The association between protein levels in 24-hour urine samples and maternal and neonatal outcomes of pregnant women with preeclampsia

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Abstract

Objective: Hypertensive diseases of pregnancy are one of the leading causes of maternal and perinatal mortality worldwide. The aim of this study was to evaluate the association between protein levels in 24-hour urine samples and maternal and perinatal outcomes in preeclamptic patients.

Material and Methods: This retrospective cohort study was conducted with pregnant women who were diagnosed with preeclampsia (PE) and delivered in our clinic between 2010 and 2018. Patients were divided into those with a proteinuria value below 300 mg/24 h (non-proteinuria), proteinuria value between 300-2000 mg/24 h (mild proteinuria), proteinuria value between 2000-5000 mg/24 h (severe proteinuria) and proteinuria value >5000 mg/24 h (massive proteinuria) and were compared in terms of maternal and perinatal outcomes. Demographic characteristics (age, body mass index in kg/m^2, gravidity), PE-related clinical symptoms (epigastric pain, neurological and respiratory symptoms), laboratory findings (24 h protein level, lactate dehydrogenase, aspartate aminotransferase, platelet count and creatine levels) were recorded in all patients.

Results: A total of 1,379 patients meeting the study criteria were included. There were 315 (23%) patients in the non-proteinuria group, 704 (51%) in the mild proteinuria group, 234 (17%) patients in the severe group and 126 (9%) patients in the massive proteinuria group. The massive proteinuria group was found to have the highest rates of maternal and prenatal complications. The Apgar score, umbilical cord pH value, birth weight, gestational week at delivery, intrauterine growth restriction and intrauterine fetal death were significantly higher in the massive proteinuria group.

Conclusion: Our data showed that the degree of proteinuria appears to be associated with maternal, fetal and neonatal outcomes among women diagnosed with PE. Women with proteinuria of >5000 mg/24 hours had notably poorer natal outcomes. (J Turk Ger Gynecol Assoc 2022; 23: 190-8)

Keywords: Hypertensive diseases, preeclampsia, 24-hour urine protein, proteinuria, intrauterine growth restriction, perinatal mortality

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Introduction

Preeclampsia (PE) is a pregnancy-specific health problem observed in 5-8% of all pregnancies, with potential serious maternal and perinatal outcomes (1). As a multisystemic disease, PE may also cause long term sequelae in the kidneys, liver, brain and coagulation system (2). PE is mainly characterised by new-onset hypertension in pregnancy accompanied by systemic signs and symptoms. There are also defined criteria for disease severity and they have been revised over the last decades. Until the early 2000s, proteinuria quantification was utilized to identify the disease severity and values above 2 g/24 h were used as the cut-off value for a decision to undertake emergency delivery (3,4). In 2013, proteinuria was removed from the main diagnostic criteria for the detection of PE, in accordance with the committee opinion of the American College of Obstetricians and Gynecologists (ACOG). Moreover, massive proteinuria (≥5 g/24 h) and

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fetal growth restriction (FGR), which were considered to be diagnostic criteria for severe PE, were also removed from the same classification (5). However, there is still no strong evidence concerning the possible effects of proteinuria on obstetric outcomes (4). Although many studies have demonstrated the relationship between massive proteinuria and adverse events in pregnancies affected by PE, poor obstetric outcomes have also been reported in pregnancies with hypertensive disorders without proteinuria (6,7).

Gestational week at the onset of PE is the most important marker to predict perinatal outcomes in PE, which is known to have a complex and unclear pathology. Perinatal outcomes are known to worsen in the presence of early onset PE and are mostly related to medically indicated preterm deliveries. When observed in early pregnancy, there is an average of 20-fold increased risk for adverse pregnancy outcomes compared to a term pregnancy (8). One fourth of preterm deliveries with medical indications are associated with PE (6). A study has shown that PE is responsible for a significant proportion of severe maternal complications seen at 30% (9,10). Furthermore, PE has been blamed for 14% of maternal deaths due to hypertensive disorders (10). Timing of delivery is crucial both for maternal and fetal well-being, but the unpredictable course of the disease makes this decision extremely challenging for the clinician.

Clarification of the severity of PE and prediction of possible complications in high-risk pregnant women can minimize undesired adverse feto-maternal outcomes. In our own practice, it was anecdotally evident that pregnancy outcomes were worse in patients with proteinuria. Considering that the diagnostic criteria of PE have been frequently reviewed in recent years, we decided that the clinical course of proteinuria and its correlation with feto-maternal outcomes should be reconsidered. Therefore, the aim of this study was to evaluate the association between different degrees of proteinuria, defined by a range of cut-off values, and maternal and perinatal outcomes in pregnant women with PE.

Material and Methods

This retrospective cohort study was conducted in a university hospital, which is a tertiary referral center both for obstetrics and neonatal care. Data regarding pregnant women who were diagnosed with PE, delivered in our hospital and whose 24-hour urine results were obtained from electronic records between the years of 2010 and 2018 were included for the study. The study was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (approval number: B.30.2.ATA.0.01.00/368). The diagnosis of PE was defined as proteinuria and/or end-organ damage accompanying new onset systolic blood pressure (BP) of 140-159 mmHg, i.e. ≥140 mmHg, and/or diastolic BP ≥90 mmHg, measured on at least two occasions 4-hours apart in the left lateral decubitus position following the 20th gestational week in a woman, who had previously normal BP, according to the criteria of the ACOG (11). The presence of >300 mg/L protein in a 24-hour urine sample was considered as proteinuria. The group without proteinuria consisted of patients with at least one of the following disorders accompanying high BP: 1) renal failure (serum creatinine level >1.0 mg/dL or a doubling of creatinine concentration); 2) liver involvement (liver transaminases >40 IU/L and/or right upper quadrant or epigastric abdominal pain); 3) neurological complications (eclampsia, stroke, visual scotoma or severe headaches); and 4) hematological complications (thrombocytopenia ≤100000/μL) (12).

Those with multiple pregnancies, those with fetal anomalies, those with suspected hepatitis A, B, C or other infectious hepatitis, those with autoimmune hepatitis, those with chronic liver disease, those with kidney disease before or during pregnancy, those with gestational hypertension and those not examined for protein level using 24 h urine samples before delivery were excluded from the study.

Four groups were designated based on the degree of proteinuria in the 24 h urine collection samples. Patients with a proteinuria value <300 mg/24 h were designated non-proteinuria, those with a proteinuria value between 300-2000 mg/24 h were designated mild proteinuria, those with a value between 2000-5000 mg/24 h were designated severe proteinuria and those with a value >5000 mg/24 h were designated massive proteinuria. These groups were compared in terms of maternal and perinatal outcomes. Demographic characteristics (age, body mass index in kg/m^2, gravidity), PE-related clinical symptoms (epigastric pain, neurological and respiratory symptoms), laboratory findings [24 h protein level, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), creatine levels and platelet count] were recorded in all patients. Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome (HELLP), eclampsia, placental abruption, oligohydramnios, premature membrane rupture, preterm delivery, mode of delivery and magnesium sulfate therapy were recorded as maternal complications. The Apgar score, presence of intrauterine growth restriction, fetal birth weight and pregnancy loss rate were examined and constituted neonatal complications. FGR was defined as an estimated fetal weight, calculated ultrasonographically, below the 10th percentile for gestational age (GA) (13). GA was calculated according to the last menstrual date confirmed by the earliest ultrasonographic findings. Patients with elevated liver function tests, prodromal symptoms of eclampsia and, preterm ruptures of membranes were delivered urgently.

Statistical analysis

The analyses were performed with SPSS, version 20 (IBM Inc., Armonk, NY, USA). The data were expressed as mean, standard deviation, median, minimum, maximum, percentage and number, as appropriate. The normal distribution of continuous variables was evaluated with the Shapiro-Wilk W-test when the sample size was <50, and the Kolmogorov-Smirnov test when the sample size was ≥50. In the comparisons between two independent groups, the independent samples t-test was used when the condition of normal distribution was met, and the Mann-Whitney U test was used when the condition was not met. For the comparison of continuous variables between more than two independent groups, the ANOVA test was used when the condition of normal distribution was met, and the Kruskal-Wallis test was used when the condition was not met. Bonferroni corrected z-test was used for multiple comparisons to compare multiple groups regarding a categorical variable. Following the ANOVA test, the Tukey post-hoc test was used for homogeneous variances, and the Tamhane's T^2 post-hoc test was used for non-homogeneous variances. Following the Kruskal-Wallis test, the Kruskal-Wallis One-Way ANOVA (k samples) test was used for post-hoc tests. In the comparison of two continuous variables, the Pearson correlation test was used when the condition of normal distribution was met, and the Spearman correlation test was used when the condition was not met. Receiver operating characteristic (ROC) curve analysis was used to determine whether the continuous variable could be used for diagnosis or not. In addition, the Youden index was used to determine cut-off values. The power of the new test to distinguish between patients and healthy individuals was determined by calculating the sensitivity, specificity, positive predictive value and negative predictive value for the validity of the diagnostic test results. A value of $p<0.05$ was considered statistically significant.

Results

A total of 1,379 patients who met the study inclusion criteria were included. Patients were divided into four groups based on degree of proteinuria. There were 315 (23%) patients with a proteinuria value below 300 mg/24 h (non-proteinuria; group1), 704 (51%) patients with a value between 300-2000 mg/24 h (mild proteinuria; group 2), 234 (17%) patients with a value between 2000-5000 mg/24 h (severe proteinuria; group 3) and 126 (9%) patients with a value >5000 mg/24 h (massive proteinuria; group 4). Demographic, laboratory and clinical data of the patients are shown in Table 1, 2. There was no significant difference between the groups in terms of age. However, gestational week at diagnosis, neurological symptoms (group 2 was significantly different from group 4; 0.03, 0.10 respectively), epigastric pain, HELLP syndrome (group 2 was significantly different from group 4; 0.05, 0.13 respectively), magnesium sulfate therapy (in group 1, group 2, group 3 and group 4; 0.07; 0.13; 0.38 and 0.83 respectively), preterm delivery (in group 1, group 2, group 3 and group 4; 0.44, 0.53, 0.78, 0.92 respectively) oligohydramnios [group 1 (0.19) was significantly different from group 4 (0.32); group 2 (0.17) was significantly different from group 3 (0.27); and group 4 (0.32)], cesarean delivery (group 1 (0.73) was different from group 2 (0.81) and group 3 (0.85)], LDH, AST, alanine aminotransferase (ALT) and creatinine (≥1.1 mg/dL) levels were significantly different between the groups ($p<0.05$) (Table 3).

Group 4 was found to have the highest rates of maternal and perinatal complications. Intrauterine growth restriction and intrauterine fetal death were significantly higher in this group. There was also a significant difference between the groups in terms of neonatal complications. The Apgar score, umbilical cord pH value, birth weight and gestational week at delivery were significantly higher in group 4. Systolic and diastolic BPs were significantly higher in group 4 ($p<0.05$). There was no significant difference between the groups in terms of premature membrane rupture. The rate of cesarean delivery was similarly

Table 1. Descriptive statistics for continuous variables of all patients

Variables	Mean ± SD	Median (minimum-maximum)
Age (year)	31±6	31 (16-58)
24-h urine protein level (mg/L of 24 h urine)	1694±2025	900 (3-9900)
AST (U/L)	36±69	22 (2-1251)
ALT (U/L)	29±67	13 (1-1045)
LDH (U/L)	316±168	282 (1-3051)
Creatinine (mg/dL)	0.83±9.3	0.5 (0.1-34)
Platelet count (μL)	222000±81000	219000 (8000-785000)
Systolic blood pressure (mmHg)	146±15	140 (100-220)
Diastolic blood pressure (mmHg)	91±10	90 (60-140)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, SD: Standard deviation

high in all groups. Obstetric outcomes are shown in Table 3 and neonatal outcomes are shown in Table 4. As a result of multinomial regression analysis, creatinine, systolic BP and neurological symptom variables were found to be significant in the model (Table 5). Systolic BP (p=0.01) and creatinine values (p=0.001) were significantly higher in group 3 compared with group 1. Creatinine, systolic BP and epigastric pain levels were found to be significantly higher in group 4 compared with group 1 (p=0.002, p<0.001 and p=0.029, respectively).

