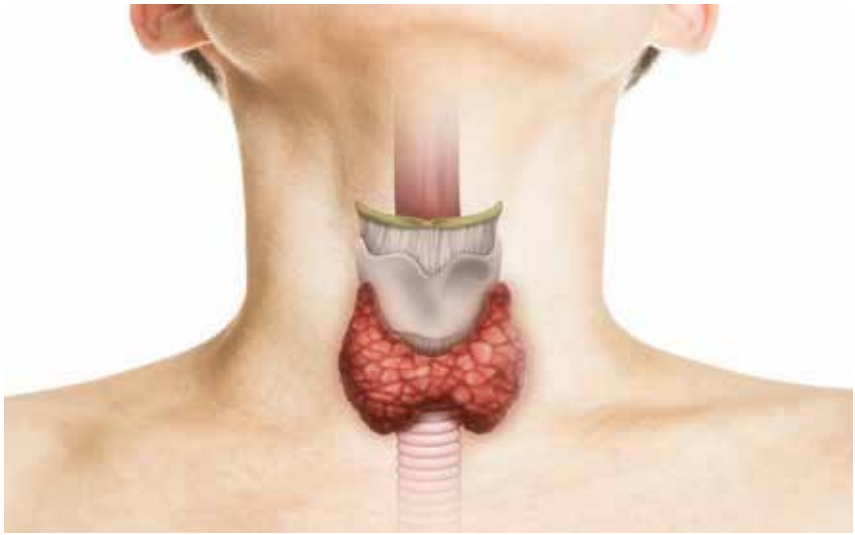
Thyroid autoantibodies and adverse pregnancy outcomes

By Karli A. McManaman, APRN, WHNP-BC, and Sandi Tenfelde, PhD, APRN, WHNP-BC

Thyroid dysfunction caused by autoimmune thyroid disease is a prevalent condition among reproductive-age women and in pregnancy. Autoimmune thyroid disease is characterized by the presence of thyroid autoantibodies including thyroid peroxidase antibodies, thyroglobulin antibodies, and/or thyroid-stimulating hormone receptor antibodies. These autoantibodies have been linked to adverse pregnancy outcomes such as miscarriage, preterm birth, infertility, and postpartum thyroiditis even when the pregnant person is euthyroid. This article reviews current evidence related to the association of these adverse outcomes in women with autoantibodies who are euthyroid and available guidance on treatments to reduce risks. Screening approaches also are discussed.

KEY WORDS: **autoimmune thyroid disease, thyroid autoantibodies, miscarriage, preterm delivery, infertility, postpartum thyroiditis, screening during pregnancy**

Womens Healthcare. 2022;10(4):20-24. doi:10.51256/WHC082220



One of the most common endocrine disturbances among reproductive-age women is thyroid dysfunction. The main etiology of thyroid dysfunction is autoimmune thyroid disease, which results from dysregulation of the immune system.[1] Autoimmune thyroid disease is characterized by the presence of thyroid autoantibodies, which include thyroid peroxidase antibodies (TPO-Abs), thyroglobulin antibodies (T-Abs), and/or thyroid-stimulating hormone receptor antibodies (TSHRAbs).[2] These antibodies attack and damage the thyroid gland, which can then potentially lead to hypothyroidism.[3]

Most reproductive-age women have a thyroid-stimulating hormone (TSH) level within normal range and are considered euthyroid. However, the presence of thyroid autoantibodies is relatively common, with a prevalence of 6% to 20% in the general population.[4] In pregnant women, the prevalence of thyroid autoantibodies ranges from 3% to 18%.[2] Women with thyroid autoantibodies who are euthyroid prepregnancy may have an increase in TSH levels during pregnancy, possibly because the ability of the thyroid to augment hormone production is compromised.[3] However, 10% to 20% of pregnant women with thyroid autoantibodies remain euthyroid.[4]

Regardless of whether thyroid function has been compromised or not, research conducted over the past two decades has shown that the presence of thyroid autoantibodies is linked to adverse pregnancy outcomes such as miscarriage, preterm birth, infertility, and the increased risk of developing postpartum thyroiditis.[1] This article reviews the current evidence related to these adverse outcomes in women with thyroid autoantibodies who are euthyroid. Management strategies are described based on guidelines from the American Thyroid Association (ATA), and screening approaches for thyroid disorders during pregnancy are discussed.

