HHS Public Access

Author manuscript

Am J Obstet Gynecol. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Am J Obstet Gynecol. 2017 December ; 217(6): 697.e1–697.e7. doi:10.1016/j.ajog.2017.09.001.

Thyroid stimulating hormone, anti-thyroid antibodies and pregnancy outcomes

Torie C PLOWDEN, M.D., M.P.H.[1,2], **Enrique F SCHISTERMAN, Ph.D.**[1], **Lindsey A SJAARDA, Ph.D.**[1], **Neil J PERKINS, Ph.D.**[1], **Robert SILVER, M.D.**[3], **Rose RADIN, Ph.D.**[1], **Keewan KIM, Ph.D.**[1], **Noya GALAI, Ph.D.**[4], **Alan H DeCHERNEY, M.D.**[2], and **Sunni L MUMFORD, Ph.D.**[1]

[1]Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, 6100 Executive Blvd, 7B03, Rockville, MD, 20852, United States

[2]Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, 10 Center Drive, Bethesda, MD, 20892, United States

[3]Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Room 2B200 SOM, 50 North Medical Drive, Salt Lake City, UT, 84132, United States

[4]Department of Statistics, University of Haifa, Mt Carmel, Haifa, Israel 31905

Abstract

Background—Overt thyroid dysfunction has been associated with adverse obstetrical outcomes. However, less is known regarding subclinical hypothyroidism or thyroid autoimmunity and their relationship to pregnancy complications.

Objective—To examine the association between pre-pregnancy anti-thyroid antibodies and subclinical hypothyroidism and preterm delivery (PTD), gestational diabetes (GDM), and preeclampsia.

Study Design—Secondary analysis of a prospective cohort of 18–40 year old women with 1–2 prior pregnancy losses (n=1193) participating in a multi-center randomized, placebo-controlled trial of low-dose aspirin. Pre-pregnancy levels of thyroid stimulating hormone (TSH), free thyroxine, thyroglobulin antibody (anti-TG) and thyroid peroxidase antibody (anti-TPO) were measured. Relative risks (RR) and 95% confidence intervals (CIs) were estimated using generalized linear models adjusting for age and body mass index (BMI).

Correspondence to: Sunni L. Mumford, Ph.D., Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, 6710B Rockledge Dr., MSC 7004, Bethesda, MD 20892 USA, mumfords@mail.nih.gov, 1-301-435-6946.

Trial Registration: The trial was registered on clinicaltrials.gov #NCT00467363.

These findings were previously presented in March 2016 at the Society of Reproductive Investigation Annual Meeting in Montreal Quebec and in June 2015 at the Society of Epidemiologic Research Annual Meeting in Denver, Colorado.

The authors report no conflict of interest.

Results—Among women with an ongoing pregnancy of >20 weeks estimated gestational age, there was no association between pre-pregnancy TSH level (>2.5 versus ≤2.5 mIU/L) and PTD (aRR 0.77; 95% CI 0.40, 1.47), GDM (aRR 1.28; 95% CI 0.54, 3.04) or preeclampsia (aRR 1.20; 95% CI 0.71, 2.04). Similarly, among women with thyroid antibodies, there was no increase in the likelihood of PTD (RR 1.26; 95% CI 0.65, 2.45), GDM (RR 1.33; 95% CI 0.51, 3.49) or preeclampsia (RR 1.02; 95% CI 0.54, 1.92), compared to women without these antibodies.

Conclusions—Among women with 1–2 prior pregnancy losses, subclinical hypothyroidism and thyroid autoimmunity were not associated with an increased risk of PTD, GDM, or preeclampsia. These data support current recommendations that low-risk asymptomatic women should not be routinely screened for thyroid dysfunction or autoimmunity.

Keywords

adverse pregnancy outcomes; anti-TG; anti-TPO; gestational diabetes; preeclampsia; preterm delivery; subclinical hypothyroidism; thyroid autoimmunity

INTRODUCTION

Thyroid disease complicates approximately 4% of all pregnancies. [1] Overt hypothyroidism has been linked to various pregnancy complications such as preeclampsia, gestational diabetes (GDM) and preterm delivery (PTD).[2,3] These adverse pregnancy outcomes contribute significant burden on families and the health care system and have important implications for the future health of the child. However, it is unclear whether less severe forms of thyroid disease, specifically, subclinical hypothyroidism (SCH), are also linked to obstetric complications.

