Positive effects of thyroid replacement therapy on assisted reproductive technology outcomes in women with subclinical hypothyroidism with positive thyroid peroxidase autoantibodies

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Objective: To study the beneficial effects of thyroid replacement therapy (TRT) on pregnancy outcomes in patients with subclinical hypothyroidism (SCl hypoT) with respect to thyroid peroxidase (TPO) autoantibodies.
Design: Retrospective study of 706 patients.
Setting: Not applicable.
Patient(s): The study evaluated 706 patients, who were divided into 3 cohorts: euthyroid patients, with pre–in vitro fertilization thyroid-stimulating hormone levels of <2.5 μIU/mL; patients with SCl hypoT, defined as thyroid-stimulating hormone levels of >2.5 μIU/mL and <4 μIU/mL, who were not treated; and patients with SCl hypoT who received TRT. The 3 cohorts were further subclassified into 2 groups, each based on TPO antibody levels.
Intervention(s): The cohorts were compared for the effects of TRT on pregnancy outcomes.
Main Outcome Measure(s): Identification of effects of TRT on assisted reproductive technology outcomes.
Result(s): Patients with SCl hypoT had significantly fewer positive pregnancy outcomes than euthyroid patients. Importantly, low-dose TRT was found to be beneficial in improving IVF success and pregnancy outcomes in patients with SCl hypoT. The original cohort of patients, further classified into 2 subgroups on the basis of antithyroid (TPO) antibodies, showed that low-dose TRT was associated with improved pregnancy outcomes in women with SCl hypoT and TPO-positive antibodies.
Conclusion(s): Our findings demonstrate that low-dose TRT may be beneficial in improving in vitro fertilization success and pregnancy outcomes in women with SCl hypoT and TPO-positive antibodies. (Fertil Steril Rep® 2022;3:32–8. ©2021 by American Society for Reproductive Medicine.)
Key Words: Subclinical hypothyroidism, in vitro fertilization, thyroid replacement therapy

The hypothalamus releases thyrotropin-releasing hormone, which in turn stimulates the pituitary gland to release thyroid-stimulating hormone (TSH), the primary marker for thyroid function (1). Thyroid-stimulating hormone stimulates the release of thyroxine (T4) and tri-iodothyronine from the thyroid gland, which exert the metabolic effects of the thyroid gland throughout the body (1). Low levels of T4 stimulate

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the release of more TSH via negative feedback on the hypothalamic-pituitary axis. Thyroid function is critical for optimal reproductive function in women, and thyroid disease may negatively affect ovulation, menstrual function, and pregnancy success (2, 3). Because of the strong inverse log-linear relationship between serum TSH and serum-free T4, serum TSH levels are generally regarded as a reliable measure to indicate thyroid function and abnormalities and are routinely screened in women with infertility (4–6). Even small changes in T4 levels produce very large changes in serum TSH levels, making TSH a reliable and sensitive indicator of thyroid function abnormalities (4–6).

With regard to reproductive function, the thyroid hormone exerts its effects at multiple levels, including estradiol metabolism, ovulation, embryo implantation, pregnancy, and live births (7–10). Hypothyroidism can manifest as overt or subclinical hypothyroidism (SCl hypoT) (11). In overt hypothyroidism, TSH levels are elevated, T4 levels are decreased, and symptoms of hypothyroidism, such as cold intolerance and constipation, may occur. In SCl hypoT, TSH levels are increased with normal T4 levels (i.e., TSH levels are >2.5 μIU/mL and ≤ 4 μIU/mL and T4 levels are 5–12 μg/dL) and there are mild to no evident symptoms of hypothyroidism (12, 13). However, a study has indicated that patients with SCl hypoT may have additional comorbidities, including increased total cholesterol levels and low-density lipoprotein, greater risk of atherosclerosis, disturbed blood coagulation, increased chronic heart failure risk, and even increased incidence of depressive disorders compared with euthyroid patients (14).

It is well established that overt hypothyroidism negatively affects reproduction and pregnancy outcomes via increased miscarriage rates, menstrual irregularities, subfertility, ovulation failure, and altered ovulatory function (15, 16). However, it is unclear to what extent SCl hypoT affects pregnancy outcomes. Although this subject remains controversial, some studies have shown that pregnant patients with SCl hypoT have a significantly higher risk of placental abruption, preterm birth, stillbirths, and miscarriage (15–18). The treatment of SCl hypoT in pregnant patients has been found to positively impact miscarriage and live birth rates for those undergoing in vitro fertilization (IVF) and is associated with a decrease in obstetric and neonatal complications (19).

