Subclinical hypothyroidism in the infertile female population: a guideline

Practice Committee of the American Society for Reproductive Medicine

The American Society for Reproductive Medicine, Washington, D.C.

There is controversy regarding whether to treat subtle abnormalities of thyroid function in infertile female patients. This guideline document reviews the risks and benefits of treating subclinical hypothyroidism in female patients with a history of infertility and miscarriage, as well as obstetric and neonatal outcomes in this population. (Fertil Steril® 2024;121:765-82. ©2024 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Thyroid-stimulating hormone, subclinical hypothyroidism, pregnancy, pregnancy loss, levothyroxine

Overt hypothyroidism can potentially have a significant impact on reproductive outcomes. Complications may include an increased incidence of infertility, miscarriage, and adverse obstetric, fetal, and neurocognitive development outcomes in offspring (1–3). There are also older data that suggest that inadequate treatment of subclinical hypothyroidism (SCH) can lead to infertility, miscarriage, and adverse obstetrical and neurodevelopmental outcomes (3–7). However, debate persists about the definition of SCH and the decision of when to screen and treat, particularly for infertile women and women attempting pregnancy.

The classic definition of SCH is a thyrotropin (thyroid-stimulating hormone [TSH]) level greater than the upper limit of the normal range (4.5–5.0 mIU/L) with normal free thyroxine (FT4) levels. With this definition, the incidence of SCH in the reproductive-age population is approximately 4%–8% (8, 9). However, the upper range of normal in the general population appears to be below the upper limit of normal as determined using the third-generation assay (10). Moreover, given the potential impact of inadequate thyroid function, the question remains whether treatment should be initiated for subtler abnormalities of thyroid dysfunction. Treatment recommendations for SCH vary between the American Society for Reproductive Medicine (ASRM), the Endocrine Society, the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists, the American College of Obstetricians and Gynecologists (ACOG), and others (11, 12). Our current understanding of the effect of thyroid dysfunction and thyroid autoimmunity (TAI) on fertility and pregnancy is based on mainly retrospective studies. Although there are limited high-quality data available, consistent trends in the literature allow for the guidelines set forth in this document.

Received December 26, 2023; accepted December 28, 2023; published online December 30, 2023.
Supported by the American Society for Reproductive Medicine (ASRM). Authors who serve on the ASRM Practice Committee were reimbursed by ASRM for expenses related to travel to Practice Committee meetings where they reviewed drafts of manuscripts. The American Society for Reproductive Medicine receives no outside funding for the development of guidelines.
Correspondence: Practice Committee, American Society for Reproductive Medicine, Washington, D.C. (E-mail: asrm@asrm.org).

Fertil Steril® Vol. 121, No. 5, May 2024 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2023.12.038

LIMITATIONS OF THE LITERATURE

Multiple challenges exist in interpreting the literature on the treatment of SCH and fertility, obstetric, neonatal, and neurodevelopment outcomes. Available studies used a wide range of TSH levels to define SCH, ranging from >2.5–10 mIU/L, meaning various studies measured different exposure levels and are challenging to compare. Most of the literature is of low to intermediate quality, placing studies at risk for bias. Very few randomized trials are available, and some questions addressed in this guideline have no randomized trials. Although several meta-analyses exist, they tend to be limited in that they all assess the same two or three randomized trials and all report on the same data. For example, there are at least eight meta-analyses addressing treatment of SCH and fertility outcomes, but only three randomized trials. Many studies were significantly underpowered and at increased risk of type I and type II errors. Thyrotropin levels are influenced by several population characteristics, and the studies included significant heterogeneity in the populations sampled.

In this updated version of the SCH guideline, the ASRM Practice Committee and assigned Task Force consciously decided to delve more

deeply into the quality of the included studies. Studies from other areas of literature have found that 8% of randomized trials have critical flaws, and 14% contain falsified data (13). Specifically, we searched for and considered trial retractions, letters of concern, and Task Force or Practice Committee members' concerns about data integrity (14).

Such studies were either excluded or considered critically in the summary and recommendation sections of the guideline. This approach, as well as including new high-quality randomized trials, resulted in different conclusions compared with the 2015 version of the same document in a few key places. It is important to note that this document does not review the screening and treatment of SCH in women with recurrent pregnancy loss (RPL). That clinical scenario is discussed in a separate guideline.

MATERIALS AND METHODS

This clinical practice guideline followed a methodological protocol established by ASRM staff and executive leadership, the ASRM Practice Committee, an independent consulting epidemiologist, and a patient representative. The ASRM Practice Committee identified the necessity of this guideline for SCH and empaneled a task force of experts to engage in its development. Members of the task force applied the Population, Interventions, Comparisons, and Outcomes (PICO) framework to formulate a focused question related to clinical practice and evidence-based treatments for SCH, as well as preliminary inclusion and exclusion criteria.

This guideline provides evidence-based recommendations for the following: defining SCH; the association of SCH with miscarriage, infertility, adverse obstetric outcomes, and neurodevelopmental outcomes in offspring; treatment of SCH to improve miscarriage, clinical pregnancy, live birth (LB), and neurodevelopmental outcomes in offspring; the association of antithyroid antibodies with adverse reproductive outcomes; and the management of SCH in patients during the first trimester of pregnancy.

A systematic literature search was performed using a combination of the following keywords: subclinical, hypothyroidism, diagnosis, level, criteria, pregnancy loss, abortion, miscarriage, infertility, pregnancy, baby, fetus, birth defect, delivery, antibody, elevated TSH levels, live-birth rate, preeclampsia, pregnancy rate, complications, death, and demise. Literature from the prior guideline published in 2015 was included, and a new search using the same search criteria was performed, restricted to MEDLINE citations of human subject research published in the English language from April 2014 to February 2020 and updated on August 24, 2022.

The literature search and examination of reference lists from primary and review articles yielded 498 studies, of which 87 met inclusion criteria. This guideline's summary statements and recommendations were based on included studies.

Per inclusion and exclusion criteria that the task force agreed on (Table 1), included for assessment were randomized controlled trials (RCTs), systematic reviews or meta-analyses of RCTs, systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies, trials without randomization, cohort studies, and case-control studies. Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions on the basis of clinical experience, and reports of expert committees were excluded from this guideline. Guidance from other international medical societies was included for contrast and comparison.

Titles and abstracts of potentially relevant articles were screened and reviewed initially according to preliminary inclusion and exclusion criteria determined by task force members. The task force reviewed the full articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in total. Disagreements about inclusion among reviewers were discussed and resolved by consensus or arbitration after consultation with an independent reviewer and epidemiologist.

Quality of Evidence

A methodological specialist extracted data from included studies into an evidence table for outcomes identified by the task force, including LB, clinical pregnancy, miscarriage, and obstetric as well as neonatal adverse outcomes. Members of the task force had no conflicts of interest in the topic and critically assessed the strengths and limitations of available evidence that met inclusion and exclusion criteria to rate the quality of each study and assign a quality grade on the basis of the rating scale below, which was recorded in the evidence table.

Assessment of the quality of the evidence allowed the task force to make distinctions among studies. The quality of the evidence was evaluated using the following grading system (Table 2). The task force chair reviewed grades of quality assigned by members of the task force and provided oversight throughout the entire development process. When no grade was assigned, the chair determined a grade of quality on the basis of a study's strengths and limitations. The study design was evaluated, and the quality of the methodology was assessed on the basis of components, including blinding, allocation concealment, appropriate control groups, intention-to-treat analysis, generalizability, and risk of bias. The consulting epidemiologist and chair of the task force confirmed agreement with the expert task force's assessment of quality on the basis of the following definitions:

The task force summarized data from the evidence table in narrative form to include the characteristics, quality, benefit, and conclusions of studies relevant to answering each treatment related to the question. The task force convened to review the literature and summarize the findings.

Included evidence related to treatments for women with SCH was searched for and collected systematically, objectively assessed, and described clearly and succinctly to inform readers relying on ASRM guidelines with trusted recommendations that were guided by the quality of available evidence. These evidence-based recommendations are intended to optimize patient care and help guide medical practice in the field of reproductive medicine. The strengths of recommendations in this guideline were based on both the quality and strength (confidence/certainty) of evidence, risks, benefits, and expert judgment of the Practice Committee and task force (Table 3)

TABLE 1

Summary of inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Randomized controlled trials (RCTs); systematic reviews or meta-analyses of RCTs; systematic reviews or meta-analyses of a combination of RCTs; controlled trials without randomization; and cohort studies; controlled trials without randomization; cohort studies; case-control studies	• Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions on the basis of clinical experience, and reports of expert committees
• Published full article in peer-reviewed journal	• Abstracts
• Human adult studies	• Animal studies
• English	• Non-English
• Studies with a comparison group, including placebo or no treatment	• Studies without a comparison group
• Outcomes, primary or secondary: live birth, clinical pregnancy, miscarriage, obstetric, and neonatal adverse events	—
• Patients with subclinical hypothyroidism and infertility	—
• Patients with subclinical hypothyroidism in the first trimester of pregnancy	—
• Medical Practice Guidelines	—

Practice Committee of the American Society for Reproductive Medicine. SCH and infertility. Fertil Steril 2024.

(Supplemental Table 1, available online). Patient perspective and feedback were elicited during the review and before the publication of this guideline.

WHAT IS THE DEFINITION OF SCH?

Nonpregnant Women

Subclinical hypothyroidism is diagnosed as a TSH concentration above the upper limit of the normal range and a serum-free thyroxine (T4) concentration within the normal range. However, this designation only applies when thyroid function has been stable for weeks, the hypothalamic-pituitary-thyroid axis is normal, and there is no recent or ongoing severe illness (15). The reference range of a given laboratory should determine the upper limit of normal for a third-generation TSH assay for nonpregnant patients. When an age-based upper limit of normal is not available, an upper limit of normal of 4.12 mIU/L should be used for patients who live in an iodine-sufficient area (15, 16). This value is based on the upper normal TSH limit for a studied reference population that was not pregnant, did not have laboratory evidence of hyperthyroidism or hypothyroidism, did not have detectable thyroglobulin antibodies (TgAbs) or thyroid peroxidase antibodies (TPOAbs), and was not taking estrogens, androgens, or lithium (15). Pooled prevalence rates for hypothyroidism calculated from studies using the 97.5th percentile as an upper limit for TSH were 0.50% for overt hypothyroidism, 3.47% for SCH, and 2.05% for isolated hypothyroxinemia (17). Ninety-five percent of individuals without evidence of thyroid disease were found to have a TSH level <2.5 mIU/L, and the normal reference range of TSH level is skewed to the right (18).

Pregnant Women

There is known variability in TSH levels during pregnancy, with a typical decrease in TSH levels during the first trimester, which can be attributed to the weak thyroid stimulatory effect of human chorionic gonadotropin (15, 19). For women who have reason for thyroid function screening, it is recommended that both TSH and serum total T4 levels be obtained. Immunoassays of free T4 in pregnancy may be altered by changes in serum proteins in pregnancy and thus are not recommended (15). The upper limit of TSH in pregnancy depends on the trimester, and laboratory-specific cutoffs should be used. When local laboratory pregnancy cutoffs are unavailable, the upper limit or normal TSH levels can be reduced by 0.5 mIU/L in the first trimester and by nonpregnant thresholds later in pregnancy (12).

Women Attempting Pregnancy

Universal screening of thyroid function is not recommended for patients who are attempting pregnancy, including those undergoing assisted reproduction (15). However, "aggressive case finding" with TSH screening can be considered for patients who are at increased risk of overt hypothyroidism, including those with autoimmune disease, psychiatric disorder, family history of thyroid disease, history of neck radiation, history of prior thyroid dysfunction or surgery, signs or symptoms of thyroid dysfunction, or palpable thyroid abnormalities on examination (15, 20). These could be considered indications for thyroid testing in pregnant and nonpregnant women. There is insufficient evidence that the pregnancy thresholds for TSH levels should be used for women attempting pregnancy. Instead, the defined age-based cutoffs for nonpregnant patients should be used until pregnancy is achieved.

Summary statement.

- There is moderate evidence that the reference range of a given laboratory should determine the upper limit of normal for a third-generation TSH assay for pregnant and nonpregnant patients. When an age-based upper limit of normal is not available, defined upper limits of normal should be used: 4.12 mIU/L for nonpregnant patients and those attempting pregnancy; reduce the upper limit by 0.5 mIU/L for pregnant patients in the first trimester; and use nonpregnant thresholds in the first and third trimesters.

TABLE 2

Rating for quality of evidence.

Quality of evidence	Definition
High quality	The target population is identified clearly. Sufficient sample size for the study design A clear description of the study design. Appropriate control(s). Generalizable results. Definitive conclusions. Minimal risk of bias. Limitations do not invalidate conclusions. Evidence is primarily based on well-designed systematic reviews or meta-analyses of randomized controlled trials.
Intermediate quality	Target population. Sufficient sample size for the study design but could benefit from larger studies. Control group identified. Reasonably consistent results whose limitations do not invalidate. Fairly definitive conclusions. Low risk of bias. Evidence is primarily based on small randomized controlled trials, systematic reviews or meta-analyses of a combination of randomized controlled trials, controlled trials without randomization, and cohort studies; controlled trials without randomization; and/or well-designed observational studies.
Low quality	Insufficient sample size for the study design. Discrepancies among reported data. Errors in study design or analysis. Missing significant information. Unclear or inconsistent results. There is a high risk of bias because of multiple flaws, so conclusions cannot be drawn. High uncertainty about the validity of conclusions.

Practice Committee of the American Society for Reproductive Medicine. SCH and infertility. Fertil Steril 2024.

Recommendation.

- It is recommended that laboratory-specific TSH cutoffs levels be used to diagnose SCH for nonpregnant patients and pregnant patients by trimester. When laboratory cutoffs are not available, defined upper limits of normal TSH levels should be used (strength of evidence: B; strength of recommendation: moderate).

IS UNTREATED SCH ASSOCIATED WITH MISCARRIAGE?

For the purposes of this document, miscarriage was used interchangeably with spontaneous abortion but was most commonly labeled as first-trimester clinical pregnancy loss. It should be noted that a few studies included pregnancy loss up to 20 weeks, which stretches beyond the first trimester. Three meta-analyses have been conducted to evaluate the association between SCH and pregnancy loss, although they each asked somewhat different questions (21–23). The first meta-analysis was conducted to determine how SCH during pregnancy impacted pregnancy outcomes in cohort and randomized trials (21). It is difficult to draw conclusions from this meta-analysis because it included multiple studies (approximately half) that did not meet the definition of SCH and did not perform a sensitivity analysis of studies meeting the above definition of SCH. Another meta-analysis was performed to examine the relationship between SCH and the risk of pregnancy loss before 20 weeks of pregnancy in cohort and randomized trials (22). Studies that examined the prevalence of first-trimester pregnancy loss in pregnant women with and without SCH were included (nine studies and over 20,000 patients). Pregnant patients with untreated SCH had a similar risk of first-trimester pregnancy loss compared with euthyroid women (relative risk [RR] 1.38; 95% confidence interval [CI] 0.65–2.96, $P=.40$). Another meta-analysis was conducted to determine whether TSH levels before conception predict outcomes of assisted reproductive technology (ART) (23). Although this study did not use a standard definition of SCH or include a sensitivity analysis of true SCH, data from almost 4,000 women showed no increased risk of miscarriage in women with TSH levels >2.5 and >3.5 mIU/L. Overall, the three available meta-analyses do not evaluate true SCH or, when they do, show no association with miscarriage.

Five prospective studies were included in this review (one low-quality and four intermediate-quality studies) that demonstrated mixed results. Three of the studies were specifically conducted in women with RPL, which this document does not address (24–26). Plowden et al. (25) conducted a prospective cohort study that sought to understand prepregnancy TSH concentrations and their impact on early pregnancy loss. In >1,200 women with unassisted pregnancies, those with TSH levels ≥2.5 mIU/L did not have an increased risk of first-trimester pregnancy loss (RR 1.07; 95% CI 0.81–1.41) compared with women with TSH levels

TABLE 3

Rating for strength of evidence.

Strength of evidence	Definition
Grade A	High confidence in the evidence. A larger or further study is very unlikely to change the reported effect. Most evidence is supported by well-constructed randomized controlled trials (RCTs) or extremely strong and consistent observational studies with generalizable results, sufficient sample sizes for the study design, adequate controls, definitive conclusions, and minimal risk of bias.
Grade B	Moderate confidence in the evidence. Larger or further studies are not likely to change the reported effect but may more precisely identify the magnitude of the effect. Most evidence comprises RCTs with potential weaknesses, including small sample size or generalizability, or moderately strong and consistent observational studies with reasonably consistent results, sufficient sample sizes for the study designs, identified appropriate controls, fairly definitive conclusions, and a low risk of bias.
Grade C	Low confidence in the evidence. Evidence is lacking to support the reported effect. Evidence comprises observational studies with significant methodological flaws and/or inconsistent findings on the basis of poor evidence, inconsistent results, insufficient sample size for study design, conclusions that cannot be drawn, and/or a high risk of bias.

Practice Committee of the American Society for Reproductive Medicine. SCH and infertility. Fertil Steril 2024.

<2.5 mIU/L, after adjustment for age and body mass index. However, this study did not include a subgroup analysis of women with true SCH. A large population-based prospective study also attempted to address this question, in which 3,315 women were screened for thyroid dysfunction at 4–8 weeks gestation in iodine-sufficient areas of China (27). Thyroid-stimulating hormone, FT4, TPOAb, and TgAb levels were measured. Compared with euthyroid women, first-trimester pregnancy loss risk was significantly higher among women in the SCH group (7.1% vs. 2.2%, adjusted odds ratio [aOR] 3.40, 95% CI 1.62–7.15, $P=.002$). It is interesting to note that even though this group had a higher first-trimester pregnancy loss rate, the overall rate in this cohort was still lower than expected in this patient population.

Twelve retrospective studies were included in this review (six low-quality and six intermediate-quality studies) and demonstrated mixed results. Several studies did not analyze data on the basis of the above definition of SCH in primary and sensitivity analyses (28–31). Li et al. (32) compared outcomes on the basis of on the ATA 2011 vs. 2017 guidelines.

Thyroid-stimulating hormone levels can change in early pregnancy, which can make this population difficult to study. A retrospective population-based cohort study (intermediate quality) included over 180,000 women (33). All participants had TSH levels drawn within 6 months of conception. Over 7,000 patients were analyzed, and SCH was associated with a higher risk of pregnancy loss (aOR 1.15; 95% CI 1.10–1.22) compared with women with TSH levels <2.50 mIU/L. Conversely, another retrospective cohort of much smaller size, with 106 patients, found no association between SCH and pregnancy loss (34). As mentioned previously, the definition of SCH varies among studies. A large retrospective cohort of intermediate quality sought to compare reproductive outcomes utilizing several categories of TSH concentrations: <2.5, 2.5–4.0, and 4.0–10.0 mIU/L (35). All the women in the study were undergoing ovarian stimulation for in vitro fertilization (IVF) treatment. Women who were using levothyroxine for treatment were excluded from the analysis. When using a TSH threshold level of 4.0 mIU/L, the prevalence of SCH was 5.1% but increased to 29.9% when using a TSH threshold level of 2.5 mIU/L. Miscarriage rates were not different in women with SCH, regardless of TSH threshold level >2.5 or 4.0 mIU/L. Another large study of >1,000 women (intermediate quality) specifically used a TSH cutoff level of 2.5 and 4.5 mIU/L to define SCH (36). This retrospective cohort of patients with first-cycle IVF treatment found no differences in the rates of clinical pregnancy, delivery, or miscarriage. Karakis et al. (28) also compared women undergoing intrauterine insemination treatment with TSH levels of 2.5–4.5 mIU/L to those with TSH levels of <2.5 mIU/L and similarly found no difference in pregnancy, miscarriage, or LB. A retrospective study among women undergoing fresh autologous IVF cycle treatment who had TSH levels drawn within 2 weeks before treatment was evaluated (37). The cohort was stratified by oocyte age and TSH level. Participants were followed until pregnancy loss or delivery. After adjusting for maternal age, early pregnancy loss was not associated with TSH level ($P>.30$) compared with euthyroid patients. Chai et al. (38) evaluated subfertile women undergoing their first IVF cycle treatment to investigate whether the LB rate was impacted by TAI and/or SCH. This low-quality retrospective cohort study found that clinical pregnancy, LB, and pregnancy loss were similar among women with and without SCH. In 2010, an intermediate-quality retrospective study evaluated whether maternal thyroid function from 11–13 weeks gestation played a role in pregnancy loss or fetal death (39). There were 202 pregnancies that ultimately resulted in first-trimester pregnancy loss or later fetal death and were compared with 4,318 normal pregnancies. In the final prediction of fetal loss using the logistic regression analysis, FT4 level was associated with pregnancy loss. In this study, it is important to note that thyroid function was used only as a linear predictor of outcomes and did not evaluate SCH.

Summary Statement

- There is moderate evidence on the basis of intermediate- and low-quality studies with some contradictory findings that SCH during pregnancy is not associated with an increased risk of miscarriage. Most intermediate-quality studies do not show an increased risk. There is moderate

evidence that TSH levels between 2.5 and 4.0 mIU/L are not associated with miscarriage.

Recommendations

- It is recommended to counsel women that SCH is not associated with an increased risk of miscarriage (strength of evidence: B; strength of recommendation: moderate).
- It is recommended to counsel women that a TSH levels between 2.5 and 4.0 mIU/L is not associated with an increased risk of miscarriage (strength of evidence: B; strength of recommendation: moderate).

IS UNTREATED SCH ASSOCIATED WITH INFERTILITY?

Five retrospective studies (four low-quality studies and one intermediate-quality study) evaluated SCH in women with infertility. One low-quality retrospective study examined 244 women with infertility compared with 155 women with confirmed fertility and sought to evaluate the prevalence of SCH and TAI in these two groups (40). Ultimately, SCH was diagnosed in 13.9% of the women with infertility vs. 3.9% in the control group ($P<.002$), suggesting a potential association between SCH and infertility. Another low-quality retrospective study evaluated a Finnish population cohort of infertile women to determine the occurrence of hypothyroidism (7). Of note, only 12 (4%) women in the cohort had abnormal TSH levels, which ranged from 5.7–32.0 mIU/L, and three of these women had been diagnosed with hypothyroidism in the past. Thyroid-stimulating hormone levels were similar in women diagnosed with ovulatory dysfunction (6.3%), unknown infertility (4.8%), tubal factor infertility (2.6%), and male infertility (1.5%). Karakis et al. (28) also compared women undergoing intrauterine insemination with TSH levels of 2.5–4.5 mIU/L to those with TSH levels of <2.5 mIU/L and similarly found no difference in pregnancy or LB.

Additionally, a retrospective study of intermediate quality aimed to determine the frequency of elevated TSH levels in women who sought treatment for infertility (41). Seven hundred-four women were evaluated, and 16 (2.3%) had abnormal TSH levels and were treated with levothyroxine. Eleven of the sixteen women in the hypothyroidism group also had ovulatory dysfunction, and seven women conceived successful pregnancies. A retrospective cross-sectional study examined data from >11,000 Danish women (low-quality) (42) and found no association of SCH with infertility ($P=.09$).

Summary Statement

- There is weak evidence that SCH is not associated with an increased risk of infertility.

Recommendation

- There is insufficient evidence to counsel women that SCH is associated with infertility (strength of evidence: C; strength of recommendation: weak).

IS SCH ASSOCIATED WITH ADVERSE OBSTETRIC OUTCOMES?

There may be an increased risk for adverse obstetric outcomes, including placental abruption, preterm birth, fetal death, and preterm premature rupture of membranes, among pregnant women with SCH or TSH levels outside of the normal range in pregnancy (1, 43–45). However, available studies are limited by the fact that clinically relevant outcomes are rare, and studies are mostly retrospective.

This guideline includes two systemic reviews (21, 46), one RCT, and 18 cohort studies (5, 29, 31, 33, 44, 45, 47–58) that address a potential association between SCH and adverse obstetrical outcomes. The bulk of the literature is graded as low-quality, the remainder is intermediate-quality, and most of the studies were retrospective cohort studies.

The studies showed significant heterogeneity in how SCH was defined. Threshold levels included 3 mIU/L (51), >2.5 mIU/L (31, 50), between 2.5 and 4.0 mIU/L (57), and +TPOAb only (59). One study did not define SCH, but subjects had an average TSH level of 28 mIU/L, which is more consistent with overt hypothyroidism (44). Each meta-analysis (21, 60) also combined primary studies that included the full range of TSH levels to diagnose SCH (levels from 2.5–4.5 mIU/L) and those that defined SCH as just the presence of antithyroid antibodies in the absence of elevated TSH levels. Many of the source studies (>50%) would not have met ASRM's criteria for SCH (nor ACOG or the ATA 2017 criteria). This heterogeneity of studies makes the results of the meta-analyses challenging to interpret and may not be informative for the diagnosis of SCH in this article.

In a moderate-quality RCT, Nazarpour et al. (46) randomized 366 women with SCH (defined at TSH levels ≥2.5 mIU/L) to treatment with levothyroxine or no treatment. The primary clinic provider and patient were not blinded, and there was no placebo control. The study leaders were blinded to group assignments. The study did not find any effect of treatment on the primary outcome of preterm delivery (10.2% vs. 11.8%, RR 0.86, 95% CI 0.47–1.55); in a secondary post hoc analysis that also added additional statistical methods of log-binomial models plus adjustments for gestation age on enrollment (neither of which were performed in primary analyses nor another secondary post hoc analysis and was not in the a priori statistical plan), there was a reduction in preterm delivery with levothyroxine treatment (RR 0.38; 95% CI 0.15–0.98). It should be noted that this analysis ignores randomization by moving a large number of patients out of their assigned randomization group. Although the overall study was an RCT, the reduction in preterm delivery should be viewed as lower-quality evidence from a cohort study.

The systematic reviews from van den Boogaard et al. (60) and Maraka et al. (21) included studies with TSH levels above 2.5–4.5 mIU/L and thyroid-positive antibodies. In an intermediate-quality systematic review (21) including randomized trials and cohort studies of pregnant women with SCH that examined adverse pregnancy and neonatal outcomes, compared with euthyroid pregnant women, pregnant women with SCH were at higher risk for placental abruption (RR 2.14; 95% CI 1.23–3.70), premature rupture of

membranes (RR 1.43; 95% CI 1.04–1.95), and neonatal death (RR 2.58; 95% CI 1.41–4.73).

In an intermediate-quality systematic review and meta-analysis (60) assessing the clinical significance of thyroid dysfunction in early pregnancy, SCH in early pregnancy, compared with normal thyroid function, was associated with an increased occurrence of preeclampsia (odds ratio, [OR] 1.7; 95% CI 1.1–2.6) and an increased risk of perinatal mortality (OR 2.7; 95% CI 1.6–4.7). However, in the meta-analysis, it appeared that it was the presence of thyroid antibodies that was associated with an increased risk of preterm birth (OR 1.9, 95% CI 1.1–3.5) compared with the absence of thyroid antibodies, and SCH in the absence of thyroid antibodies was not likely to be associated with any adverse obstetrical outcomes. As such, the meta-analyses were discrepant in their finding, and the one that excluded antithyroid antibodies in subanalysis did not find a significant risk associated with SCH and adverse obstetric outcomes.

In the only study in this section that evaluated preconception TSH levels to define SCH, Li et al. (55) retrospectively evaluated over 50,000 women with preconception TSH levels drawn from a large Chinese study. Subclinical hypothyroidism was not associated with preterm delivery, pregnancy loss, or large for gestational age births. However, in this study, SCH was associated with a slightly increased risk of small for gestational age infants (OR 1.16; 95% CI 1.01–1.33). Overall, SCH was not associated with the most adverse outcomes in the only cohort diagnosed preconceptionally. However, the same group performed a smaller retrospective cohort of 1,500 patients, overlapping with the final year of the study just discussed and only checking for TSH levels in the first trimester instead of preconceptionally (55). In this study, the first trimester SCH diagnosis was associated with pregnancy-induced hypertension, preeclampsia, preterm delivery, placenta previa, and preterm birth. It is unclear why the same center and similar patients resulted in disparate outcomes between the two studies.

In an intermediate-quality cohort study (48) of 1,017 women with singleton pregnancies, maternal serum samples in the first 20 weeks of pregnancy were screened. This study found that SCH was associated with increased fetal distress (on the basis of six cases), preterm delivery (on the basis of five cases), infants with poor vision (on the basis of two cases), fetal loss (on the basis of two cases), and infants with neurodevelopmental delay (on the basis of two cases). The small number of cases highlights the relatively small absolute risk. The study found no difference with SCH in 35 other measured obstetrical outcomes. It is difficult to draw conclusions from this small study that did not adjust for multiple comparisons.

In a large, intermediate-quality observational study of 25,756 women with singleton births, women were screened for thyroid disease (45). Elevated TSH levels above pregnancy normal values were associated with an increased risk of placental abruption (RR 3.0; 95% CI 1.1–8.2) and delivery at <34 weeks (RR 1.8; 95% CI 1.1–2.9). One weakness of the study is that it was based only on second-trimester values, which is outside of the aim of this present document.

An intermediate-quality prospective cohort study (53), including 8,012 pregnant women, was performed to evaluate the effects of SCH on maternal and perinatal outcomes during pregnancy. Subclinical hypothyroidism discovered in the third trimester had an increased risk of gestational hypertension, premature rupture of membranes, intrauterine growth restriction, and low birth weight. Women with SCH discovered in the second trimester had two cases of stillbirth vs. four in the euthyroid control group (3.7% vs. 0.1%, $P=.006$). The other 21 outcomes studied in the first and second trimesters showed no association of SCH with adverse pregnancy outcomes, and no accounting for multiple comparisons was performed. This study's overall findings do not suggest an association of first-trimester SCH with adverse obstetric outcomes.

The data on obstetrical outcomes in women with TSH levels between 2.5 and 4.0 mIU/L are limited. One intermediate-quality cohort study reviewed >1,200 ART treatment cycles and found that 23% of women had TSH levels in the range of 2.5–4.0 mIU/L (49). These patients did not demonstrate greater adverse pregnancy outcomes because of premature delivery or low birth weight.

A large, low-quality, population-based cohort study was performed to investigate the association between maternal preconception TSH levels and pregnancy outcomes (33), including 184,611 women who subsequently became pregnant. Maternal TSH levels were measured within 6 months before pregnancy. The overall incidence of adverse pregnancy outcomes was 28.6%. Comparing TSH levels <2.5 mIU/L vs. 2.50–4.29 mIU/L, midrange TSH levels were associated with preterm birth (aOR 1.09; 95% CI 1.04–1.15) and operative vaginal delivery (aOR 1.15; 95% CI 1.09–1.21). True SCH with a TSH level of 4.29–10 mIU/L was correlated with stillbirth (aOR 1.58; 95% CI 1.10–2.28), preterm birth (aOR 1.20; 95% CI 1.08–1.34), cesarean section (aOR 1.15; 95% CI 1.10–1.22), and large for gestational age infants (aOR 1.12; 95% CI 1.04–1.21).

In a low-quality retrospective cohort study of 1,981 pregnant women (29) who underwent TSH testing between 9 and 12 weeks of gestation, TSH 2.5–5.0 mIU/L showed no association with prematurity, preeclampsia, dystocia labor, or stillbirths; however, there was an increase in pregnancy loss. True SCH (TSH levels >5 mIU/L) was not associated with any adverse outcomes. Sitoris et al. (58) performed a low-quality retrospective cohort study that demonstrated SCH to be associated with preeclampsia but not with small or large for gestational age, neonatal intensive care unit admission, or preterm births.

Overall, the studies on SCH and adverse obstetric outcomes are variable in their diagnostic criteria, all low to intermediate quality, and when they do find adverse obstetrical outcomes, the findings are inconsistent across studies (e.g., preeclampsia, small for gestational age, preterm delivery, and others). Overall, the studies that showed no associations were more likely to be of intermediate quality, although the studies showing a specific difference were almost all of low quality. No study controlled for multiple comparisons, which is particularly important when assessing up to 35 different

obstetric endpoints. The studies demonstrating no adverse outcomes were more than twice as many as those demonstrating different adverse events.

Summary Statement

- There is moderate-quality evidence that SCH during pregnancy is not associated with adverse obstetric outcomes. Although some studies show an increased risk, particularly with testing later in pregnancy, higher-quality studies with preconception and first-trimester testing predominately do not show an increased risk. There is insufficient evidence that TSH levels of 2.5–4 mIU/L are associated with adverse obstetric outcomes.

Recommendation

- It is recommended to counsel women that SCH is not associated with increased obstetric risk (strength of evidence B; strength of recommendation: moderate).

DOES UNTREATED SCH AFFECT DEVELOPMENTAL OUTCOMES IN CHILDREN?

The fetal thyroid does not produce thyroid hormone before 10–13 weeks of gestation (61). Therefore, maternal thyroid hormone is imperative in early pregnancy. There is some evidence that untreated hypothyroidism during pregnancy may delay fetal neurological maturation and development as well as impair school performance and lower the intelligence quotient (IQ) of offspring (3, 62). It appears that overt maternal hypothyroidism may have adverse effects on developmental outcomes. Although an adverse impact of maternal SCH on development has been suggested by previous observational studies, more recent RCTs have not demonstrated an association (63–65).

This guideline includes three RCTs (63–65) and four observational cohort studies (48, 66–68) assessing developmental outcomes in children with SCH.

Low- or intermediate-quality studies have suggested an association between SCH and reduced intellectual development. A low-quality retrospective cohort study found that isolated levels of TSH may be a determinant of cognition (66). Children born to mothers with SCH in the second trimester had an eight-point lower IQ than controls at 25–30 months of age. Although controls were matched for many characteristics, including parental education, there was no modeling to account for parental education, and analysis of their table demonstrates more than double the likelihood of controls having maternal and paternal university-level education. In addition, childhood IQ was still above average at 110, and it is unclear whether a small difference at 25–30 months of age has any future implications for those children.

In a low-quality cohort study (48) of 1,017 women with singleton pregnancies, maternal serum samples in the first 20 weeks of pregnancy were tested for thyroid hormones. This study found that SCH was associated with increased neurodevelopmental delay (aOR 10.49; 95% CI 1.01–119.19). This was based on a single case of delay in the patients with SCH, leading to a very wide CI, and was only significant in one statistical model but not in other models the researchers used.

A low-quality cohort study (68) evaluated 39 women with SCH defined as a TSH levels >4 mIU/L and evaluated nine obstetric outcomes. Compared with 700 women without SCH, there were no differences in the neurodevelopment of their offspring. They did find a statistically significant one-point difference in the score for receptive communication in 1-year-old children (score 11.3 vs. 10.7, $P=.047$). There was no adjustment for multiple comparisons in this study, and the clinical relevance of the single finding is uncertain.

Another intermediate-quality cohort study evaluated 143 maternal TSH levels at the time of delivery in cases of preterm birth and found an association between TSH levels and neurodevelopment at 5.5 years of age. Higher TSH levels were associated with more neurocognitive issues, and even mild maternal hypothyroidism at the time of delivery (TSH levels ≥ 3 mIU/L) was associated with a significant decline in verbal and perceptual performance (67). The relevance of these data for this clinical question is unclear, given that TSH levels were evaluated at the time of delivery and not earlier during pregnancy.

There have been three RCTs that have provided evidence that SCH is not associated with adverse neurodevelopmental outcomes in offspring. Prior observational studies were limited by heterogeneous populations, variable definitions of SCH, and confounding factors (such as prematurity). In addition, different studies assess children at different ages and use different measurements of cognition.

In a high-quality study (63), an RCT assessed the cognitive function at 3 years of age in the offspring of women who underwent thyroid screening in early pregnancy and were immediately treated with levothyroxine (4.6% had high TSH, low free T4, or both levels) compared with controls whose serum was stored and tested after pregnancy (later found to be 5% positive). The median gestational age at screening was 12 weeks (interquartile range 6–13 weeks), and treatment began 1 week later. The results of IQ testing at the age of 3 years did not differ significantly between the two groups. In addition, there was no association between thyrotropin levels and IQ. The investigators concluded that there is no benefit of routine screening for maternal hypothyroidism at 6–13 weeks of gestation in the prevention of impaired childhood cognitive function, indicating that most patients began treatment in the first trimester. Another clinical trial with children at 5 years also had similar findings, suggesting that SCH was unrelated to neurodevelopmental outcomes. However, in this study, there is not a euthyroid control group for comparison (65).

In a high-quality follow-up to the above RCT (64), cognitive function at age 9 years was assessed using an in-depth battery of tests to evaluate cognitive function in children of mothers with SCH who were randomly assigned to treatment and a third group of euthyroid women. Treatment began at 16 $\pm$ 3 weeks of gestation. There was no difference in IQ <85 between children of mothers with normal gestational thyroid

function and children of mothers with SCH who were treated or untreated. The investigators concluded that there is no effect of low thyroid function on offspring intelligence or cognition and no benefit to screening or treating SCH in pregnancy with regards to neurological development.

Summary Statement

- There is strong evidence that SCH in pregnancy is not associated with adverse neurodevelopmental outcomes in offspring. There is insufficient evidence that pregnancy TSH levels between 2.5 and 4 mIU/L are associated with adverse developmental outcomes.

Conclusion

- It is recommended that women be counseled that SCH in pregnancy is not associated with adverse neurodevelopmental outcomes in offspring (strength of evidence: A; strength of recommendation: strong).

DOES TREATMENT OF SCH IMPROVE MISCARRIAGE RATES, LB RATES, AND/OR CLINICAL PREGNANCY RATES?

This guideline includes four RCTs, four systematic reviews of only RCTs, five systematic reviews of RCTs and cohort studies, one prospective cohort study, and four retrospective cohort studies that aim to determine whether levothyroxine treatment improves miscarriage rates, live-birth rates (LBRs), or clinical pregnancy rates among women with SCH. Most investigators demonstrated no improvement in these outcomes with levothyroxine treatment.

In an intermediate-quality randomized trial of 64 infertile patients with SCH undergoing IVF treatment, women were randomized to levothyroxine or no treatment groups (69). The LBR was significantly higher in the levothyroxine group than in the control group (17/32 [53.1%] vs. 8/32 [25.0%], $P=.04$). There were four miscarriages, all of which occurred in the control group. Among patients with a clinical pregnancy, the miscarriage rate was significantly higher in the control group compared with the treatment group (4/12 [33%] vs. 0/17 [0], $P=.02$). When the entire study population was included in the analysis, however, this comparison no longer achieved statistical significance (4/32 [13%] vs. 0/32 [0], $P=.11$). The difference in LB was entirely because of the 4 vs. 0 pregnancy losses between the two groups and may be at risk of type I error given the small study size. Therefore, although this small study showed the benefit of treating SCH, the data are insufficient to propose universal screening and treatment of SCH in infertile women.

A high-quality randomized trial examined rates of TPOAb positivity among euthyroid women with infertility (70). Of the 484 women included in the study, 72 (15%) tested positive for TPOAbs. These 72 women were then randomized to levothyroxine or placebo. Among the TPOAb+ women, treatment with levothyroxine did not significantly reduce the risk of miscarriage (8/24 [33%] vs. 11/21 [52%], $P=.24$) or improve the rate of LB (16/43 [37%] vs. 10/43 [23%], $P=.24$). This study did not evaluate SCH as defined in this present article.

Another high-quality RCT randomized pregnant women at 15 6/7 weeks of gestational age or less to thyroid screening or no screening (63). Screening resulted in treatment for women with SCH. As mentioned in the prior section, they found no difference in the primary outcome of neurocognitive development. Although they do not comment on pregnancy loss or LB, they did report the number of women randomized at 13 weeks, how many dropped out, and how many reported for testing of their children at 3 years of age. There was no difference in dropout between the two groups, which would be a combination of pregnancy loss and true dropout. It can be stated from their data that there is no difference in the percentage of subjects randomized to testing and treatment at 13 weeks gestation vs. randomized to the control arm that then presented with a 3-year-old child from that delivery (screen and treat: 390/499 [78.1%] vs. control 404/551 [73.3%], $P=.09$). Although this does not directly report LB, it indirectly shows that screening and treating for SCH in pregnancy does not increase the likelihood of having a birth that lives to 3 years old (and that child shows up for neurological testing with a similar dropout between groups).

A low-quality randomized trial by Abdel Rahman et al. (71) was excluded because of unclear data reporting and major data integrity concerns. The study reports outcomes as percentages only, and the *P* values do not appear consistent with the data provided. For example, the investigators reported pregnancy loss as 13% in the control arm and 9% in the treatment arm (reported $P=.03$), even though each arm only had 35 subjects. This incorrect *P* value was reported to the Editor in Chief of the journal Endocrine Practices. The Editor in Chief was unable to clarify multiple discrepancies and thereafter wrote an erratum, which recalculates the outcome assuming 13 and 9 are raw outcomes and not percentages, which then gives $P=.44$ and no difference in pregnancy loss (72). In addition, the pregnancy rate was calculated using the investigators' percentages as assumed raw numbers. Using this calculation, the editor reported pregnancy as 100% (35/35) in the treatment arm and 28% (10/35) $P<.0001$ (72). Because of the significant concerns over the validity of this trial, the investigators of the Cochrane review on this subject brought it to the adjudication of the Cochrane Gynecology and Fertility. This group decided that this article should be completely excluded because of its high risk of error in the data (73).

In this current ASRM Guideline, the decision was made to exclude the study from Abdel Rahman et al. (71). This change in how this study is graded and now excluded is the primary reason that this version of the ASRM Practice Committee Guidelines on treating SCH is different from the prior version. Unfortunately, this RCT has been included in every systematic review and meta-analysis found in the literature search, except for the Cochrane review. The study from Abdel Rahman et al. (71) had such a strong effect size on clinical pregnancy outcomes (100% with treatment and 28% without—by best guess from the editor) that its RR is 4–8 times larger than the RRs in any other randomized trial. Only one of the meta-

analyses of randomized trials from Rao et al. (74) included sensitivity analyses, removing Abdel Rahman et al. (71) from the analysis. When excluding this study, there was no difference in pregnancy, pregnancy loss, or LB in this meta-analysis. They also note that removing the Abdel Rahman et al. (71) study resulted in a change from high heterogeneity to low heterogeneity among the studies. The other meta-analyses discussed in the following paragraphs did not perform sensitivity analyses, removing this study, and their outcomes are largely driven by this single problematic trial.

Many international society guidelines cite this RCT, and the available meta-analyses are largely driven by this single RCT when discussing the one to three clinical trials that influence their recommendations for the treatment of SCH in pregnancy and women attempting pregnancy, including the last iteration of this previous ASRM Guideline. Many society guidelines discuss that the evidence is weak or lacking to demonstrate the benefit of levothyroxine treatment for SCH in women desiring pregnancy or pregnant. However, they also mentioned that levothyroxine is inexpensive and unlikely to cause harm. Our current guidelines specifically aim to look for evidence that an intervention is clearly beneficial before recommending it. An intervention being inexpensive and unlikely to cause harm was not viewed as justification for screening and treatment because there was insufficient evidence of benefit in the literature.

A high-quality systematic review and meta-analysis of four RCTs included 787 women with SCH or TAI undergoing IVF treatment (74). Levothyroxine treatment was not associated with clinical pregnancy rate (RR 1.46; 95% CI 0.86–2.48) or LBR (RR 2.05; 95% CI 0.96–4.36). In contrast, miscarriage was significantly lower in the levothyroxine group compared with the control group (RR 0.51; 95% CI 0.32–0.82). This association was driven by the results of one study that has subsequently been retracted (71). After excluding that study, this meta-analysis found no improvement in pregnancy loss with treatment. Similarly, levothyroxine treatment did not improve miscarriage rates when patients with TAI were excluded (mostly from the Negro et al. (70) study).

Another low-quality systematic review and meta-analysis included 220 women with SCH from three RCTs (75). The investigators demonstrated a significantly higher LBR (RR 2.76; 95% CI 1.2–6.4) and lower miscarriage rate (RR 0.45; 95% CI 0.24–0.82) among women treated with levothyroxine. These effects were driven largely by the RCT that has since been retracted, and excluding that study from the analyses eliminates any significant associations between levothyroxine and the outcomes of interest. There was no difference in clinical pregnancy between groups. One low-quality systematic review of RCTs and two intermediate-quality systematic reviews of RCTs and cohort studies similarly demonstrated no significant associations between levothyroxine treatment and miscarriage, LB, or clinical pregnancy (73, 76, 77). Two other intermediate-quality systematic reviews and meta-analyses did find a benefit of treatment of SCH. However, both studies combined cohort and clinic trial data. Most of the clinical trials were low to intermediate quality, and there was no benefit to treating SCH in subanalysis of only randomized trials in both meta-analyses. One additional systematic review and meta-analysis was included at the search phase of this document, but used a wide range of TSH values and TAI to define SCH, which were inconsistent with this document's definition of SCH (78, 79).

In an intermediate-quality retrospective cohort study of 5,405 pregnant women with SCH from a large administrative database, treatment with levothyroxine was associated with a significant reduction in the rate of pregnancy loss compared with no treatment (aOR 0.62; 95% CI 0.48–0.82) (80). Other low- and intermediate-quality cohort studies and systematic reviews have not demonstrated significant associations between levothyroxine and the outcomes of interest in women with SCH (21, 81, 82).

Given that there are only two RCTs that evaluate treatment in patients with SCH using TSH levels >4 mIU/L, after the exclusion of one study for data integrity concerns and one trial on the topic of thyroid immunity, there is a lack of primary clinical trial data to assess the benefit of treating SCH in women desiring pregnancy or already pregnant. Despite the lack of quality clinical trials, there are at least nine meta-analyses. Overall, primary studies (cohort and clinical trials) did not show the benefit of treating SCH for pregnancy outcomes. At the same time, the meta-analyses were largely driven by a single clinical trial with significant concerns for data integrity. Therefore, the recommendation is to not treat SCH in pregnant women or women desiring pregnancy.

Summary Statements

- There is moderate evidence that treatment of SCH with levothyroxine does not improve pregnancy loss, clinical pregnancy, or LB.

Recommendation

- It is not recommended to treat pregnant women or women desiring pregnancy who have a diagnosis of SCH with levothyroxine, as treatments have not been demonstrated to reduce pregnancy loss nor to improve clinical pregnancy or LB outcomes (strength of evidence B; strength of recommendation: moderate).
- Thyroid-stimulating hormone and T4 levels should be tested in patients with signs or symptoms of hypothyroidism (including irregular menstrual cycles) rather than in all patients with infertility (strength of evidence: B; strength of recommendation: moderate).

DOES TREATMENT OF SCH IMPROVE DEVELOPMENTAL OUTCOMES?

Although an association of SCH with decreased neurodevelopmental outcomes was reported in several observational studies of low- to intermediate-quality grading (3, 48, 62, 66, 67, 83, 84), other observational studies have found no association of early pregnancy serum TSH with infant developmental outcomes (85, 86). Since the last version of this document was published, three high-quality RCTs have

demonstrated no benefit in offspring neurocognitive development by treating SCH in pregnant women. The results of these three high-quality clinical trials have largely answered the question of screening for SCH in pregnant women to improve offspring neurocognitive development.

A high-quality RCT sought to evaluate the effectiveness of antenatal thyroid screening regarding childhood cognitive function (63). Pregnant women at a gestational age of ≤15 weeks and 6 days were allocated to a screening group with immediate analysis of TSH and free T4 levels or a control group for which serum was stored and measurements obtained shortly after delivery. Women with TSH levels above the 97.5th percentile and/or free T4 levels below the 2.5th percentile were assigned 150 μg of L-T4 per day. The primary outcome was IQ at 3 years of age in children of screen-positive women, measured by randomization allocation blinded psychologists. No significant differences in mean IQ scores were found between children of women with a positive screening and treatment compared with those in the controls. The proportion of children with an IQ <85 was not statistically different between groups.

In another high-quality RCT, women with a singleton pregnancy before 20 weeks of gestation were screened for SCH, defined as a TSH level >4 mIU/L and a normal free T4 level, and hypothyroxinemia, defined as a low free T4 level (<0.86 ng/dL) with a normal TSH level (46). In pregnant women diagnosed with SCH, 677 women were randomized to receive levothyroxine supplementation or placebo. Children born to trial participants underwent annual developmental and behavioral testing for 5 years. The primary outcome was the IQ score at 5 years of age or death at an age of <3 years. No significant differences in the median IQ score of the children were found between the levothyroxine group (IQ mean 97; 95% CI 94–99) and the placebo group (IQ mean 94; 95% CI 92–96; $P=.71$).

A third high-quality RCT examined the potential benefit of levothyroxine treatment on pregnancy outcomes in women with SCH after the children reached a mean age of 9.5 years (87). There was no difference in the primary outcome of IQ scores or any other marker of neurocognitive development.

A systematic review and meta-analysis on this topic identified the above three RCTs for inclusion and found no evidence of the benefit of levothyroxine therapy on obstetrical, neonatal, childhood IQ, or neurodevelopmental outcomes, concluding that current trial evidence does not support the treatment of SCH diagnosed in pregnancy (87).

Summary Statement

- There is strong evidence, on the basis of three randomized clinical trials, that levothyroxine therapy for women with SCH diagnosed in pregnancy has no benefit for obstetrical, neonatal, childhood IQ, or neurodevelopmental outcomes.

Recommendation

- Levothyroxine therapy for SCH diagnosed in pregnancy is not recommended for the indication of improving developmental outcomes (strength of evidence: A; strength of recommendation: strong).

ARE THYROID ANTIBODIES ASSOCIATED WITH INFERTILITY OR ADVERSE REPRODUCTIVE OUTCOMES?

It is important to emphasize that the current document does not address SCH in women with a history of RPL, which is covered in another ASRM Practice Committee Guideline. A population study found that antithyroid antibodies were more prevalent in women than men, increased with age, and were significantly associated with hypo- or hyperthyroidism, but TgAbs were not (8). However, the data are varied on whether thyroid antibodies are associated with infertility or adverse reproductive outcomes. A systematic review and meta-analysis of 38 articles found that the presence of thyroid antibodies was associated with an increased risk of unexplained subfertility (OR 1.5; 95% CI 1.1–2.0), miscarriage (OR 3.73; 95% CI 1.8–7.6), recurrent miscarriage (OR 2.3; 95% CI 1.5–3.5), preterm birth (OR 1.9; 95% CI 1.1–3.5), and maternal postpartum thyroiditis (OR 11.5; 95% CI 5.6–24) compared with the absence of thyroid antibodies (60). This meta-analysis is complicated by varied definitions of SCH, heterogeneous patient populations, and combining cohort and clinical trial evidence.

Looking further into any association with miscarriage, some studies that were prospective, retrospective, and case-control in design found an increase in miscarriage rate in patients with TAI, even in the setting of a normal TSH level (27, 70, 88–91). Conversely, a prospective cohort of 234 women screened before their first ART treatment cycle found no difference in pregnancy rates between women with and without thyroid antibodies (6). However, there was a higher miscarriage rate in women with thyroid antibodies (6). A retrospective study of 537 patients found a higher miscarriage rate in nontreated TPOAb+ patients compared with the treated group (92). Cost-effectiveness analyses have demonstrated a higher cost in women with a history of pregnancy loss and a history of untreated SCH, or autoimmune thyroid disease (ATD), that was left untreated and found universal screening for ATD to be cost-effective (81, 93). These data are heavily influenced by the reference data used to model the benefits of screening and treatment.

Not all studies support an association between TAI and pregnancy loss. One prospective cohort study of 1,228 women who had a history of one or two prior pregnancy losses found no increased risk of pregnancy loss nor decrease in LB in women with TAI (25).

When examining infertility and ART treatment outcomes, there are also conflicting study results. A retrospective study showed a higher prevalence of SCH but not of TAI in patients with infertility (40). A systematic review and meta-analyses, which included only RCTs, focused on the treatment effect of levothyroxine on the pregnancy outcomes of women with SCH and/or TAI who underwent IVF treatment. This study found a significantly decreased miscarriage risk relative to those receiving a placebo or no treatment (RR 0.51; 95% CI:

0.32–0.82) (74). However, these data were again largely driven by the results of Abdel Rahman et al. (71), which have been excluded per the reasons outlined above. With the exclusion of the data from Abdel Rahman et al. (71), there was no benefit to treating women with antithyroid antibodies. A prospective trial examining women undergoing ART treatment found a higher miscarriage rate in TPOAb-positive patients (70). Other studies did not find an effect on thyroid autoantibodies and ART treatment success (6, 38). In another study of 487 patients who successfully conceived with ART treatment, the investigators found a 22% rate of thyroid antibodies. Patients with positive thyroid antibodies had a similar pregnancy rate to those without antibodies (94). Another retrospective study of 416 euthyroid women found no differences in pregnancy and delivery rates observed between women with and without antibodies. However, women with TPOAb who failed to become pregnant or miscarried displayed higher TSH values before ART treatment compared with those who delivered and compared with women who were antibody-negative (95).

Summary Statements

- There is intermediate-quality and conflicting evidence that is insufficient to suggest an association between thyroid antibodies and miscarriage.
- There is weak evidence that women with RPL have higher rates of positive thyroid antibodies on the basis of limited case-controlled studies.
- There is insufficient evidence to recommend screening for TAI in infertile or pregnant women.

Recommendation

- It is not recommended to screen for TAI in asymptomatic women with infertility or pregnancy. Targeted screening may be considered in women with a history of RPL (strength of evidence C; strength of recommendation weak).

WHAT IS THE MANAGEMENT OF SCH PATIENTS IN THE FIRST TRIMESTER OF PREGNANCY?

Thyroid hormone requirements increase during gestation. In pregnant patients, median TSH values are lower in the first trimester than in the second, but 98th centile values are higher (19). The establishment and monitoring of TSH reference ranges by individual laboratories are crucial for the interpretation of measurements.

The literature on the management of SCH in the first trimester of pregnancy is largely from women with unknown SCH status and assessing screening strategies linked to treatment when SCH was found. Therefore, screening and treatment are linked together in these studies.

There has not been a clear consensus regarding the topic of screening for hypothyroidism in the first trimester of pregnancy (12, 96, 97). Most professional organizations recommend against universal routine screening and recommend a risk-based approach. The American College of Obstetrics and Gynecology recommends testing of thyroid function "in women with a personal or family history of thyroid disease, type 1 diabetes mellitus, or clinical suspicion of thyroid disease" and does not recommend universal screening or SCH treatment.

A retrospective study on 756 women enrolled at $\leq$12 weeks gestation demonstrated that participants with identified SCH had a significantly higher rate of spontaneous abortion (15.48% vs. 8.86%, P=.03) but no increased rates of obstetric or neonatal outcomes (50). In this study, no statistically significant decrease in the incidence of spontaneous abortion was demonstrated in women with a diagnosis of SCH who were treated with levothyroxine compared with those who remained untreated. One retrospective cohort study found a significantly higher rate of fetal deaths in the 2.2% of 9,403 women who had TSH levels $\geq$6 mIU/L compared with women whose TSH levels were <6 mIU/L (0.9%: OR 4.4; 95% CI, 1.9–9.5), although this did not represent true SCH (98).

Two studies on the basis of decision-analytic models sought to analyze the cost-effectiveness of routine screening for SCH during pregnancy (93, 99). One concluded that routine screening of TSH levels resulted in cost savings and gained quality-adjusted life years compared with no routine screening (99). The investigators of the other study reported similar findings with regard to cost-effectiveness using a combined screening approach of a first-trimester TSH level and antithyroid peroxidase antibodies (93). In this analysis, universal screening was more cost-effective than screening of high-risk women, which in turn was more cost-effective than no screening. As in other comparisons discussed in this document, these cost-effectiveness analyses are largely driven by selecting source articles demonstrating a benefit to screening and treatment, which most of the literature does not demonstrate.

Further studies on this issue have yielded conflicting results. Within a cohort of 537 consecutive iodine-supplemented women undergoing thyroid screening, patients were treated with 50 μg of levothyroxine when the TSH levels exceeded 1 mIU/L in TPOAb+ women. In this study of intermediate quality, treatment was associated with a significantly lower spontaneous abortion rate compared with no treatment (0 vs. 16%; P=.02) (92). This study, like other cohorts assessing SCH, had findings primarily on the basis of a first-trimester pregnancy loss rate of 0 in treated women, which is a result inconsistent with human reproduction and aneuploidy. As outlined previously in this guideline, a high-quality RCT reported no benefit of antenatal thyroid screening regarding childhood cognitive function (63).

Another high-quality RCT was designed to compare a universal screening strategy with a case-finding strategy on the basis of the presence or absence of risk factors for thyroid disease (100). A total of 4,562 women were randomly assigned to either immediately receive testing for FT4, TSH, and TPOAbs levels or receive the same testing only when risk factors for thyroid disease were identified. No significant differences in adverse outcomes were identified between the case-finding and universal screening groups. However,

low-risk women in the case-finding group were significantly more likely to experience one of the composite obstetric and neonatal outcomes than those in the screening group. Among low-risk women with thyroid abnormalities in the universal screening arm, at least one adverse outcome occurred in 37.3% (19/51). Among low-risk women in the case-finding arm who were later identified to be hypo- or hyper-thyroid, 36 of 39 had at least one adverse outcome (92.3%) (100).

There is currently insufficient collective evidence to support the approach of universal screening of thyroid function in the first trimester. Although it is conceivable that this may be secondary to a lack of well-powered studies, the current body of evidence supports a case-finding screening strategy targeted at specific groups of patients at increased risk of overt hypothyroidism. On the basis of expert recommendations, women with known hypothyroidism treated with levothyroxine before conception should plan to increase their dosage by 30%–60% in the first trimester (101, 102). Women with preconceptional ATD should undergo regular TSH level monitoring during pregnancy, as they are at increased risk for gestational thyroid insufficiency and postpartum thyroiditis.

Summary Statements

- There is moderate evidence that universal screening of thyroid function during pregnancy does not result in a decrease in adverse outcomes.
- There is moderate-quality evidence to support a case-finding screening strategy targeted at specific groups of patients who are at increased risk of overt hypothyroidism.

Recommendations

- Universal screening of thyroid function during pregnancy is not recommended (strength of evidence: B; strength of recommendation: moderate).
- Screening of thyroid function during pregnancy with a serum thyrotropin level is recommended in patients at increased risk of overt hypothyroidism (strength of evidence: B; strength of recommendation: moderate).

RISK CONSIDERATIONS

Although levothyroxine therapy is often considered minimally risky, it does have some associated risks. These risks include, but are not limited to, heat intolerance, sweats, chills, heart palpitations and arrhythmia, diarrhea, weight change, hair thinning, tremors, mood changes, sleep disturbances, fatigue, anxiety, and bone loss (103). In addition, the goal of achieving a TSH level <2.5 mIU/L has resulted in significant delays in women receiving the appropriate infertility treatment or initiating an IVF treatment cycle. Although prior versions of this ASRM document and recommendations from other international societies state that there may be benefit and likely low harm to levothyroxine treatment for SCH, treatment does have side effects, risks, including misdiagnosis and delay in care, and associated costs. In the absence of demonstrable benefit, practitioners are encouraged to use caution and not recommend routine screening and treatment.

CONCLUSIONS

Most of the evidence advocating for screening and treatment of SCH in women with infertility or pregnancy is based on low-quality observational data and one clinical trial, which should be withdrawn because of significant concerns over data integrity. On the basis of current evidence, it is not recommended to screen or treat for asymptomatic SCH in women with infertility or pregnancy.

UNANSWERED QUESTIONS

- Additional clinical trials evaluating the treatment of SCH to improve offspring neurocognitive development are unlikely to change the evidence that screening and treatment do not provide benefits.
- Additional clinical trials evaluating the screening and treatment of antithyroid antibodies and pregnancy outcomes are needed.
- Additional clinical trials evaluating the screening and treatment of SCH in infertile patients and in patients receiving IVF therapies could result in a change in recommendations.

RECOMMENDATIONS

- It is recommended that laboratory-specific TSH cutoff levels be used to diagnose SCH for nonpregnant patients and for pregnant patients by trimester. When laboratory cutoffs are not available, defined upper limits of normal TSH levels should be used (strength of evidence: B; strength of recommendation: moderate).
- It is recommended to counsel women that SCH is not associated with an increased risk of miscarriage (strength of evidence: B; strength of recommendation: moderate).
- It is recommended to counsel women that TSH levels between 2.5 and 4 mIU/L are not associated with an increased risk of miscarriage (strength of evidence: B; strength of recommendation: moderate).
- There is insufficient evidence to counsel women that SCH is associated with infertility (strength of evidence: C; strength of recommendation: weak).
- It is recommended to counsel women that SCH is not associated with increased obstetric risk (strength of evidence B; strength of recommendation: moderate).
- It is recommended that women be counseled that SCH is not associated with adverse neurodevelopmental outcomes in offspring (strength of evidence: A; strength of recommendation: strong).
- It is not recommended to treat women desiring pregnancy or already pregnant who have a diagnosis of SCH with levothyroxine, as treatment has not been proven to reduce pregnancy loss or to improve clinical pregnancy or LB outcomes (strength of evidence B; strength of recommendation: moderate).

- Levothyroxine therapy of SCH diagnosed in pregnancy is not recommended for the indication of improving developmental outcomes (strength of evidence: A; strength of recommendation: strong).
- It is not recommended to screen for TAI in asymptomatic women with infertility or pregnancy. Targeted screening may be considered in women with a history of RPL (strength of evidence C; strength of recommendation weak).
- Universal screening of thyroid function during pregnancy is not recommended (strength of evidence: B; strength of recommendation: moderate).
- Screening of thyroid function during pregnancy with a serum thyrotropin level is recommended for patients at increased risk. (strength of evidence: B; strength of recommendation: moderate).
- Thyroid-stimulating hormone and T4 levels should be tested in patients with signs or symptoms of hypothyroidism (including irregular menstrual cycles) rather than in all patients with infertility (strength of evidence: B; strength of recommendation: moderate).

Declaration of Interests

Per the American Society for Reproductive Medicine (ASRM) policy, all members of ASRM task forces and the Practice Committee disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients for the preceding 12 months. Committee members were reminded to update potential disclosures annually and when new potential conflicts arose during their appointments. Before live discussions or meetings, committee members were reminded verbally and in writing to disclose any new or previously undisclosed relationships. Disclosures were reviewed for conflicts by the ASRM Chief Medical Officer and the Chair of the Practice Committee. Task force members for whom conflicts were identified were excused from this project. Members of the Practice Committee who were found to have conflicts of interest on the basis of the relationships disclosed did not participate in the discussion or development of the document.

