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Plasenta Previada Birinci Trimester Tam Kan Sayımı İnflamatuar İndekslerinin Değerlendirilmesi

Evaluation of Complete Blood Count Inflammatory Indices in Pregnant Women Diagnosed with Placenta Previa

MURADİYE YILDIRIM [1] Orcid ID: 0000-0002-6583-2153
DİLEK SAHIN [2] Orcid ID: 0000-0001-8567-9048

[1] Department of Obstetrics and Gynecology, Division of Perinatology, Turkish Ministry of Health Ankara City Hospital, Ankara, Turkey

[1] University of Health Sciences, Department of Obstetrics and Gynecology, Division of Perinatology, Turkish Ministry of Health Ankara City Hospital, Ankara, Turkey

ÖZ

Amaç: Plasenta previa (PP) tanılı gebelerde sistemik inflamasyonu değerlendirmektir. PP hastalarının birinci trimester tam kan sayımı indeksleri sağlıklı gebeler ile karşılaştırıldı.

Gereçler ve Yöntem: Bu kesitsel çalışma, üçüncü basamak bir merkezde bir yıl boyunca opere edilmiş 115 PP (çalışma grubu) ve rastgele seçilmiş 231 sağlıklı gebe (kontrol grubu) olmak olmak üzere 346 tekil gebe ile yapıldı. PP olguları daha sonra iki alt gruba ayrıldı. Plasenta akreta spektrumu (PAS) nedeniyle sezaryen histerektomi yapılanlar PAS-pozitif grup, invazyon saptanmayanlar PAS-negatif grup olarak belirlendi. Hastaların demografik ve obstetrik özellikleri ile birinci trimester muayene laboratuvar sonuçları retrospektif olarak kaydedildi. Sistemik immün-enflamasyon indeksi (SII) ve sistemik inflamatuar yanıt indeksi (SIRI) değerleri hesaplandı. Elde edilen veriler, bağımsız örneklem t-testi kullanılarak karşılaştırıldı, ortalama ve standart sapma olarak sunuldu.

Bulgular: PP ve kontrol grupları arasında ortalama anne yaşı, vücut kitle indeksi ve hemogramın değerlendirildiği haftalar benzerdi. Beyaz kan hücresi ve nötrofil sayıları PP grubunda anlamlı olarak yüksekken, kırmız kan hücresi ve hemoglobin sayıları daha düşüktü (p<0.001). PP grubunun ortalama SII ve SIRI değerleri sağlıklı gebelere göre anlamlı olarak yüksek bulundu [(sırasıyla 1266±846 x10⁹/L ve 892±479 x10⁹/L) ve (sırasıyla 2±1.2 x10⁹/L ve 1.3±0.7 x10⁹/L) (p<0.001)]. SII ve SIRI, PAS pozitif grupta PAS negatif gruba göre daha yüksek olmasına rağmen istatistiksel olarak fark bulunmadı.

Sonuç: İnflamasyonun değerlendirilmesi PP hastaları ve fetüsleri için önemlidir. Yüksek riskli gebeliklerin tahmin ve takibinde diğer yöntemlerin yanı sıra her kurumda kolayca ulaşılabilen laboratuvar indekslerinden yararlanılabilir.

Anahtar kelimeler: plasenta previa, plasenta akreta spektrumu, inflamasyon, sistemik immun-inflamasyon indeksi, sistemik inflamasyon yanıt indeksi

ABSTRACT

Aim: To evaluate systemic inflammation in pregnant women diagnosed with placenta previa (PP). First-trimester complete blood count indices of PP patients were assessed.

Materials and Method: This cross-sectional study was conducted with 346 singleton pregnant women, including 115 PP cases (study group) and 231 healthy pregnant women (control group) who were operated on in a tertiary center for one year. The study group was then divided into two subgroups. Those who underwent peripartum hysterectomy due to placenta accreta spectrum (PAS) were determined as PAS-positive, and those without invasion were PAS-negative. Demographic and obstetric characteristics laboratory results were recorded retrospectively. Systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) values were calculated. Data were compared using the independent sample t-test and presented as mean and standard deviation.

