J Surg Med. 2020;4(11):952-955.
DOI: 10.28982/josam.736881

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Can hematologic inflammation markers be the indicator of early pregnancy loss?

Hematolojik enflamasyon belirteçleri erken gebelik kaybının göstergesi olabilir mi?

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Ethics Committee Approval: Noninvasive Clinic Ethical Committee of Bozok University (Decision no: 2017-KAEK-189_2019.11.13_01, date: 11/13/2019) has approved the study protocol. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolünü Bozok Üniversitesi Noninvazif Klinik etik Kurulu (Karar no: 2017-KAEK-189_2019.11.13_01, tarih: 13.11.2019) onayladı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

Abstract

Aim: Pregnancy loss occurs in 50% of human pregnancies and is the most common complication of early pregnancy. The aim of this study is to evaluate the relationship between early pregnancy loss and inflammation with hematological markers.

Methods: This case-control study was carried out between January 2016-March 2019 in our clinic to evaluate the cases of early pregnancy loss. The early pregnancy loss group consisted of 94 patients, while the control group consisted of 104 women giving normal birth. Demographic data and complete blood count results of the groups were obtained from the patient files and hospital information management systems.

Results: There were no statistically significant differences in terms of age and body mass index between the two groups. Pregnancy losses in the abortion group occurred at an average of 9.03 (3.62) weeks. In the abortus group, platelet count (P=0.003), NLR (P=0.036), PLR (P=0.032) and plateletcrit (P=0.007) were higher, while LMR (P=0.034) was lower, compared to the control group.

Conclusions: Hematological inflammation parameters are easy to perform and cost-effective examinations. In our study, the success of these parameters to predict early pregnancy loss was evaluated, and it was found that although there are significant differences in hematological inflammation markers between the groups, the sensitivity and specificity of these markers are low.

Keywords: Early pregnancy loss, Inflammation, Hematologic markers

Öz

Amaç: İnsan gebeliklerinin yaklaşık %50'sinde gebelik kaybı meydana gelmektedir ve erken gebeliğin en sık görülen komplikasyonudur. Bu çalışmanın amacı, erken gebelik kaybı ile inflamasyon arasındaki ilişkiyi hematolojik belirteçler ile değerlendirmektir.

Yöntemler: Çalışma Ocak 2016 / Mart 2019 tarihleri arasında kliniğimizde gerçekleşmiş olan erken gebelik kaybı olgularını değerlendiren, olgu-kontrol çalışmasıdır. Erken gebelik kaybı grubu 94 hasta, kontrol grubu ise 104 miadında doğum yapmış kadından oluşturuldu. Grupların demografik verilerine ve tam kan sayımı sonuçlarına hasta dosyaları ve hastane bilgi yönetim sistemi taranarak ulaşıldı.

Bulgular: İki grup arasında yaş ve vücut kitle indeksi açısından istatistiksel olarak anlamlı bir fark yoktu. Abortus grubunda gebelik kayıpları ortalama 9,03 (3,62) haftada gerçekleşmiştir. Abortus grubunda kontrol grubuna kıyasla platelet sayısı (P=0,003), NLR (P=0,036), PLR (P=0,032) ve plateletkrit (P=0,007) yüksek olarak saptanmıştır. Diğer taraftan, LMR (P=0,034) abortus grubunda düşük olarak saptanmıştır.

Sonuçlar: Hematolojik enflamasyon parametreleri kolay ulaşılabilen ve maliyet olarak ucuz tetkiklerdir. Çalışmamızda bu parametrelerin erken gebelik kaybını öngörme başarısı değerlendirilmiş ve sonuç olarak, gruplar arasında hematolojik inflamasyon belirteçlerinde anlamlı farklılıklar olmasına rağmen, bu belirteçlerin duyarlılık ve özgüllüğünün düşük olduğu bulunmuştur.