Acknowledgments

Following are members of the American Society for Reproductive Medicine (ASRM) Practice Committee who participated in the development and review of this document: Alan Penzias, M.D.; Paula Amato, M.D.; Jacob Anderson, M.B.A.; Kristin Bendikson, M.D.; Clarisa Gracia, M.D., M.S.C.E.; Tommaso Falcone, M.D.; Rebecca Flyckt, M.D.; Karl Hansen, M.D., Ph.D.; Micah Hill, D.O.; Sangita Jindal, Ph.D.; Suleena Kalra, M.D., M.S.C.E.; Tarun Jain, M.D.; Bruce Pier, M.D.; Michael Thomas, M.D.; Richard Reindollar, M.D.; Jared Robins, M.D.; Chevis N. Shannon, Dr.Ph., M.B.A., M.P.H.; Anne Steiner, M.D., M.P.H.; Cigdem Tanrikut, M.D.; and Belinda Yauger, M.D. The Practice Committee acknowledges the special contributions of Micah J. Hill, D.O. (Chair); Kathryn Goldrick, M.D.; Torie Plowden, M.D.; Barry Witt, M.D.; Jennifer Eaton, M.D.; Alex Quaas, M.D.; Mary Ellen Pavone, M.D.; Jessica Goldstein, R.N.; Zac Knight, Ph.D.; and Jeffrey Hayes, Ph.D., in the development of this document. No relevant conflicts were identified.

Disclaimer

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine (ASRM) as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, considering the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

Panel

This evidence-based guideline with recommendations for clinicians was developed by a multidisciplinary group comprising the American Society for Reproductive Medicine (ASRM) Practice Committee and a task force of medical experts, which included specialists in obstetrics and gynecology, reproductive endocrinology and infertility, assisted reproductive technology, in vitro fertilization, epidemiology, and biostatistics. Members of the task force for this clinical practice guideline consisted of medical professionals at various levels of training, including fellows and senior experts, as well as experts with <10 years of posttraining, Clinical Reproductive Scientist Training (CREST) Program scholars, a clinical epidemiologist who is also a reproductive medicine subspecialist, and a methodologic specialist. In addition, a select group of patients participated in document scoping and review.

Review process

The Practice Committee, a multidisciplinary body, reviewed this document at various stages of development. After thorough review of the final draft by the task force for this guideline as well as the Practice Committee, this document was reviewed by the American Society for Reproductive Medicine (ASRM) executive leadership. The document then proceeded to a 15-day period of open review by ASRM members, which includes patient advocates, genetic counselors, mental health professionals, nursing professionals, legal professionals, laboratory personnel, research scientists, and physicians boarded in one or more specialties. The ASRM Board of Directors also reviewed the document over a period of 15 days. The input of all was considered in the preparation of the final document.

Patient and public perspective

To incorporate the perspectives of those who might be affected most by the recommendations in this guideline, a group of patient volunteers and lay stakeholders in reproductive medicine who were not involved in the scoping or development of this guideline reviewed the document. Their feedback was considered in the preparation of the final document.

Updating policy

Document expiration: 2028

ASRM reviews and updates or retires its evidence-based guidelines every 5 years or after significant scientific developments or changes in public policy as determined by the ASRM Practice Committee.

REFERENCES

1. Davis SL. Environmental modulation of the immune system via the endocrine system. Domest Anim Endocrinol 1998;15:283–9.
2. Stagnaro-Green A, Chen X, Bogden JD, Davies TF, Scholl TO. The thyroid and pregnancy: a novel risk factor for very preterm delivery. Thyroid 2005;15:351–7.
3. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549–55.
4. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006;91:2587–91.
5. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002;12:63–8.
6. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. Hum Reprod Update 2003;9:149–61.
7. Arojoki M, Jokimaa V, Juuti A, Koskinen P, Irjala K, Anttila L. Hypothyroidism among infertile women in Finland. Gynecol Endocrinol 2000;14:127–31.
8. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, 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;87:489–99.
9. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526–34.
10. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab 2005;90:5483–8.
11. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, 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.
12. Thyroid Disease in Pregnancy: ACOG Practice Bulletin, Number 223. Obstet Gynecol 2020;135:e261–74.
13. Boughton SL, Wilkinson J, Bero L. When beauty is but skin deep: dealing with problematic studies in systematic reviews. Cochrane Database Syst Rev 2021;6:ED000152.
14. Cochrane database of systematic reviews: editorial policies. Available at: https://www.cochranelibrary.com/cdsr/editorial-policies#problematic-studies. Accessed August 24, 2022.
15. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Adults. 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, Erratum in: Endocr Pract 2013;19:175–9.
16. Fatourechi V. Subclinical hypothyroidism: an update for primary care physicians. Mayo Clin Proc 2009;84:65–71.
17. Dong AC, Stagnaro-Green A. Differences in diagnostic criteria mask the true prevalence of thyroid disease in pregnancy: a systematic review and meta-analysis. Thyroid 2019;29:278–89.
18. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Laboratory medicine practice guidelines Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003;13:3–126.
19. Haddow JE, Knight GJ, Palomaki GE, McClain MR, Pulkkinen AJ. The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. J Med Screen 2004;11:170–4.
20. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291:228–38.
21. Maraka S, Singh Ospina NM, O'Keeffe DT, Rodriguez-Gutierrez R, Espinosa De Ycaza AE, Wi CI, et al. Effects of levothyroxine therapy on pregnancy outcomes in women with subclinical hypothyroidism. Thyroid 2016;26:980–6.
22. Zhang Y, Wang H, Pan X, Teng W, Shan Z. Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: a systematic review and meta-analysis. PLOS ONE 2017;12:e0175708.
23. Zhao T, Chen BM, Zhao XM, Shan ZY. Meta-analysis of ART outcomes in women with different preconception TSH levels. Reprod Biol Endocrinol 2018;16:111.
24. Uchida S, Maruyama T, Kagami M, Miki F, Hihara H, Katakura S, et al. Impact of borderline-subclinical hypothyroidism on subsequent pregnancy outcome in women with unexplained recurrent pregnancy loss. J Obstet Gynaecol Res 2017;43:1014–20.
25. Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, et al. Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss, or live birth. J Clin Endocrinol Metab 2016;101:2358–65.
26. van Dijk MM, Vissenberg R, Bisschop PH, Dawood F, van Wely M, Goddijn M, et al. Is subclinical hypothyroidism associated with lower live birth rates in women who have experienced unexplained recurrent miscarriage? Reprod Biomed Online 2016;33:745–51.
27. Liu H, Shan Z, Li C, Mao J, Xie X, Wang W, et al. Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. Thyroid 2014;24:1642–9.
28. Karakis LS, Kiyak H, Okmen B, Ozdemir C, Turkgeldi E. Impact of preconceptional serum thyroid stimulating hormone values ranging between 2.5 and 4.5 mIU/L on live birth rates following ovulation induction and intrauterine insemination treatment for unexplained infertility. BMC Womens Health 2021;21:162.
29. Hernández M, López C, Soldevila B, Cecenarro L, Martínez-Barahona M, Palomera E, et al. Impact of TSH during the first trimester of pregnancy on obstetric and foetal complications: usefulness of 2.5 mIU/L cut-off value. Clin Endocrinol (Oxf) 2018;88:728–34.
30. De Vivo A, Mancuso A, Giacobbe A, Moleti M, Maggio Savasta L, De Dominici R, et al. Thyroid function in women found to have early pregnancy loss. Thyroid 2010;20:633–7.
31. Cakmak BD, Turker UA, Temur M, Ustunyurt E. Pregnancy outcomes of antibody negative and untreated subclinical hypothyroidism. J Obstet Gynaecol Res 2019;45:810–6.
32. Li MF, Ma L, Feng QM, Zhu Y, Yu TP, Ke JF, et al. Effects of maternal subclinical hypothyroidism in early pregnancy diagnosed by different criteria on adverse perinatal outcomes in Chinese women with negative TPOAb. Front Endocrinol (Lausanne) 2020;11:580380.
33. Chen S, Zhou X, Zhu H, Yang H, Gong F, Wang L, et al. Preconception TSH and pregnancy outcomes: a population-based cohort study in 184 611 women. Clin Endocrinol (Oxf) 2017;86:816–24.
34. Tsunemi A, Uchida T, Kuroda K, Ikemoto Y, Ochiai A, Goto H, et al. Effect of thyroxine treatment on pregnancy outcomes in infertile Japanese women with TSH levels between 2.5 μIU/mL and the upper reference limit: a retrospective study. Endocr J 2021;68:171–7.
35. Coelho Neto MA, Martins WP, Melo AS, Ferriani RA, Navarro PA. Subclinical hypothyroidism and intracytoplasmic sperm injection outcomes. Rev Bras Ginecol Obstet 2016;38:552–8.
36. Reh A, Grifo J, Danoff A. What is a normal thyroid-stimulating hormone (TSH) level? Effects of stricter TSH thresholds on pregnancy outcomes after in vitro fertilization. Fertil Steril 2010;94:2920–2.
37. Gingold JA, Zafman K, Rodriguez-Purata J, Whitehouse MC, Lee JA, Sandler B, et al. Do elevated TSH levels predict early pregnancy loss in ART patients? Gynecol Endocrinol 2016;32:973–6.
38. Chai J, Yeung WY, Lee CY, Li HW, Ho PC, Ng HY. Live birth rates following in vitro fertilization in women with thyroid autoimmunity and/or subclinical hypothyroidism. Clin Endocrinol (Oxf) 2014;80:122–7.

