ORIGINAL PAPER / OBSTETRICS

Role of platelet indices in prediction of preeclampsia

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ABSTRACT

Objectives: To compare platelet indices in preeclamptic and normotensive pregnants and to investigate the clinical use of these parameters in preeclampsia prediction.

Material and methods: This retrospective case- control study included 257 preeclampsia patients and 264 healthy pregnant women as the control group. The groups were compared in terms of platelet count (PC), mean platelet volume (MPV), platelet distribution range (PDW), plateletcrit (Pct), Pct / MPV ratio and PC / MPV ratio.

Results: Between the preeclampsia group and the control group; mean platelet count (227.22 ± 78.58 vs 236.69 ± 64.30), plateletcrit (PCT) (0.21 ± 0.06 vs 0.24 ± 0.27), and platelet distribution width (PDW) (17.11 ± 0.80 vs 17.29 ± 0.82) were not significantly different (p> 0.05). However, MPV values were significantly higher in the preclampsia group compared to the control group (9.66 ± 1.62 and 8.92 ± 1.33, respectively) (p < 0.001). In our study, the optimum cut-off value of MPV was 9.15 with 58.7% sensitivity and 61.7% specificity for the prediction of preeclampsia. Pct/MPV ratio (0.02 ± 0.007 vs 0.027 ± 0.029) (p = 0.01) and PC/MPV ratio (24.63 ± 10.90 vs 27.63 ± 10.24) (p = 0.001) were significantly lower in the preeclampsia group than in the control group.

Conslusions: In preeclampsia, changes in platelet functions, destruction and production lead to changes in platelet indices. Compared with normal healthy pregnant women, preeclamptic pregnant women have higher MPV values. In preeclampsia prediction, MPV and PC/MPV ratio are promising as a diagnostic parameter.

Key words: mean platelet volume; platelet count; preeclampsia

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INTRODUCTION

Preeclampsia is a multifactorial and multisystemic disease characterized by high blood pressure and proteinuria after 20 weeks of gestation. Preeclampsia, which has an important role in maternal morbidity and mortality, differs geographically and affects 5–8% of all pregnancies [1, 2]. Although its pathophysiology is still unclear, hemostatic changes such as endothelial cell damage, platelet activation, increased intravascular thrombin formation have been known to be the main events in the pathophysiology of preeclampsia [3].

In normal pregnancy, a small increase in platelet aggregation is observed, which is compensated by increased platelet synthesis. Mean platelet volume (MPV) also increases due to increased platelet synthesis [4, 5]. Preeclampsia which is characterized by endothelial damage; uncontrolled intra-vascular platelet activation and increased platelet destruction are expected outcome [6]. Decrease in platelet count stimulates new platelet synthesis in the bone marrow and releases young and large platelets into the circulation [7].

The role of platelets in the pathophysiology of preeclampsia and therefore MPV values may vary in preeclampsia. The aim of this study was to evaluate whether MPV and PC/MPV ratio, which can be detected in a simple whole blood count, have a place in clinical practice in predicting preeclampsia.

MATERIAL AND METHODS

This retrospective study included 521 patients admitted to the Gynecology and Obstetrics Clinic of our hospital between 2018 and 2019, a tertiary center with 12000 deliveries annualy. The study complies with the Declaration of

Helsinki. This study was approved by Bursa Yuksek Ihtisas Ethics Committee (2011-KAEK-25 2020/02-18). In our institute, which is a training and research hospital, a general informed consent from patient admission is used in retrospective studies. The patients were divided into two groups as 264 healthy normotensive pregnant women and 257 preeclampsia patients with no medical or obstetric problems other than preeclampsia. Preeclampsia was diagnosed according to the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin [8]. In a patient whose blood pressure was normal previously; systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg in two separate measurements made at least six hours and marked proteinuria (urinary protein excretion > 300 mg/24 h), after 20th gestational week were diagnostic criteria.

Women with systemic disease (hypertension, endocrinological pathology, diabetes mellitus, heart disease, renal disease, liver disease), gestational diabetes mellitus, morbid obesity (BMI ≥ 40 kg/m^2), history of thromboembolism or known thrombophilic disease, anticoagulant use, malformed fetus and multiple pregnancies, 'hemolysis, increased liver function enzymes and low platelet count' (HELLP) syndrome were excluded from the study.

Statistical Analysis

In the descriptive statistics of the data; mean, standard deviation, median, min-max, ratio and frequency values were used. The distribution of the variables was checked by Kolmogorov-Simirnov test. Independent sample t-test (two-tailed) was used for data analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

Table 1 presents the maternal demographic characteristics and delivery outcomes of both groups. The ages of the patients in the preeclampsia group (33.02 ± 5.82//26.77 ± 6.09; $p < 0.001$) and body mass index (BMI) (33.02 ± 5.82/29.75 ± 4.92; $p < 0.001$) were significantly higher than the control group. While there was no significant difference between gravida and parity numbers, the gestational week at birth (34.81 ± 3.76/38.36), 99; $p < 0.001$), birth weight of infants (2464 ± 947/3229 ± 573; $p < 0.001$) and 1st minute (8.35 ± 1.63/8.82 ± 0.84; $p < 0.001$) and 5th minute (9.28 ± 1.67/9.75 ± 0.82; $p < 0.001$) APGAR scores were significantly lower in the preeclampsia group than in the control group.

Table 2 contains laboratory data containing the platelet indices in detail. When the groups were evaluated in terms of whole blood count parameters; white blood cell (WBC), hemoglobin (hb), hematocrit (hct), platelet count (PC), platelet distribution range (PDW), plateletcrit (Pct)

Table 1. Basic demographic and clinical datas			
	Control n: 257	**Preeclampsia n: 264**	**p**
Age	26.77 ± 6.09	30.23 ± 6.52	< 0.001
BMI*	29.75 ± 4.92	33.02 ± 5.82	< 0.001
Gravidas	2.39 ± 1.50	2.58 ± 1.59	0.162
Parity	1.09 ± 1.2	1.13 ± 1.24	0.690
Gestational age	38.36 ± 1.99	34.81 ± 3.76	< 0.001
Birth weigth	3229 ± 573	2464 ± 947	< 0.001
Fetal length	50.05 ± 2.60	46.04 ± 5.89	< 0.001
Fetal head circumference	34.53 ± 1.68	32.41 ± 3.47	< 0.001
Cyistolic blood pressure	108.02 ± 12.13	155.76 ± 13.98	< 0.001
Diastolic blood pressure	64.90 ± 9.27	98.39 ± 9.34	< 0.001
APGAR 1th minute	8.82 ± 0.84	8.35 ± 1.63	< 0.001
APGA 5th minute	9.75 ± 0.82	9.28 ± 1.67	< 0.001

*BMI— Body Mass Index

Table 2. Comparison of laboratory parameters between groups			
	Control n: 257	**Preeclampsia n: 264**	**p**
Blood urea nitrogen (mg/dL)	7.92 ± 2.38	11.28 ± 5.04	< 0.001
Creatinine (mg/dL)	0.66 ± 0.33	0.76 ± 0.24	< 0.001
Aspartate aminotransferase (AST) (U/L)	20.43 ± 6.40	33.61 ± 40.96	< 0.001
Alanine Aminotransferase (ALT) (U/L)	11.19 ± 5.78	24.97 ± 39.00	< 0.001
White blood cel l (WBC) (mcL)	10.82 ± 2.94	11.21 ± 3.30	0.155
Hemoglobine (Hb) (g/dL)	11.46 ± 1.27	11.70 ± 1.44	0.045
Hematocrite (Htc) (%)	34.98 ± 3.36	35.35 ± 4.01	0.257
Platelets (PLT) (mcL)	236.69 ± 64.30	227.22 ± 78.58	0.133
Plateletcrite (PCT) (%)	0.24 ± 0.27	0.21 ± 0.06	0.093
Red cell distribution width (RDW) (%)	15.36 ± 2.50	15.42 ± 2.70	0.813
Platelet distribution width (PDW) (%)	17.29 ± 0.82	17.11 ± 0.80	0.014
Mean platelet volume (MPV) (fL)	8.92 ± 1.33	9.66 ± 1.62	< 0.001
Mean cell volume (MCV) (fL)	83.53 ± 7.16	83.82 ± 7.35	0.651
PLT/MPV	27.63 ± 10.24	24.63 ± 10.90	0.001
PCT/MPV	0.027 ± 0.029	0.02 ± 0.007	0.01

values were not significantly different; only mean platelet volume (MPV) values were significantly higher in the preeclampsia group (9.66 ± 1.62/8.92 ± 1.33; $p < 0.001$).

