OBSTETRICS

Thyroid-stimulating hormone, anti—thyroid antibodies, and pregnancy outcomes

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

OBJECTIVE: The purpose of this study was to examine the association between prepregnancy anti—thyroid antibodies and subclinical hypothyroidism and preterm delivery, gestational diabetes mellitus, and preeclampsia.

STUDY DESIGN: We conducted a secondary analysis of a prospective cohort of 18- to 40-year-old women with 1—2 previous pregnancy losses (n=1193) who participated in a multicenter randomized, placebo-controlled trial of low-dose aspirin. Prepregnancy levels of thyroid-stimulating hormone, free thyroxine, thyroglobulin antibody, and thyroid peroxidase antibody were measured. Relative risks and 95% confidence intervals were estimated with the use of generalized linear models with adjustment for age and body mass index.

RESULTS: Among women with an ongoing pregnancy of >20 weeks estimated gestational age, there was no association between prepregnancy thyroid-stimulating hormone level (>2.5 vs ≤2.5 mIU/L) and preterm delivery (adjusted relative risk, 0.77; 95% confidence interval, 0.40—1.47), gestational diabetes mellitus (adjusted relative risk, 1.28; 95% confidence interval, 0.54—3.04), or preeclampsia (adjusted relative risk, 1.20; 95% confidence interval, 0.71—2.04). Similarly, among women with thyroid antibodies, there was no increase in the likelihood of preterm delivery (relative risk, 1.26; 95% confidence interval, 0.65—2.45), gestational diabetes mellitus (relative risk, 1.33; 95% confidence interval, 0.51—3.49), or preeclampsia (relative risk, 1.02; 95% confidence interval, 0.54—1.92), compared with women without these antibodies.

CONCLUSION: Among women with 1—2 previous pregnancy losses, subclinical hypothyroidism and thyroid autoimmunity were not associated with an increased risk of preterm delivery, gestational diabetes mellitus, or preeclampsia. These data support current recommendations that low-risk asymptomatic women should not be screened routinely for thyroid dysfunction or autoimmunity.

Key words: adverse pregnancy outcome, anti-TG, anti-TPO, gestational diabetes mellitus, preeclampsia, preterm delivery, subclinical hypothyroidism, thyroid autoimmunity

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 a significant burden on families and the healthcare 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.

SCH is defined as an elevated thyroid-stimulating hormone (TSH) level with normal thyroxine (fT4)[4] and is the most common form of thyroid dysfunction in pregnancy.[5] Although 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 the assessment of thyroid function during early pregnancy, as opposed to preconception when alterations to TSH can occur as the result of the presence of human chorionic gonadotropin and other hormone changes.[10] Thyroid autoimmunity, which is characterized by the presence of thyroid autoantibodies, is also common and has been associated variably with adverse pregnancy outcomes.[5,11] In 2011, the American Thyroid Association recommended a TSH level of <2.5 mIU/L to be the ideal in early pregnancy.[1] None of the studies referenced earlier, however, examined obstetric outcomes in women with TSH of <2.5 vs ≥2.5 mIU/L. Furthermore, studies that evaluate the relationship between preconception thyroid levels and pregnancy outcomes are lacking. Thus, our objective was to determine the association between prepregnancy anti—thyroid antibodies, SCH, and adverse obstetric outcomes that included 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 multicenter, 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 1—2 previous pregnancy losses who were attempting pregnancy were recruited from 4 US medical centers from 2007—2011. A detailed description of the study design and methods has been published.[12] Institutional Review Board authorization was obtained at the data coordinating center and at all clinical centers; each participant

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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 who were 18−40 years old with regular menstrual cycles (21−42 days in length) who were actively attempting to conceive. Although they had a history of 1−2 confirmed pregnancy losses, they did not have diagnosed infertility, pelvic inflammatory disease, tubal occlusion, endometriosis, anovulation, uterine abnormality, polycystic ovarian syndrome, or any major medical disorder.[12]

Women in the study were observed through 6 cycles attempting pregnancy. If they did not conceive in 6 cycles or experienced a second periconception loss during the study, their study participation was discontinued. If they became pregnant, they were observed prospectively throughout the pregnancy and delivery. Fertility monitors (Clearblue Easy Fertility Monitor; Inverness Medical, Waltham, MA) were used to assist with the scheduling of study visits and timing of intercourse.

Thyroid function assessment

Preconception TSH, fT4, thyroglobulin antibody (anti-TG), and thyroid peroxidase antibody (anti-TPO) levels were measured in serum that was collected at a baseline visit before conception. Samples were stored at −80°C after collection until the time of assay. TSH was measured by 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 were 2.1% at 1.596 mIU/L and 2.9% at 9.037 mIU/L. FT4 level was measured with the use of an fT4 reagent/competitive immunoassay (Roche Diagnostics), with a reference range of 0.7−1.85 ng/dL. Anti-TG antibody levels were measured with a TSH reagent sandwich immunoassay (Roche Diagnostics); the interassay coefficients of variations were 7.2% at 91.4 IU/mL and 6.7% at 171 IU/mL. Anti-TPO levels were measured with an anti-TPO reagent competitive immunoassay (Roche Diagnostics); the interassay coefficients of variations were 17% at 31.5 IU/mL and 11.9% at 76.13 IU/mL. Results for anti-TG antibody were considered positive if the anti-TG level was ≥115 IU/mL; results were considered positive if the anti-TPO level was ≥35 IU/mL, according to the reference ranges at our laboratory.

Outcome measures

Reproductive, medical, and obstetric histories were obtained at baseline by questionnaire and from medical record abstraction. A clinically confirmed pregnancy was defined as evidence of a continuing intrauterine pregnancy with ultrasound examination at 6−7 weeks gestation. Gestational age was determined by an ultrasound examination that was conducted in early pregnancy (mean, 6.9 weeks gestation) for 97% of clinically confirmed pregnancies (697/720) among women who completed the trial; for the remaining 3% of pregnancies(23/720), gestational age was determined with the use of menstrual cycle dating from home-based fertility monitors that had been provided by the study. The dates and details of pregnancy outcomes were assessed by postpartum 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 zero days and 36 weeks 6 days gestation. Cases of PTD were identified prospectively during the study and underwent 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 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 1 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 cases (39%) were related to preeclampsia. Other indications included placenta previa/abruption, preterm labor, chorioamnionitis, and nonreassuring fetal heart rate tracing.

The remaining preterm births were categorized as preterm birth of uncertain indication. Physicians who provided 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 level (n=12) or whose fT4 level was not recorded (n=23) were excluded. The remaining participants were categorized into 2 groups based on TSH level: TSH <2.5 or ≥2.5 mIU/L. Although SCH is defined most often as TSH above the normal range (4.5−5.0 mIU/L) with a normal fT4 level,[14] the National Academy of Clinical Biochemistry found that 95% of patients without any symptoms of thyroid dysfunction actually had a TSH level <2.5 mIU/L. We also evaluated participants for the presence or absence of anti-TG and/or anti-TPO antibody. If women were positive for at least 1 antibody, they were included in the thyroid autoimmunity group. Descriptive statistics were used to compare characteristics between groups with the use of 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 with the use of log-binomial regression that was adjusted for age and body mass index. We also evaluated pregnancy outcomes in women with thyroid autoimmunity that was stratified by TSH level.

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