



# The role of hematological and biochemical markers in preeclampsia prediction

## Preeklampsi öngörüsünde hematolojik ve biyokimyasal belirteçlerin rolü

Prediction of preeclampsia with analysis of blood tests

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### Öz

**Giriş:** Bu çalışmanın amacı; erken gebelik dönemindeki tam kan sayımı parametrelerinin ve ilk trimester trizomi taraması sırasında bakılan biyokimyasal parametrelerin erken başlangıçlı preeklampsiyi tespit edip etmeyeceğinin araştırılmasıdır. **Gereç ve Yöntem:** Çalışmadaki 1. Grup, 18-40 yaşındaki tekil gebeliği olan ve 34. gebelik haftasından önce preeklampsi tanısı alıp 37. hafta ve sonrasında doğum yapan 214 hastadan oluşmaktaydı. Kontrol grubunu 2. grup oluşturdu. Yardımcı üreme teknikleriyle gebe kalanlar, vücut kitle indeksi >30kg/m<sup>2</sup> olanlar, kromozomal anomalili gebeliğe sahip olanlar, medikal problemi ya da öyküsü olanlar, çoğul gebelikler, antenatal dönemde vajinal kanaması olanlar ve erken doğum öyküsü olanlar çalışma dışı bırakıldı. Preeklampsi, sistolik kan basıncı 140 mmHg ve üstü, diyastolik kan basıncı 90 mmHg ve üstü hesaplanan ve 20. gebelik haftasından sonra proteinürisi olan gebelikleri tanımlamaktaydı. Tam kan sayımı, PAPP-A ve serbest beta-HCG için kan örnekleri 11+0 ile 13+6 gebelik haftaları arasında alındı. **Bulgular:** Doğumdaki gebelik haftası ve doğum ağırlıkları 1. grupta anlamlı olarak daha düşük bulundu. Nötrofil lenfosit oranı ve trombosit dağılım genişliği preeklampsi grubunda daha yüksek bulundu. Buna karşın lenfosit sayısı ve PAPP-A düzeyi preeklampsi grubunda daha düşüktü. **Tartışma:** Mevcut gebelikteki, nötrofil lenfosit oranı ve trombosit dağılım genişliğinin yüksek seviyeleri ve lenfosit sayısı ve PAPP-A'nın düşük seviyeleri ile erken başlangıçlı preeklampsi arasında güçlü bir bağlantı olduğu sonucuna ulaştık.

### Anahtar Kelimeler

Gebelik; Preeklampsi; Tarama Testleri; Trombosit; Biyokimyasal Sonuçlar

### Abstract

**Aim:** To investigate whether complete blood count parameters of early pregnancy or biochemical markers of first-trimester trisomy screening were related to the prediction of early onset preeclampsia. **Material and Method:** Group 1 (n=214) was composed of patients between 18-40 years old with a single pregnancy who was diagnosed with preeclampsia at <34 gestational weeks and had delivery at ≥37 weeks of gestation. Group 2 (n=240) was a control. Women who became pregnant by assisted reproductive technologies or had a body mass index (BMI) >30kg/m<sup>2</sup>, had a history of delivery complicated by chromosomal anomalies, current or previous medical problems, or multiple pregnancies and patients who had vaginal bleeding in the antenatal period or a history of preterm delivery were excluded. Preeclampsia for pregnancy is defined as having a systolic blood pressure ≥140 and diastolic blood pressure ≥90 as well proteinuria after the 20th gestational week. Blood samples for complete blood count, PAPP-A, and free beta-HCG were collected between 11+0 to 13+6 gestational weeks. **Results:** The mean gestational weeks at delivery and birth weight were significantly lower in Group 1 (preeclampsia) than in Group 2 (control). NRL and PDW were found significantly higher in Group 1. Lymphocyte count was significantly lower in Group 1. PAPP-A was lower in Group 1. **Discussion:** We found a strong relation between high levels of NLR and PDW, as well as low levels of lymphocyte count and PAPP-A, with early onset preeclampsia development during the current pregnancy.