Also in the preeclampsia group; the Pct/MPV ratio (0.02 ± 0.007 vs 0.027 ± 0.029) (p = 0.01) and the PC/MPV ratio (24.63 ± 10.90 vs 27.63 ± 10.24) (p = 0.001), which were simply calculated using these indices, were observed significantly lower than the control group.

Binary Logistic Regression Analysis

Results of the logistic regression analysis are shown in Table 3. In unadjusted model, increased MPV and BMI, ALT, BUN levels were significantly associated with high odds of having preeclampsia.

Receiver Operating Characteristic (ROC) Curve Analysis

The ROC curve for MPV for predicting the preeclampsia risk is shown in Figure 1. The area under the ROC curves were 0.634 (95% CI 0.587–0.682, p < 0.001) for MPV. The optimal cut-off value of MPV for detecting preeclampsia was ≥ 9.15 ng/mL, at which the sensitivity is 58.7% and specificity is 61.7%.

DISCUSSION

There are two consecutive steps in the pathogenesis of preeclampsia. In the first step, utero-placental arterial blood flow decreases and hypoxia develops due to insufficient invasion of cytotrophoblasts to the uterine wall at the maternofetal junction. Released free oxygen radicals cause placental dysfunction, release of anti-angiogenic factors of proinflammatory cytokines, and activation of neutrophils [9, 10]. In the second step, activated neutrophils infiltrate maternal vascular tissue and PE starts; platelet activation, vasoconstriction, endothelial dysfunction and end-organ ischemia occur [11]. As a result of all this; PE is clinically presented with hypertension, proteinuria, edema, headache, coagulopathy, renal and hepatic dysfunction [9, 12].

MPV is being studied with increasing interest as a potential marker for the prediction of preeclampsia, since it is easily detectable during complete blood count and reflects indirect platelet reactivity. In our study, MPV value was significantly higher in preeclamptic pregnants in the third trimester compared to normotensive pregnants. There are many studies showing that MPV value increases especially in the 2nd and 3rd trimesters in preeclampsia [11, 13–20].

These studies suggest that disruption of the microcirculation in the cascade beginning with endothelial damage in preeclampsia leads to microtrombus formation, and that platelet count decreases with increasing platelet destruction, and the increase in MPV values of younger and larger platelets as a result of stimulation of platelet production in the bone marrow reflects the increase in MPV values. However, in our study; similar to the results of the study in which Dündar and et al. [21], evaluated the platelet parameters longitudinally in preeclamptic and normotensive pregnancies during the course of pregnancy, an increase in MPV was observed without a decrease in platelet count. In preeclamptic pregnants; while the number of platelets does not change, the number of studies advocating an increase in MPV is not small [22, 23]. MPV was found to be high in many cases with vascular risk such as diabetes mellitus, hypercholesterolemia, and acute myocardial infarction that did not associated with thrombocytopenia [24]. In preeclampsia,
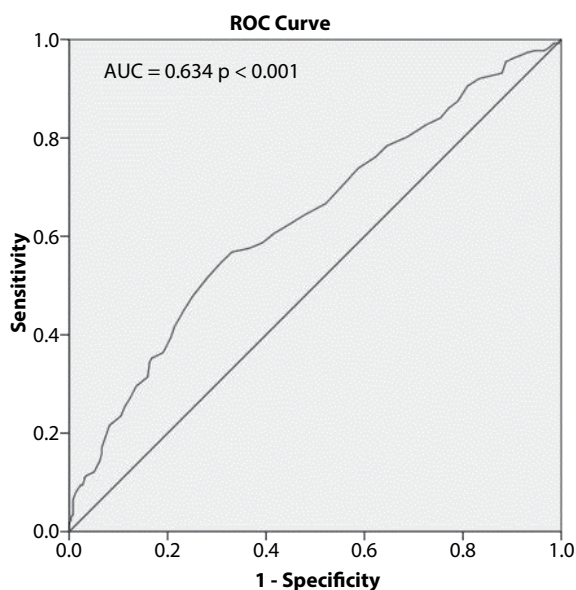
Table 3. Evaluation of the association between of MPV and age, BMI, ALT,BUN in the study population (women with and without preeclampsia) using the Binary logistic regression analysis

	OR	95% CI		p
		lower	upper	
Variables				
Age	1.046	1.011	1.083	0.009
BMI	1.140	1.091	1.191	< 0.001
MPV	1.494	1.275	1.751	< 0.001
ALT	1.074	1.040	1.108	< 0.001
BUN	1.275	1.183	1.374	< 0.001

OR — odds ratio; CI — confidence interval; a p value of < 0.05 was considered significant (*)

Figure 1. Receiver operating characteristic (ROC) curve for MPV for the prediction of preeclampsia. The estimate of the area under the ROC curve and its 95% confidence interval is shown. Cut-off value of MPV was ≥ 9.15 (sensitivity 58.7% and specificity 61.7%) for prediction of preeclampsia. AUC, area under curve. A p value of < 0.05 was considered significant (*)

the interaction between damaged endothelial cells and platelets may disrupt the coagulation process, or large and enzymatically active platelets may have a different role in the pathogenesis of preeclampsia.

To date, the results of studies examining the relationship between preeclampsia and MPV value are conflicting. In addition to numerous studies saying that MPV increases in preeclampsia, there are studies reporting that MPV value decreases [25] or MPV value does not change, and there is no predictive value [5, 26]. Although these differences are related to the analysis method used, the anticoagulant used, the time taken for analysis, factors such as study design and number of patients included may also be effective [7].

In our study, the optimum cut-off value of MPV for preeclampsia prediction was found to be ≥ 9.15 with 58.7% sensitivity and 61.7% specificity (area under the ROC curve 0.634, p < 0.001, 95% Confidence Interval). This value is indicated by Manneerts and his colleagues (16) as 8.15. In the literature, the cut-off values calculated for MPV in preeclampsia prediction ranged between 8.65 and 9.95. [27, 28]

Studies emphasize that platelet indices should not be ignored when evaluating complete blood count. Doğan et al., reported that the risk of developing PE increased by two-fold in patients with platelet counts ≤ 190 * 10^9/L, two-fold in patients with MPV ≥ 9 fL, and 2.4 fold in patients with PC/MPV ratio ≤ 19.9, but stated that changes in platelet indices were not associated with PE severity [17]. AlSheeha et al. [25], reported that in preeclamptic pregnants, platelet count decreased while MPV did not change. In our study, on the contrary, platelet count did not decrease significantly in PE, whereas MPV was found to be significantly higher and ironically, both studies concluded that PC/MPV ratio decreased significantly in preeclampsia.

In our study, the birth weeks of preeclamptic pregnant women, birth weight of infants, and APGAR scores of 1 and 5 minutes were significantly lower. PE is associated with preterm birth and low birth weight [27, 29]. Early recognition should be a primary goal for the prevention of preeclampsia. However, some studies reported that the first trimester MPV value and a meta-analysis showed that the first and second trimester MPV values were not significant in PE prediction [21, 31].

With the MPV value to be evaluated in the third trimester, the follow-up of the pregnants who are predicted to develop PE can be increased and the progression of severe preeclampsia, eclampsia and HELLP with high morbidity and mortality can be reduced and neonatal care conditions can be ensured. The limitations of this study were its retrospective design and non-longitudinal aspect.

CONCLUSIONS

In our study, MPV, one of the parameters of complete blood count, which can be evaluated as easy, fast and inexpensive in every hospital, was found to be increased in preeclampsia. In prenatal follow-up, evaluating MPV value and PC/MPV ratio may be useful in the prediction of preeclampsia.

Prospective, multicenter, large-scale studies are needed to understand the role of platelets in preeclampsia and to reduce maternal and fetal complications.

Conflict of Interest

The authors declare that there are no conflicts of interest

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