Results: The mean value of maternal age, body mass index, and gestational weeks at which hemograms were evaluated were similar between the study and control groups. While white blood cell and neutrophil counts were significantly higher in the PP group, red blood cell and hemoglobin counts were lower (p<0.001). The mean values of SII and SIRI of the PP group were found to be significantly higher than the healthy pregnant women [(1266±846 x10⁹/L and 892±479 x10⁹/L, respectively) and (2±1.2 x10⁹/L and 1.3±0.7 x10⁹/L, respectively) (p<0.001)]. Although SII and SIRI were higher in the PAS-positive group than the PAS-negative group, no statistical difference was found.

Conclusion: Evaluation of inflammation is important for PP cases. In addition to other methods, easily accessible laboratory indices can be used to manage high-risk pregnancies.

Keywords: placenta previa, placenta accreta spectrum, inflammation, systemic-immune-inflammation index, systemic inflammation response index

Sorumlu Yazar/ Corresponding Author: Muradiye YILDIRIM
Adres: Turkish Ministry of Health, Ankara City Hospital, 1604th Street, No: 9, Cankaya/Ankara, 06800 Turkey,
E-mail: my48523@gmail.com

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INTRODUCTION

Placenta previa (PP) is the condition in which the placental tissue covers the internal os of the cervix. Advanced maternal age, multiparity, smoking, systemic and intraamniotic inflammation are some of the etiological factors (1, 2). It is associated with adverse maternal and fetal outcomes (preeclampsia, peripartum hemorrhage, preterm birth, blood transfusion, perinatal morbidity, and mortality). One of the theories in the pathogenesis is that trophoblast implantation is distally due to vascularization disorder in the uterus due to previous interventions (3). Placenta accreta spectrum (PAS) is the placentation anomaly in which the chorionic villi are directly related to the myometrium without decidua (4). Decidualization defect and excessive migration of extravillous trophoblasts are involved in the pathogenesis of the PAS. Most develop at the site of microscopic endometrial defects secondary to previous surgical traumas. Despite imaging methods and a multidisciplinary approach, PAS is still the most common cause of peripartum hysterectomies (5).

Immune adaptation is required for healthy implantation and placentation. Defects in these cause abnormal trophoblast proliferation and release of various factors involved in inflammation and angiogenesis into the maternal circulation (6). Complete blood count (CBC) parameters and calculated indices have been investigated and used as indicators of inflammation and invasion. The systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) are obtained by calculating the neutrophil, platelet, monocytes, and lymphocyte counts in the CBC. SII is a hematological index that is primarily used in cancer cells circulating in the peripheral blood, and its relationship with inflammatory conditions is investigated (7). A previous study has shown that SII has a predictive value for the risk of miscarriage (8). It was hypothesized based on the similarity of trophoblast invasion and cancer cell behavior in PAS. SIRI is a marker with predictive value in adverse perinatal outcomes in pregnant women with Coronavirus disease 2019, as in infectious and chronic diseases (9, 10). These markers have been found to be associated with prognosis and disease activity in autoimmune chronic diseases (11).

We hypothesized that patients diagnosed with PP have an inflammatory condition and that possible risks can be detected in the early period. For this purpose, we compared the first-trimester examination CBC parameters and indices between uncomplicated pregnant women and those diagnosed with PP and PAS.

MATERİAL AND METHOD

The presented study was conducted on one-year patient admissions to a referral center (March 1, 2021- March 1, 2020). Ethics committee approval was obtained from the Ankara City Hospital Ethics Commission (E2-22-1506). The study was carried out following the Declaration of Helsinki Principles. The study group consisted of 115 patients who were operated on for PP in our hospital and whose first-trimester hemograms could be obtained. The control group was obtained with 231 randomly selected healthy pregnant women. They were composed of pregnant women with antenatal follow-up who had low-risk pregnancies with normal placement of the placenta and did not have any additional diseases. The study group was then divided into two subgroups. The PAS-negative group consisted of patients who were diagnosed with PP and had their placenta removed during cesarean section without any adhesion anomaly. Among the PP cases, those who underwent cesarean hysterectomy due to invasion anomaly had PAS, which was confirmed by pathological examination (4). Placenta accreta, increta, and percreta diagnoses were grouped as PAS-positive. According to the pathology results, those who invaded the myometrium instead of the decidual layer were called accreta, those who invaded the myometrium layers were called increta, and those who invaded the serosa were called percreta (4). Eligible patient information was obtained from hospital records retrospectively.

