Thyroid Autoimmunity and Reproductive Function

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Semin Reprod Med

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Abstract

Thyroid hormones are important for normal reproductive function, and maternal thyroid dysfunction has been associated with infertility, miscarriage, preterm birth, and poor neurodevelopment in the offspring. Thyroid autoimmunity is the leading cause of thyroid dysfunction in women of reproductive age. Women with thyroid autoimmunity, even with normal thyroid function, appear to be at a higher risk for poor reproductive outcomes, including miscarriage and preterm birth. Thyroxine replacement in women with thyroid autoimmunity with or without appreciable thyroid dysfunction may improve pregnancy outcomes. Thus, identification and treatment of women with thyroid autoimmunity may optimize reproductive success.

Keywords

- thyroid autoimmunity
- hypothyroidism
- infertility
- miscarriage
- pregnancy

Normal thyroid function is important for reproduction. Unfortunately, thyroid dysfunction is common in reproductive-age women.[1,2] Thyroid dysfunction has been associated with infertility and poor pregnancy outcomes including miscarriage, preterm delivery, fetal demise, and diminished IQ testing in the offspring.[3] Normal maternal thyroid function during the periconception window may be particularly important as (1) the fetus relies on maternal thyroxine until the second trimester for normal neurological development,[4] (2) miscarriage is most likely to occur during this time period,[5–7] and (3) implantation events affect risk of preeclampsia, placental pathologies, and birth outcomes.[8,9]

Thyroid autoimmunity is the most common etiology of thyroid dysfunction.[10] The presence of thyroglobulin antibodies (TG-Abs) or thyroid peroxidase antibodies (TPO-Abs) induces a chronic lymphocytic thyroiditis and can result in thyroid destruction. Thyroid Abs to TG and TPO are relatively common in women of reproductive age, occurring in 12 to 25% of women aged 18 to 45 years.[1,11] Although thyroid Abs can lead to thyroid dysfunction, most women with TPO-Ab or TG-Ab are euthyroid.[12] Thyroid autoimmunity, both with and without thyroid dysfunction, has been associated with adverse reproductive outcomes.[13–15]

Some professional societies have recommended screening for and treatment of thyroid dysfunction or autoimmunity before or during pregnancy to optimize reproductive success.[13,16–19] However, current recommendations are inconsistent among the various societies. In this review, we will discuss (1) the association between thyroid autoimmunity and reproductive function, (2) potential therapies for thyroid autoimmunity, and (3) current screening guidelines. We will specifically focus on TPO and TG autoimmunity.

Thyroid Physiology

Normal Thyroid Physiology

Normal thyroid hormone function is dependent on adequate supply of iodine through the diet. Iodine enters the thyroid gland under the influence of thyroid-stimulating hormone (TSH). In the thyroid, iodine is oxidized to elemental iodine and bound to tyrosine. Monoiodotyrosine and diiodotyrosine combine to form triiodothyronine (T3) and thyroxine (T4). Seventy percent of T3 and T4 are bound in circulation to thyroxine-binding globulin (TBG). TBG is synthesized in the liver; synthesis is increased by estrogen.

Thyroid hormones regulate TSH secretion by both suppressing thyrotropin-releasing hormone (TRH) secretion from the hypothalamus and reducing the number of TRH receptors in the pituitary. Estrogen increases the TRH receptor number in the pituitary, leading to increased TSH responsiveness in women as compared with men. TSH-secreting cells are regulated by free T4, after it is converted to T3 in the pituitary. Thus, the measurement of both free T4 and TSH provides the most accurate assessment of thyroid function.

Issue Theme Thyroid in Reproduction; Guest Editor, Clarisa R. Gracia, MD, MSCE

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DOI http://dx.doi.org/10.1055/s-0036-1593485.
ISSN 1526-8004.