Subclinical hypothyroidism is defined as an elevated thyroid stimulating hormone (TSH) with normal thyroxine (fT4),[4] and is the most common form of thyroid dysfunction in pregnancy.[5] Though several studies have evaluated the relationship between SCH in pregnancy and various adverse pregnancy outcomes, results have been conflicting.[5–9] Previous studies have been limited by assessment of thyroid function during early pregnancy, as opposed to preconception, when alterations to TSH can occur secondary to the presence of human chorionic gonadotropin and other hormone changes.[10] Thyroid autoimmunity, characterized by the presence of thyroid auto-antibodies, is also common and has been variably associated with adverse pregnancy outcomes.[5,11] In 2011, the American Thyroid Association recommended a TSH level of <2.5mIU/L as ideal in early pregnancy.[1] None of the studies referenced above, however, examined obstetrical outcomes in women with TSH of <2.5 versus ≥ 2.5 mIU/L. Furthermore, studies evaluating the relationship between preconception thyroid levels and pregnancy outcomes are lacking. Thus, our objective was to determine the association between pre-pregnancy anti-thyroid antibodies, SCH, and adverse obstetrical outcomes including PTD, preeclampsia, and GDM.

MATERIALS AND METHODS

This was a secondary prospective cohort analysis from the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial. The EAGeR trial was a multi-center, double-blind,

randomized, placebo-controlled trial that examined the effect of low dose aspirin on live birth.[12,13] Women (n=1228) with a history of one to two previous pregnancy losses and attempting pregnancy were recruited from four U.S. medical centers 2007–2011. A detailed description of the study design and methods has been described previously.[12] Institutional Review Board (IRB) authorization was obtained at the data coordinating center and at all clinical centers and each participant provided written informed consent. Patient safety was monitored by a Data Safety and Monitoring Board and the trial was registered with ClinicalTrials.gov, number NCT00467363.

Study Design and Population

Participants were women aged 18–40 years, with regular menstrual cycles (21–42 days in length) who were actively attempting to conceive. Although they had a history of one or two confirmed prior pregnancy losses, they did not have diagnosed infertility, pelvic inflammatory disease, tubal occlusion, endometriosis, anovulation, uterine abnormality, or polycystic ovarian syndrome, or any major medical disorder.[12]

Women in the study were followed through six cycles attempting pregnancy. If they did not conceive in six cycles or experienced a second periconception loss during the study, their study participation was discontinued. If they became pregnant, they were followed prospectively throughout the pregnancy and delivery. Fertility monitors (Clearblue Easy Fertility Monitor; Inverness Medical, Waltham, MA) were used to assist with scheduling study visits and timing intercourse.

Thyroid Function Assessment

Preconception TSH, fT4, thyroglobulin antibody (anti-TG), and thyroid peroxidase antibody (anti-TPO) levels were measured in serum collected at a baseline visit prior to conception. Samples were stored at −80°C after collection until the time of assay. TSH was measured via the TSH reagent sandwich immunoassay method (Roche Diagnostics, Indianapolis, IN). The reference range was 0.4 – 5 mIU/L, and the interassay laboratory coefficients of variation (CVs) were 2.1% at 1.596 mIU/L and 2.9% at 9.037 mIU/L. fT4 was measured using a fT4 reagent/competitive immunoassay (Roche Diagnostics, Indianapolis, IN) with a reference range 0.7 – 1.85 ng/dL. Anti-TG levels were measured with a TSH reagent sandwich immunoassay (Roche Diagnostics, Indianapolis, IN) and the interassay CVs were 7.2% at 91.4 IU/mL and 6.7% at 171 IU/mL. Anti-TPO levels were measured using an anti-TPO reagent competitive immunoassay (Roche Diagnostics, Indianapolis, IN) and the interassay CVs were 17% at 31.5 IU/mL and 11.9% at 76.13 IU/mL. Results for anti-TG were considered positive if anti-TG ≥ 115 IU/mL and results were considered positive if anti-TPO ≥ 35 IU/mL, according to the reference ranges at our laboratory.

