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Can systemic inflammation markers obtained from complete blood count in the first trimester play a role in predicting early pregnancy loss?

İlk trimesterde tam kan sayımından elde edilen sistemik inflamasyon belirteçleri erken gebelik kaybını tahmin etmede rol oynayabilir mi?

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Abstract

Aim: Ten percent of pregnancies result in early pregnancy loss, and in 40%, the cause is unknown. The purpose of this study is to evaluate the relationship between first trimester hematological inflammatory markers and early pregnancy loss.

Methods: This retrospective case-control study was conducted at Department of Obstetrics and Gynecology at The Private Nisa Hospital between 1 January 2015 and 1 October 2020. A total of 611 patients were evaluated, including 310 patients with early pregnancy loss, and 301 patients, who were included in the study as the healthy control group. Sociodemographic data and complete blood count results of the groups were obtained by scanning hospital files and computer registration systems.

Results: No statistically significant differences were detected between the two groups in terms of Red Cell Distribution Width (RDW), plateletcrit (PCT), Eosinophil and NLR (Neutrophil Lymphocyte Ratio) values (P>0.05 for all). In the early pregnancy loss group, PLT(P=0.004), MPV(P<0.001), PDW(P=0.005), PLR (platelet lymphocyte ratio) (P<0.001), ELR (eosinophil lymphocyte ratio) (P<0.001), and ENR (eosinophil neutrophil ratio) (P=0.004) values were higher, while WCB (P<0.001), Hemoglobin (P=0.007), Neutrophil (P<0.001), and Lymphocyte (P<0.001) values were lower, compared to the healthy control group.

Conclusions: PLT, MPV, PDW, PLR, ELR and ENR were related with early pregnancy loss. Inflammation markers, thrombocyte activation markers and allergy markers obtained from Complete Blood Count (CBC) in the first trimester pregnancy constitute a cost-effective, and easy method to predict early pregnancy loss.

Keywords: Early pregnancy loss, Systemic inflammation, Inflammatory markers, Thrombocyte activation markers, Allergy markers

Öz

Amaç: Tüm gebeliklerin %10'u erken gebelik kaybıyla sonuçlanır ve % 40'ında neden bilinmemektedir. Bu çalışmanın amacı ilk trimester hematolojik inflamatuar belirteçleri ile erken gebelik kaybının arasındaki ilişkiyi değerlendirmektir

Yöntemler: Bu retrospektif vaka kontrol çalışması 1 Ocak 2015- 1 Ekim 2020 tarihleri arasında Özel Nisa Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda yapılmıştır. Erken gebelik kaybı olan 310 hasta ve sağlıklı kontrol grubu olarak 301 hasta olmak üzere toplamda 611 hasta değerlendirildi. Grupların sosyodemografik verilerine ve tam kan sayımı sonuçları hastane dosyaları ve bilgisayar kayıt sistemleri taranarak elde edildi.

Bulgular: Her iki grup arasında RDW, PCT, Eosinofil ve NLR düzeylerinde açısından istatistiksel olarak anlamlı fark yoktu (tümü için P>0,05). Erken gebelik kayıplı grupta sağlıklı kontrol grubuna kıyasla WCB (P<0,001), hemoglobin (P=0,007), Nötrofil (P<0,001) ve Lenfosit (P<0,001) değerleri daha düşük iken PLT (P=0,004), MPV (P<0,001), PDW (P=0,005), PLO (platelet lenfosit oranı) (P<0,001), ELO (eosinofil lenfosit oranı) (P<0,001) ve ENO (eosinofil nötrofil oranları) (P=0,004), değerleri istatistiksel olarak anlamlı düzeyde yüksek olduğu saptandı (P<0,05).

Sonuç: PLT, MPV, PDW, PLO, ELO ve ENO erken gebelik kaybı ile güçlü bir şekilde ilişkiliydi. İlk trimesterde yapılan Tam kan sayımından den elde edilen trombosit ve alerji belirteçleri fetal kayıpları tahmin etmek için kullanılabilecek ekonomik ve güvenli bir yöntemdir.

