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Intrauterine Insemination Success Rates Between Patients TSH Level of 2.5 mIU / L and 2.5-4.5 mIU/L

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Abstract: The aim of this study to assess whether there is a need to decrease the TSH level below 2.5 mIU/L in unexplainable infertility patients who were undergoing intrauterine insemination and determining the difference between patients with a TSH level of 2.5 mIU / L and patients with a TSH level of 2.5-4.5 mIU/L in terms of the success of intrauterine insemination. This study conduct via cross-sectional examinations of the 272 patients who applied to Ümraniye Training and Research Hospital infertility outpatient clinic between 01.06.2017-01.10.2019, who underwent intrauterine insemination with the diagnosis of unexplained infertility. Results research the mean age of the cases participating in our study is 31.65 \pm 5.28, and the mean BMI measured as 24.17 \pm 4.30 kg / m2. TSH values range from 0.3 to 5.2, with an average of 1.84 ± 0.93; while TSH value of 174 cases (77.3%) is below 2.5 mIU/L, TSH value of 51 cases (22.7%) is between 2.5-4.5mIU/L. Within the control group with TSH <2.5 mIU/L, the cycle was canceled in 13 cases (7.5%), pregnancy did not occur in 143 cases (82.2%). While ongoing pregnancy was achieved in 17 cases (9.8%), clinical pregnancy was achieved in 1 case (0,6%). Also, within the study group with a TSH value of 2.5-4.5 mIU/L, cycles were canceled in 7 cases (13.7%), pregnancy did not occur in 40 cases (78.4%), and ongoing pregnancy was achieved in 4 patients (7.8%). There was no statistically significant difference in terms of intrauterine insemination success between the control group with TSH <2.5 mIU / L and the study group with TSH 2.5-4.5 mIU/L. Widespread randomized controlled prospective studies need to determine the optimal TSH threshold value before TSH treatment of the women receiving infertility treatment.

Keywords: Thyroid stimulating hormone; insemination; infertility,

INTRODUCTION

Thyroid hormones, which play many a role in regulating countless metabolic activities in the human body, are essential both in the implantation process in early pregnancy and for the fetus's healthy development and normal continuation of pregnancy¹. The thyroid gland functions, which embryologically derive from the endodermal epithelium, are regulated by thyrotropin-releasing hormone (TRH) and stimulating thyroid hormone (TSH). While TSH stimulates the production of thyroxine

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(T4), which is a prohormone in the thyroid gland, it also regulates the conversion of T4 to its active form, triiodothyronine (T3) in peripheral tissues². As with the many tissues of the body, the endometrium is also known to have thyroid hormone receptors that think to be associated with endometrial physiology and implantation³. According to the American National Health and Nutrition Examination Survey (NHANES); Normal free T4 levels, along with a TSH level of >4.5 mlU/L, were considered as subclinical hypothyroidism⁴. As for The American Clinical Endocrinology Association (AACE) and the American Thyroid Association (ATA), they determined the uppermost threshold of TSH levels during pregnancy as 2.5 mlU/L in the first trimester, three mlU/L in the second trimester, and 3.5 mlU/L in the third trimester⁵. The adverse effects of overt hypothyroidism on infertility are known, but the relationship between subclinical hypothyroidism and infertility has not yet been established⁶.

There are different publications in the literature about the upper limit of TSH accepted in subclinical hypothyroidism about studies conducted in patients receiving ovulation induction and intrauterine insemination therapy or in vitro fertilization therapy. The clinical practice guide published by the American Endocrine Society in 2012 recommends thyroid replacement should the TSH level before treatment be >2.5 mIU/L in infertile women⁷. The American Reproductive Medicine Association (ASRM), on the other hand, proclaims that there is not enough evidence to associate cases with TSH levels of 2.5-4 mIU / L and free T4 levels with increased risk of infertility and increased risk of miscarriage⁸.

In this study, we analyzed patients who have different TSH levels beginning of the Intrauterine insemination treatment. We aimed to investigate the relationship between TSH level and intrauterine insemination success in couples with unexplained infertility with intrauterine insemination.

MATERIALS AND METHODS

Couples who applied to the Umraniye Training and Research Hospital Infertility Clinic between June 2017 and October 2019 include in the study. Primary infertile couples who have not had a pregnancy despite one year of unprotected intercourse and had ovulation induction by clomiphene citrate and recombinant FSH with intrauterine insemination cycles, along with secondary infertile couples who could not conceive despite unprotected intercourse for six months, were retrospectively screened. 441 treatment cycles applied on 272 infertile couples, along with their treatment cycle files, were analyzed.

