Preconception Counseling and Care for Pregnant Women with Thyroid Disease

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KEYWORDS

• Thyroid disease • Preconception • Pregnancy • Thyroid autoimmunity

KEY POINTS

- Women with overt thyroid disease should receive preconception counseling regarding the risks to pregnancy and fetal outcomes and be monitored regularly during pregnancy using appropriate reference ranges for thyroid function testing.
- Universal screening for thyroid dysfunction preconception or in early pregnancy is not currently recommended.
- Antithyroid drugs are the main treatment modality for hyperthyroidism in pregnancy and the dose and choice of medication requires careful consideration.
- Treatment strategies for subclinical hypothyroidism and isolated hypothyroxinemia and thyroid autoimmunity are still debated.
- Current evidence indicates that levothyroxine administration to euthyroid TPO antibody–positive women does not improve fertility and pregnancy outcomes.

BACKGROUND

Thyroid disorders are among the most prevalent medical conditions in women of reproductive age. Normal functioning of the thyroid gland is essential for optimal conception and pregnancy.

PHYSIOLOGIC CHANGES OF THYROID FUNCTION IN PREGNANCY

Pregnancy induces dynamic changes in thyroid function throughout the course of pregnancy, designed to provide adequate concentrations of thyroid hormone to the

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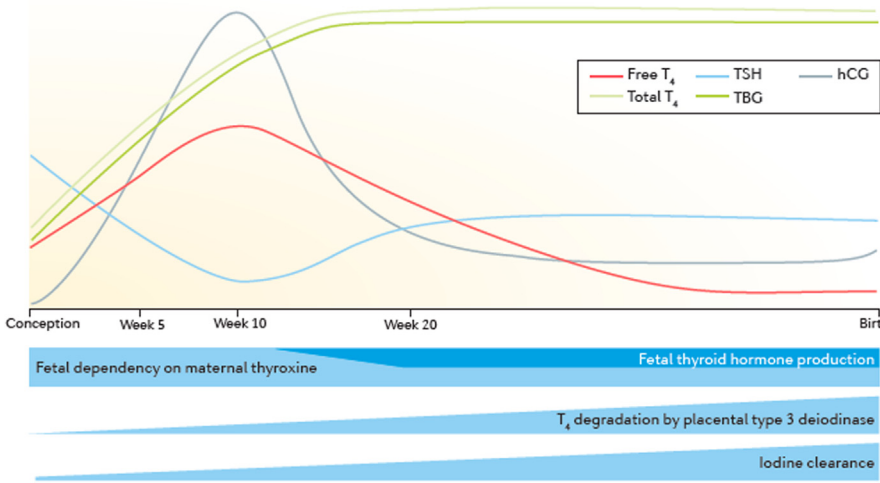

Fig. 1. Changes in thyroid physiology during pregnancy. hCG, human chorionic gonadotrophin; T4, thyroxine; TBG, thyroid-binding globulin; TSH, thyroid-stimulating hormone. (*From* Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol. 2017 Oct;13(10):610-622.)

mother and fetus (**Fig. 1**).[1–5] Overall, the demands on maternal thyroid hormone production increase by approximately 50% during pregnancy[6]; this requires an adequate supply of iodine for the biosynthesis of thyroid hormones and the absence of significant thyroid disease.

Elevated estrogen in pregnancy leads to increases in thyroid binding globulin concentrations, starting early in pregnancy, and plateauing by approximately 18 to 20 weeks of gestation. To maintain adequate free thyroid hormone concentrations, thyroxine (T4) and triiodothyronine (T3) production by the thyroid gland increases during the first half of pregnancy. By midgestation, a new steady state is reached and the synthesis of thyroid hormones returns to around prepregnancy rates. The first trimester sees increases in human chorionic gonadotrophin (hCG), which because of its weak thyroid-stimulating activity, transiently increases free T4 (fT4) and free T3 (fT3) and decreases thyrotropin (thyroid-stimulating hormone [TSH]). From midgestation, as hCG declines, serum fT4 and fT3 concentrations decline gradually, whereas serum TSH concentrations rise slightly.[7]

Iodine requirements increase considerably during pregnancy. In the mother, there is increased consumption of iodine for thyroid hormone synthesis and increased renal iodine clearance.[8] The placenta may also be an organ of storage for iodine.[9] The fetal thyroid begins to take up iodine from 10 to 12 weeks of gestation and fetal thyroid function commences at 18 to 22 weeks' gestation. Breastmilk production begins to rise from the second half of gestation, adding to further maternal iodine demand.[10]

Maternal thyroid hormones are essential for the maintenance of pregnancy and may influence placental development. Transplacental passage of maternal T4 is essential for normal fetal development, especially neurodevelopment during the first half of gestation.[11,12] The fetus is completely dependent on maternal T4 before commencement of its own thyroid hormone production, but remains reliant on maternal supply of iodine[1] and continues to receive maternal T4 until delivery.[13]

