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May the Systemic Immune-Inflammation Index be an Indicator of Premature Ovarian Insufficiency?

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Abstract

Objective: This study aimed to determine whether there was a correlation between the systemic immune-inflammation index and ovarian reserve markers such as follicle stimulant hormone, estradiol, and anti-mullerian hormone

Methods: The study comprised 65 people with premature ovarian insufficiency and 71 controls with similar demographics. The concentrations of hemoglobin, hematocrit, platelets, white blood cells, neutrophils, and lymphocytes were evaluated. The neutrophil leukocyte ratio, platelet lymphocyte ratio, and systemic immune-inflammation index were calculated. The antral follicle count reserves of all patients were evaluated by transvaginal ultrasonography. An independent t-test was used for the comparison of the study and control groups. Correlations between variables were analyzed using Pearson's correlation test. A p value of 0.05 was considered significant.

Results: The results of the neutrophil-to-lymphocyte ratio and the platelet-lymphocyte ratio showed a significant difference between the groups ($p = 0.043$). The Systemic Immune Inflammation Index value was the statistically significant difference found between the groups. There was a significant positive correlation between the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-lymphocyte ratio, and follicle stimulant hormone, while a significant negative correlation was found between the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-lymphocyte ratio, antral follicle count, and anti-mullerian hormone. In ROC analysis for SII at a cut-off level of 441.35, the sensitivity was 72.1% and the specificity was 68.9.

Conclusion: Our study was the first in this field to reveal the relationship between premature ovarian failure and the systemic immune-inflammation index. According to our study results, the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-lymphocyte ratio are significantly higher in individuals with ovarian failure.

Key words: Complete blood count, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, platelet-lymphocyte ratio, premature ovarian insufficiency

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INTRODUCTION

Indirectly measuring ovarian reserve is possible by the analysis of hormone levels or ultrasound imaging of the ovaries (1). The quantity of oocytes in an ovary is considered its ovarian reserve. The average number of oocytes in a female at birth is between half a million and one million. With follicular atresia and ovulation, the number of oocytes begins to deplete over time, followed by menopause. Although ovarian reserve declines with age, even among women of the same chronological age, there is a wide range in ovarian reserve (2). Early follicular phase assessment of follicle stimulant hormone (FSH), estradiol (E2), and inhibin B, measurement of anti-mullerian hormone (AMH) independent of cycle day, and a clomiphene citrate challenge test are biochemical measures of ovarian reserve (1).

In women under the age of 40, diminished ovarian function is called primary ovarian insufficiency (POI), and it appears as oligomenorrhea or amenorrhea, subfertility or infertility, depletion of residual follicles in the gonads, decreased estradiol levels, and increased FSH levels (3,4). POI is characterized by steroid deficiency (5). By blocking several pro-inflammatory immune pathways and inflammatory tissue responses, estrogen exerts its anti-inflammatory effect. Decreased estrogen levels result in a change in the direction of inflammation (6).

There are a few well-known hematological indicators of systemic inflammation that correlate with markers of a pro-inflammatory state, including the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR). The systemic immune-inflammation index (SII) is a new inflammatory marker that combines NLR with platelets (7–11). There are studies reporting that it is used in SII premature rupture of membranes, in demonstrating the prognosis of tumors, and in the follow-up of cranial hemorrhages (7–10).

This study aimed to determine whether SII is related to ovarian reserve tests and whether it can be used as a valid indicator in the diagnosis of POI.

METHODS

In this retrospective study, 136 women who were followed up in the gynecology polyclinic of a tertiary Training and Research Hospital between January 2018 and July 2019 were included. The study protocol was approved by the local ethics committee of our hospital. Patient file data were accessed from the hospital's digital archive system. All techniques performed on human subjects in studies conformed to the ethical norms of the institutional and/or national research committee and to the 1964 Helsinki

declaration and its later revisions or other equivalent ethical standards.

Medical diseases and conditions that may affect ovarian reserve, such as pregnancy, polycystic ovarian syndrome, chronic medical diseases, endocrine disorders, excessive exercise, poor caloric intake, pituitary or hypothalamic adenomas, chemotherapy, radiotherapy, and ovarian surgery, were excluded. Hematological, cardiovascular, renal-liver illness, asthma, arthritis, neoplastic disorders such as androgen-secreting tumors, ovarian tumors, glucocorticoid usage, infectious, and parasitic diseases were also ruled out since they could impact the results of a complete blood count.

The study comprised 65 women with POI and 71 controls with similar demographics. POI was diagnosed in women younger than 40 years of age with at least 4 months of amenorrhea, FSH levels ≥ 40 mIU/milliliter, and no or few follicles on transvaginal ultrasonography. All POI patients had 46 XX karyotypes.

The concentrations of hemoglobin, platelets, neutrophils, and lymphocytes were evaluated. The NLR was determined by dividing neutrophils by lymphocytes. Calculating PLR included splitting platelets into lymphocytes. SII was calculated using the neutrophil-platelet-lymphocyte formula.

