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Original Article *Özgün Araştırma*

THE EFFECT OF TSH LEVEL ON OVARIAN RESERVE IN WOMEN IN THE REPRODUCTIVE PERIOD

Üreme Döneminde Kadınlarda TSH Düzeyinin Yumurta Rezervine Etkisi

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ABSTRACT

Objective: One of the most common endocrinological disorders in women of reproductive age is thyroid diseases. It is known that serum Anti-Mullerian hormone level is a good indicator in determining the ovarian reserve. In this study, we investigated the effect of serum thyroid-stimulating hormone level on Anti-Mullerian hormone.

Material and Methods: The data of 198 patients aged between 20-45 years, who were consulted to the endocrinology clinic for fertility evaluation, were recorded and analyzed retrospectively. All patients were divided into 3 categories according to their thyroid-stimulating hormone level results; 1) ≤2.5 mIU/L, 2) 2.51-4.99 mIU/L, 3) ≥5 mIU/L. Serum Anti-Mullerian hormone, laboratory results and demographic characteristics were compared between all of the groups. In addition, the correlation between Anti-Mullerian hormone and thyroid-stimulating hormone was analyzed.

Results: The mean age of the patients was 29.4 (±6.4). Variables such as age (p=0.384), BMI (p=0.407), FSH (p=0.178), LH (p=0.407), estradiol (p=0.424), and Anti-Mullerian hormone (p=0.814) were not different between the groups. There was no correlation between Anti-Mullerian hormone level and serum thyroid-stimulating hormone level or body mass index results. While a statistically significant positive correlation was found between Anti-Mullerian hormone and luteinizing hormone (r=0.258, p=0.001), a negative correlation was found between Anti-Mullerian hormone and follicle stimulating hormone (r=-0.207, p=0.007) and estradiol (r=-0.198, p=0.010).

Conclusion: In conclusion, while mild thyroid-stimulating hormone changes do not appear to be effective on Anti-Mullerian hormone used in the assessment of ovarian reserve, more comprehensive studies are needed to show that ovarian reserve changes positively with thyroid hormone replacement therapy.

***Keywords**: Anti-Mullerian hormone, TSH, ovarian reserve.*

ÖZ

Amaç: Üreme çağındaki kadınlarda en sık görülen endokrinolojik bozukluklardan biri tiroid hastalıklarıdır. Serum Anti-Mullerian hormon düzeyinin yumurtalık düzeyini belirlemede iyi bir gösterge olduğu bilinmektedir. Bu çalışmada, serum tiroid uyarıcı hormon düzeyinin Anti-Mullerian hormon üzerindeki etkisini araştırdık.

Gereç ve Yöntemler: Endokrinoloji kliniğine fertilite değerlendirmesi için konsülte edilen 20-45 yaş arası 198 hastanın verileri kaydedildi ve geriye dönük olarak incelendi. Tüm hastalar TSH sonuçlarına göre 3 kategoriye ayrıldı; 1) ≤2.5 mIU / L, 2) 2.51-4.99 mIU / L, 3) ≥5 mIU / L. Tüm bu gruplar arasında serum Anti-Mullerian hormon, laboratuvar sonuçları ve demografik özellikler karşılaştırıldı. Ayrıca, Anti-Mullerian hormon ile tiroid uyarıcı hormon arasındaki korelasyon ilişkisi analiz edildi.

Bulgular: Hastaların ortalama yaşı 29.4 (±6.4) idi. Yaş (p=0.384), vücut kitle indeksi (p=0.407), follikül stimüle edici hormon (p=0.178), luteinizan hormon (p=0.407), östradiol (p=0.424) ve Anti-Mullerian hormon (p=0.814) gibi değişkenler gruplar arasında farklı değildi. Serum Anti-Mullerian hormon seviyesi ile serum tiroid uyarıcı hormon seviyesi veya vücut kitle indeksi sonuçları arasında korelasyon ilişkisi yoktu. Anti-Mullerian hormon ve luteinizan hormon (r=0.258, p=0.001) arasında istatistiksel olarak anlamlı düzeyde pozitif korelasyon bulunurken, Anti-Mullerian hormon ile follikül stimüle edici hormon (r=-0.207, p=0.007) ve estradiol (r=-0.198, p=0.010) arasında negatif korelasyon tespit edildi.