It is recommended that population-, trimester-, and manufacturer-specific reference ranges are used for the correct interpretation of thyroid function during

pregnancy. The use of reference ranges determined in similar populations, free from thyroid disease and iodine sufficient, using the same assay, is advised when specific ranges are not available. In the absence of such information it is reasonable to set an upper limit of TSH of 4.0 mIU/L in pregnancy.[14]

THYROID DYSFUNCTION: DEFINITIONS, EPIDEMIOLOGY, AND EFFECTS ON PREGNANCY

Overt Hyperthyroidism

Overt hyperthyroidism is diagnosed on the finding of a reduced serum TSH concentration with high fT4 and/or fT3 levels, using trimester- and laboratory-specific reference ranges. Overt hyperthyroidism is present in around 0.1% to 0.4% of pregnant women and the most common cause is autoimmune Graves disease.[15,16] Uncontrolled Graves thyrotoxicosis has been associated with miscarriage, preeclampsia, preterm birth, placental abruption, and fetal hyperthyroidism.[17–19]

Overt Hypothyroidism

The diagnosis of overt hypothyroidism is based on confirmation of a low fT4 concentration in combination with an elevated serum TSH concentration. The prevalence of overt hypothyroidism in pregnancy is around 0.2% to 0.6%.[4,5,20] Overt hypothyroidism is most commonly caused by autoimmune Hashimoto thyroiditis and has been associated with adverse pregnancy outcomes, such as miscarriage, hypertensive disorders of pregnancy, placental abruption, preterm delivery, and higher rates of neonates being admitted to intensive care units and lower intelligence scores in the offspring.[5,14,21]

Subclinical Thyroid Disease

Subclinical hyperthyroidism (SCHyper) and subclinical hypothyroidism (SCHypo) are biochemical diagnoses based on abnormal serum TSH concentrations in combination with normal fT4 levels. These conditions may represent the earliest stages of thyroid dysfunction and SCHypo in particular may progress to overt disease, although reversion to euthyroidism is common.[22,23] The prevalence of SCHypo (TSH higher than the reference range and fT4 within the reference range) varies widely because of inconsistent definitions and is reported to range from 3% up to 18% in pregnant women.[14,24] There is mounting evidence that SCHypo is linked to negative pregnancy outcomes, such as miscarriage, preterm birth, preeclampsia, gestational hypertension, and perinatal mortality.[25,26] The effects seem to be augmented by the presence of thyroid antibodies.[26] There is insufficient evidence to suggest a causal association between SCHypo and infertility. There is, however, consensus that subfertile women are more likely to have mildly raised TSH concentrations.

There are no known harmful effects of SCHyper in pregnancy.[27] However, fT4 concentrations that remain higher than the upper limit of the normal range, and even those at the higher end of normal, might have unfavorable effects. Studies have shown that higher fT4 concentrations are associated with lower birth weight; reduced child neurocognition; and increased risks of autism, attention-deficit/hyperactivity disorder, and epilepsy.[28–31]

Isolated Hypothyroxinemia

Isolated hypothyroxinemia is defined as serum concentrations of fT4 lower than the reference range in combination with normal TSH concentrations. It is considered a form of mild thyroid dysfunction and is predominantly associated with adverse neurobehavioral outcomes in the child.[32–34] It has a prevalence of approximately 1% to 2%

of pregnant women in iodine-sufficient populations with a higher prevalence in countries with more severe iodine deficiency.[35]

Gestational Thyrotoxicosis

Gestational hyperthyroidism, biochemically defined by elevated concentrations of fT4 and suppressed TSH, is diagnosed in approximately 1% to 3% of pregnancies. Most cases of the disease occur secondary to high hCG concentrations and in 50% of cases it coexists with hyperemesis gravidarum.[15,16,36] Patients with gestational hyperthyroidism have a higher risk of low birth weight and a higher risk of preeclampsia than patients with euthyroid pregnancies.[5]

Thyroid Autoimmunity

Thyroid autoimmunity describes the presence of circulating antithyroid autoantibodies that are targeted against the thyroid and can occur with or without affecting thyroid function. The three most clinically important antibodies are thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies, and TSH receptor antibodies (TRAb).