Anahtar kelimeler: Erken gebelik kaybı, Sistemik inflamasyon, İnflamasyon belirteçleri, Trombosit aktivasyon belirteçleri, Alerji belirteçleri

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Introduction

Early pregnancy loss is the absence of the embryo or heartbeat in the gestational sac in the first trimester of pregnancy [1]. Ten percent of all pregnancies result in early pregnancy loss. A total of 80 % of pregnancy losses are detected within the first twelve gestational weeks [1,2]. Genetic, infectious, endocrinologic, anatomical, and immunologic implantation abnormalities are known causes in its etiology. The cause is unknown in 40% of early pregnancy losses [3,4].

In the literature, it has been stated that systemic inflammatory markers are important in pathogenesis [5]. The aim of this study was to compare systemic inflammation markers obtained from the complete blood counts (CBC) of pregnant women in their first trimester, including white blood cell count (WBC), hemoglobin (Hb), neutrophil, lymphocyte, platelet distribution width (PDW), platelet count (PLT), mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), eosinophil to lymphocyte ratio (ELR), platelet to lymphocyte ratio (PLR), and eosinophil to neutrophil ratio (ENR), to predict early pregnancy loss. All the above-mentioned markers are easy to obtain and cost-effective [6,7]. They are used to predict inflammatory diseases, complicated pregnancies, gynecological cancers [8], ovarian hyperstimulation syndrome [9], early ovarian failure [10], endometriosis [11], hyperemesis gravidarum [12], gestational diabetes [13], preeclampsia [14], intrahepatic pregnancy cholestasis [15] in numerous studies in the literature.

Materials and methods

The study was approved by Istanbul Medipol University Clinical Research Ethics Committee and conducted in accordance with the 1964 Helsinki Declaration and local guidelines regarding studies with human participants. Written approval was obtained from Private Nisa Hospital before the data collection phase (Reference number: 10840098-772.02-E.58403 Date: 16/10/2020).

This retrospective case control study reviewed the data of the pregnant patients who were followed up in Yenibosna Private Nisa Hospital Maternity Outpatient Clinic between January 1, 2017 and October 1, 2020, which were obtained from the hospital files and hospital registry.

Patients between the ages of 18-35 years with pregnancy losses in the first trimester were included in the study group, while those within the same age range who gave live births at ≥37 gestational weeks were included in the control group.

Patients with insufficient data, multiple pregnancy, a history of recurrent miscarriage or infertility, any other medical conditions, known thrombophilia, complicated pregnancy, and congenital uterine anomalies, smokers, along with those requiring chronic drug treatment, were excluded from the study.

The study was based on chart review. Among 8937 patients, a total of 611 patients were evaluated in the present study, including 310 patients with early pregnancy loss who met the inclusion and exclusion criteria, and 301 patients as the healthy control group.

The medical data of the patients were examined, and the age, gravida, parity, gestational week, Body Mass Index (BMI=Weight (kg) Height^{-2} (m)) of the patients were recorded.

The basal complete blood count values of patients with early pregnancy loss were obtained as they first visited our clinic, when fetal heart beats were observed, and that of patients who carried healthy pregnancies to term were obtained during their first visit for routine pregnancy follow-up. The blood samples were drawn into tripotassium ethylene diamine tetra acetic acid (EDTA) tubes. All hematological parameters were analyzed with a Beckman Coulter Blood Count Analyzer (XT2000i, Sysmex, Osaka, Japan) 15 minutes after drawing blood.

Statistical analysis

Numbers (n), percentages (%), mean, Standard Deviation (SD), Standard Error (SE), median, Interquartile Range (IQR), minimum (Min) and maximum (Max) values were used in the analysis of the data. The fitness of the data to normal distribution was tested with Kolmogorov-Smirnov Test. Mann Whitney-U test was used to compare intergroup mean values. ROC Analysis was performed to determine the cut-off values. Statistical significance level was $P<0.05$. The data were analyzed with SPSS 22.0 Statistical Package Program.

