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HEMATOLOJİK İNFLAMATUAR PARAMETRELERİN DÜŞÜKLERLE İLİŞKİSİ

ASSOCIATION OF HAEMATOLOGICAL INFLAMMATORY PARAMETERS WITH ABORTUS IMMINENS

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ÖZ

Amaç: Abortus imminens öngörüsünde sistemik immün-inflamasyon indeksi ve pan-immün-inflamasyon değerinin gebeliğin devamını öngörmede belirteç olarak kullanılabilirliğini bulmayı amaçladık.

Materyal method: Bu vaka-kontrol çalışması Ankara Etlik Şehir Hastanesi kadın hastalıkları ve doğum kliniğinde retrospektif olarak yapılmıştır. Kanama nedeniyle hastanemize başvuran ve abortus imminens tanısıyla hastaneye yatırılıp abort eden hastalar ve ayaktan takip edilip gebeliği devam eden hastalar iki gruba ayrıldı. Gebeliği düşük ile sonuçlanmayan (grup 1) ve düşük ile sonuçlanan (grup 2) hastalar arasında hemogram sonuçlarından derive edilmiş indeksler karşılaştırıldı ve indekslerin gebeliğin devamını öngörmedeki performansını değerlendirildi.

Bulgular: Yaş, vücut kitle indeksi ve parite açısından eşleştirilmiş 232 vaka (abort eden grup) ve 232 kontrol (gebeliği devam eden grup) çalışmaya dahil edilmiştir. Gebeliğin düşükle sonuçlanıp sonuçlanmayacağını belirlemek için tam kan sayımından elde edilen indeksler değerlendirildiğinde, SII, SIRI, PIV, NLR, PLR ve MLR arasında sadece SII ayırt edici güce sahiptir. (cut-off: > 720; p: 0.039, duyarlılık: %63, özgüllük: %52).

Sonuç: Anne kanındaki yüksek SII seviyeleri, düşük tehdidi tanısı konan hastalarda gebeliğin devamını öngörebilir. Bu durum, gebeliğin sürdürülmesinde maternal immün toleransın ve immün sistemin önemini vurgulamaktadır. Yüksek SII'li hastalarda ek tedavilerle gebelik sürdürülebilir. Ancak, sonuçlarımızı doğrulamak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: abortus imminens, platelet, gebelik, sistemik ımmun-inflamatuar index

ABSTRACT

Aim: We aimed to find out whether the systemic immune-inflammatory index and the pan-immune inflammatory score can be used as markers for predicting a continuation of pregnancy in the prediction of threatened abortion.

Materials and Method: This case-control study was conducted retrospectively in the gynecology and obstetrics clinic of Ankara Etlik City Hospital. Patients who were admitted to our hospital due to bleeding and were hospitalized with a diagnosis of abortus imminens and had an abortion, and patients who were followed up as outpatients and whose pregnancy continued were divided into two groups. The indices derived from the hemogram results were compared between the patients whose pregnancies did not result in miscarriage (Group 1) and those whose pregnancies ended in miscarriage (Group 2), and the performance of the indices in predicting the continuation of pregnancy was evaluated.

Results: We recruited 232 cases (miscarriage) and 232 controls (pregnancy continued), matched for age, body mass index, and parity. When complete blood count derived indices were evaluated to determine whether the pregnancy would result in miscarriage or not, only SII had discriminative power among SII, SIRI, PIV, NLR, PLR and MLR. (cut-off: > 720; p: 0.039, sensitivity: 63%, specificity: 52%).

Conclusion: High SII levels in maternal blood can predict continuation of pregnancy in patients diagnosed with threatened miscarriage. This emphasises the importance of maternal immune tolerance and the immune system in maintaining pregnancy. In patients with high SII, pregnancy can be maintained with additional treatments. However, further studies are needed to confirm our results.

Key word; Abortion, Missed, Blood Platelets , Pregnancy, Systemic immune-inflammation index

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GİRİŞ

A pregnancy loss of less than 20 weeks is called a miscarriage. Miscarriage occurs in approximately 15.0-30.0% of all pregnancies and in 8-15% of pregnancies confirmed by ultrasound and histopathology (1,2). It is responsible for 7.9% of maternal deaths (3). Many factors, including genetic abnormalities, endocrinological disorders and immunological diseases, have been associated with miscarriage. Many factors such as advanced maternal age, obesity, thyroid disorders, autoimmune diseases, thrombophilic gene mutations, infertility treatments with assisted reproductive technologies, nulliparity, smoking during pregnancy or in the past, the presence of fibroids or uterine malformations and cervical insufficiency cause miscarriages (4).

