Could red cell distribution width in the first trimester be used to predict preeclampsia?

Abstract

Aim: It has been reported that red cell distribution width (RDW) and hypertension are somehow related, but there is no well-established evidence about the probable relationship between RDW and preeclampsia. The present study aimed to determine whether RDW in the first trimester can be used to predict the presence and severity of preeclampsia. Material and Method: This is a retrospective review of 57 healthy pregnant women, 42 women with mild preeclampsia, and 18 women with severe preeclampsia who delivered at the study center. These three groups were compared with respect to complete blood count parameters obtained during the first trimester. Results: When compared with the control group, systolic blood pressure, diastolic blood pressure, leukocyte count, RDW, blood urea nitrogen, and proteinuria were significantly higher in the severe preeclampsia group (respectively p<0.001, p<0.001, p=0.036, p<0.001, p<0.001, and p<0.001). The median RDW values of control, mild, and severe preeclampsia groups were 12.51% (range: 10.6-15.02%), 13.2% (range: 10.45-15.5%), and 13.7% (range: 11.9%-14.7%). RDW was significantly higher in the severe preeclampsia group than in the control group (p<0.001) and mild preeclampsia group (p<0.001). However, mild preeclampsia and control groups had statistically similar RDW values (p>0.05). Discussion: Increased RDW in the first trimester can be utilized to predict severe preeclampsia, but RDW values do not seem to correlate with the severity of preeclampsia.

Keywords

Preeclampsia; Pregnancy; Red Cell Distribution Width
Preeclampsia and red cell distribution width

Introduction
Preeclampsia is one of the most common medical complications of pregnancy, with a reported incidence between 2 and 8 percent [1, 2]. Preeclampsia traditionally refers to high blood pressure (BP) and proteinuria which appears after the 20th gestational week. This complication is frequently associated with both maternal and fetal morbidity, and even mortality [3, 4]. Preeclampsia is thought to be caused by inadequate placental cytotrophoblast invasion, followed by widespread maternal endothelial dysfunction [4]. Research has demonstrated that excess quantities of the antiangiogenic factors soluble fms-like tyrosine kinase 1 and soluble endoglin are released by the placenta into maternal blood, causing widespread endothelial dysfunction which results in clinical manifestations of preeclampsia [5]. Additionally, disruption of the renin–aldosterone–angiotensin II axis, increased oxidative stress, hypoxia, inflammation, impairment of immune adaptation, and genetic susceptibility may all contribute to the pathogenesis of preeclampsia [6].

Red cell distribution width (RDW) is one of the parameters in the standard complete blood count [7]. This parameter shows the heterogeneity in erythrocyte volume (anisocytosis) and, thus, it is conventionally used to differentiate microcytic anemias including iron deficiency anemia, thalassemia, and other hemoglobinopathies [8]. However, recent studies have reported that RDW is increased in hypertension [9], atherosclerosis [9], ischemic cardiac diseases [10], acute and chronic cardiac failure [11], inflammatory bowel diseases, [12] and prostate cancer [13]. Although the exact mechanism behind this relationship has not been clarified, high RDW levels are believed to reflect an inflammatory process [14].

It has been reported that RDW and hypertension are somehow related, but there is no well-established evidence about the probable relationship between RDW and preeclampsia. The present study aimed to determine whether RDW in the first trimester can be used to predict the presence and severity of preeclampsia.

Materials and Method
This retrospective case-control study was approved by the Institutional Review Board and Ethical Committee of Gaziosmanpasa University Hospital.

Study Design and Participants
This is a retrospective review of 117 women with singleton pregnancy who delivered at the study center between January 2011 and January 2015. The participants were categorized into control group (n=57), mild preeclampsia group (n=42), and severe preeclampsia group (n=18). The control group was carefully chosen so that the age, gravidity, parity and gestational age of the control and preeclampsia groups could be matched. Mild preeclampsia was defined as the onset of hypertension occurring after 20 weeks of gestation in a woman whose BP has been previously normal (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg on two occasions at least 6 hours apart) and consistent proteinuria (>1 + by dipstick or >300 mg/24 hour).

Severe preeclampsia was defined as a BP greater than or equal to 160/110 mmHg. Eclampsia, pulmonary edema, increased serum creatinine and transaminases, oliguria (<500ml/24 hour), significant fetal growth restriction, and symptoms suggestive of significant end-organ involvement (headache and visual disturbance) were accepted as other findings of the severe disease.

