Maternal antithyroid antibodies and euploid miscarriage in women with recurrent early pregnancy loss

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Objective: To determine whether an association exists between maternal antithyroid antibodies and euploid miscarriage in women with recurrent early pregnancy loss (REPL).
Design: Observational cohort study.
Setting: Two academic medical centers.
Patient(s): Women seen between 2004-2015 with a history of REPL, who were euthyroid or had subclinical hypothyroidism, had maternal antithyroid antibody testing and had at least one subsequent early pregnancy loss (<10 weeks' gestation).
Intervention(s): Thyroid function and antibodies were measured at consultation. Subsequent miscarriages were assessed by conventional cytogenetic analysis, and when indicated, microsatellite analysis and/or comparative genomic hybridization/single nucleotide polymorphisms were performed.
Main Outcome Measure(s): Determine whether maternal antithyroid antibodies are associated with euploid miscarriage.
Result(s): Cohort consisted of 74 subjects with REPL who had 130 subsequent early pregnancy losses. The prevalence of maternal antithyroid antibodies in the cohort was 17.6%. Mean TSH was significantly higher among subjects with maternal antithyroid antibodies. Otherwise, no significant differences in demographics were noted. When comparing types of early pregnancy losses between the two groups, a trend toward having more miscarriages than nonvisualized pregnancy losses was noted among subjects with maternal antithyroid antibodies (70% and 30%) compared with subjects without maternal antithyroid antibodies (55% and 43%). No significant difference was noted in the frequency of euploid miscarriage between subjects with and without maternal antithyroid antibodies (42% vs. 56%).
Conclusion(s): Our study did not demonstrate an association between euploid miscarriage and maternal antithyroid antibodies in subjects with a history of REPL. Therefore, testing or treatment in this cohort may not be warranted. (Fertil Steril® 2018;110:452–8. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Recurrent pregnancy loss, antithyroid antibodies, euploid miscarriage

Of reproductive aged couples 1%–5% are affected by recurrent pregnancy loss (RPL) (1, 2). Recurrent pregnancy loss is a multifactorial condition that is characterized by repeated pregnancy demise. It is a disorder that is physically, mentally, and emotionally challenging. Recurrent early pregnancy loss (REPL) is more strictly defined as two or more pregnancy losses of <10 weeks' gestation (3).

It is important to acknowledge that chromosome errors, such as trisomy, monosomy, polyploidy, and unbalanced translocations, are responsible for 50%–70% of miscarriages that occur before 10 weeks of gestation (4, 5). If a miscarriage is found to be due to a random chromosome error, it is an "explained" miscarriage, and it does not increase a woman's likelihood of a subsequent miscarriage beyond her age-related risk (6).

However, once a woman has a history of two "unexplained" miscarriages, she and her partner should be evaluated for factors associated with REPL. According to the American Society for Reproductive Medicine's guidelines from 2012, the standard evaluation consists of screening for a maternal or paternal translocation, structural uterine factors, antiphospholipid syndrome, diabetes mellitus, PRL abnormalities,

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and thyroid disorders (7). In addition, performing an endometrial biopsy to test for chronic endometritis and treating those who are positive with antibiotics has been supported in recent literature (8, 9). After evaluation, 60% of couples with REPL will have at least one or more factors identified (10).

Normal physiologic changes during early pregnancy, such as increased plasma blood volume, decreased iodine concentrations, and increased production of thyroid-binding globulin, which binds circulating thyroid hormones, all lead to an amplified demand placed on the thyroid during pregnancy to increase the production of thyroid hormones (11, 12). Inability to meet this increased demand is thought to be problematic. In their most recent practice bulletin on thyroid disease in pregnancy, the American College of Obstetrics and Gynecology characterized overt hypothyroidism as an elevated TSH and low circulating thyroid hormones (free T_4) (13). Effects of overt hypothyroidism include increased risk of miscarriage, low birthweight, premature delivery, placental abruption, hypertensive disorders of pregnancy, and lower intelligence quotient scores (14–17). Due to these adverse outcomes, there is a strong consensus to treat women with overt hypothyroidism with levothyroxine (14, 15, 17, 18).