Outcome Measures

Reproductive, medical, and obstetric history was obtained at baseline via questionnaire and from medical record abstraction. A clinically confirmed pregnancy was defined as evidence of a continuing intrauterine pregnancy on ultrasound at 6–7 weeks' gestation. Gestational age was determined by an ultrasound conducted in early pregnancy (mean 6.9 weeks' gestation) for 97% (697/720) of clinically confirmed pregnancies among women who

completed the trial; for the remaining 3% (23/720) of pregnancies, gestational age was determined using menstrual cycle dating from home-based fertility monitors provided by the study. The dates and details of pregnancy outcomes were assessed by post-partum phone interview and through medical record abstraction by trained research staff.

Primary outcomes for this analysis included PTD, GDM, and preeclampsia. PTD was defined as delivery between 20 weeks and zero days and 36 weeks and six days' gestation. Cases of PTD were prospectively identified during the study and had further review of abstracted medical records by a maternal-fetal medicine physician to vet and categorize the outcome as spontaneous, medically indicated, or a preterm birth of uncertain indication. Spontaneous preterm birth was defined as any preterm birth preceded by spontaneous labor (cervical change or 4 cm or greater cervical dilation in the presence of contractions), preterm premature rupture of membranes, or both. Medically indicated preterm birth was defined as any preterm birth not classified as spontaneous preterm birth for which at least one medical indication for delivery was noted in the medical record. In this cohort of patients, the major indication for medical delivery was preeclampsia. The overall number of patients with medically indicated preterm birth was small (N=28). Of these, 11 (39%) were related to preeclampsia. Other indications included placenta previa/abruption, preterm labor, chorioamnionitis, and non-reassuring fetal heart rate tracing.

The remaining preterm births were categorized as a preterm birth of uncertain indication. Physicians providing prenatal care to patients made a diagnosis of preeclampsia or GDM based on standard clinical and laboratory criteria. Trained EAGeR research staff abstracted these diagnoses from participants' delivery records.

Statistical Analysis

Women with an abnormal fT4 (n=12) or whose fT4 was not recorded (n=23) were excluded. The remaining participants were categorized into two groups based on TSH level: TSH <2.5 or ≥ 2.5 mIU/L. Though subclinical hypothyroidism is most often defined as TSH above the normal range (4.5–5.0 mIU/L) with a normal fT4,[14] the National Academy of Clinical Biochemistry (NACB) found that 95% of patients without any symptoms of thyroid dysfunction actually had a TSH below 2.5 mIU/L. We also evaluated participants for the presence or absence of anti-TG and/or anti-TPO. If women were positive for at least one antibody, they were included in the thyroid autoimmunity group. Descriptive statistics were used to compare characteristics among groups using Fisher's exact test and t-tests where appropriate. Risk ratios (RR) and 95% confidence intervals (CI) for PTD, GDM, and preeclampsia by TSH level (<2.5 or ≥ 2.5 mIU/L) and by thyroid autoimmunity status were estimated using log-binomial regression adjusted for age and body mass index (BMI). We also evaluated pregnancy outcomes in women with thyroid autoimmunity stratified by TSH level.

As pregnancy outcomes are conditional upon becoming pregnant, we restricted our analysis to women who had an ongoing pregnancy > 20 weeks estimated gestational age. As such, we utilized inverse probability weights to control for potential selection bias introduced by restricting the analytical cohort since low-dose aspirin treatment was shown to be associated with the probability of pregnancy among women with a single recent loss [13,15,16]. Of note,

low dose aspirin treatment was not associated with GDM, PTD, or preeclampsia, and we also did not observe associations between thyroid exposures and pregnancy loss or fecundity [17]. Weights were based on factors associated with becoming pregnant, including maternal age, parity, marital status, number of prior losses, and treatment assignment. Weighted log-binomial regression was used to estimate RRs and 95% CIs. When evaluating PTD, we also stratified by indication (spontaneous versus medically-indicated). The number of cases was too low to estimate the RR in some models; therefore, odds ratio (OR) is reported in those instances. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

