Original Article

Correlation Between White Blood Count Parameter (Neutrophil/ Lymphocyte Ration) and Follicle Stimulating Hormone in Females with Premature Ovarian Insufficiency

Saira Nasir[1], Naheed Waris[2], Hiba Anjum[3]

[1]Postgraduate Resident of Gynae and OBS, Jinnah Hospital, Lahore
[2]Senior Registrar of Gynae and OBS, Services Hospital, Lahore
[3]Women Medical Officer, Jinnah Hospital, Lahore

Correspondence: *Dr. Saira Nasir*
PGR, Jinnah Hospital, Lahore
sranasir5362@gmail.com

Abstract

Objective: To determine correlation between Neutrophil/Lymphocyte ratio (NLR) in white blood cell count and follicle stimulating hormone in females with premature ovarian insufficiency.

Methodology: A cross-sectional study was conducted in the Department of Obstetrics and Gynecology at Jinnah Hospital, Lahore, from May 2019 to November 2019. A 5 ml venous blood sample was collected from each participant under aseptic conditions. The blood samples were placed in laboratory tubes containing EDTA and analyzed using an automated hematology analyzer within 60 minutes of venipuncture. The levels of Follicle-Stimulating Hormone (FSH) and the Neutrophil/Lymphocyte ratio in white blood cell count were measured for each case. All data was collected by study proforma.

Results: The overall average age of patients was 30.44 ± 6.34 years. 95(48.5%) cases had Amenorrhea and 101(51.5%) cases had Oligomenorrhea. Mean FSH level was 60.37 ± 11.05 (mIU/ml) and the mean neutrophil/lymphocyte ratio was 1.72 ± 0.82. The correlation between Neutrophil/Lymphocyte ratio in white blood cell count and follicle stimulating hormone in females with premature ovarian insufficiency was calculated as, r = 0.666 (p- 0.001).

Conclusion: The observed correlation between NLR and follicle stimulating hormone in females with premature ovarian insufficiency was positively significant. However the ratio can be used as novel predictor marker for diagnosis of premature ovarian insufficiency.

Keywords: WBC, Neutrophil/Lymphocyte ratio, FSH, premature ovarian insufficiency

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Introduction

Natural menopause typically occurs in women between the ages of 46 and 55,[1] marking the end of their reproductive years as ovarian function gradually declines. However, premature ovarian insufficiency, also known as early menopause, occurs when ovarian function declines before the age of 40, either due to spontaneous causes or as a result of medical treatments.[1] It is known by several names. While most commonly referred to as POI or premature ovarian failure, it is also sometimes called premature menopause, hyper-gonadotropic amenorrhea, hypergonadotropic hypogonadism and primary ovarian failure.[2] It is a diverse condition that impacts approximately 1% of women under the age of 40.[3,4] Its varied nature stems from multiple contributing factors, including genetic abnormalities, autoimmune damage to the ovaries, metabolic disorders, environmental influences, and medical interventions such as surgery and cancer treatments.[3,5] In the majority of cases, the exact cause of premature ovarian insufficiency remains unknown, leading to its classification as idiopathic POI.[3]

In cases of oligo- or amenorrhea (whether primary or secondary) lasting 4 to 6 months, the diagnosis of premature ovarian insufficiency (POI) can be made in

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any woman under 40 years old if hyper-gonadotropic hypogonadism is present.[6] However, the clinical picture of premature ovarian insufficiency (POI) can be influenced by symptoms of hypoestrogenism, the decline in ovarian function, and the speed of these events. Consequently, the clinical manifestations of POI are varied and can include underlying etiological factors as well as signs of hypoestrogenism. These may manifest as dyspareunia, sleep disturbances, hot flashes, vaginal dryness, and the decreased libido.[6,7]

However literature has indicated that inflammatory markers play a significant role in the etiopathogenesis of premature ovarian insufficiency (POI). Ovarian biopsies from patients with POI have demonstrated the presence of inflammatory cells, which are associated with lymphocytic infiltration and various immune responses.[6,8,9]

