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The association of thyroid stimulating hormone levels and intrauterine insemination outcomes of euthyroid unexplained subfertile couples

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ABSTRACT

Objective: To investigate the effect of different TSH (0.5–2.49 mIU/L and 2.5–4.5 mIU/L) levels on intrauterine insemination (IUI) outcomes of euthyroid unexplained subfertile patients who are negative for thyroid antibodies.

Study design: In this retrospective cohort study, data of euthyroid subfertile patients who underwent IUI due to unexplained infertility at a university-based infertility clinic between January 2013 and December 2014 were reviewed. A total of 156 patients of them were categorized into two groups according to pre-conceptional TSH levels. The first study group consisted of patients with serum TSH levels 0.5–2.49 mIU/L and the second study group consisted of patients with serum TSH levels 2.5–4.5 mIU/L. The primary outcome measure was live birth rate.

Results: Demographics and cycle characteristics of the study groups were similar. There were no statistically significant differences between the study groups regarding main outcome measures (live birth rate, P = 0.82; clinical pregnancy rate, P = 0.64; miscarriage rate, P = 0.57).

Conclusion: Pre-conceptional TSH levels ranging between 0.5–4.5 mU/L does not appear to have a significant effect on IUI outcome of euthyroid women who are negative for thyroid antibodies.

Introduction

Hypothyroidism is a common health problem which affects women more than men. Prevalence of overt hypothyroidism ranges between 0.1%–2% depending on the population studied and is significantly higher in patients with infertility [1,2]. Thyroid function abnormalities can alter normal menstrual function and may result in oligomenorrhea, amenorrhea, or hypermenorrhea/menorrhagia. Menstrual irregularities are three times more frequent in hypothyroid patients when compared to normal population, and the most common irregularity is oligomenorrhea [3]. Although screening for thyroid disorders is not mandatory, during infertility evaluation most clinicians check for thyroid functions as it can result in pregnancy loss and anovulation.

While the impact of overt hypothyroidism is clear, debate continues on the possible negative effect of subclinical hypothyroidism on assisted reproduction outcomes. Some authors advocate treatment of subclinical hypothyroidism. Higher implantation and live birth rates are reported in subclinical hypothyroidism patients who are treated by levothyroxine during controlled ovarian stimulation, regardless of thyroid antibody status [4]. The American Association of Clinical Endocrinologists recommend consideration of treatment with L-thyroxine in women of childbearing age with serum TSH levels between 2.5 mIU/L and the upper limit of normal for a given laboratory's reference range if they are in the first trimester of pregnancy or planning a pregnancy including assisted reproduction in the immediate future [5].

On the other hand, among patients treated by assisted reproductive technology (ART), no differences were observed in clinical pregnancy, miscarriage or delivery rates between TSH thresholds of 2.5 mIU/L and 4.5 mIU/L as the upper limit [6]. In a recent study, preconceptional TSH levels and outcomes of intrauterine insemination (IUI) were evaluated in euthyroid infertile patients [7]. The high-normal TSH levels (2.5–4.9 mIU/L) were not found to be associated with adverse outcome. Presence of thyroid antibodies may have adverse effect on IUI success and pregnancy outcome. However, the exact effect of TSH level on IUI success in euthyroid-subfertile patients with no thyroid antibodies needs to be determined.

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In this retrospective study, we aimed to investigate the effect of different TSH levels on IUI outcomes of euthyroid unexplained subfertile patients who are negative for thyroid antibodies.

Materials and methods

Trial population and study protocol

In this retrospective cohort study, data of euthyroid subfertile patients who underwent IUI at a university-based infertility clinic between January 2013 and December 2014 were reviewed. The study was approved by the Institutional Review Board of Ankara University School of Medicine. The inclusion criteria were age 18–40 years, unexplained subfertility, duration of infertility at least two years, follicle stimulating hormone level <12 IU/ml, serum TSH level between 0.5 mIU/L and 4.5 mIU/L, full thyroid function tests and thyroid antibody testing performed within last three months of ovulation induction. The exclusion criteria were body mass index >30 kg/m^2, overt thyroid dysfunction with elevated or decreased serum free T3 and/or free T4, being positive for thyroid antibodies (anti-TG and/or anti-TPO), being under thyroid medication, history of ovarian and/or tubal surgery and documented endometriosis. The first stimulation cycle for each subject was included in the study to prevent possible crossover bias between groups. All patients had a standard infertility evaluation that included medical history, physical examination, assessment of tubal patency by hysterosalpingography, confirmation of ovulation by mid-luteal serum progesterone, and semen analysis (abnormal semen test results confirmed by a second analysis at least 6 weeks apart). Couples with normal sperm parameters, bilateral patent fallopian tubes, and regular ovulatory cycles were diagnosed with unexplained infertility. The first study group consisted of patients with serum TSH levels 0.5–2.49 mIU/L and the second study group consisted of patients with serum TSH levels 2.5–4.5 mIU/L. The primary outcome measure was live birth rate. Clinical pregnancy was defined an intrauterine pregnancy ring.