Demographic data such as age, body mass index, and gravida for all cases were recorded. Ovarian reserves of all patients were evaluated by transvaginal ultrasonography (Samsung HS70) between the second and fifth days of menstruation. Follicles between 2 and 10 mm in both ovaries (antral follicle count) were counted and recorded. AMH and FSH were studied from 10 cc of antecubital venous blood. AMH levels, 3rd-day hormone profiles, and total blood counts of all individuals were studied. The NLR, PLR, and RPR values of both patients and controls were determined. An automated hematology analyzer was used to measure the complete blood count (Beckman UniCel DXL 600 Coulter Cellular, California, United States). The electrochemiluminescence immunological test (CLIA) was used to measure the serum AMH level (Beckman UniCel Dxl 600 Immunoassay, California, United States).

Statistical Analysis

SPSS version 23.0 was used for statistical analysis (SPSS, Chicago, IL, USA). Data were given as mean + standard deviation (SD). The compatibility of the data set with the normal distribution was confirmed by the Kolmogorov-Smirnov test. An independent t-test was used for the comparison of the study and control groups. Pearson's correlation test was used to examine correlations between variables. The confidence interval for the difference analysis was 95%, and the confidence interval for the correlation analysis was between 95% and 99%. A p value of 0.05 was regarded as

statistically significant. The ROC curve was analyzed to determine the best threshold for SII.

RESULTS

There were a total of 130 participants, including 65 people with POI and 65 healthy controls. In terms of age, body mass index, neutrophils, lymphocytes, and platelets, there was no significant difference between the groups ($p > 0.05$) (Table 1). The comparison of FSH, AMH, and AFC revealed, as was to be expected, that there was a difference between the groups (p 0.05). NLR was determined by dividing the mean of the neutrophils by the mean of the lymphocytes, and the results showed that there was a significant difference between the groups ($p = 0.043$). There was a significant difference between the groups in the PLR that was obtained by dividing the mean of the platelets by the mean of the lymphocytes ($p = 0.041$) (Table 1). To obtain SII, the neutrophil x platelet / lymphocyte formula was used, the SII value was calculated, and A statistically significant difference was found between the groups. There was a significant positive correlation between SII, NLR, and PLR and FSH, while a significant negative correlation was found between SII, NLR, and PLR and AFC and AMH (Table 2). In ROC analysis for SII at a cut-off level of 441.35, the sensitivity was 72.1% and the specificity was 68.9 (Figure 1).

Table 1. The table shows the demographic data of the groups

	Study (n=65)	Control (n=71)	P value*
Age (year)	33.71±4.12	34.40±3.93	0.228
BMI (kg/m^2)	25.31±4.12	24.90±4.02	0.199
Hemoglobin (g/dL)	12.18 ± 1.89	11.89 ± 1.73	0.213
Neutrophile count (10e3/uL)	3.75 ± 1.30	3.43 ± 1.17	0.143
Lymphocyte count (10e3/uL)	2.24 ± 0.52	2.43 ± 0.57	0.164
Platelet count (10e3/uL)	257.81 ± 53.25	244.70 ± 57.78	0.112
FSH (mIU/ml)	23.56 ± 3.89	7.19 ± 1.29	***0.001***
AMH (mIU/ml)	0.75 ± 0.21	3.10 ± 1.43	***0.001***
AFC	2.25 ± 0.35	9.23 ± 3.27	***0.001***
NLR	1.69 ± 0.68	1.41 ± 0.61	***0.043***
PLR	118.61 ± 32.85	103.54 ± 21.25	***0.041***
SII	433.45 ± 61.23	348.45 ± 63.72	***0.021***

Data is presented mean ± std. *Independent t test. AMH: Anti-müllerian Hormone, FSH: Follicle stimulating hormone, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SII: Systemic Immune-Inflammation Index.

Tablo 2. Correlations between ovarian reserve tests and inflammation markers

	FSH		AMH		AFC	
	r	p	r	P	r	p
NLR	0.32	***0.042***	-0.24	***0.023***	-0.31	***0.032***
PLR	0.21	***0.052***	-0.19	***0.051***	-0.21	***0.021***
SII	0.41	***0.001***	-0.45	***0.002***	-0.28	***0.005***

AMH: Anti-müllerian Hormone, FSH: Follicle stimulating hormone, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SII: Systemic Immune-Inflammation Index.