Thyroid autoantibodies and miscarriage

Miscarriage, defined as spontaneous loss of pregnancy that occurs prior to 20 weeks' gestation, affects 17% to 31% of all pregnancies.[3] Recurrent pregnancy loss, defined as the loss of two or more pregnancies regardless of consecutiveness, affects 1% to 5% of pregnancies.[2,5] Although the underlying etiology for miscarriage is often unknown, a physiologic alteration in endocrine and thyroid function may predispose some patients to recurrent loss.

Since 1990, researchers have conducted studies to evaluate potential links between the presence of thyroid autoantibodies, primarily TPO-Abs, and miscarriage. These studies are consolidated in published guidelines from the ATA for the diagnosis and management of thyroid disease during pregnancy and postpartum.[3] Several recently published studies reveal strong evidence linking TPO-Ab positivity to a greater risk of miscarriage.[6–8] The underlying mechanisms for this association are not clear, and while there is a correlation between thyroid autoantibodies and miscarriage, causality has not been proved.

To date, there is little evidence to support treatment strategies for euthyroid women with TPO-Ab positivity either prior to attempting pregnancy or during early pregnancy to decrease the risk for miscarriage. Variables in research design, participant characteristics, and protocols for levothyroxine initiation and dose adjustments in studies complicate generalizability.

In one prospective randomized control trial (RCT), over 8,000 pregnant women were screened for TSH and thyroid autoantibodies in their first trimester of pregnancy. In this sample, 400 women (~ 5% of the sample) were euthyroid women with thyroid autoantibodies. They were randomized to receive either levothyroxine initiation or no treatment, and dose was determined by initial TSH levels. There were no significant differences in miscarriage rates among patients who were treated with levothyroxine and those who were not.[9] Previous pregnancy loss was not an inclusion criterion for this study.

Women with a history of miscarriage or infertility may have unique needs. The TABLET study looked specifically at levothyroxine treatment for euthyroid women with TPO-Ab positivity and a history of miscarriage or infertility. This large, multicenter, prospective RCT concluded that for the 540 participants who became pregnant during the study, levothyroxine at a dose of 50 µg started prior to pregnancy and continued to the end of the pregnancy was of no benefit in increasing the proportion who attained a live birth at or beyond 34 completed weeks' gestation.[10] The T4Lifetrial, another multicenter, prospective RCT, examined the effect of levothyroxine treatment in 187 euthyroid pregnant women with TPO-Ab positivity and a history of recurrent pregnancy loss. Compared with placebo, levothyroxine treatment did not result in higher live birth rates (defined as birth of a living fetus > 24 weeks' gestation).[11] Findings from both the TABLET study and the T4Lifetrial support that the use of levothyroxine is not beneficial to prevent miscarriage in women with recurrent pregnancy loss who are euthyroid and positive for TPO-Ab.[10,11]

The 2017 ATA guidelines provide evidence-based recommendations for clinicians caring for pregnant women with thyroid conditions. The guidelines note that there is not enough evidence to convincingly determine a beneficial impact of levothyroxine administration on the reduction of pregnancy loss in newly pregnant TPO-Ab-positive euthyroid women with a history of pregnancy loss.[3] However, despite the lack of strong evidence, the guidelines acknowledge the risks of prescribing levothyroxine (25–50 µg) for euthyroid TPO-Ab-positive women with a history of pregnancy loss are low. This recommendation was made prior to the reported results of the TABLET study and the T4Lifetrial.

Thyroid autoantibodies and preterm birth

Preterm births, defined as those occurring prior to 37 weeks' gestation, make up 11% of all births in the United States.[3] Although studies investigating the association between TPO-Abs in euthyroid women and preterm birth have had mixed results, data from several studies including one older meta-analysis have demonstrated an association.[12–14]

Interventional studies examining whether levothyroxine treatment is beneficial in reducing preterm birth rates in euthyroid women who are

TPO-Ab positive are sparse. One prospective randomized study did not find that levothyroxine was effective in the reduction of preterm birth rates.[9] Another prospective randomized study, however, using the same intervention protocol provided evidence to suggest that levothyroxine treatment does aid in the reduction of preterm birth among TPO-Ab-positive pregnant women by 70%.[15]

Noting insufficient evidence, the 2017 ATA guidelines do not recommend for or against treating TPO-Ab-positive euthyroid women with levothyroxine to prevent preterm birth.[3] The TABLET study completed after the ATA 2017 guidelines were released concluded that treatment with levothyroxine did not decrease the occurrence of preterm birth.[10] Overall, more research is needed to recommend for or against levothyroxine treatment to prevent preterm delivery in TPO-Ab-positive women.

