

# Impact of subclinical hypothyroidism and thyroid autoimmunity on clinical pregnancy rate after intrauterine insemination in euthyroid women

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## ABSTRACT

**Objective:** This study aimed to evaluate the association between subclinical hypothyroidism and thyroid autoantibodies with clinical pregnancy rate after intrauterine insemination (IUI) in euthyroid women.

**Methods:** In this prospective cohort study, we recruited 497 women who underwent IUI treatment. We assessed thyroid function tests, thyroid antibodies and clinical pregnancy rates of the patients.

**Results:** The patients were divided into two groups according to TSH values: normal group, n=387, and subclinical hypothyroidism group 2, n=110. The clinical pregnancy rate was 15.2% in the Control Group and 17.3% in the study group ( $p=0.656$ ). In the Study Group, 35% of the patients had anti-TPO positivity ( $p=0.531$ ) and 42.1% of the patients had anti-TG positivity ( $p=0.285$ ). There was no statistically significant difference in clinical pregnancy rates between the groups in terms of antithyroid antibody positivity ( $p=0.54$ ;  $p=0.559$ , respectively).

**Conclusion:** Anti-TPO antibodies and subclinical hypothyroidism had no impact on clinical pregnancy rates in the women submitted to IUI.

**Keywords:** Autoantibody, clinical pregnancy, intrauterine insemination, subclinical hypothyroidism, thyroglobulin, thyroid peroxidase.

## INTRODUCTION

Thyroid disorders are one of the most common endocrinological diseases affecting women of reproductive age (Negro & Mestman, 2011; Krassas *et al.*, 2010; Sarac & Koc, 2018). They are associated with adverse reproductive outcomes such as spontaneous abortion and infertility (Krassas *et al.*, 2010; Kalem *et al.*, 2016; Liu *et al.*, 2005). Hypothyroidism is responsible for harmful effects on fetal health, the guidelines suggest that TSH (thyroid stimulating hormone) levels should be  $<2.5$  mIU/L in pregnant or first trimester pregnant women (Burman, 2009; Garber *et al.*, 2012). The 2012 guidelines of the American Thyroid Association and the American Society of Clinical Endocrinologists recommend limiting serum TSH to 2.5 mIU/L in euthyroid patients planning to become pregnant (Garber *et al.*, 2012). However, in 2017 the American Society of Thyroid Guidelines recommended the upper reference limit of TSH to 4.0 mIU/L (Alexander *et al.*, 2017). There is no clear consensus on the efficacy of an upper value for TSH and the effects on fertility outcomes (Miko *et al.*, 2017).

Chronic autoimmune thyroiditis (named Hashimoto thyroiditis) (HT), is the most common endocrinopathy in premenopausal women in developed countries (Friedrich *et al.*, 2008). All over the world, iodine deficiency is still the most common cause of thyroid dysfunction (Hayashi *et al.*, 1986). Various studies have shown that HT is associated

with various gynecological problems, recurrent miscarriage, unexplained infertility, and *in vitro* fertilization failure (Dendrinis *et al.*, 2000; Poppe *et al.*, 2007; van den Boogaard *et al.*, 2011; Aydın *et al.*, 2008).

There is a negative association between maternal thyroid dysfunction and low birth weight, preterm birth, preeclampsia and decreased intelligence (De Groot *et al.*, 2012). Subclinical hypothyroidism without thyroid autoantibodies seems to be related to the problems mentioned above (Negro *et al.*, 2010; Benhadi *et al.*, 2009). Therefore, hypothyroidism treatment during pregnancy is essential. Recommendations for the treatment of subclinical hypothyroidism before and during pregnancy also differ (Vila *et al.*, 2014).

Intrauterine insemination (IUI) is widely used to treat infertility, and it is considered a non-invasive and less expensive treatment when compared to assisted reproduction techniques (ART) such as *in vitro* fertilization (IVF) (Dilbaz *et al.*, 2011). The clinical pregnancy rates differ between indications in 8-20% per cycle (Merviel *et al.*, 2014; Dilbaz *et al.*, 2011). Fertility treatment outcome in the presence of thyroid problems is challenging (Practice Committee of the American Society for Reproductive, 2015; Tan *et al.*, 2014; Tuncay *et al.*, 2018).

In this study, we aimed to evaluate a possible association between subclinical hypothyroidism and thyroid autoantibodies with clinical pregnancy rates after intrauterine insemination in euthyroid women.

