ORIGINAL ARTICLE: INFERTILITY

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.

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 ≥ 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 ≥ 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

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 infer-

tile 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 ≥ 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

polycystic ovary syndrome. The AMIGOS trial (N = 900) was a multicenter, prospective, randomized, clinical trial of aromatase inhibitors vs. clomiphene citrate vs. gonadotropins combined with IUI for the treatment of unexplained infertility. Inclusion and exclusion criteria for this analysis were intentionally structured with common criteria to allow for contribution of patients from both trials to maximize power. Inclusion criteria required normal TSH, as determined locally by the recruiting center. Patients with uncorrected thyroid disease (defined as TSH <0.2 mIU/L or >5.5 mIU/L) were excluded. Institutional review board approval was obtained at each participating institution, and written informed consent was obtained. A separate consent was obtained for storage and use of deidentified samples for future research.

In both trials, serum samples were collected before fertility treatment, stored at −80°C, and subsequently assayed centrally at the Ligand Assay Core laboratory at the University of Virginia for both TSH and anti-TPO antibodies. Thyroid-stimulating hormone was measured using the Immulite 2000 system (range: euthyroid = 0.4–4 uIU/mL, hyperthyroid = <0.01 uIU/mL; intra-assay coefficient of variation [CV] 3.6%; interassay CV 4.7%; Siemens). Assays for anti-TPO antibodies were not part of the original study protocol and were only performed on samples authorized for future research. Anti-TPO antibodies were measured using the antithyroid peroxidase antibody assay on the Immulite 2000 system (range: positive >35 IU/mL. Interassay CVs performed at three levels: 20 IU/mL (10%), 70 IU/mL (5%), and 200 IU/mL (5%). Pregnancies were detected by serum hCG levels, then followed by transvaginal ultrasound between 6 and 9 weeks' gestation to document fetal viability. Pregnancy outcomes were confirmed by review and detailed follow-up of medical records.

We defined elevated TSH as TSH ≥2.5 mIU/L and euthyroidism as a TSH <2.5 mIU/L. We defined positive anti-TPO antibodies as >35 IU/mL, per assay specifications. Outcomes of interest for this study included cumulative rates of conception, clinical pregnancy, first-trimester miscarriage, and live birth. Conception was defined as a rising serum level of hCG on two consecutive tests (AMIGOS) or a serum level of hCG of >10 mIU/mL (PPCOS II). Clinical pregnancy was confirmed by the ultrasound finding of a gestational sac with a fetal heartbeat. Miscarriage included biochemical pregnancies and losses within the first trimester. Live birth was noted with the birth of a live-born infant after 20 weeks' gestation. For this analysis women who were noted to use thyroid medication during the study or screening (n = 157) were excluded.

Bivariate analyses, including Wilcoxon rank–sum tests, χ^2 analyses, and Fisher's exact tests, were performed, where appropriate, to assess the relationship between other covariates with TSH ≥2.5 mIU/L and presence of TPO antibodies. Such bivariate analyses were used to compare each outcome (conception, miscarriage, and live birth) by TSH ≥2.5 mIU/L and presence of TPO antibodies and covariates. Subsequently, logistic regression models were created to determine the independent association between elevated TSH or thyroid autoimmunity and each outcome, adjusting for age, treatment arm, body mass index (BMI), prior live birth, duration of infertility, history of smoking, educational status, and ovarian reserve. Sensitivity analyses were also conducted using TSH as a

continuous variable. These covariates were selected on the basis of existing analyses for the same data (18). SAS 9.3 (SAS Institute) was used for all analyses. A two-tailed P value <.05 was considered statistically significant.

RESULTS

There were 1,650 women enrolled in the two trials (750 couples in the PPCOS II trial and 900 couples in the AMIGOS trial). After excluding thyroid medication users (n = 157) and patients with missing TSH values (n = 30), 1,468 were eligible for TSH analysis. After accounting for patients who did not consent for future studies, 1,429 were available for analysis of anti-TPO antibodies.

At baseline the participants had a mean (±SD) age of 30.5 ± 4.5 years, with a mean BMI of 30.7 ± 8.9 kg/m². The sample was 79.2% white and 13.8% Hispanic. Sixty-five percent of the women studied reported being a college graduate or having some college education, and 19.3% had a graduate degree or beyond. On average, couples had been attempting to conceive for more than 3 years at the time of enrollment. Although most women were never-smokers, 11.7% were current smokers (Table 1).

