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Prevalence of premature ovarian failure in patients with autoimmune thyroiditis

Otoimmün tiroiditi olan hastalarda prematür ovaryan yetmezlik sıklığı

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ABSTRACT

Introduction and Aim: Premature ovarian failure is the loss of ovaries' functions under the age of forty that autoimmunity is a factor in some cases. Reserve of overs can be assessed with AMH measurements accurately. This study aimed to evaluate the ovarian reserve by AMH levels in women who were diagnosed with autoimmune thyroiditis. **Methods**: This is a retrospective study, covers the 10-year period between January 2011 and May 2021. Women under the age of 35 who were followed up and treated for autoimmune thyroiditis constitute the sample of the study. Participants' ovarian reserves were analyzed using age specific Anti-Müllerian hormon levels. Measurements of thyroid hormones were performed in the radioimmunoassay laboratory in the health center where the study was conducted. **Results**: Some participants did not have infertility (66.6%). 147 (38.7%) of the participants were euthyroid. 197 participants (51.8%) had a low ovarian reserve, 229 (60.3%) of the participants had high anti-TPO and 217 (57.2%) had high anti-TG levels. Participants with low ovarian reserve show a significant difference statistically ($p<0.05$). **Conclusions**: It was determined that the participants with hypothyroidism had a lower mean AMH and ovarian reserve compared to the other groups.

ÖZ

Giriş ve Amaç: Premature ovaryan yetmezlik, bazı durumlarda otoimmünitenin etken olduğu, overlerin kırk yaşın altında fonksiyonlarını kaybetmesidir. Anti-Müllerian hormon, over foliküllerinin granüloza hücreleri tarafından salgılanmaktadır. Over rezervi Anti-Müllerian hormon ölçümleri ile doğru bir şekilde değerlendirilebilir. Bu çalışmada otoimmün tiroidit tanısı alan kadınlarda Anti-Müllerian hormon düzeyine göre over rezervinin değerlendirilmesi amaçlanmıştır. **Materyal ve Metot**: Bu retrospektif bir çalışmadır, Ocak 2011-Mayıs 2021 arasındaki 10 yıllık dönemi kapsamaktadır. Çalışmanın örneklemini 35 yaş altı otoimmün tiroidit nedeniyle takip ve tedavi edilen kadınlar oluşturmaktadır. Katılımcıların over rezervleri yaşa özel AMH seviyeleri kullanılarak analiz edilmiştir. Araştırmanın yürütüldüğü sağlık merkezindeki radyoimmunoassay laboratuvarında tiroid hormon düzeyleri ölçülmüştür. **Bulgular**: Bazı katılımcılar, 253 kişide (%66.6) fertil idi yoktu. Katılımcıların 147'si (%38,7) ötiroid idi. 197 katılımcının (%51,8) over rezervi düşük, 229 katılımcının (%60,3) yüksek anti-TPO ve 217 katılımcının (%57,2) yüksek anti-TG düzeyi vardı. Over rezervi düşük olan katılımcılar tiroid hormon analiz sonuçları açısından anlamlı farklılık göstermektedir ($p<0.05$). **Sonuç**: Hipotiroidili katılımcıların ortalama AMH ve over rezervinin daha düşük olduğu belirlendi.

INTRODUCTION

Premature ovarian failure (POF) is the loss of ovaries' functions under the age of forty. It is a picture characterized by high gonadotropin (FSH, LH) levels and low estrogen levels in patients with symptoms of hypoestrogenism. Although the incidence of POF varies between populations, it's incidence is approximately 1% (1,2).

There is evidence that autoimmunity is a factor in some of the POF cases (3). Changes in the immune system can lead to impaired ovarian function and decreased ovarian reserve. Prevalence of thyroid dysfunction in reproductive aged women is approximately %15 . Changes in thyroid functions affect various functions of the body (3,4).

It is known that folliculogenesis, ovulation, fertilization, and ovarian reserves are adversely affected by hypothyroidism. It has been reported that the menstrual cycle of Hashimoto patients is adversely affected by the disease, and the incidence of infertility is higher in women with thyroid-related problems (5,6).

