

Are pan-immune-inflammation value, systemic inflammatory response index and other hematologic inflammatory indexes clinically useful to predict first-trimester pregnancy loss?

Are inflammatory indices important in predicting first trimester pregnancy loss?

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Abstract

Aim: The purpose of the study is to investigate the importance of hematological inflammatory parameters in predicting pregnancy loss in the first trimester. **Material and Methods:** This study was conducted retrospectively between February and May 2022 in Aksaray University Training and Research Hospital, Obstetrics and gynecology outpatient clinic. Fifty-five of 110 patients diagnosed with first trimester pregnancy loss were included in the study. The control group consisted of 55 pregnant women with first trimester pregnancies.

Results: When the whole groups were compared, no statistically significant difference was observed in terms of hemoglobin, platelet, neutrophil, lymphocyte count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), derived NLR ratio (dNLR), systemic inflammatory index (SII), systemic inflammatory response index (SIRI) and pan-immune-inflammation value (PIV).

Discussion: NLR, PLR, LMR, dNLR, SII, SIRI and PIV parameters were not associated with first trimester abortions. In this study, unlike previous studies, no hematological parameters, including the pan-immune-inflammation value, were found to have a role in predicting first trimester pregnancy loss.

Keywords

First-Trimester Abortion, Systemic Inflammatory Index, Systemic Inflammatory Response Index, Pan-Immune-Inflammation Value

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Introduction

First trimester pregnancy loss (FPL) is the most common complication of early pregnancy, covering the first 12 weeks of pregnancy. 75% of all abortions occur before 16 weeks of gestation [1], of which 7.9% result in maternal death [2]. Many factors such as genetic anomalies, endocrinological disorders and immunological diseases have been associated with abortion [3]. Complications such as severe vaginal bleeding, endometrial damage, and infection can be observed during the FPL process. It may take time for women to realize that they have developed FPL because the symptoms are not specific. The diagnosis of FPL is difficult until confirming the dead fetus with ultrasound [4]. According to studies, it is clear that changes in maternal adaptive and immune response are important for a healthy pregnancy [5]. In recent studies, it has been suggested that the rates generally accepted as inflammation markers, neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), change in some conditions such as pregnancy-related complications, genital cancers, and infection [6-9].

Although many studies have stated that inflammation plays a key role in the pathophysiological mechanism of FPL, there are very few studies evaluating hematological parameters for this purpose. Bas et al. evaluated the hematological parameters for spontaneous abortions in the first and second trimesters [10]. Ardestani et al.'s study showed that NLR, MLR, PLR and derived NLR ratio (dNLR) levels were significantly higher in COVID-19 patients. In addition, NLR, LMR and dNLR were found to be significantly higher in those who died due to COVID-19 [11]. In the literature, studies have reported that it is possible to predict the development and severity of the diseases by looking at NLR and PLR levels [12,13].

Systemic inflammatory index (SII) and systemic inflammatory response index (SIRI) have started to be used in studies on cancers, acute pancreatitis, death prediction after coronary artery bypass surgery and other inflammatory processes [13-15]. However, pan-immune-inflammation value (PIV) is a new marker used specifically for cancers [16-19]; PIV in first-trimester pregnancy loss has never been studied before. A Complete blood count (CBC) is one of the first tests routinely requested after the presence of pregnancy is learned. In the present study, we purposed to evaluate parameters of the blood sera and inflammation indices obtained from these parameters, which is an easily accessible, inexpensive, and easily evaluated method for predicting first-trimester abortions.

Material and Methods

Purpose and Type of the Study

This retrospective study was conducted to evaluate CBC parameters in terms of whether there is a relationship between first trimester pregnancy loss and inflammation and to show whether pregnancy loss is predictable accordingly.

Sampling and participants

One hundred and ten pregnant women who applied to Aksaray University Training and Research Hospital, Gynecology and Obstetrics Polyclinic between January 2022 and December 2022 and were diagnosed with first trimester pregnancy and met the criteria were included in this study. The present study included 55 patients with a diagnosis of first-trimester pregnancy loss

and 55 patients with healthy pregnancies. The present study was approved by Aksaray University Local Ethics Committee (protocol number: 157-SBKAEK).