Results

The two groups were similar in terms of age, BMI, gravida, and parity, and both groups were homogenous with regards to these characteristics ($P>0.05$ for all) (Table 1).

Table 1: Demographic and clinical features

Variables	Control group (n=301) Mean (SD)	Median	Min-Max	Early pregnancy loss group (n=310) Mean (SD)	Median	Min-Max	*P*-value
Age (year)	31.96 (5.59)	32	17-40	32.29 (5.15)	33	17-42	0.478
BMI (kg/m^2)	28.43 (2.96)	28.04	22.04-40.15	28.81 (3.38)	28.58	22.03-40.15	0.418
Gravida(number)	1.98 (0.99)	2	1-6	1.90 (0.93)	2	1-6	0.469
Parity(number)	0.98 (0.99)	1	0-5	0.90 (0.92)	1	0-5	0.445

Mann-Whitney U, BMI: Body mass index

The comparison of laboratory results of the groups is shown in Table 2. There were significant differences between the groups in terms of WBC ($P<0.001$), hemoglobin ($P=0.007$), PLT ($P=0.004$), MPV ($P<0.001$), PDW ($P=0.005$), neutrophil ($P<0.001$) and lymphocyte ($P<0.001$) values. PLR ($P<0.001$), ELR ($P<0.001$), and ENR ($P=0.004$) were significantly higher in patients with early pregnancy loss.

The ROC analysis of the predictive performance of PLR for early pregnancy loss is shown in Figure 1. The area under the curve was 0.681 (0.022) (95% Confidence Interval (CI), 0.639-0.723). The best PLR cut-off value was 113.71, with 68.1% sensitivity, and 42.7% specificity for early pregnancy loss prediction.

The ROC analysis of the predictive performance of ELR for early pregnancy loss is presented in Figure 2. The area under the curve was 0.591(0.023) (95% CI, 0.545-0.636). The best ELR cut-off value was 0.04, with 59.0% sensitivity and 45.3% specificity for early pregnancy loss prediction.

The ROC analysis of the predictive performance of ENR for early pregnancy loss is shown in Figure 3. The area under the curve was 0.567(0.023) (95% CI, 0.522-0.613). The

best ENR cut-off value was 0.01, with 56.8% sensitivity, and 43.2% specificity for early pregnancy loss prediction.

Table 2: Laboratory values of the groups

Parameters	Control group (n=301) Mean (SD)	Median	Min-Max	IQR	Early pregnancy loss group (n=310) Mean (SD)	Median	Min-Max	IQR	*P*-value*
WBC(/mm³×10³)	9.45 (2.73)	9.14	2.48-27.40	3.30	8.38 (2.71)	7.89	0.16-21.60	2.81	<0.001
HB(g/dL)	11.76 (1.18)	11.80	8.30-17.20	1.60	11.96 (1.24)	12.10	8.00-14.80	1.53	0.007
RDW(%)	14.29 (7.16)	13.40	3.20-134.00	1.80	13.97 (2.46)	13.20	11.10-32.30	2.50	0.051
PLT(/mm³×10³)	230.24 (65.90)	222.00	91.00-551.00	79.00	241.56 (61.68)	235.50	13.10-480.00	80.25	0.004
MPV(fL)	10.68 (1.15)	10.60	5.40-14.80	1.50	10.17 (1.14)	10.20	0.80-13.20	1.30	<0.001
PDW(%)	13.39 (2.64)	12.90	8.50-24.70	3.30	12.93 (2.79)	12.20	7.90-22.30	3.93	0.005
PCT(%)	0.24 (0.06)	0.23	0.11-0.50	0.08	0.24 (0.06)	0.24	0.07-0.47	0.07	0.511
N(×10³/uL)	6.45 (2.25)	6.25	1.05-18.03	2.72	5.95 (2.34)	5.46	2.26-18.50	2.30	<0.001
L(×10³/uL)	2.18 (0.71)	2.13	0.31-6.10	0.79	1.84 (0.57)	1.77	0.12-4.18	0.67	<0.001
E(×10³/uL)	0.09 (0.09)	0.07	0.00-0.78	0.08	0.11 (0.10)	0.09	0.00-0.75	0.10	0.065
NLR	3.31 (1.99)	2.90	0.89-21.32	1.52	3.68 (3.28)	3.01	1.06-48.00	1.68	0.141
PLR	115.25 (52.48)	106.94	36.80-606.45	49.39	145.72 (102.50)	132.34	6.52-1700.00	54.16	<0.001
ELR	0.05 (0.05)	0.04	0.00-0.48	0.04	0.06 (0.09)	0.05	0.00-1.31	0.05	<0.001
ENR	0.02 (0.02)	0.01	0.00-0.08	0.02	0.02 (0.02)	0.06	0.00-0.16	0.02	0.004

