Ann Med Res 2021;28(7):1346-50

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.06.630

Original Article

Subclinical hypothyroidism of unexplained infertility patients does not affect intrauterine insemination success: A case-control study

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Abstract

Aim: This study aimed to assess the importance of preconceptional thyroid-stimulating hormone (TSH) values on the achievement of intrauterine insemination (IUI) in unexplained infertile patients.

Materials and Methods: This study was conducted retrospectively by evaluating the medical records of euthyroid 192 patients who experienced IUI between January 2017 and December 2018. The study population was classified as serum TSH levels of 0.5-2.49 mIU/L (group A) and 2.5-4.5 mIU/L (group B). Clinical pregnancy, miscarriage and live birth rates of the groups were evaluated.

Results: The demographic characteristics, laboratory levels, and cycle characteristics of the study population were similar. There were no statistically significant differences between group A and group B in terms of clinical pregnancy (11.03%, and 8.51%, respectively, p=0.62), miscarriage (3.55%, and 1.13%, respectively, p=0.65), and live birth rates (7.58%, and 6.38%, respectively, p=0.78).

Conclusion: Clinical pregnancy, miscarriage, and live birth rates were similar between the two groups. We indicate that subclinical hypothyroidism does not adversely affect the clinical pregnancy, miscarriage, and live birth rates in IUI cycles of euthyroid unexplained infertile couples.

Keywords: Clinical pregnancy; intrauterine insemination; thyroid-stimulating hormone; unexplained infertility

INTRODUCTION

Thyroid hormones affect the menstrual pattern directly on the ovaries and mediately on prolactin (PRL), sex hormone-binding globulin (SHBG), and gonadotropin-releasing hormone (GnRH) secretion and clotting factors (1). In various animal species and in vitro studies, thyroid-stimulating hormone (TSH) and thyroid hormones have been proved to influence oocyte development and implantation (2-5). Cell culture studies are reported that thyroid hormones have a stimulating impact on the thecal and granulosa cells of the ovary (6-8).

The presence of thyroid dysfunction adversely affects normal ovarian function by affecting thyroid-ovarian interaction and can cause menstrual irregularity, infertility, and increased adverse reproductive outcomes (9, 10). The most sensitive diagnostic marker for determining thyroid function is the serum TSH level (11). Abnormal TSH levels are higher among infertile patients with ovulatory dysfunctions or unknown infertility than control groups (12). In a retrospective study, the oocyte donor had a TSH value of ≥2.5 mIU/L, independent of the recipient's TSH level, with lower rates of clinical pregnancy (13).

Subclinical hypothyroidism (SCH) is a biochemical determination in which serum TSH values elevate, but thyroxine (fT4) levels are within normal ranges (14). SCH is seen in 4-20% of the grown-up people, and it is more frequent in women and white ethnicity (15). SCH patients have no symptoms or have much fewer symptoms than patients with overt hypothyroidism (14). The rate of subfertility was higher in patients with SCH than in women with normal TSH (14). The 2017 guideline of the American Thyroid Association (ATA) recommends examining the TSH levels of patients presenting for infertility (16). A recent meta-analysis, which included 14 randomized controlled trials, found that levothyroxine (LT4) treatment significantly improved fertilization and clinical pregnancy rates (17). But currently, the determined standard peak TSH level in SCH is still controversial. In 2012, it was recommended that LT4 treatment should be considered in patients of reproductive age with serum TSH values between 2.5 mIU/L and the standard peak value of the laboratory if she is in the first trimester of gestation or scheduling a gestation (18). But then, the 2017 guideline of the ATA advised that the standard peak value of normal TSH for childbearing women is 4 mIU/L (16). Moreover,

Received: 18.06.2020 **Accepted:** 24.08.2020 **Available online:** 09.07.2021
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recent studies do not suggest treating SCH patients who attempt to conceive spontaneously to improve the probability of conception by thyroid hormone replacement (16,19).

We hypothesized that in infertile patients, preconceptional TSH levels ≥ 2.5 mIU/L might be associated with the reproductive success of intrauterine insemination (IUI) cycles. This study sought to evaluate the importance of preconceptional TSH values on the achievement of IUI in unexplained infertile couples.