The women with underlying diseases (chronic hypertension, metabolic syndrome, malignancies, endocrinopathies, as well as cardiovascular, hematological, inflammatory, renal and hepatic diseases) and the women with high risk pregnancies (multiple gestation, perinatal infections, premature rupture of membranes, and polyhydramnios) were excluded.

The women in the control and preeclampsia groups were compared with respect to the complete blood count parameters that were specified within the first trimester of pregnancy. Complete blood count was performed by means of an automated commercial counter in the study center (Coulter LH 780 Hematology Analyzer, Beckman Coulter Inc., Brea, CA, USA).

Statistical Analysis
Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (range: minimum-maximum) or median (interquartile range) whereas categorical variables were denoted as numbers or percentages where appropriate. Smirnov-Kolmogorov test was used to test the distribution of variables. One-way analysis of variance test, Kruskal-Wallis test, Tukey HSD test, and Tamhane’s T2 test were used for comparisons. Two-tailed p values less than 0.05 were considered as statistically significant.

Results
Table 1 demonstrates the clinical and biochemical characteristics of the control, mild, and severe preeclampsia groups. These three groups were statistically similar with respect to maternal age, gestational age at delivery, gravidity, parity, miscarriage number, hemoglobin, platelet count, neutrophil/lymphocyte ratio, and creatinine (p=0.101, p=0.097, p=0.462, p=0.550, p=0.232, p=0.837, p=0.163, p=0.677, and p=0.701 respectively). When compared with the control group, systolic blood pressure, diastolic blood pressure, leukocyte count, RDW, blood urea nitrogen, and proteinuria were significantly higher in the severe preeclampsia group (respectively p<0.001, p<0.001, p=0.036, p<0.001, p<0.001, and p<0.001). The median RDW values of control, mild and severe preeclampsia groups were 12.51% (range: 10.6-15.02%), 15.2% (range: 10.45-15.5%) and 13.7% (range: 11.9%-14.7%). RDW was significantly higher in the severe preeclampsia group than in the control group (p<0.001) and mild preeclampsia group (p=0.001). However, mild preeclampsia and control groups had statistically similar RDW values (p=0.05) (Figure 1).

Figure 2 shows that leukocyte count in the severe preeclampsia group was significantly higher than that of the control and mild preeclampsia groups (p=0.036). A statistically insignificant positive correlation was found between the leukocyte and RDW values of the participants (r=0.101, p=0.281, Figure 3).

Discussion
The control, mild, and severe preeclampsia groups were statistically similar with respect to maternal age, gestational age,
Preeclampsia and red cell distribution width

Gravidity, parity, hemoglobin, platelet count, creatinine, and neutrophil/lymphocyte ratio. The blood pressures, leukocyte count, RDW, blood urea nitrogen, and proteinuria were significantly higher in the severe preeclampsia group than the control group. However, mild preeclampsia and control groups had statistically similar RDW values. A weak positive correlation was also found between the leukocyte and RDW values of the participants.

Preeclampsia is a two-stage disease [15]. Stage 1 corresponds to the first and second trimesters of a pregnancy [15, 16]. At stage 1, genetic factors, immunological abnormalities (natural killer cell/human leukocyte antigen-C axis), and other factors such as oxidative stress and inflammation cause abnormal placentation and reduced placental perfusion which leads to chronic placental dysfunction [16]. At stage 2, this chronic placental dysfunction suppresses the release of angiogenic factors and triggers the release of anti-angiogenic factors and other inflammatory mediators [17]. When combined with other maternal factors (i.e., preexisting poor vascular health, obesity, smoking), stage 2 is enhanced [18].

RDW values were found to correlate with the severity of cardiovascular diseases [11, 19]. As for the pathogenesis of preeclampsia, the accumulation of fibrinoid material and foam cells in the spiral arteries disrupts blood flow, reduces placental perfusion and causes placental hypoxia [20]. Troeger et al. observed that the combination of placental hypoxia and enhanced inflammatory reactions stimulates erythropoiesis in preeclamptic women [6]. As a result, neutrophils, monocytes, and macrophages synthesize free oxygen