Sonuç: Sonuç olarak, hafif tiroid uyarıcı hormon değişiklikleri yumurtalık rezervinin değerlendirilmesinde kullanılan Anti-Mullerian hormon üzerinde etkili görünmemekle birlikte, yumurtalık rezervinin tiroid hormon replasman tedavisi ile olumlu yönde değiştiğini göstermek için daha kapsamlı çalışmalara ihtiyaç vardır.

***Anahtar Kelimeler**: Anti-Mullerian hormone, TSH, yumurtalık rezervi.*

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INTRODUCTION

Thyroid diseases are the most common endocrinological pathology in women in the reproductive period. Since there are thyroid hormone receptors on oocytes, changes in thyroid hormone levels affect ovarian functions. For example, hypothyroidism can lead to menstrual irregularities, amenorrhea, and anovulation. For all these reasons, pathological changes in thyroid hormone levels are associated with female infertility (1-3). It is known that some factors play a role in hypothyroidism increasing the risk of female infertility; changes in peripheral estrogen metabolism, its effect on prolactin levels and abnormal changes in Gonadotroin-Releasing Hormone (GnRH) secretion (4).

Approximately 20% of infertile women have subclinical hypothyroidism, which is characterized by increased thyroid-stimulating hormone (TSH) and normal free T4 hormone levels. The mean TSH levels of infertile women were found to be higher compared to normal fertile women (3,5). It was found that levothyroxine treatment initiated in patients with subclinical hypothyroidism with mildly high TSH levels caused spontaneous pregnancy and shortened infertility periods (6,7).

Ovarian reserve can be evaluated with some measurements in the early follicular phase of the menstrual cycle; investigation of antral follicle count (AFC) and ovarian volume, serum follicle stimulating hormone (FSH), estrodiol (E2), Anti-Mullarian hormone (AMH) and inhibin-B measurement (9-14). AMH is a member of the transforming growth factor-beta super family and is especially expressed from granulosa cells of preantral and small antral follicles. AMH production decreases with advancing age (15,16). AMH has been shown to be a suitable marker for determining ovarian reserve in women in the reproductive period (17). It is even claimed to be the best marker (18).

There are many studies showing that autoimmune thyroid diseases and overt hypothyroidism affect menstrual cycle and fertility. The aim of this study is to show the relationship between TSH and AMH in euthyroid and subclinical hypothyroid patients.

MATERIALS AND METHODS

This study design was retrospective and it was evaluated cross-sectionally. The data of 198 patients between the ages of 20-45, who were consulted to the endocrinology clinic for fertility evaluation between January 1, 2018 and May 31, 2020, were recorded and analyzed retrospectively. Chronic inflammatory disease, autoimmune disease, pregnancy, breastfeeding, and history of recent surgery were considered as exclusion criteria because of the possibility of affecting the results. In addition, hormone therapy or drugs known to affect the hypothalamic-pituitary-gonadal axis were questioned and the patient was excluded from the study in their presence. Anthropometric data of all patients were recorded. The early follicular period FSH, LH, estradiol, AMH and TSH results of the patients were recorded by scanning the patient data archive and were evaluated. Serum AMH was studied in Beckman Access II device with chemiluminescence immunoassay (CLIA) method, while other hormone parameters were studied with CLIA method in Beckman Unicel DX1800 device.

All patients included in the study were divided into 3 categories according to their TSH results; 1) ≤2.5 mIU/L, 2) 2.51-4.99 mIU/L, 3) ≥5 mIU/L. Between all these groups, serum AMH, laboratory results and demographic characteristics were compared. In addition, the correlation relationship between AMH and TSH was analyzed.

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An informed signed voluntary consent form was received from all participants. The study was approved by the local ethics committee (Yozgat Bozok University Rectorship, Ethics Committe of Clinical Research, date: 22.07.2020; number: 2020-06-146.).

Statistical Analysis: Data analysis was performed by using SPSS-22 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z). Visual (histograms, probability plot) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) were used to determine the distribution properties of the variables. We performed analyses to describe and summarize the distributions of variables. Numerical variables were expressed as mean and standard deviation or median and interquartile range depending on their distribution characteristics. If parametric test conditions were fulfilled, independent groups were examined by t test and if not, Mann Whitney U test was preferred. Correlation coefficients and significance were calculated using the Spearman correlation test when examining the relationships between those that did not show normal distribution. A p-value of <0.05 was accepted as statistically significant.