## MATERIALS AND METHODS

### Sample and Data

We recruited 497 women who applied to the reproductive endocrinology and infertility clinics of the Zekai Tahir Burak Women's Health Education and Research Hospital from October 2015 to June 2017 in this prospective cohort study. The study was approved by the Local Ethics Committee of the institution (05.27.2015 #20), and the universal principles of the Declaration of Helsinki were applied (World Medical Association, 2013). We excluded those with tubal factor infertility, male infertility, endometriosis, and systemic disorders such as overt diabetes mellitus, cardiac pathologies and known thyroid diseases (medications such as levothyroxine or anti-thyroid drugs). Semen samples were obtained by masturbation after 2-3 days of sexual abstinence. Sperm preparation was undertaken using the swim-up technique and stored at room temperature until the time of insemination. IUI was performed using a soft IUI catheter. Semen parameters were analyzed according to the WHO 2010 criteria (Cooper *et al.*, 2010). All patients received clomiphene citrate treatment (50-100 mg/day) (Klomen®, Kocak Farma, Istanbul, Turkey) orally or 37.5-150 IU of pure FSH or human menopausal gonadotropin (hMG) (Gonal-F®, Merck Sereno/ Menogon®, Ferring Pharmaceuticals Istanbul, Turkey), respectively starting on 3-5 cycle days of menstruation and lasting until 7-9 cycle days of menstruation for ovulation induction. The drug dosage was individualized according to patient response and/or the data from the previous cycles. We performed

serial transvaginal ultrasonography (TVUS) examinations. We administered a dose of 10,000 IU of urinary HCG or 250 mg of recombinant HCG (Pregnyl®, Organon, Istanbul, Turkey, respectively) when at least one follicle of  $\geq 18$  mm was seen upon transvaginal ultrasonography. To prevent multiple pregnancies, we included only cycles with mono and bi-follicular growth ( $>18$  mm) in the analysis.

We evaluated the demographic features, infertility types, infertility duration, endometrial thickness on HCG day, basal hormonal parameters (FSH, E2), thyroid function tests [free tri-iodothyronine (fT3) and free thyroxine (fT4) and TSH], thyroid antibodies [antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG) antibodies] and clinical pregnancy rates of the patients. We ran a qualitative serum  $\beta$ -HCG test 14 days after insemination if menstruation had not started. Clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal heartbeat by ultrasound at least 4 weeks after IUI.

### Laboratory Analysis

Blood samples were taken from the participants' antecubital veins. All serum parameters included in this analysis were obtained on the 3rd to the 5th day of the menstrual cycle with IUI. In our department, the normal range for TSH is 0.34-5.6 $\mu$ IU/ml; for fT3 it is 2.5-3.9pg/ml; for fT4 it is 0.61-1.12ng/dl; 0-9IU/ml for anti-TPO; and 0-4IU/ml for anti-TG. These normal ranges were calculated by the laboratory and all examined serum parameters were determined in the ISO-certified central laboratory of the Dr. Zekai Tahir Burak Women's Health Care University of Health Sciences, Education and Research Hospital, Ankara, TURKEY, using commercially available assays using the Elecsys electrochemiluminescence immunoassays on a Cobas 6000 immunoanalyzer (Roche Diagnostics, Mannheim, Germany). The inter and intra assay CVs were  $<2\%$  and  $<6.5\%$  for TSH,  $\leq 2\%$  and  $<5\%$  for fT4,  $\leq 2\%$  and  $<5\%$  for fT3,  $<5\%$  and  $\leq 7\%$  for anti-TPO,  $<2\%$  and  $\leq 5\%$  for anti-TG. The TSH measuring range was 0.005-100  $\mu$ IU/mL; for fT3 it was 0.3-10 nmol/L; for fT4 it was 0.101-7.77 ng/dL; for anti-TPO it was 5-600 IU/ml; for anti-TG it was 10-4000 IU/ml.

### Statistical Analysis

We used the statistical Package for the Social Sciences, version 23.0 (SPSS Inc., Chicago, IL) for the statistical analysis. The sample size calculation for the entire study population, a two-sample comparison with a 5% level of significance ( $\alpha$ ) and a power of 0.80 with an allocation ratio of 3:1, gave a study population of 315 vs. 104

women in each group. Sample size calculations were performed using the G\*Power v3.1.5 general power analysis program (Faul *et al.*, 2007). For quantitative data, we used mean values and standard deviations, whereas for quantitative data we used numbers and percentages. We used the Kolmogorov-Smirnov and Shapiro-Wilk tests to assess the normal distribution of the univariate variables. In order to analyze the variables that did not have normal distribution we used non-parametric methods. Non-parametric variables between groups were compared through the Mann-Whitney U test. For categorical variables we used the Fisher's exact or the Pearson Chi-Square test, where appropriate. We ran an ROC curve analysis to determine a cut-off value for pregnancy prediction.  $p$  values less than 0.05 indicated statistical significance. The  $p$ -value presented in our statistical analysis are for two-tailed tests.