Thyroid-stimulating hormone averaged 1.9 ± 1.0 mIU/L, median 1.7 mIU/L and interquartile range 1.2–2.4 mIU/L, with a full range of 0.0075–7.16 mIU/L. A total of 322 patients (21.9%) had TSH ≥2.5 mIU/L. Among those with TSH ≥2.5

TABLE 1

Study population demographics and baseline ovarian reserve parameters.

Variable	All patients (N = 1,468)
Age (y)	30.5 ± 4.5
BMI (kg/m²)	30.7 ± 8.9
Race	
White	1,163/1,468 (79.2)
Black or African American	171/1,468 (11.7)
Other	134/1,468 (9.1)
Ethnic group	
Not Hispanic or Latino	1,266/1,468 (86.2)
Hispanic or Latino	202/1,468 (13.8)
Reason for infertility	
No diagnosed reason for infertility	829/1,468 (56.5)
Ovulatory dysfunction (PCOS)	602/1,468 (41.0)
Other reason	37/1,468 (2.5)
Length of attempting conception (mo)	37.8 ± 31.7
Prior live birth	292/1,468 (19.9)
Education	
High school graduate or less	226/1,468 (15.4)
College graduate or some college	959/1,468 (65.3)
Graduate degree	283/1,468 (19.3)
History of smoking	
Current smoking	172/1,468 (11.7)
Quit smoking	400/1,468 (27.3)
Never smoked	896/1,468 (61.0)
Fasting serum FSH (mIU/mL)	6.7 ± 3.0
Baseline E₂ (pg/mL)	43.5 ± 36.3
Baseline AMH (ng/mL)	5.2 ± 5.7
Antral follicle count: both ovaries	33.3 ± 24.6

Note: Values are mean ± SD or number of subjects/total number (percentage). AMH = anti-müllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; PCOS = polycystic ovary syndrome.

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mIU/L, the average TSH value was 3.3 ± 0.8 mIU/L. One hundred twenty-three women (8.6%) had positive anti-TPO antibodies.

When grouped by presence of elevated TSH and presence of anti-TPO antibodies, there were no statistically significant differences in age, FSH, or antimüllerian hormone (AMH) between those with and without TSH ≥ 2.5 mIU/L or between those with and without anti-TPO antibodies. Women with TSH ≥ 2.5 mIU/L were more likely to be Caucasian and had significantly higher BMI and baseline E_2 levels compared with euthyroid women as defined for this study. Women with anti-TPO antibodies were more likely to be Caucasian. Women with no diagnosed reason for infertility were less likely to have a TSH ≥ 2.5 mIU/L or have anti-TPO antibodies. There were no significant differences in demographic characteristics or ovarian reserve parameters of basal FSH, basal E_2, or AMH between the groups with anti-TPO antibodies or without. Current smokers were more likely to have a TSH < 2.5 mIU/L and to be negative for anti-TPO antibodies compared with past smokers and never-smokers (Table 2).

Pregnancy rates, miscarriage rates, and live birth rates were not significantly different between women with TSH levels ≥ 2.5 mIU/L and women with TSH levels < 2.5 mIU/L according to the bivariate analysis (Table 3). Multivariable logistic regression indicated that there was no difference in the odds of conception, clinical pregnancy, miscarriage, or live birth in women with TSH levels ≥ 2.5 mIU/L compared with women with TSH levels < 2.5 mIU/L (Fig. 1). To further

investigate the lack of association between TSH levels and pregnancy and miscarriage rates, a logistic regression was conducted with TSH as a continuous variable, and again no association was observed.

In women with detectable anti-TPO antibodies, the miscarriage rate was significantly higher and the live birth rate was significantly lower than that of women without anti-TPO antibodies (Table 3). Conception and clinical pregnancy rates did not differ by presence of TPO antibodies. Multivariable regression indicated that women with antithyroid antibodies had 2.17 times (95% confidence interval [CI] 1.12–4.22) the odds of miscarriage than women without antibodies (Fig. 1). Women with antibodies did not have decreased odds of conception or clinical pregnancy, but they were significantly less likely to have a live birth, according to adjusted analyses (odds ratio 0.58, 95% CI 0.35–0.96) (Fig. 1). When using anti-TPO as a continuous variable, no significant association between the level of anti-TPO antibodies and miscarriage (adjusted odds ratio 1.001, 95% CI 0.999–1.002, $P = .42$) or live birth (adjusted odds ratio 1.000, 95% CI 0.999–1.001, $P = .67$) was found.