**Mann-Whitney U, HB: Hemoglobin, WBC: white blood cell count, RDW: red cell distribution width, PLT: platelet, PDW: count platelet distribution width, MPV: mean platelet volume, PCT: plateletcrit, N: Neutrophil, L: Lymphocyte, E: Eosinophil, NLR (Neutrophil/Lymphocyte), PLR: PLT / Lymphocyte, ELR: Eosinophil / Lymphocyte, ENR: Eosinophil / Neutrophil

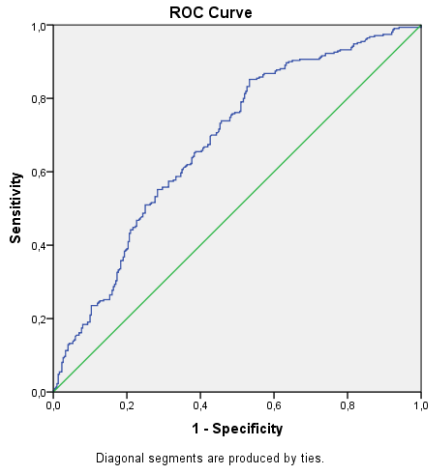

Figure 1: ROC analysis performed to examine the role of PLR in preedicting early pregnancy loss (AUC=0.681, *P*<0.001).

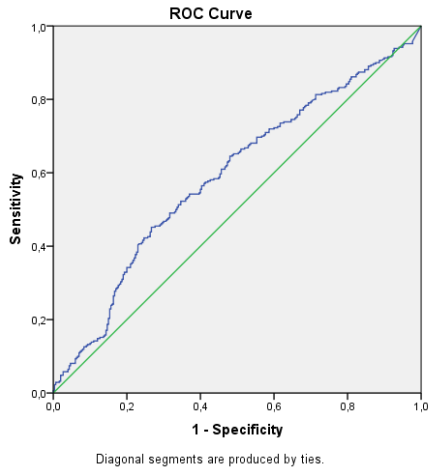

Figure 2: ROC analysis performed to examine the role of ELR in predicting early pregnancy loss (AUC=0.591 (0.023), *P*<0.001)

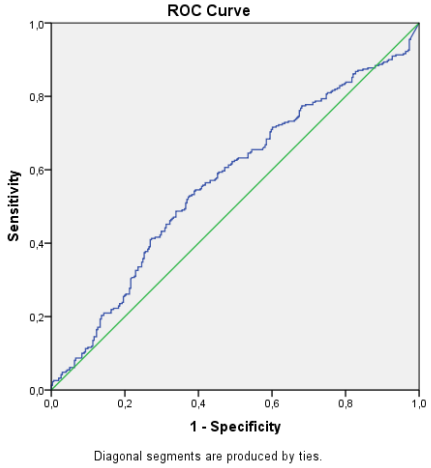

Figure 3: ROC analysis performed to examine the role of ENR in predicting early pregnancy loss (AUC=0.567 (0.023), *P*=0.004).

