Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Assessment of decreased ovarian reserve and systemic inflammatory markers

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Article Info

Article history:

Received: August 25, 2024
Accepted: October 27, 2024
Published: November 30, 2024

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Abstract

Given the significance of investigating ovarian reserve in infertile women, the limitations of existing diagnostic tests, and the absence of similar studies in this area, the present study aimed to examine the relationship between systemic inflammatory markers in patients with diminished ovarian reserve referred to the fertility clinic of Alzahra Hospital in Rasht in the year 2023. This cross-sectional analytical study was conducted on 174 patients referred to the Alzahra Hospital fertility clinic in Rasht. Patients were divided into two categories based on their serum levels of anti-Müllerian hormone (AMH):AMH >1.1 (ng/ml) and AMH < 1.1(ng/ml). Demographic and laboratory variables, including age, BMI, parity, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red cell distribution width-to-platelet ratio (RPR), and follicle-stimulating hormone (FSH), were compared between the two groups. Significant difference between the two study groups regarding age and BMI, with the mean age and BMI of patients in the group with normal ovarian reserve being lower than those in the group with poor ovarian reserve. There was a significant difference in FSH levels, the group with poor ovarian response had higher FSH levels. Age and FSH were identified as independent predictive variables associated with diminished ovarian reserve in patients. According to the present study, a significant association between diminished ovarian reserve and inflammatory markers (NLR, PLR, and RPR) was not observed. However, FSH levels were significantly higher in the Diminished Ovarian Reserve (DOR) group. Furthermore, a meaningful correlation was only found between diminished ovarian reserve and age.

Keywords: Inflammation, Infertility, Ovarian Reserve, Complete Blood Count

1. Introduction

Recent technological advancements have significantly contributed to the success of assisted reproductive methods, particularly in vitro fertilization (IVF)[1]. A limiting factor in the success of IVF is poor ovarian response, which is observed in 10 to 15% of women undergoing IVF procedures[2]. Diminished Ovarian Reserve (DOR), as defined by the American Society for Reproductive Medicine (ASRM), refers to women of reproductive age with regular menstrual cycles who exhibit reduced fertility potential or poor ovarian response (POR) following gonadotropin stimulation, in comparison to women of similar age[3]. This condition is largely attributed to the decline in ovarian function associated with the natural aging process[4], distinguishing it from menopause or premature ovarian failure[5]. The most common causes of Diminished Ovarian Reserve (DOR) vary among patients of different age groups. For older patients, DOR seems more closely associated with a natural decline in ovarian function due to advanced chronological age, significantly reducing ovarian reserve and oocyte quality.[6, 7]. However, in younger patients, DOR is frequently linked to genetic factors, environmental influences, and etiologic elements such as previous pelvic surgery or ovarian-related issues[8] Therefore, evaluating ovarian reserve before implementing assisted reproductive treatments becomes imperative[9] and may serve as a predictive indicator of ovarian response during Controlled Ovarian Stimulation (COS)[10]. For assessing ovarian reserve and predicting poor ovarian response, the estimation of Antral Follicle Count (AFC) and Anti-Müllerian Hormone (AMH) levels is commonly employed[1]. However, both indicators present pros and cons. For instance, AFC is primarily influenced by sonographic experience and subjectivity, while the reliability of AMH is heavily dependent on diagnostic methodologies. Nevertheless, ovarian reserve markers can significantly

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Doi: http://dx.doi.org/10.14715/cmb/2024.70.11.21

contribute to Controlled Ovarian Stimulation (COS) protocols, optimizing ovarian response and minimizing undesirable consequences of excessive ovarian stimulation [10]. Additionally, other examinations for evaluating ovarian reserve include the determination of Follicle-Stimulating Hormone (FSH) levels, serum Inhibin B levels, and Antral Follicle Count (AFC)[11–13], each associated with diagnostic limitations.

2. Materials and Methods

2.1. Background

Given the limitations of the tests above, there is a pressing need to identify markers with high precision and cost-effectiveness. Comprehensive blood count parameters have recently been introduced as diagnostic biomarkers for several inflammation-associated disorders[14].

2.2. Inflammatory Indicators

Platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and red blood cell distribution width-to-platelet ratio (RPR) are emerging inflammatory indicators that can be readily assessed through complete blood count. Based on studies, PLR and NLR might serve as valuable immunologic and inflammatory markers within the body [15, 16] However, there is limited quantitative research on the relationship between inflammatory indicators in patients with infertility[17–19].