RESULTS

For euthyroid ≤2.5 TSH group, euthyroid >2.5 TSH group and hypothyroid group, the mean age was 28.9±6.2, 29.3±6.4, and 31.1±7.2, respectively (p= 0.384). Median BMI (IQR = interquartile range) values were 24.34 (22.27-26.77), 24.21(22.67-26.71), and 25.51 (23.12-27.51), in the same order (p= 0.407). Clinical and laboratory features were summarized in Table 1. There was a significant difference in TSH level between the first (euthyroid ≤2.5 TSH) and second groups (euthyroid >2.5 TSH) (p<0.001), between the second and third groups (p<0.001), and between the first and third groups (hypothyroid) (p<0.001). However, no statistically significant difference was found in any of the levels FSH (p=0.178), LH (p=0.407), and estradiol (p=0.424) variables between the groups (Table 1). Also, there was no difference between the groups in terms of serum AMH assessment (p= 0.814) (Figure 1).

In addition, the relationship between serum AMH level and TSH, BMI, FSH, LH and estradiol levels were evaluated by correlation analysis.

No correlation was found between AMH level and both serum TSH level and BMI results. While a statistically significant positive correlation was found between AMH and LH (r=0.258, p=0.001), a significant negative correlation was found between AMH and FSH (r=-0.207, p=0.007) and estradiol (r=-0.198, p=0.010) (Table 2).

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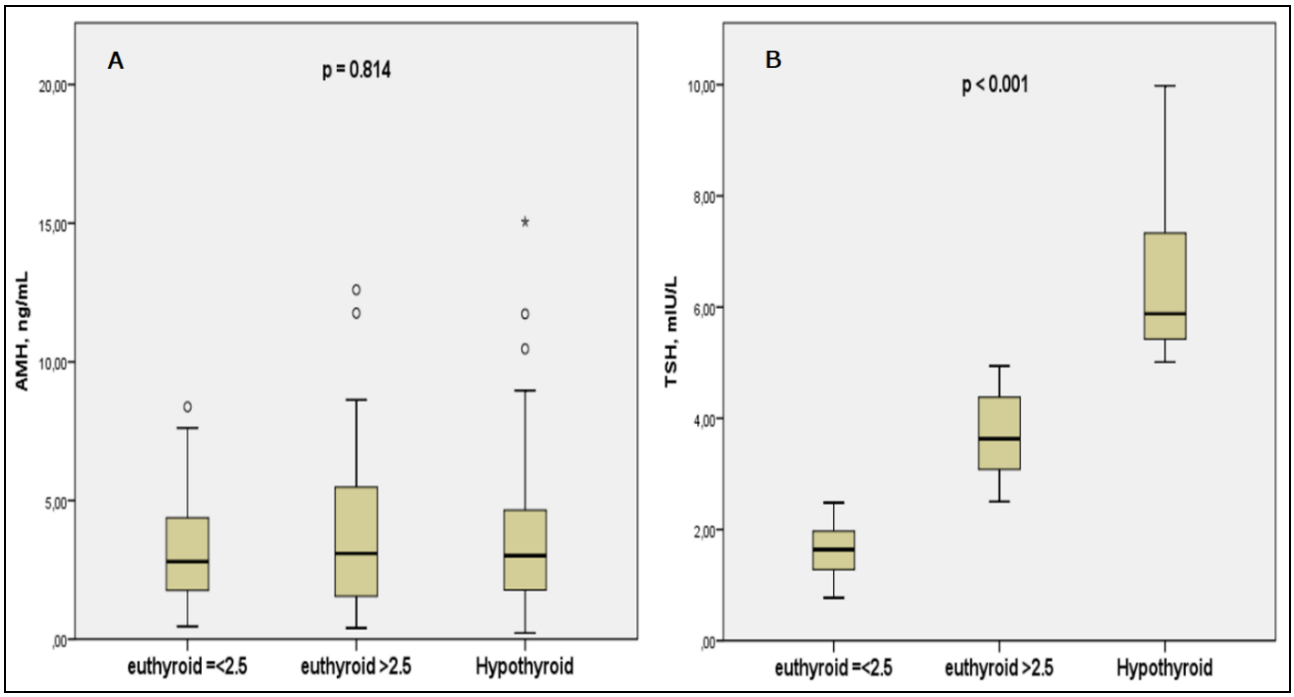

Figure 1: Comparison of AMH (A) and TSH (B) results according to TSH≤2.5 mIU / L, 2.5 <TSH <5 mIU / L, and TSH≥5 mIU / L groups, respectively.

Table 1: Comparison of laboratory results and demographic characteristics according to TSH subgroups.