### Keywords

Pregnancy; Preeclampsia; Screening Tests; Platelets; Biochemical Results

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## Introduction

Preeclampsia affects approximately 6-8% of pregnancies [1]. It is one of the most fatal events seen during pregnancy, it presents with hypertension (systolic blood pressure  $\geq 140$  and diastolic blood pressure  $\geq 90$ ) and proteinuria ( $\geq 300$  mg/24 hours or 1+ persistent by dipstick) that may arise from early weeks of pregnancy (but generally after the 20th gestational week); it has a high morbidity and mortality rate [2]. While numerous factors have been accused as contributors to the disease, still the pathogenesis is not clear, and therefore early prediction is impossible [3]. Pathologic trophoblastic invasion of maternal vessels causes impairments in placental perfusion, thereby damaging the maternal endothelial cells and destroying their functions by the mediators that flow into maternal circulation. This mechanism is suspected for preeclampsia pathogenesis [2]. It is known that more than half of maternal and fetal mortality due to hypertensive diseases can be prevented [4]. However, termination of pregnancy is still the most effective treatment. Therefore, any of the effective determinants may have great importance in prediction and treatment of preeclampsia.

A balance between the coagulation and anti-coagulation system is essential in the formation and continuation of pregnancy. Many biochemical determinants like D-dimer (DD), soluble fms-like tyrosine kinase-1 (sFlt-1), and platelet distribution width (PDW) have been studied [5-7]. Studies have focused on neutrophil/lymphocyte ratio (NLR), and thrombocyte/lymphocyte ratio (TLR) and researchers have shown that the ratio between blood cell subtypes might be promising in diagnosing and determining the prognosis of the diseases related to a chronic low level of inflammation [8-10].

Pregnancy-associated plasma protein-A (PAPP-A) is one of the most frequently studied first-trimester biochemical markers, especially in pregnancies complicated with intrauterine growth retardation and preeclampsia [11]. PAPP-A is related to fetal growth and trophoblastic invasion of deciduas. Its level increases, especially from the 22nd gestational week to term [12]. PAPP-A is a metalloproteinase that proteolyzes the intrinsic growth factor binding protein-4 (IGFBP-4). In-vitro studies showed that PAPP-A plays a role in cellular response to vascular damage and its increased levels in circulation have been determined as a marker of oxidative stress [13].

In this study, we aimed to investigate whether complete blood count parameters of early pregnancy or biochemical markers of first-trimester trisomy screening (PAPP-A, free beta-HCG) were related to prediction of early onset (before the 34th gestational week) preeclampsia.

## Material and Method

This was a retrospective case-control study of preeclamptic nulliparous women who gave birth at the Department of Obstetrics and Gynecology in Medipol University, Faculty of Medicine, from January 2013 to December 2016. The study was based on chart review. In total, 12,960 patients were searched. The study group was composed of patients between 18-40 years old with a single pregnancy who were diagnosed with preeclampsia at  $< 34$  gestational weeks and had delivery at  $\geq 37$  weeks of gestation who were routinely followed up in our hospital beginning from the first antenatal examination and had

first-trimester trisomy screening. The study group patients did not have any previous history of chronic diseases. Our control group was composed of 18-40 year-old women with singleton pregnancies without any complications during pregnancy and who gave birth at  $\geq 37$  weeks of gestation in the same period. Women who became pregnant by assisted reproductive technologies or had a body mass index (BMI)  $> 30$  kg/m<sup>2</sup>, had a history of delivery complicated by chromosomal anomalies, current or previous medical problems, or multiple pregnancies were excluded. Furthermore, patients who had vaginal bleeding during the antenatal period or a history of preterm delivery were excluded.

Preeclampsia for pregnancy is defined as having a systolic blood pressure  $\geq 140$  and diastolic blood pressure  $\geq 90$  as well proteinuria (300 mg/24 hours or 1+ persistent by dipstick) after the 20th gestational week. Blood pressure was measured at least two times within a 6-hour interval, and it was confirmed that the patient had at least 30 minutes of rest before measurement. Gestational age was calculated based on the first day of the last menstruation period and/or crown-rump length measurement of the first-trimester ultrasound. Blood samples for complete blood count, PAPP-A, and free beta-HCG were collected between 11+0 to 13+6 gestational weeks.

Group 1 (study group) consisted of 214 patients who had early onset preeclampsia whereas Group 2 (control group) was formed from 240 patients. The two groups were compared with each other due to their demographic features and obstetric and biochemical results.