TPOAb are the most common antithyroid autoantibody, present in 90% of cases of Hashimoto thyroiditis, 75% of Graves disease, and 10% to 20% of nodular goiter or thyroid carcinoma. However, around 10% to 15% of biochemically euthyroid individuals also have elevated TPOAb titers.[37,38] The prevalence observed among unselected pregnant women ranges from 2% to 17%, with higher prevalence seen in iodine-deficient populations.[39] Some studies have reported higher rates of TPOAb positivity in women considered to be "high risk" (eg, with subfertility or history of recurrent pregnancy loss).[40] However, a large prevalence study of more than 19,000 women with history of miscarriage or subfertility showed no difference in prevalence whether women had one or two miscarriages, three or more miscarriages, or if they had subfertility (9.8%, 9.7%, and 9.5% prevalence of TPOAb, respectively).[41]

Studies have shown that the presence of thyroid autoantibodies leads to significantly increased odds of miscarriage and preterm birth for women from low- and high-risk obstetric populations compared with women without thyroid autoantibodies.[26,40] Associations between TPOAb positivity and subfertility, and increased risks of postpartum thyroiditis, have also been established.[42] Euthyroid women who are positive for TPOAb are more likely to develop impaired thyroid function during pregnancy and are particularly at risk of developing SCHypo.[43,44]

PRECONCEPTION CARE

In view of the known adverse effects of overt thyroid disease on pregnancy outcomes, it is crucial for women with preexisting thyroid disease to be counseled on the importance of having a normal thyroid function before conception. Women with poorly controlled thyroid disease should be managed by the relevant endocrinologists and such women should also receive prepregnancy counseling from obstetric specialists.

Preconception Counseling for Women with Known Overt Hyperthyroidism

All women of reproductive age who develop thyrotoxicosis should have a discussion regarding potential future pregnancy. The risks and benefits of all treatment options including antithyroid drugs, radioactive iodine (^{131}I) administration, or surgery should be discussed. Thyroid function should be controlled and stable on two measurements 2 months apart before conception. If the woman is on levothyroxine (LT4) replacement following definitive thyroid ablation or thyroidectomy, then optimal TSH and fT4 concentrations (TSH <2.5 mU/L with normal fT4) should be achieved preconception.[14]

Following radioiodine treatment TRAb concentrations may rise, increasing the risk of fetal Graves disease caused by transplacental passage of maternal TRAb, even when maternal thyroid function tests are normal.[45,46] It is advised that following ^{131}I, pregnancy should be delayed by 6 months.[47] Surgery may be the better option in women with high TRAb concentrations because antibody levels usually normalize within months after a thyroidectomy,[48] and cure is immediate. However, the risks of surgery and lifelong need for LT4 replacement have to be considered.

For women who continue on antithyroid drugs, propylthiouracil (PTU) is the preferred drug preconception and during the first trimester, because this has a lower teratogenic risk than methimazole (MMI). The lowest possible dose of antithyroid drugs to maintain euthyroidism should be used.[49–51] Consideration should be given to discontinuation preconception once euthyroidism is achieved for at least 6 months.[14,52] Early discontinuation to reduce teratogenic risks needs to be weighed against risks of a hyperthyroid flare in the periconception period, which has the attendant risks of increased adversity in pregnancy.

Preconception Counseling for Women with Known Overt Hypothyroidism

In women with hypothyroidism, preconception encouragement of treatment compliance and adequate replacement may reduce the risk of early pregnancy hypothyroidism. A preconception target TSH less than or equal to 2.5 mU/L is recommended.[52,53] In pregnancy, the required LT4 dose increment may vary depending on the cause of hypothyroidism and the prepregnancy TSH concentrations. A self-initiated empirical dose increase by approximately 25% to 30% as soon as there is a positive pregnancy test can significantly reduce the risk of developing hypothyroidism in pregnancy, without any adverse consequences on the pregnancy provided regular thyroid function monitoring in pregnancy is performed. This empirical dose increase is usually recommended as doubling of the dose on 2 days of the week[14] or alternatively implementing a dose increment of 25 μg per day for women taking 100 μg or less T4 daily and a dose increment of 50 μg per day for women taking greater than 100 μg T4 daily.

Preconception Counseling for Women with Subclinical Hypothyroidism with or without Thyroid Peroxidase Antibodies

There is a universal consensus that women with SCHypo who have TSH levels higher than 10 mIU/L should be treated preconception with LT4, aiming for a target TSH of less than 2.5 mIU/L before pregnancy. There is also a general agreement that women with moderately raised levels of TSH that is higher than the laboratory assay range (usually 4–5 mIU/L) and 10 mIU/L should receive LT4 treatment. As for overt hypothyroidism, it is recommended that women with SCHypo have an empirical dose increase following a positive pregnancy test in view of the risk of progression to overt hypothyroidism as a consequence of increased demands on T4 requirements.

