Thyroid function after assisted reproductive technology in women free of thyroid disease

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Objective: To evaluate thyroid function in women undergoing a first assisted reproductive technology (ART) procedure and to compare women with ongoing pregnancy or miscarriage.
Design: Prospective cohort study.
Setting: Tertiary referral center.
Patient(s): Seventy-seven women free of thyroid disease.
Intervention(s): Serum TSH and FT4 were determined before and 2, 4, and 6 weeks after ET. All women received the same ART protocol.
Main Outcome Measure(s): Thyroid function.
Result(s): Forty-five women had ongoing pregnancies, and 32 suffered a miscarriage after 6.7 weeks (range 5–11). Mean age and number of ET were similar in both groups. Compared with baseline values, TSH and FT4 increased significantly 2 weeks after ET (ongoing pregnancies group: TSH 2.5 ± 1.3 vs. 1.6 ± 0.8 mU/L and FT4 13.8 ± 1.4 vs. 12.4 ± 1.8 ng/L; miscarriage group: TSH 2.1 ± 1.0 vs. 1.5 ± 0.7 mU/L and FT4 14.2 ± 2.0 vs. 12.4 ± 1.9 ng/L). Pregnancy outcome did not affect thyroid function and its evolution over time.
Conclusion(s): In women free of thyroid diseases, thyroid function changed significantly after ART, but these changes were not different between women with ongoing pregnancy and miscarriage. (Fertil Steril® 2005;83: 1753–7. ©2005 by American Society for Reproductive Medicine.)

Key Words: Thyroid, infertility, assisted reproductive technology, miscarriage

Miscarriage occurs in approximately 30% of all pregnancies and is an important psychological burden for women. Only 10% of these miscarriages are clinically obvious, most pass without the women's awareness (biochemical pregnancy).

The etiology of miscarriage is diverse and encompasses genetic anomalies, uterine factors, the presence of anticardiolipin antibodies, and hormonal abnormalities (1–3).

Previous work indicated that thyroid dysfunction (hypo- and hyperthyroidism) and the presence of thyroid antibodies (TAI+) increases the risk of infertility and miscarriage (4–8). The pathophysiology underlying the association between TAI and miscarriage remains largely speculative. Moreover, women with spontaneous abortion may have significantly lower thyroxine levels compared with women with ongoing pregnancy (9).

With the awareness that subclinical forms of thyroid dysfunction and TAI+ are potentially adverse contributors in pregnancy outcome, we performed the present study to investigate whether the status of thyroid function in a cohort of women free of thyroid disease and undergoing an assisted reproductive technology (ART) procedure was different between women who had ongoing pregnancies and women who had spontaneous miscarriages.

While doing so, we wanted to avoid the confounding effects of thyroid autoimmunity.

MATERIALS AND METHODS

Research Question

Among women pregnant after ART, do TSH and FT4 differ between women with ongoing pregnancies and women suffering a miscarriage?

Overall Study Design

Women presenting at the Center of Reproductive Medicine were systematically screened for thyroid hormone function (serum TSH and FT4) and for the presence of thyroid autoimmunity (thyroperoxidase antibodies [TPO-ab] and thyroglobulin antibodies [Tg-ab]). A diagnosis of thyroid disease was further evaluated from medical history on thyroid disease, and/or the use of thyroid medication. Only euthyroid women (normal serum TSH and FT4 levels) without thyroid antibodies (TAI−) with a clinically proven pregnancy after having received a first ART cycle were included in the study.

Causes of infertility were as follows: male infertility (50%), tubal diseases (19%), endometriosis (9%), ovulatory disorders (7%), and idiopathic (15%).

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Thyroid function tests were further determined after confirmation of pregnancy as well as 2, 4, and 6 weeks after the ET, i.e., until the moment of miscarriage.

Embryo transfer took place 5 to 7 days after the end of ovulation induction (OI).

The median term for miscarriage was 6.7 weeks (range, 5–11). The institutional review board at our institution approved the study protocol.

Assisted Reproductive Technology Treatment

All female partners received ART treatment as previously described (10, 11).

Pregnancy was diagnosed at least 10 days after ET by rising hCG levels of at least 20 IU/mL in serum on two occasions. Clinical pregnancies were diagnosed by ultrasonography performed 5 weeks after embryo transfer.