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Thyroid Autoimmunity

Thyroid autoimmunity is defined as the presence of TPO-Ab or TG-Ab. Thyroid antibodies to TG and TPO are relatively common in women of reproductive age, occurring in 12 to 25% of females aged 18 to 45 years.[1,11] In the United States, the prevalence in males are approximately half that of women. Antibody prevalence increases with age and appears to differ between races, with whites and Mexican Americans having a higher prevalence than blacks.[1] Seventy percent of people with TG-Abs also have concomitant TPO-Abs, whereas TPO-Abs are more likely to be seen in isolation.[1] Antithyroid antibodies are probably the manifestation of genetic susceptibility and environmental interplay. Genetic predisposition is most likely polygenic, involving several low-penetrance, low-risk alleles. Environmental factors such as low birth weight, iodine excess, selenium deficiency, and reproductive life span may also play a role in the development of antibodies.[20]

Women with autoantibodies to TG and TPO (previously known as thyroid microsomal antigen) may exhibit a range of thyroid function from normal to transient dysfunction, to subclinical hypothyroidism (an elevated TSH with normal range T4), and to overt hypothyroidism (an elevated TSH level with low T4). A strong relationship exists between the diagnosis of overt hypothyroidism and the presence of antibodies to TPO (odds ratio [OR]: 39.7, 95% confidence interval [CI]: 11.6–136.1).[1] In addition, thyroid function in an individual is not stagnant. Women with thyroid autoimmunity have approximately a 5% annual conversion rate from subclinical to overt hypothyroidism.[21]

Physiologic Thyroid Function Changes in Pregnancy

Although the fetus does not make thyroxine until the second trimester, it does indirectly influence the maternal supply of thyroxine to itself. Studies of pregnant women have shown that human chorionic gonadotropin (hCG), which is produced by the developing embryo, moderates maternal and subsequent fetal T4 levels (►**Fig. 1**).[22,23] hCG is detectable in maternal serum as early as 4 weeks of gestation. hCG binds to the luteinizing hormone receptors on the corpus luteum, increasing estradiol production. Estradiol stimulates the production of TBG by the liver, and there is a 1.5- to 2-fold increase in TBG during pregnancy.[24] TBG binds T4 and lowers the levels of biologically active free T4. In addition, hCG, which has structural homology with TSH, can bind to the TSH receptor on maternal thyroid epithelial cells, leading to stimulation of T4 production.[25,26] Thus, the conceptus, through production of hCG, indirectly increases the demand for T4 and also directly stimulates the maternal thyroid to produce T4. In a woman without thyroid dysfunction with a viable pregnancy, thyroxine equilibrium is maintained. However, women with a history of hypothyroidism, unable to compensate for the greater thyroid hormone requirements during pregnancy, commonly need to increase their thyroxine replacement dose in pregnancy to maintain normal TSH levels.[27]

Several studies have sought to characterize changes in thyroid function during pregnancy using a mixture of cross-sectional and longitudinal data.[22,28,29] Subjects have been recruited as early at 6 weeks of gestation, and thyroid function assessed in each trimester of pregnancy. Free T4