The area of uncertainty is regarding the management of women who are actively seeking pregnancy from certain high-risk populations. For women undergoing assisted-reproductive technologies the 2017 American Thyroid Association guideline recommends the following: “subclinically hypothyroid women undergoing in vitro fertilization or intracytoplasmic sperm injection should be treated with LT4. The goal of treatment is to achieve a TSH concentration less than 2.5 mU/L.”[14] This has led to widespread practice in many countries of initiating LT4 treatment in any subfertile woman undergoing in vitro fertilization or intracytoplasmic sperm injection treatment with a TSH value greater than 2.5 mIU/L; however, the evidence of benefit with this management strategy is limited.

The Endocrine Society Clinical Practice Guideline also makes the recommendation of aiming for a preconception TSH of less than 2.5 mIU/L for all subfertile women, and extends this to women with history of miscarriage or preterm birth.[53] This strategy is controversial, because data showing evidence of benefit are conflicting and often do not consider thyroid antibody status. Furthermore, there is insufficient evidence suggesting reduced fertility outcomes or higher miscarriage rates exist in women with mild thyroid dysfunction.

In summary, there is wide variation in clinical practice in the management of mild thyroid dysfunction, in particular in women with history of subfertility or pregnancy loss. The ongoing controversy is regarding the initiation of LT4 treatment in women with high normal/mildly raised thyroid dysfunction, that is, TSH levels 2.50 to 5.00 mIU/L, especially for women considered high risk with a history of subfertility or miscarriage or who are positive for thyroid antibodies.

Finally, there is no evidence of benefit with LT4 treatment, commenced preconception, in euthyroid women who are positive for TPOAb. The evidence is discussed in detail later.

Universal Preconception Screening for Thyroid Disease

There is great debate regarding the need and the cost-effectiveness of routinely screening for thyroid disease and for thyroid autoimmunity in women who are planning for pregnancy.

Proponents of universal screening have argued that a case for screening for overt hypothyroidism can be made because it is a condition that has serious adverse consequences in pregnancy and on the newborn.[54] Furthermore, it is detectable by a safe and simple thyroid function test, and is treated with LT4 to reduce the chances of adverse outcomes. A large prevalence study of thyroid disease in asymptomatic preconception women from "high-risk" populations (women with history of miscarriage or subfertility) found that 0.4% of women had undiagnosed overt hypothyroidism[41]; this demonstrates that a proportion of women will be missed without universal screening. However, the overall cost-effectiveness remains debatable.

If a universal thyroid function screening approach is adopted, overt thyroid disease will constitute only a small proportion of the abnormal thyroid function detected. Most will fall into the gestational hyperthyroidism, SCHypo, and isolated hypothyroxinemia groups, where the benefit of treatment remains controversial.

Targeted Preconception Screening for Thyroid Disease in High-Risk Populations

There is a lack of consensus on what factors should trigger thyroid function screening and risk-based thyroid function screening remains controversial.[55] The American Thyroid Association 2017 guidelines recommend that all patients seeking pregnancy who have any of the following risk factors should undergo clinical evaluation and have serum TSH testing (**Box 1**).[14]

The guideline also states that there is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations preconception, with the exception of women planning assisted reproduction or those known to have TPOAb positivity.[14] The European Society for Human Reproduction and Embryology (ESHRE) guideline for recurrent pregnancy loss recommends routine thyroid function testing in women who have suffered two or more previous miscarriages.[56]

One of the criteria that a screening test should meet, in accordance with World Health Organization guidance, is that there should be an accepted and proven treatment of the disease.[54,55] Regarding TPOAb, there is currently no evidence in support of any treatment, which can improve pregnancy outcomes for women with TPOAb. At

Box 1
American Thyroid Association 2017 guidance on high-risk populations who require preconception TSH testing

Risk factors that warrant preconception TSH screening
- A history of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction
- Known thyroid antibody positivity or presence of a goiter
- History of head or neck radiation or prior thyroid surgery
- Age greater than 30 years
- Type 1 diabetes or other autoimmune disorders
- History of pregnancy loss, preterm delivery, or infertility
- Multiple prior pregnancies (two or more)
- Family history of autoimmune thyroid disease or thyroid dysfunction
- Morbid obesity (body mass index $\geq$40 kg/m^2)
- Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
- Residing in an area of known moderate to severe iodine insufficiency

present the ESHRE guideline recommends routine testing of TPOAb in women with recurrent pregnancy loss,[56] but this was based on the potential benefit with LT4 treatment suggested by two small studies. The ESHRE guideline predates the results of two of the biggest trials on the subject.[57,58]

An important counterargument in favor of TPOAb testing is that the presence of TPOAb represents the primary cause leading to hypothyroidism in pregnant women. Thus, knowing TPOAb status allows identification and stratification of the women at higher risk of progression to thyroid disease in pregnancy, consequently requiring thyroid function monitoring. This is particularly important for women undergoing ovarian stimulation within the process of assisted-reproductive technologies. TSH levels have been shown to be maintained at high levels for prolonged periods in women with TPOAb undergoing ovarian stimulation. However, there is a need for detailed clinical and cost-effectiveness analyses to determine whether routine testing for TPOAb is beneficial, or whether routine thyroid function testing in pregnancy should be performed instead.

