The Role of Platelet Counts in the Etiology of Missed Abortion

Trombosit Sayımlarının Gecikmiş Düşük Etiyolojisindeki Rolü

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ÖZ

Amaç: Ortalama trombosit hacmi (MPV) ve trombosit (PLT) sayımlarının başarısız gebeliği özellikle gecikmiş düşüğü tahmin edip edemeyeceğini belirlemek için normal gebeliklerin ve düşük yapan hastaların MPV değerlerini ve PLT sayılarını araştırmak.

Gereç ve Yöntemler: Bu retrospektif vaka-kontrol çalışmamızda, abortuslu vakaların ve kontrol grubunun MPV değerleri ve PLT sayıları araştırıldı. Gebeliği normal seyreden gebeler ile gecikmiş düşükle sonuçlanan gebelerin MPV ve PLT değerleri karşılaştırıldı. Çalışma grubuna dahil edilen gecikmiş düşük tanılı 238 hasta ve kontrol grubuna dahil edilen 226 sağlıklı gebe olmak üzere toplam 464 kişi çalışmaya dahil edildi.

Bulgular: Gecikmiş düşük tanılı grupta ortalama yaş 33.50 iken, kontrol grubunda ortalama yaş 32 yıl idi. İki grup arasında yaş açısından istatistiksel anlamlı fark mevcuttu (p=0.01). Gecikmiş düşük grubunda gebelik yaşı, kontrol grubuna göre istatistiksel anlamlı daha yüksekti (p<0.001). Gebelik sayısı (p<0.001) ve canlı doğum sayısı (p=0.002) açısından istatistiksel anlamlı farklılık saptandı. Gecikmiş abortus grubunun % 39,5'inin birinci, kontrol grubunun % 63,2'sinin ilk gebeliği idi. Gecikmiş düşük grubunun % 35,7'si ikinci graviteye sahipken, kontrol grubunun% 63,2'si ikinci graviteye sahipti. Gecikmiş düşük grubunun% 54,6'sında, kontrol grubunun ise% 67,3'ünde parite görülmedi. İlk parite, gecikmiş düşük grubunun% 37,8'inde ve kontrol grubunun% 31,4'ünde görüldü. Gecikmiş düşük grubunda sigara kullanımı (% 32,3), kontrol grubuna (% 14,1) göre anlamlı derecede yüksekti (p <0,001). Eritrosit dağılım genişliği (RDW-SD) (p <0.001) ve hematokrit (Htc) (p = 0.032) açısından iki grup arasında anlamlı fark vardı. MPV (p = 0.155; OR = 1.097; CI = 0.966_1.247), Trombosit dağılım genişliği (PDW) (p = 0.695; OR = 0.991; CI = 0.947_1.037), plateletcrit (PCT) (p = 0.468) ile gecikmiş düşük arasında anlamlı bir korelasyon yoktu. Gecikmiş düşük grubunda sigara içen hasta sayısı, kontrol grubuna göre daha yüksekti (p<0.001). RDW-SD (p<0.001) ve Htc (p=0.032) değerleri gruplar arasında anlamlı farklılık gösterdi. MPV (p = 0.155; OR = 1.097; CI = 0.966_1.247), PDW (p = 0.695; OR = 0.991; CI = 0.947_1.037), PCT (p = 0.468) değerleri ve gecikmiş düşük arasında anlamlı bir korelasyon bulunmadı.

Sonuç: Çalışmamızda gösterildiği üzere, MPV gibi hematolojik parametrelerin gecikmiş düşük için tarama veya tanı testi olarak kullanılması uygun bulunmamıştır.

Anahtar Kelimeler: Gecikmiş Düşük, Ortalama trombosit hacmi, Trombosit dağılım genişliği, Trombosit indeksleri.

ABSTRACT

Aim: To investigate mean platelet volume (MPV) values and platelet (PLT) counts of normal pregnancies and patients with missed abortions to determine whether MPV and PLT counts can predict unsuccessful pregnancy particularly missed abortion.

Materials and Methods: This retrospective case-control study investigated the MPV) values and PLT counts of patients with missed abortion and the control group. Among 464 cases, 238 participants with missed abortion and 226 healthy pregnant women were included.

Results: The mean age of the missed abortion group was 33.50 years and the mean age of the control group was 32 years. Age showed a statistically significant difference between the two groups (p = 0.010). The missed abortion group was in the 4th week of gestation age and the control group was in the 2nd week of gestation age which showed statistically significant difference (p < 0.001). Significant differences between the two groups in gravidity (p < 0.001) and parity (p = 0.002) were observed. 39.5% of the missed abortion group had the first gravidity while 63.2% of the control group had the first gravidity. 35.7% of the missed abortion group had the second gravidity while 63.2% of the control group had the second gravidity. No parity was observed in 54.6% of the missed abortion group and in 67.3% of the control group. First parity was observed in 37.8% of the missed abortion group and 31.4% of the control group. Smoking was significantly higher in the missed abortion group (32.3%) than that in the control group (14.1%) (p < 0.001). There was a significant difference between the two groups in Red cell distribution width (RDW-SD) (p < 0.001) and in hematocrit (p = 0.032). There was no significant correlation between MPV (p = 0.155; OR = 1.097; CI = 0.966_1.247), Platelet distribution width (PDW) (p = 0.695; OR = 0.991; CI = 0.947_1.037), plateletcrit (PCT) (p= 0.468) and missed abortion.