Patients with the following features excluded from the study; patients with hypothyroidism and hyperthyroidism during treatment, patients with previous thyroid surgery history, patients with TSH > 4.5 mIU/L, thyroid antibody positivity, or using thyroid hormone preparation, patients with hypogonadotropic hypogonadism, patients with endometriosis, history of ovulatory surgery or tube surgery, patients with conditions that cause cavity deformations such as fibroids, polyps, and congenital uterine malformations, patients with male infertility factors, and patients who have experienced spontaneous ovulation and not inseminated.

A total of 225 cycle implementations performed in 151 infertile couples with unexplained infertility, whose chosen criteria were as follows: patients with TSH <4.5 mIU/L and normal free T3 and free T4 values during treatment ovulatory dysfunction and

unexplained infertility, the functioning of at least one tube/one-way tubal transition according to the results of hysterosalpingography, a uniform endometrial space structure, and couples with the male partner possessing a "total post-washing progressive motile sperm count" as greater than 15 million. Unexplained infertile patients are divided into two groups: ones with TSH value <2.5 mIU/L being the control group and ones with TSH value 2.5-4.5 mIU/L being the study group. Body mass index (BMI) had been measured as; BMI (kg/m2)= Body weight (kg)/Height2(m)

Ovulation Induction

Basal FSH, LH, and estradiol levels of the patients were analyzed with the Abbott Architect i200 SR device by the manufacturer's recommendations. The patients applied to our outpatient clinic on the third day of their cycle, when the basal endometrium thickness and antral follicle analysis perform. Ovulation induction was performed between the 5th and 9th days of the process via Clomiphene Citrate (CC) with a daily dose range of 50-150 mg/day. Ovulation induction via gonadotropin and the follicle follow-up procedure was started on the 3rd day of the cycle via recFSH (Gonal-f Merck İlaç Ecza ve Kimya Tic. A.Ş., Puregon Merck Sharp Dohme İlaçları Ltd. Şti., Fostimon IBSA İlaç San. Ve Tic. Ltd. Şti.), Human FSH (Fostimon IBSA İlaç San. Ve Tic. Ltd. Şti.) and FSH+LH (Menogon, Ferring, Kiel, Germany) administration, with a daily starting dose of 75 IU/day. In comparison, the amount was increased by 37.5 IU/day in tandem with follicle development. As soon as the dominant follicle reached 18mm in size, ovulation was triggered with 250 mcg re HCG. Ultrasonography ((Hitachi Aloka Prosound F37) use for basal ultrasound examinations and follicle follow-up of patients.

Sperm Preparation

After 3-7 days of sexual abstinence, sperm samples take to our university's andrology laboratory on the morning of intrauterine insemination. Sperm samples to use in insemination prepared by two-layer gradient swim-up technique.

Intrauterine Insemination

Thirty-six hours after the application of RecHCG by experts certified in fertilization treatment techniques and employed by our hospital's infertility clinic, a sperm sample was collected from the patient's partner, and intrauterine insemination performs through a soft cannula. Before the procedure, the cervix sterilizes with a sterile saline solution, and the cervical mucus, if any existed, was slowly removed. In our hospital, an ultrasonography device does not use during insemination procedures. Patients give a 15-minute rest period to rest, and patients did not provide luteal phase support therapy. To apply legal regulations in our country and to prevent multiple pregnancy cases, RecHCG was not used to avoid the presence of more than two follicles equal to or greater than 16 mm, the insemination procedure was canceled, and couples were advised not to have sexual intercourse. As the primary evaluation criterion in our study, Beta-HCG examines in the patient's blood 14 days after intrauterine insemination. A value of 50 and above was evaluated as a positive pregnancy test result, while pregnancies reached 12 weeks and assessed above as ongoing pregnancy. (Ovulation induction treatments, follicle followups, and intrauterine insemination procedures regarding infertile couples performed by certified specialists employed in our hospital specialized in fertilization treatment techniques).

This study approves by the Local Ethics Committee of Umraniye Training and Research Hospital (Ethics Committee Approval No: B.10.1TKH.4.34.H.GP.0.01/206).

The study conduct by the World Medical Association's Helsinki Declaration for Human Studies.

Statistical Analysis

Statistics were performed with the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used. Simultaneously, the study data evaluate—the suitability of quantitative data for normal distribution tested by Shapiro-Wilk test and visual examinations. The student's T-test use to compare the normal distribution quantitative variables between two groups, and the Mann-Whitney U test use to reach the quantitative variables that did not show normal distribution between the two groups. To make a comparison between the qualitative data, the Pearson Chi-Square test, and Fisher-Freeman-Halton test use. Statistical significance has been determined at p <0.05 levels for all values.

