnancy are quite different than the nonpregnant normative ranges because of the effects of hCG and T4 during pregnancy. As a result, nonpregnant normative ranges cannot be used to direct therapy during pregnancy.[10–12] Notably, TSH levels rarely exceed 2.5 mIU/L during the first trimester or 3.0 mIU/L during the second and third trimesters. Furthermore, the lower limits of the TSH reference range are significantly lower than nonpregnant references ranges (0.1 vs 0.4 mIU/L). Using nonpregnant reference ranges, hypothyroid women could be misclassified during pregnancy as being euthyroid (TSH >2.5 but <4.0 mIU/L), and euthyroid pregnant women could be classified as being hyperthyroid (TSH <0.4 but >0.1 mIU/L). Accordingly, multiple societies (ATA, ES, ATA + AACE) now endorse the use of validated method- and trimester-specific TSH reference ranges in the diagnosis and management of thyroid disease in pregnant women. In contrast, ACOG does not yet endorse the use of trimester-specific ranges.

The development of method- and trimester-specific TSH reference ranges is challenging because they vary with immunoassay platforms, geographic area of study, iodine status, age, sex, ethnicity, body mass index, hCG variants, and multiple pregnancy.[25–27] A normal euthyroid pregnant reference population would require sensitive testing for unrecognized thyroid disease and still may not allow widespread application. Early studies reported a relatively narrow TSH normative range in pregnant women. In an analysis comprising 8 studies in women carefully screened for thyroid disease, the 2.5th to 97.5th centile normative lower limit of TSH in the first trimester was 0.03 to 0.12 mIU/L, and the upper limit was 2.15 to 3.67 mIU/L, respectively.[28] More recent work indicates broader normative ranges during pregnancy, which is puzzling (Table 2). These differences could reflect the difficulties in obtaining a disease-free population for TSH sampling, or multiple other factors previously addressed. Furthermore, even when the same immunoassay system is used in carefully designed protocols by experienced investigators, TSH median values can vary up to 20%.[29] At present, trimester-specific TSH ranges in carefully screened pregnant populations using common commercial laboratory assays are not available.

Despite the ACOG position, there are data that argue for the adoption of trimester-specific TSH ranges in the management of hypothyroidism during pregnancy. In the absence of validated immunoassays for pregnancy, the consensus for the identification and management of

TABLE 2
Trimester-Specific TSH Reference Ranges (mIU/mL)

Reference	1st Trimester	2nd Trimester	3rd Trimester
Marwaha et al[95]	0.06–5.00	0.44–5.78	0.74–5.7
Fereidoun et al[96]	0.2–3.9	0.5–4.1	0.6–4.1
Santiago et al[97]	0.23–4.18	1.78–3.89	2.01–4.3
Yan et al[98]	0.03–4.51	0.05–4.50	0.47–4.54

women with thyroid disease is an upper limit TSH value of 2.5 mIU/L during the first trimester, 3.0 mIU/L in the second trimester, and 3.0 to 3.5 mIU/L in the third trimester.[11,12]

TT4 and FT4 Assays

In selected cases, diagnostic and therapeutic decisions for hypothyroid women will require the results of both TSH and FT4 assays. The most reliable method for measuring FT4 is ultrafiltration or equilibrium dialysis followed by immunoassay or liquid chromatography/tandem mass spectrometry.[15] Unfortunately, this methodology is expensive and not routinely available. In clinical practice, FT4 is measured using commercial immunoassays. However, pregnancy-induced changes in binding globulins, albumin, and nonesterified fatty acids can alter the performance and accuracy of FT4 estimates using current commercial platforms. Furthermore, only 0.02% of T4 is not bound to binding proteins. Therefore, the requirement to measure very small amounts of free ligand in the setting of much higher levels of TT4 adds additional complexity and uncertainty. Evidence exists that the precision of FT4 estimates using commercial immunoassays during pregnancy is variable and therefore subject to diagnostic errors, including both false-positive and false-negative results.[30,31]

The American Congress of Obstetrics and Gynecology does not specifically address the limitations of FT4 assays during pregnancy. In contrast, the ES advises that clinicians "cautiously interpret" the results of FT4 levels obtained during pregnancy.[10] As an alternative to FT4 estimates, surrogate markers are now endorsed. The 2 most common methods include measuring TT4 levels or the FT4 index (product of TT4 and thyroid hormone–binding ratio).[10,12] When using TT4 levels, it is necessary to adjust for the predictable rise in TT4 (150%) that accompanies the rise in TBG during pregnancy. More simply, the TT4 level should fall within the nonpregnant reference range when the reference range is multiplied by a factor of 1.5.

While the rationale for TT4 measures is compelling, there are potential pitfalls. Thyroid-binding globulin levels rise linearly during the first trimester and may not reach equilibrium until the second trimester.[13] Therefore, the use of TT4 in early gestation may be subject to diagnostic error, and the ES endorses the use of TT4 beginning in the second trimester. Second, the formula assumes that the TBG reference range is narrow and nonheterogeneous across gestation, a concept that has been recently challenged.[32] While method- and trimester-specific reference ranges using direct immunoassay for FT4 are endorsed, they are not yet established. At present, providers should rely on nonpregnant reference ranges for evaluation of FT4 measures or modified reference ranges for TT4 in clinical decisions.

