

# The role of the first trimester inflammation markers at early and late preeclampsia

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#### Abstract

**Objective:** Our aim was to compare the difference between the levels of first trimester neutrophil/lymphocyte rate (NLR), platelet/lymphocyte rate (PLR), red blood distribution width (RDW), mean platelet volume (MPV) in patients developing early-onset or late-onset preeclampsia during their pregnancies.

**Methods:** In our clinic, 118 patients diagnosed as preeclampsia were evaluated retrospectively. The patients were separated into two groups as early-onset and late-onset preeclampsia. First trimester laboratory data were collected and the two groups were evaluated in terms of inflammation markers.

**Results:** No significant difference was found among two groups in terms of inflammation markers. Birth week, mean birth weight and mean newborn percentile values  $(33.12\pm3.05 \text{ weeks}, 1703\pm640 \text{ g}$  and  $11.15\pm15.54$  percentile, respectively) of early precelampsia group were found to be significantly lower than the late preeclampsia group  $(37.42\pm1.50 \text{ weeks}, 2760\pm580 \text{ g}$  and  $29.16\pm30.36$  percentile, respectively; p<0.001, p<0.001, p=0.002). The rate for delivery by cesarean section and the incidence for baby with growth retardation in the early preeclampsia group (100% and 64%, respectively) was significantly higher than the late preeclampsia group (86% and 37%, respectively; p=0.024, p=0.018).

**Conclusion:** High rate of growth retardation in early preeclampsia brings to mind that a placental pathology has a significant role in this group. We found no difference when we evaluate the systemic reflection of this pathology in terms of the inflammation markers in early weeks of gestation.

Keywords: Inflammation, preeclampsia, platelet, neutrophil/lymphocyte rate, platelet/lymphocyte rate.

## Özet: Erken ve geç preeklampside birinci trimester inflamasyon belirteçlerinin yeri

Amaç: Çalışmamızda gebeliğinde erken başlangıçlı veya geç başlangıçlı preeklampsi gelişen hastaların birinci trimester nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR), eritrosit dağılım genişliği (RDW) ve ortalama trombosit hacmi (MPV) düzeyleri arasındaki farkın karşılaştırılması amaçlanmıştır.

**Yöntem:** Kliniğimizde preeklampsi tanısı almış 118 hasta retrospektif olarak değerlendirildi. Hastalar erken başlangıçlı ve geç başlangıçlı preeklampsi olarak iki gruba ayrıldı. Birinci trimester laboratuvar verileri toplandı ve iki grup inflamasyon belirteçleri açısından incelendi.

**Bulgular:** Her iki grup arasında inflamasyon belirteçleri açısından anlamlı fark saptanmadı. Erken preeklampsi grubunda doğum haftası, ortalama doğum kilosu ve ortalama yenidoğan persantil değerleri (sırasıyla 33.12 $\pm$ 3.05 hafta, 1703 $\pm$ 640 gram ve 11.15 $\pm$ 15.54 persantil) geç preeklampsi grubuna göre anlamlı derecede düşük saptandı (sırasıyla 37.42 $\pm$ 1.50 hafta, 2760 $\pm$ 580 gram ve 29.16 $\pm$ 30.36 persantil; p<0.001, p<0.001, p=0.002). Erken preeklampsi grubunda sezaryen ile doğum oranı ve gelişme geriliği olan bebek sıklığı ise (sırasıyla %100 ve %64) geç preeklampsi grubuna göre anlamlı derecede fazla bulundu (sırasıyla %86 ve %37; p=0.024, p=0.018).

**Sonuç:** Erken preeklampside gelişme geriliği sıklığının daha fazla olması plasental bir patolojinin bu grupta daha ön planda olduğunu düşündürmektedir. Biz bu patolojinin sistemik yansımasını erken gebelik haftalarındaki inflamasyon belirteçleri açısından değerlendirdiğimizde herhangi bir fark saptayamadık.

Anahtar sözcükler: İnflamasyon, preeklampsi, trombosit, nötrofil/lenfosit oranı, trombosit/lenfosit oranı.

