

Subclinical Hypothyroidism in Women Planning Conception and During Pregnancy: Who Should Be Treated and How?

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Subclinical hypothyroidism (SCH), a mild form of hypothyroidism defined as elevated TSH with normal free thyroxine levels, is a common diagnosis among women of reproductive age. In some, but not all, studies, it has been associated with infertility, an increased risk of adverse pregnancy and neonatal outcomes, and possibly with an increased risk of neurocognitive deficits in offspring. Despite well-established recommendations on treatment of overt hypothyroid pregnant women, a consensus has not yet been reached on whether to treat women with SCH. This review focuses on examining the evidence informing the clinical strategy for using levothyroxine (LT4) in women with SCH during pregnancy and those who are planning conception. A crucial first step is to accurately diagnose SCH using the appropriate population-based reference range. For pregnant women, if this is unavailable, the recommended TSH upper normal limit cutoff is 4.0 mIU/L. There is evidence supporting a decreased risk for pregnancy loss and preterm delivery for pregnant women with TSH > 4.0 mIU/L receiving LT4 therapy. LT4 treatment has been associated with better reproductive outcomes in women with SCH undergoing artificial reproductive techniques, but not in those who are attempting natural conception. Thyroid function tests need to be repeated throughout pregnancy to monitor LT4 therapy. In addition to potential harms, LT4 contributes to treatment burden. During a consultation, clinicians and patients should engage in a careful consideration of the current evidence in the context of the patients’ values and preferences to determine whether LT4 therapy initiation is the best next step.

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Subclinical hypothyroidism (SCH) is a mild form of hypothyroidism defined as an elevated TSH concentration in conjunction with normal free thyroxine (FT4) levels [1]. It is a common diagnosis among women of reproductive age (4% to 8%) and as such it can affect women planning conception and pregnant women [2]. Owing to the nonspecific nature of the hypothyroidism-related symptoms (e.g., fatigue), the diagnosis of SCH is based on laboratory testing [1].

Abbreviations: ATA, American Thyroid Association; CATS, Controlled Antenatal Thyroid Screening; FT4, free thyroxine; hCG, human chorionic gonadotropin; IVF, *in vitro* fertilization; LT4, levothyroxine; RR, relative risk; SCH, subclinical hypothyroidism; TPOAb, thyroid peroxidase antibody.

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In contrast to the known negative impact on conception and pregnancy of overt hypothyroidism (*e.g.*, increased risk of pregnancy loss, premature birth, lower offspring intelligence quotient), in which TSH is elevated and the FT4 level is below normal, the impact of SCH remains unclear. In some studies, it has been associated with infertility [3], an increased risk of adverse pregnancy and neonatal outcomes [4–14], and possibly with an increased risk of neurocognitive deficits in the offspring [15]. However, other studies have not found an association of SCH with adverse outcomes [16–19].

The recommended treatment of maternal overt hypothyroidism is administration of oral levothyroxine (LT4). The question that clinicians are called to answer is the following: Is SCH also a disease requiring treatment or is it just a biochemical diagnosis of no clinical consequences? Although there are a few observational studies suggesting a beneficial effect of LT4 treatment in pregnant women with SCH [20], results from large randomized trials suggest the opposite [21, 22].

This review discusses the evidence informing the clinical strategy for using LT4 in women with SCH during pregnancy and those who are planning conception, focusing on the benefits and risks of treatment. We also consider issues related to the monitoring and duration of treatment.

1. Sources and Selection Criteria

References were identified through searches of publications listed by PubMed, Ovid MEDLINE, the Cochrane Controlled Trials Register, Ovid EMBASE, Web of Science, and Scopus from each database's inception to January 2018. Controlled vocabulary supplemented with keywords was used to search for studies of SCH in women planning conception and during pregnancy. References were also identified from relevant review articles and through searches of the authors' files. We included randomized and observational studies published in English, prioritizing studies with low risk of bias as well as meta-analyses, reviews, and clinical guidelines for hypothyroidism and pregnancy.