In this study, we evaluated the impact of thyroid replacement therapy (TRT) on pregnancy outcomes and whether TRT can overcome the adverse effects of antithyroid antibodies on pregnancy outcomes in women with SCl hypoT.

MATERIALS AND METHODS

Patient Population

Our retrospective study was approved by our institutional review board. The approved clinical research assisted reproductive technology (ART) data gathering complies with the US law on ARTs (The Fertility Clinic Success Rate Act 1992 [Wyden bill]). The study analyzed data from 706 patients undergoing ART between 2017 and 2018 at the South Florida Institute for Reproductive Medicine. Of the 706 patients, the total number of patients with preimplantation genetic testing for aneuploidy (PGTA) was 217, and the number of patients with non-PGTA was 489. Patients were categorized into 3 groups. Group 1, euthyroid, consisted of patients who had pre-IVF TSH levels of <2.5 μIU/mL. Patients with SCl hypoT (TSH levels of >2.5 μIU/mL but ≤ 4 μIU/mL) were divided into 2 groups (groups 2 and 3) on the basis of whether they were given low-dose thyroid supplementation (treatment): group 2 included patients with SCl hypoT who were not treated and group 3 included those who were treated. The information on the thyroid peroxidase (TPO) antibodies was used to classify each of the 3 groups (euthyroid, SCl hypoT untreated, and SCl hypoT treated) into 2 subgroups TPO-negative (TPO levels of <11 IU/mL) and TPO-positive (TPO levels of >11 IU/mL). Serum TSH and TPO antibodies were measured within 1–2 months before treatment initiation. All women underwent standard controlled ovarian stimulation protocols following the typical practice in our IVF center.

Oocyte Retrieval, Embryo Biopsy, and Culture Conditions

Patients underwent controlled ovarian stimulation using standardized protocols. When at least 2 follicles had reached ≥ 18 mm in diameter, human chorionic gonadotropin (hCG) and/or gonadotropin-releasing hormone agonist was administered, and oocyte retrieval was scheduled 35–36 hours later. Conventional insemination or intracytoplasmic sperm injection was performed, and embryo culture proceeded to the blastocyst stage, at which time embryo transfer, embryo cryopreservation, or embryo biopsy was performed, as previously described (20, 21). Preimplantation genetic testing for aneuploidy was performed for different indications (recurrent miscarriage, repetitive implantation failure, advanced maternal age, or male factor infertility). All patients subsequently underwent embryo transfer pregnancy, miscarriage and ongoing pregnancy rates were recorded. A total of 220 patients underwent PGTA, of which 3 were fresh embryo transfers and 217 were frozen embryo transfers. The number of non-PGTA cases was 486, of which 274 were fresh embryo transfers and 212 were frozen embryo transfers (Supplemental Table 1, available online).

Statistical Analysis and Sample Size Calculation

Variables are presented as mean and standard deviation or as median and interquartile values based on the sample distribution. Intrinsic and extrinsic variables with fixed and random effects are considered in the analysis. GraphPad Prism (GraphPad Software [https://www.graphpad.com]) was used for statistical analysis. All data are presented as mean $\pm$ standard error of the mean. The statistical significance between the 2 groups was estimated by an unpaired two-tailed t test. Multiple group comparisons were performed using a one-way analysis of variance with the least significant difference test. In all cases, $P<.05$ was considered statistically significant.