Whether to treat women with subclinical hypothyroidism (SCH), defined by the American College of Obstetrics and Gynecology as an elevated TSH with normal levels of circulating thyroid hormones (13), is controversial. In a systematic review, Vissenberg et al. (14) concluded that there is not enough evidence to state that the treatment of SCH improves pregnancy outcomes. Bernardi et al. (15) and Van Dijki et al. (16) independently reported there was no significant difference in subsequent pregnancy outcomes in a cohort of women with a history of RPL when comparing those with and without subclinical hypothyroidism.

The effects of maternal antithyroid antibodies, namely antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG), and their association with REPL are also not clear. According to the recent American Thyroid Association (ATA) guideline from 2017, the literature supports an association between sporadic pregnancy loss and women who are positive for maternal antithyroid antibodies. However, the ATA reports that an association between maternal thyroid antibodies and REPL in euthyroid women is controversial, based on the literature that is currently available (17). We hypothesize that if there is an association between maternal antithyroid antibodies and REPL, the frequency of euploid miscarriage should be increased in women with maternal antithyroid antibodies. Therefore, the objective of this study was to evaluate whether maternal antithyroid antibodies are associated with euploid miscarriage in women with a history of REPL.

MATERIALS AND METHODS

Patients

Institutional Review Board approval was obtained from the University of Chicago to prospectively collect data and tissue from women and their partners seen in the University of Illinois at Chicago Recurrent Pregnancy Loss Program from July 2004 to December 2011 for future research. All of the women gave written informed consent. In addition, Institutional Review Board approval was obtained from the University of Illinois at Chicago to retrospectively review charts from women seen in the University of Illinois at Chicago Recurrent Pregnancy Loss Program from 2013 to 2015.

Women were identified from a previously published cohort by Bernardi et al. (15) consisting of women with a history of REPL who were euthyroid or had subclinical hypothyroidism. Additional women seen between July 2013 and September 2015 in the University of Illinois at Chicago Recurrent Pregnancy Loss Program were also included.

Criteria for Inclusion and Abnormal Test Results

Inclusion criteria consisted of a history of REPL, defined as two or more unexplained pregnancy losses of <10 weeks of gestation. Women who were euthyroid (TSH, 0.3–2.5 mIU/L) or had subclinical hypothyroidism (TSH, >2.5 mIU/L, with normal free T_4 or free T_4 index) (15) and had serum testing for anti-TPO and/or anti-Tg antibodies at the time of their REPL evaluation were included. Presence of maternal antithyroid antibodies was defined as anti-TPO antibodies >4 IU/mL or anti-Tg antibodies >9 IU/mL. In addition, a woman must have had at least one subsequent miscarriage of <10 weeks of gestation that was monitored in one of the RPL programs.

Management Strategy

Each subject underwent a diagnostic screening protocol, which was previously described by Bernardi et al. (15) to assess for concomitant factors associated with REPL. In the screening protocol were genetic, endocrine, anatomical, autoimmune, and infectious factors. For each REPL factor identified, the current and highest level of evidence was discussed with the patient along with the risks and benefits of each proposed treatment.

A subsequent pregnancy was confirmed with a serum β-hCG (≥ 5 mIU/mL) drawn 1–2 days after missed menses. The serum β-hCG was redrawn 1 week later and then all subjects were scheduled for a transvaginal ultrasound, which was performed at approximately 6 weeks of gestation. All subjects were offered close monitoring and supportive care during the first trimester (every 1–2 weeks), which consisted of transvaginal ultrasounds and in-office visits with their provider, who was the senior author. At the end of the first trimester, ongoing obstetric care was transferred to the provider of their choice or a maternal fetal medicine subspecialist if warranted. Pregnancy outcomes were obtained from the subject's provider and/or hospital records.

Conventional cytogenetic analysis with Giemsa banding was performed at the time of miscarriage in a subsequent monitored pregnancy. With a 46,XX result, microsatellite analysis or comparative genomic hybridization/single nucleotide polymorphisms was performed to assess for maternal cell contamination (19).

Definitions

At time of initial consultation, prior documented pregnancies required a positive urinary or serum β-hCG and/or ultrasound