2. Definition and Prevalence of SCH

Crucial in the biochemical diagnosis of SCH is the use of appropriate reference ranges, which should be based on local population laboratory reference values [23]. For nonpregnant adults, the TSH upper normal limit is typically 4.2 to 4.5 mIU/L. A repeat test at least 6 to 8 weeks later showing a persistent TSH elevation above the normal limit with normal FT4 constitutes a diagnosis of SCH. The prevalence of SCH in nonpregnant women of childbearing age has been reported from 4% to 8% [2, 24].

The thyroid laboratory reference values will vary in conditions such as pregnancy where the reference values change in each trimester [1]. To meet the increased metabolic needs during pregnancy, there are changes in thyroid physiology that are reflected in altered thyroid function tests and a TSH normal range lower than among nonpregnant adults. During pregnancy, the thyroxine binding globulin increase results in an increase of total T4 levels. Additionally, owing to homology between human chorionic gonadotropin (hCG) and TSH resulting in cross-reactivity, hCG can bind at the TSH receptor and stimulate the thyroid hormone production, leading collectively to a decrease in the TSH secretion by the pituitary, particularly in the first trimester [25]. Guidelines published by the American Thyroid Association (ATA) in 2011 recommended establishing a laboratory trimester-specific reference range for TSH [26]. If unavailable, then a population-based reference range could be used [26]. However, as often this was not possible either, the ATA recommended a TSH normal reference range of 0.1 to 2.5 mIU/L for the first trimester, 0.2 to 3.0 mIU/L for the second trimester, and 0.3 to 3.0 mIU/L for the third trimester [26]. Similar guidelines were published by the Endocrine Society a year later [27]. Based on these diagnostic criteria using a fixed TSH upper limit cutoff if population-based reference ranges were unavailable, the prevalence of SCH in the United States was then estimated as high as ~15% [28] as

compared with the historically reported prevalence of 2% to 3% before these criteria were established [29]. However, further studies suggested that these TSH reference ranges are probably not valid worldwide. Values may vary with geographic region and ethnic origin [30–32]. Analyzing 14 sufficiently sized population-based studies on reference ranges [33], it was noted that although reference ranges differ according to population characteristics such as iodine status, ethnicity, and body mass index, 12 of these studies (n = 63,362 participants) reported an upper trimester-specific TSH limit (defined as mean + 2 SD) that was >2.5 or 3.0 mIU/L. These data strongly suggested that a large proportion of women worldwide would be overdiagnosed with SCH when fixed upper limits of TSH of 2.5 or 3.0 mIU/L are used instead of population-based reference ranges.

To overcome this limitation, the updated ATA guidelines published in 2017 [1] still strongly recommend using a laboratory or population-based pregnancy-specific TSH reference range. However, when this is unavailable, taking into consideration the latest findings, the recommended TSH upper normal limit cutoff is 4.0 mIU/L, which usually corresponds to a reduction of ~0.5 mIU/L compared with the nonpregnant TSH reference range.

3. Screening and Causes of SCH

Based on an exhaustive review of the literature, the expert panel concluded that there is insufficient evidence to recommend for or against universal screening of thyroid dysfunction in early pregnancy or preconception, with the exception of women planning assisted reproduction or those known to have thyroid peroxidase antibody (TPOAb) positivity [1]. Instead, it is recommended that all patients seeking pregnancy, or newly pregnant, should undergo clinical evaluation and when any of 11 risk factors (*e.g.*, symptoms/signs of thyroid dysfunction, type 1 diabetes or other autoimmune disorders, history of infertility) for thyroid dysfunction is identified, testing for serum TSH is recommended. Previous studies have shown that case finding by using the risk factors proposed by the 2011 ATA guideline and the 2007 Endocrine Society guideline will miss up to 60% of the women who need treatment [34–36]. A recent study [37] also showed that symptoms and signs during early pregnancy will not help a clinician detect women at risk for thyroid hypofunction.

