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ARAŞTIRMA/RESEARCH

The value of red cell distribution width for predicting subsequent preeclampsia

Eritrosit dağılım genişliğinin sonradan gelişen preeklampsiyi öngörmedeki değeri

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Abstract

Purpose: The purpose of our study was too assess the diagnostic value of red cell distribution width and other inflammatory markers such as white blood cell count and mean platelet volume during the first trimester of gestation for predicting the subsequent development of preeclampsia.

Material and Methods: A retrospective study was performed on 137 patients with preeclampsia and 150 normotensive pregnant women. Study group was assessed for presence of preeclampsia and the values of first trimester red cell distribution width, white blood cell count and mean platelet volume. The receiver operator curve was used to evaluate cut-off, sensitivity and specificity values.

Results: The optimal cut-off points to predict preeclampsia were a white blood cell count 10200 cells/mm3 or higher with a sensitivity of 75.1% and specificity of 44.1%, a mean platelet volume 8.6fL or lower with a sensitivity of 62.5% and specificity of 64.4% and a red cell distribution width 15.3% or lower with a sensitivity of 31.2% and specificity of 79.7%.

Conclusion: Regarding the association between first trimester red cell distribution width, white blood cell count and mean platelet volume, statistical analysis revealed that these markers were weak predictors of preeclampsia.

Key words: Mean platelet volume, preeclampsia, red cell distribution width, white blood cell count

Öz

Amaç: Bu çalışmanın amacı ilk trimester eritrosit dağılım genişliği, lökosit sayısı ve ortalama platelet hacmi gibi inflamatuar markerların sonradan gelişen preeklampsiyi belirlemedeki tanısal değerini belirlemektir.

Gereç ve Yöntem: Preeklampsili 137 hasta ve 150 normal tansiyonlu hasta retrospektif olarak incelendi. Çalışma grubu preeklampsinin varlığına ve ilk trimester eritrosit dağılım genişliği, lökosit sayısı ve ortalama platelet hacmi açısından değerlendirildi. Eşik değeri, sensitivite ve spefisite değerlerini belirmek için ROC eğrisi kullanıldı.

Bulgular: Preeklampsiyi öngörmede lökosit için optimal eşik değeri ≥10200 hücre/mm3, sensitivite %75.1 ve spesifisite %44.1; ortalama platelet hacmi için optimal eşik değeri ≤ 8.6fL, sensitivite %62.5 ve spesifisite %64.4; eritrosit dağılım genişliği için optimal eşikd eğeri %15.3, sensitivite %31.2 ve spesifisite %79.7 olarak belirlendi.

Sonuç: İlk trimester eritrosit dağılım genişliği, ortalama platelet hacmi ve lökosit değerleri preeklampsiyi öngörmede zayıf öngörücü belirteçlerdir.

Anahtar kelimeler: Eritrosit dağılım genişliği, lökosit, ortalama platelet hacmi, preeklampsi

INTRODUCTION

Preeclampsia affects 3-5% of pregnant women[1]. It is one of the common complications of pregnancy which is responsible for 12% of worldwide maternal mortality[1]. It is characterized by new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive pregnant woman[1]. Although the risk factors for preeclampsia such as advanced maternal age, presence of hypertension before pregnancy, diabetes mellitus or obesity, positive self-history or family history of preeclampsia and nulliparity are well-known, the exact pathogenic mechanism is still unclear[2]. On the other hand, many etiological factors including uncontrolled inflammatory changes during

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pregnancy have been proposed to explain the pathological changes in the disease[3].

Massive influx of proinflammatory macrophages and natural killer cells in human decidua in the first trimester are demonstrated as early as 4 weeks of gestation by Sacks et al[4]. Moreover, Faas et al. reported that, single low dose endotoxin administration to rats on the 14th day of gestation resulted in hypertension and proteinuria throughout the gestation, specifically in pregnant rats[5]. The results of these researches gave us the idea that, the initiation of this pathogenic mechanism of preeclampsia in the first trimester can be determined by assessing the systemic inflammatory markers in that period. Predetermined values of these systemic inflammatory markers might have been utilized as the precursors of preeclampsia which may develop in the future.

Recently, red cell distribution width (RDW) is gaining interest as a risk predictor in various clinical circumstances. Elevated RDW is reported to be associated with hypertensive disorders, increased mortality in coronary artery diseases, and in all-cause mortality6. However, predictive value of first trimester RDW in early diagnosis of preeclampsia still remains unclear and has not been analyzed previously in English literature to our knowledge.

The aim of this study was to assess the diagnostic value of inflammatory markers such as RDW, white blood cell (WBC), and mean platelet volume (MPV), during the first trimester of gestation for predicting the subsequent development of PE.