Ovulation induction and intrauterine insemination

A transvaginal ultrasonography was performed on cycle day 3. Cycles of women with ovarian cysts ≥15 mm were postponed. All of the patients stimulated with rFSH (Gonal-F®; Serono, Istanbul, Turkey or Puregon®; Schering-Plough, Istanbul, Turkey) with a starting dose of 75 IU/day (BMI < 25 kg/m^2) and 100 IU/day (BMI ≥ 25 kg/m^2) were examined because of the duration of infertility. rFSH injections were commenced on cycle day 2-4. The first ultrasonography was performed on the 6th day of stimulation and rFSH dose was adjusted according to ovarian response. Ovarian response and endometrial thickness were strictly monitored by transvaginal ultrasonography. When the average diameter of the leading follicle reached ≥18 mm 10,000 IU hCG (Pregnyl®, Schering-Plough, Istanbul, Turkey) was administered. A single IUI was performed 36–40 hours after hCG injection. Semen samples used for insemination were processed within one hour after ejaculation, using a density gradient centrifugation followed by washing with culture medium. No luteal phase support was given.

Thyroid assays

Enzyme-linked immunosorbent assays (ELISA) were used for measurements of serum TSH, free T3, and free T4 (IMMULITE 2000 chemiluminometric assay; Siemens Healthcare Diagnostics, Deerfield, Ill., USA) and serum anti-TPO and anti-Tg (Varelisa thyroglobulin and TPO antibodies; Pharmacia Diagnostics, Freiburg, Germany). Thyroid autoimmunity (TAI) was defined as serum concentration of anti-Tg or anti-TPO ≥100 IU/ml.

Statistical analyses

Data analyses were performed by using SPSS Version 21.0 (IBM Corporation, Armonk, NYC, USA). Samples were tested with Shapiro-Wilk test to determine normality of distributions. According to the results, non-parametric tests were preferred. Continuous variables were compared with Mann-Whitney U test. Categorical variables were compared with Chi-square test. A *P* value of <0.05 was considered statistically significant.

Results

A total of 232 euthyroid subfertile patients who underwent IUI due to unexplained infertility were found to be eligible for the analysis. Among those 24 (10.3%) patients with BMI > 30 kg/m2, 16 (6.8%) patients with positive thyroid antibody, 10 (4.3%) patients with elevated or suppressed serum free T3/T4, and 26 (11.2%) patients who were under thyroid medication were excluded from the study. As a result, 156 patients were selected for the final analysis. The first study group consisted of 118 patients with TSH levels 0.5–2.49 mU/L and the second study group consisted of 38 patients with TSH levels 2.5–4.5 mU/L. None of the women included in the study had previous parity; twenty-three patients in the first study group and six patients in the second had one miscarriage history before the treatment and the others were primary subfertile. Demographic data and cycle characteristics are presented in Table 1. The main outcome measures including live birth rates, clinical pregnancy and miscarriage rates are presented in Table 2. There were no statistically significant differences between the study groups regarding main outcome measure.

Table 1
Demographics and cycle characteristics of the study groups.

	Group I TSH 0.5-2.49 mIU/L (N = 118)	Group II TSH 2.5-4.5 mIU/L (N = 38)	*P* value
Age (years)	28 (23-44)	30 (22-36)	0.19
BMI (kg/m^2)	23 (18-30)	24 (20-29)	0.98
Duration of infertility (years)	4 (2-8)	3 (2-6)	0.51
Day 3 FSH (IU/ml)	8,3 (1.7-12)	7.4 (5.8-12)	0.87
TMSC (x10^6)	37 (5-120)	27 (5–58)	0.06
Total gonadotropin dose (IU)	1000 (400-1769)	825 (375-1625)	0.76
Duration of stimulation (days)	10 (5-20)	11 (5-21)	0.17
Pre-ovulatory follicles >17 mm (n)	1 (1-4)	1 (1-2)	0.94
Peak estradiol (pg/ml)	106 (100-915)	48 (38-790)	0.74
ET on day of hCG (mm)	10.9 (7.0-14.0)	12.0 (8.0-15.0)	0.14

Note: The values are presented as median (min-max). TMSC: total motile sperm count; ET: endometrial thickness.