In developed countries, the main cause of primary hypothyroidism is autoimmune thyroiditis [38]. Thyroid autoantibodies are detected in about half of pregnant women with SCH. The 2017 ATA guidelines recommend that all pregnant women with TSH concentrations >2.5 mIU/L should be evaluated for TPOAb status [1]. Importantly, however, note that because the immune system is suppressed during pregnancy [39], thyroid antibody titers decrease on average by 60% in the second half of pregnancy; thus, the currently used cut-offs for TPOAb positivity based on a nonpregnant established reference range may be too high [40]. The role of thyroid ultrasound in diagnosing autoimmune thyroiditis in pregnancy has not been established. In developing countries, the main cause of primary hypothyroidism is iodine deficiency [38]. This has resulted in a recommendation by many organizations that all women planning pregnancy, pregnant, and breastfeeding should receive daily iodine supplementation [1, 27, 41, 42]. All pregnant women should ingest ~250 µg of iodine daily. To achieve a total of 250 µg of iodine ingestion daily, strategies may need to be varied based on country of origin. In most regions, including the United States, women who are planning pregnancy or are currently pregnant are recommended to supplement their diet with a daily oral supplement that contains 150 µg of potassium iodide, optimally starting 3 months in advance of planned pregnancy [1].

4. Impact of SCH

A. On Conception

Normal functioning of the thyroid gland is essential for successful conception and pregnancy [43]. Hypothyroid women with TSH concentrations >15 mIU/L have a high rate of irregular

menses (68%) compared with a 12% rate of menstrual irregularities reported by euthyroid women [44]. In contrast to overt hypothyroidism, where most evidence appears to support an association with an increased risk of infertility, the data for SCH are less clear. A prospective study [45] of 538 women showed that the mean TSH level was statistically higher in infertile women (1.3 mIU/L) compared with controls (1.1 mIU/L), but this difference did not appear clinically significant. Additionally, the study found no difference in the prevalence of TSH > 4.2 mIU/L in the infertile group vs the control group. Similarly, a cross-sectional study [46] analyzed the sera of 704 women undergoing infertility treatment and found only 16 with a raised TSH level (2.3%), which is similar to general population rates. Moreover, a prospective cohort study found that among healthy fecund women with a history of pregnancy loss, a TSH level ≥ 2.5 mIU/L was not associated with fecundity, pregnancy loss, or live birth [47]. However, other researchers have suggested that SCH is more prevalent (0.7% to 10.2%) in infertile women (particularly when they have ovulatory dysfunction) [48, 49]. For example, a retrospective study [3] of 394 women found a significantly higher incidence of SCH affecting 13.9% of infertile women compared with controls (3.9%). Additionally, the Danish General Suburban Population Study, with a cross-sectional design using biochemical results and self-administered questionnaire, demonstrated that SCH was associated with a risk of not having children and a risk of not getting pregnant [50]. Overall, 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. In 2015, the American Society for Reproductive Medicine found insufficient evidence to conclude that SCH is associated with infertility [51].

B. On Pregnancy and Neonatal Outcomes

In a large prospective study of >16,000 pregnant women, those with SCH were at higher risk for placental abruption and preterm delivery compared with euthyroid women [4]. Also, their offspring were more likely to be admitted in the neonatal intensive care unit and have respiratory distress syndrome [4]. Other large studies comparing women with SCH to women with normal thyroid function during pregnancy have also shown an association of SCH with miscarriage [9, 14, 52], preterm delivery [7, 52], gestational diabetes [11], gestational hypertension [5, 6], eclampsia [5], premature rupture of membranes [14], intrauterine growth restriction [13], and low birth weight [16]. The presence of TPOAb seems to play a synergistic role with the elevated TSH concentrations in increasing the risk for pregnancy complications. A recent, large, prospective study from China [8] showed that pregnant women with higher TSH were 3.4-fold more likely to experience a miscarriage compared with euthyroid women, and this risk tripled when these women had also positive TPOAb. Alternatively, two large prospective studies in the United States [16] and Finland [17, 18] did not find any effect of SCH on pregnancy outcomes. A meta-analysis [53] of 18 cohort studies studying 3995 pregnant women with SCH found that pregnant women with SCH were twofold more likely to have pregnancy loss and 2.6-fold more likely to suffer a neonatal death compared with euthyroid women. They were also at higher risk for placental abruption and premature rupture of membranes. It was noted that the included studies were at low to moderate risk of bias mainly due to limitations in the representativeness of study samples, lack of blinding when assessing the outcomes, and lack of adjustment for confounders.