Conclusion: MPV may not be used as a screening or diagnostic test for unsuccessful pregnancies particularly missed abortion as shown in the current study.

Keywords: Mean platelet volume, Missed abortion, Platelet distribution width, Platelet indices.

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INTRODUCTION

The term "missed abortion" is defined as a clinical abortion which does not cause spontaneous expulsion of the conception products. About 15% of the pregnancies which are diagnosed clinically constitute is missed abortion (1). In other words, missed abortion is the death of the embryo or fetus in the uterus before the 20th week of gestation while the pregnancy is retained in the long term (2).

Missed abortion is caused due to anatomic, genetic, endocrine factors, and thrombophilia. Thrombophilia has been reported in many studies to cause missed abortion and pregnancy loss (3,4).

Platelets (PLT) play a major role in hemostasis. PLT size has been demonstrated to reflect the activity of PLT and Mean platelet volume (MPV) is used to measure its size. Large-sized PLT are more reactive thereby producing more prothrombotic factors (5,6). Large platelets have higher functional capabilities than small ones and the patients who have small platelets will experience more frequent bleeding diathesis (7). When normal pregnancies occur, there have been increased PLT aggregations, which increased PLT volume and increased synthesis compensated for it (8,9).

Kosus et al. evaluated changes of MPV in missed abortion group as compared with normal pregnancies (10). Some studies have shown a significant increase in MPV in subjects with acute myocardial infarction (MI) (11). Platelet Distribution Width (PDW) and plateletcrit (PCT) values were found high in MI patients (12).

The aim of this study was to investigate MPV values and platelet counts of normal pregnancies and patients with missed abortions to determine whether MPV and PLT counts can predict unsuccessful pregnancy particularly missed abortion.

MATERIALS AND METHODS

The present study was planned as a retrospective case-control study . Patients who were diagnosed as missed abortion and were admitted to Adana City Training and Research Hospital Obstetrics and Gynecology outpatient clinic between January 2014 and December 2019 were included in this study. The inclusion criteria included missed abortion, and the exclusion criteria included multiple pregnancies, ectopic pregnancy, not having fetal pole observed before 5 weeks of viable pregnancy, hypertension, diabetes, immunological, renal, hematological or heart diseases.

This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants 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. The study was carried out with the permission of Research Ethics Committee of Adana City Training and Research Hospital (Permission granted /CAAE number: 2020/06.5, Decision no: 850). The

retrospective electronic medical records of 238 patients diagnosed with missed abortion and 226 healthy pregnant women were examined and MPV values and PLT counts were compared between the two groups. The control group was selected among healthy pregnant women who had no complications for pregnancy. Missed abortion means that there is no fetal heart rate detected before the 20th gestational weeks.

Gestational age, age, gravidity, parity, Body-mass index (BMI), height and weight and laboratory values such as Hematocrit (Htc) , Hemoglobin (Hb), leucocytes, neutrophils, lymphocytes, monocytes , PLT, MPV, mean corpuscular volume (MCV), platelet distribution width (PDW) , red cell distribution width (RDW-SD) , and PCT were recorded.

When the sample size was calculated with the G-Power 3.1 (http://www.gpower.hhu.de/) program, the total mean of the two groups compared based on the Student's t-test with the effect size of 16%, power of 90% and 0.05 type 1 error, was found to be at least 432 patients.

Statistical Assessment

All of the statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS) 22.0 software (IBM, Armonk, NY). For evaluating the normal distribution of data, the Kolmogorov-Smirnov test was used. All the variables were considered non-parametric according to the normality test. Hence, the differences between groups were evaluated by the chi-square test for categorical variables and the Mann-Whitney test for continuous non-parametric variables. Multivariate binary logistic regression test was performed by including all factors with $P < 0.2$ on the univariate study. Also, to evaluate the accuracy of platelet indices to predict the missed abortion, receiver operator characteristics analysis (ROC) was performed. Values < 0.05 were considered as statistical significance in all of the analyses tests.