### Blood sample collection and laboratory methods:

Venous blood samples were collected by vacuum tubes for biochemical analyses. After the blood had coagulated the sample was centrifuged for ten minutes at 3000 RPM. The electro-chemiluminescence immunoassay (ECLIA) method was used for measuring the quantity of free b-HCG and PAPP-A. For this technique, the Immulite 2000 immunoassay system by Siemens was used. Tubes containing K3EDTA were used for CBC investigation. The quantity of CBC parameters were measured by automated hematology analyzer (XT2000i, Sysmex, Osaka, Japan).

### Statistical Method

Data were analyzed by using the Statistical Package Social Sciences (SPSS) Version 15.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used for numerical variables and presented as the mean and standard deviation. Kolmogorov-Smirnov test was used for analyzing normally distributed variables and Mann-Whitney U test was used in the comparison of subgroups.

## Results

In total 454 patients' data was analyzed. The mean age was similar for the two groups, being  $28.7 \pm 3.4$  for Group 1 and  $27.5 \pm 3.5$  for Group 2. The mean gestational weeks at delivery and birth weight were significantly lower in Group 1 compared to Group 2 ( $37.6 \pm 1.1$  vs.  $40.5 \pm 1.5$  weeks,  $p < 0.01$  and  $2845 \pm 334$  vs.  $3320 \pm 331$  g,  $p < 0.01$ , respectively). Nevertheless, there was no statistically significant difference for gravidity, smoking status, and BMI before the pregnancy between the two groups (Table 1).

Table 1. Demographic and obstetric features of two groups (for the explanation of gravidity, mean and minimum-maximum values were used; for smoking status, the number of patients and their percentages were used).

	Group 1 (n=214)	Group 2 (n=240)	p-value
maternal age (years)	28.7±3.4	27.5±3.5	0.98
gravidity	2(1-3)	1(0-2)	0.13
smoking status	7 (3.2%)	8 (3.4%)	0.90
gestational weeks at delivery (weeks)	37.6±1.1	40.5±1.5	<0.01
BMI (kg/m <sup>2</sup> )	22.9±3.2	22.7±3.5	0.09
Birth weight (g)	2845±334	3320±331	<0.01

Table 2. Comparing two groups for hematological and biochemical markers

	Group 1 (n=214)	Group 2 (n=240)	p-value
leukocyte counts (x10 <sup>3</sup> /mm <sup>3</sup> )	8.7± 1.5	8.5± 1.4	0.57
neutrophil counts (x10 <sup>3</sup> /mm <sup>3</sup> )	6.8±2.1	6.6±1.4	0.54
lymphocyte counts (x10 <sup>3</sup> /mm <sup>3</sup> )	1.8±0.49	2.3± 0.79	<0.01
platelet counts (x10 <sup>3</sup> /mm <sup>3</sup> )	235± 53	238±41	0.13
NLR	3.96± 1.23	3.22± 1.24	0.05
PLR	119± 51	120± 43	0.87
MPV	10.3±0.85	10.4±1.1	0.24
PCT	0.251±0.04	0.248±0.05	0.77
PDW	12.5±2.1	11.6± 1.87	<0.01
PAPP-A (MoM)	0.78±0.3	1.19±0.84	<0.01
free-b-HCG (MoM)	0.99±0.51	1.05±0.47	0.36

NLR and PDW were found significantly higher in Group 1 compared to Group 2 (3.96±1.23 vs. 3.22±1.24, p<0.05 and 12.5±2.1 vs. 11.6±1.87, p<0.01). The lymphocyte count was significantly lower in Group 1 (1.8±0.49 vs. 2.3±0.79 x10<sup>3</sup>/mm<sup>3</sup>, p<0.01). Furthermore, PAPP-A was found to be lower in Group 1 (0.78±0.3 vs. 1.19±0.84 MoM, p<0.01). Other CBC parameters, as well as free b-HCG, were found to be similar in the two groups.

### Discussion

In this study, it was shown that first-trimester biochemical markers such as NLR, PAPP-A, and hematologic parameters might be useful in the early detection of preeclampsia. Despite the fact that many studies have been conducted on early prediction of preeclampsia, none to date has identified any single marker that is simple, quick, non-invasive, reliable, and low-cost [14].