There were no differences in age, race, and education level in participants with TSH <2.5 compared to those with a TSH ≥ 2.5. Women with a TSH level ≥ 2.5 had a higher BMI and were more often nulliparous compared to women with lower TSH [Table 1]. Women with positive tests for anti-thyroid antibodies were similar in age and BMI compared to those testing negative. Of the 1018 women without thyroid antibodies 962 were non-Hispanic white (94.5%), compared to 98.2% non-Hispanic white among women with thyroid antibodies (p = 0.04). There was no difference in prior number of live births or pregnancies between groups.

Among women who became pregnant during the study with an ongoing pregnancy > 20 weeks, there was no increased risk of PTD (RR 078; 95% CI 0.41, 1.48), GDM (OR 1.27; 95% CI 0.50, 3.20) or preeclampsia (OR 1.16; 95% CI 0.63, 2.15) in women with TSH <2.5 versus those with TSH ≥ 2.5 either before or after adjustment for potential confounders [Table 2]. Similarly, anti-thyroid antibodies also were not associated with any of these adverse obstetric outcomes. We further explored if any differences were noted when stratifying by indication for preterm delivery (spontaneous versus medically-indicated), and found no differences.

We also evaluated obstetric outcomes in the cohort of women with both SCH (TSH ≥ 2.5 mIU/L) and thyroid autoimmunity (n= 45), since this cohort may be at elevated risk. However, the combination of these two assay results was not associated with PTD (OR 0.77; 95% CI 0.19, 3.13), GDM (RR 3.24; 95% CI 0.30, 34.55) or preeclampsia (RR 1.53, 95% CI 0.38, 6.09) [Table 3].

COMMENT

SCH and thyroid antibodies were not associated with adverse pregnancy complications among healthy fecund women with an ongoing pregnancy >20 weeks estimated gestational age. Furthermore, among women with thyroid autoimmunity, there were no differences in PTD, preeclampsia, or GDM even when stratifying by TSH level. These results support current recommendations that low-risk asymptomatic women should not be routinely screened for thyroid dysfunction or autoimmunity.

Previous research on SCH has explored a variety of adverse pregnancy outcomes with inconsistent results. In part this may be due to varied definitions of SCH among studies. Our

results for PTD are in agreement with findings from a recent systematic review and meta-analysis [18] that reported no relationship between PTD and SCH, though an increased risk of PTD was noted among women with overt hypothyroidism in that study.

Though available data regarding SCH and preeclampsia is mixed, our results are consistent with a prior retrospective study and meta-analysis that also showed no difference in rates of preeclampsia [6] or gestational hypertension in relation to SCH.[5] Though an association between SCH and severe preeclampsia (but not gestational hypertension or mild/moderate preeclampsia) was reported in one large study, it is of note that SCH was defined as TSH > 4.13; [8] as such the results are not directly comparable to our study. Our findings also differ from those of a large Chinese cohort that observed a link between SCH and gestational hypertension.[7] However, their results were not adjusted for BMI which may have confounded their findings and they did not examine preeclampsia as an outcome[7]. In contrast, overt hypothyroidism has been associated with severe preeclampsia [19–21], and adverse cardiovascular effects,[20,22,23] which in turn may be associated with vascular-related pregnancy complications.

Our findings are also in agreement with several investigations of SCH and GDM. Many groups found no association between SCH and GDM, including two recent cohort studies.[7,9] A meta-analysis examining SCH and pregnancy outcomes also did not detect a link between GDM and SCH (OR 1.38; 95% CI 0.97, 1.96).[5] Here, we extend these findings confirming no relationship between SCH and GDM, even with thyroid function measured prior to pregnancy.