MATERIALS and METHODS

Study Population

The current study was carried out retrospectively by evaluating the medical records of euthyroid patients experienced IUI in Diyarbakir Gazi Yasargil Training and Research Hospital between January 2017 and December 2018. Institutional Ethics Committee approved the study (15.05.2020/463). Of the IUI performed during this period, 192 patients were enrolled in this research with predetermined criteria. These criteria were duration of infertility at least one year, unexplained infertility, serum TSH level 0.5-4.5 mIU/L, standard thyroid function tests performed in the last three months before ovulation induction, no past or current treatment of thyroid disease, body mass index (BMI) < 30 kg/m2, no previous ovarian and/or tubal surgery, serum follicle-stimulating hormone (FSH) level < 12 IU/ml and no male factor to cause infertility. All free triiodothyronine (fT3) and fT4 values were within the normal range among the participants. For the diagnosis of unexplained infertility, mid-luteal serum progesterone value was examined to confirm the ovulation (≥5 ng/mL), semen analyses performed, tubal patency was evaluated via hysterosalpingography and/or laparoscopy. If the semen test result was abnormal, it was repeated at least six weeks later to confirm the abnormal result. Couples with ovulatory cycles, bilateral patent uterine tubes, and normal semen analyses were considered as unexplained infertility. The exclusion criteria were as follows: oligo/anovulation, bilateral tubal pathology, BMI >30 kg/m2, history of tubal or ovarian surgery, documented endometriosis, overt thyroid dysfunction with increased or reduced serum fT3 or fT4, being under thyroid disorder treatment, other endocrine disorders, and male factor infertility. Canceled cycles were also excluded. All the included IUIs were the first treatment cycles of the patients. We classified the patients as serum TSH levels 0.5-2.49 mIU/L (group A) and 2.5-4.5 mIU/L (group B) (19).

Clinical and Laboratory Procedures

Ovulation induction was initiated after the transvaginal ultrasound (TvUS) scan on the third day of her period. In all patients, ovulation induction was performed with recombinant FSH (rFSH). The beginning gonadotropin dose was determined depending on the patient's age, BMI, the hormonal profile on the 3rd day, and the antral follicle number. The patients were followed up with a TvUS scan, and follicle size, count, and endometrial thickness were evaluated. rFSH dose re-adjusted as needed according to ovarian response. During this period, estradiol and LH levels of the patients were measured. When the leading follicle achieved a mean diameter of 18 mm, 250 µg recombinant human chorionic gonadotropin (hCG) was done for the final follicular maturation. IUI was performed 34-36 hours following the hCG dose. After 48-72 hours of sexual abstinence, semen specimens were taken from the patient's husband in the laboratory two hours before IUI. These semen samples were processed and inseminated with a soft catheter. Progesterone capsules (200mg, 2x1) were given to the patient to provide luteal phase support after the IUI. The primary outcome measure was the rate of clinical pregnancy. It was diagnosed by detecting an intrauterine gestational sac and/or fetal heartbeat on TvUS 2-3 weeks following the beta-hCG testing day. Miscarriage was described as the loss of gestation before 20 weeks. We described the live birth as the birth of a newborn after 24 weeks of gestation who breathes with a heartbeat.

Electrochemiluminescence immunoassay (ECLIA) was used for serum TSH, fT3, and fT4 measurements (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Science Software (SPSS) Version 21.0 (Chicago, IL, USA). Measured variables were presented as mean±standard deviation (std), and categorical variables were presented as numbers and percentages (%). Shapiro-Wilk test was used to determine whether the numerical data matched the normality distribution. The independent t-test was used to compare the normally distributed data. Mann-Whitney U test was used to compare the non-normally distributed data. A Chi-square test and Fisher's exact test were used to compare qualitative variables. A p-value < 0.05 was considered statistically significant.