Maternal adaptation and immune response are important for a healthy pregnancy (5). Recent studies have demonstrated the effects of haematological parameters, particularly platelets and white blood cells, on inflammation and the immune response and have shown that platelets are more important for the immune response than their effects on haemostasis (6). The innate immune system responds to molecules associated with pathogens and releases inflammatory mediators. The cascades formed by these messengers activate monocytes, lymphocyte(LYM), macrophages, neutrophils(NEUT), natural killer cells, and mast cells (7). In addition to white blood cells, platelets(PLT) also play an important role in the release of mediators that cause local changes in the inflammatory process. It is increasingly recognized that platelets play a crucial role in inflammation and immune responses and not only in hemostasis (8). Blood parameters have begun to be used to assess the systemic inflammatory status of the immune system. While the first studies used neutrophil to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR) values for immune response, a new parameter calculated by the formula NEUT × PLT/LYM was found in 2014 and is called the systemic immune inflammation index (SII) (9). The SII is more stable than NLR, PLR and MLR and accurately indicates the inflammatory status of patients. The SII is more accurate than others because it considers multiple factors to represent inflammation. The SII has generally been studied in oncology and cardiovascular disease (10,11). Recently, its association with pregnancy complications and early pregnancy loss has also been studied (12,13).

The complete blood count (CBC) is one of the tests routinely ordered at the first pregnancy visit. In this study, we aimed to evaluate the blood parameters, which are an easily accessible, inexpensive and evaluable method for predicting continuation of pregnancy, and their relationship to the inflammation indices obtained from these parameters in patients who had bleeding or pain in the first trimester and were diagnosed with abortus imminens.

MATERIALS AND METHODS

In this study, we retrospectively analysed the data of women who were diagnosed with threatened abortion in our clinic between October 2022 and October 2023. The study included women over the age of 18 who were diagnosed with abortion in the first 20 weeks of pregnancy. A control group was formed from women with healthy pregnancies at the same gestational week who had no systemic diseases that could affect haemogram values and who had no complications in the follow-up period up to delivery.

Patients with a history of multiple pregnancies, haematological, autoimmune and inflammatory diseases, recurrent miscarriages, thyroid dysfunction, history of thrombosis, history of drug use, uterine abnormalities and active infections were excluded.

Patients' age, gestational age, parity, gravidity, history of single or multiple pregnancy, obstetric ultrasound findings and laboratory results were extracted from the hospital's electronic medical records. Pregnant women with vaginal bleeding with a closed cervix were categorised as abortus imminens.

In the first 20 weeks, haemogram parameters including platelet (PLT) count, neutrophil(NEUT) count and lymphocyte (LYM) count were determined. Haemoglobin (HGB), NEUT, PLT and LYM were determined using the ADVIA® 120 haematology system (Siemens Healthcare Diagnostics Inc., Deerfield, Illinois). PLR was calculated as the number of platelets divided by the number of lymphocytes and NLR was calculated as the number of neutrophils divided by the number of lymphocytes. The SII was calculated using the formula neutrophil count x platelet count/lymphocyte count (9) and PIV was calculated usind the formula neutrophil count × platelet count × monocyte count)/ lymphocyte count (14)

Statistical analyses

All statistical analyses were performed using the RStudio integrated development environment for statistical computing to analyze the data. The variables were examined using visual (histogram and probability plots) and analytic (Kolmogorov–Smirnov/Shapiro–Wilk's test) methods to determine whether

the variables were normally distributed. The Levene test was used to assess the homogeneity of the variance. Descriptive studies were presented using medians and quartiles (Q1–Q3) for non-normally distributed numerical data. The Mann–Whitney U tests were used to compare these parameters between groups. Descriptive analyses for categorical variables were presented using frequency and percentage. The relationships between categorical variables were analyzed using the Chi-square test or Fisher's exact test (when the Chi-square test assumptions did not hold due to low expected cell counts). The capacity of SII to predict miscarriage was analyzed using receiver operating characteristics (ROC) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity, area under the curve (AUC) value, and positive and negative probability ratios were presented. A 5 % type I error level was used to determine statistical significance. A p value of less than 0.05 was considered statistically significan

RESULTS

Of the 329 patients who had a miscarriage in our clinic between October 2022 and October 2023, 27 had a recurrent miscarriage, 18 had gestational diabetes, 8 had hypertension, 4 had rheumatologic disease, 2 had a previous uterin surgery and 2 patients had valvular heart disease. and 36 patients were excluded from the study because their data could not be accessed, resulting in a patient group of 232 patients (Group II). Taking into account the randomisation rules, 232 patients with threatened abortion whose pregnancies did not result in abortion were included in the control group (Group I). There was no difference between the groups in terms of the week in which the imminent abortion was diagnosed, but maternal age, gravida, parity, multiparity, miscarriage, vaginal delivery and delivery by caesarean section were higher in the control group (Table 1).