Studies regarding thyroid autoimmunity and pregnancy complications also have yielded mixed results. In this study, we found no difference in PTD, GDM, or preeclampsia among women with thyroid autoimmunity, even among those with an additional finding of subclinical hypothyroidism. Our results are consistent with several groups who also found no relationship between thyroid antibodies and GDM and preeclampsia; however, these studies found a positive relationship between these antibodies and PTD [11,24–26] which is in contrast to our study. Of note, in one of these studies an association was only observed with the outcome of very preterm birth (<34 weeks) and no adjustments for potential confounders were made.[25] However, anti-TPO positivity was associated with PTD in other studies, including a recent meta-analysis, that adjusted for relevant confounding factors[11,24,26] though some of the prior studies assessed for the presence of only TPO antibodies or used differing definitions of positive antibody status. These differences in study design may account for some of the differences in findings among studies.

This study has several strengths. First, the original trial was prospective, allowing for preconception assessment of fT4, TSH and thyroid antibody levels, and thus the assessment of thyroid function was not affected by changes in thyroid function during pregnancy. An important difference between previous work and the current study is our assessment of thyroid function prior to pregnancy. As thyroid function is known to change during early pregnancy, this could have important implications for interpreting these findings.[10] Furthermore, we were able to evaluate the clinical utility of using a cut point of a TSH ≥ 2.5 mIU/L. Our results extend previous work by utilizing preconception measurements and

exploring the association with a more strict and more common definition of SCH. We were also able to adjust for potential confounders in our analyses. Moreover, all outcomes were assessed prospectively and our population was comprised of young, healthy women with a history of pregnancy loss. As such, these results are generalizable to a large population of women. Additionally, the original trial had a high compliance rate, with the majority of women completing study follow-up (88%). There are some limitations to our study as well. We had a small number of adverse outcomes making our ability to detect small differences somewhat limited. Additionally, the majority of this population consisted of Caucasian, middle-class, well-educated women, which may limit generalizability.

In conclusion, we found no relationship between PTD, GDM, or preeclampsia and preconception SCH and thyroid autoimmunity, defined as presence of either anti-TPO or anti-TG antibodies, among women with proven fecundity. To date, the American College of Obstetricians and Gynecologist does not recommend screening of TSH or anti-thyroid antibodies in low risk, asymptomatic patients, and our data support this guideline. These findings can offer reassurance to women with subclinical hypothyroidism or thyroid autoimmunity and their healthcare providers.

Acknowledgments

We would like to especially thank the EAGeR study participants for their extraordinary commitment to the study.

Financial Support: Intramural Research Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland (Contract Nos. HHSN267200603423, HHSN267200603424, HHSN267200603426). The funding source had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

References

1. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011; 21(10):1081–1125. [PubMed: 21787128]
2. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010; 31(5):702–755. [PubMed: 20573783]
3. Mannisto T, Mendola P, Grewal J, Xie Y, Chen Z, Laughon SK. Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. J Clin Endocrinol Metab. 2013; 98(7):2725–2733. [PubMed: 23744409]
4. Practice Committee of the American Society for Reproductive Medicine. Electronic address Aao. Subclinical hypothyroidism in the infertile female population: a guideline. Fertil Steril. 2015; 104(3):545–553. [PubMed: 26239023]
5. Chan S, Boelaert K. Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. Clin Endocrinol (Oxf). 2015; 82(3):313–326. [PubMed: 25200555]
6. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol. 2005; 105(2):239–245. [PubMed: 15684146]
7. Chen LM, Du WJ, Dai J, et al. Effects of subclinical hypothyroidism on maternal and perinatal outcomes during pregnancy: a single-center cohort study of a Chinese population. PLoS One. 2014; 9(10):e109364. [PubMed: 25353960]
8. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical thyroid disease and the incidence of hypertension in pregnancy. Obstet Gynecol. 2012; 119(2 Pt 1):315–320. [PubMed: 22270283]