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Overies have thyroid hormone receptors. These highlights the importance of thyroid hormones for functions over. However, physiopathology of hypothyroidism on follicles is controversial. Some studies have found that poor thyroid hormone levels (hypothyroidism) result in ovarian atrophy. In some similar studies, data supporting the relationship between hypothyroidism and decreased ovarian reserve were obtained (7-10).

Measurement of reserve of overies can be assessed with Anti-Müllerian hormone (AMH) accurately. AMH levels vary according to age. While it is 3.0 ng/mL during the reproductive age, it decreases below 0.5 ng/mL after menopause. Thyroid disorders are correlated with low ovarian reserve, and there is a possible correlation between thyroid autoimmune disease (TAD) and decreased ovarian reserve. The prevalence of low ovarian reserve in patients with poor thyroid hormone levels has not been fully determined (11-13).

Autoimmune thyroiditis is a common endocrinopathy in POF patients. However, there are not enough studies on the prevalence of this condition. Aim of this study to evaluate the reserve of overs by AMH level in women under 35 who was autoimmune thyroiditis.

MATERIALS AND METHODS

Our retrospective study covers the 10-year period between January 2011 and May 2021. Women under the age of 35 who were followed up and treated for autoimmune thyroiditis in the endocrinology clinic of our hospital constitute the sample of our study. The total number of participants is 380. AMH levels of the participants were examined in terms of ovarian reserve. Demographic characteristics of the participants were given as descriptive statistics. The parameters examined and analyzed for statistical significance are:

- AMH, free T4 (FT4),
- Thyroid stimulating hormone (TSH),
- Antithyroglobulin antibody (anti-TG),
- Antithyroid peroxidase antibody (anti-TPO).

The data of the participants were obtained from the files of the participants. The file with missing data was not excluded . Participation was on a voluntary basis. Ethic permission was obtained.

Patients' eligibility criteria:

Inclusion criteria for the research:

1. Follow-up with the diagnosis of autoimmune thyroiditis,

2. Having an AMH test,

3. Being under the age of 35

Exclusion criteria for the research:

1. Having thyroid diseases other than autoimmune thyroiditis

2. Not having an AMH test,

3. Being over the age of 35

AMH

AMH analyzes were performed with the Immunotech (IOT) Beckmann Coulter assay. This test is a used for AMH levels in serum and lithium heparin plasma (14).

Ovarian Reserve Categories:

Participants' ovarian reserves were analyzed using age specific AMH levels. In this way, AMH levels were reliably calculated for each participant. Age-specific AMH values (annual) were taken into account to classify the participants and graphs were generated for the entire patient cohort. According to the graphs created and by using the reference values of the participants' AMH levels were analyzed in three different ovarian reserve categories:

- Low
- Normal
- High

Thyroid Hormones, TSH and anti-TPO Antibodies

Thyroid hormone measured in the radioimmunoassay laboratory in the health center where the study was conducted. TSH and free FT4 were analyzed by electrochemiluminescence immunoassay (Roche Diagnostics). The amount of anti-TG and anti-TPO antibodies were analyzed with a radioimmunoassay kit (BRAHMS Diagnostics) (15,16).

- Serum TSH and FT4 levels were classified as low, normal, and high,
- Anti-TG and anti-TPO levels were classified as low and high by using the reference values.

The records of the participants with low ovarian reserves were scanned to identify the risk factors that would potentially further reduce the ovarian reserves. As a result of this procedure, the participants were divided into the following groups in terms of risk factors that will reduce their ovarian reserves:

- Non-Hormonal Factors (Endometriosis, Tubal Factor and Male Factor etc.)

- Unexplained
- POF
- Anovulation

Other Analyzes

Participants were divided into two groups (aged ≤ 25, aged 26-36). The parity status of the participants was grouped as no pregnancy, single pregnancy, and two or more pregnancies and included in the analysis. Participants were also grouped according to the presence of infertility.

Statistical Analysis

Some socio-demographic characteristics and the frequencies of the values obtained from the measurements are presented in the table.

