Subclinical hypothyroidism in the infertile female population: a guideline

Practice Committee of the American Society for Reproductive Medicine

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There is controversy regarding whether to treat subtle abnormalities of thyroid dysfunction in the infertile female patient. 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 obstetrical and neonatal outcomes in this population. (Fertil Steril® 2015;104:545–53. ©2015 by American Society for Reproductive Medicine.)

Key Words: Thyroid-stimulating hormone, levothyroxine treatment, infertility, fertility treatment, screening

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LITERATURE SEARCH

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 thyroid-stimulating hormone (TSH), live-birth rate, preeclampsia, pregnancy rate, complication, death, and demise.

The search was restricted to MEDLINE citations of human subject research published in the English language from 1966 to March 2014. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials), that assessed the effectiveness of a procedure correlated with outcome measure (pregnancy, implantation, or live-birth rates), meta-analyses, and relevant articles from bibliographies of identified articles.

The quality of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography:

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

The strength of the evidence was evaluated as follows:

Level A: There is good evidence to support the recommendations, either for or against.

Level B: There is fair evidence to support the recommendations, either for or against.

Level C: There is insufficient evidence to support the recommendations, either for or against.

BACKGROUND

Overt hypothyroidism potentially can have a significant impact on reproductive outcomes. Complications may include an increased incidence of infertility, miscarriage, and adverse obstetric and fetal outcomes (1–3). There is also evidence to suggest that inadequate treatment of overt hypothyroidism or subclinical hypothyroidism (SCH) can lead to infertility, miscarriage, and adverse obstetrical and neurodevelopmental outcomes (3–7). However, debate persists in the definition of SCH and the decision of when to treat,

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particularly for women attempting pregnancy. The classic definition of SCH is a thyrotropin (TSH) level greater than the upper limit of 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 by third-generation assay (10). Moreover, given the potential impact of inadequate thyroid function, the question remains whether treatment should be initiated with subtler abnormalities of thyroid dysfunction. The Endocrine Society, the American Thyroid Association (ATA), and the American Association of Clinical Endocrinologists (AACE) have established guidelines on whether and when to treat thyroid dysfunction (11). Our current understanding of the effect of thyroid dysfunction and thyroid autoimmunity on fertility and pregnancy is based largely on retrospective studies. Although there are limited Level I data available, there are consistent trends in the literature that allow for the guidelines set forth in this document.

WHAT IS THE DEFINITION OF SCH?

Normative data for TSH have been established by the National Health and Nutrition Examination Survey (NHANES III) population (8). The data from this examination suggest a median serum level for TSH of 1.50 mIU/L with the corresponding 2.5 and 97.5 percentiles of 0.41 and 6.10, respectively, for a disease-free population. However, according to the National Academy of Clinical Biochemistry (NACB), 95% of individuals without evidence of thyroid disease have a TSH level <2.5 mIU/L, and the normal reference range is skewed to the right (12). Therefore, the NACB suggests that a TSH level of 2.5 mIU/L should be the upper limit of normal for all patients (10). However, if the upper limit of normal was lowered to 2.5 mIU/L, an additional 11.8%–14.2% of the United States population, 22–28 million individuals, would be diagnosed with hypothyroidism. This compares with 2.3%–4.3% (4.6–8.6 million) people being diagnosed according to the classic definition (TSH >5 mIU/L) (8, 13).

Although antithyroid antibodies are not used for the diagnosis of SCH, they are often measured and elevated levels have been associated with an increased likelihood of converting to overt hypothyroidism (14). Normative data for antithyroid antibodies have also been established by the NHANES III population (8). While both antithyroglobulin and antithyroid peroxidase antibodies (TPO-Abs) were positive in approximately 10%–12% of the population, only anti-TPO-Abs were associated with thyroid dysfunction and thought to be of clinical significance.