Table 2
Comparison of outcome measures among the study groups.

	Group I TSH 0.5-2.49 mIU/L (N = 118)	Group II TSH 2.5-4.5 mIU/L (N = 38)	*P* value
Clinical pregnancy, n (%)	18 (15.2)	4 (10.5)	0.64
Live birth, n (%)	14 (11.8)	4 (10.5)	0.82
Miscarriage, n (%)	4 (3.3)	0 (0)	0.57

Discussion

In the present study, we aimed to assess the association of pre-conceptional TSH levels on IUI outcome of euthyroid subfertile with thyroid antibody negative patients. According to the results of this retrospective study, serum TSH level being above or under 2.5 mIU/L prior to ovulation induction does not appear to have a significant effect on live birth rate in euthyroid subfertile women undergoing IUI.

Since maternal hypothyroidism has been shown to be related to an increased risk of adverse pregnancy outcomes such as premature birth, low birth weight, pregnancy loss and damaged optimal development of fetal brain, normal TSH levels are crucial during pregnancy, particularly in the first trimester [8–10]. The American Thyroid Association published a guideline in 2011 recommending the upper reference limit for serum TSH concentration during pregnancy as 2.5 mU/L in the first trimester, and 3.0 mU/L in the second and third trimesters [11].

The impact of preconceptional TSH levels on ART outcome has been an issue of debate [6,12]. Several studies couldn't have found significant effect of TSH levels on ART outcome [6,13,14]. In a recent meta-analysis, the effect of LT4 treatment on pregnancy rates of ART patients with subclinical hypothyroidism was evaluated [15]. The authors concluded that, LT4 supplementation should be recommended to improve clinical pregnancy outcome in women with subclinical hypothyroidism and/or thyroid autoimmunity undergoing ART [15].

Recently, Jatzko et al. reported a retrospective analysis of their IUI cycles [16]. On multivariate analysis treatment of subclinical hypothyroidism with TSH levels above 2.5 mU/L was associated with higher pregnancy rates among women undergoing IUI [16]. However, they also reported that patients with TSH > 2.5 mU/L were treated for subclinical hypothyroidism and all patients had TSH < 2.5 mU/L at the time of insemination. Interestingly, they found no significant effect of TSH level, thyroid antibody status, and treatment for overt hypothyroidism on IUI outcome. In another recent study, Karmon et al. evaluated preconceptional TSH values of 4064 IUI cycles from 1477 women [7]. The authors reported no significant difference between IUI outcome of patients among several TSH categories. Same results were reported in two retrospective cohort studies consistent with Karmon *et al.*'s study [7,17,18]. Furthermore, they found increased odds of live birth and decreased odds of miscarriage for patients with TSH > 2.5 mU/L. While they interpreted this result as 'no adverse effect of high normal TSH values', also discussed ignorance of thyroid antibody status as a limitation of the study. Although not significant, we observed a similar pattern in our study population too. There were 4 and no miscarriages among patients with TSH < 2.5 mU/L and with TSH > 2.5 mU/L, respectively. We interpret this finding as a result of low subject number in group II.

Our study has some discrepancy from the aforementioned studies per design. First of all, we included only unexplained patients in order to have a more homogenous study population and to avoid unfavorable effects of infertility etiology. In addition, we excluded patients with hypo-/hyperthyroxinaemia, and under thyroid medication. Although a recent large scale retrospective cohort study found no association between presence of thyroid autoimmunity and IUI success, we excluded patients who are positive for thyroid antibody [19,20]. Because, an association between thyroid antibodies and pregnancy loss was suggested in some studies [5,21]. And, eliminating this co-factor may add credence to our findings. Moreover, to the best of our knowledge this is the third study that reports association between serum TSH level and IUI outcome of euthyroid women with thyroid autoimmune negative.

The major limitations of our study were the retrospective design and the low number of subjects, particularly in the second study group. However, we could not include more subjects such a study with strict inclusion and exclusion criteria conducted in a single center. Another limitation of the study was the lack of a hypothetical power analysis.

In conclusion, pre-conceptional TSH levels ranging between 0.5–4.5 mU/L does not appear to have a significant effect on IUI outcome of euthyroid women who are negative for thyroid antibodies. Further large prospective studies are needed to determine the exact effect of pure TSH level on IUI outcome.

Declaration of competing interest

The authors report no conflicts of interest and no financial disclosure.

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Ethical approval

It is a restrospective study so ethical approval was not obtained. This study was reviewed by the appropriate ethics committee and was performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

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