## RESULTS

The area under the ROC curve revealed that no cut-off value of TSH can predict pregnancy in intrauterine insemination cycles (the area under the ROC curve was 0.495 (%95 CI: 0.424-0.566) ( $p$ -value=0.887). Therefore, the patients were divided into two groups as TSH values between 0.35-2.49mIU/L (group 1,  $n=387$ ) and 2.52-4.88 mIU/L (group 2,  $n=110$ ). The groups were statistically comparable in terms of the variables mentioned.

Demographic features of the subjects are shown in Table 1. Of these, 387 women (77.2%) had TSH values between 0.35-2.49 mIU/L (control group), and 110 women (22.8%) had TSH values between 2.52-4.88 mIU/L (study group). There were no statistically significant differences between the groups in terms of age, BMI, infertility duration, infertility type (primer/secondar), ovulation induction protocol and clinical pregnancy rates ( $p>0.05$ ). The clinical pregnancy rate was 15.2% in the Control Group and 17.3% in the study group ( $p=0.656$ ). There was no statistically significant difference between the groups in terms of FSH, E2 and endometrial thickness on the ovulation trigger day (Table 2).

Anti-TPO positivity was present in 35% vs. 29.2% of patients in the Study and Control groups, respectively ( $p=0.531$ ); while anti-TG positivity was present in 42.1% vs. 29% in the Study and Control groups, respectively ( $p=0.285$ ) (Table 2). There was no statistically significant difference for clinical pregnancy rates between the groups in terms of antithyroid antibody positivity (Figures 1 and 2). No statistically significant difference between the

**Table 1.** Comparison of the subjects' demographic features

	Control Group (n=387)	Study Group (n=110)	p-value
Age (years)	27 (18-44)	26 (19-34)	0.395**
BMI (kg/m <sup>2</sup> )	24.44 (16.44-40.39)	24.69 (18.73-38.71)	0.313**
Infertility duration	3 (1-14)	3 (1-14)	0.176**
Infertility -Primary -Secondary	298 (77%) 89 (23%)	85 (77.3%) 25 (22.7%)	1.00*
Ovulation Induction clomiphene citrate rFSH hMG	248 (64.1%) 128 (33.1%) 11 (2.8%)	67 (60.9%) 40 (36.4%) 3 (2.7%)	0.813*
Clinical pregnancy rate, n (%)	59 (15.2%)	19 (17.3%)	0.656*