RESULTS

Impact of TRT on Pregnancy Outcomes

To study the impact of TRT on pregnancy outcomes, a total of 706 patients were considered. Among these, the total number of patients with PGTA were 210, of which 3 were fresh embryo transfers and 207 were frozen embryo transfers. The number of non-PGTA cases were 486, of which 274 were fresh embryo transfers and 212 were frozen embryo transfers. The number of non-PGTA patients with fresh embryo transfer were significantly greater than that of non-PGTA or PGTA patients with frozen embryo transfer ($P<.05$). In contrast, the number of non-PGTA patients with frozen embryo transfer were not significantly different from the number of PGTA patients with frozen embryo transfer (confirming that PGTA and non-PGTA as classes do not confound the ART outcomes) ($P>.05$) (Supplemental Table 1). After excluding the 3 patients with fresh embryo transfers from the PGTA category, the patients were stratified into 3 classes on the basis of treatment and preretrieval TSH levels of <2.5 or >2.5 μIU/mL. Group 1 (n = 525) consisted of euthyroid women with preretrieval TSH level of <2.5 μIU/mL who did not receive TRT. Group 2 (n = 50) consisted of women with SCl hypoT with preretrieval TSH level of >2.5 μIU/mL who did not receive TRT. Group 3 (n = 131) consisted of women with SCl hypoT with preretrieval TSH of >2.5 μIU/mL who received TRT. These 3 groups were compared for pregnancy outcomes. The results showed that the overall pregnancy rate was significantly lower in women with SCl hypoT without treatment than in the euthyroid participants ($P<.05$). On the contrary, treated women with SCl hypoT (group 3) showed no significant differences compared with the euthyroid women (group 1) ($P>.05$) (Table 1 and Fig. 1).

Negative Effects of Antithyroid Antibodies on Pregnancy Outcomes in Hypothyroid and SCl hypoT Women

Recent studies suggest that thyroid autoimmunity may adversely impact pregnancy outcomes (22, 23). Although the adverse effects of antithyroid antibodies have been well studied in hypothyroid pregnant women, their effects in euthyroid women and in women with SCl hypoT are not well evaluated. As a first step, we studied the effects of TPO antibodies on ART outcomes after embryo transfer in all women. For this purpose, patients were further classified into 2 groups on the basis of the TPO antibodies—negative (<11 IU/mL) and positive (>11 IU/mL)—and were compared for ART outcomes. Among the 582 TPO-negative patients, 450 were pregnant and 132 were not pregnant, and were found not to be significantly different ($P>.05$) from the 124 patients who were TPO-positive, of which 94 were pregnant and 30 were not pregnant. Next, we studied the effects of TRT on ART outcomes after embryo transfer in women with SCl hypoT with respect to the presence of TPO antibodies. Among the 525 women in group 1 (euthyroid), 453 were TPO-negative (358 pregnant, 95 not pregnant) and 72 were TPO-positive (54 pregnant, 18 not pregnant). Group 2 included 50 women with SCl hypoT who were not treated. Of these, 42 patients were TPO-negative (28 pregnant, 14 not pregnant) and 8 were TPO-positive (3 pregnant, 5 not pregnant). Group 3 included 131 women who were treated. Of these, 87 patients were TPO-negative (64 pregnant, 23 not pregnant) and 44 were TPO-positive (37 pregnant, 7 not pregnant). The pregnancy outcomes were compared in each of the subgroups via a 3-way analysis of variance. The results showed that women with SCl hypoT who were TPO-positive had significantly fewer pregnancies than women with SCl hypoT who were TPO-negative ($P<.05$) (Table 2 and Fig. 2). Additionally, TRT significantly improved the pregnancy outcomes in patients with SCl hypoT who were TPO-positive ($P<.05$). Moreover, the difference between pregnancy outcomes between patients in group 1 vs. group 3 was nonsignificant ($P>.05$).

DISCUSSION

Subclinical hypothyroidism is an early and mild form of hypothyroidism (24, 25). The recently published guidelines of the American Thyroid Association and the earlier guidelines of the Endocrine Society and the European Thyroid Association recommend the treatment of SCl hypoT in the mother during pregnancy. However, the benefits of treating SCl hypoT with TRT before conception and in pregnancy are unclear and controversial (11). For instance, some studies suggest that SCl hypoT during pregnancy is associated with multiple adverse maternal and neonatal outcomes; however, no association is reported between recurrent pregnancy loss and SCl hypoT and levothyroxine does not improve subsequent pregnancy outcomes (11, 26). On the other hand, some studies show that the effects of levothyroxine in pregnant women with SCl hypoT are not the same for all pregnancy outcomes and can indeed reduce pregnancy loss in some patients (27). Our study focus is on evaluating whether SCl hypoT may negatively impact the IVF success level and pregnancy outcomes; whether low-dose TRT may be beneficial in improving IVF success and pregnancy outcomes in women with SCl hypoT; whether the antithyroid antibodies have any deleterious effects on pregnancy outcomes in women with SCl hypoT; and whether low-dose TRT may be beneficial in improving IVF success and pregnancy outcomes in women with SCl hypoT with TPO-positive antibodies.