Thyroid autoantibodies and infertility

Infertility is defined as the inability to conceive after 12 months of regular unprotected sexual intercourse or with therapeutic donor insemination.[2] Limited evidence suggests that women with female-factor infertility are more likely to be TPO-Ab positive than age-matched women who are not infertile.[3] Current studies have investigated the association between TPO-Ab positivity and infertility and have revealed a positive link.[16–18]

More research is needed on the most effective management for thyroid autoimmunity and infertility. Current literature reveals mixed study findings on the association between levothyroxine therapy and fertility outcomes. In a 2017 meta-analysis of RCTs that studied the effects of levothyroxine supplementation on pregnancy outcomes in women with thyroid dysfunction, the authors concluded that levothyroxine was beneficial for women with thyroid dysfunction to prevent miscarriage and increase fertilization and clinical pregnancy rates, but data remain limited to conclude whether levothyroxine supplementation is an effective treatment in TPO-Ab-positive euthyroid patients.[19] A meta-analysis of RCTs that included women with thyroid autoimmunity and/or subclinical hypothyroidism undergoing assisted reproduction found that supplementation with levothyroxine was not associated with improved clinical pregnancy rates or live birth rates. Results did suggest significantly lower miscarriage rates.[20]

The ATA guidelines do not provide any recommendation for the administration of levothyroxine in TPO-Ab-positive euthyroid women with infertility attempting natural conception (not undergoing assisted reproductive therapy), based on insufficient evidence for improved fertility.[3] However, the guidelines note that levothyroxine supplementation of 25 to 50 µg may be considered for women who are TPO-Ab positive undergoing assisted reproductive therapies given its potential benefit and minimal risk.

Thyroid autoantibodies and postpartum thyroiditis

Postpartum thyroiditis (PPT) is an inflammatory autoimmune condition that occurs in about 8% of women who are euthyroid prior to pregnancy. This condition most commonly occurs around 6 weeks postpartum, but it can present up to 12 months after giving birth.[2] Women who develop PPT may experience a biphasic presentation, beginning with transient thyrotoxicosis, in which there is an increased release and circulation of thyroid hormones T3 and T4. Thyrotoxicosis is then followed by transient hypothyroidism, with an eventual return to euthyroid by 12 months postpartum. Up to 50% of women present only with transient hypothyroidism. Over the years, research has shown that women who are positive for TPO-Abs are 5 to 7 times more likely to develop postpartum thyroiditis compared to women who are negative for TPO-Abs.[2]

There are limited data evaluating treatment modalities that can be initiated during pregnancy to prevent the occurrence of PPT in euthyroid women with TPO-Ab positivity. Older available studies do not support the use of levothyroxine, iodide, or selenium during pregnancy for this purpose.[21–23] The ATA guidelines recommend against treatment of euthyroid, TPO-Ab-positive pregnant women with levothyroxine, iodide, or selenium to prevent PPT.[3]

Screening for thyroid dysfunction

ATA and the American College of Obstetricians and Gynecologists (ACOG) prefer to utilize a targeted approach when screening women for thyroid disorders prior to pregnancy or in early pregnancy.[3,24] With this approach, serum TSH levels are obtained in women with identified risk factors. Women considered at risk include those with a history or current manifestations of thyroid disease, known TPO-Ab positivity, history of prior thyroid surgery or head/neck radiation, all women 30 years of age and older, history of type 1 diabetes/autoimmune disorders, history of pregnancy loss, preterm births, or infertility, multiple pregnancies (> 2), family history of thyroid disease, morbid obesity, use

Well-designed studies are needed to learn more about the mechanisms for the association between thyroid autoantibody positivity and adverse pregnancy outcomes.

of thyrotoxic agents (amiodarone, lithium, or iodine contrast), or those residing in known areas of iodine insufficiency.[3]