RESULTS AND DISCUSSION

174 cycle cases with TSH <2.5 mIU/L were accepted as the control group, whereas 51 cycle cases with TSH values between 2.5-4.5 mIU/L taken as the study group. Among the groups, there was no statistically significant difference between parameters such as age, BMI distributions, smoking status, male ages, previous methods of protection, and duration of unprotected intercourse. Among groups, there was a statistically significant difference between education levels. The proportion of primary school graduates in the study group was higher than the control group (p=0,008). In the case of smoking among spouses, a statistically significant difference was found between the groups. The rate of smoking in the study group was higher than that of the control group (p=0,006). Among groups, a statistically significant difference was found between the number of intercourse per week. In the study group, the number of intercourse per week was higher than the control group (p=0,004). The demographic characteristics of the groups shown in Table 1.

There was a statistically significant difference between baseline FSH levels on the 3rd day of menstruation between the two groups (p=0,032). The FSH measurements of the study group were lower than the control group. Simultaneously, there was no difference found in basal LH, E2, and prolactin levels. (Table 2). There was no statistically significant difference found between the agents used for ovulation induction in both groups. (Table 3). In both groups, no statistically significant difference was found between the endometrium thicknesses and insemination successes on the day of intrauterine insemination (Table 4).

Thyroid hormones play an essential role in fetal development and pregnancy, ranging from fertilization to implantation¹. The relationship of overt hypothyroidism with poor obstetric outcomes and infertility demonstrated, but there are many different publications on subclinical hypothyroidism's effects on infertility. This difference is related to the different TSH limit values for the diagnosis of subclinical hypothyroidism. ASRM proclaims that there is no sufficient evidence to relate the cases, where TSH levels are 2.5-4 mIU/L, and free T4 levels are normal, with an increased risk of miscarriage infertility⁸. However, AACE and ATA determined the upper threshold value for TSH during pregnancy as 2.5 mIU/L in the first trimester, 3 mIU/L in the second trimester, and 3.5 mIU/L in the third trimester⁵.

Table 1: Demographic Features of Both Groups

		Control group (n=174)	Study group (n=51)	ρ
Age (year)	Min-Max (Median) Overall±Ss	21-46 (31) 31.80±5.24	20-48 (30) 31.14±5.42	^a 0.432
BMI (kg/m²)	Min-Max (Median) Overall±Ss	16-41.8 (24) 24.33±4.13	18-36 (22) 23.65±4.84	^a 0.328
Education Level	Primary education Secondary education Associate/Undergraduate	32 (18.4) 86 (49.4) 56 (32.2)	20 (39.2) 18 (35.3) 13 (25.5)	^c 0.008**
Smoking	None Present	135 (77.6) 39 (22.4)	39 (76.5) 12 (23.5)	^c 0.867
Age of spouse (year)	Min-Max (Median) Overall±Ss	22-50 (34) 34.81±4.76	25-45 (33) 33.63±4.58	^a 0.117
Spouse smoking	None Present	109 (62.6) 65 (37.4)	21 (41.2) 30 (58.8)	^c 0.006**
Previous protection methods	None Coitus interruptus Barrier methods Hormonal methods IUD	96 (55.2) 40 (23.0) 30 (17.2) 7 (4.0) 1 (0.6)	30 (58.8) 12 (23.5) 6 (11.8) 3 (5.9) 0 (0)	^d 0.808
Duration of unprotected intercourse (month)	Min-Max (Median) Overall±Ss	6-144 (24) 29.76±22.44	6-84 (18) 25,69±17.99	^b 0.167
Number of intercourse per week	Min-Max (Median) Overall±Ss Less than ≤1 Twice Thrice More than ≥4	0-5 (3) 2.60±0.83 11 (6.3) 64 (36.8) 81 (46.6) 18 (10.3)	1-5 (3) 2.98±0.88 3 (5.9) 10 (19.6) 24 (47.1) 14 (27.5)	^b 0.004**
	Present	53 (30.5)	8 (15.7)	

^aStudent t Test, ^bMann Whitney U Test, ^cPearson Chi-Square Test ^dFisher Freeman Halton Test, *p<0.05, **p<0.01

Table 2: Laboratory Results of Both Groups

	rable	2. Laboratory Rest	alls of both Groups	
		Control group	Study group	p
		(n=174)	(n=51)	
Basal FSH	Min-Max (Median)	1-10.1 (5.8)	2.8-7.5 (5.4)	^a 0.032*
	Overall±Ss	5.85±1.54	5.33±1.43	
Basal LH	Min-Max (Median)	1.4-13.3 (4.1)	2-8.7 (4.2)	^a 0.947
	Overall±Ss	4.40±1.75	4.38±1.65	
Basal E2	Min-Max (Median)	11-170 (43)	20-128 (41)	^b 0.826
	Overall±Ss	47.49±24.18	46.59±18.76	
Basal	Min-Max	1.3-91 (13.4)	6.3-48 (14.7)	^b 0.192
Prolactin	(Median)			
	Overall±Ss	15.67±10.52	16.23±7.28	
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^aStudent t Test, ^bMann Whitney U Test, *p<0.05