### Introduction

Preeclampsia (PE) is a disease characterized by hypertension (HT) appearing after 20 weeks of gestation in a pregnant women known to be previously normotensive and by accompanying proteinuria.<sup>[1]</sup> This disease seen in 3-5% of pregnancies is responsible for 12% of maternal

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Received: January 24, 2014; Accepted: April 30, 2014

Available online at: www.perinataljournal.com/20140223003 doi:10.2399/prn.14.0223003 QR (Quick Response) Code:



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mortality seen worldwide.<sup>[1,2]</sup> When the appearance of the disease findings before 34 weeks of gestation is defined as early-onset PE, detecting them after 34 weeks of gestation is defined as late-onset PE.<sup>[3]</sup>

Many pathological mechanisms have been asserted in order to explain preeclampsia. It was reported in the literature that defective trophoblastic invasion at first trimester caused PE.<sup>[4]</sup> Another mechanism suggested is that the changes in the immune system of pregnant woman causes improper placentation due to increased inflammatory response and as a result, increase in permeability, microvascular thrombosis and increase in vascular tone.<sup>[4,5]</sup> In a study carried out on the rats, HT and proteinuria appeared only in the pregnant rats which were administered low dose endotoxin on the 14th day of pregnancy.<sup>[6]</sup> This is significant for showing us that an inflammatory reaction during implantation and placentation may result with PE at further periods.

Inflammation has a role in HT pathogenesis seen non-pregnant patients, and in the onset and progression of cardiovascular system diseases (CVD).<sup>[7-9]</sup> Preeclampsia defined also as gestational proteinuric HT having similar characteristics with CVD which appears in non-pregnant patients brings to mind that both diseases may have a common pathological process based on increased systemic inflammation.<sup>[10]</sup> In practice, the level of systemic inflammation in these diseases can be easily evaluated by using some blood parameters or formulas.

Recently, the studies carried out on the markers shows systemic inflammation such which neutrophil/lymphocyte rate (NLR), platelet/lymphocyte rate (PLR) and red blood distribution width (RDW), and can be easily obtained by a simple full blood count (hemogram) have been drawn attention. It has been reported in these studies that high NLR is associated with increased cardiovascular risk and increased mortality in some malignancies.<sup>[7,11]</sup> PLR and mean platelet volume (MPV) which is an indicator of increased platelet activation were found to be associated with the onset and progression of atherosclerosis.<sup>[7,11]</sup> RDW was found to be associated with severity and presence of hypertension in non-pregnant patients and also with non-dipper hypertension.<sup>[12,13]</sup> There is limited number of studies in the literature researching PE patients for the first trimester level of NLR, PLR and RDW which are considered as the indicators of systemic inflammation and widely used clinically. In our study, it was aimed to compare the difference between first trimester NLR, PLR, MPV and RDW levels of the pregnant women diagnosed to have early and late preeclampsia.

#### Methods

One hundred and eighteen patients established with preeclampsia diagnosis at the Perinatology Department of Tepecik Training and Research Hospital between January 2010 and January 2013 were included in our study. The diagnosis of preeclampsia was established according to the criteria of 'American College of Obstetrics and Gynecology<sup>,[14]</sup> All PE patients diagnosed were between 22 and 40 weeks of gestation and those diagnosed before 34 weeks were grouped as early preeclampsia and those diagnosed at or after 34 weeks were grouped as late preeclampsia. First trimester (7-14 weeks) hemogram values of all patients were screened and if there was more than one hemogram result, the values closest to the 7 weeks were accepted. When accessing delivery data of 92 patients, the data of 26 patients could not be reached since they delivered at an external center.

Patients which had any systemic disorder, acute or chronic inflammatory disease, any hematopoietic system disease history, malignancy history or any drug use that may affect blood condition were excluded from the study.

Demographic data, first trimester hemogram values, diagnosis week, delivery type of patients and sex, birth weight and percentile information of newborns were obtained by reviewing patient records retrospectively.

Coulter LH 750 device (Beckman Coulter, Brea, CA, USA) was used in the laboratory of our full blood count center. Neutrophil/lymphocyte rate was calculated by dividing absolute neutrophil by absolute lymphocyte number and PLR was calculated by dividing absolute platelet number by absolute lymphocyte number. Fetal percentile values were calculated by using Hadlock formula, and the values below 5 percentile were considered as small for gestational age (SGA).<sup>[15]</sup>

The study group was evaluated in terms of the first trimester inflammation markers between early and late PE groups. The statistical analysis of data was done by using SPSS software, version 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were given as mean± standard deviation (SD). In the comparison of both groups, Mann-Whitney U and  $\chi^2$  tests were used. For all tests, p<0.05 was considered statistically significant.