Those with hypertensive disease, diabetic diseases, and those with additional systemic and chronic diseases were excluded from the study. At the same time, fetal chromosomal and structural anomalies were excluded. The control group consisted of randomly selected low-risk, healthy pregnant women with normal placenta placement. Maternal age (year), body mass index (BMI) (kg/m²), numbers of gravidity, parity, previous cesarean, the gestational week when CBC was obtained, white blood cell (WBC) (x10³/L), neutrophil (x10³/L), lymphocyte (x10³/L), monocytes (x10³/L), red blood cell (x10¹²/L) counts, hemoglobin (g/dL) value, and platelet (x10³/L) count were recorded. CBC parameters were recorded from the first-trimester examination. SII by multiplying the neutrophil and platelet counts divided by the lymphocyte count (x10³/L); SIRI values were found by multiplying the neutrophil and monocyte counts and dividing by the lymphocyte count (x10³/L).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY. The Kolmogorov-Smir-

nov test evaluated the normality of variables. Descriptive statistics were given as the mean standard deviation for normally distributed numerical data. Parametric data were compared with an independent sample t-test. The relationship of the variables with each other was shown with the error-bar graph. Differences with a p-value of <0.05 were considered statistically significant.

The power of our study, which included a total of 346 patients, including 115 as the case group and 231 as the control group, was 98% with an effect size of 0.5 (moderate) and a margin of error of 5% (12).

RESULTS

The comparison of the sociodemographic and laboratory results of the PP patients and the control group is given in Table 1. Mean and standard deviation values in the study group, maternal age 31 ± 5 years, BMI 26.6 ± 3.4 kg/m² , gravidity 3 ± 2, parity 2 ± 1. The mean value of previous cesarean section number 1±0, gestational week at which CBC was performed 8 ± 3, WBC count 10.8 ± 3.4 10/L, neutrophil count 8.2±3.1 10/L, lymphocyte count 2.3±0.7 10/L, monocyte count 0.4±0.2 10/L, RBC count 4±0.5 10^{12}/L, Hb 11.5 ±1.4 g/dL, thrombocyte count was calculated as 250±90 10/L.

The mean value of maternal age of the control group was 30±5, bmi 27.1±3.5, gravida 2±1, parity 1±0, previous cesarean section number 1±0, gestational week at which CBC was performed 7±2. In the control group, the mean value of WBC was 8.9±2.7 10/L, neutrophil count 6.2±2.2 10/L, lymphocyte count was 1.9±0.6 10/L, monocyte count was 0.4±0.2 10/L, RBC 4.4±0.4 10^{12}/L, and hemoglobin value 12.4±1.3 g/dL, thrombocyte count was 261±74 10/L. The mean values of maternal age, BMI, and weeks of blood count were similar between groups (p-values 0.072, 0.063, 0.154; respectively). WBC and neutrophil counts were significantly higher in the study group, while RBC and hemoglobin were lower (p<0.001).

Table 1: Comparison of socio-demographic and laboratory data of case and control groups

	Case (n=115)	Control (n=231)	p-value
Age (years)	31±5	30±5	.061*
BMI (kg/m²)	26.6±3.4	27.1±3.5	.334*
Gravidity (n)	3±2	2±1	<.001*
Parity (n)	2±1	1±0	<.001*
Previous cesarean (n)	1±0	1±0	.237*
Gestational week	8±3	7±2	.271*
WBC (x10^9/L)	10.8±3.4	8.9±2.7	<.001*
Neutrophil (x10^9/L)	8.2±3.1	6.2±2.2	<.001*
Lymphocyte (x10^9/L)	2.3±0.7	1.9±0.6	.314*
Monocyte (x10^9/L)	0.4±0.2	0.4±0.2	.189*
RBC (x10^{12}/L)	4±0.5	4.4±0.4	<.001*
Hb (g/dL)	11.5±1.4	12.4±1.3	<.001*
Thrombocyte (x10^9/L)	250±90	261±74	.138*
SII (x10^9/L)	1266±846	892±479	<.001*
SIRI (x10^9/L)	2±1.2	1.3±0.7	<.001*

Abbreviations: BMI, body mass index; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; SII, Systemic immune-inflammation index; SIRI, systemic inflammatory response index.