RESULTS

Patients' characteristics

226 subjects were included in the control group and 238 patients were evaluated in the missed abortion group. The subjects' general and clinical characteristics of the two groups were investigated. According to the results, the mean age of the missed abortion group was 33.50 years with a standard deviation of around 8 years and the mean age of the control group was 32 years with a standard deviation of around 8 years. There was no statistically significant difference between the two groups in terms of age (p = 0.01). The missed abortion group was in the 4th week of gestation age (with the standard deviation of 4 weeks) and the control group was in the 2nd week of gestation age (with the standard deviation of 2 weeks) which showed statistically significant difference (p < 0.001).

Significant difference in gravidity (p < 0.001) was observed between the two groups. 39.5% of the missed abortion group had the first gravidity while 63.2% of the control group had the first gravidity. 35.7% of the missed abortion group had the second gravidity while 63.2% of the control group had the second

gravidity. Third gravidity was observed in 16.3% of the missed abortion group and 3.6 % in the control group. There was also significant difference between the two groups in parity (p= 0.002). No parity was observed in 54.6% of the missed abortion group and 67.3% of the control group. First parity was observed in 37.8% of the missed abortion group and in 31.4% of the control group.

Smoking was significantly higher in the missed abortion group (32.3%) than that in the control group (14.1%) (p < 0.001). There was a significant difference between the two groups in RDW-SD (p < 0.001) and hematocrit (p = 0.032). RDW-SD was 33.50 (4.10) in the missed abortion group and 34.50 (9.10) in the control group. Htc was 36.55 (5.70) in the missed abortion group and 37.5 (4.60) in the control group. Other variables didn't differ significantly between two groups (p > 0.05). The general and clinical characteristics of the individuals in the two groups are shown in Table 1.

Table 1. Baseline and clinical characteristics of patients.

Parameters		Missed Abortion (n = 238)	Control (n = 226)	p-value
Age (year)		33.50 (8)	32 (8)	0.010
Weight (kg)		76 (19)	75 (17.3)	0.557
Height (m)		1.66 (0.07)	1.66 (0.08)	0.454
BMI (kg/m^2)		27.5 (7.02)	27.1 (6.53)	0.868
Gestational age (week)		8 (4)	6 (2)	< 0.001
Gravidity	1	94 (39.5)	143 (63.2)	< 0.001
	2	85 (35.7)	75 (33.2)	
	3	39 (16.3)	8 (3.6)	
	4	16 (6.8)	0	
	5	1 (0.4)	0	
	6	3 (1.3)	0	
Parity	0	130 (54.6)	152 (67.3)	0.002
	1	90 (37.8)	71 (31.4)	
	3	16 (6.7)	3 (1.3)	
	4	2 (0.9)	0	
Smoking		77 (32.3)	32 (14.1)	< 0.001
Leucocytes		7.20 (3.21)	7.01 (3.07)	0.638
Neutrophils		4.2 (3.13)	4.14 (3.03)	0.431
Lymphocytes		2.16 (0.91)	2.14 (0.85)	0.715
Monocytes		0.54 (0.26)	0.56 (0.31)	0.394
Basophils		0.05 (0.03)	0.05 (0.04)	0.311
Hb		12.35 (2.20)	12.70 (1.70)	0.104
RDW-SD		33.50 (4.10)	34.50 (9.10)	< 0.001
PLT		245500 (59000)	248000 (87500)	0.940
MPV		9.80 (1.73)	9.78 (1.50)	0.271
PDW		11.85 (7.90)	12.10 (6.20)	0.941
PCT		0	0	0.306
MCV		87.60 (4.80)	87.60 (6.60)	0.683
Htc		36.55 (5.70)	37.5 (4.60)	0.032

BMI : Body mass index , Hb: Hemoglobin RDW-SD : Red cell distribution width, PLT: Platelet , MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit Htc:Hematocrit

2.2. Binary logistic regression

All the independent variables were evaluated by logistic regression. Univariate logistic regression showed there was no significant correlation between MPV (p = 0.155; OR = 1.097; CI = 0.966_1.247), PDW (p = 0.695; OR = 0.991; CI = 0.947_1.037), PCT (p= 0.468) and missed abortion.

However, following the univariate logistic regression, MPV (p < 0.2) was added in the multivariate logistic regression adjusted for RDW-SD (p < 0.001, OR = 1.143, CI = 1.090_1.198), Htc (p = 0.031, OR = 1.057, CI = 1.005_1.112), age (p = 0.011, OR = 0.956, CI = 0.923_0.990), gestational age (p < 0.001, OR = 0.664, CI = 0.596_0.741), parity (p < 0.001, OR = 0.561, CI = 0.406_0.775), Gravidity (p < 0.001, OR = 0.407, CI = 0.310_0.534) and smoking (p < 0.001, OR = 2.889, CI = 1.826_4.603).

Continuous variables are expressed as median (interquartile range) and categorical variables are expressed as n (%).

Table 2 shows the results of logistic regression analysis of MPV. The relationship between MVP and the outcome in unadjusted and adjusted models was insignificant (p-value > 0.05).