#### Results

Of 118 preeclampsia patients included in our study, 43 patients had early preeclampsia diagnosis and 75 patients

	Early PE group (n=43)	Late PE group (n=75)	p value
Maternal age (y)*	28.7±6.37	28.6±5.76	0.868
Pregnancy number*	2.34±1.41	2.51±1.49	0.595
Diagnosis week (w)*	29.57±2.62	36.69±1.55	<0.001
Duration between diagnosis and delivery (d)	14.05±20.07	3.43±6.98	<0.001
Delivery week (w)*	33.12±3.05	37.42±1.50	<0.001
Birth weight (g)*	1703±640	2760±580	<0.001
Percentile*	11.15±15.54	29.16±30.36	0.002
SGA rate	22/34 (0.64)	22/58 (0.37)	0.018
Cesarean section rate (%)	100	86	0.024
Female-male ratio	16/18 (0.88)	22/36 (0.61)	0.511

Table 1. The comparison of the general characteristics of the study group.

\*The values have been given as mean±standard deviation. y: year; w: week; d: day; g: gram.

had late preeclampsia diagnosis. The comparison of general characteristics of both groups is shown in the Table 1. While mean age value of early preeclampsia was 28.7 (range: 18-41), it was 28.6 (range: 17-43) in the late preeclampsia group. There was no difference between two groups in terms of age, pregnancy number and baby gender (p=0.868, p=0.595 and p=0.511, respectively). The diagnosis weeks of early and late preeclampsia groups were found as 29.57±2.62 and 36.69±1.55, respectively. Birth week, mean birth weight and mean newborn percentile values (33.12±3.05 weeks, 1703±640 g and 11.15±15.54 percentile, respectively) of early preeclampsia group were found to be significantly lower than the late preeclampsia group (37.42±1.50 weeks, 2760±580 g and 29.16±30.36 percentile, respectively; p<0.001, p<0.001, p=0.002). The rate for delivery by cesarean section and the incidence for SGA baby in the early preeclampsia group (100% and 64%, respectively) was significantly higher than the late preeclampsia group (86% and 37%, respectively; p=0.024, p=0.018). In terms of the duration between diagnosis and delivery, it was seen that the patients in early preeclampsia group was followed up for a longer period and that the period was significantly shorter in late preeclampsia group  $(14.05\pm20.07 \text{ days and } 3.43\pm6.98 \text{ days, respectively; } p<0.001).$ 

When the patients were evaluated in terms of first trimester inflammation markers, mean white blood cell count (WBC), MPV, neutrophil, lymphocyte and platelet values were higher in early preeclampsia group; however, there was no significant difference compared to late preeclampsia group (p=0.792, p=0.678, p=0.954, p=0.689, and p=0.896, respectively). NLR, PLR and RDW as other inflammation markers were lower in early preeclampsia group; however, there was also no significant difference compared to late preeclampsia group; however, there was also no significant difference compared to late preeclampsia group; however, there was also no significant difference compared to late preeclampsia group (p=0.608, p=0.637, and p=0.498, respectively). The comparison of inflammation markers of both groups is shown in the **Table 2**.

#### Discussion

It is seen that early- and late-onset preeclampsia differ by at some points in terms of clinical outcomes. It was reported that the newborns in early preeclampsia were shorter and weak, and the newborns in late preeclampsia

Table 2. The comparison of inflammation markers in early- and late-onset preeclampsia groups.

Marker*	Early PE group (n=43)	Late PE group (n=75)	p value
WBC (10 <sup>3</sup> / mm <sup>-3</sup> )	10.07±2.62	9.94±2.27	0.792
Neutrophil (10 <sup>3</sup> / mm <sup>-3</sup> )	7.01±2.40	6.99±1.81	0.954
Lymphocyte (10 <sup>3</sup> / mm <sup>-3</sup> )	2.22±0.58	2.17±0.67	0.689
Platelet (10 <sup>3</sup> / mm <sup>-3</sup> )	258.28±62.34	256.77±58.34	0.896
RDW (%)	14.11±1.86	14.47±3.15	0.498
MPV (fL)	8.44±0.97	8.35±1.20	0.678
NLR	3.31±1.22	3.42±1.04	0.608
PLR	123.19±39.38	126.91±41.91	0.637

\*The values have been given as mean±standard deviation.

might be weak as well as overweight.<sup>[16]</sup> Both diseases having two different presentations in terms of fetal growth and early preeclampsia causing more apparent placental failure bring to mind that there may be some difference during implantation and placentation process.