Data collection tools

The demographic information of the patients included in the study (age, number of pregnancies, number of miscarriages) and CBC parameters obtained from the hospital automation system were evaluated. CBC values during routine scans were used. CBC parameters evaluation was performed using an automated blood analyzer. The diagnosis of FPL was made by clinical examination and ultrasound records. All patients were 6-12 weeks pregnant from the first day of their last menstrual period. FPL was defined as the monitoring of an intrauterine gestational sac with no fetal heartbeat but greater than 10 mm in diameter. The inclusion criteria were pregnant mothers between the ages of 18-40 years with gestational age between 6-12 weeks who had singleton pregnancies. Patients with any congenital uterine anomaly, cervical insufficiency, hydatiform mole or multiple pregnancies, large uterine fibroids, and known history of thrombophilia were excluded from the patients diagnosed with FPL. Blood samples from the antecubital veins of these women were obtained after admission to the hospital before any treatment was administered. A complete blood count was performed as a standard laboratory procedure. Hemogram parameters were recorded. NLR, PLR, LMR, dNLR (neutrophil count divided by the result of WBC count minus neutrophil count), SII (neutrophil x platelet/lymphocyte count), SIRI (neutrophil x monocyte/lymphocyte count), and PIV (neutrophil x platelet x monocyte/lymphocyte count) were calculated. Accessible data (age, number of pregnancies, number of miscarriages) and hemogram parameters of the patient and control groups were evaluated. No extra blood was drawn from the patients for the study.

Statistical analysis

IBM SPSS 22 statistical program was used for statistical analysis. Two independent groups were compared with Student's t-test. Values that did not fit the normal distribution were compared using the Mann-Whitney U test. Statistically significant p-value was accepted as <0.05.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The difference observed between those who had abortions and those who were healthy in terms of age, count of gravida and parity were not statistically significant ($p=0.152$, $p=0.21$, $p=0.144$) (Table 1). On the other hand, the number of abortions in FPL group was significantly higher than in the healthy group ($p=0.04$). A comparison of all parameters of the control and abortion groups are shown in Table 1.

Discussion

Most of the fetal deaths observed during pregnancy occur in the first trimester. Although many studies have stated that inflammation plays a key role in the pathophysiological mechanism of FPL, there are very few studies evaluating hematological parameters for this purpose. In the present study, we investigated CBC parameters, which are included

Table 1. Comparison of all parameters in first-trimester abortions in healthy pregnant women (n=110).

Parameters	FPL group (n=55) Median (min-max)	Healthy (n=55) Median (min-max)	P
Age (years) Mean ± SD	29.7 ± 6.6	26.2 ± 5.6	0.152¥
Gestational age (weeks) Mean ± SD	7.9 ± 1.7	8.4 ± 1.9	0.403¥
Gravida	2 (1-6)	2 (1-5)	0.21*
Parity	1 (0-5)	0.8 (0-3)	0.144*
Abortus	0.5 (0-4)	0.3 (0-2)	0.04*
Hemoglobin (g/dl)	13 (10.4-15.6)	13.1 (10.5-15.0)	0.862*
Neutrophil (10 ⁹ /L)	5.5 (2.6-16.9)	5.8 (3.4-10.2)	0.647*
Lymphocyte (10 ⁹ /L)	2.1 (0.8-4.1)	1.9 (0.6-3.1)	0.656*
Platelet (10 ⁹ /L)	249 (137-413)	254 (166-446)	0.77*
NLR	2.93 (1.28-11.52)	2.98 (1.5-8.9)	0.414*
PLR	126.1 (58.1-382.7)	127.5 (71.3-358.1)	0.362*
LMR	0.21 (2.7-9.3)	0.23 (1.3-7.9)	0.799*
dNLR	-4.7 (-16.04 , -2.2)	-5.1 (-9.5,-2.8)	0.652*
SII	731.9 (285.4-3328.4)	782.6 (381.3-2539.9)	0.252*
SIRI	1.25 (0.38-6.1)	1.29 (0.53-3.6)	0.552*
PIV	321.8 (85.3-1764.1)	324.7 (115.6-1152.7)	0.435*