Overt Hypothyroidism

Untreated overt hypothyroidism during pregnancy is unquestionably associated with an increased risk of adverse fetal/maternal complications.[5,33,34] In a recent study that assessed a total of 223,512 singleton pregnancies across 12 ethnically and racially diverse centers, a total of 3183 cases of primary hypothyroidism were identified according to discharge data. Primary hypothyroidism was associated with an increased risk of preeclampsia (odds ratio [OR], 1.47), superimposed preeclampsia (OR, 2.25), gestational diabetes (OR, 1.57), cesarean delivery (OR, 1.31), preterm birth (OR, 1.3), and neonatal intensive care unit admission (OR, 2.08).[35] Although confirming an increased risk of obstetric complications, the study was unable to assess whether inadequate treatment was the root cause of the increased morbidity. Nevertheless, previous studies indicate that adverse outcomes are reduced in women adequately treated for thyroid disease.[36,37] The American Congress of Obstetrics and Gynecology and all specialty and subspecialty societies endorse L-T4 treatment of overt hypothyroidism during pregnancy.

Subclinical Hypothyroidism

Numerous studies report an increased risk of adverse obstetric complications in women with subclinical hypothyroidism including spontaneous miscarriage, preterm delivery, preeclampsia, abruption, and maternal hypertension.[38–40] In addition, the offspring of mothers with subnormal T4 levels during pregnancy may be at increased risk for neurocognitive disorders, including intellectual impairment, which may be attenuated with treatment.[41] The American Congress of Obstetrics and Gynecology does not support treatment of subclinical hypothyroidism during pregnancy, whereas the ES and ATA + AACE endorse L-T4 treatment in women with subclinical hypothyroidism both preconceptually and when diagnosed during pregnancy. On the other hand, the ATA recommends L-T4 treatment in pregnant women who are both positive for thyroid peroxidase antibodies (TPOAbs) and have subclinical hypothyroidism of any degree, or in antibody-negative women with a TSH of more than 10 mU/L (note that the ATA guidelines consider a pregnant woman with a TSH of more than 10 mU/L to have overt hypothyroidism) (Table 1).

The lack of a clear consensus for treatment of subclinical hypothyroidism reflects the inconsistent obstetric hazards reported from study to study. Some observational trials indicate minimal or no increase in obstetric risk,[4,42] whereas others report an increased risk.[39,43] The inclusion of women with a mixture of diagnoses, including undertreated overt hypothyroidism and subclinical hypothyroidism, adds additional uncertainty to the risk analysis.[5] Only 1 interventional trial has evaluated obstetric outcomes in women screened for hypothyroidism.[39] Pregnant women were randomly assigned to either a universal screening or case-finding group to detect thyroid dysfunction in early gestation (hypothyroid = TSH >2.5 mIU/L + TPOAbs or hyperthyroid = undetectable TSH and elevated FT4). Women in either the high-risk case-finding group or the universal screening group were treated with levothyroxine to maintain TSH levels within trimester-specific ranges. In the case-finding low-risk group, thyroid function tests were assayed only in the postpartum period, and women in this group were not treated. Universal screening did not decrease the rate of maternal/fetal adverse outcomes compared with the case-finding group. However, in a post hoc analysis, low-risk women in the universal screening group who were identified and treated for thyroid dysfunction had a lower composite risk of adverse outcomes compared with untreated low-risk women in the case-finding group. Although this study is cited as an investigation of the "treatment of subclinical hypothyroidism and screening,"[10] only a single first-trimester assay for thyroid function was performed. In addition, the use of a composite index for obstetric outcome data, where individual outcome variables may be codependent, is a recognized limitation in the data analysis.

While some retrospective and prospective studies suggest that treating women who have subclinical hypothyroidism with L-T4 improves obstetric outcomes, there is no evidence of improved infant neurocognitive outcomes. In a recent controlled interventional trial, L-T4 treatment was not shown to modify neurocognitive risk.[44] The Controlled Antenatal Thyroid Screening Study screened 22,000 women for thyroid disease within the 16th week of gestation. Women with FT4 levels lower than the 2.5th centile and/or TSH levels above the 97.5th centile were randomized to a treatment arm (L-T4) or a control arm. Neuropsychological testing (Wechsler Preschool and Primary Scale of Intelligence - Third Edition) at 3 years of age showed no significant difference in IQ scores in the intention-to-treat analysis. In a secondary analysis, the percentage of offspring with a mean IQ of less than 85 was significantly higher in the control group (15%) versus the treated group (9%). A recognized limitation of the study design is that L-T4 was often not administered until 12 weeks' gestation or later (mean, 12.5 weeks), whereas the critical period for maternal thyroid hormone effects on fetal brain development may occur before 12 weeks' gestation. Whether earlier intervention would have altered outcomes is unknown.

Based on the limited data, it is not surprising that treatment guidelines for subclinical hypothyroidism are diverse and contentious. In many respects, it is sensible and fundamentally sound to treat subclinical hypothyroidism during pregnancy. There is good evidence that TSH normative reference ranges are different between pregnant and nonpregnant women. Therefore, TSH values that fall outside trimester-specific ranges are likely abnormal and indicative of thyroid dysfunction. Second, evidence exists that women with thyroid dysfunction during pregnancy are at an increased risk for maternal/fetal morbidity. Finally, the risk of replacement doses of L-T4 during pregnancy is marginal, and therefore the "potential benefits outweigh the potential risks."[10] We are supportive of treatment of subclinical hypothyroidism based on these findings. Women with subclinical hypothyroidism can be treated with L-T4 to achieve a preconceptual TSH of 2.5 mIU/L and maintain TSH levels within trimester-specific ranges during pregnancy. L-Thyroxine therapy can be stopped after pregnancy, and thyroid function reassessed. In a recent longitudinal study with a mean follow-up of nearly 5 years, 75% of women with the diagnosis of subclinical hypothyroidism during pregnancy had normal TSH levels after pregnancy.[45]