A. **Nonpregnant women.** Despite the findings that TSH levels are skewed in the general population, current evidence does not support treating nonpregnant women for subtle thyroid abnormalities (TSH <5 mIU/L). There is no benefit (with respect to lipid profile and/or cardiovascular risk) of treatment for a TSH level between 5 and 10 mIU/L (15). Thus, any potential benefit of treatment for individuals with TSH <5mIU/L is questioned (15). While there is potential risk of overtreatment, particularly for women who could suffer bone loss, this study further suggests that the positive predictive value (PPV) for hypothyroidism of a TSH between 2.5 and 5 mIU/L is small. Given the absence of demonstrable benefit of treatment, the low PPV and the increased health-care costs of identification and treatment, population screening, and/or lowering the upper limit of normal reference for TSH are not supported. Given the lack of evidence for treatment of nonpregnant individuals using these cutoffs, the Endocrine Society guidelines do not support changing the cutoff outside of pregnancy. The recommendation from the Endocrine Society is the following: The reference range of a given laboratory should determine the upper limit of normal for a third generation TSH assay. The normal TSH reference range changes with age. If an age-based upper limit of normal for a third generation TSH assay is not available in an iodine sufficient area, an upper limit of normal of 4.12 mIU/L should be considered (11).

B. **Pregnant women.** It has been recommended that the normal range of TSH for pregnancy be modified (16). This is because human chorionic gonadotropin (hCG) can bind to the TSH receptor and influence TSH values. Accordingly, the Endocrine Society recommends the following: The reference range of TSH in pregnancy is to be dependent on the trimester: 2.5 is the recommended upper limit of normal in the first trimester, 3 in the second and 3.5 in the third (11).

C. **Women attempting pregnancy.** Because the reference range of TSH changes when a woman becomes pregnant, some advocate using pregnancy thresholds for the treatment of women attempting conception in order to minimize the potential risks associated with SCH in pregnancy (17). This strategy has been controversial, since data are difficult to interpret. Their validity is hindered by a variety of methodological limitations, including the lack of proper controls, recall bias, and failure to control for confounders (i.e., age, medical conditions) that are known to influence reproductive outcomes. Most importantly, the studies use different TSH cutoffs to define subclinical hypothyroidism.

The next sections summarize the studies assessing the association between subclinical hypothyroidism and treatment for risk of miscarriage, infertility, and adverse pregnancy outcomes.

ASSOCIATIONS

Is Untreated SCH Associated with Miscarriage?

Overt hypothyroidism is associated with an increase in miscarriage rate (18). However, data about whether or not SCH is associated with an increase in the incidence of miscarriage are conflicting; some studies show a possible increased risk, while others show no effect (19–24). The contradictory results may be due to the small number of fetal losses with thyroid deficiency, differences in timing of thyroid

screening, and differences in TSH cutoffs. In addition, most study populations were tested in the late first trimester and second trimester and do not provide information regarding early first-trimester miscarriages.

Several studies have found that elevated TSH levels in pregnancy are associated with an increased risk of miscarriage in patients without a diagnosis of hypothyroidism (20, 21, 25–27). Most of these studies have assessed thyroid function during the late first trimester rather than before pregnancy. For example, one study found TSH values were elevated at 11–13 weeks' gestation in 202 women with singleton pregnancies that subsequently miscarried compared with 4,318 singleton pregnancies with no history of thyroid disease that resulted in live birth after 34 weeks (25). Similarly, a study of 2,497 pregnant women without thyroid disease participating in a large population-based cohort study of Amsterdam-born children and their development found an association between thyroid indices and miscarriage (27). In this study, TSH and FT4 level were measured prior to 27 weeks' gestation (average 13 weeks' gestation). The mean TSH and FT4 levels in the women who miscarried were 1.48 mIU/L and 9.82 pmol/L compared with 1.11 mIU/L and 9.58 pmol/L respectively in women who did not miscarry. The incidence of miscarriage increased by 60% (odds ratio [OR] 1.60; 95% confidence interval [CI], 1.04–2.47) for every doubling in TSH concentration. This association remained significant after adjustment for known confounders (adjusted odds ratio [AOR] 1.80; 95% CI, 1.07–3.03). However, in the 2,497 pregnant women in the study, there were only 27 miscarriages. It is worthwhile to note that these miscarriages occurred after 11 weeks' gestation, and, although statistically different, the TSH values of both groups were within the normal range and less than <2.5 mIU/L. More recently, several investigators performed an analysis of a subset of TPO-ab-negative women (n = 4,123) with TSH levels at or below 5.0 mIU/L from a prospective study that was evaluating treatment impact for thyroid dysfunction (20). These women had TSH levels measured within the first trimester and were receiving no treatment. They were divided into two groups based on their initial TSH: group A, TSH level below 2.5 mIU/L; and group B, TSH level between 2.5 and 5.0 mIU/L. The rate of pregnancy loss (defined as any loss prior to 20 weeks' gestation) was significantly higher in group B compared with group A (6.1% vs. 3.6%, respectively, P=.006). Although this study did report a statistical difference, the clinical significance can be questioned given that the miscarriage rates reported are less than expected for the general population.