Several studies have suggested that the effects of treated subclinical or overt hypothyroidism on IVF success are variable. Interestingly, Scoccia et al. (28) showed that even treated patients with hypothyroidism had worse pregnancy outcomes (decreased implantation, clinical pregnancy, and live birth rates) than euthyroid patients. In contrast, Busnelli et al. (29) showed that treated hypothyroid patients had no difference in pregnancy rate and live births compared with euthyroid patients.

There are several potential mechanisms that can contribute to these differing findings. For example, the controlled ovarian hyperstimulation causes higher estradiol levels, which in turn lead to elevated thyroid-binding globulin levels. This decreases the levels of free T4 and increases the TSH levels due to the hypothalamic-pituitary feedback

TABLE 1

Distribution of patients with respect to the preretrieval TSH levels, PGTA status, age of the patients, and pregnancy outcomes (nonpregnant, SAb, biochem, delivered, and ectopic) into 3 groups (group 1, euthyroid; group 2, SCl hypoT untreated; and group 3, SCl hypoT that received treatment).

Group 1

Pre, TSH < 2.5 μIU/mL, nontreated

	PGTA		non-PGTA			
Pregnancy outcome	**No. of Patients**	**%**	**No. of Patients**	**%**	**Mean age**	**SD**
Not pregnant	27	15.70	86	24.36	97.50	0.85
SAb	16	9.30	42	11.90	86.18	1.30
Biochem	17	9.88	36	10.20	79.89	0.82
Delivered	112	65.12	189	53.54	195.62	1.53
Ectopic	0	0.00	0	0.00	35.00	0.00
Total	172	100	353	100		

Group 2

Pre, TSH ≥ 2.5 μIU/mL, nontreated

	PGTA		non-PGTA			
Pregnancy outcome	**No. of Patients**	**%**	**No. of Patients**	**%**	**Mean age**	**SD**
Not pregnant	5	50	14	35	34.49	1.60
SAb	2	20	1	2.5	16.84	1.30
Biochem	1	10	6	15	33.50	0.98
Delivered	2	20	19	47.5	50.08	2.27
Ectopic	0	0	0	0	0.00	0.00
Total	10	100	40	100		

Group 3

Pre, TSH ≥ 2.5 μIU/mL, treated

	PGTA		non-PGTA			
Pregnancy outcome	**No. of Patients**	**%**	**No. of Patients**	**%**	**Mean age**	**SD**
Not pregnant	5	14.29	25	26.04	35.66	1.18
SAb	7	20.00	8	8.33	35.88	1.78
Biochem	4	11.43	6	6.25	33.84	2.02
Delivered	19	54.29	57	59.38	71.40	2.58
Ectopic	0	0.00	0	0.00	0.00	0.00
Total	35	100	96	100		

Note: PGTA = preimplantation genetic testing for aneuploidy; SAb = spontaneous abortion; SCl hypoT = subclinical hypothyroidism; SD = standard deviation; TSH = thyroid-stimulating hormone.

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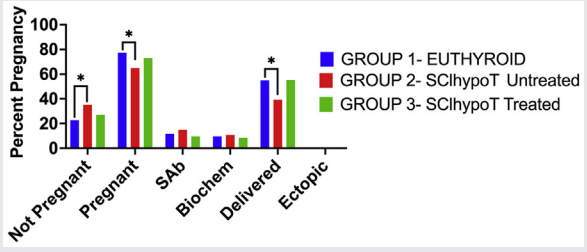
FIGURE 1



Impact of treatment with thyroid replacement therapy on pregnancy outcomes in the 3 groups (group 1, euthyroid; group 2, SCl hypoT untreated; and group 3, SCl hypoT that received treatment). SAb = spontaneous abortion; SCl hypoT = subclinical hypothyroidism. *$P<.05$.

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mechanism. Euthyroid patients have appropriate control of this feedback loop and can synthesize more T4 to compensate for this response; however, patients with hypothyroidism who are on fixed doses of TRT may be unable to adequately compensate and may actually be undertreated, leading to lower pregnancy success rates (28). Additionally, hCG administration to trigger ovulation can affect thyroid hormone levels. Thyroid-stimulating hormone and hCG share 85% homology as they have a common α-subunit. This leads to a cross-reaction of hCG on TSH receptors, which increases the T4 levels. In euthyroid patients, the increase in free T4 due to hCG cross-reactivity and the decrease in free T4 due to increased thyroid-binding globulin levels are balanced (28). However, these mechanisms are not intact in patients with hypothyroidism and can affect the IVF success depending on the adequacy of the TRT. Therefore, close monitoring of

TABLE 2

Distribution of patients with respect to the TPO antibodies, preretrieval TSH levels, treatment, PGTA status, age of the patients, and pregnancy outcomes (nonpregnant, SAB, biochem, Delivered, Ectopic) into 3 groups (group 1, euthyroid; group 2, SCl hypoT untreated; and group 3, SCl hypoT that received treatment).

