

## Effects of Thyroid Stimulating Hormone (TSH) level on clinical pregnancy rate via In Vitro Fertilization (IVF) procedure

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### Abstract

**Background:** Subclinical hypothyroidism may adversely affect In Vitro Fertilization (IVF) outcomes. However the cutoff of thyroid-stimulating hormone (TSH) for diagnosis and treatment is controversial. The aim of this study was to find the association of clinical pregnancy rate with regard to TSH levels in women undergoing IVF.

**Methods:** A historical cohort study of 816 infertile patients who underwent IVF in 2011 and 2012 was conducted. The study subjects were categorized in two groups according to their baseline TSH level; one with  $0.5 \leq \text{TSH} < 2.5$  mIU/L and other with  $2.5 \leq \text{TSH} < 4.5$  mIU/L. All patients were followed up for 6 weeks after embryonic transfer. The outcomes of the study were consisted of rates for Human Chorionic Gonadotropin (HCG) and evaluation of their clinical pregnancies.

**Results:** About 60% of the study subjects had serum TSH level  $< 2.5$  mIU/L and 40%  $\geq 2.5$  mIU/L. There were no statistically significant differences in age, years of infertility, BMI, baseline FSH and estradiol level of patients and the type of induction protocols between the study groups. The HCG rise was occurred in 30.4% of the subjects with TSH level  $< 2.5$  mIU/L versus 26.3% of the subjects with TSH  $\geq 2.5$  mIU/L (p value= 0.2). The clinical pregnancy rates in the group of patients with TSH  $< 2.5$  mIU/L and those with  $\geq 2.5$  mIU/L were 27.1% and 23.9% respectively (p value= 0.3).

**Conclusion:** Our results were similar to various studies in which reported lack of association between TSH level in the range of 0.5- 4.5 mIU/L and IVF outcomes. It seems that lowering the upper limit of normal TSH should be still considered as a scientific debate.

**Keywords:** Thyroid stimulating hormone, clinical pregnancy, In Vitro Fertilization. Subclinical hypothyroidism.

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### Introduction

Overt hypothyroidism is one of the known causes of women infertility problems and adverse perinatal outcomes. Hypothyroidism can result in impaired ovulation, fertilization, placental abruption, abortion and fetal death (1). Treatment of hypothyroidism before and during pregnancy will improve the fertility and minimize the risks of pregnancy complications (2).

Subclinical hypothyroidism which represents milder thyroid failure is a condition with normal serum of free T4 and free T3 levels with elevated serum TSH level (3). This condition could also adversely affect fertility and decreases the chance of clinical pregnancy and increases the risk of preterm delivery of infertile women undergoing in vitro fertilization therapy (4).

Although most of the endocrinological

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references suggest (consider) the serum TSH  $> 4.5$  mIU/L as a subclinical hypothyroidism (3). However other studies support unique findings in women anticipating pregnancy and recommend to consider TSH  $\geq 2.5$  mIU/L considered to be the cut off point for subclinical hypothyroidism which requires treatment in the early stage of disease (5, 6).

There are also some evidences that infertile women who undergone in vitro fertilization (IVF), the TSH  $\geq 2.5$  mIU/L could result in lower gestational age at delivery and low birth weight compared to those with TSH  $< 2.5$  mIU/L (7). Moreover the T4 replacement in women with subclinical hypothyroidism, will improve the pregnancy rate and delivery in women who become pregnant through IVF (8). However it has also been argued that considering the cutoff point of 2.5 mIU/L might be more applicable for iodine-sufficient and higher cutoff for upper limit of normal in an iodine deficient populations (7). The purpose of this study was to determine the association of IVF outcomes in women undergoing in vitro fertilization, with regard to their TSH levels.

## Methods

This study was a historical cohort study on infertile women undergoing IVF therapy in 2011 and 2012. The study population consisted of 816 infertile women candidate for IVF with TSH level between 0.5 and 4.5 and free T4 and T3 level in normal range. The serum TSH level of all was measured within 6 month prior to procedure IVF. History of overt thyroid dysfunctions or uses of thyroid medications were considered as exclusion criteria.

All women became pregnant through IVF with fresh or freeze embryos by standard or short protocols for ovarian stimulation. In addition they were followed for 6 weeks after the transfer. The serum beta Human Chorionic Gonadotropin (HCG) was measured two weeks after embryo transfer, and vaginal ultrasound performed 6 weeks after embryo transfer. Outcomes of the study were consisted of pregnancy rates with various HCG level two weeks after embryo transfer, and evaluation of clinical pregnancy (presence of gestational sac and fetal cardiac activity by transvaginal ultrasonography in week 6).

Comparisons were made for outcome variables in women with  $0.5 \leq \text{TSH} < 2.5$  mIU/L versus  $2.5 \leq \text{TSH} < 4.5$  mIU/L. Statistical analysis was done using Stata 10 software statistical analysis package. Student t-test was also used for comparing means and chi square test for comparing categorical variables. Two-sided P values  $< 0.05$  were considered statistically significant.

## Results

Of the 816 women with history of  $6.6 \pm 4.4$  years (mean  $\pm$  SD) infertility complaint, 487 (59.7%) had serum TSH level  $< 2.5$  mIU/L and 329 (40.3%) TSH  $\geq 2.5$  mIU/L. Baseline characteristics of the study groups are presented in Table 1. There were no statistically significant differences in age, years of infertility, BMI, baseline FSH and estradiol level of patients with a TSH  $< 2.5$  mIU/L versus those with TSH  $\geq 2.5$  mIU/L.