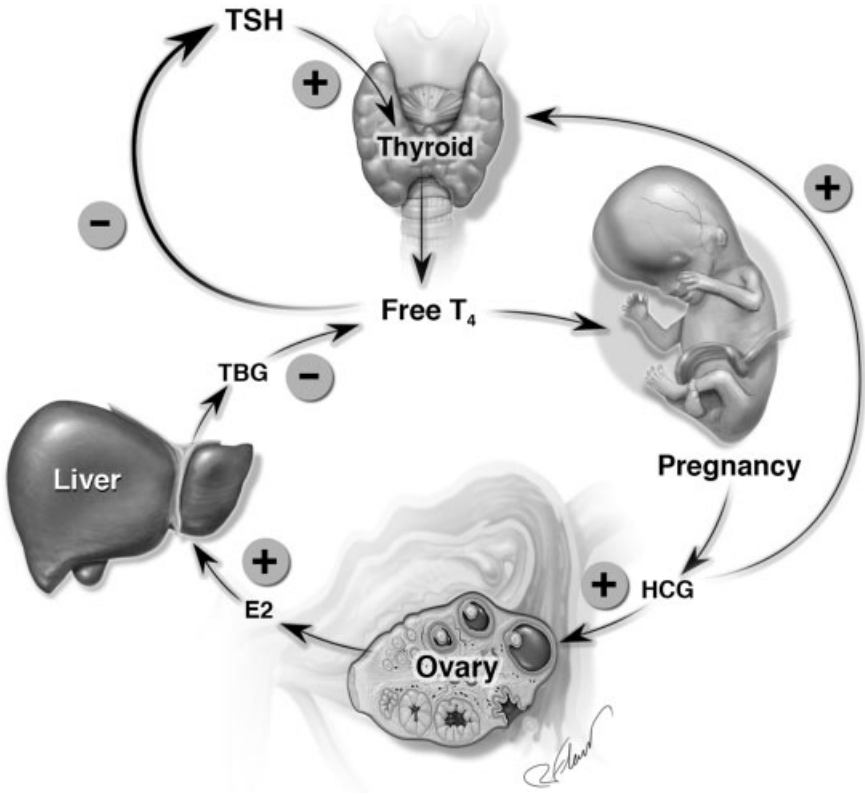

Fig. 1 Physiologic thyroid hormone function changes in pregnancy. E2, estradiol; HCG, human chorionic gonadotropin; T4, thyroxine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone.

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appears to peak concomitant with the hCG peak at 9 to 13 weeks of gestation and then subsequently declines followed by a plateau in the late second trimester.[29] TSH is the best measure of thyroid function during the weeks following conception and reflects thyroxine activity in peripheral tissues.[30,31] TSH values mirror changes in T4, with the lowest levels seen at the peak in hCG levels.[14] As TSH values change during pregnancy, trimester-specific normative values are provided. TSH rarely exceeds 2.5 mIU/L in the first trimester or 3.0 mIU/L in the second or third trimester.[13,14,16]

Studies of thyroid function during the transition from preconception to early conception in women without preexisting thyroid disease have been limited. Poppe et al compared prepregnancy and early pregnancy thyroid function in women undergoing in vitro fertilization (IVF) without history of thyroid disease ($n = 77$). They found that at 2 weeks after embryo transfer (~4 weeks of gestation) both TSH and free T4 were significantly higher than prior to pregnancy.[32] However, elevated estradiol levels due to ovarian hyperstimulation may have led to the elevation in TSH observed in these women.[33,34] A study at our institution evaluated thyroid hormone levels before and during early conception in women without preexisting thyroid disease or infertility ($n = 60$). Pre-pregnancy TSH values were significantly higher than those in early pregnancy, although no such changes in free T4 values were noted.[35] Thus, it appears that thyroid hormone levels differ in preconception versus early pregnancy, which should be taken into consideration when crafting screening guidelines.

Thyroid antibodies lead to epithelial thyroid cell destruction through antibody-dependent cell-mediated cytotoxicity.[36] On average, women with TPO-Ab or TG-Ab have significantly higher TSH levels than women who are antibody negative.[1] However, many women with thyroid antibodies will not exhibit thyroid dysfunction preconception, because the thyroid gland is able to function normally in the nonstressed, nonpregnant state. As the demand on the thyroid increases during pregnancy, women with thyroid autoimmunity may become overtly hypothyroid as pregnancy progresses.[3,10,37,38] Thus, the timing and choice of screening tests needs to be carefully considered when considering a program to screen for thyroid dysfunction to improve reproductive outcomes.

Reproductive Outcomes

There is biologic evidence that T4 is important for early fetal development and implantation. T4 is found in coelomic fluid as early as 5.6 weeks.[39] Both syncytiotrophoblasts and cytotrophoblasts exhibit T4 receptors.[40] T3 has been shown to act synergistically with epidermal growth factor in the regulation of implantation.[41] However, the fetus does not produce T4 until the middle of the second trimester.[42] In the first trimester, the fetus is dependent on maternal T4 production and transfer across placental membranes.[4] Thus, it is biologically plausible that maternal deficiencies in T4 production my result in aberrant placentation and subsequent miscarriage. As women with thyroid Abs are more likely to have thyroid dysfunction or develop thyroid dysfunction during pregnancy, these women are at risk for poor reproductive outcomes.