Group 1

	Pre, TSH < 2.5 μIU/mL, nontreated, TPO−						Pre, TSH < 2.5 μIU/mL, Nontreated, TPO+					
	PGTA		non-PGTA				PGTA		non-PGTA			
Pregnancy outcome	No. of patients	%	No. of patients	%	Mean age	SD	No. of patients	%	No. of patients	%	Mean age	SD
Not pregnant	26	16.77	69	23.15	35.31	0.53	1	5.88	17	30.91	37.83	1.18
SAb	14	9.03	36	12.08	35.9	0.76	2	11.76	6	10.91	38.38	1.85
Biochem	14	9.03	29	9.73	35.89	0.57	3	17.65	7	12.73	33.8	1.06
Delivered	101	65.16	164	55.03	72.14	0.82	11	64.71	25	45.45	69.94	2.25
Ectopic	0	0.00	0	0.00	35	0.00	0	0.00	0	0.00	0	0.00
Total	155	100	298	100			17	100	55	100		

Group 2

	Pre, TSH ≥ 2.5 μIU/mL, Nontreated, TPO−						Pre, TSH ≥ 2.5 μIU/mL, Nontreated, TPO+					
	PGTA		non-PGTA				PGTA		non-PGTA			
Pregnancy outcome	No. of patients	%	No. of patients	%	Mean age	SD	No. of patients	%	No. of patients	%	Mean age	SD
Not pregnant	4	44.44	10	30.30	35.57	1.08	1	100	4	57.14	33.4	2.11
SAb	2	22.22	1	3.03	33.67	2.60	0	0	0	0.00	0	0.00
Biochem	1	11.11	5	15.15	32	1.97	0	0	1	14.29	35	0.00
Delivered	2	22.22	17	51.52	68.16	2.55	0	0	2	28.57	32.00	2.00
Ectopic	0	0.00	0	0.00	0	0.00	0	0	0	0.00	0	0.00
Total	9	100	33	100			1	100	7	100		

Group 3

	Pre, TSH ≥ 2.5 μIU/mL, treated, TPO−						Pre, TSH ≥ 2.5 μIU/mL, treated, TPO+					
	PGTA		non-PGTA				PGTA		non-PGTA			
Pregnancy outcome	No. of patients	%	No. of patients	%	Mean age	SD	No. of patients	%	No. of patients	%	Mean age	SD
Not pregnant	5	19.23	18	29.51	36.46	0.89	0	0.00	7	20.00	34.86	1.47
SAb	6	23.08	5	8.20	33	0.69	1	11.11	3	8.57	38.75	2.87
Biochem	2	7.69	2	3.28	33.5	0.87	2	22.22	4	11.43	34.17	3.18
Delivered	13	50.00	36	59.02	72.33	1.75	6	66.67	21	60.00	70.46	3.41
Ectopic	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	26	100	61	100			9	100	35	100		

Note: PGTA = preimplantation genetic testing for aneuploidy; SAb = spontaneous abortion; SCl hypoT = subclinical hypothyroidism; SD = standard deviation; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.