C. On Neurocognitive Function of the Offspring

Thyroid hormones are essential for early brain development [54]. Maternal thyroid hormones are required by the fetus until its own thyroid starts to function at ~14 to 18 weeks of gestation [55, 56]. A retrospective study by Haddow *et al.* [15] initially reported that the IQ of children born to untreated, predominantly overt hypothyroid mothers was significantly lower than those of control children. However, mean IQ scores and IQ scores <85 were not significantly different comparing children born to mothers who were treated or not ($P = 0.20$ and $P = 0.90$, respectively), although the treatment groups were small. Since then, several studies

reported that higher levels of maternal TSH during pregnancy may be associated with a negative impact on the offspring's neurocognitive function [10, 57–60], but this was not confirmed by others [61–63]. A recent meta-analysis [64] including 11 observational studies showed that, as compared with normal thyroid function, maternal SCH was associated with indicators of intellectual disability in offspring (OR, 2.14; 95% CI, 1.20 to 3.83; $P = 0.01$).

Overall, the inconsistent results between SCH and adverse outcomes may, in part, be explained by the variable TSH cut-off points used across studies to define SCH, by analyzing TPOAb⁺ and TPOAb⁻ cases together, and by differences in the timing of the thyroid function evaluation. Additionally, thyroid function may change during pregnancy, and as a result a woman diagnosed with SCH at the beginning of her pregnancy may ultimately progress to overt hypothyroidism [65] or spontaneously revert to euthyroidism [31]. However, observational studies do not consistently follow the pregnant women with serial TSH level measurements to determine their thyroid status throughout the pregnancy. Therefore, owing to all the limitations of observational studies, any shown associations (or lack of) should be considered with caution.

5. Treatment of SCH

A. Diagnosed Before Conception

There has been no randomized controlled trial examining whether LT4 therapy improves outcomes for infertile women with SCH not undergoing assistive reproductive techniques. A retrospective study examining LT4 therapy on 69 infertile women reported that 84% became pregnant with treatment although 29% had a miscarriage afterward [66]. There is insufficient evidence for or against routine LT4 therapy to aid conception in thyroid autoantibody-negative infertile women with SCH who are not undergoing artificial reproductive techniques [1]. However, the ATA has issued a weak recommendation that administration of LT4 may be considered in this setting given its ability to prevent progression to overt hypothyroidism once pregnancy is achieved [1].

In patients undergoing artificial reproductive techniques, evidence from randomized controlled trials shows that LT4 therapy improves pregnancy and miscarriage rates in women with SCH. In one trial, women with SCH (TSH > 4.0 mIU/L) undergoing *in vitro* fertilization (IVF)/intracytoplasmic sperm injection were randomized to 50 µg of LT4 therapy with a goal to normalize TSH before IVF or placebo (35 women in each group) [67]. The LT4 arm had a lower miscarriage rate (9% vs 13% for control, $P = 0.03$) and a higher live birth rate (26% vs 3% for control, $P = 0.02$). Similar results were seen in another randomized control trial of 64 infertile women with SCH (TSH > 4.5 mIU/L) undergoing IVF/intracytoplasmic sperm injection [68]. The 32 women randomized to 50 µg of LT4 with a goal to reach and maintain TSH of <2.5 mIU/L had a lower miscarriage rate (0% vs 33%, $P = 0.02$) and higher live birth rate (53% vs 25%, $P = 0.04$) compared with the control group. A recent randomized controlled study showed that LT4 treatment, titrated to keep the TSH level at <2.5 mIU/L and <3.0 mIU/L in first and second to third trimesters, respectively, did not benefit euthyroid women (TSH of 0.50 to 4.78 mIU/L) with positive TPOAb undergoing IVF [69]. A stratified analysis by TSH level >4.0 mIU/L did not show any benefit with regard to pregnancy loss between treated and untreated women; importantly, however, note that by study design there were only 17 women with TSH of >4.0 mIU/L. Finally, a large prospective study of 270 patients with SCH undergoing IVF who received LT4 therapy showed similar miscarriage and live birth rate between those who achieved a target TSH level of 0.2 to 2.5 mIU/L compared with a TSH level of 2.5 to 4.2 mIU/L [70]. These data suggest that there may be no benefit in strictly controlling TSH levels (<2.5 mIU/L) for those women with SCH receiving LT4 therapy who are undergoing assistive reproductive techniques.