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild preeclampsia</td>
<td>Severe preeclampsia</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>29.95±5.81</td>
<td>31.22±6.48</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>141.9±3.97</td>
<td>164.45±10.43</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>92.26±6.07</td>
<td>102.22±5.48</td>
</tr>
<tr>
<td>Gestational age at delivery, weeks</td>
<td>34.2±3.27</td>
<td>32.94±4.02</td>
</tr>
<tr>
<td>Gravidaity</td>
<td>2.52±1.23</td>
<td>3.06±2.29</td>
</tr>
<tr>
<td>Parity</td>
<td>1.31±1.02</td>
<td>1.83±2.26</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>0.21±0.47</td>
<td>0.28±0.46</td>
</tr>
<tr>
<td>Red cell distribution width, %</td>
<td>11.99±3.69</td>
<td>13.54±4.18</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>12.7±1.29</td>
<td>12.79±0.96</td>
</tr>
<tr>
<td>Platelets, x10^3/µL</td>
<td>205.26±66.97</td>
<td>173.72±53.41</td>
</tr>
<tr>
<td>Red cell distribution width, %</td>
<td>13.15±1.65</td>
<td>14.57±1.77</td>
</tr>
<tr>
<td>Neutrophil/Lymphocyte</td>
<td>4.97±4.35</td>
<td>6.07±4.42</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dl</td>
<td>10.41±4.80</td>
<td>12.7±4.55</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.66±0.22</td>
<td>0.64±0.16</td>
</tr>
<tr>
<td>Proteinuria, g/dl</td>
<td>427[300-1012]</td>
<td>1008[284.35-456.8]</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or median [interquartile range].

*Different letters (a,b,c) in the same row (ANOVA) indicate a statistically significant difference (p<0.05).

Figure 1. Red cell distribution widths in the mild preeclampsia, severe preeclampsia and control groups.

Figure 2. White blood cell counts in the mild preeclampsia, severe preeclampsia and control groups.
increased significantly after the 34th week of gestation until that RDW was a risk factor for PHD (odds ratio 2.683; 95). The national hypertension and 70 healthy pregnant women showed later, a logistic regression analysis of 149 women with gestational hypertension and 50 healthy pregnant women [24].

Kurt et al. were the first to compare the RDW values of normal and preeclamptic pregnant women [23]. Although they were unable to detect a significant difference between RDW values of 52 pregnant women with preeclampsia and 50 healthy pregnant women, they reported that RDW levels were significantly higher in patients with severe preeclampsia than in patients with mild preeclampsia [23]. On the contrary, a Sudan study concluded that there was no association between RDW values and the presence and severity of preeclampsia in a cohort of 65 healthy pregnant women and 65 preeclamptic women [24].

Later, a logistic regression analysis of 149 women with gestational hypertension and 70 healthy pregnant women showed that RDW was a risk factor for PHD (odds ratio 2.683; 95), the optimal RDW-CV threshold was 14.1% to predict gestational hypertension with a sensitivity of 72.5% and specificity of 78% [22]. Yilmaz et al. compared 118 women with preeclampsia and 120 healthy pregnant women and found that RDW values were significantly higher in the preeclampsia group than the control group and RDW values were significantly higher in the severe preeclampsia group than the mild preeclampsia group [25].

The findings of this study suggest that increased RDW in the first trimester can be utilized to predict severe preeclampsia. This relationship between RDW and preeclampsia can be attributed to an augmentation in inflammatory response [26, 27]. As shown by the increase in tumor necrosis factor alpha and interleukin-6 levels of preeclamptic women, there is a close relationship between enhanced inflammation and pathogenesis of preeclampsia [26]. In case of inflammation, RDW levels increase, possibly due to increased destruction of the red blood cells in the liver, impaired erythropoietin response, and changes in iron metabolism [27]. Moreover, it has been designated that inflammatory cytokines inhibit red blood cell maturation, direct immature erythrocytes to enter into the circulation, and, thus, cause anisocytosis [28]. The determination of a weak positive correlation between leukocyte counts and RDW values in this study can be interpreted as evidence for the probable relationship between enhanced inflammation and anisocytosis in preeclampsia. However, the power of these findings is limited by its retrospective design, small cohort size, and lack of longitudinal data. Further research is warranted to determine the predictive power of first trimester RDW and understand the probable role of RDW in the pathogenesis of preeclampsia.

**Scientific Responsibility Statement**

The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

**Animal and human rights statement**

All procedures performed in this study 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. No animal or human studies were carried out by the authors for this article.

**Funding: None**

**Conflict of interest**

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

**References**


How to cite this article: