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Original Article

Decreased mean platelet volume is associated with the developing stage of fetoplacental unit in spontaneous abortion

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Abstract: Aim: The aim was to evaluate the place of mean platelet volume (MPV) in predicting spontaneous miscarriage and to identify any differences in its values following miscarriage after biochemical and clinical pregnancy. Material and method: We retrospectively evaluated the data of 305 spontaneous miscarriages and 168 control subjects. The miscarriage subjects were evaluated in two groups: miscarriage after biochemical pregnancy (n=79) (BA group) and miscarriage after clinical pregnancy (n=226) (CA group). Demographic and laboratory data of all subjects were statistically compared. Results: No statistically significant difference was found between the miscarriage and control subjects in terms of demographic data and Hb, Htc, WBC, and Plt values. The mean platelet volume (MPV) value in the miscarriage group (8.99±1.47 fl) was statistically significantly lower than in the control group (9.66±1.64 fl) (P<0.001). A statistically significant difference was present between the BA, CA and control group, with the lowest MPV value in the BA group (8.64±1.34 fl, 9.11±1.49 fl, and 9.66±1.64 fl, respectively) (P<0.001). Discussion: MPV was significantly lower in patients with miscarriage than the control group, and this was correlated with the gestational stage when the miscarriage occurred.

Keywords: Mean platelet volume, biochemical abortion, clinic abortion, prediction

Introduction

Spontaneous miscarriage is identified as the loss of pregnancy before the 20th gestational week and is the most common pregnancy complication [1, 2]. The risk decreases the gestational week increases. A miscarriage occurs in 40% of pregnancies before they are defined clinically and 8-22% afterwards [3, 4]. Miscarriage can occur after biochemical pregnancy (BA) or after clinical pregnancy (CA) on laboratory and ultrasonographic evaluation. Many factors are associated with this pregnancy complication, including endocrinology imbalance, immune dysfunction, genetic disorders, advanced maternal age, gravity, body mass index (BMI) >25 or <18, genital infection, environmental toxins, anatomic uterine defects, and chromosomal abnormalities [5-9].

Platelets are blood cells that are especially important in hemostasis. Larger platelets are thought to have granules with more mediators and to be more active. MPV is the indicator most commonly used as an activation marker in past studies. Increased MPV has been associated with coronary heart disease, diabetes mellitus, atherosclerosis, hypertension, and Polycytic Ovarian Syndrome (PCOS) in particular [10-19]. Changes in platelet activity and volume in normal and complicated pregnancy (especially preeclampsia and intrauterine growth retardation) have been evaluated in a large number of studies [14]. However, there are only a few studies on using MPV evaluation to predicting miscarriages.

The aim of our study was to evaluate the place of MPV in predicting miscarriage following biochemical or chemical pregnancy.

Material and method

Study design

We retrospectively evaluated the hospital records of all patients who presented with delayed menstruation to Adiyaman University

Table 1. Demographic characteristics and Complete Blood Counts of the Study Populations

	Abortion group	Control Group	
	n: 305	n: 168	P
Age (year) (mean ± SD)	27.16±4.59	27.62±4.41	0.286
Gravidy (median (min-max))	2 (1-8)	2 (1-8)	0.674
Parity (median (min-max))	1 (0-7)	1 (0-7)	0.898
WBC ($10^3/mm^3$)	9.04±2.29	9.33±2.41	0.190
Hemoglobin (g/dl)	10.98±1.69	11.21±1,51	0.138
Hematocrit (%)	33.43±4.49	33.92±3.91	0.240
Platelets ($10^3/mm^3$)	274.24±43.32	267.11±62.65	0.146
PDW (%)	17.31±2.99	17.78±3.28	0.125
MPV (fl)	8.99±1.47	9.66±1.64	<0.001

n: number of patient, SD: standart deviation, WBC: White blood cell, MPV: mean platelet volume, PDW: platelet distribution width.

Medical Faculty Training and Research Hospital's Obstetrics and Gynecology Clinic between January 2013 and January 2014. We first reviewed the files of patients who had been diagnosed with a miscarriage within the identified period. A miscarriage was identified as birth following a pregnancy of under 20 gestational weeks and/or 500 g. A total of 305 females with miscarriage who met the study criteria made up the patient group, and 168 females who had given birth at term without complication made up the control group. The miscarriage group was divided into two subgroups as the biochemical pregnancy (BA) (n=79) and clinical pregnancy (CA) (n=226) groups according to clinical follow-up, laboratory, and ultrasonographic data. The demographic and laboratory values and laboratory values at first presentation (hemoglobin (Hb) and hematocrit (Htc) level, white blood cell (WBC), number of platelets, MPV, and platelet distribution width (PDW)) were recorded were statistically compared.

We ensured that the control group subjects had first been examined before the 20th gestational weeks.

Descriptions

Pregnancy was diagnosed using maternal blood HCG level and ultrasonographic evaluation. BA was described as miscarriage without any pregnancy-related structure being seen on ultrasonography together with a positive pregnancy test after delayed menstruation. CA was described as the development of pregnancy with an intrauterine location and heartbeat on sonography, followed by miscarriage. Gestational age was determined using the last menstrual date (LMD) and verified with ultrasonographic measurements. Gestational week was calculated based on the first hospital ultrasonographic measurement in women with unknown LMD.

Inclusion criteria: Patients characteristic included age of 18 to 35 years; no smoking or alcohol use; no chronic disease, such as hypertension, diabetes mellitus, vasculitis, or thyroid disorder; no defined hematological and rheumatological disease; no history of thrombosis or habitual abortion; and no uterine anomaly on ultrasonographic evaluation.

Sample collection and analysis

Blood samples were obtained before the vaginal bleeding in all patients. If HCG doubling-time (for BA group) and ultrasonographic evaluation (for CA group) were not suitable for normal pregnancy course, the patents were accepted abortion. All samples were evaluated within one hour. The MPV and other parameters were studied at the Adiyaman University School of Medicine Department of Biochemistry Laboratory. In all cases, complete blood counts were measured by an automatic blood counter (CELL-DYN Sapphire, Abbott, Illinois, United States) within one hour. All blood samples were received from the antecubital vein into Vacutainer System (Becton Dickinson, Franklin Lakes, NJ, USA), containing 0.04 ml 7.5% K3 ethylene diamin tetra-acetic acid (K3EDTA). The MPV, Hb, WBC, and Plt range were determined as 6.9-10.6 fl, 11.5-16.5 g/dl, 3.7-10.1×10^3/mm^3, and 155-366×10^3/mm^3, respectively.

Statistical analysis

Data were analyzed with SPSS software, version 15.0 for Windows (SPSS for Windows, Chicago, IL). Continuous variables were presented as mean ± SD. One-sample Kolmogorov-Smirnov test was used to analyze the normality of the continuous variables. An independent samples *t*-test or Mann-Whitney U-test was

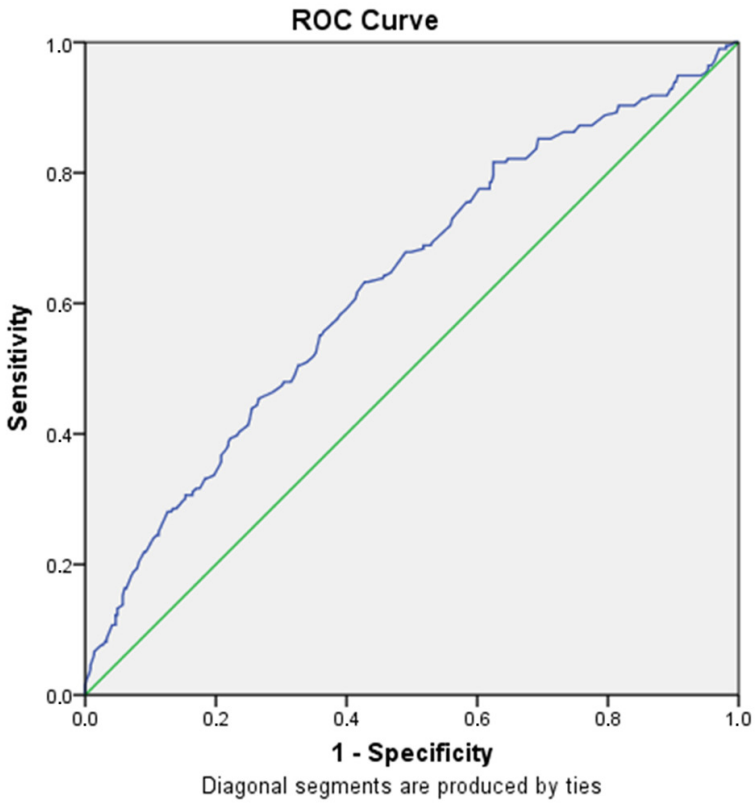

Figure 1. ROC curve for MPV in predicting development of miscarriage (AUC: 0.621).

used to compare continuous variables where appropriate. Pearson's correlation test was used for correlation analysis. In order to estimate the sensitivity and specificity of MPV values for predicting spontaneous abortıon, receiver-operator curve (ROC) analysis was performed. A *p*-value 0.05 was accepted as statistically significant.

Results

No significant difference was found in terms of maternal age, gravida, or parity between the miscarriage and control groups (P=0.286, P=0.674, P=0.898, respectively) (**Table 1**). There was also no statistically significant difference in terms of the WBC count, Hb, Htc, Plt and PDW value (P=0.190, P=138, P=0.240, P=0.146, P=0.125, respectively) (**Table 1**). The MPV value in the miscarriage group (8.99±1.47 fl) was statistically significantly lower than in the control group (9.66±1.64 fl) (P<0.001) (**Table 1**). A cut-off value of 9.25 in the ROC analysis performed to investigate the effect of MPV value in predicting miscarriage produced a sensitivity of 60% and specificity of 60%. The area under the curve (AUC) for the MPV 0.621 (95% CI: 58-67%, P<0.001) (**Figure 1**).

Comparison of the spontaneous miscarriage subgroups of BA and CA with the control group revealed no statistically significant differences in terms of WBC, Hb, Htc, Plt count, and PDW values (P=0.118, P=0.328, P=0.081, P=0.315, P=0.291, respectively). There was, however, a statistically significant difference between the groups for MPV value, with the lowest value in the BA group (P<0.001) (**Table 2**).

Discussion

Platelets have an anuclear discoid structure and a relatively stable morphology throughout their lives. Recent studies have shown that a change in platelet morphological structure results in a change in platelet activity [17]. Platelet activity can also be changed by various physiological and pharmacological agents. Although the best known platelet functions are protection of vascular integrity and controlling bleeding, platelets also play a role in the physiopathogenesis of thromboembolic disorders [18]. Platelets also serve in the development of the placenta, especially in the remodeling of the maternal spiral artery in obstetric practice [19].

Pregnancy is a hypercoagulability situation. The sensitive role of platelets in maintaining the balance between prothrombotic tendency and placental development is vital for the continuation of a pregnancy [19]. An imbalance can cause an increased hemostatic response. The result would be uteroplacental vascular thrombosis and loss of the pregnancy. Changes in the number and function of platelets have been reported for up to 12 weeks following a miscarriage. However, it was stated that the reason for

Table 2. Complete Blood Counts of the Biochemical Abortion, Clinical Abortion and Healthy Control Groups

	Biochemical Abortion (mean ± SD)	Clinic Abortion (mean ± SD)	Control group (mean ± SD)	P	P*	
n	79	226	168			
WBC (×10³/mm³)	9.39±2.70	8.91±2.11	9.33±2.41	0.118		
Hemoglobin (g/dl)	11.00±1.75	10.96±1.68	11.21±1.51	0.328		
Hematocrit (%)	34.23±5.54	33.16±4.05	33.92±3.91	0.081		
Platelets (×10³/mm³)	272.03±44,83	275.02±42.85	267.11±62.65	0.315		
PDW (%)	17.21±3.65	17.35±2.73	17.78±3.28	0.291		
MPV (fl)	8.64±1.34	9.11±1.49	9.66±1.64	<0.001	1	0.053
					2	<0.001
					3	0.001

n, number of patient; SD: standart deviation, WBC: White blood cell, MPV: mean platelet volume; PDW: platelet distribution width; *, 1, BA versus CA; 2, BA versus Control group; 3, CA versus control group.

these changes could be environmental and hormonal factors as well as the pregnancy and miscarriage themselves [20].

Increased platelet volume is a direct indicator of increased platelet synthesis. Increased MPV reflects an increase of active platelets in circulation and in platelet aggregation capacity [21]. Platelets with high MPV are accepted as having more granules containing mediators and being more active. Increased MPV is associated with both arterial and venous vascular pathologies, such as stroke, myocardial infarction, and venous thromboembolism. A close relationship has been shown between high MPV and CHD, DM, atherosclerosis, PCOS, and the complications of these disorders [12, 13].

The MPV parameter is included in routine whole blood count requested at patient admission in obstetric practice and does not require an additional cost. Every laboratory has a specific normal range, but there are no generally accepted mean values. On the other hand, the measurement is significantly affected by both environmental and laboratory conditions such as environmental temperature, storage temperature, and time until measurement. It is therefore difficult to determine a general risk cutoff value. However, it is attractive as an indicator because there is no additional procedure or cost. When evaluating MPV, one needs to know whether the patient is suffering from a disorder affecting the number and function of platelets such as aplastic anemia-induced thrombocytopenia, immune thrombocytopenia, or thrombocytosis.

As pregnancy advances, platelet count decreases, with no significant change in MPV [22]. The number and activities of platelets in complicated pregnancies have been evaluated in a large number of studies. Preeclampsia, premature rupture of membranes (PROM), and IUGR are the most commonly studied pregnancy complications. These studies have reported that increased MPV (and therefore increased platelet activity) increases placental platelet aggregation, causing thrombosis and placental deficiency [23, 24]. A significant correlation was found between second trimester abnormal uterine Doppler blood flow and MPV changes in retrospective evaluations of patients suffering from pregnancy complications such as preeclampsia and IUGR. This indicates that placental failure starts in the early weeks of pregnancy [25].

Miscarriage is the most common complication of pregnancy and many factors play a role in its etiology. Thrombosis and the resulting placental deficiency are major factors in the etiology of miscarriage. We would normally expect a change in MPV value that is measured in circulation due to the migration of active platelets to the uteroplacental region in miscarriage cases [26]. It has been reported that platelet aggregation and thrombosis during early placental development can cause miscarriage, and this can be associated with high MPV values [27]. However, other articles report no such change [28].

We found the MPV values to be low at hospital presentation in our patients suffering a miscar-

riage before any relevant clinical findings. The miscarriage group was divided into two subgroups for a more detailed analysis. The group with a miscarriage after biochemical pregnancy had the lowest MPV value. These results can be evaluated from two perspectives. First, platelets with high activity can shift the sensitive balance between placental development and thrombosis development toward thrombosis, which can play a role in miscarriage. Evidence supporting platelet activity as inducing miscarriage by itself is insufficient. However, the relationship between venous thrombosis and increased cardiovascular disease risk should not be ignored [21, 29]. Additional factors such as the antiphospholipid syndrome during placental development may also contribute. Second, disorders that develop during the placental development stage increase inflammation, attracting a larger number of active platelets to the region [30]. The result is a decrease in the MPV level in circulation. It is possible that with miscarriages, a larger number of active platelets migrate to the region in earlier gestational weeks. This may be similar to the decrease in MPV during the active period of disorders such as ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) [17].

Conclusion

In our study, MPV was higher in healthy pregnant women than in women who had suffered miscarriage. On the other hand, MPV was at a low level according to the gestational stage when the miscarriage occurred. We believe that the reason for this is the migration of more active platelets to the uteroplacental region, with a high level of inflammation. However, the presence of overlapping values and its low sensitivity and specificity restrict the use of MPV. Studies on a larger number of cases combining various inflammatory markers can help elucidate the relationship between miscarriage and MPV.

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Disclosure of conflict of interest

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