B. Diagnosed During Pregnancy

Despite well-established clinical guidelines on treatment of overt hypothyroid pregnant women [1], a consensus has not yet been reached on whether to treat women with SCH. The

American Congress of Obstetricians and Gynecologists in 2007 found insufficient evidence to recommend treatment of SCH during pregnancy [71]. Then, the ATA in 2011 recommended to treat pregnant women with SCH, but only when they have positive TPOAb levels [26]. One year later, the Endocrine Society published their recommendation of universally treating all pregnant women with SCH, acknowledging that this recommendation was based on low-quality evidence [27]. A recent appraisal of all the clinical practice guidelines on the management of hypothyroidism in pregnancy [72] found that their quality is highly variable and that the 2017 ATA guideline ranked overall the highest, mainly due to achieving the highest scores in the domains of scope and purpose, rigor of development, and editorial independence. The study concluded that these guidelines need substantial improvement, especially in the rigor of development and applicability domains.

The findings of the prospective study from Negro *et al.* [73] strongly informed the guidelines published in 2011 to 2012. In this study, ~4500 women were randomized by the 11th week of pregnancy to universal screening for thyroid dysfunction vs case finding based on the presence of risk factors for thyroid disease. All pregnant women at the universal screening were checked for thyroid dysfunction and started on therapy when confirmed. From the case finding group only the high-risk women were checked, whereas the low-risk group had their stored serum checked at the end of pregnancy; therefore, these women never received therapy. LT4 was started for hypothyroidism defined as TSH >2.5 mIU/L and positive TPOAb, so by definition women with overt hypothyroidism were included, which was one of the limitations of the study. The primary outcome for the study was a composite endpoint of 18 obstetrical and neonatal complications with variable importance, making the interpretation of the results challenging. There was no significant difference between the total number of adverse outcomes in the universal screening and the case finding group. Considering only the cohorts of low-risk women, complications were less likely to occur among women in the “universal screening” group than women in the “case finding” group (OR, 0.43; 95% CI, 0.26 to 0.70) driven by the events that happened to the undetected and untreated patients with hypothyroidism (adverse outcomes were less likely to occur in low-risk universal vs case finding, but no difference in high risk). However, the untreated group was a substantially smaller group (n = 34), so the study was profoundly underpowered.

In a prospective study in China, pregnant women with SCH were recommended to have LT4 treatment [14]. Comparing the 28 women who actually opted to be treated to the 168 women who remained untreated, there was not any difference in the rates of pregnancy loss [relative risk (RR), 0.46; CI, 0.12 to 1.84], preterm delivery (RR, 0.31; CI, 0.02 to 5.13), gestational hypertension (RR, 3.00; CI, 0.28 to 31.99), low birth weight (RR, 0.65; CI, 0.04 to 11.71), or low Apgar score (RR, 0.65; CI, 0.04 to 11.71). This study was limited owing to its observational design and small sample size, leading to imprecise results and confounding.

In 2012, the results of the Controlled Antenatal Thyroid Screening (CATS) study were published [22]. It was a multicenter, randomized study by Lazarus *et al.* where 21,846 women were randomized at ~12 weeks of gestation to a group of screening for thyroid dysfunction or to a control group. Treatment with 150 µg of LT4 was started at ~13+ weeks of gestation when a woman at the screening group was found to have a TSH >97.5th percentile, an FT4 <2.5th percentile, or both. The study found no difference in the IQ of children at 3 years of age (treated mean IQ 99 vs untreated mean IQ 100) and the percentage of children with IQ <85. A subgroup analysis including only the women meeting the criteria for SCH had similar results. The study received criticism for the late initiation of LT4 therapy (possibly too late in gestation to have a major influence on brain development) and for the relatively high, fixed LT4 dosing. Moreover, it was questioned whether we can assess accurately the IQ in a 3-year-old child. However, the recently published data from the CATS-II study showed that LT4 therapy did not improve the child cognition at age 9.5 years, confirming long term the results of the CATS study [74]. Finally, it is possible that the study was underpowered to detect subtle cognitive differences, as the power calculation was based on an IQ difference of 6 points as found by Haddow *et al.* [15].

A retrospective single-center study [75] found that LT4 therapy of pregnant women with SCH was associated with less risk for low birth weight and low Apgar score, but there was no statistically significant difference in other adverse pregnancy and neonatal outcomes. Although the available data on multiple potential confounders, most notably socioeconomic measures and obstetric comorbid conditions, allowed for adjusted analyses, this study was limited by its retrospective nature and the risk of selection and referral bias. In another study by Ma *et al.* [76] lower odds of miscarriage and macrosomia were reported in pregnant women with SCH who received LT4 treatment (OR, 0.34; CI, 0.21 to 0.56 and OR, 0.46; CI, 0.28 to 0.74, respectively). This study was also limited by high risk for selection bias.

Recently, a multicenter randomized trial funded by the National Institutes of Health was completed [21]. Pregnant women with TSH >4.0 mIU/L and normal FT4 levels were randomized to LT4 treatment vs placebo. The study did not find any benefit of LT4 treatment with regard to IQ score of offspring at 5 years, selected adverse pregnancy outcomes (preterm delivery, gestational hypertension, preeclampsia, gestational diabetes, placental abruption), and adverse neonatal outcomes (neonatal death, low Apgar score, admission to the neonatal intensive care unit, low birth weight, congenital malformations). A *post hoc* analysis found no significant interaction according to TPOAb level. However, similarly to the study by Lazarus *et al.* [22], LT4 therapy was actually initiated at the second trimester of pregnancy, at 17 weeks of gestation on average. Owing to the late randomization, the study was not able to adequately assess the outcome of pregnancy loss.

The results from the first national study in the United States were also published recently [20]. Using a large national database, 843 pregnant women with SCH who received thyroid hormone treatment were compared with 4562 women who did not. The treated women had 38% less risk for pregnancy loss compared with the untreated women. However, thyroid hormone treatment was associated with increased risk for preterm delivery, diabetes, and preeclampsia. A stratified analysis by TSH groups showed that the treated women with a higher TSH level were the ones who had the benefit of fewer pregnancy losses and not the ones with milder TSH elevation. This lack of benefit together with the noted risk of adverse events raised the concern of possible overtreatment for women with TSH between 2.5 and 4.0 mIU/L. This study was limited by its retrospective observational design and use of administrative claims data—specifically, the potential for misclassification of treatment and confounders, lack of clinical detail (*e.g.*, gestational age at initiation of LT4 therapy, TPOAb status), and selection biases related to health plan enrollment, diagnostic testing, and treatment choice.

In support of these findings were the results from the recent single-blinded randomized trial by Nazarpour *et al.* [77]. Despite no beneficial effect of LT4 therapy in reducing preterm delivery in SCH TPOAb⁻ women with TSH of 2.5 to 10.0 mIU/L, a subgroup analysis showed that LT4 could decrease this complication using the newly recommended TSH cut-off ≥ 4.0 mIU/L (RR, 0.38; 95% CI, 0.15 to 0.98; $P = 0.04$). Similarly, the Tehran Thyroid Study showed a 70% and 83% decrease in preterm delivery and neonatal hospital admissions, respectively, in LT4-treated pregnant women who were TPOAb⁺ [78]. The beneficiary effect of LT4 treatment was mainly observed among TPOAb⁺ women with TSH ≥ 4.0 mIU/L.