2.3. Literature Context

Associations Between Inflammatory Indices and Female Infertility: A Limited Study Perspective Limited studies have indicated a significant positive correlation between Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) with infertility[20]. Additionally, other investigations have revealed links between Premature Ovarian Insufficiency (POI) and systemic immune-related inflammation markers, demonstrating notably higher Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in individuals with POI [14, 21, 22]. In a particular study, NLR has been suggested as a potential predictive indicator before disease onset or in the early stages of POI, aiding in appropriate fertility treatment choices [23].

2.4. Study Objective

While the primary cause of POI remains unidentified, genetic factors, familial history, and autoimmune diseases are among the prominent influential elements. However, POI might also be associated with ovarian tissue damage from viral infections or other related insults. Neutrophils and lymphocytes are pivotal in inflammatory processes, possibly altering their quantities during inflammatory events. The Neutrophil-to-Lymphocyte Ratio (NLR) is a simple biological indicator of inflammation. In recent studies, the Neutrophil-to-Lymphocyte Ratio (NLR) has gained attention as a diagnostic and predictive indicator. Several studies have reported an association between elevated NLR in peripheral blood and poor prognosis [24, 25]. Given the significance of investigating ovarian reserve in infertile women, the limitations of diagnostic methods, and the absence of similar studies in this domain, the present study aimed to investigate the relationship between systemic inflammatory markers in patients with diminished ovarian reserve referring to the infertility clinic of Alzahra Hospital in Rasht in the year 2023.

2.5. Methodology

This cross-sectional analytical study was conducted on patients aged 18 to 40 who presented at the Alzahra Hospital Infertility Clinic in Rasht in 2023.

2.6. Sample Size

Sampling for this study was carried out using the availability method and based on the study by İlhan [26], with a type I error of 5%, test power of 95%, and a 20% dropout rate. The minimum sample size for each group was estimated to be 87 individuals.

2.7. Exclusion Criteria

Exclusion criteria encompassed patients with secondary amenorrhea causes, including polycystic ovary syndrome, chronic medical conditions (uncontrolled diabetes mellitus or celiac disease), hypothalamic amenorrhea, intense exercise, low-calorie intake, hyperprolactinemia, thyroid hyperactivity, hypothalamic or pituitary lesions, endometriosis, smoking, women with a history of chemotherapy, pelvic surgery, exposure to radiation, or premature ovarian insufficiency due to extensive ovarian surgery. Additionally, patients with diseases that might interfere with complete blood count parameters were excluded, including hematologic, cardiovascular, renal, or hepatic diseases, asthma, arthritis, neoplastic diseases such as androgen-secreting tumors, ovarian tumors, use of glucocorticoids, infectious diseases, and parasitic infections[26].

2.8. Data Collection

After obtaining written informed consent from the patients, a phlebotomy session was conducted, and parameters, including complete blood cell counts and anti-Müllerian hormone (AMH) levels, were assessed in a centralized laboratory.

2.9. Comparison Parameters

Based on the AMH levels, the patients were categorized into two groups: AMH $\leq$ 1.1 (POR group) and AMH $>$ 1.1 (control group), according to the Bologna criteria for defining patients with Primary Ovarian Insufficiency (POR). Patients with preserved normal ovarian function were defined as AMH between 1.1 and 3.5 . Then, the two groups were compared in terms of demographic findings (age, BMI, parity, history of previous pregnancy, and miscarriage) and laboratory results (Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Red Blood Cell Distribution Width to Platelet Ratio (RPR), and Anti-Müllerian Hormone (AMH).

2.10. Statistical analysis

After data collection, statistical analysis was performed using SPSS software. The Mann-Whitney U test was employed to compare means between the two groups with non-normal distribution, and for comparing frequencies between groups, the Chi-square test was used. Linear regression analysis was utilized for modeling estimation. The differences were analyzed at a 95% confidence interval, and correlation analysis was conducted within the 95-99% confidence interval. A significance level of $p < 0.05$ was considered statistically significant.

Table 1. Comparison of Demographic, Laboratory, and Hormonal Variables Between the Two Study Groups.

		Ovarian Insufficiency Response Group (N=87)	Ovarian Reserve Normal Group (N=87)	P value
age(Mean±SD)		34.98±3.64	33.01±4.81	*0.01
BMI(Mean±SD)		27.07±4.32	25.66±3.41	*0.01
parity N(%)	0	(%86.2)75	(%90.8)79	**0.34
	1 and above	(%13.8)12	(%9.2)8	
NLR(Mean±SD)		1.92±1.17	1.93±0.73	*0.49
PLR (Mean±SD)		348.81824±0.86	348.47±275.44	*0.64
RPR (Mean±SD)		0.005±0.001	0.010±0.064	*0.95
FSH (Mean±SD)		14.75±18.78	7.36±4.44	0.001>*

*Mann–Whitney, ** Chi-squared

Table 2. Results of Logistic Regression Fitting for Determining Factors Associated with Diminished Ovarian Reserve.