MANAGEMENT OF THYROID DISEASE IN PREGNANCY

Overt Hyperthyroidism

Treatment with antithyroid drugs represents the mainstay of treatment of active hyperthyroidism in pregnancy. Minor adverse effects of antithyroid drugs, including skin rash, occur in 3% to 5% of patients. Serious adverse effects are rare and include agranulocytosis occurring in 0.15% with either drug and liver failure in 0.1%, the latter pertaining almost exclusively to PTU.[59]

If a woman has been euthyroid for 6 months or more on a low dose of an antithyroid drug (<10 mg MMI daily or <200 mg PTU daily), consideration should be given to discontinuing antithyroid drugs, before the period of highest teratogenic risk (6–10 weeks of gestation).[14,60,61] This period of time also coincides with rising hCG concentrations, which may exacerbate any residual hyperthyroidism, thus it is recommended that there is close monitoring of thyroid function from early gestation until the midtrimester of pregnancy.

The lowest effective dose of antithyroid drugs should be used targeting serum fT4 at the upper end, or slightly higher than the normal reference range, or total T4 at 1 to 1.5 times the upper limit of the nonpregnant reference range to minimize the risk of fetal hypothyroidism from transplacental passage of the drug.[51,62] Titration should not be

primarily based on TSH concentrations, and there is no role for fT3 and total T3 measurements.

Large population studies have indicated that the use of PTU during early pregnancy is associated with a slightly lower risk of adverse reactions and outcomes, and less severe fetal anomalies, compared with MMI.[36,49,51] Therefore, it is advised that women who are receiving MMI and are in need of continuing therapy during pregnancy are switched to PTU as early as possible and remain treated with PTU up until the 16th week of pregnancy.[14]

Even with successful antithyroid drug therapy, there is a relapse rate of Graves disease of around 30% to 50% in the nonpregnant population.[63] It has been observed that women whose Graves disease is biochemically controlled prepregnancy with stable low doses of MMI (5–10 mg) or PTU (100–200 mg) have a lower chance of relapse than women with uncontrolled disease. If a relapse has occurred following cessation of antithyroid medication this usually occurs after a few months in those women who are susceptible.[61] To minimize the potential harmful effects of antithyroid drugs on the fetus, clinicians can discuss the possibility of stopping treatment in women who wish to become pregnant or at the point of a first positive pregnancy test in unplanned pregnancies. However, if antithyroid drugs are discontinued, it is recommended that clinicians monitor thyroid function closely at regular intervals (eg, every 1–2 weeks).[14]

Monitoring for the fetus

Clinicians should perform a baseline assessment of concentrations of TRAb in patients with Graves hyperthyroidism. If TRAb concentrations are elevated, the fetus should be monitored every 4 to 6 weeks by assessing the fetal heart rate, fetal growth, and/or fetal thyroid appearance via ultrasonography from midpregnancy until birth. Together with maternal thyroid function, these measures are a reflection of the fetal thyroid hormone status.[64,65]

Gestational Thyrotoxicosis

It is important to differentiate gestational thyrotoxicosis from Graves disease. New-onset Graves disease requires prompt treatment in pregnancy and is far less common than gestational thyrotoxicosis. The clinical features, including palpitations, tremor, anxiety, and tachycardia, are seen in both conditions and therefore diagnosis cannot be determined by symptoms alone. However, the lack of symptoms of thyrotoxicosis and weight loss before a pregnancy, the absence of a goiter, ophthalmopathy or a personal/family history of thyroid disease, and the presence of significant nausea and vomiting are more suggestive of gestational hyperthyroidism. Serum blood tests are done for TRAb and serum T3 concentrations, because these are raised in Graves disease but generally not in gestational hyperthyroidism.[15,36] Serum hCG concentrations are not useful in distinguishing the two conditions.[66] Where there is doubt, a repeat thyroid function test 2 weeks from the initial test, demonstrating a declining fT4 concentration without antithyroid treatment, is suggestive of gestational hyperthyroidism. TSH concentrations take longer to recover, and often remain suppressed, making this a less useful test.