Table 1: Demographic and clinical characteristics of the study population.

Variable	**GROUP 1** **n: 232**	**GROUP 2** **n: 232**	**TOTAL** **n: 464**	**p**
Age (years)	28 (24-33)	26 (22-32)	27 (23-32)	**0.002**
Gestational age (week)	9 (6-13)	10 (6-13)	9 (6-13)	0.192
Gravida (number)	2 (2-3)	1 (1-2)	2 (1-3)	**<0.001**
Parity (number)	1 (0-2)	0 (0-0)	0 (0-1)	**<0.001**
Primiparous n (%)	44 (19)	169 (72.8)	213 (45.9)	**<0.001**
Multiparous n (%)	188 (81)	63 (27.2)	251 (54.1)	
Miscarriage (number)	0 (0-1)	0 (0-0)	0 (0-0)	**<0.001**
Vaginal delivery (number)	0 (0-1)	0 (0-0)	0 (0-1)	**<0.001**
Ceserean delivery (number)	0 (0-1)	0 (0-0)	0 (0-0)	**<0.001**
Volume of haematoma$^{\Phi}$ (mm^3)	224 (100-515)	218 (114-343)	222 (100-473)	0.509

Taking into account the randomisation rules, 232 patients with threatened abortion whose pregnancies did not result in abortion were included in the control group (Group I). There was no difference between the groups in terms of the week in which the imminent abortion was diagnosed, but maternal age, gravida, parity, multiparity, miscarriage, vaginal delivery and delivery by caesarean section were higher in the control group (Table 1).

When evaluating the results of the complete blood count and the indices calculated from it, there were no differences between the groups with regard to leucocytes, haemoglobin, haematocrit, thrombocytes, monocytes, neutrophils, lymphocytes, NLR, PLR, MLR, SIRI. The SII and PIV values were statistically significantly higher in group II than in group I. (Tablo 2)

Table 2: Comparison of hemogram parameters, hemogram-derived ratios at hospital admission between groups.

Variable	GROUP 1 n: 232	GROUP 2 n: 232	TOTAL n: 464	p
WBC (10^3/μL)	8.3 (7-10.4)	8.6 (7.3-10.2)	8.5 (7.1-10.2)	0.541
Hemoglobin (g/dl)	12.4 (11.7-13)	12.5 (11.7-13.2)	12.5 (11.7-13.1)	0.931
Hematocrit (%)	37.5 (35.5-39.2)	37.8 (35.6-39.4)	37.6 (35.5-39.3)	0.529
Platelets (10^3/μL)	255 (206-312)	252 (222-298)	253 (217-305)	0.982
Monocytes (10^3/μL)	0.39 (0.31-0.49)	0.40 (0.32-0.49)	0.40 (0.32-0.49)	0.336
Neutrophils (10^3/μL)	5.7 (4.6-7.4)	6.1 (4.8-7.4)	5.93 (4.6-7.4)	0.324
Lymphocytes (10^3/μL)	2 (1.6-2.3)	1.8 (1.5-2.3)	1.9 (1.6-2.3)	0.141
NLR	3 (2.3-3.9)	3.2 (2.4-4.2)	3.1 (2.4-4)	0.075
PLR	130 (103-159)	136 (112-171)	133 (109-166)	0.052
MLR	0.20 (0.16-0.25)	0.21 (0.17-0.26)	0.21 (0.17-0.26)	0.064
SII (ml)	707 (521-1120)	823 (602-1145)	785 (550-1126)	**0.040**
SIRI (ml)	1.08 (0.76-1.92)	1.22 (0.92-1.69)	1.2 (0.83-1.84)	0.058
PIV (μL)	239 (170-587)	333 (228-478)	285 (192-538)	**0.044**

When analysing the indices derived from the complete blood count to determine whether the pregnancy would lead to a miscarriage or not, only the SII had discriminatory power. (cut-off: > 720; p: 0.039, sensitivity: 63%, specificity: 52%) (Table 3) (Figure 1).