DISCUSSION

In this large study of prospectively recruited infertile women, we found no association of preconceptional TSH levels between 2.5 and 5 mIU/L with conception, miscarriage, or

TABLE 2

Demographic characteristics and baseline ovarian reserve measures compared by TSH levels and presence of antithyroid antibodies.

Variable	TSH < 2.5 mIU/L (n = 1,146)	TSH ≥2.5 mIU/L (n = 322)	P value	Negative anti-TPO antibody (n = 1,306)	Positive anti-TPO antibody (n = 123)	P value
Age (y)	30.5 ± 4.5	30.6 ± 4.5	.77	30.4 ± 4.6	31.0 ± 4.2	.22
BMI (kg/m²)	30.2 ± 8.5	32.3 ± 10.1	.004	30.8 ± 9.0	30.1 ± 8.5	.49
Race			.001			.04
White	888/1,146 (77.5)	275/322 (85.4)		1,028/1,306 (78.7)	107/123 (87.0)	
Black or African American	152/1,146 (13.3)	19/322 (5.9)		159/1,306 (12.2)	6/123 (4.9)	
Other	106/1,146 (9.3)	28/322 (8.7)		119/1,306 (9.1)	10/123 (8.1)	
Ethnic group			.54			.43
Not Hispanic or Latino	985/1,146 (86.0)	281/322 (87.3)		1,127/1,306 (86.3)	103/123 (83.7)	
Hispanic or Latino	161/1,146 (14.0)	41/322 (12.7)		179/1,306 (13.7)	20/123 (16.3)	
Reason for infertility			.01			.047
No diagnosed reason for infertility	665/1,146 (58.0)	164/322 (50.9)		722/1,306 (55.3)	70/123 (56.9)	
Ovulatory dysfunction (PCOS)	458/1,146 (40.0)	144/322 (44.7)		555/1,306 (42.5)	46/123 (37.4)	
Other reason	23/1,146 (2.0)	14/322 (4.4)		29/1,306 (2.2)	7/123 (5.7)	
Length of attempting conception (mo)	37.3 ± 31.2	39.3 ± 33.4	.48	37.8 ± 32.0	39.4 ± 31.8	.25
Prior live birth	235/1,146 (20.5)	57/322 (17.7)	.27	263/1,306 (20.1)	17/123 (13.8)	.09
Education			.66			.83
High school graduate or less	172/1,146 (15.0)	54/322 (16.8)		205/1,306 (15.7)	17/123 (13.8)	
College graduate or some college	755/1,146 (65.9)	204/322 (63.4)		850/1,306 (65.1)	83/123 (67.5)	
Graduate degree	219/1,146 (19.1)	64/322 (19.9)		251/1,306 (19.2)	23/123 (18.7)	
History of smoking			.31			.02
Current smoking	142/1,146 (12.4)	30/322 (9.3)		163/1,306 (12.5)	5/123 (4.1)	
Quit smoking	308/1,146 (26.9)	92/322 (28.6)		353/1,306 (27.0)	38/123 (30.9)	
Never smoked	696/1,146 (60.7)	200/322 (62.1)		790/1,306 (60.5)	80/123 (65.0)	
Fasting serum FSH (mIU/mL)	6.6 ± 3.0	6.8 ± 3.0	.10	6.7 ± 3.1	6.3 ± 1.7	.14
Baseline E_2 (pg/mL)	42.2 ± 33.3	48.5 ± 45.0	.02	43.4 ± 33.1	47.9 ± 63.2	.87
Baseline AMH (ng/mL)	5.2 ± 5.7	5.1 ± 5.9	.19	5.3 ± 5.7	5.3 ± 6.7	.39
Antral follicle count: both ovaries	32.8 ± 23.6	35.1 ± 28.0	.65	33.6 ± 25.1	33.1 ± 22.1	.91

Note: Values are mean ± SD or number of subjects/total number (percentage). AMH = antimüllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; PCOS = polycystic ovary syndrome; TPO = anti-thyroid peroxidase; TSH = thyroid-stimulating hormone.

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TABLE 3

Unadjusted reproductive outcome measures.

Variable	Conceptions	P value	Clinical pregnancies	P value	First-trimester pregnancy losses[a]	P value	Live birth	P value
Study (n = 1,498)		.40		.30		.99		.59
AMIGOS	286/775 (36.9)		228/775 (29.4)		77/286 (26.9)		195/775 (25.2)	
PPCOSII	241/693 (34.8)		187/693 (27.0)		65/241 (27.0)		166/693 (24.0)	
TSH groups (n = 1,498)		.83		.32		.21		.37
TSH <2.5 mIU/L	413/1,146 (36.0)		331/1,146 (28.9)		106/413 (25.7)		288/1,146 (25.1)	
TSH ≥2.5 mIU/L	114/322 (35.4)		84/322 (26.1)		36/114 (31.6)		73/322 (22.7)	
Thyroid antibody groups (n = 1,459)		.51		.22		<.01		.04
Negative anti-TPO Ab	474/1,306 (36.3)		376/1,306 (28.8)		120/474 (25.3)		332/1,306 (25.4)	
Positive anti-TPO Ab	41/123 (33.3)		29/123 (23.6)		18/41 (43.9)		21/123 (17.1)	
TSH and thyroid antibody combined groups (n = 14,59)		.29		.35		.02		.14
TSH <2.5 and anti-TPO Ab negative	375/1,040 (36.1)		304/1,040 (29.2)		89/375 (23.7)		267/1,040 (25.7)	
TSH <2.5 and anti-TPO Ab positive	29/73 (39.7)		20/73 (27.4)		14/29 (48.3)		15/73 (20.6)	
TSH ≥2.5 and anti-TPO Ab negative	99/266 (37.2)		72/266 (27.1)		31/99 (31.3)		65/266 (24.4)	
TSH ≥2.5 and anti-TPO Ab positive	12/50 (24.0)		9/50 (18.0)		4/12 (33.3)		6/50 (12.0)	

Note: Values in parentheses are percentages. Ab = antibody; AMIGOS = Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation; PPCOS II = Pregnancy in Polycystic Ovary Syndrome II; TPO = anti-thyroid peroxidase; TSH = thyroid-stimulating hormone.
[a] Pregnancy losses before 13 weeks/conception.

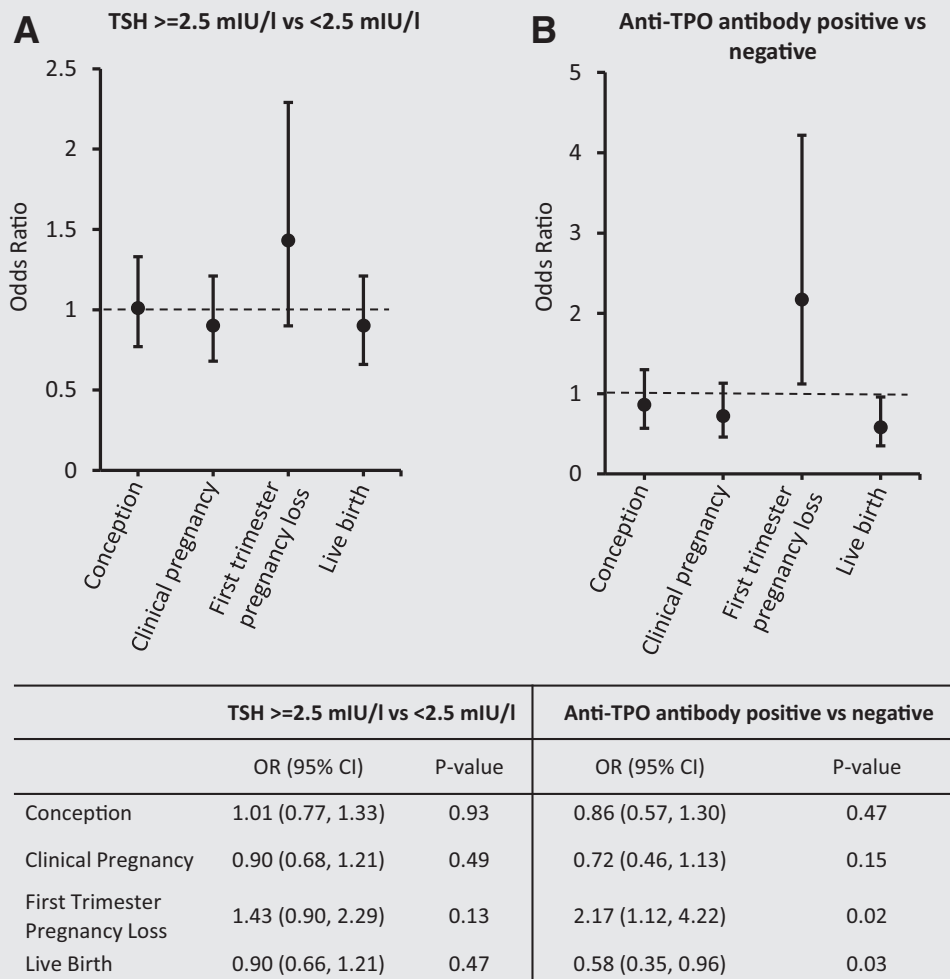*Seungdamrong. Thyroid function and live birth. Fertil Steril 2017.*