	Results*			**p value**
	TSH ≤2.5 mIU/L (n=90)	2.5< TSH <5 mIU/L (n=81)	TSH ≥5 mIU/L (n=27)	
Age (years)	28.9 (±6.2)	29.3 (±6.4)	31.1 (±7.2)	0.384
BMI (kg/m^2)	24.34 (22.27-26.77)	24.21 (22.67-26.71)	25.51 (23.12-27.51)	0.407
FSH (mIU/mL)	6.91 (±2.23)	7.31 (±1.93)	6.65 (±1.22)	0.178
LH (mIU/mL)	4.90 (3.67-6.67)	5.32 (4.25-6.56)	4.32 (3.80-8.26)	0.407
Estradiol (pg/mL)	42.62 (29.54-59.75)	46.00 (32.31-65.05)	49.95 (32.59-79.92)	0.424
TSH (mIU/L)	1.64 (1.28-1.98)	3.63 (3.08-4.38)	5.88 (5.40-7.39)	<0.001
AMH (ng/ml)	2.80 (1.76-4.42)	3.09 (1.55-5.53)	3.01 (1.76-4.68)	0.814

Abbreviations: BMI; body mass index, TSH; thyroid-stimulating hormone, FSH; follicle-stimulating hormone, LH; luteinizing hormone, AMH; anti-mullerian hormone.

*Descriptive results for continuous variables were expressed as mean and standard deviation or median and interquartile range, depending on normal distributions.

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Table 2: Correlation analysis results between serum AMH level and other variables.

	Correlation analysis (Spearman correlation test)	
	r value	p value
TSH	0.037	0.608
BMI	-0.011	0.882
FSH	-0.207	0.007
LH	*0.258*	0.001
Estradiol	-0.198	0.010

Abbreviations: BMI; body mass index, TSH; thyroid-stimulating hormone, FSH; follicle-stimulating hormone, LH; luteinizing hormone

DISCUSSION

In our study, serum AMH level, which shows the ovarian reserve quite well, was compared between subclinical hypothyroid and euthyroid patient groups, and no difference was observed. Similar results were obtained in the study of Kucukler et al. and Polyzos et al. (19,20). In these two studies, autoimmune thyroid patient group and control group were also compared in terms of AMH levels and no significant difference was found. In another prospective study of 775 patients with a 12-year follow-up period in which the relationship of thyroid hormone levels and thyroid autoimmunity with ovarian reserve was evaluated, the initial anti-TPO level was found to be significantly higher in the group with low ovarian reserve (21). In addition, an increase in anti-TPO titers was observed in the group with low ovarian reserve. Similarly, the same results have been published by Monteleone et al. and Chen et al. (8,22). The hypothesis of the results obtained in these studies was attributed to the conclusion that increased TSH and hyperandrogenic state in hypothyroid patients caused AMH hypersecretion in granulosa cells. In the studies conducted by Pirgon and Erol in adolescent girls and Tüten et al. in women of reproductive age, it was reported that AMH levels were found to be significantly higher in patients with thyroid autoimmunity compared to the control group (23-25). In our study, we wanted to emphasize whether the gradual but mild increase in TSH levels of women in reproductive age who have not yet developed clinical hypothyroidism has an effect on ovarian reserve. However, we came to the conclusion that it does not affect.

In a study questioning the relationship between thyroid functions and infertility, a significant negative correlation was found between serum AMH and TSH (26). In a study reported by Weghofer A. et al, significantly better ovarian reserve was observed in patients with TSH <3, even when the effect of thyroid auto-antibody and age variables were corrected (27). There are studies showing that thyroid hormone replacement therapy initiated at high normal TSH levels (in the range of 2.5-4.99 mIU / L), especially in women with fertility expectancy, improves the pregnancy potential (6,7,28,29). However, the results we obtained were in conflict with this theory. This may be due to the relatively small number of participants or the cross-sectional evaluation of our study. In addition, in our study, the BMIs of the patients were similar according to the groups, and there was no correlation between them and AMH. This result was consistent with the literature (30).

The limitations of the study include the single center conduct of the study, not defining the etiology of hypothyroidism (autoimmunity, secondary to surgery, etc.), not using other methods (antral follicle number, inhibin measurement, etc.) to determine ovarian reserve other than AMH.

While mild TSH changes do not appear to be effective on AMH used in the assessment of ovarian reserve, more comprehensive studies are needed to show that

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ovarian reserve changes positively with thyroid hormone replacement therapy.

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