¥: Student's t-test; *: Man-Whitney U test, FPL: First trimester pregnancy loss, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte ratio, LMR: Lymphocyte-to-Monocyte Ratio, dNLR: Derived NLR ratio (neutrophil count divided by the result of WBC count minus neutrophil count), SII: Systemic inflammatory index (neutrophil x platelet/lymphocyte count) , SIRI: Systemic inflammatory response index (neutrophil x monocyte/lymphocyte count) and PIV: Pan-immune inflammation value (neutrophil x platelet x monocyte/lymphocyte count).

in routine screening tests in the first trimester of pregnancy, between FPL and healthy control groups. Studies up to date have shown that high neutrophil count may be a marker of inflammation, infection, bleeding, tissue necrosis, stress-related conditions, and gestational diabetes mellitus [8,9]. In recent studies, neutrophil counts and NLR have been associated with several conditions such as HELLP syndrome, recurrent pregnancy loss, hyperemesis gravidarum, or spontaneous abortion, particularly in the first trimester [10,19,20]. In study of Bas et al., when compared with the control group, in the first and second trimester abortion groups, platelet volume, platelet-lymphocyte ratio levels decreased, and neutrophil, lymphocyte and NLR increased [10]. In this study, we detect no significant differences in neutrophil, platelet, and lymphocyte count, NLR, PLR, and SII ratios between FPL cases and the control group (p > 0.05) (Table 1). The different results of this study from previous studies can be explained by the fact that FPL has a much different pathogenesis; this also means that not all pregnancy products can trigger inflammatory responses to the same degree.

Recent studies have shown that NLR, PLR and dNLR indicate inflammation [11]. Murad et al.'s study on determining the prognostic predictive value of Body Mass Index (BMI), NLR, SIRI and BMI in patients with laryngeal squamous cell carcinoma, found that NLR ≥ 2.02 + Low BMI or SIRI ≥ 1160.85 + Low BMI increased the risk of death [13]. In this study, we found no correlation between FPL and hematologic parameters. However, in this study, PIV, which is one of the newest markers, has been studied mostly in the field of cancer and was found to be significantly higher in worse overall survival [17-19, 22]. PIV has not been studied so far in women who had a first trimester abortion. Therefore, the present results have provided

important information for the literature.

Clinically, it is unreasonable to expect a high degree of significance from the rates obtained, since the hematological conditions of the individuals before the diagnosis of FPL are not identical. In addition, disease progression may also move the hematological parameters in the direction opposite to that is expected. For example, deepening of thrombocytopenia with the development of disseminated intravascular coagulopathy may cause a decrease in LII. Conversely, with an increase in any systemic inflammation, there may be an increase in neutrophil count, with a corresponding decrease in lymphocyte count and thus an increase in SII. Therefore, it is possible to obtain different results in similar studies. As a matter of fact, in our study, unlike the literature, we showed that the inflammatory parameters of FPL were not significantly different compared to the control group.

Therefore, it is important to state that there was no statistically significant difference between the groups in our study in terms of age, gestational week, gravidity and parity. We may owe to the fact that the CBC parameters are not very different from each other, due to the excellent similarity of all demographic parameters except the health status of the pregnancy. However, the result should be supported by further prospective large-scale studies.

Conclusion

As a conclusion, we showed that there is no relationship between hematologic parameters and inflammatory indexes in FPL. The limitations of the study are that it is a single-center and small-scale study. However, despite these limitations, it is important because it is the first study to investigate the pan-immune-inflammatory value in first trimester abortions.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Massalska D, Zimowski J G, Bijok J, Pawelec M, Czubak-Barlik M, Jakiel G, et al. First trimester pregnancy loss: clinical implications of genetic testing. *J Obstet Gynaecol Res.* 2018; 43(1): 23-29.
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health.* 2014; 2(6): 323-33.
3. Kaplanoglu M, Yuca T, Bulbul M. Decreased mean platelet volume is associated with the developing stage of fetoplacental unit in spontaneous abortion. *Int J Clin Exp Med.* 2015; 8(7): 11301.
4. Zhang X, Li J, Gu Y, Zhao Y, Wang Z, Jia G. A pilot study on environmental and behavioral factors related to missed abortion. *Environ Health Prev Med.* 2011; 6(4): 273-8.
5. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol.* 2010; 63(6): 425-33.
6. Panwar M, Kumari A, Anand H, Rashmi A, Vishwajeet S, Reeta B. Raised neutrophil lymphocyte ratio and serum beta hCG level in early second trimester of pregnancy as predictors for development and severity of preeclampsia. *Drug Discov Ther.* 2019; 13(1): 34-37.