Taking into account the latest findings, the ATA recommendations for the treatment of SCH in pregnancy have changed in the recently released guidelines [1]. More notably, owing to the noted additive risk of having positive TPOAb, the recommendations were stratified by antibody status. Currently, LT4 treatment is recommended for pregnant women positive for TPOAb when TSH is above 4.0 mIU/L (strong recommendation; moderate quality evidence) and may be considered for pregnant women positive for TPOAb if TSH is >2.5 mIU/L (weak recommendation; low-quality evidence) or for TPOAb⁻ women when TSH is 4.0 to 10.0 mIU/L (weak recommendation; low-quality evidence). On the basis of all available evidence, continuing to offer thyroid hormone treatment to decrease the risk of pregnancy loss and preterm delivery in pregnant women with TSH concentrations >4.0 mIU/L is reasonable.

6. Monitoring and Maintenance of LT4 Therapy

A. LT4 Dosage

A-1. For women started on treatment before conception

Women who were started on LT4 before conception often require a higher dose of LT4 during pregnancy to remain euthyroid due to the increased metabolic demands. A community-based study found that most LT4-treated women have early gestational TSH levels above the recommended targets with an increased risk of miscarriage [79]. The current clinical practice guidelines recommend that LT4-treated hypothyroid patients who are newly pregnant should independently increase their dose of LT4 by ~25% to 30% without first measuring serum TSH upon a missed menstrual cycle or positive pregnancy test and notify their caregiver promptly [1]. However, the study by Verga *et al.* [80] showed that this increase might be insufficient, as their patients needed to increase the LT4 dose from 45% to 70%. The degree of LT4 dose increase appears to vary with etiology of hypothyroidism: athyreotic women require larger dose increases (~50% increase) compared with women with thyroid cancer (21% increase) and autoimmune hypothyroidism (16% increase) [81]. Therefore, it has been suggested that to best achieve optimal TSH levels very early in pregnancy, the thyroid status on LT4 needs to be optimized even before a woman becomes pregnant [82]. A recently published study directly compared two LT4 dose adjustment algorithms in pregnant hypothyroid women (empiric dose increase followed by ongoing adjustment using a pill-per-week approach vs ongoing adjustment only using a micrograms-per-day approach) and demonstrated that both algorithms maintained maternal TSH within trimester-specific reference ranges for the majority of pregnancy [83]. Moreover, the study showed that the three women with twin pregnancies did not exhibit greater TSH suppression or require more LT4 dose changes compared with the overall study cohort [83].

A-2. For women diagnosed with SCH and started on treatment during pregnancy

For women who were diagnosed with SCH during pregnancy, there is no official recommendation regarding the starting LT4 dose. Clinical (*e.g.*, weight) or biochemical characteristics (*e.g.*, TSH or TPOAb levels) could potentially play a role in the required LT4 dosage; however, evidence is lacking. Starting at a low dose of 50 µg of LT4 and titrate as necessary appears reasonable [1].

B. Goals and Monitoring

The ATA recommends the treatment of maternal hypothyroidism to target maternal TSH concentrations <2.5 mIU/L [1]. The ATA also suggests repeating thyroid function tests at least every 4 weeks during the first half of pregnancy and again at least once near 30 weeks gestation [1]. Alternatively, the Endocrine Society suggests repeating thyroid function tests every 4 to 6 weeks throughout pregnancy [27] and, similar to the ATA, recommends LT4 dose adjustments to maintain TSH within trimester-specific goal ranges.

Following delivery, LT4 should be reduced to the patient's preconception dose. Additional thyroid function testing should be performed at ~6 weeks postpartum [1]. For women who initiated LT4 during pregnancy, LT4 could potentially be discontinued, especially when the LT4 dose is <50 µg. The decision to discontinue LT4, if desired, should be made by the patient and her provider. If LT4 is discontinued, serum TSH should be evaluated in ~6 weeks [1]. A retrospective single-center study [75] found that 54% of pregnant women with SCH who were started on LT4 supplementation discontinued treatment after delivery/miscarriage.