MATERIALS AND METHODS

We performed a retrospective study among 137 pregnant women with a diagnosis of preeclampsia and 150 normotensive pregnant women admitted to a tertiary care center. The study was approved by the Independent Bioethics Committee for Scientific Research of our center and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

The diagnosis of preeclampsia was made in accordance with American College of Obstetrics and Gynecology criteria between 22 to 40 weeks of gestation[7]. One hundred and fifty primigravid women between 38 to 41 weeks, who gave birth to appropriate for gestational age fetuses, were defined as the control group. Patients with previous history of any hematopoietic system disorders, malignancies, systemic diseases, acute or chronic inflammatory diseases, and the patients who were taking any medication that could affect the complete blood cell count (CBC) results were not included in the study. All 287 cases' first trimester (7-14 weeks) CBC were obtained. CBC test was performed at our center using a Coulter LH 750 device (Beckman Coulter, Brea, CA, USA). When more than one CBC results were available, the result which is closest to 7 weeks of gestation was used for statistical analysis.

The following clinical and delivery data of patients were collected from patient medical reports: demographic characteristics, first trimester CBC results, gestational age at the time of diagnosis, the time and type of delivery, gender, birth weight and percentile of the newborn. Fetal weight percentile was calculated by the Hadlock formula and less than 5 percentile was accepted as small for gestational age[8]. Twenty six of the preeclamptic patients' delivery data could not be obtained because of transference to another medical center for various reasons after the initial diagnosis.

Study group was assessed for presence of preeclampsia and the values of first trimester inflammation markers (WBC count, MPV, and RDW values). Statistical analysis was performed using the SPSS software, version 15.0 (Statistical package for social sciences, Inc., Chicago, IL, USA). Collected data was assessed by Student's t-test, Mann–Whitney U-test, Pearson's chi-square test and Kolmogorov–Smirnov test. Relative risks with 95% confidence intervals were calculated. A P value < 0.05 was considered to indicate statistical significance. A receiver operating characteristic (ROC) curve was used to evaluate cut-off, sensitivity and specificity values.

RESULTS

Mean maternal age of the study and control groups were 28.3 years (range, 17–43) and 27.5 years (range, 17–39) respectively. Mean gestational age at the time of initial diagnosis was 34 weeks (range, 22–40) in preeclampsia patients. Female to male ratio were 0.76 and 1.02 respectively in preeclampsia and control groups, which was statistically insignificant ($p = 0.084$). In preeclampsia group 43.4% of the fetuses were small for gestational age. Also gestational age at delivery, birth weight and

percentile values were significantly lower and cesarean delivery rate was significantly higher in preeclampsia group as expected. Table 1 summarizes the clinical characteristics of the study and control groups.

The mean first trimester WBC counts were significantly higher in the preeclampsia group (9990 ± 2440 cells/mm^3) than the control group (8920 ± 2000 cells/mm^3; $p < 0.001$). The mean MPV, and RDW values were significantly lower in the preeclampsia group (8.38 ± 1.12 fL , 14.34 ± 2.75% respectively) than the control group (9.02 ± 1.08 , 15.47 ± 2.57% ; $p < 0.001$, $p = 0.047$). The ROC curve indicated that a first trimester WBC count 10200 cells/mm3 or higher with a sensitivity of 75.1% and specificity of 44.1%, a MPV value 8.6 or lower with a sensitivity of 62.5% and specificity of 64.4% and a RDW value 15.3 or lower with a sensitivity of 31.2% and specificity of 79.7% was optimum for predicting preeclampsia. MPV was found to be the strongest marker for predicting preeclampsia in our study. The ROC findings indicating the utility of MPV, RDW and WBC count as predictive markers of the diagnosis of preeclampsia, are shown in Figure 1 and Table 2.

Table 1. Clinical characteristics of the study groups

Markers	Preeclampsia group (n = 137)	Normotensive group (n = 150)	P value
Maternal age (y)*	28,3 ± 5.98	27.5 ± 5.01	0.226
Gestational age at diagnosis (w)*	34.20 ± 3.85	N/A	N/A
Female to male ratio	48/63(0.76)	76/74(1.02)	0.084
Time of delivery (w)*	35.7 ± 2.95	39.3 ± 1.17	< 0.001
Birth weight (g)*	2297 ± 762	3343 ± 399	< 0.001
Birth percentile*	19.9 ± 26.9	39.73 ± 25.77	< 0.001
Number of gestations*	2.41 ± 1.41	1	N/A
Cesarean delivery rate (%)	92	62	< 0.001
BMI at enrollment*	26.1 ± 3.2	25.7 ± 3.5	0.459
WBC (103/ mm-3)*	9.99 ± 2.44	8.92 ± 2.00	< 0.001
MPV (fL)*	8.38 ± 1.12	9.02 ± 1.08	< 0.001
RDW (%)*	14.34 ± 2.75	15.47 ± 2.57	0.047

*Values are expressed as mean ± standard deviation. BMI, body mass index; MPV, mean platelet volume; RDW, red cell distribution width; WBC, white blood cell count; N/A, not available