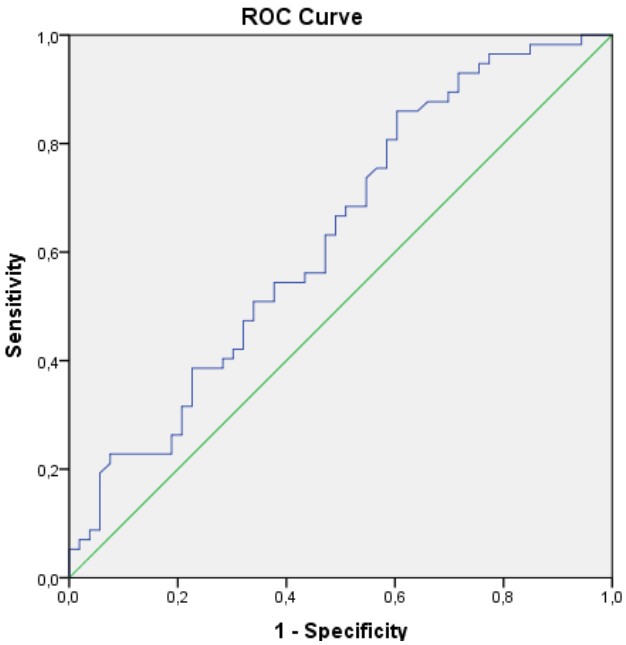

Figure 1. ROC curve. AUC:0.630 (95% CI: 0.525–0.734). (AUC:area under the curve, CI: confidence interval, ROC:receiver operating characteristic).

DISCUSSION

To our knowledge, this study provides the first information about POI and its effect on NLR, PLR, and SII levels. According to our findings, it increases SII in POI. This is the first study in the literature examining the relationship between SII and POI.

There are studies reporting that inflammation reduces ovarian reserve (12). When the inflammatory process in the ovary was reduced, the reproductive window was prolonged, and ovarian aging was postponed, according to a study conducted on animals to investigate the potential influence of inflammation on ovarian reserve. In parallel, it has been shown that rising inflammation in the ovary consumes the follicles over time and causes ovarian aging (12).

Ilhan et al studied the relationship between NLR, PLR, and RDW and premature ovarian failure. They measured FSH and AMH for the diagnosis of ovarian reserve. They found a positive correlation between NLR and FSH and a negative correlation between NLR and AMH (13). Although there was a positive correlation between NLR and FSH and a negative correlation between NLR and AMH, similar to theirs, in our study, we studied a new inflammation index, SII, and added AFC to ovarian reserve tests.

NLR has been frequently used to evaluate the intensity of inflammation and has been demonstrated to be raised in a variety of disorders (14–21). PLR was identified as an independent risk factor for decreased survival

in individuals with a variety of cancers (22–25). Some studies have evaluated the value of some blood cell count indices, especially NLR and PLR, and reported that these biomarkers may be related to POI (3,13).

Although an increased FSH level is a reliable indicator of decreased ovarian reserve, it cannot reveal an earlier loss in ovarian reserve. AMH levels begin to decrease before FSH levels begin to increase (26). When compared to levels of early follicular phase hormone, AMH levels are a more sensitive indicator of ovarian reserve than those levels. Numerous studies have concluded that AFC and AMH are equally effective in providing evidence of ovarian reserve (27). As a result, when conducting research on ovarian reserve tests, we examined not only FSH but also AMH and AFC to determine how closely these factors are related to inflammation.

In the etiopathogenesis of POI, one can identify genetic abnormalities, metabolic illnesses, autoimmune conditions, iatrogenic events such as chemotherapy and infections, and environmental variables. Idiopathic describes conditions for which the etiological origin is uncertain (28). Recent research has demonstrated that inflammation plays a crucial role in the etiology of POI. Inflammatory cells linked with lymphocytic infiltration and other immune responses have been demonstrated in ovarian biopsies (12,29). Aging causes the appearance of inflammatory cells in the ovaries, which play a significant role in idiopathic and unknown cases (30). In addition, studies have shown that lower estrogen levels stimulate proinflammatory processes, whereas estrogen supplementation reduces inflammatory cell levels (6).

Demir et al. reported that 47 patients with POI had substantially higher than average white blood cell and MPV values, platelet counts, and lymphocyte counts. However, they did not report significant differences between groups for NLR and PLR. They also did not detect any correlation between blood parameters and hormone levels. In our results, NLR, PLR, and SII were significantly higher in the POI group (31).

Ovarian aging causes a decline in estrogen production and an increase in inflammatory mediators. Thus, the ovarian reserve is diminished, and the number of inflammatory cells increases. When the ovarian reserve diminishes, fertility declines. The effectiveness of in vitro fertilization may even be predicted by measuring inflammatory indicators in the patient's complete blood count, according to some research (32).

One of our limitations was the retrospective nature of our study and the relatively small number of cases. In addition, although diseases and conditions that may affect the CBC's inflammation markers have been excluded, they may have been affected by unpredictable conditions. Another limitation was that the

ultrasonography image can be affected by conditions such as weight, gas, device resolution, and the interpretation of the person performing the measurement in the AFC count. Our research results should be supported by a large number of prospective studies.

CONCLUSION

In conclusion, our study was the first in this field to reveal the relationship between premature ovarian failure and SII. According to our study results, SII, NLR, and PLR are significantly higher in individuals with ovarian failure. It can be used as a marker for the diagnosis of POI when supported by well-designed, forward-looking, large-scale studies.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethics committee at SBU Trabzon Kanuni Training and Research Hospital with file number 2019/48.

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