Infertility

An increased prevalence of thyroid autoimmunity has been observed in infertile women as compared with fertile controls. In a study of 108 women with infertility, Roussev et al found that the prevalence of thyroid antibodies was significantly higher in infertile women as compared with controls (65 vs. 7%, respectively).[43] Poppe et al also found that women with infertility ($n = 438$) had a significantly higher prevalence of TPO-Ab as compared with fertile controls (18 vs. 8%, respectively). In this study, women with endometriosis, which has also been associated with immune system dysfunction, were most likely to have thyroid autoimmunity (29% prevalence).[38] Abalovich et al ($n = 244$) also demonstrated an increased prevalence in women with endometriosis as compared with controls, although the finding was not statistically significant (25 vs. 14% among controls).[44] Janssen et al ($n = 175$) found that women with polycystic ovarian syndrome also were more likely to have thyroid autoimmunity (27 vs. 8% of healthy controls).[45] A recent meta-analysis (4 studies included in analysis, $n = 2{,}013$) reported that Ab-positive women had 1.5 times the odds of infertility as compared with women without thyroid autoimmunity (95% CI: 1.1–2.0).[15] Although human oocytes have thyroid hormone receptors,[46,47] the mechanism by which isolated thyroid autoimmunity may impact infertility is largely still unknown.

Controlled ovarian hyperstimulation (COH) is commonly used in the treatment of infertility. COH is associated with a rise in serum estradiol levels over the course of stimulation, which likely drives an increase in hepatic production of TBG. Correspondingly, TSH levels increase over the course of stimulation.[32,33,48,49] In a study of 35 women undergoing COH for IVF, Poppe et al showed that women with thyroid autoimmunity had a greater increase in TSH levels than women who were Ab negative over the course of stimulation.[49] Therefore, it is recommended that women with thyroid autoimmunity receive thyroxine supplementation as needed to achieve a TSH level below 2.5 mIU/L before COH.[3,13]

There has been significant research on the impact of thyroid autoimmunity on IVF outcomes. Zhong et al evaluated women undergoing IVF ($n = 766$), and found that compared with women without antibodies, those with thyroid Abs had significantly lower rates of fertilization (64 vs. 75%), implantation (18 vs. 27%), and clinical pregnancy (33 vs. 47%).[50] Conversely, Fumarola et al retrospectively evaluated women undergoing IVF ($n = 164$) and revealed no difference in number of oocytes retrieved, number of embryos transferred, or quality of embryos between women with TPO-Ab and those without. However, there was a significantly lower rate of pregnancy in women with TPO-Ab (0 vs. 24%).[51] Kim et al found that even among euthyroid women, those women with TPO-Ab or TG-Ab were less likely to conceive (26 vs. 39% in women without thyroid Abs, $N = 79$). In this study, there was no difference in number of oocytes retrieved, fertilization rates, or number of embryos transferred.[52] In contrast, Poppe et al failed to observe any association between thyroid autoimmunity and IVF outcome among euthyroid patients ($n = 234$).[53] In a meta-analysis, van den Boogaard (7 studies, $n = 1{,}760$) found no significant association between thyroid

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autoimmunity and pregnancy rates after IVF (OR: 0.67, 95% CI: 0.36–1.4).[15] Subsequent additional retrospective studies in euthyroid women undergoing IVF have also shown no association between thyroid Abs and pregnancy rates.[54–56] Thus, we conclude that thyroid autoimmunity is unlikely to affect IVF pregnancy rates.

Early Pregnancy and Miscarriage

Studies are mixed regarding the rate of early pregnancy loss after IVF in women with thyroid autoimmunity. This population is unique, as pregnancy after IVF is often detected at an earlier stage than in spontaneous conceptions. Early pregnancy loss or implantation failure may be easier to identify in the IVF population. In women treated with IVF, Zhong et al observed a higher miscarriage rate in women with thyroid Abs compared with those without (27 vs. 12%, respectively).[50] The previously cited study by Poppe et al also supported this finding, with 53% of pregnancies in TPO-Ab-positive women ending in miscarriage as compared with 23% in TPO-Ab-negative women.[53] Kim et al also reported a higher miscarriage rate in women undergoing IVF with TPO-Ab as compared with those without (40 vs. 18%, respectively).[52] While these studies suggest that miscarriage rates following IVF are higher in women with thyroid autoimmunity, a recent meta-analysis (5 studies, $n = 1{,}819$) failed to find a statistically significant association (pooled odds ration [OR]: 1.6, 95% CI: 0.76–3.5).[15]