Other studies have shown no increased risk of miscarriage with subtle thyroid abnormalities (19, 22–24, 28). In a subset of patients (n = 10,990) from the First And Second Trimester Evaluation of Risk (FASTER) Trial, thyroid function tests were performed to determine if thyroid hypofunction diagnosed during the first or second trimesters affects obstetric outcomes (23). In this study, 2.2% of patients were found to have TSH ≥2.5 mIU/L, and the risk of miscarriage in this group was no different than in those with TSH <2.5 mIU/L (AOR 0.69; 95% CI, 0.1–5.0) even when adjusted for potential confounders (age, body mass index [BMI], smoking, medical conditions). However, because patients were enrolled between 10 and 13 weeks' gestation, the study was not able to assess pre-pregnancy TSH values or association with early first-trimester losses. Nested within the prospective population-based China-Anhui Birth Defects and Child Development Study was another study of 1,017 women with singleton pregnancies. This study found no association with miscarriage rates and TSH values drawn within the first 20 weeks of pregnancy. Of note, only 2.1% of pregnancies resulted in a miscarriage (24).

Few studies have examined if miscarriage rates are increased with a TSH level >2.5 mIU/L and less than the upper range of normal at the time of conception (19, 28). The studies examining this association are mostly retrospective and in an infertile population. One study reviewed more than 1,200 cycles and found that 23% of women had moderately elevated TSH values in the range of 2.5 to 4.0 mIU/L (28). This population had stimulation and pregnancy outcomes similar to women with TSH values <2.5 mIU/L, with a miscarriage rate of 20% in both groups. The findings are similar to those in another study in which 248 patients with mildly elevated basal TSH (>2.5 mIU/L) were compared with 807 patients with a normal TSH (<2.5 mIU/L), and no difference in pregnancy outcomes were noted (19).

Summary statement. There is fair evidence that SCH, defined as a TSH level >4 mIU/L during pregnancy, is associated with miscarriage, but insufficient evidence that TSH levels between 2.5 and 4 mIU/L are associated with miscarriage.

Is Untreated SCH Associated with Infertility?

The data assessing the effect of SCH on fertility are limited due to varied definitions of SCH (different TSH cutoffs) and lack of adequate control groups. Overall, the incidence of SCH is similar in infertile women and the general female population (29, 30), although the mean TSH level may be slightly higher in a population of infertile women compared with controls (30). Some investigators have suggested that SCH is more prevalent in infertile women (0.7%–10.2%), and the prevalence appears to be highest among women with ovulatory disorders (7, 29, 31). One study of 704 infertile women seeking treatment for infertility found an elevated TSH level in 2.3% of women; 64% of these 16 women had ovulatory dysfunction (29). A few studies have found an association between SCH and unexplained infertility (7, 16). In a retrospective study, an elevated serum TSH was found in 4% of 335 infertile Finnish women with no known history of thyroid dysfunction (7). The prevalence was highest in those with ovulatory dysfunction (6%) and unexplained infertility (5%). A retrospective study found a 14% incidence of SCH in 244 infertile women and 4% in 155 healthy fertile controls in Argentina (16). Subclinical hypothyroidism is not increased in other infertile populations, including those with tubal factor (7).

Summary statement. There are insufficient data to conclude that SCH is clearly associated with infertility.

Is SCH Associated with Adverse Obstetric Outcomes?

The relationship between SCH with TSH levels outside of the normal pregnancy range and pregnancy complications suggests that there may be an increased risk for adverse obstetric outcomes including placental abruption, preterm birth, fetal death, and preterm premature rupture of membranes (PPROM) (1, 2, 32, 33). However, available studies are limited by the fact that clinically relevant outcome events are rare, and studies are mostly retrospective.