There is also a persuasive argument against treatment. According to the US Preventative Services Task Force, screening and treatment of asymptomatic individuals require evidence of measurable success (Agency for Healthcare Research and Quality). Therefore, the recommendation to universally endorse treatment of subclinical hypothyroidism may be premature and should await the results of randomized prospective clinical trials that prove benefit. The "Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy" sponsored by the National Institutes of Health and the Maternal Fetal Medicine Units Network will help clarify the role of L-T4 treatment for subclinical hypothyroidism and isolated hypothyroxinemia. In this study, roughly 120,000 pregnant women have been screened for thyroid disease. The intervention arm consists of L-T4 treatment to normalize TSH or FT4 values and a nontreated control arm. The off spring

will undergo neurocognitive screening at 5 years of age (Wechsler Preschool and Primary Scale of Intelligence - Third Edition), and the study is projected to be completed in 2015.

Isolated Hypothyroxinemia

Isolated hypothyroxinemia is characterized by low T4 levels (generally below the 2.5th centile of the T4 reference range) but normal TSH levels. The pathogenesis of this disorder is unclear, but the prevalence is higher (20%–30%) in regions of iodine deficiency and lower (1%–1.5%) in iodine-sufficient regions.[46] The clinical impact of isolated hypothyroxinemia on fetal/maternal health is unclear, with some but not all studies reporting fetal and maternal complications. The major risk of maternal isolated hypothyroxinemia is the potential for impaired neurodevelopment in offspring.[47–49]

The investigation of the risks of isolated hypothyroxinemia during pregnancy is complicated. In 1 study, only 14% of women who initially had low FT4 during early pregnancy remained hypothyroxinemic during pregnancy.[47] In a recent study done in the Greater Boston area, which is iodine sufficient, the authors failed to find a relationship between fetal intellectual development and maternal serum T4 levels.[50] Furthermore, in 2 large observational studies including more than 28,000 women, isolated hypothyroxinemia was not associated with adverse pregnancy outcomes.[3,4] The ES supports partial replacement therapy of isolated hypothyroxinemia at the discretion of the caregiver. In contrast, given the inconsistent results and lack of randomized trials that prove a benefit with treatment, ACOG, ATA, and ATA + AACE do not specifically endorse screening or treatment of isolated hypothyroxinemia.

Thyroid Antibodies

Autoimmune disease is the most common cause of thyroid failure and is characterized by elevated titers of thyroid antibodies (antithyroglobulin antibodies [TGAbs], antimicrosomal/TPOAbs, and anti-TSH receptor antibodies). The presence of thyroid antibodies confers an increased lifetime risk of developing hypothyroidism (4.3%/year vs 2%/year without TPOAbs).[51] Particularly relevant to obstetric providers, both thyroid dysfunction during pregnancy and postpartum thyroiditis are increased in women with thyroid antibodies.[52,53] In 2 prospective studies, roughly 20% of women with TPOAbs or TGAbs monitored during pregnancy had TSH levels that exceeded trimester-specific thresholds, and 33% to 50% developed postpartum thyroiditis.[54,55]

The presence of thyroid antibodies in otherwise euthyroid women is linked to an increased risk of miscarriage. The association was first reported in 1990 and subsequently confirmed in multiple observational studies.[56] An initial meta-analysis of 18 studies indicated a 3-fold increased risk of miscarriage.[57] A more recent meta-analysis of 31 studies reported a 4-fold increased risk of miscarriage in cohort studies (n = 19; OR, 3.90; confidence interval [CI], 2.48–6.12; $P < 0.001$) and a more modest risk for case-control studies (n = 12; OR, 1.80; CI, 1.25–2.60; $P = 0.002$).[58] The association of thyroid antibodies in women with recurrent pregnancy loss is less clear, with some studies showing an increased risk and others not.[59–62]

Only 1 interventional trial demonstrated a decreased risk of sporadic miscarriage in thyroid peroxidase (TPO)–positive women who spontaneously conceived and were treated with L-T4.[55] In a prospective randomized trial, euthyroid TPOAbs-positive women were either treated with a graded L-T4 dose (0.5–20 g/kg per day) or received no treatment during pregnancy. Treated women had a lower first-trimester miscarriage rate (3.5%) compared with untreated TPOAbs-positive women (13.8%). However, several methodological concerns about this trial have been raised. First, the study was not blinded or placebo controlled, and the control group had higher TSH and lower T4 levels (but still within the reference range). The average gestational age of miscarriage was 8.5 weeks' gestation, but the average date of institution of treatment was 10.5 weeks. All but one of the losses occurred before 11 weeks' gestation, and only 40% of women were on treatment by 8 weeks' gestation. Finally, the study was conducted in Italy, where iodine deficiency is prevalent, and iodine status was not determined.

Although multiple obstetric complications are linked to the presence of thyroid antibodies, the most consistent observation is an association with preterm delivery. While a number of investigators have reported an increased risk,[54,63–66] larger observational studies comparing preterm delivery rates (<37 weeks) in antibody-positive versus antibody-negative women including Männistö et al (5.9 vs 4.3%),[4,42] Haddow et al[67] (7.5 vs 6.4%) and Abbassi-Ghanavati et al[68] (6.6 vs 5.7%) failed to support these findings. A large meta-analysis including 11 prospective cohort studies and more than 35,000 women reported a modest increased risk in women with positive TPOAbs (risk ratio, 1.69; CI, 1.19–2.41; $P = 0.003$), but not in women with positive TGAbs. When the analysis was restricted to studies that carefully excluded women with thyroid dysfunction, the association was more robust (risk ratio, 1.98; CI, 1.29–3.04; $P = 0.002$).[69]