One Way Anova was used to analyze whether there was a difference between the ages of the participants, thyroid hormone and thyroid antibody levels, and ovarian reserves determined using AMH analyses. Post Hoc test was performed to determine from which groups the detected difference originated.

Results were considered significant when $p < 0.05$.

RESULTS

Although a significant relationship was not obtained, the frequencies of infertility causes were examined. Accordingly, in the light of the data obtained from the participants, the causes of infertility due to non-hormonal factors such as endometriosis, tubal factor, and male factor are quite low (4.5%). POF was the most common among hormonal factors. This was followed by unexplained causes and anovulation.

The socio-demographic and other characteristics are in Table 1. It was determined that 253 participants (66.6%) were fertile . When the causes of infertility were examined in the participants with infertility, it was determined that the most common group was those who experienced infertility due to POF . 147 (38.7%) of the participants were euthyroid. According to the AMH analysis, 197 participants (51.8%) had a low ovarian reserve. It was determined that 229 (60.3%) of the participants had high anti-TPO and 217 (57.2%) had high anti-TG levels.

The relationship between the FT4 analysis results of the participants and those with low ovarian reserve according to their AMH values was examined. As it can be seen in Table 2, participants with low ovarian reserve show a significant difference statistically between the groups of thyroid hormone analysis results ($p<0.05$). According to the results of the Post Hoc test performed to determine which groups the said difference was due to; it was found that the difference was due to the significant difference between those with hypothyroidism and the other groups. Those with hypothyroidism have a lower mean AMH and ovarian reserve than other groups.

In the examinations performed according to TSH, anti-TPO, and anti-TG results of the participants with low ovarian reserve, the values obtained from the analysis are not shown in the tables.

The correlation between the anti-TPO values and anti-TG results of the participants and the ovarian reserve according to the AMH values was examined, and a statistically significant difference was found between the variables ($p<0.05$). The difference is due to the variation between those with low ovarian reserve and other groups according to AMH values. Those with low ovarian reserve according to AMH values have higher anti-TG and anti-TPO levels compared to other groups (Table 3).

The relationship between the ovarian reserves of the participants and their TSH and FT4 values was also examined ; the values obtained from the analysis are not shown in the tables.

According to the AMH values of the participants, ovarian reserves were analyzed in terms of their relationship with socio-demographic characteristics and causes of infertility. No significant relationship was found between these variables in the studies.

DISCUSSION

In non-pregnant women normal range of TSH is 0.5 to 5.0 mIU/L. Experts recommends that levels of TSH be kept between 0.2-<3.0 mIU/L in pregnancy. Normal FT4 levels are 0.7 to 1.9ng/dL. According to the main results obtained from our research, there is a statistically significant difference in ovarian reserve in terms of thyroid hormone analysis results. It was determined that the participants with hypothyroidism had a lower mean AMH and ovarian reserve compared to the other groups. TSH, anti-TPO, and anti-TG results did not differ in terms of AMH average and ovarian reserve.

Another result obtained from our research is that those with low ovarian reserve according to AMH values have higher anti-TG and anti-TPO levels compared to other groups. However, no significant relationship was found between ovarian reserves, TSH and FT4 values. Results obtained from studies on the subject report that abnormal thyroid hormone levels, especially in women in the childbearing period, may cause ovarian dysfunction (4,9,13)

The mechanism of the relationship between autoimmune thyroid disease and ovarian reserves is currently

unknown. It is thought by researchers that anti-TPO antibodies damage the growing follicles and oocytes by crossing the barrier between the blood and the follicles during the development of the follicles. It has been determined that hypothyroidism, which is common in autoimmune thyroid disease, also affects the menstrual cycle. Although some studies argue that women with hypothyroidism commonly experience oligomenorrhea during the menstrual cycle, some claim the opposite (17,18)