9. Tudela CM, Casey BM, McIntire DD, Cunningham FG. Relationship of subclinical thyroid disease to the incidence of gestational diabetes. Obstet Gynecol. 2012; 119(5):983–988. [PubMed: 22525909]
10. Fantz CR, Dagogo-Jack S, Ladenson JH, Gronowski AM. Thyroid function during pregnancy. Clin Chem. 1999; 45(12):2250–2258. [PubMed: 10585360]
11. He X, Wang P, Wang Z, He X, Xu D, Wang B. Thyroid antibodies and risk of preterm delivery: a meta-analysis of prospective cohort studies. Eur J Endocrinol. 2012; 167(4):455–464. [PubMed: 22826476]
12. Schisterman EF, Silver RM, Perkins NJ, et al. A randomised trial to evaluate the effects of low-dose aspirin in gestation and reproduction: design and baseline characteristics. Paediatr Perinat Epidemiol. 2013; 27(6):598–609. [PubMed: 24118062]
13. Schisterman EF, Silver RM, Lesher LL, et al. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. Lancet. 2014; 384(9937):29–36. [PubMed: 24702835]
14. Practice Committee of the American Society for Reproductive M. Subclinical hypothyroidism in the infertile female population: a guideline. Fertil Steril. 2015; 104(3):545–553. [PubMed: 26239023]
15. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004; 15(5):615–625. [PubMed: 15308962]
16. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000; 11(5):550–560. [PubMed: 10955408]
17. Plowden TC, Schisterman EF, Sjaarda LA, et al. Subclinical Hypothyroidism and Thyroid Autoimmunity Are Not Associated With Fecundity, Pregnancy Loss, or Live Birth. J Clin Endocrinol Metab. 2016; 101(6):2358–2365. [PubMed: 27023447]
18. Sheehan PM, Nankervis A, Araujo Junior E, Da Silva Costa F. Maternal Thyroid Disease and Preterm Birth: Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2015; 100(11): 4325–4331. [PubMed: 26383905]
19. Patel S, Robinson S, Bidgood RJ, Edmonds CJ. A pre-eclamptic-like syndrome associated with hypothyroidism during pregnancy. Q J Med. 1991; 79(289):435–441. [PubMed: 1924678]
20. Alfadda A, Tamilia M. Preeclampsia-like syndrome that is associated with severe hypothyroidism in a 20-week pregnant woman. Am J Obstet Gynecol. 2004; 191(5):1723–1724. [PubMed: 15547551]
21. Inversetti A, Serafini A, Manzoni MF, Dolcetta Capuzzo A, Valsecchi L, Candiani M. Severe hypothyroidism causing pre-eclampsia-like syndrome. Case Rep Endocrinol. 2012; 2012:586056. [PubMed: 22937297]
22. Stabouli S, Papakatsika S, Kotsis V. Hypothyroidism and hypertension. Expert Rev Cardiovasc Ther. 2010; 8(11):1559–1565. [PubMed: 21090931]
23. Kotsis V, Alevizaki M, Stabouli S, et al. Hypertension and hypothyroidism: results from an ambulatory blood pressure monitoring study. J Hypertens. 2007; 25(5):993–999. [PubMed: 17414663]
24. Kumru P, Erdogdu E, Arisoy R, et al. Effect of thyroid dysfunction and autoimmunity on pregnancy outcomes in low risk population. Arch Gynecol Obstet. 2015; 291(5):1047–1054. [PubMed: 25388918]
25. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. J Clin Endocrinol Metab. 2011; 96(6):E920–924. [PubMed: 21411559]
26. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab. 2013; 98(11):4382–4390. [PubMed: 24037884]

Am J Obstet Gynecol. Author manuscript; available in PMC 2018 December 01.