Variable	Estimate	Standard Error	Odds Ratio	Significance Level (P value)	95% Confidence Interval
Age	0.114	0.042	1.121	0.006	(0.822,0.969)
BMI	0.086	0.044	1.089	0.051	(0.842,1.000)
FSH	0.100	0.031	1.106	0.001	(0.852,0.961)

3. Results

Out of the 174 participating patients in the current study, 87 individuals exhibited AMH levels Smaller than 1.1(AMH<1.1) , indicating the group with poor ovarian response. In contrast, 87 individuals with AMH levels between 1.1 and 3.5 were classified as the group with preserved normal ovarian function. The comparison of demographic, laboratory, and hormonal variables is presented in Table 1. The results revealed a statistically significant difference between the two study groups regarding age and BMI, wherein the mean age and BMI of patients in the preserved normal ovarian function group were lower than those in the poor ovarian response group. No significant differences between the two study groups regarding hematological laboratory variables were observed. However, a statistically significant difference in FSH levels was detected between the two groups, with the poor ovarian response group having higher FSH levels (Table 1). To identify factors associated with diminished ovarian reserve, logistic regression results indicated that among the parameters including age, BMI, parity, NLR, PLR, RPR, and FSH, age and FSH were independent predictors significantly linked to diminished ovarian reserve in patients. For each unit increase in age, the chance of decreased ovarian reserve was 1.12 times higher (p = 0.006), and for each unit increase in FSH, the chance of decreased ovarian reserve was 1.10 times higher (p = 0.001) (Table 2).

4. Discussion

The correlation between Diminished Ovarian Reserve (DOR) and poor fertility outcomes poses a significant challenge to women's health[27]. Research has indicated that a poor ovarian response is the initial sign of ovarian aging[28]. The annual cost associated with diminished ovarian reserves places a substantial burden on healthcare systems in various countries[29]. The diagnosis of DOR has been on the rise in recent years[30]. Various biomarkers have been proposed to address this issue, differing in sensitivity, specificity, cost, and accessibility[31]. Among the primary constraints in biomarker research are test accuracy and cost. Suitable biomarkers should be as cost-effective and non-invasive as possible[32].The Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Red Blood Cell Distribution Width-to-Platelet Ratio (RPR) are inflammatory ratios that can be easily calculated through a simple blood test. These indicators reflect inflammatory burden and have often been investigated as predictive factors in various medical domains. The timely diagnosis of diminished ovarian reserve is important for preserving remaining reserves and preventing infertility [33].

Given the lack of studies exploring the relationship between inflammatory factors such as NLR and PLR with DOR and ovarian reserve reduction, the present study is somewhat pioneering. Consequently, for result comparison in the discussion, references from studies focusing on Primary Ovarian Insufficiency (POI) were employed. The study demonstrated no significant association between NLR and diminished ovarian reserve in the investigated patients. These findings align with studies by Demir and Akdemir[22][34] but contrast with the studies by Sanverdi[14] and İlhan [26], which found a close relationship between NLR and ovarian reserve indicators like FSH and AMH. A study has suggested that NLR might be a promising indicator before disease onset or in the early stages of Premature Ovarian Insufficiency (POI) as an option for appropriate fertility treatment choices[23] .While the primary cause of POI remains unknown, genetics, family history, and autoimmune diseases are major influencing factors. However, POI may also be associated with ovarian tissue damage due to viral infections or other related factors. Neutrophils and lymphocytes are cells that play a crucial role in inflammatory processes. The number of neutrophils and lymphocytes may change in the presence of inflammation. The Neutrophil-to-Lymphocyte Ratio (NLR) is a simple biological marker for inflammation. In recent studies, NLR has garnered attention as a diagnostic and predictive indicator[24][25] .