7. Wang J, Zhu Q-W, Cheng X, Liu J, Zhang L, Tao Y-M, et al. Assessment efficacy of neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio in preeclampsia. *J Reprod Immunol*. 2019;132: 29-34.
8. Ethier J-L, Desautels D, Templeton A, Oza A, Amir E, Lheureux S. Is the neutrophil-to-lymphocyte ratio prognostic of survival outcomes in gynecologic cancers? A systematic review and meta-analysis. *Gynecol Oncol*. 2017; 145(3): 584-94.
9. Russell C, Parajuli A, Gale H, Bulteel N, Schuetz P, Jager C, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. *J Infect*. 2019; 78(5): 339-48.
10. Bas FY, Tola EN, Sak S, Cankaya BA. The role of complete blood inflammation markers in the prediction of spontaneous abortion. *Pak J Med Sci*. 2018; 34(6): 1381.
11. Ardestani SK, Salehi MR, Attaran B, Hashemi SY, Sadeghi S, Ghaffarpour S, et al. Neutrophil to Lymphocyte Ratio (NLR) and Derived NLR Combination: A Cost-effective Predictor of Moderate to Severe COVID-19 Progression. *Iran J Allergy Asthma Immunol*. 2022; 21(3): 241.
12. Erdal H, Yasar E, Tuncer SÇ. Determination of calprotectin levels in patients with cataract surgery. *Ann Clin Anal Med*. 2023;14(2):148-51.
13. Ozcan D, Kurtul BE, Ozcan SC, Elbeyli A. Increased Systemic Immune-Inflammation Index Levels in Patients with Dry Eye Disease. *Ocul Immunol Inflamm*. 2020;30(3): 588-92.
14. Murad LD, Silva TQ, Schilithz AOC, Monterio MC, Murad LB, Fialho E. Body Mass Index Alters the Predictive Value of the Neutrophil-to-Lymphocyte Ratio and Systemic Inflammation Response Index in Laryngeal Squamous Cell Carcinoma Patients. *Nutr Cancer*. 2021; 7: 1-9.
15. Tiwari B, Sharma A, Vashishtha V. Comprehensive Assessment of Inflammatory Indices to Predict Outcomes in Acute Pancreatitis. *J Invest Surg*. 2023; 36(1): 2152914.
16. Urbanowicz T, Michalak M, Olasińska-Wiśniewska A, Rodzki M, Witkowska A, Gąsecka A, et al. Neutrophil Counts, Neutrophil-to-Lymphocyte Ratio, and Systemic Inflammation Response Index (SIRI) Predict Mortality after Off-Pump Coronary Artery Bypass Surgery. *Cells*. 2022; 11(7): 1124.
17. Lin F, Zhang LP, Xie SY, Huang HY, Chen XY, Jiang TC, et al. Pan-immune-inflammation value: A new prognostic index in operative breast cancer. *Front Oncol*. 2022; 12:830138.
18. Yeh C-C, Kao H-K, Huang Y, Tsai T-Y, Young C-K, Lu C-Y, et al. Discovering the Clinical and Prognostic Role of Pan-Immune-Inflammation Values on Oral Cavity Squamous Cell Carcinoma. *Cancers*. 2023; 15(1):322.
19. Zhao H, Chen X, Zhang W, Cheng D, Lu J, Wang C, et al. Pan-immune-inflammation value is associated with the clinical stage of colorectal cancer. *Front Surg*. 2022; 9:996844.
20. Susok L, Said S, Reinert D, Mansour R, Scheel C-H, Becker J-C, et al. The pan-immune-inflammation value and systemic immune-inflammation index in advanced melanoma patients under immunotherapy. *J Cancer Res Clin Oncol*. 2022; 148(11) 3103-8.
21. Aynioglu O, Isik H, Sahbaz A, Harma M, Isik M, Kokturk F. Can plateletcrit be a marker for recurrent pregnancy loss? *Clin Appl Thromb Hemost*. 2016; 22(5): 447-52.
22. Sisti G, Faraci A, Silva J, Upadhyay R. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and complete blood count components in the first trimester do not predict HELLP syndrome. *Medicina*. 2019; 55(6): 219.

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