In a large, observational study of 25,756 women with singleton births, 2.3% were found to have elevated TSH at 15 weeks' gestation (absolute values were not reported; TSH values >97.5 percentile with normal free thyroxine) (33). When comparing those women with elevated TSH with those with a normal TSH, 1% vs. 0.3% of patients experienced placental abruption (relative risk [RR] 3.0; 95% CI, 1.1–8.2), and 4% vs. 2.5% delivered ≤34 weeks (RR 1.8; 95% CI, 1.1–2.9) (33). A case-control study in which TSH levels were obtained at 15 weeks' gestation showed similar findings (2). Cases included all women with preterm delivery (N = 124), and controls were randomly selected from among the 829 women who delivered at term. The cases were stratified in the following way: 28 gravidas who delivered very preterm (<32 completed weeks' gestation), and 96 gravidas who delivered moderately preterm (32 to <37 completed weeks' gestation). Investigators found that 4 of 28 patients had very preterm births and elevated maternal TSH levels (>3.0 mIU/L) at 15 weeks' gestation compared with the 7 of 107 patients who delivered at term (AOR = 3.13; 95% CI, 1.02–9.63). The risk of very preterm delivery with elevated TSH did not change with additional adjustment of cigarette smoking (AOR = 3.37; 95% CI, 1.18–9.63).

There are few studies evaluating the risk of SCH and other pregnancy complications (23, 34). One study found a significantly higher rate of fetal deaths in the 2.2% of 9,403 women who had TSH levels ≥6 mIU/L compared with women whose TSH was <6 mIU/L (0.9%:OR 4.4; 95% CI, 1.9–9.5) (34).

The FASTER trial, a study evaluating noninvasive prenatal diagnostic testing, found a 15% incidence of TPO-Ab and antithyroglobulin antibodies during the first trimester and 14% in the second trimester of pregnancy (23). In this study, there was a significantly increased risk of PPROM when both antibodies were positive in either trimester (P=.002 and P<.001, respectively). This may be related to an underlying inflammatory process; however, there was no consistent maternal/fetal risk associated with maternal SCH. It is important to note that none of these studies have looked at obstetrical outcomes in women with TSH levels between 2.5 and 4 mIU/L prior to conception.

Summary statement. There is fair evidence that SCH during pregnancy is associated with adverse obstetric outcomes in pregnant patients with TSH outside of the normal reference range in pregnancy. However, there are no data to evaluate whether pre-pregnancy TSH levels between 2.5 and 4 mIU/L are associated with adverse obstetric outcomes.

Does Untreated SCH Affect Developmental Outcomes in Children?

The fetal thyroid does not produce thyroid hormone before 10–13 weeks of gestation (35). Therefore, maternal thyroid hormone is imperative in early pregnancy. There is 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 (36). While it appears that overt maternal hypothyroidism has adverse effects on developmental outcomes, the impact of maternal SCH on development has not been well established. Whether SCH is associated with decreased cognition in offspring is difficult to determine. Studies are 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 an attempt to determine if untreated maternal hypothyroidism during pregnancy affected the child's neuropsychological development, TSH levels were measured in 25,216 stored serum samples from pregnant women in the second trimester (3). Investigators identified 47 women with TSH concentrations ≥99.7 percentile of the values for pregnant women (TSH level >8 mIU/L) and 15 women with values from the 98 to 99.6 percentiles (all TSH values >5 mIU/L) and compared these women to 124 matched controls with normal values. Compared with children born of euthyroid women, 7- to 9-year-old children born of women with serum TSH levels at or above the 98th percentile performed 4 points lower on the Wechsler Intelligence Scale for Children, 3rd Edition (P=.06). Children of women with untreated hypothyroidism scored 7 points lower in full-scale IQ testing compared with normal controls (P=.005). Furthermore, 19% of children born to women with untreated hypothyroid had IQ scores below 85, compared with 5% in the euthyroid controls. In this study the average TSH value was 13.2 mIU/L, and the free thyroxine was below the reference range at 0.71 ng/dL. Another large, observational study reported similar results (37). After controlling for socioeconomic status, that study showed an OR of having an IQ >1 standard deviation below the control mean of 4.7 (P=.006) for women with TSH values ≥99.7th percentile in the second trimester, compared with those with a TSH below the 98th percentile (37).

More recently, a study found that isolated levels of TSH may be a determinant of cognition (38). Investigators collected serum from 1,268 women in the second trimester and compared neurodevelopment outcomes in the children of patients with isolated SCH (18 cases) (TSH level >4 mIU/L, normal levels of T4 and FT4, and negative TPO-Ab), hypothyroxinemia (19 cases), and euthyroid patients with elevated titers of TPO-Ab (34 cases). They compared cognition in 134 matched euthyroid and TPO-Ab-negative women and found that increased maternal serum TSH, decreased maternal serum T4, and maternal TPO-Ab titers measured during the second trimester of pregnancy were significant predictors of reduced motor and intellectual development scores at 25–30 months.

Whether or not TSH values between 2.5 and 4 mIU/L are associated with developmental outcomes has not been well determined. A recent study evaluated maternal TSH levels at the time of delivery in cases of preterm birth and found an association between TSH and neurodevelopment in the child at 5.5 years. Higher TSH levels were associated with more cognitive issues, but even mild maternal hypothyroidism at the time of delivery (TSH levels ≥3 mIU/L) effected a significant decline in verbal and perceptual performance (39). However, another study examined IQ and cognition of children born to hypothyroid mothers who were treated to maintain TSH ≤2.5 mIU/L prior to gestation and had TSH values >3 mIU/L vs. ≤3 mIU/L during the first half of gestation (40). These investigators found that IQ level and cognitive performance in the children born of levothyroxine-treated hypothyroid mothers who had TSH >3 mIU/L during their pregnancy were similar to those levothyroxine-treated hypothyroid mothers who maintained a normal serum TSH during pregnancy. Similar findings were seen in Japanese pregnant women: serum TSH levels higher than 2.5 mIU/L in the first half of gestation had no effect on fetal maturation scores or child developmental tests in their infants (41, 42). Other investigators have found an association between thyroid dysfunction and cognitive function with low thyroxine values (43). They evaluated 1,761 children and their mothers and found that low serum levels of free thyroxine (<5th percentile) were associated with a decrease in "mental" scores during the second year of life using the Bayley Scales of Infant Development (43). However, in this study TSH values were not recorded.

Summary statement. There is good evidence that overt hypothyroidism and fair evidence that SCH diagnosed in pregnancy are associated with adverse neurodevelopmental outcomes. However, there is no evidence that prepregnancy TSH levels between 2.5 and 4 mIU/L are associated with adverse developmental outcomes.

TREATMENT

Does Treatment of SCH Improve Miscarriage Rates, Live-birth Rates, and/or Clinical Pregnancy Rates?

Two small, randomized trials have evaluated whether treatment for SCH improves pregnancy outcomes (44, 45). Of note, all studies define SCH as a TSH level >4 mIU/L. In 2011, several investigators performed a randomized trial on a population of 64 infertile patients with SCH (TSH level >4.5 mIU/L with a normal FT4 level) who had undergone 64 in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles (44). Subjects were randomized into either the levothyroxine treatment group (50 mcg levothyroxine starting at day 1 of ovarian stimulation) or the control group. They found that treatment did not alter the number of eggs retrieved or the percent that reached maturity. However, they observed a significant increase in the number of grade I or II embryos (P=.007) and in the implantation rate (26.9% vs. 14.9%, P=.044). The miscarriage rate was significantly lower in the levothyroxine treatment group (0 vs. 33.3%; P=.021), and as a result the live-birth rate was significantly higher in the levothyroxine treatment group (53.1% vs. 25%, P=.039). When pregnant, the levothyroxine dosage was titrated to maintain serum TSH concentrations of <2.5 mIU/L in the first trimester. Another study randomized 70 women with SCH (defined as an elevated TSH >4.2 mIU/L, with normal FT4) to receive either 50–100 mcg levothyroxine daily or placebo (45). This study found that the number of retrieved oocytes was similar, the miscarriage rate was significantly lower (9% vs. 13%, respectively), while the clinical pregnancy rate (35% and 10%) and delivery rate (26% and 3%) were both significantly higher in the treatment group compared with placebo. In addition, there have been some observational studies in the general population that have found inadequate treatment of hypothyroidism (levels ≥4 mIU/L) linked to an increase in miscarriage (5, 46).

There are no randomized trials assessing the efficacy of levothyroxine therapy in women with TSH levels between 2.5 and 4 mIU/L. One observational study showed a nonstatistically significant improvement in miscarriage rates when treatment was initiated with a TSH level of >2.5 mIU/L (21).

Summary statement. There is good evidence that levothyroxine treatment in women with SCH defined as TSH >4.0 mIU/L is associated with improvement in pregnancy and miscarriage rates. There is insufficient evidence that levothyroxine therapy in women with TSH levels between 2.5 and 4 mIU/L is associated with improvement in pregnancy and miscarriage rates.

Does Treatment of SCH Improve Developmental Outcomes?