Table 1

Demographics and baseline characteristics by TSH level and thyroid autoimmunity among women with normal fT4 (0.7 to 1.85 ng/dL)

Characteristics N (%)		TSH			Anti-thyroid antibodies (presence of anti-TPO or anti-TG antibodies)		
	Total	<2.5 mIU/L n=884	≥2.5 mIU/L n=303	P value	Negative n=1018	Positive n=168	P value
Age, y	28.7 ± 4.8	28.8 ± 4.8	28.5 ± 4.7	0.37	28.7 ± 4.8	28.8 ± 4.7	0.86
BMI, kg/m^2	26.3 ± 6.5	25.9 ± 6.2	27.4 ± 7.3	0.001	26.1 ± 6.3	27.1 ± 7.4	0.08
Race							
White	1126 (94.9)	835 (94.5)	291 (96)	0.28	962 (94.5)	165 (98.2)	0.04
Others	61 (5.1)	49 (5.5)	12 (4)		56 (5.5)	3 (1.8)	
Education *							
≤ High School	160 (13.5)	122 (13.8)	38 (12.5)	0.58	144 (14.2)	16 (9.5)	0.10
> High School	1026 (86.5)	761 (86.2)	265 (87.5)		873 (85.8)	152 (90.5)	
Household income (annual) *							
≥ $100,000	474 (40)	348 (39.4)	126 (41.6)	0.77	398 (39.1)	72 (42.9)	0.30
$75,000–$99,999	144 (12.1)	110 (12.5)	34 (11.2)		124 (12.2)	21 (12.5)	
$40,000–$74,999	175 (14.8)	136 (15.4)	39 (12.9)		155 (15.2)	21 (12.5)	
$20,000–$39,999	302 (25.5)	221 (25)	81 (26.7)		267 (26.3)	36 (21.4)	
≤ $19,999	91 (7.7)	68 (7.7)	23 (7.6)		73 (7.2)	18 (10.7)	
Employed *							
Yes	868 (75.7)	632 (74.4)	236 (79.7)	0.06	741 (75.5)	125 (76.2)	0.85
No	278 (24.3)	218 (25.6)	60 (20.3)		240 (24.5)	39 (23.8)	
Time from last loss to randomization (months) *							
≤ 4 Months	629 (53.8)	460 (52.8)	169 (56.9)	0.49	544 (54.2)	87 (53)	0.31
5–8 Months	214 (18.3)	163 (18.7)	51 (17.2)		179 (17.8)	35 (21.3)	
9–12 Months	96 (8.2)	70 (8)	26 (8.8)		80 (8)	17 (10.4)	
>12 Months	230 (19.7)	179 (20.5)	51 (17.2)		201 (20)	25 (15.2)	
Number of previous pregnancies, not including losses							
0	506 (42.6)	363 (41.1)	143 (47.2)	0.12	429 (42.1)	76 (45.2)	0.76
1	421 (35.5)	315 (35.6)	106 (35)		364 (35.8)	57 (33.9)	
2	239 (20.1)	191 (21.6)	48 (15.8)		208 (20.4)	31 (18.5)	

Characteristics N (%)		TSH			Anti-thyroid antibodies (presence of anti-TPO or anti-TG antibodies)		
	Total	<2.5 mIU/L n=884	≥2.5 mIU/L n=303	P value	Negative n=1018	Positive n=168	P value
3	21 (1.8)	15 (1.7)	6 (2)		17 (1.7)	4 (2.4)	
Number of previous live births							
0	550 (46.3)	392 (44.3)	158 (52.1)	0.01	463 (45.5)	86 (51.2)	0.36
1	430 (36.2)	321 (36.3)	109 (36)		374 (36.7)	57 (33.9)	
2	207 (17.4)	171 (19.3)	36 (11.9)		181 (17.8)	25 (14.9)	
Smoking in past year*							
Never	1033 (87.8)	764 (87.1)	269 (89.7)	0.46	880 (87)	153 (92.7)	0.08
<6 times/week	83 (7.1)	64 (7.3)	19 (6.3)		76 (7.5)	5 (3)	
Daily	61 (5.2)	49 (5.6)	12 (4)		55 (5.4)	7 (4.2)	
Alcohol consumption in past year*							
Often	26 (2.2)	16 (1.8)	10 (3.3)	0.13	21 (2.1)	5 (3)	0.22
Sometimes	369 (31.5)	285 (32.7)	84 (28)		325 (32.3)	43 (25.9)	
Never	777 (66.3)	571 (65.5)	206 (68.7)		659 (65.6)	118 (71.1)	

BMI, body mass index; fT4, free thyroxine; TSH, thyroid stimulating hormone.