T4 supplementation in women with thyroid autoimmunity undergoing IVF may improve reproductive outcomes. Negro et al conducted a study of 484 women undergoing IVF. Seventy-two of the women were TPO-Ab positive without thyroid dysfunction. These women were randomized to treatment with levothyroxine (LT4) or no treatment.[57] There was no significant difference in pregnancy rates between women with TPO-Ab and those without TPO-Ab or between women with TPO-Ab who received treatment and those who did not. However, TPO-Ab-positive women who did not receive LT4 supplementation had a significantly higher miscarriage rate compared with TPO-Ab-positive women treated with LT4 and compared with women without antibodies (52 vs. 33 vs. 26%, respectively).[57]

It appears that euthyroid women, who conceive spontaneously in the presence of TPO-Ab or TG-Ab, have a two- to fivefold increase in risk of miscarriage.[10,13,52,57–67] A recent meta-analysis by Thangaratinam et al (19 studies, $n = 8{,}522$) found up to a 3.9 times the odds of miscarriage in women with thyroid Abs as compared with those without (95% CI: 2.5–6.1).[68] Liu et al evaluated women in early pregnancy ($n = 3{,}315$) and found that women with isolated thyroid autoimmunity had 2.7 times the odds of miscarriage as compared with controls (95% CI: 1.4–5.1).[67] Women with thyroid antibodies with concurrent thyroid dysfunction are at greater risk for miscarriage. The risk of pregnancy loss increases with the degree of thyroid dysfunction. Women with thyroid antibodies and a TSH >2.5 mIU/L and <5.2 mIU/L have five times the odds of miscarriage (95% CI: 2.8–8.9) and women with a TSH >5.2 mIU/L and <10 mIU/L have 9.6 times the odds of miscarriage (95% CI: 3.8–24.3) as compared with controls.[67]

T4 replacement in women with thyroid autoimmunity appears to reduce miscarriage risk. In women with thyroid autoimmunity and thyroid dysfunction, thyroxine supplementation clearly reduces the likelihood of miscarriage.[3,13,69,70] However, thyroid supplementation may also be beneficial in euthyroid pregnant women with thyroid autoimmunity. In a study of pregnant women ($n = 984$) by Negro et al,[64] women with TPO-Ab and no other evidence of thyroid dysfunction were randomized to levothyroxine (LT4) supplementation (ranging from 0.5 to 1.0 μg/kg/day, based on TSH levels) or no supplementation at an average gestation of 10 weeks. In the LT4-supplemented group, 3.5% of women subsequently miscarried versus 13.8% in the placebo group ($p < 0.05$). In a retrospective analysis, Lepoutre et al examined pregnant women at the first prenatal visit ($n = 537$) and found a significant reduction in the rate of miscarriage between TPO-Ab-positive women who received LT4 treatment (0%) and TPO-Ab-positive women who were not treated with LT4 (16%).[71] A meta-analysis (2 studies, $n = 160$) suggests that miscarriage rates are reduced with LT4 supplementation in euthyroid, Ab-positive, pregnant women (RR: 0.5, 95% CI: 0.3–0.9).[68] However, evidence supporting routine supplementation during the periconception window to further reduce miscarriage risk in Ab-positive women is lacking.

The association between thyroid autoimmunity and recurrent miscarriage is less clear. A meta-analysis by van den Boogaard (8 studies, $n = 2{,}383$) revealed that women with recurrent miscarriage more often had thyroid Abs (OR: 2.3, 95% CI: 1.5–3.5).[15] Subsequently, Yan et al evaluated women ($n = 716$) with recurrent miscarriage (three or more miscarriages of less than 20 weeks in gestational age) and found no difference in the prevalence of TPO-Ab between women with explained or unexplained miscarriage (12 vs. 11%, respectively). In this study, some women with unexplained miscarriage and TPO-Ab were treated with LT4. No difference in miscarriage rates was observed between TPO-Ab women treated with LT4 (53%), TPO-Ab women without treatment (58%), and TPO-Ab-negative women (64%).[72] Recently, Vissenberg et al retrospectively evaluated euthyroid women with a history of recurrent miscarriage ($n = 202$). Women with TPO-Ab who did not receive LT4 treatment had a lower live birth rate as compared with either TPO-Ab-positive women with treatment or Ab-negative women (29% vs. 60 and 51%, respectively).[73] An ongoing, a multicenter randomized, double-blind placebo controlled trial (the T4-LIFE study) seeks to determine the benefit of T4 supplementation in women with recurrent miscarriage and TPO-Ab.[74]