Studies have shown that hypothyroidism is significantly higher in women with low ovarian reserve due to genetic reasons. According to the results of one study, approximately half of women with low ovarian reserve due to Turner syndrome have subclinical hypothyroidism. In the same study, positive anti-TPO antibodies were detected in approximately 30% of the participants. These findings suggest that Turner syndrome are associated with a higher prevalence of hypothyroidism. This association seen in Turner syndrome was not seen in other chromosomal disorders. Similar studies in Turner syndrome have obtained values similar to this prevalence. For a study, the prevalence of hypothyroidism was found to be 31% (13,19–21)

In our study, no relationship was found between low ovarian reserve and TSH values. Some of the results obtained from studies on the subject support the results obtained in our study. A study shows that low ovarian reserve women have higher TSH levels compared to others. In this study, the presence of anti-thyroid antibodies in the ovarian follicle fluid of women with autoimmune thyroid disease was demonstrated. A positive correlation has been confirmed. The mechanism of this determined relationship can be explained by the fact that anti-TPO and anti-TG antibodies cross the barrier between blood and follicles and cause a cytotoxic environment by damaging the maturing oocyte (4,13,22)

Findings from some other studies have produced different results. Various studies are reporting that the evidence regarding the relationship between low ovarian reserve and TAD is controversial (8,13,23,24)

In a prospective study conducted on the subject, it was determined that there was no significant change in the reserve of overs in TAD. In the study, higher TSH levels were found in those with reduced ovarian reserve, but it was reported that there was not enough evidence that thyroid disorders were associated with ovarian reserve (17).

A study states that the levels of anti-thyroid show a positive correlation in women with TAD. Results from another study show that thyroid autoantibodies do not affect ovarian reserve in euthyroid women with normal TSH levels. In a similar study, the relationship between TAD and decreased ovarian reserve was analyzed. According to the results, the euthyroid women's antibodies does not show any effect on ovarian reserve (18,25,26).

According to the results of a study, it was observed that the AMH level increased significantly in anti-TG positive and anti-TPO negative patients after external administration of FT4. Kuroda et al. emphasized that this result should be investigated in larger patient subgroups (27).

There are various methods used to detect ovarian reserve. Among them, the most frequently used ones are FSH, Inhibin B, AMH, AFC, clomiphene test. In a study in which ovarian volume was measured by ultrasound, it was emphasized that AMH, whose levels were constant throughout the menstrual cycle, was the most reliable biomarker for the detection of ovarian reserve (17). The presence of preantral follicles that could produce AMH and could not be detected by ultrasound may have affected the results of the study. AMH was used in the determination of ovarian reserve in our study; in addition, taking into account age specific AMH values, the creation of graphs for all participants according to age shows the reliability of our data (28)

In hypothyroidism, slowing down of metabolism is an expected situation. Therefore, approximately 30% of this patient group has weight gain. In studies examining the relationship between autoimmune thyroid diseases and low ovarian reserve, the relationship between the ovarian reserve and body mass index (BMI) has also been frequently examined. While some results obtained in studies show that there is a relationship between ovarian reserves and BMI, there are also studies claiming the opposite (13,29)

Although both anti-TPO and anti-TG markers are indicative of autoimmune thyroiditis, anti-TPO levels are considered to be more sensitive. According to the NHANES III study, which is one of the most important studies in this field, in the absence of anti-TPOs, the relationship of anti-TGs alone with autoimmune thyroiditis can be questioned. For this reason, in some studies, thyroid dysfunction was examined on the basis of TSH and anti-TPO, but anti-TG antibodies were not examined. This study, the relationship of both anti-TPO and anti-TG antibodies with low ovarian reserve was investigated. This feature of our study increases the quality of our data regarding the relationship between autoimmune thyroiditis and low ovarian reserve (30).

Strength & Limitations

Our research has some strengths and some limitations. The sample size of our research is sufficient. Many studies

on the subject have been conducted with a very low number of participants. In our study, the main variables of thyroid disease were examined. Ovarian reserves were examined with AMH, and this method is accepted as the most reliable method today. Anti-TPO and anti-TG, markers of autoimmune thyroiditis, were both analyzed. Ovarian reserves of the participants were calculated by considering age specific AMH values.

The fact that the BMI of the participants were not examined can be considered as a limitation of our study.

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