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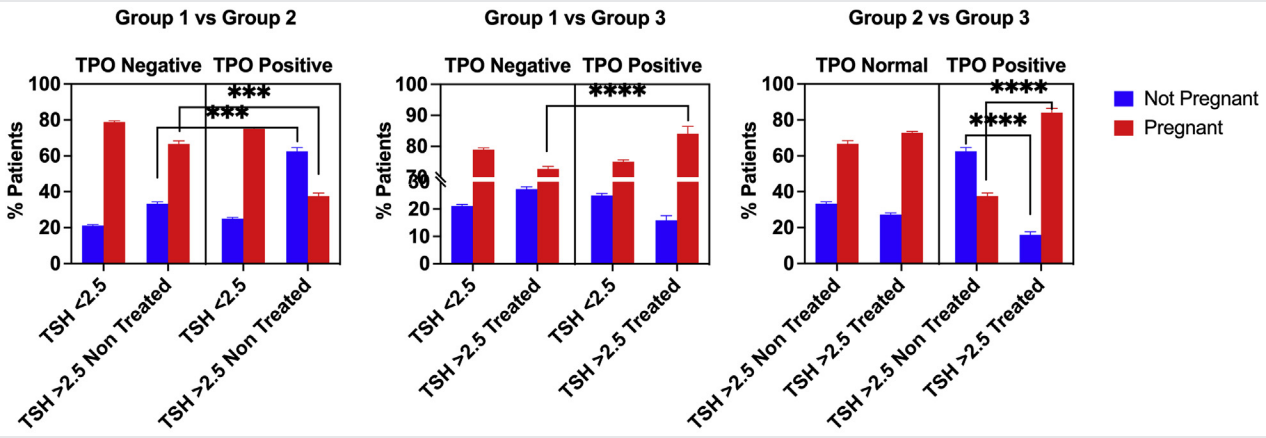
TSH levels during treatment for subclinical or clinical hypothyroidism is critical in determining successful pregnancy outcomes.

Our study focused on patients with SCl hypoT treated with TRT. Although different studies suggest reference ranges for SCl hypoT, which vary drastically from 0.45–4.5 μIU/mL, for selecting the patients with SCl hypoT, we considered TSH range of 2.5–4.0 μIU/mL based on >30 years of clinical practice experience (30–32). We evaluated the implications of TRT, TSH, and TPO antibodies on improving the pregnancy success rates in these patients. We found that SCl hypoT negatively impacts IVF success and pregnancy outcomes. Patients with SCl hypoT benefit from a low dose of TRT with improved IVF success and pregnancy outcomes. Moreover, we found that antithyroid antibodies have deleterious effects on pregnancy outcomes in women with SCl hypoT, and low-dose TRT improves IVF success and pregnancy outcomes in these women. However, our study has the following limitations. Group 2, which represents patients with SCl hypoT who did not receive TRT, was a small group with a limited number of patients. The existence of this group was influenced by clinician's discretion whether to administer TRT, which could be important, but that is beyond the scope of analysis in the present study. On comparing the pregnancy outcomes in patients with SCl hypoT with TPO-negative antibodies who did and did not receive TRT, we could not observe a significant difference. This suggests, to some extent, that the TPO antibodies influence the treatment efficacy. However, to validate this observation, more detailed analysis on other factors that could potentially confound the outcomes, which are but not limited to body mass index, percent body fat, high-sensitivity C-reactive protein, elevated estradiol, and so on,

FIGURE 2



Impact of treatment with thyroid antibodies and thyroid replacement therapy on pregnancy outcomes in the 3 groups with respect to each other (group 1, euthyroid; group 2, SCl hypoT untreated; and group 3, SCl hypoT that received treatment). SCl hypoT = subclinical hypothyroidism; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.
****$P<.001$.
****$P<.0001$.

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is required. Further in-depth studies are ongoing to evaluate parameters such as the presence of anti-thyroglobulin antibodies and other specific treatment strategies, which may have an additional effect on the success of the IVF outcomes.

CONCLUSION

Serum TSH is often screened in women planning to conceive to evaluate thyroid function, given its association with adverse neonatal and obstetric outcomes. Thyroid hormone replacement (levothyroxine) is the standard of care for women with clinical hypothyroidism, and it can be consumed daily or as otherwise prescribed (33, 34). The general recommendation is to target a TSH level of <2.5 μIU/L with levothyroxine treatment for optimal outcomes for patients with primary hypothyroidism (35–37). However, no specific TSH value within the recommended ≤ 2.5 μIU/L range for pregnancy has been found to predict better IVF outcomes (38). Our study showed that the TRT has significant positive effects on ART outcomes in women with SCl hypoT. Additionally, we found that TPO antibodies can have deleterious effects on pregnancy outcomes in women with SCl hypoT. TRT can improve the overall pregnancy outcomes in women with SCl hypoT with TPO-positive antibodies. Our findings are consistent with the updated recommendations for thyroid replacement in pregnant women by the American Thyroid Association. Further in-depth studies are ongoing considering parameters such as the antimüllerian hormone, body mass index, and additional specific treatment strategies, which may affect successful IVF outcomes (33, 34).

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