Investigators performed a randomized trial to determine if treatment for TSH elevations above the 97.5 percentile (absolute values not reported) would change IQ scores in children at 3 years of age (47). This study collected sera from pregnant women at a gestation of 15 weeks and 6 days or less and randomly assigned each woman to a screening group (in which measurements were obtained immediately) or a control group (in which serum was stored and measurements were obtained shortly after delivery). Women with elevated TSH in the screening group were assigned to 150 mcg of levothyroxine per day. Levels of TSH and FT4 were checked 6 weeks after the start of levothyroxine therapy and at 30 weeks' gestation, with dose adjustment as necessary. The target TSH level was 0.1 to 1.0 mIU/L. Investigators found no significant difference in IQ scores between 3-year-old children born to women who were randomly assigned to the screening group and treated for reduced thyroid function before 20 weeks' gestation and children born to women with reduced thyroid function who were randomly assigned to the control group. There were no between-group differences in the analyses that were limited to the women who adhered to treatment.

Summary statement. There is fair evidence based on the only randomized clinical trial that levothyroxine treatment for SCH (defined as TSH outside the normal pregnancy range) does not improve developmental outcomes.

Are Thyroid Antibodies Associated with Infertility or Adverse Reproductive Outcomes?

The data are mixed on whether thyroid antibodies are associated with infertility or adverse reproductive outcomes. The prevalence of isolated thyroid autoimmunity may be higher among infertile women, especially when infertility is caused by endometriosis or ovulatory dysfunction (30). In a prospective study comparing 438 infertile women and 100 age-matched healthy, fertile controls, the prevalence of TPO-Ab was 18% in infertile women compared with 8% in controls ($P<.05$) (30). However, the prevalence of women with thyroid antibodies did not increase in a retrospective study comparing a general population of 688 women undergoing assisted reproductive technology (ART) and 200 healthy, reproductive-aged controls (50).

Some studies suggest an association between thyroid antibodies and miscarriage even in the absence of thyroid dysfunction (4, 22, 48–51). Most data that suggest an association between thyroid antibodies and miscarriage are from case-control studies in populations with recurrent miscarriage. In addition, the populations were tested late in the first trimester and second trimester, and the studies do not provide information regarding early first-trimester miscarriages. However, there are a few prospective studies. In one prospective study of 534 pregnant women, thyroid antibodies were measured and then the patients were followed to determine if there was a pregnancy loss or live birth (51). Investigators found that the overall rate of miscarriage (prior to 20 weeks' gestation) was 2.4% (13 of 534) and that the incidence of miscarriage was significantly higher among women with TPO-Ab (10.3%) who presented with a TSH >3.8 mIU/L (12.5%). They also showed that, when adjusted for age and TSH, the presence of thyroid antibodies was associated with a 4-fold increase in risk of miscarriage. However, there were only 29 patients with thyroid antibodies in this study, and 3 of them miscarried. In a randomized study of euthyroid women with antithyroid antibodies, it was found that thyroid antibodies were associated with miscarriage and preterm birth (4). In this study, 984 pregnant women were studied, and 11.7% were TPO-Ab positive. The patients were divided into 3 groups: group A (n = 57) was treated with levothyroxine (4), and group B (n = 58) was not treated. The 869 TPO-Ab–negative patients (group C) served as a normal population control group. Groups A and C showed no difference in miscarriage rate (3.5% and 2.4%, respectively), but their rates were significantly lower than group B (13.8%) ($P<.05$; RR 1.72; 95% CI, 1.13–2.25; and $P<.01$; RR 4.95; 95% CI, 2.59–9.48, respectively). Group B displayed a 22.4% rate of premature deliveries, which was higher than group A (7%) ($P<.05$; RR 1.66; 95% CI, 1.18–2.34) and group C (8.2%) ($P<.01$; RR 12.18; 95% CI, 7.93–18.7).

Other studies suggest that there is no relationship between thyroid antibodies and reproductive outcomes (52, 53). One study tested for thyroid antibodies from 74 nonpregnant women with a history of recurrent pregnancy loss and from 75 healthy, fertile control subjects (52). Twenty-two of the women with a history of recurrent pregnancy loss (29.3%) and 28 of the control subjects (37%) had positive results for either one or both of the thyroid autoantibodies ($P>.05$). Another study found that the future risk of pregnancy loss in women with unexplained recurrent miscarriage is not associated with thyroid antibodies (53). In this study, investigators measured thyroid antibodies and followed 870 consecutive, nonpregnant women with a history of three or more pregnancy losses and normal parental karyotypes. Thyroid antibodies were found in 162 (19%) women. Thirteen women had a history of thyroid disease, and an additional 15 women were found to have abnormal thyroid function. In the group proven euthyroid, 14 of 24 untreated pregnancies resulted in live births (58%). Among the 710 thyroid antibody-negative women, 47 of 81 untreated pregnancies resulted in live births (58%).