Late Pregnancy Complications

Overt thyroid dysfunction has been shown to be associated with poor obstetric outcomes.[13,16,75] In addition, studies suggest that pregnant women with thyroid antibodies are at increased risk for placental abruption,[76,77] gestational diabetes,[78] premature rupture of membranes,[79–81] preterm birth (PTB),[82–84] and offspring with low birth weight and perinatal mortality.[85] It is not known if the complications are due to thyroid dysfunction or the autoimmunity itself.

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The most consistently observed pregnancy complication associated with thyroid autoimmunity is PTB. Negro et al prospectively followed up euthyroid women during pregnancy ($n = 3,593$) and found a significantly higher rate of early PTB (<34 weeks) in women with thyroid Abs as compared with Ab-negative women (4.5 vs. 1.8%).[82] Using the Generation R study cohort ($n = 5,791$), a Norwegian population-based pregnancy cohort, Korevaar et al revealed a significant increase in PTB in women with TPO-Ab as compared with Ab-negative women. Specifically, in women with TPO-Ab, the risk of birth at less than 37 weeks was increased 1.7-fold and the risk of birth at less than 34 weeks was increased 2.5-fold.[83] Recently, Kumru et al prospectively followed up a group of low-risk pregnant women screened for thyroid disease at a gestational age of 10 to 12 weeks ($n = 395$). Women with TPO-Ab were 2.5 times as likely to have PTB (95% CI: 1.06–5.89) as compared with women without thyroid dysfunction or Abs.[84] However, some recent, large, observational studies have failed to find an increase in PTB among women with thyroid autoimmunity.[76,80,85] In a meta- analysis, van den Boogaard et al (3 studies, $n = 2,263$) found that the presence of thyroid Abs in euthyroid women was associated overall with an increased risk of PTB (OR: 1.9, 95% CI: 1.1–3.5).[15]

Women with TPO-Ab and subclinical hypothyroidism appear to have an even greater risk of PTB. A recent study by Kumru et al ($n = 395$) found an increase in PTB among women with both TPO-Ab and subclinical hypothyroidism (OR: 4.85, 95% CI: 1.89–12.42) as compared with euthyroid women without thyroid Abs.[84] Using the Generation R study cohort, Korevaar et al reported that the risk of PTB increased in TPO-Ab-positive women with the degree of subclinical hypothyroidism. In pregnant women with TPO-Ab ($n = 295$), the odds of PTB was 2.7 times higher with a TSH greater than 2.5 mIU/L (95% CI: 0.95–7.5) and 3.3 times higher with a TSH greater than 4.0 (95% CI: 1.15–9.29) as compared with TPO-Ab-positive women without a TSH elevation.[83]

Treatment of euthyroid women with thyroid autoimmunity may decrease the rate of PTB. In the only study evaluating LT4 treatment in euthyroid women with TPO-Ab, Negro et al reported that women with untreated TPO-Ab had a significantly higher rate of PTB as compared with TPO-Ab-positive women treated with LT4 (22 vs. 7%, respectively).[64] A meta-analyses by Vissenberg et al (2 studies, $n = 257$) found that LT4 supplementation in women with both subclinical hypothyroidism and thyroid autoimmunity was associated with significant reduction in PTB (RR: 0.41, 95% CI: 0.24–0.68).[86]

Neonatal Outcomes

The fetus is dependent on maternal thyroid hormones for normal neuronal migration and brain development during the first half of pregnancy. Deficiencies in maternal thyroid hormones have been shown to negatively impact fetal neurological development and LT4 replacement is currently recommended for pregnant women with subclinical and clinical hypothyroidism.[13,16,87,88]

There is limited research on the association between isolated maternal thyroid autoimmunity and offspring IQ. In a small study ($n = 230$), Pop et al reported significantly lower intelligence scores in children born to euthyroid TPO-Ab-positive women as compared with Ab-negative women (OR: 10.5, 95% CI: 3–34).[89] Furthermore, in a study of pregnant Chinese women ($n = 1,268$), Li et al found that children of women with TPO-Ab had significantly lower intelligence and motor skill scores as compared with women without Abs (OR: 6.7, 95% CI: 2.3–19 and OR: 8.3, 95% CI: 3.3–21, respectively).[90] Currently, no studies have evaluated the potential benefit of treating euthyroid women with thyroid autoimmunity to improve neurodevelopmental outcomes in their offspring.