Initial retrospective and uncontrolled studies suggest that L-T4 treatment may reduce the risk of

obstetric complications in women with thyroid antibodies. However, there is only 1 interventional trial that has evaluated L-T4 treatment on obstetric outcomes. In this trial, preterm births were lower in the L-T4–treated group compared with untreated women (7 vs 22.4%).[55] In a recent observation study of 5791 pregnant women (Generation R study), there was a 1.7-fold increased risk of preterm (<37 weeks) and a 2.5-fold increase risk of very preterm delivery (<34 weeks) in women with positive TPOAbs.[70] When the analyses were adjusted for serum TSH and FT4 levels, the risk of prematurity persisted, suggesting that the risk of preterm delivery is related to the effects of autoimmune disease and not thyroid dysfunction. Interestingly, there was an increased risk for prematurity in women with hypothyroxinemia but not in women with subclinical hypothyroidism who were TPOAbs-negative, suggesting that subclinical hypothyroidism is not a risk factor for preterm delivery. Based on limited published data, routine screening for thyroid antibodies and treatment of euthyroid but antibody-positive women during pregnancy is not recommended at this time.

The ACOG guidelines do not address surveillance strategies for women with positive TPOAbs during pregnancy. According to the ES and ATA, TPOAbs-positive women should be monitored every 4 to 6 weeks for elevation of TSH above the reference range for pregnancy and at least once between 26 and 32 weeks of pregnancy.[10,11] The surveillance of euthyroid but antibody-positive women advocated by the subspecialty organizations is reasonable. Euthyroid women with positive antibodies can develop overt or subclinical hypothyroidism during pregnancy, although the exact prevalence of this complication is unknown. It is hoped that future studies will better define the role of treatment; such studies include the TABLET (Thyroid AntiBodies and LEvoThyroxine) trial, a multicenter, placebo-controlled, double-blind trial designed to determine the efficacy of L-T4 treatment on miscarriage and preterm delivery rates in euthyroid women.

Women on Levothyroxine

Most women with hypothyroidism are diagnosed and treated with L-T4 prior to pregnancy. It is important to recognize that adequate preconceptual replacement therapy may be inadequate to maintain physiologic levels of thyroid hormones during pregnancy, depending on the degree of glandular damage and functional capacity. In fact, the majority of women (50%–85%) with thyroid disease require a dose adjustment during pregnancy to keep TSH levels within the desirable range.[71]

The American Congress of Obstetrics and Gynecology endorses appropriate L-T4 treatment during pregnancy to maintain euthyroidism, but the methods of monitoring and treatment goals are not clearly specified. In contrast, other subspecialty guidelines (ES, ATA, and ATA + AACE) endorse a preconception TSH level of less than 2.5 mIU/mL in women on L-T4 with the goal to minimize the potential adverse effects of low T4 levels on fetal/maternal health (Table 1). During pregnancy, the treatment goal is to maintain TSH levels within trimester-specific normative ranges. In early pregnancy, there are 2 options to achieve this goal. A TSH level can be measured at the onset of pregnancy and the dose of T4 adjusted accordingly. Alternatively, the preconceptual dose of T4 can be increased by 30% (2 extra tablets per week) as soon as pregnancy is diagnosed.[11] An empiric dose adjustment is a reasonable approach for the obstetrician who is unable to evaluate patients in very early gestation, or when subspecialty consultation is not readily available. A recent prospective data trial is supportive of this strategy.[72] In the recent Therapy Trial, 23 women on L-T4 were randomized to receive either 2 or 3 extra tablets per week beginning in early gestation (mean, 6.3 weeks). In the group that had 2 extra tablets per week, 85% were euthyroid in the first trimester, and only 25% of women required a dose adjustment during later gestations. Two women (8%) had a low TSH (<0.1 mIU/mL), but only 1 had an elevated FT4 index. In this study, thyroid function testing was performed every 2 weeks; however, 92% of abnormal tests were evident by testing every 4 weeks.

Dose adjustments of L-T4 are related to the severity of thyroid disease. Replacement doses in women with a compromised but partially functional thyroid gland (eg, autoimmune thyroid disease) are less compared to athyroidic women.[73] Furthermore, dose adjustments are related to preconception TSH levels. In 1 study, only 17% of women with a preconception TSH of less than 1.2 mIU/mL required a dose adjustment in the first trimester.[74] While the optimal TSH target range and dosage schedule are unknown, women on T4 should have thyroid function tests every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks' gestation.[10,12] The postpartum dose of L-T4 should be reduced to prepregnancy levels following delivery. The ATA recommends thyroid function testing 6 weeks after delivery, and the ES recommends testing at 6 months or earlier if clinically indicated.

Postpartum thyroid dysfunction can occur within the first 12 months after delivery,[53] with the majority of cases due to postpartum thyroiditis.[50] The clinical presentation is generally transient hyperthyroidism followed by transient hypothyroidism.[51] Risk factors for postpartum thyroiditis include positive TPOAbs, type 1 diabetes, chronic viral hepatitis, systemic lupus erythematosus, and previous Graves disease.[11] Longitudinal studies indicate a high risk of hypothyroidism (nearly 40% at 12 years of follow-up) in women with postpartum thyroid dysfunction, and the risk is increased in women with positive TPOAbs and TSH values of more than 2.6 mIU/mL at time of diagnosis.[75] The ATA recommends TSH testing every 2 months until 1 year postpartum in women with postpartum thyroiditis. The ES recommends TSH screening 6 months postpartum in TPO-positive women. In women with type 1 diabetes, Graves disease in remission, or viral hepatitis, screening at 3 and 6 months is recommended. Annual TSH testing is also advised in women with a history of postpartum thyroiditis.