Anahtar kelimeler: Erken gebelik kaybı, Enflamasyon, Hematolojik belirteçler

How to cite/Atıf için: Onat T, Kırmızı DA, Çaltekin MD, Başer E, Yalvaç ES. Can hematologic inflammation markers be the indicator of early pregnancy loss? J Surg Med. 2020;4(11):952-955.

Introduction

Early pregnancy loss (abortus) is defined as loss of pregnancy before the 20th gestational week [1]. The World Health Organization defined abortus as pregnancy losses in which the fetus weighed less than 500 gr. It is the most common complication in the early pregnancy period [1]. Its incidence in clinically diagnosed pregnancies is around 8-20% [2]. Abortus occurs mostly in the first 12 weeks [3]. Early pregnancy loss reduces in women who gave birth. Considering all pregnancy losses, only about 50% of fertilized oocytes result in a live birth [4]. The most important risk factor is maternal age. Increasing maternal age increases also the risk of abortus and it reaches about 80% at the age of 45 [5]. Having a miscarriage history, smoking, and a body mass index of <18.5 and >25 kg/m2 can be deemed as other risk factors [6-8]. In about half of the abortus cases, chromosome anomalies were found as a cause [9].

Inflammation was most identified in the pathological evaluation of abortus materials [3]. On the other hand, inflammation in the early stages of pregnancy, in particular, is deemed as one of the physiological features of pregnancy [10]. The severity of inflammation plays an active role in the process to progress to a successful implantation or abortus [10]. In the etiology of abortus, it is not known exactly at what stage and how inflammation is effective.

Inflammation plays a key role in many diseases today. Therefore, many studies are carried out on the evaluation of inflammation. Direct measurement of inflammatory mediators, neutrophil and lymphocyte count, and parameters such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) are among the methods used. Studies show that these markers have prognostic value in coronary artery disease, ulcerative colitis, and preeclampsia [11-13]. In addition, these markers are used for predicting mortality and morbidity in various types of cancer [14,15]. These markers were additionally studied to predict obstetric complications such as preeclampsia, intrauterine growth retardation, and preterm delivery [16-19].

This study aims to evaluate the relationship between early pregnancy loss and inflammation with hematological markers.

Materials and methods

This retrospective case-control study was carried out by evaluating the files of the abortus cases that occurred in our clinic between January 2016-March 2019 and hospital information management systems after obtaining ethics approval from the Noninvasive Clinic Ethical Committee of Bozok University (Decision no. 2017-KAEK-189_2019.11.13_01, dated 13/11/2019).

Patients with chronic diseases (thyroid, kidney, liver, type I-II diabetes mellitus), acute-chronic inflammatory diseases, uterine anomalies which cause abortus, along with those who became pregnant with assisted reproductive techniques were excluded from the study. Patients who became pregnant spontaneously and gave normal birth were included in the control group.

Age, body mass index (BMI), gravida, parity and first trimester hematological parameters (leukocyte, neutrophil, lymphocyte, monocyte, hemoglobin, platelet, plateletcrit and average platelet volume) of both groups were noted. Neutrophil-leukocyte ratio (neutrophil count/leukocyte count), platelet-lymphocyte ratio (platelet count/lymphocyte count), and lymphocyte-monocyte ratio (lymphocyte count/monocyte count) were calculated.

Statistical analysis

Analysis of the study data was performed using the SPSS 20.0 program. $P<0.05$ was considered statistically significant. Histogram and Kolmogorov-Smirnov test were used to evaluate the distribution of data. Numerical data were shown as mean (standard deviation). Correlation analyses of the data were made by Pearson or Spearman test, as needed. The diagnostic cut-off values of the tests were determined by Receiver Operations Curve (ROC) analysis.