Management of gestational hyperthyroidism is predominantly supportive with symptomatic relief through antiemetics, rehydration, and correction of electrolyte imbalances if the woman has hyperemesis gravidarum. There may be a need for temporary treatment with β-blockers to control symptoms of thyrotoxicosis and tachycardia.[16,36] There is no evidence that treatment with antithyroid drugs improves obstetric and fetal outcomes in women with transient gestational hyperthyroidism.[67]

Overt Hypothyroidism

There have not been any randomized controlled trials investigating the effect of LT4 treatment of overt hypothyroidism during pregnancy. However, in view of the well-established adverse effects of overt hypothyroidism on pregnancy outcomes and fetal development, the general consensus is that overt hypothyroidism during pregnancy should be treated as early as possible.[14] The placental transfer of maternal T4 to the fetus is essential for optimal fetal brain development, and because LT4 supplementation is the treatment of choice for overt hypothyroidism, the therapy should be initiated as soon as possible. Patients using LT4 and liothyronine combination therapy or desiccated thyroid extracts often have a T4/T3 ratio that is lower than that of patients with normal thyroid function. Therefore, in these patients, the placental transfer of maternal T4 to the fetal brain might be insufficient. These findings indicate that patients using combination therapy or desiccated thyroid extracts who desire to become pregnant should be switched to LT4.

Following the initial empirical dose increase in women taking LT4 preconception, up to 40% may require further dose adjustments in either direction.[14,68] Hence regular thyroid function monitoring is required, especially in the first half of the pregnancy. This is the period over which thyroid-binding globulin concentrations are rising, in conjunction with the other previously outlined physiologic changes in pregnancy. The ultimate LT4 dose increments depend on the underlying cause of hypothyroidism. Studies have shown that there are higher dose requirements in subjects with radioiodine- or surgery-induced hypothyroidism[69] compared with patients with autoimmune thyroiditis.[70] The aim of dose titration is to maintain euthyroidism by replicating the normal dynamic changes of pregnancy that affect thyroid hormone requirements.

Subclinical Hypothyroidism, Isolated Hypothyroxinemia, and Thyroid Peroxidase Antibodies Positivity

Thyroid hypofunction

Because of the association between adverse pregnancy outcomes and SCHypo (defined as serum TSH higher than the pregnancy-specific reference range), it is recommended that SCHypo is treated preconception, and during pregnancy, with LT4 therapy (**Table 1**). In contrast, evaluation of the effects of isolated hypothyroxinemia on maternal and fetal outcomes has yielded conflicting data. Some studies have shown an association between hypothyroxinemia and poor cognitive development of the offspring.[28,32–34] Effects on prematurity and low birth weight are uncertain[26,28,32] and results from observational studies of isolated hypothyroxinemia on pregnancy outcomes are conflicting.[7,71]

It remains unclear if treatment of SCHypo and isolated hypothyroxinemia with thyroid hormone-replacement therapy is beneficial. The two separate large randomized controlled trials evaluating treatment of SCHypo and isolated hypothyroxinemia with T4, regardless of anti-TPO status, commencing at a median gestation beyond 12 weeks of gestation, demonstrated no benefit to offspring intelligence scores and obstetric and neonatal outcomes. However, these studies were limited by the late timing of the intervention, that is, after completion of the first trimester of pregnancy.[72,73] Moreover there is mounting evidence that overzealous replacement with LT4 may be associated with adverse pregnancy outcomes.[74,75]

A post hoc analysis of the randomized controlled trial by Negro and colleagues[76] demonstrated a potential benefit in reducing adverse pregnancy outcomes with LT4 intervention starting in the first trimester in TPOAb-positive women with very mild

Table 1
A summary of all the published and ongoing randomized studies on management of subclinical hypothyroidism, isolated hypothyroxinemia, and TPOAb-positive euthyroidism in preconception and pregnancy

Author/Year/ Country	Population/Number of Participants in Trial	Thyroid Dysfunction Group of Interest	TSH Ref Range (mIU/L)	Intervention	Comparison	Main Findings
Negro et al,[77] 2005 Italy	Women undergoing assisted reproduction N = 72	Euthyroid TPOAb positive	0.27–4.2	LT4 1 mg/kg/d	Placebo	No difference in pregnancy rate between the groups. TPOAb-positive women had higher miscarriage rate than TPOAb-negative. LT4 treatment in TPOAb-positive women did not affect delivery rate.
Negro et al,[43] 2006 Italy	Pregnant women in first trimester N = 115	Euthyroid TPOAb positive	0.27–4.2	LT4: dose dependent on TSH	No treatment	At baseline, TPOAb-positive women had higher TSH compared with TPOAb-negative. LT4 treatment may be able to lower the chance of miscarriage and premature delivery.