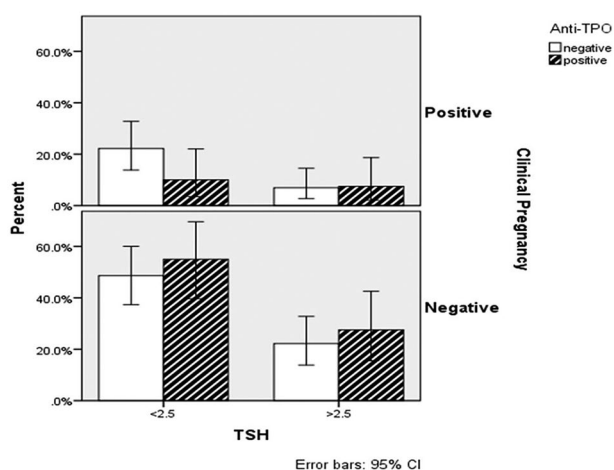
\*Fisher's exact

\*\*Mann Whitney U

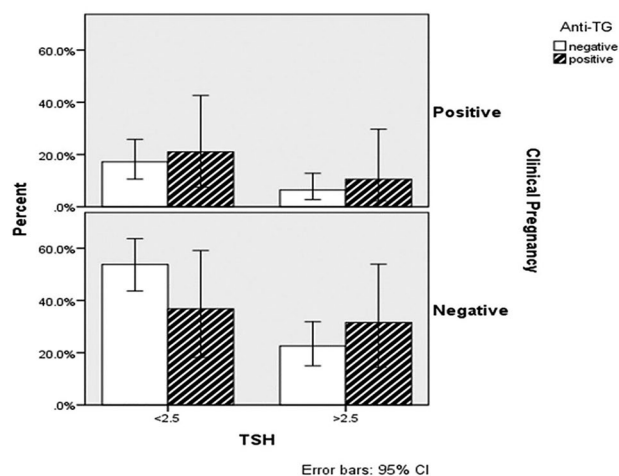
Table 2. Laboratory parameters			
	Control group (n=387)	Study group (n=110)	p-value
FSH	6.51 (4-15)	6.7 (3.2-55.7)	0.879**
E2	42 (5-163)	39.77 (5-84)	0.567**
Endometrial Thickness	9 (4-15)	8.5 (5-17)	0.528**
TSH	1.36 (0.35-2.49)	3.15 (2.52-4.88)	<0.0001**
ft3	3.09 (2.12-4.65)	3.16 (2.3-4.8)	0.54**
ft4	0.91 (0.56-3.24)	0.92 (0.68-1.54)	0.559**
Anti-TPO (%)	29.2%	35%	0.531*
Anti-TG (%)	29%	42.1%	0.285*

\*Fisher's exact

\*\*Mann Whitney U



**Figure 1.** The clinical pregnancy rate of patients concerning TSH and anti-TPO positivity



**Figure 2.** The clinical pregnancy rate of patients about TSH and anti-TG positivity

groups was seen in terms of ft3 and ft4 results ( $p=0.54$ ;  $p=0.559$ , respectively) (Table 2).

## DISCUSSION

The fertility treatment outcome in the presence of thyroid autoimmunity (TAI) and subclinical hypothyroidism is contradictory (Unuane *et al.*, 2017; Medenica *et al.*, 2015; Karmon *et al.*, 2015; Jatzko *et al.*, 2014; Tuncay *et al.*, 2018). In this study, we investigated the fertility outcome in euthyroid women treated with IUI concerning the TSH threshold and antithyroid antibodies. We found no significant differences in fertility outcomes among euthyroid women between the groups. The clinical pregnancy rate was similar between the two groups. 59 patients (15.2%) out of the 397 patients in the low-TSH group (Control Group) became pregnant, whereas the clinical pregnancy rate was 19/110 (17.3%) in the subclinical hypothyroidism group (Study Group).

In the euthyroid patient group with women of normal upper TSH values we have found similar IUI outcomes compared to women with baseline TSH <2.5 mIU/L. Unexpectedly, some of the previous studies also showed results similar to those from our study; the women with a TSH score of >2.5 mIU/L before IUI had a higher birth rate after a clinical pregnancy and lower spontaneous abortion risk (Tuncay *et al.*, 2018; Jatzko *et al.*, 2014). Reh *et al.* (2010) observed that there was no significant difference in clinical pregnancy or birth rates between TSH levels of 0.4-2.4 mIU/L and women above 2.5 mIU/L in the infertile population. They did not report any difference in miscarriage rates in the low and high TSH groups (Reh *et al.*, 2010). In another study carried out by Karmon *et al.* (2015), there was no significant difference in clinical pregnancy rates among women with TSH levels of 0.4-2.4 mIU/L and levels > 2.5 mIU/L. In addition, they found that preconceptional TSH levels were inversely associated with spontaneous abortion and positively associated with live birth after clinical pregnancy (Karmon *et al.*, 2015).

The American Thyroid Association supported the 2012 guidelines on hypothyroidism management in pregnancy (Garber *et al.*, 2012). The document strengthens the idea of keeping TSH levels at <2.5 mIU/L in women with hypothyroidism during the first trimester of pregnancy. Guidelines should also recommend treatment if TSH levels for euthyroid women are 2.5 mIU/L or higher in the first trimester or in those planning a pregnancy. This supports the view that physiologically HCG cross-reacts with the TSH receptor and causes a decrease in TSH levels (Gilbert *et al.*, 2008).

In addition, many studies have redefined the TSH reference intervals in pregnancy and argued that there should be lower values in the first trimester (Springer *et al.*, 2009;

Garber *et al.*, 2012; Ödöl *et al.*, 2009). However, there is no evidence that pre-pregnancy outcome in early euthyroid women with high normal TSH levels has altered early cycle and pregnancy outcomes. Furthermore, since general screening is not recommended, it is difficult to make a decision to intervene in the high normal TSH values found incidentally in a non-pregnant asymptomatic patient (Committee on Patient Safety and Quality Improvement; Committee on Professional Liability, 2007).