Euthyroid Women With TSH Between 2.5 and 4.5 mIU/L

Whether the upper limit of normal for the TSH reference range should be changed is a question of intense debate.[76] According to the National Academy of Clinical Biochemists, 95% of TSH levels fall below 2.5 mIU/L in a population without thyroid disease.[77] In addition, mean and median values are approximately 1.5 mIU/L, suggesting that the reference range is skewed to the right, possibly due to the inclusion of individuals with undiagnosed thyroid disease. The debate is further complicated as the upper limit of the TSH reference range increases with aging[26] and is also influenced by race/ethnicity and sex.[25] Arguments against lowering the upper limit of the TSH reference range include a reanalysis of the National Health and Nutrition Examination Survey III data where the TSH reference range was calculated in a disease-free population that also excluded individuals with thyroid antibodies. In this study, the upper limit of the TSH reference range dropped only marginally (4.5–4.1 mIU/L).[1] Similarly, in the Hanford Thyroid Disease Study, the upper limit of the reference range was 4.1 mIU/L in an iodine-sufficient cohort without evidence of thyroid disease, thyroid autoantibodies, or abnormal thyroid imaging studies.[78]

An important clinical question is whether women contemplating pregnancy with a TSH in this range are at increased risk of maternal and fetal morbidity. The American Congress of Obstetrics and Gynecology does not cite a position, but 2 subspecialty organizations now support empiric preconceptual L-T4 treatment in women with a baseline TSH between 2.5 and 4.5 mIU/L. Notably, in a recent joint document published by the AACE and the ATA, the task force concluded that treatment with L-T4 should be considered in women of child-bearing age with serum TSH levels between 2.5 mIU/L and the upper limit of normal for a given laboratory's reference range if they are "in the first trimester of pregnancy or planning a pregnancy." The ES also supports "prenatal" treatment with low-dose T4 when the TSH level is more than 2.5 mIU/L on repeated values. A frequently cited study reported that miscarriage risk was significantly increased in euthyroid and TPO-negative women with a TSH between 2.5 and 5 mIU/L compared with a similar group with a TSH of less than 2.5 mIU/L (6.1% vs 3.6%). The risk of preterm delivery was not increased.[79] The findings of this study are provocative but limited in that TSH values were not obtained in the preconception period, but were drawn during early pregnancy (within the first 11 weeks of gestation).

Whether a single TSH value of more than 2.5 and less than 4.5 mIU/L is precise enough to endorse a change in clinical management is debatable. Thyroid-stimulating hormone production is pulsatile and has a diurnal rhythm with peak levels in the early morning or late evening.[80,81] Thyroid-stimulating hormone values can vary by up to 40% in serial samples performed during a single day, and up to 50% of abnormal TSH levels are normal after repeat testing.[82,83] Strenuous exercise, sleep deprivation, and endocrine disorders can all alter TSH levels. In a recent study, 50% of women with an abnormal preconception TSH (>3.0) had a normal value (<2.5) during early pregnancy, a finding that raises the possibility of either overtreating or undertreating.[84] Furthermore, population studies indicate that sex, ethnicity, and age all impact TSH normative ranges,[25] and the positive predictive value in the diagnosis of hypothyroidism is low when TSH values between 2.5 and 5.0 mIU/L are used.[76]

In the absence of interventional outcome data to support a treatment benefit, the decision for preconceptual treatment with L-T4 for TSH values between 2.5 and 4.5 mIU/L is at the discretion of the provider. We support treatment because L-T4 for this indication carries minimal risk and has the potential to decrease the risk of maternal/fetal complications associated with hypothyroidism, which can develop in this population during pregnancy. At a minimum, monitoring of thyroid function in untreated women during gestation should be considered. If TSH levels exceed trimester-specific

ranges, then treatment with L-T4 is appropriate. In women treated with L-T4, the monitoring of thyroid function tests with dose adjustments is analogous to the recommendations for women on L-T4 for hypothyroidism.

Iodine

Iodine is a critical trace element required for thyroid hormone synthesis. During pregnancy, the demand for iodine increases with increasing thyroid hormone production, renal clearance of iodine, and fetal requirements. Iodine deficiency is the most common cause of maternal hypothyroidism worldwide, and severe iodine deficiency is associated with significant fetal/maternal risks including fetal neurocognitive deficits (cretinism) and obstetric morbidity.[85,86] Intervention trials in areas of severe iodine deficiency indicate that the incidence of cretinism is reduced with iodine treatment initiated before or during early pregnancy.[87] Furthermore, iodine supplementation is effective in reducing obstetric risks.[88,89] The benefits of iodine treatment for mild or moderate iodine deficiency are less clear, but neurocognitive outcomes may be improved with iodine supplementation when administered to women in iodine-deficient areas.[90]

While most Americans consume adequate levels of iodine (diet and iodized salt), roughly 15% of reproductive-age women and 17% of pregnant women in the United States have low urinary iodine levels (<50 g/L).[91] Moreover, only 20% of pregnant, lactating, or nonpregnant women take iodine supplements. The avoidance of iodized salts, decreasing amounts of iodine in the US food supply, and other dietary habits contribute to low iodine intake. The recommended prepregnancy daily intake of iodine is 150 to 200 μg/day, and during pregnancy and lactation 250 to 300 μg/day. Unfortunately, there are no simple clinical tests to determine the adequacy of iodine intake; so many clinical specialists endorse iodine supplements, which contain at least 150 μg of potassium iodide or iodate taken daily. Prenatal vitamins can be a source of iodine, but in 1 study only 51% of prenatal vitamins contained iodide, and the dose was inconsistent from product to product.[92,93] Thus, it is prudent to confirm that prescribed supplements contain the appropriate amount of iodine. Excessive iodine may exacerbate autoimmune thyroid disease, and the fetal thyroid is also sensitive to excessive iodine ingestion. However, total doses of iodide less than 500 to 1100 μg are considered safe during pregnancy.[94]