Results

A total 203 pregnant women were included in our study, 94 of which constituted the abortus group, and 109 age- and BMI-compatible pregnant women constituted the control group. The mean age of the pregnant women included in our study was 30.7 (6.37) years, and their mean BMI values were 25.79 (1.61) kg/m^2 (Table 1). Pregnancy losses in the abortus group occurred in an average of 9.03 (3.62) weeks. There was no difference between the abortus and control groups in terms of age, BMI, gravida, parity, leukocyte count, neutrophil count, lymphocyte count, monocyte count, mean platelet volume (MPV), and hemoglobin values (Table 2) ($P>0.05$). In the abortion group, platelet count ($P=0.003$), NLR ($P=0.036$), PLR ($P=0.032$) and plateletcrit ($P=0.007$) were higher compared to the control group, while LMR ($P=0.034$) was lower. The optimal ROC cut-off value of plateletcrit for abortus was calculated as 0.26 with a sensitivity of 60.6% and a specificity of 52.3% (AUC: 0.609) (Figure 1, Table 3). The optimal ROC cut-off value of platelet for abortus was calculated as 227.0 (x10^3/μL) with a sensitivity of 71.3% and a specificity of 47.7% (AUC: 0.621) (Figure 1, Table 3).

Table 1: Demographic features

Parameters	All participants (n:203)
Age	30.7 (6.37)
Average abortus period (week)	9.03 (3.62)
BMI (kg/m^2)	25.79 (1.61)
Gravida	2.86 (1.48)
Parity	2.00 (1.20)
Leukocyte (x10^3/μL)	9.47 (2.49)
Hemoglobin (gr/dl)	12.4 (1.36)
Platelet (x10^3/μL)	249.0 (72.0)

Table 2: Comparison of variables between groups

	Abortus group (n:94)	Control group (n:109)	*P*-value[∝]
Age (year)	31.51 (6.72)	30.00 (5.99)	0.097
VKİ (kg/m^2)	25.89 (1.62)	25.71 (1.61)	0.341
Gravidity	3.05 (1.58)	2.69 (1.67)	0.120
Parity	1.41 (1.13)	1.58 (1.24)	0.415
Leukocyte (x10^3/ μL)	9.37 (2.68)	9.56 (2.30)	0.266
Neutrophil (x10^3/ μL)	6.52 (2.56)	6.79 (1.86)	0.102
Lymphocyte (x10^3/ μL)	2.10 (0.60)	2.08 (0.61)	0.818
Monocyte (x10^3/ μL)	0.57 (0.16)	0.61 (0.16)	0.193
Hemoglobin (gr/dl)	12.56 (1.45)	12.30 (1.27)	0.090
Platelet (x10^3/ μL)	263.55 (68.70)	237.04 (72.87)	0.003
Plateletcrit (%)	0.27 (0.06)	0.25 (0.07)	0.007
MPV (fl)	10.45 (0.99)	11.51 (8.99)	0.175
NLR	3.46 (2.48)	3.45 (1.14)	0.036
LMR	3.49 (1.37)	3.79 (1.22)	0.034
PLR	134.13 (48.11)	121.31 (45.77)	0.032

[∝] Mann-Whitney U test, MPV: Mean platelet volume, NLR: Neutrophil-leukocyte rate, LMR: Lymphocyte-monocyte rate, PLR: Platelet- lymphocyte rate

Table 3: Sensitivity and specificity of hematological markers

Parameters	Area Under Curve	*P*-value	Sensitivity (%)	Specificity (%)
Platelet	0.621	0.003	71.3	47.7
Plateletcrit	0.609	0.007	60.6	52.3
LMR	0.414	0.034	52.3	31.9
NLR	0.414	0.036	56.4	33.1
PLR	0.587	0.032	59.6	51.4

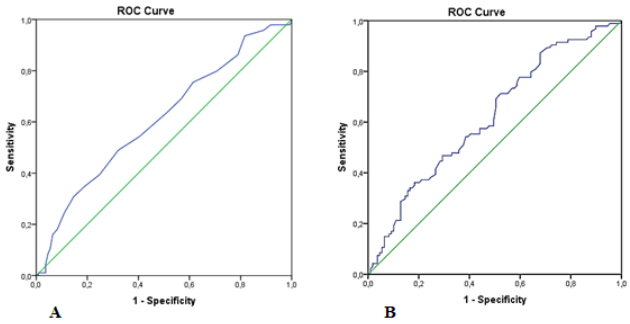

Figure 1: Diagnostic performance of plateletcrit (A) and platelet (B) in prediction of early pregnancy loss