In general, conflicting results regarding the relationship between NLR and Premature Ovarian Insufficiency (POI) exist in various studies, suggesting a need for further investigations. On the other hand, studies conducted on patients with POI have reported varied pathological features and contradictory results could stem from the distinct pathology of POI compared to diminished ovarian reserve. Considering the significance of early diagnosis of diminished ovarian reserve for preserving the remaining reserves and preventing infertility [33], the need for conducting additional studies on the association between inflammatory factors and diminished ovarian reserve becomes apparent. In the present study, a significant correlation between diminished ovarian reserve and Platelet-to-Lymphocyte Ratio (PLR) was not observed, which aligns with similar findings from other studies such as Sanverdi [14], Demir[22] and İlhan[29], which also did not find a significant difference in Platelet-to-Lymphocyte Ratio. Another hematological parameter investigated in this study was the Red Blood Cell Distribution Width-to-Platelet Ratio (RPR). It was found that there was no significant association between diminished ovarian reserve and RPR, in line with the results of Sanverdi[14] and İlhan [26] studies. Still, contrasting with Demir et al.[22]. Since there are reported studies regarding the relationship between inflammatory factors in patients with Premature Ovarian Insufficiency (POI), which differ from the studied population in the present research, these differences can be justified due to the distinct primary pathology of POI and diminished ovarian reserve. The most common causes of Diminished Ovarian Reserve can also vary across different age groups.

For older patients, Diminished Ovarian Reserve (DOR) seems to be associated with a natural decline in ovarian function due to advancing chronological age and a significant reduction in egg quality and quantity[6, 7] .However, in younger patients, DOR is often linked to genetic inheritance, environmental factors, and exogenous factors such as previous pelvic or ovarian surgeries [8]. Therefore, the need for further research in patients with diminished ovarian reserve becomes apparent.

The current study also examined the relationship between diminished ovarian reserve and inflammatory factors (NLR, PLR, and RPR) concerning demographic variables (age, BMI, parity). The findings revealed that only the age variable significantly impacted diminished ovarian reserve. In the study by Rastemi, being outside the normal weight range was identified as a risk factor for diminished ovarian reserves [35]. This could justify the observed association in individuals with lower BMI, where lower fat content might lead to poorer follicle quality [36, 37]. A significant correlation was observed in the present study in investigating the relationship between Follicle-Stimulating Hormone (FSH) and diminished ovarian reserve. This finding is consistent with previous studies such as Sanverdi[14], Alipour [38], and JIAO [39], where FSH levels were significantly higher in the diminished ovarian reserve group. During the menstrual cycle, serum FSH levels are typically measured on days 2-3 to assess ovarian reserves in women. At this point in the menstrual cycle, low FSH levels are expected. As a result of diminished follicles, FSH levels increase. Therefore, elevated FSH levels indicate diminished ovarian reserves [40, 41].

However, multiple studies have indicated that Anti-Mullerian Hormone (AMH) is more sensitive and specific than FSH in diagnosing Primary Ovarian Insufficiency (POI). AMH can be measured throughout the entire menstrual cycle, giving it an advantage over FSH, which is only measured during specific days of the cycle. For this reason, AMH is superior to FSH in diagnosing POI [38, 40, 41].

5. Conclusion

The current study revealed no significant correlation between diminished ovarian reserve and inflammatory factors (NLR, PLR, RPR). However, the FSH levels were significantly higher in the DOR group. A meaningful association was also observed between diminished ovarian reserve and demographic characteristics, precisely age.

Conflict of Interest

The authors declare that there is no conflict of interest.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

The study was approved by the ethics committee of Guilan University of Medical Sciences (IR.GUMS.REC.1401.524). All stages of this research have been performed according to the Helsinki Declaration. All procedures of the study were explained clearly to the participants who had the eligible inclusion criteria. Moreover, all participants voluntarily filled out the written informed consent form before they joined the study and they were free to decide whether or not to attend or withdraw at any time and for any reason without changing the medical care.

Availability of data and material

Supporting data are available in the Reproductive Health Research Center, Department of Obstetrics & Gynecology, Al-Zahra Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.

Authors' contributions

Roya Kabood Mehri: Concept, Design
Seyedeh Shahed Shoarishoar and Maryam Karimian: Literature Search
Fereshteh Fakor: Design
Zahra Rafiei Sorouri and Mandana Mansour-Ghanaei and Forozan Milani: Concept
Roya Faraji Darkhaneh: writing
Seyedeh Fatemeh Dalil Heirati: Data Collection or Processing , Analysis or Interpretation
Zahra Heidarpour: Data Collection or Processing , Literature Search

Funding

This study was financially supported by the Vice-Chancellorship of Research and Technology, Guilan University of Medical Science.

Acknowledgments:

The authors gratefully acknowledge the following support personnel Reproductive Health Research Center, Guilan University of Medical Sciences, Rasht, Iran.

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