Preconceptional antithyroid peroxidase antibodies, but not thyroid-stimulating hormone, are associated with decreased live birth rates in infertile women

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Objective: To study whether preconceptual thyroid-stimulating hormone (TSH) and antithyroid peroxidase (TPO) antibodies are associated with poor reproductive outcomes in infertile women.

Design: Secondary analysis of data from two multicenter, randomized, controlled trials conducted by the Reproductive Medicine Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. Multivariable logistic regression analyses were performed to assess the association between preconceptual TSH levels and anti-TPO antibodies.

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Setting: Not applicable.
Patient(s): Serum samples from 1,468 infertile women were utilized.
Intervention(s): None.
Main Outcome Measure(s): Cumulative conception, clinical pregnancy, miscarriage, and live birth rates were calculated.
Result(s): Conception, clinical pregnancy, miscarriage, and live birth rates did not differ between patients with TSH $\geq$2.5 mIU/L vs. TSH $<$ 2.5 mIU/L. Women with anti-TPO antibodies had similar conception rates (33.3% vs. 36.3%) but higher miscarriage rates (43.9% vs. 25.3%) and lower live birth rates (17.1% vs. 25.4%) than those without anti-TPO antibodies. Adjusted, multivariable logistic regression models confirmed elevated odds of miscarriage (odds ratio 2.17, 95% confidence interval 1.12–4.22) and lower odds of live birth (oddr ratio 0.58, 95% confidence interval 0.35–0.96) in patients with anti-TPO antibodies.
Conclusion(s): In infertile women, preconceptional TSH $\geq$2.5 mIU/L is not associated with adverse reproductive outcomes; however, anti-TPO antibodies are associated with increased risk of miscarriage and decreased probability of live birth.
Clinical Trial Registration Number: PPCOS II NCT00719186; AMIGOS NCT01044862. (Fertil Steril® 2017;108:843–50. ©2017 by American Society for Reproductive Medicine.)
Key Words: Antibodies, autoimmunity, infertility, pregnancy, spontaneous abortion, thyroid

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Elevations in thyroid-stimulating hormone (TSH) and the presence of anti–thyroid peroxidase (TPO) antibodies during pregnancy have been associated with miscarriage, preterm birth, and adverse perinatal outcomes (1). Therefore, in infertile women, thyroid supplementation is commonly prescribed to keep TSH levels to $<$2.5 mIU/L, in accordance with recommendations made in 2012 by the Endocrine Society (2). However, evidence supporting the relationship between TSH levels or anti-TPO antibodies and pregnancy-related outcomes of conception, miscarriage, and live birth in infertile women is lacking.

Thyroid hormones seem to play an important role in implantation and early pregnancy (3, 4). Thyroid dysfunction in the form of hypothyroidism affects 4.6% of the US population (5). Subclinical hypothyroidism, defined as a TSH level above the 97.5th percentile for gestational age and a free T_4 level within normal limits, has been found in 2.3% of pregnant women (6, 7) and is associated with an increased risk of subfertility and adverse perinatal outcomes (1, 2), including gestational complications, placental abruption, preterm birth (2, 7), and miscarriage (3, 4). Thyroid autoimmunity, the most common cause of hypothyroidism, has also been independently associated with adverse reproductive outcomes. Moreover, in euthyroid women with TSH levels $<$2.5 mIU/L, antithyroid antibodies have been associated with preterm delivery (5, 8, 9) and miscarriage (6, 7, 10).

In 2012 the Endocrine Society recommended evaluation of thyroid function in infertile women before pregnancy. Treatment with thyroid supplementation was advised to achieve a TSH level $<$2.5 mIU/L (1, 2). Thyroid autoimmunity was not included as a criterion for thyroid supplementation in these recommendations. These recommendations were based on the findings of a large study in early pregnancy, which showed that anti-TPO antibody–negative women with first-trimester TSH levels $>$2.5 mIU/L but $<$5.0 mIU/L had a higher miscarriage rate as compared with women with TSH levels $<$2.5 mIU/L (3). Women in this study were not infertile and conceived without treatment. Evaluation of thyroid function was performed in early pregnancy, rather than before conception. Despite these nuances, preconceptional screening of infertile women for thyroid dysfunction and treatment of subclinical hypothyroidism with thyroid supplementation was recommended (2). However, in infertile women, the role of preconceptional TSH levels of 2.5–5 mIU/L and anti-TPO antibodies on fertility and pregnancy outcomes in an infertile population is unknown. Current American College of Obstetricians and Gynecologists recommendations do not advise universal screening in pregnancy for either thyroid function or antithyroid antibodies (11), and recent American Society for Reproductive Medicine guidelines (12) question the relationship of TSH levels to infertility and miscarriage. While acknowledging the low quality of existing evidence, the American Thyroid Association recommends that thyroid supplementation be considered in women with subclinical hypothyroidism or TPO antibodies undergoing assisted reproductive technology (13).

To help address this clinical question, we sought to investigate the impact of preconceptional elevated TSH levels and presence of anti-TPO antibodies on reproductive success in infertile women. We hypothesized that in infertile women, preconceptional TSH levels $\geq$ 2.5 mIU/L would be associated with lower conception and live birth rates and that the presence of preconceptional anti-TPO antibodies would be associated with higher rates of miscarriage.

MATERIALS AND METHODS

A secondary analysis of data from two multicenter, randomized, controlled trials conducted by the Reproductive Medicine Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development was performed. Methods for the design and recruitment of patients in the Pregnancy in Polycystic Ovary Syndrome II (PPCOS II; clinicaltrials.gov NCT00719186) (14, 15) and the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS; clinicaltrials.gov NCT01044862) (16, 17) have previously been reported. The PPCOS II trial (N = 750) was a multicenter, prospective, double-blind, randomized, clinical trial of clomiphene citrate vs. letrozole for the treatment of infertility in patients with