The data are conflicting in studies evaluating the impact of thyroid immunity following ART (48, 49, 54, 55). One study measured thyroid antibodies in 487 patients who were undergoing ART and found 106 women who were antibody positive for antithyroglobulin, TPO-Ab, or both, and 381 who were negative (54). The overall incidence of positivity was 22%. In the antibody-positive group, there was a significant increase in clinical miscarriage rate compared with the antibody-negative group (32% vs. 16%, respectively; $P=.002$). There was no significant difference between the groups in age, gravidity, or number of prior pregnancy losses.

A large study of women preparing for ART prospectively identified an incidence of TPO-Ab in 14% of 234 women and found that the miscarriage rate was 53% with TPO-Ab and 23% without TPO-Ab, with an OR of 3.77 (95% CI, 1.29–11.05; $P=.016$) (49). However, other investigators in a retrospective, multicenter study found TPO-Ab in 16% of 873 women undergoing IVF and 15% in 200 healthy reproductive-aged controls. There was no difference in biochemical pregnancy rates, clinical pregnancy loss rates, or live-birth rates between women with or without TPO-Ab (48). An additional retrospective study found TPO-Ab in 10% of 416 euthyroid women undergoing ART and found no differences in pregnancy and/or delivery rates between women with and without antibodies (55). However, women who were thyroid antibody-positive failed to become pregnant or miscarried and had higher TSH values before ART (2.8 mIU/L) compared with women who delivered (1.6 mIU/L; $P=.032$) and were TPO-Ab negative (1.1 mIU/L; $P=.018$). In a prospective, randomized IVF trial, 72 women with TPO-Ab, and on average normal TSH, were randomized to receive levothyroxine therapy or placebo; additional controls included 412 euthyroid women without TPO-Ab (56). Although the risk of miscarriage was higher in the TPO-Ab positive groups when compared with controls (RR 2.01; 95% CI, 1.13–3.56; $P=.028$), there was no difference in pregnancy outcomes between the treated and untreated TPO-Ab groups.

Summary statement. There is good evidence that thyroid autoimmunity is associated with miscarriage and fair evidence that it is associated with infertility. Levothyroxine treatment may improve pregnancy outcomes in women with positive thyroid antibodies, especially if the TSH level is over 2.5 mIU/L.

In summary, SCH (serum TSH concentration above the upper limit of the reference range with a normal FT4) is associated with miscarriage and adverse obstetric and fetal outcomes, and thyroid supplementation is beneficial. Although there is evidence that SCH is associated with developmental outcomes, treatment has not proved to modify long-term neurological development in offspring. There are limited data on whether TSH values >2.5 mIU/L and less than the upper range of normal during pregnancy are associated with adverse pregnancy outcomes. Therefore, treating SCH when the TSH is between 2.5 mIU/L and the upper range of normal prior to pregnancy remains controversial. However, given that there appears to be benefit in some subgroups and minimal risk, it is reasonable to treat even though the evidence is weak. Alternatively, it is reasonable to monitor levels and treat above nonpregnant and pregnancy ranges.

Should There Be Universal Screening for Hypothyroidism in the First Trimester of Pregnancy?