live birth rates. In contrast, we found that preconceptional anti-TPO antibodies were associated with increased miscarriage rates as well as decreased live birth rates. Our data suggest that preconceptional TSH levels ≥2.5 mIU/L are not a risk factor for poorer reproductive outcomes, but instead that preconceptional presence of anti-TPO antibodies may be of concern. These findings call into question the practice of preconceptional identification and treatment of women with TSH levels ≥2.5 mIU/L but less than the upper limit of normal to improve obstetric outcomes (10, 12). The conundrum remains whether preconceptional identification of euthyroid infertile women who have antithyroid antibodies is beneficial, and whether treatment, if any, improves pregnancy chances and outcomes.

Our study did not demonstrate an association between elevated preconception TSH levels in infertile women and pregnancy, miscarriage, or live birth rates. Our findings differ from a number of prior studies that found associations between lower pregnancy rates and elevated TSH levels but that included patients who were recruited in early pregnancy rather than preconceptionally (3, 7, 19). The lack of association between preconceptional TSH levels and pregnancy rates is in agreement with recent studies conducted in populations of infertile women (20, 21). In regard to miscarriage risks, our data did not demonstrate a correlation of TSH levels with miscarriage rates, which is in contrast to observations in prior reports (20, 22). Our findings are similar to those of other, smaller studies, where TSH was assessed before treatment of infertile women (21, 23, 24) and those with a history of pregnancy loss (25). In contrast, a recent study of infertile women who underwent IUI found significantly lower odds of miscarriage and higher odds of live birth in women with elevated preconception TSH values (2.5–4.9 mIU/L) (20). Our results also differ from those of a number of studies that have found that higher TSH values, when assessed during pregnancy, are associated with miscarriage (3, 22). Thus, the timing of screening for TSH level is likely important, with questionable value of screening for TSH preconceptionally. Nonetheless, the value of screening using TSH levels even in pregnancy is still controversial and not established. In addition, it may be possible that the discrepant results between studies may be related to the etiology of miscarriage. Studies to date have not established an association between hypothyroidism and euploid pregnancy losses. It should be noted that a majority of miscarriages are caused by aneuploidy, and it could be possible that high TSH levels are a marker of a pregnancy destined to fail because of aneuploidy rather than a causative factor.

The literature has been inconsistent regarding the association between thyroid antibodies and miscarriage risks. One study postulated that miscarriages within a population of euthyroid women with positive antithyroid antibodies are due to deficiencies in thyroid function that manifest not preconceptionally but during early pregnancy (26). A smaller study observed higher TSH levels in patients with thyroid autoimmunity but no difference in the miscarriage rate (27). As in prior studies, we found a significant association of antithyroid antibodies with both higher miscarriage rates and lower live birth rates (10). We found that presence of antithyroid antibodies preconceptionally increases the probability of miscarriage and lowers the probability of live birth after treatment of infertile women. A number of smaller studies have described similar findings (10, 28), and yet others report no association

FIGURE 1

	TSH >=2.5 mIU/l vs <2.5 mIU/l		Anti-TPO antibody positive vs negative	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Conception	1.01 (0.77, 1.33)	0.93	0.86 (0.57, 1.30)	0.47
Clinical Pregnancy	0.90 (0.68, 1.21)	0.49	0.72 (0.46, 1.13)	0.15
First Trimester Pregnancy Loss	1.43 (0.90, 2.29)	0.13	2.17 (1.12, 4.22)	0.02
Live Birth	0.90 (0.66, 1.21)	0.47	0.58 (0.35, 0.96)	0.03

1. The association between pregnancy outcomes and (**A**) thyroid-stimulating hormone (TSH) level or (**B**) the presence of anti-thyroid peroxidase (TPO) antibodies.