* Independent sample t-test
Data are shown with mean and standard deviation

The SII 1266±846 (x10/L) and SIRI 2±1.2 (x10/L) were calculated in the study group. 892±479 (x10/L) and 1.3±0.7 (x10/L) were found to be in the control group, respectively. The mean values of SII and SIRI were statistically significantly higher in the PP group (p-values <0.001). The data are presented in Table 1. A comparison of clinical and obstetric characteristics and laboratory test results between PAS-positive and PAS-negative subgroups is presented in Table 2. All hemogram parameters were similar (p-values 0.1, 0.135, 0.540, 0.660, 0.805, 0.532, 0.261; respectively). Although SII and SIRI were higher in the PAS-positive group, no statistical difference was found between indices (p-values 0.562, 0.375; respectively).

SII and SIRI comparisons of pregnant women with PP and healthy pregnant women is presented with error bar in figures 1a and 1b. SII and SIRI comparisons between PAS-positive and negative cases are shown with error bar in figures 2a and 2b.

Table 2: Comparison of sociodemographic and laboratory data results of subgroups of placenta previa cases

	PAS-positive (n=28)	PAS-negative (n=87)	p-value
Age (years)	30±5	32±5	.072*
BMI (kg/m²)	24.3±2.7	27.4±3.1	.063*
Gravidity (n)	3±2	4±2	<.001*
Parity (n)	1±1	3±2	<.001*
Previous cesarean (n)	1±1	2±1	<.001*
Gestational week	8±2	7±3	.154*
WBC (x10^9/L)	11±3.3	10.1±3.3	.100*
Neutrophil (x10^9/L)	8.3±3.2	7.6±2.8	.135*
Lymphocyte (x10^9/L)	2.2±0.3	1.8±0.7	.540*
Monocyte (x10^9/L)	0.4±0.2	0.4±0.2	.660*
RBC (x10^{12}/L)	4±0.5	4±0.5	.805*
Hb (g/dL)	11.5±1.4	11.3±1.3	.532*
Thrombocyte (x10^9/L)	246±84	262±106	.261*
SII (x10^9/L)	1286±897	1207±666	.562*
SIRI (x10^9/L)	2±1.6	1.8±1.1	.375*

Abbreviations: BMI, body mass index; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; SII, Systemic immune-inflammation index; SIRI, systemic inflammatory response index.

* Independent sample t-test

Data are shown with mean and standard deviation

DISCUSSION

This study compared first-trimester CBC parameters and calculated indices between PP patients and healthy pregnant women. We found that the WBC and neutrophil counts were statistically higher in the study group. Red blood cell count and hemoglobin levels were significantly statistically lower. We showed that SII and SIRI were higher in the patient group diagnosed with PP, which supports our hypothesis of inflammatory status. However, this increase was not sufficient to predict PAS development.

Adaptation of pregnancy to semi-allograft fetus is due to changes in the immune system. Many molecular arrangements, especially T cell regulation, are required for a successful pregnancy outcome. An excessive immune response develops in pregnant women with PP and invasion anomaly, and immunological inflammation occurs. In patients with PP diagnosed with intact membranes and preterm labor, both histological inflammation and the presence of intraamniotic inflammation have been demonstrated (1). To date, inflammation plays a major role in the pathogenesis of many chronic and systemic diseases. In a study performed with biopsy from the placental bed, trophoblast and inflammatory cell infiltration were found to be higher in myometrial spiral arterioles in PP patients (3). Increased interleukin-1beta, interleukin 6, tumor necrosis factor-alpha, and interferon-gamma were found in the serum of pregnant women diagnosed with PP (13). Angiogenesis, inflammation, and invasion continue to be investigated processes in the pathogenesis of PAS (14). These findings support the inflammatory state in this patient group. SII and SIRI, which we evaluated in our study, are low-grade indices previously investigated in immune and infective diseases and cancer (7, 9).

The plasma volume increases more than the erythrocyte volume, with the effect of aldosterone and estrogens during pregnancy, causing hemodilution. Due to the estrogenic effect and increase in bone marrow activity, there is an increase in the number of leukocytes, neutrophils, and polymorphonuclear leukocytes (15). Since these hematological and hemodynamic changes occur especially in the third trimester, we compared the first trimester complete blood indices in this study. The presented study, investigated the complete blood values obtained at the first visit because hemodilution develops with the advancing weeks of pregnancy. In this study, while hemoglobin and RBC values were lower in the PP group than in healthy pregnant women, lymphocyte and monocyte counts did not change. In a case-control study investigating inflammatory CBC parameters in unexplained stillbirth cases, lymphocyte-monocyte ratio and hemoglobin-lymphocyte ratio in the first trimester were found to be significantly different from uncomplicated pregnant women (16). They found that the lymphocyte counts were higher in the first trimester and the monocyte counts were lower at the time of delivery. This supports secondary responses to hemodynamic changes in pregnancy (16).