Negro et al,[76] 2010 Italy	Pregnant women (natural conception) in first trimester N = 4562 randomized to universal or case finding screening	High-normal TSH/mild SCHypo Mixed TPOAb positive and negative	0.27–4.2	LT4 (if TSH >2.5 mIU/L and TPOAb positive)	No treatment if TSH <2.5 mIU/L	Universal screening compared with case finding did not result in a decrease in adverse outcomes. Treatment of hypothyroidism or hyperthyroidism identified by screening a low-risk group was associated with a lower rate of adverse outcomes.
Lazarus et al,[73] 2012 United Kingdom	Pregnant women $\leq 15^{+6}$ wk with subclinical hypothyroidism (median gestation 12 + 3 wk) N = 794	SCHypo and isolated hypothyroxinemia Mixed TPOAb positive and negative	>97.5th centile (>3.3 mIU/L)	Being screened and detected as SCHypo LT4 commenced 150 μg/d Dose titrated to maintain TSH level 0.1–1.0 mIU/L	Control group, not screened	Antenatal screening and maternal treatment of hypothyroidism did not result in improved cognitive function in children at 3 y of age.
Negro et al,[80] 2016 Italy	Pregnant women in first trimester N = 413	Euthyroid and TPOAb positive	0.2–2.5 mIU/L	LT4; women with TSH 0.5–1.5 mIU/L were begun on 0.5 μg/kg/d, women with a TSH 1.5–2.5 mIU/L were begun on 1 μg/kg/d	No treatment in first trimester	LT4 intervention had no impact on the rate of miscarriage and preterm delivery in euthyroid thyroid antibody–positive women.
Casey et al,[72] 2017 United States	Pregnant women with a singleton pregnancy <20 wk gestation (median gestation 17 wk) N = 677	SCHypo (n = 677) isolated hypothyroxinemia (n = 526) Mixed TPOAb positive and negative	>4.0 mIU/L	LT4 100 μg/d	Placebo	No significant effect of T4 replacement therapy, compared with placebo, on child cognitive function and other indexes of neurodevelopment up to 5 y of age.

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Table 1
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Author/Year/ Country	Population/Number of Participants in Trial	Thyroid Dysfunction Group of Interest	TSH Ref Range (mIU/L)	Intervention	Comparison	Main Findings
Wang et al,[58] 2017 China	Women being treated for infertility N = 600	Euthyroid and TPOAb positive	0.50–4.78	LT4, dose dependent on TSH	Placebo	Treatment with LT4, compared with no LT4 treatment, did not reduce miscarriage rates or increase live-birth rates.
Nazarpour et al,[81] 2017 Iran	Pregnant women in first trimester N = 131	SCHypo and TPOAb positive	2.5–10	LT4, dose dependent on TSH	No treatment	Treatment with LT4 decreases the risk of preterm delivery in women who are positive for TPOAb.
Nazarpour et al,[82] 2018 Iran	Pregnant women in first trimester N = 366	SCHypo and TPOAb negative	2.5–10	LT4, morning dose of 1 μg/kg/d	No treatment	Using the TSH cutoff of 2.5 mIU/L, no significant difference in preterm delivery was observed. However, analysis based on a cutpoint of 4.0 mIU/L demonstrated a significantly lower rate of preterm delivery in LT4-treated women compared with those who received no treatment.

Dhillon-Smith et al,[57] 2019 United Kingdom	Women with history of miscarriage or subfertility N = 952	Euthyroid and TPOAb positive	0.44–3.63	LT4 50 μg/d	Placebo	LT4 treatment, compared with placebo, showed no improvement in live birth at or beyond 34 wk or any secondary pregnancy, maternal or neonatal outcomes.
Vissenberg et al (publication awaited) Netherlands	Women with history of recurrent pregnancy loss N = 240	Euthyroid and TPOAb positive	0.5–5.0	LT4, dose dependent on weight	Placebo	Not available.

hypothyroidism (defined as a TSH >2.5 mIU/L). However this was a small sample size (n = 83 treated vs n = 34 untreated) and adverse pregnancy outcome was not the primary outcome of this trial.

Thyroid peroxidase antibodies–positive euthyroidism

Evidence from older published studies suggested benefit with LT4 treatment in euthyroid TPOAb-positive women.[43,77] However, newer evidence from much larger studies has contested this.

The POSTAL trial randomized 600 euthyroid TPOAb-positive women undergoing assisted reproduction.[58] In contrast to the previous studies, this study reported no difference in clinical pregnancy or miscarriage rates between women who received LT4 therapy and those that did not.

In the most recent and largest trial on the subject, the TABLET trial, there was no improvement in live birth outcome at or beyond 34 weeks in those taking LT4 and no difference in any secondary pregnancy or neonatal outcomes, including pregnancy rates and miscarriage. Subgroup analyses were performed looking at individual populations; no difference was seen for those with a history of miscarriage or those with subfertility.[57]

Previous studies have shown the presence of thyroid antibodies can increase the risk of progression from euthyroid to subclinical or overt hypothyroidism in pregnancy.[78] Overall, data from the TABLET trial found 7% of euthyroid women with TPOAb developed SCHypo, either before or during pregnancy. In view of this, women found to be TPOAb positive should have regular monitoring (at least once per trimester) of their thyroid function during pregnancy, starting from around 7 to 9 weeks' gestation.