Recent studies in pregnant women in Asia (China, Korea, and India) have shown that there is only a minimal reduction in the upper reference level (Li *et al.*, 2014; Moon *et al.*, 2015). According to these results, in the recent guidelines of the American Thyroid Association, the lower reference range of TSH decreased by about 0.4 mIU/L, the upper reference range decreased by about 0.5 mIU/L. This corresponds to a TSH upper limit of 4.0 mIU/L for patients in the first trimester (Alexander *et al.*, 2017). In our study, no cut-off limit for TSH can be found to predict pregnancy. A recent guide from the Practice Committee of the American Society for Reproductive Medicine (2015) states that there is insufficient data to indicate that TSH levels between 2.5 and 4 mIU/L are associated with abortion and pregnancy side effects.

In a study by Negro *et al.* (2010), in 4,123 thyroid antibody-negative women, it was reported that the loss of pregnancy below 11 weeks was higher in people with TSH levels of 2.5-5 mIU/L. There may be a few reasons for this. The authors did not work on the infertile population, but included women who were in their first trimester with spontaneous pregnancies. In their study, all TSH levels were measured in the preconceptional period. This difference can be explained in part as follows; women with TSH levels  $\geq 2.5$  mIU/L in the first trimester may have higher levels before pregnancy if TSH drops in early gestation, as suggested in the literature (Gilbert *et al.*, 2008). In addition, over-stimulation appears to influence TSH levels (Gracia *et al.*, 2012). Future studies should clarify the potential benefits of treatment of women with high normal TSH levels who are already pregnant and asymptomatic, or who plan to become pregnant (naturally or otherwise).

The strengths of this study include the large sample size and its unique population of women undergoing IUI, which allowed the uniform assessment of preconceptional levels of TSH. A related point is that all the patients in our center routinely undergo TSH measurement before receiving IUI treatments.

Despite these advantages, an associated limitation is that the live birth, spontaneous abortion and other obstetric or fetal end points of our subjects were not available. Further evaluation of this relation is necessary to rule out the possibility of chance and unmeasured confounding.

TSH and TAI were independently associated with pregnancy outcomes after spontaneous conception or ART (Thangaratinam *et al.*, 2011). One review showed antithyroid antibodies were not associated with increased reproductive loss in patients submitted to ART treatments (Leiva *et al.*, 2017). In two meta-analyses carried out with ART (Busnelli *et al.*, 2016; Toulis *et al.*, 2010), TAI has a potentially harmful effect on pregnancy. In a meta-analysis involving twelve studies, Busnelli *et al.* (2016) showed a negative TAI effect in terms of an increased risk of miscarriage and a decreased chance of live birth. In another meta-analysis involving four studies, Toulis *et al.* (2010) showed a 2-fold increase in risk of miscarriage for TAI-positive patients, but no significant effect on clinical pregnancy and live birth rates. In another study, pregnancy outcomes of 114 TAI-positive and 495 TAI-negative infertile women were compared and there was no significant difference in implantation, fertilization rate, pregnancy rates and live birth rates (Łukaszuk *et al.*, 2015). Tan *et al.* (2014) concluded that pregnancy outcome was comparable between

women with and without TAI after-ICSI, but TAI status did not affect ICSI outcomes alone.

Several hypotheses have been proposed to explain the possible causal relationship between TAI and negative obstetric outcome. First, TAI can lead to a general immune imbalance, implantation failure targeting the reproductive tract. Thus, thyroid antibodies are considered to be among the causes of fertility problems and recurrent pregnancy loss. Second, thyroid antibodies may cause thyroid function decline as an undesirable pregnancy outcome. A positive TAI status increases the risk of developing (sub) clinical hypothyroidism (Medici *et al.*, 2014). In Unuane's study, the baseline characteristics of both patient groups were similar. There was a significant higher mean TSH in the anti-TPO positive group upon the fertility treatment onset (Unuane *et al.*, 2017).

In conclusion, with this large prospective cohort study we could not find any significant difference in clinical pregnancy rates in women with and without anti-TPO antibodies and subclinical hypothyroidism who underwent IUI. We could not confirm that a TSH level above 2.5 mIU/l has a negative effect on pregnancy rates. More prospective studies are needed to confirm our results, which will shed new light on the impact of thyroid function on IUI success. Future studies will also be useful to clarify which TSH threshold for thyroid hormone replacement should be used for infertile women.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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