39. Ashoor G, Maiz N, Rotas M, Jawdat F, Nicolaides KH. Maternal thyroid function at 11 to 13 weeks of gestation and subsequent fetal death. Thyroid 2010;20:989–93.
40. Abalovich M, Mitelberg L, Allami C, Gutierrez S, Alcaraz G, Otero P, et al. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. Gynecol Endocrinol 2007;23:279–83.
41. Lincoln SR, Ke RW, Kutteh WH. Screening for hypothyroidism in infertile women. J Reprod Med 1999;44:455–7.
42. Feldthusen AD, Pedersen PL, Larsen J, Toft Kristensen T, Ellervik C, Kvetny J. Corrigendum to "Impaired Fertility Associated with Subclinical Hypothyroidism and Thyroid Autoimmunity: The Danish General Suburban Population Study". J Pregnancy 2017;2017:9864034, Erratum for: J Pregnancy 2015;2015:132718.
43. Stagnaro-Green A, Dong A, Stephenson MD. Universal screening for thyroid disease during pregnancy should be performed. Best Pract Res Clin Endocrinol Metab 2020;34:101320.
44. Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol 1993;81:349–53.
45. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 2005; 105:239–45.
46. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Minooee S, Rahmati M, et al. Effects of levothyroxine on pregnant women with subclinical hypothyroidism, negative for thyroid peroxidase antibodies. J Clin Endocrinol Metab 2018;103:926–35.
47. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol 2008;112:85–92.
48. Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, et al. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. J Clin Endocrinol Metab 2011;96:3234–41.
49. Michalakis KG, Mesen TB, Brayboy LM, Yu B, Richter KS, Levy M, et al. Subclinical elevations of thyroid-stimulating hormone and assisted reproductive technology outcomes. Fertil Steril 2011;95:2634–7.
50. Wang S, Teng WP, Li JX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. J Endocrinol Investig 2012;35:322–5.
51. Furukawa S, Miyakawa K, Shibata J, Iwashita M. Women with subclinical hypothyroidism are at low risk of poor pregnancy outcome in Japan. Tohoku J Exp Med 2017;242:167–72.
52. Goel P, Kaur J, Saha PK, Tandon R, Devi L. Prevalence, associated risk factors and effects of hypothyroidism in pregnancy: a study from north India. Gynecol Obstet Invest 2012;74:89–94.
53. Chen LM, Du WJ, Dai J, Zhang Q, Si GX, Yang H, et al. Effects of subclinical hypothyroidism on maternal and perinatal outcomes during pregnancy: a single-center cohort study of a Chinese population. PLOS ONE 2014;9:e109364.
54. Ma L, Qi H, Chai X, Jiang F, Mao S, Liu J, et al. The effects of screening and intervention of subclinical hypothyroidism on pregnancy outcomes: a prospective multicenter single-blind, randomized, controlled study of thyroid function screening test during pregnancy. J Matern Fetal Neonatal Med 2016;29:1391–4.
55. Li M, He Y, Mao J, Yang L, Chen L, Du J, et al. Preconception thyroid-stimulating hormone levels and adverse pregnancy outcomes. Clin Endocrinol 2022;97:339–46.
56. Li J, He Y, Ren B, Zhang Z, Meng F, Zhang X, et al. The thyroid condition and residual clinical signs in 31 existing endemic neurological cretins after 42 years of iodine supplementation in China. Front Endocrinol (Lausanne) 2022;13:911487.
57. Qian X, Sun Y, Xu X. Effect of levothyroxine sodium tablets on pregnancy outcome and offspring development quotient of SCH during pregnancy. J Healthc Eng 2022;2022:9001881.
58. Sitoris G, Veltri F, Kleynen P, Cogan A, Belhomme J, Rozenberg S, et al. The impact of thyroid disorders on clinical pregnancy outcomes in a real-world study setting. Thyroid 2020;30:106–15.
59. Yuan N, Sun J, Li Z, Chai S, Zhang X, Ji L. Relationship between anti-thyroid peroxidase antibody positivity and pregnancy-related and fetal outcomes in Euthyroid women: a single-center cohort study. BMC Pregnancy Childbirth 2020;20:491.
60. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update 2011;17:605–19, Erratum in: Hum Reprod Update 2016;22:532–619.
61. Rosen F, Ezrin C. Embryology of the thyrotroph. J Clin Endocrinol Metab 1966;26:1343–5.
62. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 1999;50:149–55.
63. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med 2012;366:493–501.
64. Hales C, Taylor PN, Channon S, Paradice R, McEwan K, Zhang L, et al. Controlled antenatal thyroid screening II: Effect of treating maternal suboptimal thyroid function on child cognition. J Clin Endocrinol Metab 2018;103:1583–91.
65. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. N Engl J Med 2017;376:815–25.
66. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol (Oxf) 2010;72:825–9.
67. Williams F, Watson J, Ogston S, Hume R, Willatts P, Visser T, et al. Mild maternal thyroid dysfunction at delivery of infants born ≤34 weeks and neurodevelopmental outcome at 5.5 years. J Clin Endocrinol Metab 2012;97:1977, 85.
68. Wang Q, Jiang Y, Lv H, Lu Q, Tao S, Qin R, et al. Association of maternal mild hypothyroidism with offspring neurodevelopment in TPOAb-negative women: a prospective cohort study. Front Endocrinol (Lausanne) 2022;13:884851.
69. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 2011;95:1650–4.
70. Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. Hum Reprod 2005;20:1529–33.
71. Abdel Rahman AH, Aly Abbassy H, Abbassy AA. Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocr Pract 2010;16:792–7, Erratum in: Endocr Pract 2011;17:526.
72. Braverman L. Correction. Endocr Pract 2011;173:526.
73. Akhtar MA, Agrawal R, Brown J, Sajjad Y, Craciunas L. Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. Cochrane Database Syst Rev 2019;6:CD011009.
74. Rao M, Zeng Z, Zhao S, Tang L. Effect of levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism and thyroid autoimmuneity undergoing in vitro fertilization/intracytoplasmic sperm injection: an updated meta-analysis of randomized controlled trials. Reprod Biol Endocrinol 2018;16:92.
75. Velkeniers B, Van Meerhaeghe A, Poppe K, Unuane D, Tournaye H, Haentjens P. Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. Hum Reprod Update 2013;19:251–8.
76. Maraka S, Ospina NM, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, et al. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. Thyroid 2016;26:580–90.
77. Vissenberg R, van den Boogaard E, van Wely M, van der Post JA, Fliers E, Bisschop PH, et al. Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. Hum Reprod Update 2012;18:360–73.
78. Bein M, Yu OHY, Grandi SM, Frati FYE, Kandil I, Filion KB. Levothyroxine and the risk of adverse pregnancy outcomes in women with subclinical

hypothyroidism: a systematic review and meta-analysis. BMC Endocr Disord 2021;21:34.
79. Geng X, Chen Y, Wang W, Ma J, Wu W, Li N, et al. Systematic review and meta-analysis of the efficacy and pregnancy outcomes of levothyroxine sodium tablet administration in pregnant women complicated with hypothyroidism. Ann Palliat Med 2022;11:1441–52.
80. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Singh Ospina NM, et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. BMJ 2017;356:i6865.
81. Bartáková J, Potluková E, Rogalewicz V, Fait T, Schöndorfová D, Telička Z, et al. Screening for autoimmune thyroid disorders after spontaneous abortion is cost-saving and it improves the subsequent pregnancy rate. BMC Pregnancy Childbirth 2013;13:217.
82. Bernardi LA, Cohen RN, Stephenson MD. Impact of subclinical hypothyroidism in women with recurrent early pregnancy loss. Fertil Steril 2013;100:1326–31.
83. Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, Garcia-Esteban R, et al. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiology 2013;24:150–7.
84. Klein RZ, Sargent JD, Larsen PR, Waisbren SE, Haddow JE, Mitchell ML. Relation of severity of maternal hypothyroidism to cognitive development of offspring. J Med Screen 2001 Mar 1;8:18–20.
85. Orito Y, Oku H, Kubota S, Amino N, Shimogaki K, Hata M, et al. Thyroid function in early pregnancy in Japanese healthy women: relation to urinary iodine excretion, emesis, and fetal and child development. J Clin Endocrinol Metab 2009;94:1683–8.
86. Behrooz HG, Tohidi M, Mehrabi Y, Behrooz EG, Tehranidoost M, Azizi F. Subclinical hypothyroidism in pregnancy: intellectual development of offspring. Thyroid 2011;21:1143–7.
87. Yamamoto JM, Benham JL, Nerenberg KA, Donovan LE. Impact of levothyroxine therapy on obstetric, neonatal and childhood outcomes in women with subclinical hypothyroidism diagnosed in pregnancy: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2018;8:e022837.
88. Sieiro Netto L, Medina Coeli C, Micmacher E, Mamede Da Costa S, Nazar L, Galvão D, et al. Influence of thyroid autoimmunity and maternal age on the risk of miscarriage. Am J Reprod Immunol 2004;52:312–6.
89. López-Tinoco C, Rodríguez-Mengual A, Lara-Barea A, Barcala J, Larrán L, Saez-Benito A, et al. Impact of positive thyroid autoimmunity on pregnant women with subclinical hypothyroidism. Endocrinol Diabetes Nutr (Engl Ed) 2018;65:150–5.
90. Glinoer D, Riahi M, Grün JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. J Clin Endocrinol Metab 1994;79:197–204.
91. Iravani AT, Saeedi MM, Pakravesh J, Hamidi S, Abbasi M. Thyroid autoimmunity and recurrent spontaneous abortion in Iran: a case-control study. Endocr Pract 2008;14:458–64.
92. Lepoutre T, Debiève F, Gruson D, Daumerie C. Reduction of miscarriages through universal screening and treatment of thyroid autoimmune diseases. Gynecol Obstet Invest 2012;74:265–73.
93. Dosiou C, Barnes J, Schwartz A, Negro R, Crapo L, Stagnaro-Green A. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. J Clin Endocrinol Metab 2012;97:1536–46.
94. Singh A, Dantas ZN, Stone SC, Asch RH. Presence of thyroid antibodies in early reproductive failure: biochemical versus clinical pregnancies. Fertil Steril 1995;63:277–81.
95. Negro R, Formoso G, Coppola L, Presicce G, Mangieri T, Pezzarossa A, et al. Euthyroid women with autoimmune disease undergoing assisted reproduction technologies: the role of autoimmunity and thyroid function. J Endocrinol Invest 2007;30:3–8.
96. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 2012;22:1200–35.
97. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2543–65.
98. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 2000;7:127–30.
99. Thung SF, Funai EF, Grobman WA. The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. Am J Obstet Gynecol 2009;200:267.e1, 7.
100. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. J Clin Endocrinol Metab 2010;95:1699–707.
101. Mandel SJ, Spencer CA, Hollowell JG. Are detection and treatment of thyroid insufficiency in pregnancy feasible? Thyroid 2005;15:44–53.
102. Abalovich M, Vázquez A, Alcaraz G, Kitaigrodsky A, Szuman G, Calabrese C, et al. Adequate levothyroxine doses for the treatment of hypothyroidism newly discovered during pregnancy. Thyroid 2013;23:1479–83.
103. Eghtedari B, Correa R. Levothyroxine. 2023. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.

Hipotiroidismo subclínico en la población de mujeres infértiles: una guía

Existe controversia sobre si se deben tratar las anomalías sutiles de la función tiroidea en pacientes femeninas infértiles. Este documento de guía revisa los riesgos y beneficios del tratamiento del hipotiroidismo subclínico en pacientes femeninas con antecedentes de infertilidad y aborto espontáneo,así como los resultados obstétricos y neonatales en esta población.