Values are mean ± standard deviation or n (%) as indicated.

*Data on covariates were missing for education (n=1), income (n=1), employment (n=41), time from last loss to randomization (n=18), smoking (n=10), and alcohol (n=15)

Table 2

Pregnancy outcomes by TSH levels and presence of anti-thyroid antibodies among women with normal fT4 (0.7 to 1.85 ng/dL)

	Model	TSH (TSH ≥ 2.5 mIU/L versus < 2.5 mIU/L)	Anti-thyroid antibodies (Positive versus negative)
		Among Pregnancies (>20 weeks) RR (95% CI)	Among Pregnancies (>20 weeks) RR (95% CI)
Preterm Delivery (n =51)	Unadjusted	0.76 (0.40, 1.45)	1.29 (0.67, 2.48)
	Adjusted	0.78 (0.41, 1.48)	1.28 (0.66, 2.48)
Spontaneous Preterm Delivery (n =18)	Unadjusted	0.54 (0.15, 1.92)	0.31 (0.04, 2.44)
	Adjusted	0.59 (0.17, 2.10)	0.34 (0.04, 2.71)
Medically Indicated Preterm Delivery (n =28)	Unadjusted	0.90 (0.39, 2.08)	2.05 (0.93, 4.51)
	Adjusted	0.89 (0.39, 2.05)	1.90 (0.86, 4.19)
Gestational Diabetes (n =22)	Unadjusted	1.41 (0.59, 3.37)	1.63 (0.62, 4.28)
	Adjusted[+]	1.27 (0.50, 3.20)	1.32 (0.46, 3.77)
Pre-eclampsia (n =57)	Unadjusted	1.26 (0.74, 2.14)	1.19 (0.63, 2.26)
	Adjusted[+]	1.16 (0.63, 2.15)	1.00 (0.47, 2.09)

Adjusted for age and BMI

Models restricted to women who had an ongoing pregnancy >20 weeks, with inverse probability weights used to control for potential selection bias introduced by restricting to women who achieved pregnancy. Weights were based on factors associated with becoming pregnancy, including age, parity, marital status, number of prior losses and treatment assignment. Weighted log-binomial regression was used to estimate risk ratios and 95% confidence intervals.

[+]Odds Ratio used when relative risks would not converge

Table 3

Association between thyroid autoimmunity and pregnancy outcomes among women with elevated TSH (≥ 2.5 mIU/L)

		Anti-thyroid antibodies among women with TSH ≥ 2.5 mIU/L (Positive versus negative)	
	Model	**Overall**	**++ Among Pregnancies (>20 weeks)**
Preterm Delivery (n = 10)	Unadjusted	0.96 (0.30, 3.07)	0.99 (0.31, 3.24)
	Adjusted+	0.73 (0.18, 2.96)	0.77 (0.19, 3.13)
Medically Indicated Preterm Delivery (n = 8)	Unadjusted	0.69 (0.17, 2.80)	0.61 (0.15, 2.39)
	Adjusted	0.61 (0.15, 2.50)	0.45 (0.11, 1.92)
Gestational Diabetes (n = 5)	Unadjusted	4.00 (0.46, 34.66)	4.24 (0.47, 38.57)
	Adjusted+	3.06 (0.31, 30.57)	3.24 (0.30, 34.55)
Pre-eclampsia (n = 10)	Unadjusted	1.50 (0.45, 5.02)	1.56 (0.47, 5.15)
	Adjusted+	1.44 (0.37, 5.59)	1.53 (0.38, 6.09)

+Odds Ratio

++Models restricted to women who had an ongoing pregnancy >20 weeks, with inverse probability weights used to control for potential selection bias introduced by restricting to women who achieved pregnancy. Weights were based on factors associated with becoming pregnancy, including age, parity, marital status, number of prior losses and treatment assignment. Weighted log-binomial regression was used to estimate risk ratios and 95% confidence intervals.

Note: there was only 1 spontaneous preterm delivery among women with positive anti-thyroid antibodies.