Summary

We have presented the major differences in the management of hypothyroidism during pregnancy between ACOG and other subspecialty organizations whose primary focus is the care for women with thyroid disease. Although treatment strategies differ in many key areas, there is universal agreement that women with hypothyroidism require appropriate treatment to reduce maternal and fetal morbidity. In women on L-T4 therapy, the use of trimester-specific TSH thresholds to monitor and adjust L-T4 treatment is preferable when compared with nonpregnant TSH reference ranges. In the absence of laboratory-specific TSH ranges, trimester-specific TSH cutoff values established by the ES and ATA can be used.

Observational studies support L-T4 treatment in women with subclinical hypothyroidism with a preconception TSH of less than 2.5 mIU/L as a treatment goal. The risks of L-T4 therapy in this group are minimal, but the actual benefit in terms of maternal and fetal risk reduction awaits the completion of interventional trials. The benefit of preconceptual treatment of euthyroid women with a TSH of more than 2.5 but less than 4.5 mIU/L or euthyroid women with thyroid antibodies is less clear, and the use of L-T4 treatment is at the discretion of the provider. At a minimum, TSH values should be monitored during pregnancy in these categories because of an increased risk for developing hypothyroidism during pregnancy. Finally, obstetric providers should encourage iodine supplementation during pregnancy by recommending or prescribing prenatal vitamin products with adequate source of iodine.

REFERENCES

1. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T (4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489–499.
2. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:526–534.
3. 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.
4. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol*. 2008;112:85–92.
5. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. *Endocr Rev*. 2010;31:702–755.
6. Rinaldi MD, Stagnaro-Green AS. Thyroid disease and pregnancy: degrees of knowledge. *Thyroid*. 2007;17:747–753.
7. Haymart MR. The role of clinical guidelines in patient care: thyroid hormone replacement in women of reproductive age. *Thyroid*. 2010;20:301–307.
8. Hallengren B, Lantz M, Andreasson B, et al. Pregnant women on thyroxine substitution are often dysregulated in early pregnancy. *Thyroid*. 2009;19:391–394.
9. McClain MR, Lambert-Messerlain G, Haddow JE, et al. Sequential first- and second-trimester TSH, free thyroxine, and thyroid antibody measurements in women with known hypothyroidism: a FaSTER trial study. *Am J Obstet Gynecol*. 2008;199:129.e1-129.e6.

10. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2012;97:2543–2565.
11. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*. 2011;21:1081–1125.
12. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18:988–1028.
13. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev*. 1997;18:404–433.
14. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. *N Engl J Med*. 1994;331:1072–1078.
15. Soldin OP, Tractenberg RE, Hollowell JG, et al. Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations during gestation: trends and associations across trimesters in iodine sufficiency. *Thyroid*. 2004;14:1084–1090.
16. Glinoer D, De Nayer P, Robyn C, et al. Serum levels of intact human chorionic gonadotropin (hCG) and its free α and β subunits, in relation to maternal thyroid stimulation during normal pregnancy. *J Endocrinol Invest*. 1993;16:881–888.
17. Haddow JE, McClain M, Lambert-Messerlian G, et al. Variability in thyroid-stimulating hormone suppression by human chorionic [corrected] gonadotropin during early pregnancy. *J Clin Endocrinol Metab*. 2008;93:3341–3347.
18. Williams GR. Neurodevelopment and neurophysiological actions of thyroid hormones. *J Neuroendocrinol*. 2008;20:784–794.
19. Morreale de Escobar G. The role of thyroid hormone in fetal neurodevelopment. *J Pediatr Endocrinol Metab*. 2001;14 (suppl 6):1453–1462.
20. Haddow JE. Maternal thyroxine and fetal brain development: the latest chapter, a look back, and considerations for the future. *J Clin Endocrinol Metab*. 2013;98:1388–1390.
21. Henrichs J, Ghassabian A, Peeters RP, et al. Maternal hypothyroxinemia and effects on cognitive functioning in childhood: how and why? *Clin Endocrinol*. 2013;79:152–162.
22. Gronowski AM, Haddow J, Kilpatrick S, et al. Thyroid function during pregnancy: who and how should we screen? *Clin Chem*. 2012;58:1397–1401.
23. Lazarus JH. Screening for thyroid dysfunction in pregnancy: is it worthwhile? *J Thyroid Res*. 2011;2011:397012.
24. Vila L, Velasco I, González S, et al. On the need for universal thyroid screening in pregnant women. *Eur J Endocrinol*. 2014;170:R17–R30.
25. Boucai L, Hollowell JG, Surks MI. An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. *Thyroid*. 2011;21:5–11.
26. Surks MI, Boucai L. Age- and race-based serum thyrotropin reference limits. *J Clin Endocrinol Metab*. 2010 95:496–502.
27. Männistö T, Surcel H-M, Ruokonen A, et al. Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population. *Thyroid*. 2011;21:291–298.
28. Glinoer D, Spencer CA. Serum TSH determinations in pregnancy: how, when and why? *Nat Rev Endocrinol*. 2010;6:526–529.
29. Haddow JE, Palomaki GE, McClain MR. Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges [letter to the editor]. *Obstet Gynecol*. 2006;107:205–206.
30. Lee RH, Spencer CA, Mestman JH, et al. Free T4 immunoassays are flawed during pregnancy. *Am J Obstet Gynecol*. 2009; 200: 260.e1–260.e6.
31. Sapin R, d'Herbomez M. Free thyroxine measured by equilibrium dialysis and nine immunoassays in sera with various serum thyroxine-binding capacities. *Clin Chem*. 2003;49:1531–1535.
32. Midgley JE, Hoermann R. Measurement of total rather than free thyroxine in pregnancy: the diagnostic implications. *Thyroid*. 2013;23:259–261.
33. Leung AS, Millar LK, Koonings PP, et al. Perinatal outcome in hypothyroid pregnancies. *Obstet Gynecol*. 1993;81:349–353.
34. Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. *Obstet Gynecol*. 1988;72:108–112.
35. Männistö T, Mendola P, Grewal J, et al. Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. *J Clin Endocrinol Metab*. 2013:98;2725–2733.
36. Tan TO, Cheng YW, Caughey AB. Are women who are treated for hypothyroidism at risk for pregnancy complications? *Am J Obstet Gynecol*. 2006;194:e1–e3.
37. Matalon S, Sheiner E, Levy A, et al. Relationship of treated maternal hypothyroidism and perinatal outcome. *J Reprod Med*. 2006;51:59–63.
38. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol*. 2005;105: 239–245.
39. Negro R, Schwartz A, Gismondi R, et al. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab*. 2010;95:1699–1707.
40. van den Boogaard E, Vissenberg R, Land JA, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum Reprod Update*. 2011;17:605–619.
41. 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.
42. Männistö T, Vääräsmäki M, Pouta A, et al. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *J Clin Endocrinol Metab*. 2009;94:772–779.
43. Ashoor G, Maiz N, Rotas M, et al. Maternal thyroid function at 11 to 13 weeks of gestation and subsequent fetal death. *Thyroid*. 2010;20:989–993.
44. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med*. 2012;366:493–501.
45. Shields BM, Knight BA, Hill AV, et al. Five-year follow-up for women with subclinical hypothyroidism in pregnancy. *J Clin Endocrinol Metab*. 2013;98:E1941–E1945.
46. Moleti M, Vermiglio F, Trimarchi F. Maternal isolated hypothroxinemia: to treat or not to treat? *J Endocrinol Invest*. 2009;32:780–782.
47. Pop VJ, Brouwers EP, Vader HL, et al. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)*. 2003;59:282–288.
48. Kooistra L, Crawford S, van Baar AL. Neonatal effects of maternal hypothyroxinemia during early pregnancy. *Pediatrics*. 2006;117:161–167.
49. Henrichs J, Bongers-Schokking JJ, Schenk JJ, et al. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R study. *J Clin Endocrinol Metab*. 2010;95:4227–4234.
50. Oken E, Braverman LE, Platek D, et al. Neonatal thyroxine, maternal thyroid function, and child cognition. *J Clin Endocrinol Metab*. 2009;94:497–503.
51. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995;43:55–68.
52. Lazarus JH. The continuing saga of postpartum thyroiditis. *J Clin Endocrinol Metab*. 2011;96:614–616.
53. Stagnaro-Green A. Approach to the patient with postpartum thyroiditis. *J Clin Endocrinol Metab*. 2012;97:334–342.
54. Glinoer D, Riahi M, Grün JP, et al. Risk of subclinical hypothyroidism in pregnant women with asymptomatic thyroid disorders. *J Clin Endocrinol Metab*. 1994;79:197–204.
55. Negro R, Formoso G, Mangieri T, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab*. 2006;91:2587–2591.