It has been shown that some pathologies occurring during placentation and implantation processes in pregnant women cause changes in maternal peripheral blood values. Tzur et al. found in their studies that preeclamptic patients had higher first trimester platelet levels.<sup>[17]</sup> This may associate with placental hypoxia increasing erythropoietin secretion and stimulating bone marrow and causing increase in megakaryocytes and platelets.<sup>[18]</sup> Also, when preeclamptic and non-preeclamptic patients were compared in terms of platelet activation at early pregnancy period, it was seen that there was difference between two groups.<sup>[19]</sup> It was shown that the platelets were active before preeclampsia begins clinically, and platelet activation was defined as an early marker for preeclampsia.[19-21] Another indicator of platelet activation is the MPV value in full blood count.<sup>[22]</sup> Mean platelet volume also reflects inflammation and it was shown that it increases in chronic inflammatory diseases.<sup>[22]</sup> Also, high MPV value is independent risk factor for hypertension and myocardial infarction and it is a poor prognosis marker for CVD.<sup>[23,24]</sup> There are controversial results in the studies researching the value of mean platelet volume for predicting preeclampsia.<sup>[22]</sup> In the study of Altinbas et al., it was expressed that MPV is insufficient to predict the development and severity of preeclampsia; in another study, higher MPV values were found in the preeclampsia group compared to the control group.  $^{\scriptscriptstyle [22,25]}$ 

NLR and PLR values though to be indicating systemic inflammation were studied in many diseases. It was reported that high NLP and PLR values indicate increased inflammation and associate with worsening renal functions in diabetic patients, increased mortality in malignancy patients and poor prognosis in CVD patients.<sup>[7,11,26,27]</sup> Increased neutrophil number in high NLR value is associated with increased inflammation and low lymphocyte number is associated with impairment in general health condition, increased cortisol levels and increased apoptosis due to physiological stress.<sup>[17,28]</sup> High NLR and PLR values were also found in non-dipper hypertension seen together with end organ damage and cardiovascular mortality.<sup>[29]</sup> Organ damage in non-dipper hypertension depends on hypertension causing endothelial damage as in preeclampsia.<sup>[29]</sup> There is limited number of studies on NLR and PLR in preeclampsia, and their results are controversial. Kurt et al. compared NLR

in preeclampsia and control groups and also in severe and mild preeclampsia groups, but they could not find a significant difference; however, in the recent study made by Oylumlu et al., NLR was found to be significantly higher in preeclampsia group compared to the control group.<sup>[25,30]</sup>

RDW, another marker used in clinic, is a parameter showing the distribution of red blood cell volume in hemogram examinations. RDW values increase as a result of defective erythropoiesis, increased inflammation or hemolysis.<sup>[30,31]</sup> There are many conditions except anemia that red blood distribution width is associated clinically. Increased RDW values are associated with the presence and severity of hypertension and non-dipper hypertension.<sup>[12,13]</sup> It has also relationship with poor prognosis in cardiac diseases, cardiac failure and myocardial infarction, and it is considered that this relationship is related with chronic inflammation and increased inflammatory activity.<sup>[30,32]</sup> In pregnant women, RDW does not change much and remains stable between 16 and 34 weeks of gestation.<sup>[32]</sup> In the study of Kurt et al. which is one of the rare publications analyzing RDW level in preeclampsia, the authors found RDW levels higher in preeclamptic pregnant women, particularly in severe preeclamptic pregnant women, and expressed that this may be associated with increased inflammation.<sup>[30]</sup>

When we compared the data of the patients, we found that the incidence of SGA newborn was higher in early preeclampsia group. This condition which is also consistent with the literature shows that the pathology in early preeclampsia group causes more placental damage. No significant difference was found between two groups when evaluating early and late preeclampsia groups in terms of first trimester NLR, PLR, RDW and MPV. Although this seems to be inconsistent with the literature, analyzing the values at the week when preeclampsia diagnosis is established more than the first trimester values of the patients in other studies may explain this difference. While our results show that there is no difference between two groups in terms of systemic inflammation at first trimester, excluding normotensive control group from the study as a limitation as well does not show that there is no inflammation increase at first trimester generally in preeclampsia. For more clarification, more randomized prospective studies are required.

#### Conclusion

High rate of SGA in early preeclampsia brings to mind that a placental pathology has a significant role in this group. Not observing the systemic reflection of this pathology in inflammation markers of early weeks of gestation brings to mind that there are other factors not reflected in the blood values.

Conflicts of Interest: No conflicts declared.

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