Serum Assay

Serum TSH and FT4 were measured using a third-generation electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany).

The reference values were 0.27–4.2 mU/L for TSH and 9.3–18.0 ng/L (12 to 23.2 pmol/L) for FT4 (1 ng/L FT4 = 1.29 pmol/L).

Thyroid autoimmunity (TAI+) was excluded when TPO-ab (>34 kU/L) and/or Tg-ab (>115 IU/mL) were absent. TPO-ab was determined using an RIA-kit (BRAHMS Diagnostica, Berlin, Germany). The reference range was 0–34 kU/L.

Antithyroglobulin antibodies (Tg-ab) were measured with an automated competitive immunoassay (Modular E170; Roche Diagnostics). The reference range was 0–115 IU/mL.

Statistical Analysis

We performed a formal sample size calculation based on information from a previous study from our group (10). According to this analysis, a projected total sample of 62 patients is required to detect a difference in serum TSH concentration of 1.3 mU/L between ongoing and miscarrying patients with an 80% power at an overall alpha risk of .05 (two-tailed), assuming a common standard deviation of 1.8 mU/L (12).

To compare changes between pre- and post-ART values of TSH and FT4 in the early stage of pregnancy (i.e., between baseline values and values at week 2 after ET) the paired Student's *t*-test was used. The unpaired Student's *t*-test was used to compare differences in thyroid function between ongoing pregnancy group and miscarriage group at baseline and week 2. A one-way (single-group) repeated measures analysis of variance (ANOVA) was conducted to explore the effect of time on TSH and FT4 serum values collected at four periods during the first months of pregnancy, i.e., before ART (time 0), and at weeks 2, 4, and 6 after ET. A two-way (between-groups) repeated measures ANOVA was conducted to explore the impact of the outcome status (ongoing pregnancy vs. miscarriage) on thyroid function, as measured by serum TSH and FT4 values during the first months of pregnancy.

Given the numerous comparisons, the alpha threshold of .05 should not be applied to the *P* values for comparisons other than the primary outcome measure (repeated measures ANOVA on thyroid function). In this regard, a Bonferroni correction is required to avoid an alpha error. We chose to regard a level of $P<.006$ as significant for these numerous comparisons (representing a Bonferroni correction of .05 divided by eight comparisons). All data analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL).

RESULTS

Baseline Characteristics

Table 1 shows the clinical and biochemical characteristics of all women included (N = 77), stratified according to the pregnancy outcome. In the entire study group, the women's mean age was 31 ± 5 years (range 21–42), and their mean ± SD serum TSH and FT4 at baseline were 1.6 ± 0.8 mU/L and 12.4 ± 1.8 ng/L, respectively. There were no significant differences between the ongoing pregnancy and the miscarriage groups with regard to age, baseline serum TSH and FT4 values, or the number of transferred embryos.

Thyroid Function Before ART and Two Weeks After ET

Compared with baseline values, serum TSH and FT4 values were significantly higher 2 weeks after ET in both groups. In the ongoing pregnancy group the TSH values increased from 1.6 ± 0.8 mU/L at baseline to 2.5 ± 1.3 mU/L at 2 weeks ($P<.0001$), and the FT4 values from 12.4 ± 1.8 ng/L to 13.8 ± 1.48 ng/L ($P<.0001$). In the miscarriage group the TSH values increased from 1.5 ± 0.7 mU/L at baseline to 2.1 ± 1.0 mU/L at 2 weeks ($P<.0001$), and the FT4 values from 12.4 ± 1.9 ng/L to 14.2 ± 2.0 ng/L ($P<.0001$). There were no statistically significant differences between the two groups for serum TSH and FT4 values at baseline ($P=.504$ and $P=.906$, respectively) and 2 weeks after ET ($P=.132$ and $P=.399$, respectively).

Serum hCG levels were comparable at this stage of pregnancy (Table 2).

Thyroid Function During the First Weeks of Pregnancy

Figure 1 shows the pattern of changes in serum TSH and FT4 values during the first weeks of pregnancy stratified according to outcome status (ongoing pregnancy vs. miscarriage). In both groups there was a statistically significant effect for time on TSH, as well as on FT4 (one-way repeated measures ANOVA for TSH and FT4: $P<.001$). When analyzed according to outcome status, however, both the serum TSH and