56. Stagnaro-Green A, Roman SH, Cobin RH, et al. Detection of at-risk pregnancy by means of highly sensitive assays for thyroid antibodies. *JAMA*. 1990;264:1422–1425.
57. Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. *Eur J Endocrinol*. 2004;150:751–755.
58. Thangaratinam S, Tan A, Knox E, et al. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ*. 2011;342:d2616.
59. Pratt DE, Kaberlein G, Dudkiewicz A, et al. The association of antithyroid antibodies in euthyroid nonpregnant women with recurrent first trimester abortions in the next pregnancy. *Fertil Steril*. 1993;60:1001–1005.
60. Rushworth FH, Backos M, Rai R, et al. Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid autoantibodies. *Hum Reprod*. 2000;15:1637–1639.
61. Esplin MS, Branch DW, Silver R, et al. Thyroid autoantibodies are not associated with recurrent pregnancy loss. *Am J Obstet Gynecol*. 1998;179:1583–1586.
62. Yan J, Sripada S, Saravelos SH, et al. Thyroid peroxidase antibody in women with unexplained recurrent miscarriage: prevalence, prognostic value, and response to empirical thyroxine therapy. *Fertil Steril*. 2012;98:378–382.
63. Negro R, Soldin OP, Obregon MJ, et al. Hypothyroxinemia and pregnancy. *Endocr Pract*. 2011;17:422–429.
64. Ghafoor F, Mansoor M, Malik T, et al. Role of thyroid peroxidase antibodies in the outcome of pregnancy. *J Coll Physicians Surg Pak*. 2006;16:468–471.
65. Tierney K, Delpachitra P, Grossmann M, et al. Thyroid function and autoantibody status among women who spontaneously deliver under 35 weeks of gestation. *Clin Endocrinol (Oxf)*. 2009;71:892–895.
66. Stagnaro-Green A. Maternal thyroid disease and preterm delivery. *J Clin Endocrinol Metab*. 2009;94:21–25.
67. Haddow JE, Cleary-Goldman J, McClain MR, et al. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery. *Obstet Gynecol*. 2010;116:58–62.
68. Abbassi-Ghanavati M, Casey BM, Spong CY, et al. Pregnancy outcomes in women with thyroid peroxidase antibodies. *Obstet Gynecol*. 2010;116:381–386.
69. He X, Wang P, Wang Z, et al. Endocrinology in pregnancy: thyroid antibodies and risk of preterm delivery: a meta-analysis of prospective cohort studies. *Eur J Endocrinol*. 2012;167:455–464.
70. Korevaar TIM, Schalekamp-Timmermans S, de Rijke YB, et al. Hypothyroxinemia and TPO-antibody positively are risk factors for premature delivery: the Generation R study. *J Clin Endocrinol Metab*. 2013;98:4382–4390.
71. 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.
72. 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.
73. Loh JA, Wartofsky L, Jonklaas J, et al. The magnitude of increased levothyroxine requirements in hypothyroid pregnant women depends upon the etiology of the hypothyroidism. *Thyroid*. 2009;19:269–275.
74. Abalovich M, Alcaraz G, Kleiman-Rubinsztein J, et al. The relationship of preconception thyrotropin levels to requirements for increasing the levothyroxine dose during pregnancy in women with primary hypothyroidism. *Thyroid*. 2010;20:1175–1178.
75. Stuckey BGA, Kent GN, Ward LC, et al. Postpartum thyroid dysfunction and the long-term risk of hypothyroidism: results from a 12-year follow-up study of women with and without postpartum thyroid dysfunction. *Clin Endocrinol*. 2010;73:389–395.
76. Surks MI, Goswami G, Daniels GH. Controversy in clinical endocrinology. The thyrotropin reference range should remain unchanged. *J Clin Endocrinol Metab*. 2005;90:5489–5496.
77. Baloch Z, Carayon P, Conte-Devolx B, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid*. 2003;13:3–126.
78. Hamilton TE, Davis S, Onstad L, et al. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2008;93:1224–1230.
79. 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.
80. Bartalena L, Martino E, Falcone M, et al. Evaluation of the nocturnal serum thyrotropin (TSH) surge, as assessed by TSH ultrasensitive assay, in patients receiving long term L-thyroxine suppression therapy and in patients with various thyroid disorders. *J Clin Endocrinol Metab*. 1987;65:1265–1271.
81. Sturgess I, Thomas SH, Pennell DJ, et al.. Diurnal variation in TSH and free thyroid hormones in patients on thyroxine replacement. *Acta Endocrinol (Copenh)*. 1989;121:674–676.
82. Caron PJ, Nieman LK, Rose SR, et al. Deficient nocturnal surge of thyrotropin in central hypothyroidism. *J Clin Endocrinol Metab*. 1986;62:960–964.
83. Karmisholt J, Andersen S, Laurberg P. Variation in thyroid function tests in patients with stable untreated subclinical hypothyroidism. *Thyroid*. 2008;18:303–308.
84. Balthazar U, Steiner AZ. Periconceptional changes in thyroid function: a longitudinal study. *Reprod Biol Endocrinol*. 2012;10:20–25.
85. Qian M, Wang D, Watkins WE, et al. The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China. *Asia Pac J Clin Nutr*. 2005;14:32–42.
86. Pharoah POD, Buttfield IH, Hetzel BS. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet*. 1971;297:308–310.
87. DeLong GR, Leslie PW, Wang SH, et al. Effect on infant mortality of iodination of irrigation water in a severely iodine-deficient area of China. *Lancet*. 1997;350:771–773.
88. Chaouki ML, Benmiloud M. Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. *Eur J Endocrinol*. 1994;130:547–551.
89. O'Donnell KJ, Rakeman MA, Zhi-Hong D, et al. Effects of iodine supplementation during pregnancy on child growth and development at school age. *Dev Med Child Neurol*. 2002;44:76–81.
90. Berbel P, Mestre JL, Santanmaria A, et al. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid*. 2009;19:511–519.
91. Perrine CG, Herrick K, Serdula MK, et al. Some subgroups of reproductive age women in the United States may be at risk for iodine deficiency. *J Nutr*. 2010;140:1489–1494.
92. Gregory CO, Serdula MK, Sullivan KM. Use of supplements with and without iodine in women of childbearing age in the United States. *Thyroid*. 2009;19:1019–1020.
93. Leung AM, Pearce EN, Bravermann LE. Iodine content of prenatal multivitamins in the United States. *N Engl J Med*. 2009;360:939–940.
94. Stagnaro-Green A, Sullivan S, Pearce EN. Iodine supplementation during pregnancy and lactation. *JAMA*. 2012;308:2463–2464.
95. Marwaha RK, Chopra S, Gopalakrishnan S, et al. Establishment of reference range for thyroid hormones innormal pregnant Indian women. *Br J Obstet Gynecol*. 2008;115:602–606.
96. Fereidoun A, Ladan M, Atieh A, et al. Establishment of the trimester-specific reference range for free thyroxine index. *Thyroid*. 2013;23:354–359.
97. Santiago P, Berrio M, Olmedo P, et al. Reference values for thyroid hormones in the population of pregnant women in Jaen (Spain). *Endocrinol Nutr*. 2011;58:62–67.
98. Yan YQ, Dong ZL, Dong L, et al. Trimester- and method-specific reference intervals for thyroid tests in pregnant Chinese women: methodology, euthyroid definition and iodine status can influence the setting of reference intervals. *Clin Endocrinol (Oxf)*. 2011;74:262–269.