7. Treatment Safety and Burden

With regard to the safety of LT₄, overtreatment resulting in exogenous hyperthyroidism can occur more often than is recognized. During pregnancy, hCG stimulates the maternal thyroid as previously discussed, but in contrast to TSH, hCG production is not regulated via negative feedback from FT₄. Therefore, LT₄ treatment during pregnancy may lead to high FT₄ levels, particularly when treatment starts before the hCG peak (at ~10 weeks). Indeed, in the CATS study where the starting dose for LT₄ was 150 µg, 10% of the treated women needed dose reduction [22]. High thyroid function has also been associated with preeclampsia and decreased birth weight [33], indicating that more data are needed on the effects of high thyroid hormone levels and LT₄ treatment. However, it has been suggested that the typically small doses required for the treatment of SCH should not cause any physical harm. Although it is possible that overtreatment could result in low TSH levels and increase the risk for arrhythmias, studies have not found any significant difference between treated and untreated pregnant women [20, 21].

As well as the potential harms, LT₄ contributes to treatment burden. Taking this drug often demands modification of daily habits, for example, dosing 30 to 60 minutes before a meal, monitoring of effects, and clinic and laboratory visits. It can also increase the anxiety of the often otherwise healthy expectant mother and lead to increased financial costs to the patient. LT₄ has become the most prescribed drug in the United States and the third most prescribed drug in the United Kingdom [84]. The LT₄ 3-month out-of-pocket cost to patients in the United States varies considerably, from \$4 to \$100. In addition to the LT₄ prescription cost, assessments of the economic burden of LT₄ therapy should also take into account the costs to patients and other payers of thyroid testing, follow-up clinical visits, and possible lifelong monitoring. A study evaluating the patients' perspective can provide more insight regarding the degree of the treatment burden in this population.

8. Future Studies

The first challenge for the management of SCH is defining normal TSH ranges and recognizing the level that is associated with adverse outcomes. Although population- or laboratory-specific TSH reference ranges are recommended, most patients will receive care using fixed cut-off levels of TSH. It is imperative to conduct studies that can help clinicians provide care using appropriate reference ranges.

Although randomized clinical trials assessing the effect of LT₄ therapy on the clinical outcomes of patients with SCH are available, identifying patients who will benefit from treatment is still a challenge, mostly due to the limitations of these studies. One important limitation of these trials is the initiation of LT₄ therapy on average after organogenesis. It would be expected that if LT₄ will have an impact on early adverse pregnancy outcomes (*e.g.*, miscarriage), this therapy should be started as close to conception as possible. Additionally, these studies have included mostly healthy patients; it is possible that those at higher risk for complications are the ones who will benefit from treatment. Lastly, the current body of evidence has identified important predictors for adverse outcomes in patients with SCH such as thyroid autoimmunity status and degree of TSH elevation. To improve the quality of evidence for the treatment of SCH during pregnancy, large multicenter randomized clinical trials in which LT₄ is started early, with preplanned subgroups analysis based on risks for complications, would be needed to determine not only if there is a positive effect from LT₄ therapy but which patients are more likely to benefit. Although clinical evidence is available, little is known about the physiologic mechanism by which mild thyroid dysfunction could lead to adverse pregnancy outcomes or how LT₄ therapy will lead to better outcomes. Until further evidence is available, clinicians and patients should discuss the need for LT₄ therapy and tools that can support this conversation can help support patient-centered care in the setting of uncertainty.

9. Conclusion

SCH is associated with multiple adverse pregnancy and neonatal outcomes. LT4 treatment has been associated with better reproductive outcomes in women undergoing artificial reproductive techniques and decreased risk for pregnancy loss and preterm delivery when TSH is >4.0 mIU/L. However, well-conducted, large randomized trials with LT4 intervention at an early stage of pregnancy or preconception are still needed in this field to refine the available information. In the meantime, both clinicians and patients with SCH in pregnancy still face uncertainty about the effect of thyroid hormone treatment on maternal and neonatal outcomes. During a consultation, clinicians and patients should engage in a long and careful consideration of the current evidence in the context of the patients' values and preferences to determine whether LT4 therapy initiation is the best next step [85].

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