It is well established that estrogens have a significant impact on inflammatory and immune processes. A decrease in estrogen levels results in a shift towards a pro-inflammatory state.[2] Currently low serum levels of Follicle-Stimulating Hormone (FSH) and Anti-Müllerian Hormone (AMH) are used to diagnose cases of premature ovarian insufficiency (POI). Recent studies have indicated that AMH levels decrease as the number of antral follicles decreases. However, AMH testing is not available in many hospitals, and where it is offered, the cost of measuring AMH can be quite high, making it less accessible for many patients.[10]

Furthermore, there are very few biomarkers available for diagnosing cases of premature ovarian failure. However, some complete blood count parameters have been identified as potential diagnostic biomarkers for various disorders linked to inflammatory processes.[10] Specifically, the Neutrophil-to-Lymphocyte Ratio (NLR) has emerged as a simple and practical prognostic and diagnostic biomarker for several conditions.[11,12] It has been used as an inexpensive and additional easily determinable biomarker for systemic inflammation which is calculated from peripheral neutrophil counts and lymphocyte count. According to a recent study, the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, was significantly elevated in individuals with ovarian failure.[13] However, due to insufficient local evidence, the current study was designed to explore the correlation between the Neutrophil-to-Lymphocyte Ratio (NLR) in white blood cell counts and Follicle-Stimulating Hormone (FSH) levels in females with premature ovarian insufficiency within the local population, aiming to establish NLR as a novel diagnostic marker for premature ovarian insufficiency.

Methodology

A descriptive cross sectional study was done at department of Obs and Gynecology Jinnah Hospital Lahore during 6 months after approval of research proposal from CPSP. Duration of study was seven months from May 2019 to Nov 2019. Non-probability consecutive sampling technique was used. A total of 196 cases are estimated using α =5%, β = 10% and correlation between Neutrophil/Lymphocyte ratio in white blood cell count and a follicle stimulating hormone in females with premature ovarian insufficiency as 0.23.[5] All the patients aged 16 to 39 years, with diagnosed with premature ovarian insufficiency were included. Women with secondary causes of amenorrhea including pregnancy(urine pregnancy test), polycystic ovarian syndrome(on clinical record), chronic systemic disorders such as diabetes mellitus, hypothalamic amenorrhea, hyper-prolactinemia, Impaired Thyroid function, hypothalamic or pituitary disorders, previous ovarian surgery, allergic rhinitis, asthma, smoking history and ovarian tumor were excluded. The study was started after obtaining informed consent from all participating females. After taking demographic information a 5 ml venous blood sample was obtained from each case in aseptic measures. Blood samples were obtained to laboratory tubes with EDTA and were analyzed by automated hematology analyzer within 60 minutes following venipuncture. The values for follicle stimulating hormone and Neutrophil/Lymphocyte ratio in white blood cell count was assessed and analyzed. All data was collected by self-made proforma and all the data were entered and analyzed via SPSS version 25.

Results

A total number of patients were 713, out of which 33(4.62%) were diagnosed as having GDM (Fasting VPG >92 gm/dl), while 680 (95.37 %) were having normal glycemic control according to ADA criteria. Mean maternal age was 29.00$\pm$4.63 years, mean gestational age was 26.54$\pm$5.28 weeks, mean weight was 67.28$\pm$10.24 kg, and mean BMI was 26.07$\pm$3.96 kg/m^2. Mean fasting CBG was 89.94$\pm$7.17md/dl, mean fasting VPG was 84.06$\pm$7.32 mg/dl, and mean the difference between the two values was 5.89$\pm$3.17mg/dl.

The mean age of patients was 30.44 ± 6.34 years with minimum and maximum age as 16 and 39 years. According to status of period, 95(48.5%) cases had Amenorrhea and 101(51.5%) cases had Oligomenorrhea. There were 76(38.8%) obese and 120(61.2%) cases were non-obese. The mean FSH level was 60.37 ± 11.05 (mIU/ml) with minimum and maximum value as 40.30 and 79.60. The mean neutrophil/lymphocyte ratio was 1.72 ± 0.82 with minimum and maximum value as 0.30 and 3. Table -1

Table I: Descriptive statistics of demographic and clinical variables.

Variables	Statistics	
Age of the women	Mean +SD	30.44 +6.34 years
	Minimum	16.00 years
	Maximum	39.00 years
FSH	Mean +SD	60.37+11.05 mIU/ml
	Minimum	40.30 mIU/ml
	Maximum	79.60 mIU/ml
Neutrophil/Lymphocyte ratio	Mean +SD	1.72+0.82
	Minimum	.30
	Maximum	3.00
BMI	Normal	120(61.22%)
	Overweight	76(38.78%)
Status of peroids	Amenorrhea	101(51.53%)
	Oligomenorrhea	95(48.47%)

The correlation between Neutrophil/Lymphocyte ratio in white blood cell count and follicle stimulating hormone in females with premature ovarian insufficiency was calculated as, r = 0.666 (p-value < 0.01). Table II

Table II: Correlation between FSH (mIU/ml) versus Neutrophil/Lymphocyte ratio.

	FSH (mIU/ml) versus NLR
Correlation	0.666**
p-value	<0.001**
No. of cases	196

NLR= **Neutrophil/Lymphocyte ratio**

The correlation across different age groups, menstrual status, and BMI categories revealed a consistent relationship. In the 18-40 age group, there was a strong positive correlation (r = 0.705, p < 0.001) based on 82 cases. Similarly, in the 41-75 age group, the correlation remained strong (r = 0.640, p < 0.001) across 114 cases. Regarding menstrual status, individuals with amenorrhea showed a very strong correlation (r = 0.794, p < 0.001, 95 cases), while those with oligomenorrhea demonstrated a moderately strong correlation (r = 0.562, p < 0.001, 101 cases). For BMI, obese individuals exhibited a strong correlation (r = 0.655, p < 0.001, 76 cases), and non-obese individuals displayed a similarly strong correlation (r = 0.666, p < 0.001, 120 cases). Table III

Table III: Correlation between FSH (mIU/ml) versus NLR with respect to age, periods status and BMI. (years)

Variables		FSH (mIU/ml) versus NLR
Age groups		
18-40 (years)	Correlation	.705**
	Sig. (2-tailed)	<0.001**
	No. of cases	82
41-75 (years)	Correlation	0.640
	Sig. (2-tailed)	<0.001**
	No. of cases	114
Status of period		
Amenorrhea	Correlation	.794**
	Sig. (2-tailed)	<0.001**
	No. of cases	95
Oligomenorrhea	Correlation	.562**
	Sig. (2-tailed)	<0.001**
	No. of cases	101
Obesity		
Obese	Correlation	.655**
	Sig. (2-tailed)	<0.001**
	No. of cases	76
Non- Obese	Correlation	0.666**
	Sig. (2-tailed)	<0.001**
	No. of cases	120

NLR= **Neutrophil/Lymphocyte ratio**

Discussion

Premature ovarian insufficiency (POI) significantly affects the quality of life for women, largely due to the incomplete understanding of its etiology and the complexity of the condition. This study was conducted on 196 women having POI to explore the correlation between the Neutrophil-to-Lymphocyte Ratio (NLR) in white blood cell counts and Follicle-Stimulating Hormone (FSH) levels, with an overall mean age of 30.44 ± 6.34 years. In aligns to this study Demir B et al[6] reported mean age of women with POI was 31.6±7.05 years. On the other hand Erin KB et al[13] also conducted the study to investigate whether a correlation exists between the systemic immune-inflammation index and markers of ovarian reserve and in their study mean age

of the women was 33.71±4.12 years. According to studies, the typical mean age for premature ovarian insufficiency (POI) is around 30 to 33 years, which is noteworthy for several reasons. Firstly, this age falls within a critical reproductive period for women, during which the onset of POI can significantly impact fertility and overall quality of life. Early diagnosis and management are important, as women may face challenges in conceiving and experience a range of symptoms associated with ovarian dysfunction.

In this study a significant correlation found between the Neutrophil-to-Lymphocyte Ratio (NLR) in white blood cell counts and Follicle-Stimulating Hormone (FSH) levels in females with premature ovarian insufficiency, with a correlation coefficient of $r = 0.666$ ($p < 0.01$). Furthermore analysis across different age groups, menstrual status, and BMI categories indicated consistent relationships. In the 18-40 age group, a strong positive correlation was observed ($r = 0.705$, $p < 0.001$), while the 41-75 age group also showed a strong correlation ($r = 0.640$, $p < 0.001$). Women with amenorrhea had a very strong correlation ($r = 0.794$, $p < 0.001$), and those with oligomenorrhea had a moderately strong correlation ($r = 0.562$, $p < 0.001$).

Additionally, both obese ($r = 0.655$, $p < 0.001$) and non-obese individuals ($r = 0.666$, $p < 0.001$) exhibited strong correlations. In the comparison to this study Sanverdi I[10] compared 96 women diagnosed with POI to 110 healthy women, assessing various basal hormone levels and complete blood count parameters. Their findings indicated that the Neutrophil-to-Lymphocyte Ratio (NLR) was significantly elevated in the POI group (P-0.003). In aligns to our findings Erin KB et al[13] reported the NLR levels in the POI group were significantly higher than those values obtained from the control group, indicating that NLR might serve as a potent biomarker for evaluating ovarian reserve and predicting the dynamics of POI. In the study by Yldrm G et al[15] concluded that the CRP do not appear to be effective discriminative markers for identifying premature ovarian insufficiency (POI). In contrast, the Neutrophil-to-Lymphocyte Ratio (NLR) emerges as a significant and promising marker, particularly in the early stages of POI or even prior to its presentation.

Hence the NLR's potential utility in this context could facilitate the development of tailored fertility treatment options; enhancing patient management and outcomes.[15] In the line of this series Duan YN et al[16] conducted the study to predict endometriosis using the Neutrophil-to-Lymphocyte Ratio (NLR) and the Platelet-to-Lymphocyte Ratio (PLR). The researchers observed a positive correlation between these two ratios, reinforcing the idea that inflammation plays a key role in the pathogenesis of ovarian endometriosis.

According to their results, both PLR and NLR have the potential to serve as novel biomarkers for diagnosing endometriosis, providing a new approach to enhancing diagnostic accuracy and improving patient management.[16] Tunc SY et al[17] reported that serum levels of LH, FSH, NLR and TSH were significantly elevated in the POI group and they recommended that NLR may serve as a useful marker for diagnosing and monitoring premature ovarian insufficiency (POI), whereas GDF-15 did not show the identical potential.[17]

On the other hand, while elevated NLR is commonly associated with inflammation and autoimmune disorders, some studies have suggested that not all cases of POI are autoimmune in origin. This underscores the need for further research to clarify the relationship between NLR and the underlying causes of POI.[18,19] In the study by Yıldırım G et al[15] repoted that the Neutrophil-to-Lymphocyte Ratio (NLR) was significantly decreased in women with premature ovarian insufficiency (POI), suggesting a potential association between lower NLR levels and the condition. However, on the other hand, some studies have reported inconsistent findings.[6,20] Although this study possesses significant limitations, particularly a small sample size and the lack of a control group to assess the differences. Furthermore, the study's findings may not be applicable to larger populations due to its limited coverage. As a result, future research should include large scale and multicenter trials to evaluate the significance of NLR as a potential indicator of premature ovarian insufficiency (POI).

Conclusion

It is concluded that the correlation between Neutrophil/Lymphocyte ratio and follicle stimulating hormone in females with premature ovarian insufficiency was positively significant. Once validated the findings by future large-scale studies, the Neutrophil/Lymphocyte ratio in white blood cell count could be used as a novel predictive marker for the diagnosis of premature ovarian insufficiency.

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