Discussion

Abortus is the most common pregnancy complication seen in the early pregnancy period. With the advancing health services and technology, the frequencies of severe hemorrhage and infection have decreased [20]. In the evaluation of abortus materials, inflammation was shown in the decidua in the implantation area [21]. Investigating the changes of systemic inflammation markers in abortus cases, our study was planned to seek an answer to whether these markers can be used in the diagnosis of failed pregnancy in the early pregnancy period. We found that platelet count, plateletcrit, NLR, PLR, and LMR values were significantly different.

Since platelets also function as acute-phase reactants in the human body, an increased number of platelets and changes in platelet markers can be an indication of inflammation [22]. However, platelet functions can also change physiologically. Platelets play a role in the development of spiral arteries to adapt to pregnancy [23]. We found that platelet count and plateletcrit were significantly higher in the abortus group. However, in terms of MPV, there was no significant difference between the two groups. There is contradictory information on this subject in the literature. Kara et al. [24] compared spontaneous abortus and healthy pregnancy patients and found that MPV were similar, while the platelet count of the abortus was significantly higher. In addition to platelet counts, Kaplanoglu et al. [25] found a difference in MPV, as well. Eroglu et al. [25], on the other hand, suggested that MPV cannot be used as a diagnostic test. In the light of these results, we think that the platelet count increases in response to inflammation as an acute phase reactant. MPV directly shows platelet functions. Large platelets are more active in proinflammatory and prothrombotic aspects. In abortus cases, large platelets are thought to migrate to the damaged area through the circulation in parallel to inflammation and MPV is thought to decrease consequently [26].

Increased plateletcrit and PLR have been shown to affect the prothrombotic and proinflammatory processes [27]. Plateletcrit and PLR, therefore, have been studied in many obstetric complications. Yücel et al. [16] found that the rate of plateletcrit decreased significantly in severe preeclampsia patients. In our opinion, the fact that the severe preeclampsia cases are high in this study leads to a decrease in the platelet counts, which causes MPV to increase and plateletcrit to decrease significantly. However, in our study, we observed that with the increase of platelet count parallel to inflammation, MPV decreased and plateletcrit increased significantly. Ata et al. [28] obtained similar results in their study. Again, a statistically significant moderate positive correlation between plateletcrit and PLR and a highly positive correlation between plateletcrit and platelet count found in our study help explain this situation. We think that PLR, on the other hand, increases as an indicator of inflammation.

NLR and LMR, other hematologic inflammatory markers, were significantly different between the two groups in our study. LMR has been studied in the recent years to predict the success of prognosis and treatment, especially in several types of cancer [14, 29]. Based on our research in the literature, we found that the relationship between LMR and abortus was not priorly investigated. Therefore, ours is the first study evaluating LMR along with other parameters. The fact that inflammation indicators, NLR and LMR, were significantly higher in abortus cases supports the inflammatory markers.

It is not yet clear whether the inflammatory process is the cause or the consequence. The fact that anti-inflammatory therapy does not increase live birth rates suggests that inflammation is a consequence [30].

Limitations

The retrospective and single-center nature of our study, being based on a single complete blood count result, and the fact that we did not investigate other inflammatory markers appear to be factors which reduce its strength.

Conclusion

We found that plateletcrit and platelet counts were superior to others, and that there was a significant relationship between plateletcrit, platelet count, NLR, PLR, and LMR and abortus. However, this relationship is not enough to predict abortus. Given the contradictory data in the literature, more comprehensive and prospective studies are needed to confirm our results.

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