RESULTS

During the study period, 421 patients underwent IUI. Two hundred twenty-nine couples were excluded per the exclusion criteria (Figure 1). A total of 192 euthyroid unexplained infertile couples who underwent their first IUI cycle were enrolled in this research. Patients were categorized into two groups, defined by TSH values. Group A was composed of 145 women with TSH values of 0.5-2.49 mIU/L, and group B was composed of 47 women with TSH levels 2.5-4.5 mIU/L. When the obstetric anamnesis of the patients enrolled in the study was examined, no history of parity was present. The demographic characteristics, laboratory levels, and cycle features of the study population are presented in Table 1. There were no statistically significant differences between the two groups in terms of age, duration of infertility, BMI, day 3 FSH, antral follicle count, duration of stimulation, total rFSH dose used, and the number of preovulatory follicles according to TSH level. The IUI outcomes of the patients are presented in Table 2.

There were no statistically significant differences between the two groups for the clinical pregnancy, miscarriage, and live birth rates according to the TSH level.

Table 1. Demographic characteristics, laboratory levels and cycle features of the patients*

	Group A TSH 0.5-2.49 mIU/L (n=145)	Group B TSH 2.5-4.5 mIU/L (n=47)	P value
Age (years)	29 (21-44)	30 (22-39)	0.21
Duration of infertility (years)	4.2±1.9	3.7±1.4	0.62
BMI** (kg/m^2)	22 (17.5-30)	23 (19-29)	0.10
FSH*** (IU/ml)	7.9 (1.7-12)	7.4 (5.8-12)	0.95
fT3**** (pg/mL)	2.96±0.65	2.71±0.58	0.29
fT4***** (pg/mL)	0.92±0.27	0.96±0.24	0.33
Antral follicle count	13.4±6.2	12.7±5.9	0.76
Progesterone, ng/mL	12.2±6.4	13.6±7.3	0.48
TPMSC****** (x10^6)	33 (6-101)	27 (7-52)	0.11
Normal sperm morphology(%)	4.7±0.3	5.2±0.6	0.24
Duration of stimulation (days)	10 (5-20)	11 (5-21)	0.21
Total rFSH dose used (IU)	925 (400-1775)	875 (375-1625)	0.12
Number of preovulatory follicles ≥18mm (n)	1.8±0.6	1.6±0.2	0.95

*Data are shown as mean±standard deviation or median (minimum-maximum). **BMI: Body mass index, ***FSH: Follicle-stimulating hormone ****fT3: free triiodothyronine *****fT4: free thyroxine ******TPMSC: Total progressive motile sperm count. Age, BMI, FSH, TPMSC, duration of stimulation, and total rFSH dose used were analyzed using the Mann-Whitney U test. Duration of infertility, fT3, fT4, antral follicle count, progesterone, normal sperm morphology, and the number of preovulatory follicles were analyzed using the independent t-test

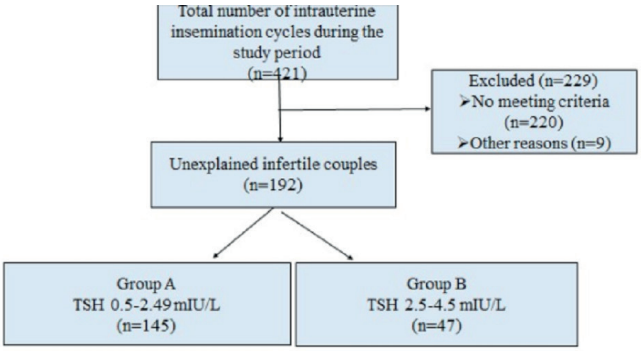

Figure 1. Flow chart of the study

Table 2. The IUI outcomes of the patients according to the TSH level

	Group A TSH 0.5-2.49 mIU/L (n=145)	Group B TSH 2.5-4.5 mIU/L (n=47)	P value
Clinical pregnancy, n (%)	16 (11.03)	4 (8.51)	0.62
Miscarriage, n (%)	5 (3.55)	1 (1.13)	0.65
Live birth, n (%)	11 (7.58)	3 (6.38)	0.78

*Data are shown as number (percentage). A Chi-square test and Fisher's exact test were used to compare qualitative variables.