Screening and Treatment Guidelines

To prevent adverse outcomes to offspring, some professional societies (Endocrine Society [ES], American Thyroid Association [ATA], American Congress of Obstetrics and Gynecology [ACOG], and American Association of Clinical Endocrinologists [AACE]) have recommended screening for thyroid disorders before or during pregnancy. It has been assumed that these screening mechanisms will identify the correct women, those with thyroid dysfunction who would benefit from treatment. The cutoff values are derived from cross-sectional data from the general population and from women presenting for prenatal care in the first trimester. It is important to note that use of cross-sectional data assumes that (1) pregnancy-induced changes in thyroid function are the same for all women, (2) women with normal pre-pregnancy thyroid levels will have normal pregnancy thyroid levels, and (3) values outside of 95% CI limits for the population represent thyroid dysfunction.

Universal screening for thyroid disease, at preconception and/or in early pregnancy, is currently either not recommend (ACOG, AACE) or no consensus could be made (ATA, ES).[13,16–18] Risk-factor–based screening for high-risk women either at preconception (ACOG, ES, AACE) or in early pregnancy (ACOG, ATA, ES) is currently recommended.[13,16–18] However, the risk factors defined by ES and ATA, which include age more than 30 years, infertility, history of miscarriage or PTB, family history of autoimmune or thyroid disease, or symptoms of thyroid disease, have led to a large proportion of reproductive-aged women being screened preconception or in early pregnancy.[13,16]

There are no consistent guidelines regarding screening for thyroid antibodies before or during pregnancy. The ES and ACOG do not recommend screening for thyroid Abs.[13,18] The ATA did not draw a conclusion on a screening recommendation due to insufficient evidence.[16] In contrast, the AACE recommends considering TPO-Ab screening in women with subclinical hypothyroidism.[17] Interestingly, in a recent cost-effectiveness study, universal screening of pregnant women for thyroid autoimmunity (with TPO-Ab and TSH) was shown to be cost-effective as compared with both risk-factor–based screening and no screening.[91]

Current treatment guidelines support treatment with LT4 in women (at preconception or in early pregnancy) with thyroid dysfunction, including subclinical hypothyroidism, to a goal TSH of <2.5 mIU/L.[13,16,19] Although guidelines for treatment in euthyroid women with thyroid Abs are less clear,

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these women are at risk for developing thyroid dysfunction in pregnancy. Thus, women with thyroid autoimmunity require, at a minimum, close monitoring for the development of thyroid disease. Current ES and ATA guidelines recommend monitoring Ab-positive women with a TSH every 4 to 6 weeks during pregnancy to detect development of thyroid dysfunction.[13,16] The current evidence from randomized, controlled trials suggests that miscarriage and PTB rates are reduced with levothyroxine treatment of euthyroid women with antithyroid antibodies.[57,64] Hopefully the ongoing TAB-LET (Thyroid AntiBodies and LEvoTyroxine) trial, a UK-based double-blind, placebo-controlled trial evaluating miscarriage and PTB rates after treatment with LT4 in euthyroid women with thyroid Abs, will provide definitive evidence of the reproductive benefits of levothyroxine therapy in euthyroid women with thyroid antibodies.

Summary

Thyroid hormones are important for normal reproductive function, and thyroid autoimmunity is the leading cause of thyroid dysfunction in women of reproductive age. Women with thyroid autoimmunity, even with normal thyroid function, appear to be at a higher risk for poor reproductive outcomes, including miscarriage and PTB. This risk appears to be further magnified in the setting of concurrent thyroid dysfunction. Current evidence suggests that there may be some benefit to thyroxine supplementation in Ab-positive, pregnant women. Thus, identification and treatment of women with thyroid autoimmunity may optimize reproductive success. Guidelines should consider normal periconception and early pregnancy thyroid physiology and the potential impact of thyroid autoimmunity in the choice, timing, and interpretation of thyroid testing.

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