Table 2. Independent predictors of missed abortion in women according to MPV in unadjusted and adjusted models.

Model	OR	p-value
Unadjusted	1.097	0.155
Adjusted	1.071	0.412

DISCUSSION

The aim of this study was to investigate MPV values and PLT counts of normal pregnancies and patients with missed abortions. The findings showed that there was a significant difference between the two groups in terms of age so that the mean age of the women in the missed abortion group was higher than that of the healthy women. The gestational age of the control group was lower than that of the missed abortion group. Those who were in the missed abortion group smoked more than those in the control group. RDW-SD was significantly higher in the control group than in the missed abortion group. Htc was significantly lower in the control group than in the missed abortion group.

The complete blood count is an easily available, and economical test that involves parameters as Hct, Hb, White Blood cell (WBC), Mean corpuscular hemoglobin (MCH), RBC, MCV, RDW-SD, PLT, MPV, Mean Corpuscular Hemoglobin Concentration (MCHC) and PDW. Studies have found a relationship between some blood count values and different clinical conditions (13). Pregnancy is a state of hypercoagulation in which the concentrations of coagulation factors change. PLT activity is also reported to increase during pregnancy (14).

Pregnancy is a state of hypercoagulation where there is a change in the coagulation factors concentrations and pregnancy is reported to increase PLT activity (15) while Lamparelli et al. (16) have reported that there was a decrease in PLT count with advancing pregnancy and no significant change in MPV was found. In a study, MPV was found to be higher than 9.1 indicating that there was a strong association between MPV and PCT values and with first-trimester miscarriage, indicating PLT indices as a useful tool for prediction of fetal loss while our study showed no

correlation between MVP and missed abortion (15).

In a study showed significantly lower MPV in patients with miscarriage than the control group, and the correlation between it and the gestational stage when the miscarriage occurred, which is not consistent with our study result (17).

Several studies have evaluated the platelet number and activities in complicated pregnancies (17). PLT are characterized by a relatively stable morphology and an anuclear discoid structure throughout their lives. Recent studies have shown a change in PLT activity due to the change of PLT morphological structure (18). It has been reported that changes in the number and function of PLT have been made 12 weeks after a miscarriage. However, these changes may occur due to hormonal and environmental factors and also the pregnancy and miscarriage (19).

The missed abortion group showed higher gestational age than the control group did, which is not supported by the result of the study conducted by Bıyık (20). There was also a significant difference between the two groups in terms of gravida and parity which is not also in line with (20). RDW-SD and hematocrit showed significant differences between groups, which is in line with the study by Bıyık (20).

In a study by Al-Aghbary (21), only parity showed a significant difference between the two groups which was in line with our study result but our study also showed a significant difference between the two groups in terms of gestational age and gravidity which was not in line with (21). Our study was shown that the missed abortion group also had a higher smoking experience than the control group had.

The primary cause of clotting was PLT which play a major role in thrombophilias and vascular pathologies. The indicators of PLT activity were PLT volume indices such as PCT, MPV, PDW, and PLT count, which are routinely reported in automated full blood counts (22). PDW represented the variability range of PLT size, and large PDW may be an indicator of prothrombotic status (23).

Kosus et al. compared 100 missed abortion cases with 100 normal pregnant women in terms of MPV and PLT values and found that MPV values were similar in both groups, showing that MPV values were similar in missed abortion and control groups, which is in line with our study result (10).

In a study found higher PLT and PCT levels in the abortion group while no statistical difference was found between the abortion and healthy pregnancy group in terms of the MPV values, which is in line with our study result (24).

On the contrary, there were significantly higher MPV, PCT, and PDW in studies on the PLT parameters in the recurrent pregnancy loss group (25,26), which was not consistent with our study which found no significant correlation between MPV and PCT and missed abortion.

Eroglu et al. (2) showed a slight not statistically significant increase in MPVs in threatened miscarriage and missed abortions, while our study showed no significant difference between MPV and missed abortion.

Sever et al. (13) in their study found that complete blood count parameters including high RDW, PCT, MPV, and low MCHC

may be an important predictor of recurrent miscarriage, while our study showed that the missed abortion group had lower RDW than the control group had and that there was no significant correlation between MPV and PCT and missed abortion. Another study (27) found that women with recurrent pregnancy loss had higher RDW values than the control group had, which is not consistent with our findings.

CONCLUSION

It is concluded that there was a significant difference between the two groups in terms of age. Two groups also showed significant differences in RDW-SD and Htc. There was no significant correlation between hematological parameters such as MPV, PDW, PCT and missed abortion. It was concluded that since there were overlapping values between normal pregnancy group and missed abortion group as shown in our study, it may not be possible to use MPV or PLT counts as a screening or diagnostic test for unsuccessful pregnancies particularly missed abortion at present.

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