Discussion

The implantation of the embryo into the endometrium depends on the harmonious interaction between the placenta, fetus, and maternal circulation [16]. An imbalance between the physiological regulation of immune response, physiologically increased inflammation and the semi-allogenic fetus during pregnancy may result in spontaneous or recurrent miscarriage, preeclampsia, premature birth, and intrauterine growth restriction [17,18].

Many studies show that maternal circulation is responsible for the immune mechanism, and the pathogenesis of early pregnancy loss includes oxidative inflammation caused by thrombosis [18,19]. MPV, PDW, and PCT are considered platelet activation markers. Large platelets with high MPV values decrease placental perfusion, leading to pregnancy loss [18,20]. Platelets also have roles in strong immune modulation. In the study of Aynioglu et al. [21], PLT, PCT and RDW were significantly higher in patients with pregnancy loss. In this study, we found that PLT, MPV, PDW levels were higher in the early pregnancy loss group.

Based on increased immune response, neutrophils increase, and lymphocytes decrease in number. NLR is an important marker in the diagnosis of inflammatory diseases. It increases in many inflammatory diseases like Hyperemesis gravidarum [12], gestational diabetes [13], preeclampsia [14], intrahepatic pregnancy cholestasis [15], and in complicated pregnancies. In the literature, there were a small number of studies in which NRL was evaluated in early pregnancy loss, reporting differing results. In the studies conducted by Oglak et al. [6] to evaluate 285 patients, NLR was higher in patients with early pregnancy loss than in healthy controls' and no statistical difference was detected in other studies [7,22]. In this study, we found that NLR values were similar among the two groups.

In recent years, PLR was reported to predict chronic inflammatory diseases and malignancies, in addition to thromboembolic diseases [23,24]. It was researched in early membrane rupture, preeclampsia, gestational diabetes, and pancreatitis [14,25,26]. Platelet activation and elevated PLR values cause damage, especially to the endothelia of spiral arterioles, and thrombosis and impaired implantation ensue [27]. There are a few studies in which high PLR values were detected in early pregnancy loss [6,7]. In the study of Ata et al. [7], AUC

was 0.686 for PLR in EPL (P<0.001), with a sensitivity and specificity of 78% and 50%, respectively at >115.41 threshold. Similarly, in this study, we found that PLR values were higher in early pregnancy loss. In EPL group, the PLR cut-off value was 113.71. Any value above this had 68.1% sensitivity and 42.7% specificity for the prediction of miscarriage (Area Under Curve: 0.681 (0.022), 95% Confidence Interval (CI): 0.639-0.723).

Eosinophil, Eosinophil to Neutrophil Ratio (ENR) and Eosinophil to Lymphocyte Ratio (ELR) values, which can be easily calculated with CBC, are hematological allergy markers. Among the causes of eosinophilia (high number of eosinophils) are allergies, parasitic infections, leukemia, and polyarthritis nodosa autoimmune disease [28]. Eosinopenia does not have any specific cause, 0% eosinophil is considered normal [29]. Eosinophil decreases physiologically with gestational age [30]. Allergic markers were evaluated in preeclampsia in a small number of studies [31,32]. However, there is no study that evaluates allergic markers in early pregnancy loss. In this study, ELR and ENR values were higher at statistically significant levels in the EPL group compared to the healthy controls. In the EPL group, the cut-off value of ELR was 0.04, with 59.0% sensitivity and 45.3% specificity for early pregnancy loss prediction. The ENR cut-off value was 0.01 and had 56.8% sensitivity and 43.2% specificity.

As a major strength, this is the first study which evaluates almost all inflammation markers obtained from CBC, such as neutrophils, lymphocytes, NLR, PLR, thrombocyte activation markers such as PLT, MPV, PDW, and allergy markers such as ELR and ENR in the prediction of early pregnancy loss. The limitations of this study include the use of a retrospective design, small sample size, and the lack of generalizability of data.

Conclusion

PLR, MPV, PDW, ELR, ENR values are cheap and easily obtainable markers in predicting early pregnancy loss. Further randomized, prospective, controlled trials with high number of subjects are warranted to evaluate allergy markers together with inflammatory markers.

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