The results of the T4Life trial, which focuses on LT4 treatment for euthyroid TPOAb-positive women with history of recurrent pregnancy loss, are eagerly awaited.[79]

Given the lack of benefit shown with LT4 in euthyroid TPOAb-positive women, across all populations, this treatment strategy should not be implemented routinely into clinical practice.

DISCUSSION

There is international consensus on the management of overt thyroid disease preconception and during pregnancy. However, as highlighted in this review there are many areas of controversy within thyroid disease and pregnancy. **Box 2** highlights the key areas with ongoing uncertainty and that require further research.

Box 2
Areas for further research

Screening
- Cost effectiveness of preconception or early pregnancy universal screening of thyroid dysfunction
- In select high-risk groups, such as subfertile women with recurrent pregnancy loss, routine preconception TPOAb testing to identify and monitor those at risk of disease progression versus routine TSH measurements in each trimester of pregnancy

Management
- Effect of LT4 commenced preconception or early pregnancy on obstetric outcomes in women with mild SCHypo/isolated hypothyroxinemia
- Effect of LT4 on obstetric outcomes in women with SCHypo and raised TPOAb; with particular focus on women undergoing assisted conception

Research Collaborative for Thyroid Disease and Pregnancy

An international consortium, led by thyroid specialists in the Netherlands, has been set up to produce large scale individual-participant data meta-analyses by collating data from all relevant clinical studies into thyroid disease and pregnancy. The work generated by this group will add significantly to the knowledge of thyroid disease and pregnancy and help to identify areas where new primary research is needed. Examples of work published by this group include an individual-participant data meta-analysis demonstrating the association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth.[26] Another study published in 2020, found that high-normal levels of fT4 in pregnancy are associated with low birthweight, adding to the argument that there may be harm from LT4 overtreatment.[83]

SUMMARY

This review provides an overview of the latest evidence-based recommendations for management of women with thyroid disease preconception and during pregnancy. In addition, we have highlighted areas of controversy and areas for future research.

CLINICS CARE POINTS

- Population-, trimester-, and laboratory-specific reference ranges for serum TSH and fT4 should be used when determining thyroid function in pregnancy.
- Women with overt thyroid disease should receive preconception counseling from the appropriate specialists, regarding the risks of their condition in pregnancy. Such women should have a stable thyroid function for at least 2 months before trying for a pregnancy.
- There is currently insufficient evidence to recommend universal screening for all women trying for pregnancy.
- Routine preconception thyroid function tests should be offered to women with identified risk factors for thyroid disease, in particular women with history of recurrent pregnancy loss and women undergoing fertility treatment.
- Women with overt thyroid disease require regular thyroid function monitoring in pregnancy and should be managed jointly by endocrinologists and obstetricians.
- New-onset hyperthyroidism during pregnancy requires differentiation between Graves disease and transient gestational thyrotoxicosis.
- Graves disease in pregnancy should be treated with antithyroid drugs and the lowest possible dose should be administered; PTU is the preferred medication preconception and in the first trimester of pregnancy.
- Women positive for TRAb antibodies need increased fetal surveillance.
- Untreated moderate SCHypo (TSH 4.0–10.0 mIU/L) is associated with early pregnancy loss and other adverse pregnancy outcomes.
- Evidence for reducing adverse outcomes in women with SCHypo with LT4 therapy is limited; however, best practice is still to treat preconception and during pregnancy.
- There is insufficient evidence of adverse pregnancy outcomes for women with high-normal TSH levels (2.5–4.0 mIU/L) and therefore insufficient evidence of LT4 therapy in this group.
- There is conflicting evidence that isolated hypothyroxinemia is harmful in pregnancy.
- There is no benefit from LT4 treatment in improving pregnancy outcomes for euthyroid TPOAb-negative women.
- Knowing TPOAb status allows for stratification of women who will require thyroid function monitoring during pregnancy. The options of performing TPOAb testing for "high-risk"

women (eg, undergoing assisted reproductive technologies) versus routine early pregnancy thyroid function testing are both acceptable strategies, until clinical and cost-effectiveness analyses are available.

- If a woman is known to be TPOAb-positive, measurement of serum TSH concentration should be taken at 7 to 9 weeks and then in each subsequent trimester, because of the risk of progression to SCHypo and overt hypothyroidism.
- Further studies are needed to determine the role of LT4 therapy in women with mildly elevated TSH levels with or without raised TPOAb.

DISCLOSURE

The authors have nothing to disclose.

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