Population screening is warranted only if thyroid replacement avoids the problems of fetal morbidity and mortality associated with untreated maternal hypothyroidism (34). While a cost-effectiveness study suggested a cost-risk benefit (57–59), subsequent randomized trials found there was no benefit to universal screening for SCH in pregnancy (20, 47). One study was designed to determine whether treatment of thyroid disease during pregnancy decreases the incidence of adverse outcomes and to compare the ability of universal screening vs. case finding to detect thyroid dysfunction (20). In this study, 4,562 pregnant women were randomized within the first 11 weeks of gestation and stratified into low risk vs. high risk for thyroid disease based on risk factors. If high risk, patients were immediately screened and treated. Overall, investigators found there were no significant differences in adverse outcomes between the case-finding and universal-screening groups. However, when thyroid dysfunction was detected and treated in the "low-risk" pregnancies, there was a significant reduction in adverse outcomes. A subsequent study randomized 21,846 women to either a universal screening group (in which measurements were obtained immediately) or a control group (in which serum was stored and measurements were obtained shortly after delivery). At a median age of 12 weeks' gestation, investigators found that maternal treatment for hypothyroidism (TSH >97.5 percentile) during pregnancy did not result in improved cognitive function in children at 3 years of age (47). Among the children of women with elevated TSH levels, the mean IQ scores were 99.2 and 100.0 in the screening and control groups, respectively (difference, 0.8; 95% CI, −1.1 to 2.6; P=.40 by intention-to-treat analysis). Proportions of children with an IQ <85 were 12.1% in the screening group and 14.1% in the control group (difference, 2.1 percentage points; 95% CI, −2.6 to 6.7; P=.39).

The Endocrine Society does not recommend universal screening of healthy women before pregnancy (11). However, their guideline could not reach agreement with regard to screening recommendations for all newly pregnant women. The AACE does not recommend universal screening for patients who are pregnant or planning pregnancy, including assisted reproduction patients (60). The American College of Obstetricians and Gynecologists does not recommend routine screening for hypothyroidism in pregnancy (61). However, screening women at high risk (family or personal history of thyroid disease, physical findings or symptoms suggestive of goiter or hypothyroidism, type 1 diabetes mellitus, infertility, history of miscarriage or preterm delivery, or personal history of autoimmune disorders) is advised. Additional testing may be advised in the face of prior head or neck irradiation, history of infertility, or recurrent miscarriage or preterm delivery (16, 62).

Summary statement. There is good evidence against recommending universal screening of thyroid function before or during pregnancy. Screening is not recommended beyond those women with clinical evidence suggesting ovulatory abnormality and those identified as "high risk" as described previously.

SUMMARY

- Subclinical hypothyroidism is defined as a TSH level greater than the upper limit of normal range (4.5–5.0 mIU/L) with normal FT4 levels.
- The normal reference range for TSH changes in pregnancy. The upper limit of normal in most laboratories is 4 mIU/L for nonpregnant women and 2.5 mIU/L in the first trimester of pregnancy.
- This guideline was conducted because it is controversial whether or not to use first-trimester pregnancy thresholds for upper limit of TSH (i.e., >2.5 mIU/L) to diagnose and treat SCH in women attempting pregnancy.
- There is insufficient evidence that SCH (defined as TSH >2.5 mIU/L with a normal FT4) is associated with infertility.
- There is fair evidence that SCH, defined as TSH levels >4 mIU/L, is associated with miscarriage, but insufficient evidence that TSH levels 2.5–4 mIU/L are associated with miscarriage.
- There is fair evidence that treatment of SCH when TSH levels are >4.0 mIU/L is associated with improved pregnancy rates and decreased miscarriage rates.
- There is fair evidence that SCH when TSH levels are >4 mIU/L during pregnancy is associated with adverse developmental outcomes; however, treatment did not improve developmental outcomes in the only randomized trial.
- There is fair evidence that thyroid autoimmunity is associated with miscarriage and fair evidence that it is associated with infertility. Levothyroxine treatment may improve pregnancy outcomes in women with positive thyroid antibodies, especially if the TSH level is over 2.5 mIU/L.
- There is good evidence against recommending universal screening of thyroid function during pregnancy.

RECOMMENDATIONS

- Currently available data support that it is reasonable to test TSH in infertile women attempting pregnancy. If TSH

concentrations are over the nonpregnant lab reference range (typically >4 mIU/L), patients should be treated with levothyroxine to maintain levels below 2.5 mIU/L. (Grade B)

- Given the limited data, if TSH levels prior to pregnancy are between 2.5 and 4 mIU/L, management options include either monitoring levels and treating when TSH >4 mIU/L, or treating with levothyroxine to maintain TSH <2.5 mIU/L. (Grade C)
- During the first trimester of pregnancy it is advisable to treat when the TSH is >2.5 mIU/L. (Grade B)
- While thyroid antibody testing is not routinely recommended, one might consider testing anti-thyroperoxidase (TPO) antibodies for repeated TSH values >2.5 mIU/L or when other risk factors for thyroid disease are present. (Grade C)
- If anti-TPO antibodies are detected, TSH levels should be checked and treatment should be considered if the TSH level is over 2.5 mIU/L. (Grade B)

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