CONCLUSION

In this study, we investigated the indices calculated from haematological parameters indicative of maternal immune inflammatory status to predict continuation of pregnancy in patients diagnosed with threatened abortion. In contrast to other studies, we used several new indices instead of a single index.

The maternal immune response is one of the most important factors for the development and maintenance of a healthy pregnancy. Since the fetus is a semi-graft, a successful pregnancy requires mechanisms to prevent rejection of the allograft. Adaptation of the immune system is critical to prevent rejection of the semi-allograft conceptus during pregnancy (15). Dysregulation of immune responses can lead to reproductive disorders such as recurrent pregnancy loss, implantation failure, preterm labor, intrauterine fetal growth restriction, and pre-eclampsia (16). Cytokines produced by immune and non-immune cells are important players in controlling the immune response (17). IL-10 is a suppressive, anti-inflammatory cytokine that has been linked to pregnancy outcomes and may be used as a therapeutic pathway to prevent natural pregnancy loss in a mouse model (18). The current inflammatory environment can be determined by the release of cytokines as well as by these new inflammatory indices measured in maternal blood. Başkıran et al. used the

subclinical inflammatory markers NLR, MLR and PLR indices in their study on abortus imminens. They found an increase in inflammatory indices in abortus imminens compared to the control group (19).

Studies have shown that maternal immune status is important for fetal rejection. The immune indices we investigated in our study are inexpensive and easily accessible tests compared to other parameters. While a suppressed immune system is required for the continuation of pregnancy, our study found that the systemic immune-inflammatory index was higher in patients who had an abortion than in the control group. Studies have mostly investigated the relationship between recurrent pregnancy losses and the immune system of the mother. Carpenter et al. argued that TNFα, a proinflammatory cytokine, is elevated in recurrent miscarriage and that TNFα blockers can be used in recurrent pregnancy loss (20). This suggests that the current inflammatory environment may have affected paracrine and autocrine mechanisms, causing cytokine release and abortion.

Previous studies have shown that a high neutrophil count may be a marker for inflammation, infection, haemorrhage, tissue necrosis, and stress-related conditions (21). In our study, no difference was found between the groups in terms of WBC, haemoglobin, haematocrit, platelets, monocytes, neutrophils, lymphocytes, NLR, PLR, MLR, SIRI when blood count parameters were examined.

Genç et al. reported that there was no difference in pan-immune inflammatory indices between first trimester spontaneous abortions and the control group (22). In contrast to this study, the pan-immune index in our study was found to be different and statistically significant between the groups.

In another study, haematological inflammatory markers in early pregnancy loss were compared with markers in patients with healthy deliveries. Although there was a difference between the two groups, the results were insufficient for sensitivity (23).

MPV can be used universally in routine blood counts with automated haemograms and is a simple and easy method for assessing platelet function. Dempsey et al. have shown that platelet function is reduced in patients with miscarriages. Their study suggests that platelets may play a role in the pathophysiology of miscarriage (24). Compared to smaller platelets, larger platelets have more granules, aggregate faster with collagen, have higher thromboxane A2 levels, and express more glycoprotein Ib and IIb/IIIa receptors. Therefore, MPV can be considered an indicator of platelet reactivity, and results have shown that high MPV values reflect platelet activation and expansion (25). In our study, MPV values were not analysed between the groups, but no difference was found between the groups when only platelet count was evaluated. The fact that MPV values were not analysed is a missing aspect of our study.

There are differences in the age and gravity of the patients. Age and gravity were found to be lower in the abortion group. Studies have shown that the risk of miscarriage increases with age and gravida (26), but in our study the opposite was the case, making the relationship between miscarriage and systemic immune inflammation stronger in patients.

It is important to point out that this study has certain limitations. First, the patients were selected from only one institution, and because the study was conducted on a single race, the sample size is relatively small. Therefore, our results may not be fully representative of the wider population. However, if multicenter studies with larger patient cohorts are conducted in the future, we may obtain more precise and accurate results that reflect the general population.

TARTIŞMA

In conclusion, high concentrations of SII and PIV in maternal blood indicate an inflammatory process leading to an unfavorable outcome of pregnancy in pregnant women diagnosed with threatened miscarriage and can be used to predict a continuation of pregnancy and they can help our treatment decisions to prevent a miscarriage. However, further studies are needed to confirm our findings.

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Ethics approval: The study was performed by according to the rules of the Declaration of Helsinki and approved by the Ethics Committee of Ankara Etlik City Hospital. (Date June 20, 2023/ No: AESH-EK1- 2023/313)

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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