The ATA guidelines do note that evidence is insufficient to recommend for or against universal screening for abnormal TSH levels in early pregnancy.[3] Some clinicians prefer to implement universal screening rather than targeted screening with the rationale that fewer women with thyroid disorders will be missed.[25] Universal screening is deemed appropriate when a condition has a significant prevalence, an association with adverse health outcomes, and is treatable. In addition, an effective form of therapy must exist that is not only practical but also effectively deliverable and cost effective.[3] Subclinical hypothyroidism and euthyroid anti-thyroid antibody positivity meet the significant prevalence and association with adverse health outcomes in pregnancy criteria, but less so having strong evidence to support supplementation as an effective form of therapy to improve outcomes.[3,24]

Specific to thyroid autoantibodies, ATA and ACOG recommend against universal testing for TPO-Abs in women planning a pregnancy or pregnant who are euthyroid due to limited evidence that thyroid hormone replacement for these individuals may not improve pregnancy outcomes[3,24] However, euthyroid women who are positive for thyroid autoantibodies may be at risk for development of hypothyroidism during pregnancy. The ATA recommends that pregnant women who are known to be positive for thyroid autoantibodies have a serum TSH drawn at the time of pregnancy confirmation and every 4 weeks through mid-pregnancy.[3]

Implications for practice

Many women considering pregnancy will have thyroid autoantibodies, specifically positive TPO-Abs. Although exact mechanisms are not fully understood, current evidence overall supports an association between TPO-Ab positivity and potential adverse pregnancy outcomes that include miscarriage, preterm birth, infertility, and postpartum thyroiditis. Clinicians who provide reproductive and obstetric healthcare must provide patients who are TPO-Ab positive with information based on the best evidence available and also in tailoring management based on individual needs and desires. Established guidelines will evolve as more research is completed and the exact mechanisms of the association of TPO-Ab positivity and adverse pregnancy outcomes are better understood.

Levothyroxine therapy has been the most studied of interventions to improve pregnancy outcomes. Recommendations from ATA were based on evidence available at the time the 2017 guidelines were developed. These guidelines include recommendations related to management of TPO-Ab positivity in reproductive-age women who are seeking pregnancy or who are pregnant.

There is insufficient evidence to support the use of levothyroxine administration in newly pregnant TPO-Ab-positive euthyroid women without a history of loss to reduce the incidence of miscarriage.[3] Levothyroxine administration (25–50 µg) may be considered for euthyroid TPO-Ab-positive women with a history of pregnancy loss due to the potential benefits of therapy outweighing the risk of any adverse outcomes. The evidence is insufficient to recommend for or against treating TPO-Ab-positive euthyroid women with levothyroxine to prevent preterm birth. There is no recommendation for the administration of levothyroxine in TPO-Ab-positive euthyroid women with infertility attempting natural conception, based on insufficient evidence for improved fertility. Levothyroxine supplementation of 25 to 50 µg may be considered for women undergoing assisted reproductive therapies given its potential benefit and minimal risk. No evidence supports treatment of euthyroid, TPO-Ab-positive pregnant women with levothyroxine, iodide, or selenium to prevent PPT. Debate continues about universal screening or targeted screening for thyroid dysfunction during pregnancy. Clinicians can choose whichever screening approach they prefer based on their own clinical judgment.

Conclusion

Several limitations exist in research done thus far exploring thyroid autoantibodies in euthyroid women, potential adverse pregnancy outcomes, and potential treatment to improve these outcomes. Current

research is limited by small sample sizes, use of nonrandomized and noncontrolled study designs, timing of lab tests, and timing of initiation and dose of levothyroxine therapy, and variable inclusion criteria all limit generalizability. Ongoing large, randomized-controlled, multicenter studies may provide further guidance for practice. Well-designed studies are needed to learn more about the mechanisms for the association between thyroid autoantibody positivity and adverse pregnancy outcomes. ■

Karli A. McManaman is a women's health nurse practitioner in Jupiter, Florida, and Sandi M. Tenfelde is Associate Professor and Director of the Women's Health/Gender Related Nurse Practitioner Program at the Marcella Neihoff School of Nursing, Loyola University, in Chicago, Illinois. **The authors have no actual or potential conflicts of interest in relation to the contents of this article.**

References

1. Crawford NM, Steiner AZ. Thyroid autoimmunity and reproductive function. *Semin Reprod Med*. 2016;34(6):343-350.
2. De Leo S, Pearce EN. Autoimmune thyroid disease during pregnancy. *Lancet Diabetes Endocrinol*. 2018;6(7):575-586.
3. Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum *Thyroid*. 2017;27(3):315-389.
4. Nazarpour S, Ramezani Tehrani F, et al. Thyroid dysfunction and pregnancy outcomes. *Iran J Reprod Med*. 2015;13(7):387-396.
5. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril*. 2020;113(3):533-535.
6. Iqbal S, Ghani F, Qureshi R. Frequency of thyroid peroxidase antibody and its association with miscarriages among pregnant women. *J Coll Physicians Surg Pak*. 2016;26(10):831-834.
7. Dhillon-Smith RK, Tobias A, Smith PP, et al. The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility. *J Clin Endocrinol Metab*. 2020;105(8):2667-2677.
8. Farquhar CM, Bhattacharya S, Repping S, et al. Female subfertility. *Nat Rev Dis Primers*. 2019;5(1):7.
9. Negro R, Schwartz A, Stagnaro-Green A. Impact of levothyroxine in miscarriage and preterm delivery rates in first trimester thyroid antibody-positive women with TSH less than 2.5 mIU/L. *J Clin Endocrinol Metab*. 2016;101(10):3685-3690.
10. Dhillon-Smith RK, Middleton LJ, Sunner KK, et al. Levothyroxine to increase live births in euthyroid women with thyroid antibodies trying to conceive: the TABLET RCT. *Efficacy Mech Eval*. 2019;6(11):1-102.
11. van Dijk MM, Vissenberg R, Fliers E, et al. Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2022;10(5):322-329.
12. Han Y, Mao LJ, Ge X, et al. Impact of maternal thyroid autoantibodies positivity on the risk of early term birth: Ma'anshan birth cohort study. *Endocrine*. 2018;60(2):329-338.
13. Rajput R, Yadav T, Seth S, Nanda S. Prevalence of thyroid peroxidase antibody and pregnancy outcome in euthyroid autoimmune positive pregnant women from a tertiary care center in Haryana. *Indian J Endocrinol Metab*. 2017;21(4):577-580.
14. Thangaratinam S, Tan A, Knox E, et al. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ*. 2011;342:1-8.
15. Nazarpour S, Ramezani Tehrani F, Simbar M, et al. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. *Eur J Endocrinol*. 2017;176(2):253-265.
16. Bahri S, Tehrani FR, Amouzgar A, et al. Overtime trend of thyroid hormones and thyroid autoimmunity and ovarian reserve: a longitudinal population study with a 12-year follow up. *BMC Endocr Disord*. 2019;19(1):47.
17. Korevaar TIM, Lidia Mínguez-Alarcón L, Carmen Messerlian C, et al. Association of thyroid function and autoimmunity with ovarian reserve in women seeking infertility care. *Thyroid*. 2018;28(10):1349-1358.
18. Meena M, Chopra S, Jain V, Aggarwal N. The effect of anti-thyroid peroxidase antibodies on pregnancy outcomes in euthyroid women. *J Clin Diagn Res*. 2016;10(9):QC04–QC07.
19. Li J, Shen J, Qin L. Effects of levothyroxine on pregnancy outcomes in women with thyroid dysfunction: a meta-analysis of randomized controlled trials. *Altern Ther Health Med*. 2017;23(2):49-58.
20. Rao M, Zeng Z, Zhao S, Tang L. Effect of levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism and thyroid autoimmunity undergoing in vitro fertilization/intracytoplasmic sperm injection: an updated meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol*. 2018;16(1):92.
21. Kämpe O, Jansson R, Karlsson FA. Effects of L-thyroxine and iodide on the development of autoimmune postpartum thyroiditis. *J Clin Endocrinol Metab*. 1990;70(4):1014-1018.
22. Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147(4):217-223.
23. Negro R, Greco G, Mangieri T, et al. The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies. *J Clin Endocrinol Metab*. 2007;92(4):1263-1268.
24. American College of Obstetricians and Gynecologists. Practice bulletin no. 223: Thyroid disease in pregnancy. *Obstet Gynecol*. 2020;135(6):e261-e274.
25. Stagnaro-Green A, Dong A, Stephenson MD. Universal screening for thyroid disease during pregnancy should be performed. *Best Pract Res Clin Endocrinol Metab*. 2020;34(4):101320.