In a retrospective study, uncomplicated pregnancies were compared with pregnancies with severe and moderate preeclampsia, and it was shown that platelet count was negatively related to the severity of preeclampsia [15]. In support of this, another study showed that preeclamptic pregnant women had lower platelet counts compared to non-complicated pregnant women and non-pregnant women [16]. Furthermore, AlSheeha et al. showed lower platelet count in preeclamptic women, but they could not find any relation between the platelet count and severity of preeclampsia [17]. We could not find any statistically significant difference between the study group and the control group for platelet

count. Our findings were supported by a previous study that concluded that preeclampsia impaired platelet function in spite of platelet count abnormalities [1].

During pregnancy, platelet turnover increases in maternal circulation. While larger platelets are metabolically and enzymatically much more active, they have increased thrombotic potential. Previous studies from Turkey had conflicting results. While one study showed statistically significant higher levels of MPV in preeclamptic women [18], another study displayed no difference between two groups for CBC and MPV [19].

MPV is a determinant of platelet function and activation. Its level has been shown to increase in conditions that are related to endothelial cell injury, such as preeclampsia [20]. Endothelial cell injury causes microthrombus formation, increased thrombus turnover, and increased the level of younger platelets in circulation and so increases the MPV level. Furthermore, it was shown that the probability of preeclampsia was two times higher in those pregnant women who had a MPV level lower than 8.5 fL in gestational weeks 24-28 [18]. In contrast, we could not find any significant difference in MPV levels between our study and control groups.

Later studies have focused on NLR and PLR, which are two parameters of CBC thought to indicate systemic inflammation due to decreased lymphocyte rate. It has been found that high levels of NLR and PLR were correlated with renal function impairment in diabetic patients and with increased mortality rate in malignancies [21,22]. Despite the fact that NLR was found to be higher in preeclamptic patients [23], there is conflicting evidence about the association between the severity of preeclampsia and NLR [23-25]. In the present study, NLR was found to be significantly higher in the preeclampsia group than in the control group, while there was no significant difference for PLR. In support of our study, another study from our country could not find any difference for PLR in preeclamptic patients [26].

PDW is a well-known parameter of platelet activation and endothelial cell injury [26]. It was thought to be a much more specific marker of platelet activation than MPV since its level was not affected by platelet distention [7]. Although some studies have not found any statistically significant difference for PDW in preeclamptic patients [17,27]. In most studies, PDW was found higher in preeclamptic patients [7,16,28]. In our study, consistent with most studies in the literature, PDW was found higher in the preeclampsia group. Furthermore, regardless of NLR, PDW occurred at different levels when comparing severe and moderate preeclampsia patients [7].

Plateletcrit (PCT) is calculated with platelet count and MPV [29]. A rate of PCT under 0.1% is an indirect sign of platelet transfusion requirement, and it is a more specific determinant than platelet number in thrombocytopenic patients [30]. Although we found a similar rate between our study and control groups, it is clear that more studies are needed in this field.

Preeclamptic women who had chromosomally normal babies were found to have low levels of PAPP-A, but its predictive value was not found to be convincing enough [31]. Despite this, in another study, low levels of PAPP-A were determined as a statistically significant marker of late-onset preeclampsia [32]. In a study of 973 pregnant women, 111 had preeclampsia,

and their PAPP-A level was found between 0.53 to 1.08, with a mean value of 0.8 MoM [33]. Similarly, we found a mean PAPP-A value of 0.78 MoM in the preeclampsia group. Furthermore, a measurement of the PAPP-A level below the 10th percentile was related to an increased preeclampsia rate (OR 1.6, 95% CI: 1.3-2.6) (32). Despite the fact that our findings did not reveal any critical value of PAPP-A level for prediction of preeclampsia, we found it to have a level lower in the preeclampsia group.

In our study, we found a strong relation between high levels of NLR and PDW, as well as low levels of lymphocyte count and PAPP-A, with early onset preeclampsia development during the current pregnancy. While our results need to be confirmed with larger studies, we believe that patients who have similar hematological and biochemical results to our study should be assessed for preeclampsia.

### Competing interests

The authors declare that they have no competing interests.

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