The IVF type performed in each group is shown in Table 2. There was no difference in the frequency of cycles using frozen or fresh embryos and in the frequency of dif-

Table 1. Baseline characteristics of the study groups before treatment for IVF cycles

	TSH $< 2.5$ mIU/L (n=487)	TSH $\geq 2.5$ mIU/L (n=329)	p Value
Age (years)	$30.4 \pm 5.04$	$30.64 \pm 5.78$	0.53
History of infertility (years)	$6.61 \pm 4.2$	$6.68 \pm 4.53$	0.82
BMI (kg/m <sup>2</sup> )	$26.2 \pm 4.1$	$26.8 \pm 4.3$	0.079
FSH (IU/L)	$6.66 \pm 2.8$	$6.65 \pm 2.7$	0.93
Estradiol	$56.1 \pm 50.7$	$54.7 \pm 60.7$	0.72
TSH (mIU/L)	$1.49 \pm 0.56$	$3.39 \pm 0.68$	$< 0.0001$

Table 2. Comparison of IVF characteristics in study groups

	TSH<2.5 mIU/L (n=487)	TSH ≥ 2.5 mIU/L (n=329)	P Value
Number of metaphase II oocyte	6.75 ± 4.4	6.57 ± 3.9	0.67
Number of Egg Transferred	2.85 ± 0.96	2.86 ± 1.03	0.87
Embryo type			0.47
Fresh	84.2%	86.0%	
Frozen	15.8%	14.0%	
Induction protocol in Fresh embryos			0.65
Long	93.7%	91.9%	
Antagonist	5.1%	6.7%	
Mini	1.2%	1.4%	

Table 3. Comparison of HCG rise and clinical pregnancy in groups

	TSH<2.5 mIU/L (n=484)	TSH ≥ 2.5 mIU/L (n=327)	P Value
HCG rise	147 (30.4%)	86 (26.3%)	0.2
Clinical pregnancy	131 (27.1%)	78 (23.9%)	0.3

ferent induction protocols between the those of women with TSH<2.5 mIU/L and cohort with TSH ≥ 2.5 mIU/L.

The HCG rise was occurred in 28.7% and clinical pregnancy in 25.7% of the women. There was no statistically significant difference in pregnancy outcomes between the two groups of the study (table 3). The risk ratio of negative clinical pregnancy was 1.04 (95% CI: 0.96-1.13) with TSH ≥ 2.5 mIU/L compared with TSH <2.5 mIU/L.

Further analysis to compare HCG rise and clinical pregnancy rates in four different groups of TSH levels i.e. 0.5-1.5, 1.5-2.5, 2.5-3.5, and 3.5-4.5 mIU/L did not show statistically significant difference ( $p > 0.05$ ).

## Discussion

The prevalence of a mildly elevated TSH (2.5 – 4.5 mIU/L) was near 40% in women. Michalakakis et al. has reported that 23% of infertile women had TSH >2.5 mIU/L and <4 mIU/L (9). Our study showed that TSH level in the range of 0.5- 4.5 mIU/L was not associated with clinical pregnancy rate in infertile women undergoing IVF. This finding was in agreement with the results of the other studies that found clinical pregnancy rate, adverse fetal and maternal outcomes in group of women with TSH ≥ 2.5 mIU/L were similar to the group with TSH< 2.5 mIU/L (5, 9, 10). The observation that mildly elevated basal TSH (2.5-4.5 mIU/L) does not impact clinical preg-

nancy rate, was consistent with results of the studies by Konstantinos et al and Reh et al. (5, 9). They found no difference in clinical pregnancy, delivery, or miscarriage in women with mildly elevated basal TSH compared to a normal TSH level (0.4 - 2.5 mIU/L). Baker et al also did not find statistically significance correlation between TSH level and spontaneous abortion rate; however they reported that gestational age at delivery and birth weight in women who become pregnant through IVF were lower in cycles with TSH ≥ 2.5 mIU/L compared with TSH <2.5 mIU/L (8).

Moreover there is also debate on TSH threshold for initiation of treatment on infertile women undergoing assisted reproduction therapies. The Endocrine Society guideline recommends that for women with previously diagnosed clinical hypothyroidism the upper limit of the reference range of TSH should be 2.5 mIU/L (6). However, the usage of this stricter TSH level could not necessarily lead to more success rates of clinical pregnancy, delivery, or miscarriage (5). This would also result in an increase in the number of women being identified as subclinical hypothyroid with unnecessary treatment (5). In a recent meta-analysis of 3 randomized controlled trials study the effect of levothyroxine treatment on pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction therapy revealed that levo-

thyroxine treatment had significantly lowered miscarriage rate and resulted in higher delivery rate with no effect on clinical pregnancy rate. However, the authors had used TSH cut-of level of 4.0 or 4.5 mIU/l for diagnosis of subclinical hypothyroidism and therefore reported the benefits of treatment with levothyroxine in these studied cases (11).

This study had retrospective design but the data for late pregnancy outcomes was not available. However, the accurate registry files of the patients made it possible to consider the potential confounding effect of age, years of infertility, and BMI in our analysis.

### Conclusion

We found no evidence that clinical pregnancy rate was reduced among women with preconception elevations in TSH level of 2.5 - 4.5 mIU/L when compared to those with a normal TSH level prior to ovarian stimulation.

However, this does not refute the potential benefits of TSH screening in infertile women to find overt and subclinical thyroid dysfunctions and early treatment them (12).

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