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(19,25,29–31). Many studies are limited by small numbers of outcomes, inconsistent timing of thyroid testing, and incomplete follow-up. Comparison of results from various studies is further complicated by inclusion of different populations. Nonetheless, a systematic review of nine studies concluded that pregnant women with anti-TPO antibodies have higher miscarriage rates (32). One study postulated that miscarriages within a population of euthyroid women with positive antithyroid antibodies are due to deficiencies in thyroid function that manifest not preconceptionally but during early pregnancy (26). A study by Korevaar et al. (33) also concluded that antithyroid antibodies are associated with diminished adaptation of the thyroid gland to pregnancy. They studied the relationship between TSH levels and hCG rise in early pregnancy and found that in women with thyroid antibodies, the thyroidal response to hCG was attenuated (33).

At least one study suggests that treatment of women with TPO antibodies and no other evidence of thyroid dysfunction with levothyroxine supplementation decreases the risk of

miscarriage (19). Yet others postulate that thyroid dysfunction is associated with alterations in cytokines and T-helper cells (34). Our findings support an association between the preconceptional presence of antithyroid antibodies and an increased risk of miscarriage. Currently there is no established therapy for thyroid autoimmunity to improve reproductive outcomes.

This study has a number of strengths. Our investigation was conducted in multiple academic centers throughout the United States and therefore represents a sample population of multiple ethnicities from multiple geographic areas. This is in contrast to prior well-performed, large trials that were limited in generalizability owing to the single-site nature of their patient population (3). Patients in our study were followed through multiple cycles of infertility treatment within a highly standardized comprehensive study design and observed throughout pregnancy and delivery. This comprehensive evaluation of study participants from initiation of treatment through live birth is unique and provides an important perspective (35).

All assays for TSH and antithyroid antibodies were performed in a centralized laboratory. This reduced potential variability between assays and also reduced variations in categorization of elevated TSH levels or antithyroid antibody levels. One important aspect of our study is that patients were recruited before widespread adoption of the 2012 Endocrine Society guidelines. Therefore, many patients were untreated but fell into the subclinical hypothyroid range according to Endocrine Society definitions, providing a robust comparison group without the confounding factor of thyroid supplementation. Last, this study encompassed infertile patients with both polycystic ovary syndrome and unexplained infertility. Because these two diagnoses are common, this is a substantial patient subset within the population of infertile women. However, this selection may have induced bias because male factor and tubal disease patients are not included.

Our findings are limited by our use of a single, cross-sectional evaluation of TSH and antithyroid antibodies. Prior studies have demonstrated acute changes in thyroid function within an episode of ovarian stimulation (36); however, because repeated measures of thyroid parameters were not included in this analysis, we could not assess any possible effects of elevated serum estrogen levels from ovarian stimulation. Additionally, free T_4 levels were not included in this analysis. This may have resulted in inclusion of women with undiagnosed thyroid dysfunction. However, TSH levels alone are typically used for screening for thyroid function in most clinical settings, and if normal, no further testing is done. Last, this study did not address the effect of thyroid supplementation for women with thyroid autoimmunity. Although patients taking thyroid supplementation were excluded from the analysis, the number of subjects taking thyroid supplementation was less than 10% of the total population, and their exclusion did not change the results.

In conclusion, this study highlights an association between anti-TPO antibodies and increased miscarriage rates and lower live birth rates, and a lack of association between preconception TSH levels ≥ 2.5 mIU/L and conception, miscarriage, and live birth rates among infertile women undergoing fertility treatment. These results suggest that thyroid supplementation in infertile women with TSH levels ≥ 2.5 mIU/L but <5.0 mIU/L may not be beneficial, whereas women with preconceptional anti-TPO antibodies may be at risk for decreased reproductive success. These findings differ from those that formed the basis for the current Endocrine Society recommendations for screening and subsequent treatment of infertile women with preconceptional TSH levels >2.5 mIU/L. This analysis characterizes a key group of infertile patients, euthyroid women with anti-TPO antibodies, who may be at risk for adverse pregnancy outcomes and eventually overt thyroid disease and for whom increased thyroid surveillance is potentially beneficial. Future interventional studies should seek to determine whether these women will benefit from increased thyroid surveillance and/or treatment with T_4 supplementation and whether anti-TPO antibodies are simply a marker of other processes impeding the course of pregnancy or are the cause of poorer reproductive success.

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