Table 3: Comparison of Both Groups According to the Agents Used for Ovulation Induction

		Control group (n=174)	Study group (n=51)	р
Agents used	Clomiphene Citrate	38 (22.0)	9 (18.0)	°0.545
	Gonadotropins	135 (78.0)	41 (82.0)	
	rFSH	117 (67.2)	37 (72.5)	^d 0.752
	hFSH	11 (6.3)	3 (5.9)	
	FSH+LH	7 (4.0)	1 (2.0)	
	Spontaneous IUI	1 (0.6)	1 (2.0)	

^dFisher Freeman Halton Test

Table 4: Evaluation of Result Properties According to TSH Level

		Control group	Study group	р
		(n=174)	(n=51)	
IUI day	Min-Max	5-16.5 (9)	6-16 (9.3)	^a 0.123
Endometrial	(Median)			
thickness	Overall±Ss	8.88±1.96	9.35±1.83	
Success of IUI	Negative	143 (82.2)	40 (78.4)	^d 0.542
	Ongoing pregnancy	17 (9.8)	4 (7.8)	
	Cancellation of cycles	13 (7.5)	7 (13.7)	
	Clinical	1 (0.6)	0 (0)	
	pregnancy			

^aStudent t Test, ^dFisher Freeman Halton Test

In literature, some related studies have shown that miscarriage rates are higher and live birth rates are lower in pregnant women with subclinical hypothyroidism compared to the euthyroid group^{9,10}. However, it is interesting that in these studies, the TSH threshold level for subclinical hypothyroidism was higher than the values suggested by AACE and ATA during pregnancy. According to Çalışkan et al.'s studies in patients undergoing in-vitro fertilization therapy (IVF), pregnancy rates per embryo transfer cycle, clinical pregnancy rates, and live birth rates were lower with euthyroidism as far as the group with subclinical hypothyroidism is concerned¹¹. However, in this study, the cases with TSH values >4.5 mIU / L and normal free T4 values were accepted as subclinical hypothyroidism, which considers above TSH threshold values recommended by AACE ATA during pregnancy. In a study among 1055 infertile patients receiving IVF treatment, the group with TSH value above 2.5 mIU/L and the group with TSH value below 2.5 mIU/L compared, and there was no significant difference found between the two groups in terms of pregnancy rates and miscarriage rates¹².

Subsequently, in a study among 4064 patients who received intrauterine insemination, there was no significant difference between the group with pre-pregnancy TSH values of <2.5 mIU/L and the group with TSH level 2.5-4.9 mIU/L in terms of clinical pregnancy rate and live birth rate¹³. Also compared infertile patients with TSH <2.5 mIU/L and infertile patients with TSH 2.5-3.5 mIU/L and found no significant difference between cumulative pregnancy rates and miscarriage rates¹⁴. Our study in the patient group with unexplained infertility, 255 intrauterine insemination cycles, which conduct after ovulation induction via CC and Gonadotropins compared regarding TSH levels and cycle successes. In the control group where the TSH value was <2.5 mIU/L, and in the study group which took no proper thyroid medication and whose TSH level is between 2.5 and 4.5 mIU/L, there was no statistical difference between the ongoing pregnancy rates after intrauterine insemination treatment (9.8%, 7.8% respectively). Whether we peruse this study or other studies in the current literature which concern infertile patients, there appears to be no difference in infertile patients with TSH <2.5 mIU/L and patients with TSH <2.5 mIU/L in terms of pregnancy success^{12,13,14}.

Our study's restricted features include its retrospective nature, low number of cycles assessed, and the inability of postpartum follow-up of babies born due to insemination treatment. In current practice, it knows that a lot of infertility patients who have a TSH value between 2.5-4.5 mIU/L receive thyroid hormone replacement therapy to make sure that their TSH value is below 2.5mIU/L before infertility treatment. This fact not only causes unnecessary drug use for patients but also increases health expenditures. In a 2004 review, the requirement of thyroid hormone replacement therapy was also questioned in individuals with subclinical hypothyroidism with a TSH value of <5mIU/L¹5. Widespread randomized controlled prospective studies need to determine the optimal TSH threshold value required before TSH treatment of the women receiving infertility treatment.

CONCLUSION

There was no statistically significant difference in terms of intrauterine insemination success between the control group with TSH <2.5 mIU / L and the study group with TSH 2.5-4.5 mIU/L. In current practice, it knows that a lot of infertility patients who have a TSH value between 2.5-4.5 mIU/L receive thyroid hormone replacement therapy to make sure

that their TSH value is below 2.5mIU/L before infertility treatment. Widespread randomized controlled prospective studies need to determine the optimal TSH threshold value required before TSH treatment of the women receiving infertility treatment.

CONFLICT OF INTEREST

The authors declare no competing interest.

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