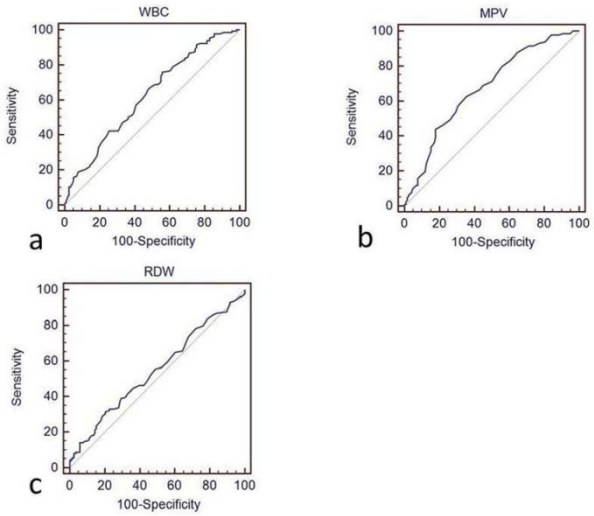

Figure 1. Receiver operating characteristic (ROC) curves for white blood cell (WBC) counts (a), mean platelet volume (MPV) (b), and red cell distribution width (RDW) (c) used to make the clinical decision regarding preeclampsia.

The areas under the ROC were 0.62, 0.67 and 0.54, respectively.

Table 2. Evaluation of the efficacy of RDW, MPV and WBC counts aiding in the clinical diagnosis at preeclampsia.

Markers	Cut off value	Sensitivity	Specificity	Area under the curve	P value
WBC (103/ mm-3)	10.2	75.1	44.1	0.623	<0.001
MPV (fL)	8.6	62.5	64.4	0.672	<0.001
RDW (%)	15.3	31.2	79.7	0.547	0.202

MPV, mean platelet volume; RDW, red cell distribution width; WBC, white blood cell.

DISCUSSION

Several pathogenic mechanisms have been proposed for preeclampsia but the exact reason still remains unknown. In previous publications, altered immune system of the gravid causing excessive maternal inflammation in the first trimester was reported to be responsible for the deficient trophoblastic invasion and poor placentation[9,10]. Therefore, the value of inflammation markers in the first trimester of pregnancy as a sign of excessive inflammation in preeclampsia is needed to be understood.

RDW is a measure of the erythrocyte volume showing the variability in size of the erythrocytes in the circulation6. Shortening of the lives of erythrocytes by defective erythropoiesis, by inflammation or hemolysis, results in elevation of RDW11. Elevated RDW level has been used as a marker for increased systemic inflammation[11]. Recent studies have reported that high RDW level is also associated with non-dipper hypertension, presence and severity of hypertension in non-pregnant people and poor prognosis in various clinical circumstances such as heart failure and coronary artery diseases6. The possible explanation of this correlation was made by accusing chronic inflammation and increased inflammatory activity in these conditions[12]. Although the influence of pregnancy over RDW is unclear, no changes between 16 to 34 weeks of gestation were previously reported[13]. Elevated RDW levels were found to be associated with the presence and severity of preeclampsia, however, the association between RDW in the first trimester and preeclampsia has not been studied widely yet[11].

MPV is also another commonly studied inflammatory marker in the literature, which is a determinant of platelet activity. It was reported as an independent risk factor for hypertension, myocardial infarction, and poor prognosis in cardiovascular disease[14]. Elevated MPV was shown to reflect the severity of inflammatory process in several diseases such as, chronic Hepatitis B, myocardial infarction, rheumatoid arthritis, and cardiovascular disease[16,17]. High MPV was also observed in patients with preeclampsia[2,18].

In addition, altered platelet reactivity was reported before the clinical onset of preeclampsia[19]. It was suggested that the activation of platelets during trophoblast invasion in early pregnancy can differ in preeclamptic patients from normal pregnancies. Therefore, an association between MPV in the first trimester and preeclampsia might be suggested.

The mean RDW and MPV were significantly low in preeclampsia group than the control group in our study, conflicting with the results of previous studies which have performed the CBC test after the diagnosis of preeclampsia[2,11,17]. However, in a study designed similar to ours, Myatt et al. have reported higher first trimester MPV levels in patients who later developed preeclampsia[20]. Their results were also conflicting with our findings.

Kurt et al. and Oylumlu et al. have reported higher WBC counts and neutrophil counts in preeclamptic patients, implying that there is an increased inflammatory state[11,18]. The relation between increased WBC and preeclampsia has been explained by increased inflammation in these patients. In this report, we detected elevated WBC counts in patients with preeclampsia also at the first trimester. However, contrary to our findings Myatt et al. have reported no significant difference in first trimester WBC count in patients who later developed preeclampsia[20]. The limitation of our study is the small population size and retrospective design. We did not evaluate all possible etiologies leading to alterations in serum markers due to missing data. However, our study was not designed to provide a pathophysiological explanation of preeclampsia. Despite the limitations, this is the first study in the literature evaluating the predictive value of RDW in the first trimester of gestation for subsequent development of preeclampsia.

In conclusion, although the mean first trimester WBC, MPV, and RDW values were significantly different in the preeclampsia group compared with the control group and MPV was the strongest marker, the ROC analysis revealed that these markers were weak predictors of preeclampsia to be used in clinical practice. There is a need for further studies in order to completely understand the relationship between RDW, and future preeclampsia, and to explain the contradiction between the results of our study and previous literature.

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