The presented study demonstrated that WBC and neutrophil counts were higher in the case group and lymphocyte counts did not change. There was no difference between the PAS-positive group and the negative group. Neutrophils, which comprise most WBC, form the first line of defense and provide active nonspecific inflammation in immune defense. As a result of physiological changes in the hematological system during pregnancy, the number of neutrophils increases. Moreover, due to the inflammatory response, the neutrophil count increases while the lymphocyte count decreases. In a case-control study examining leukocyte platelet indices in PP patients, last-trimester neutrophil counts were found to be significantly increased compared to healthy pregnant women (17). In a study conducted to predict placental invasion, preoperative neutrophil, platelet counts, and neutrophil-platelet ratios were found to be higher in cases with invasion anomaly (18).

Platelets play an essential role in response to inflammation as well as their role in hemostasis. They are involved in both endothelial response and aggregation (19). Platelet indices have been suggested as a predictor of adverse maternal and fetal outcomes in high-risk pregnancies (20). In the current study, although platelet counts decreased in both the PP group compared to healthy pregnant women and in the PAS-positive group compared to the negative group, it was not found to be statistically different. A previous study revealed higher thrombocyte count and lower mean platelet volume in PP compared to healthy pregnant women (21).

This study showed that pregnant women with PP had a statistically higher SII than the control group. SII is a marker by which systemic inflammation and local immune response are evaluated. There are reference intervals for SII determined for each trimester (22). It has been previously studied in high-risk pregnancy situations. A positive correlation was found between SII value and ketonuria in hyperemesis gravidarum, the pathogenesis of which is systemic inflammation in early pregnancy (23). In a previous study, SII was shown to predict miscarriage in pregnant women with threatened miscarriage (8). For the first time, the relationship between mass size and survival in cancer cases has been demonstrated (7). PAS is the invasion of over-invading trophoblasts to the endometrium, myometrium, and serosa. Glycoproteins expressed from malignant tissues were also detected histopathologically in PAS cases (24). In this study, SII was found insufficient to predict the development of PAS. Mean values of SII were not different between PAS-positive cases and negative cases. In a retrospective case-control study, SII was found to be significantly higher in the PAS group than in PP patients, and no relationship was found with histological subtypes (25). The higher number

of PAS and PP cases in this study may be the reason for the difference from the current study.

This study showed that SIRI and SII are insufficient to predict PAS. Although both indices were found to be higher in PP cases than in healthy pregnant women, PAS prediction could not be made. SIRI is a biomarker associated with disease severity and prognosis in many chronic, systemic diseases and conditions accompanying pregnancy (26). In a retrospective cohort study of stroke patients, it was suggested that SIRI was superior to other indices in predicting mortality (27). Another study in pregnant women with Coronavirus disease 2019 demonstrated that SII and SIRI were significantly higher than in healthy pregnant women. Cut-off values were determined for critical diseases, NICU need, and maternal mortality (10).

Early diagnosis, multidisciplinary team preparation, and management of the process are vital in PP patients. Ultrasonography, various markers, and magnetic resonance imaging are used both in diagnosing and predicting morbid adhesion. By helping these methods, adding hemogram indices, which can be easily accessed in every institution, to routine examinations can help evaluate the patient.

The strengths of this study are that it was performed in a tertiary referral center and that first trimester hemograms were studied before maternal hemodynamic changes occurred. The limitations of the study can be stated as its retrospective design and relatively low number of patients. Not detailing the histopathological types of PAS patients is also among the limitations. In prospective studies with larger series, cut-off values can be determined and together with other parameters, may help predict placental invasion. There is a need for prospective studies with large patient series that include neonatal outcomes and operative parameters such as maternal blood transfusion requirement.

CONCLUIONS

Increased inflammatory indices were shown in the first trimester examination CBC of patients diagnosed with PP. Clinical and imaging methods should be given priority for adhesion prediction. We think that easily applicable tests routinely used in clinical practice can be useful in managing high-risk pregnancies by integrating them with other methods.

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