DISCUSSION

This study sought to assess the importance of preconceptional TSH values on the achievement of IUI in unexplained infertile couples. According to the consequences of this retrospective study, patients with preconception TSH levels between 0.5-2.49 mIU/L had similar IUI outcomes to patients with TSH levels between 2.5-4.5 mIU/L.

Semen analysis is critical in predicting the IUI's success (20). In this study, couples with normal sperm parameters were included for all IUI cycles. Thus, the likelihood of a malefactor causing infertility to reduce the success of IUI was eliminated. In both groups, the total progressive motile sperm count (TPMSC) was over 10x10^6, and according to the Kruger's strict criteria, morphologically normal sperm rates were above 4%. The TPMS count and sperm morphology were similar between the two groups.

Both TSH and thyroid function tests are performed in all patients presenting to our hospital for infertility. This is because thyroid diseases can cause infertility, and maternal hypothyroidism increases adverse pregnancy outcomes, including pregnancy loss, premature birth, and lower motor and intellectual improvement (14, 21, 22). Therefore, the TSH level of the patient during pregnancy is essential. The 2017 guidelines of the American Thyroid Society recommend that the upper limit of TSH in non-pregnant patients should be 4 mIU/L.

The effect of preconceptional TSH values on the results of patients receiving infertility treatment is still controversial. In the study of Karmon et al., it was shown that preconceptional TSH levels between 2.5-4.9 mIU/L were not related to adverse IUI outcomes (23). On the other hand, Karmon et al.'s study with oocyte donors showed that the donor TSH level of ≥ 2.5 mIU/L, independent of the recipient's TSH level, increased the clinical pregnancy rates (13). In contrast with the oocyte donation study, many

recent studies have shown similar clinical pregnancy rates for patients with pre-conceptional TSH levels between 0.5-2.49 mIU/L and 2.5-4.5 mIU/L (24,25). Consistent with the most recent studies, in our study, similar clinical pregnancy rates were observed in euthyroid women with TSH values between 0.5-2.49 mIU/L and those with TSH values between 2.5-4.5 mIU/L.

There are also contradictory results between preconceptional TSH values and miscarriage and live birth rates. A recent comprehensive study suggested that thyroid hormones play a role in the formation and functioning of the placenta. They stated that thyroid disorders are associated with miscarriage and adverse pregnancy outcomes (26). In a nested case-control study, the rate of miscarriage was higher in women with TSH values between 2.5-4.87 mIU/L in the first trimester than those in the range of 0.4-2.5 mIU/L (27). On the other hand, a retrospective study examining the effect of TSH level on the IUI's success with donor sperm in fertile women found that TSH value before IUI had no influence on clinical pregnancy and live birth rates (28). In this research, similar miscarriage and live birth rates were observed in euthyroid women with TSH values between 0.5-2.49 mIU/L and those with TSH values between 2.5-4.5 mIU/L. This result is consistent with the study of the ATA recommending the preconceptional higher limit of TSH as 4 mIU/L.

To avoid contradictory results between the laboratories, all laboratory tests performed in our hospital's laboratory. The day 3 FSH and sperm parameters of the patients included in the study were normal and similar. There was no history of parity in obstetric anamnesis of both groups. The fact that these characteristics of the patients included in the study were within normal limits increases the power to observe the effect of pure TSH level on the primary outcome of the study.

LIMITATIONS

The major limitations of this study were the retrospective design, the lack of hypothetical power analysis, and the low sample size, particularly in group B. However, we could not enroll more participants in this retrospective single-center study because of the strict inclusion and exclusion criteria. Another limitation of our study was the lack of thyroid autoantibodies.

CONCLUSION

This study indicates that among euthyroid patients, preconceptional TSH values between 2.5-4.5 mIU/L do not adversely affect the success of IUI cycles. Therefore, a stricter preconceptional TSH cut-off value may not improve the IUI outcomes. Further large prospective studies are needed to determine the effect of TSH levels on the reproductive success of IUI cycles, in which thyroid autoantibody results are also evaluated.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: The current study was carried out retrospectively by evaluating the medical records of euthyroid patients experienced IUI in Diyarbakir Gazi Yasargil Training and Research Hospital between January 2017 and December 2018. Institutional Ethics Committee approved the study (15.05.2020/463).

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