ROC curve analysis revealed the area under the curve (AUC) for HELLP syndrome, giving a cut-off value, sensitivity and specificity of 1338,000, 51.2% and 65.2%. Similarly, for placental abruption these values were 3495,000, 29.1% and 84.4%, for magnesium sulfate they were 2324,500, 62.7% and 87.4%, for oligohydramnios 2250,000, 35.6% and 78.2%, for preterm delivery 1075,000, 53.4% and 76.2%, for vaginal delivery 1075,000, 32.4% and 56.5% and cesarean delivery were 402,500, 74.5% and 36.8% (Figure 1). ROC curve analysis demonstrated the AUC for neonatal mortality giving sensitivity, specificity and cut off values of 64.8%, 62.4% and 1185,000, respectively. Similarly, for FGR the cut-off value, sensitivity and specificity were 985,000, 53.4% and 57.3% (Figure 2).

Discussion

Discussions continue about the significance and clinical utility of a cut-off value of proteinuria, which is among the commonly used diagnostic criteria in PE (14). Although international guidelines recommend a cut-off value of 300 mg/24 h and greater for significant proteinuria, there are also studies that have reported only a weak association between these levels of proteinuria and maternal and perinatal outcomes (11). The findings of this retrospective study including 1,379 patients showed that AST, ALT, LDH, creatinine and BP levels increased with increasing proteinuria levels. Also, presence of HELLP syndrome, magnesium sulfate therapy requirement, preterm delivery and oligohydramnios were significantly more common in the group with massive proteinuria. Birth weight was higher, gestational week at delivery was later, intrauterine

Table 2. Descriptive statistics for discrete variables of patients

Variables		**Number of patients**	**%**
Primigravida		335	24
Multigravida		1045	76
24-h urine protein level	Group 1	315	23
	Group 2	704	51
	Group 3	234	17
	Group 4	126	9
Proteinuria in spot urine	0	614	45
	+1	328	24
	+2	214	16
	+3	199	15
	+4	16	1
Epigastric pain		99	7
Neurological symptoms		66	5
Eclampsia		15	1
HELLP syndrome		82	6
Placental abruption		55	4
Magnesium sulfate therapy		308	22
Oligohydramnios		281	20
Preterm delivery		812	59
Premature membrane rupture		129	9
Vaginal delivery		278	20
Caesarean delivery		1102	80
		Median	**Min.-max.**
Gravidity		3	1-8
Parity		2	0-6

HELLP: Elevated liver enzymes and low platelets, min.: Minimum, max.: Maximum

growth restriction more likely, umbilical cord pH higher and Apgar score lower in the massive proteinuria group. In addition, PE was diagnosed in the earlier weeks, and characteristics of severe PE were observed in the group with high 24 h proteinuria levels. As a result, these data demonstrated that there is an association between proteinuria and maternal, fetal and neonatal outcomes among pregnant women diagnosed with PE, which was especially strong in the subgroup with massive proteinuria. Early-onset PE is significantly associated with adverse maternal and neonatal outcomes. The rate of these adverse outcomes is significantly higher in early onset PE than late-onset PE. In the present study, the gestational week at diagnosis was significantly earlier in group 4 than in the other groups. However, severe PE may be associated with both early onset and high proteinuria levels. Today, the only effective treatment for PE is termination of pregnancy at the most appropriate time for both maternal and fetal well-being (15). Although urinary protein excretion increases significantly in normal pregnancy, protein excretion is considered abnormal when a value exceeding >300 mg/L in the 24 h urine sample (15). However, proteinuria is not present at initial admission with clinical symptoms in 10% of women with clinical and/or histological findings of PE and 20% of women with frank eclampsia (16). This may be due to the fact that multiple organ dysfunction, affecting the kidneys and liver, can occur without significant proteinuria, and the amount of proteinuria does not predict the severity of disease progression (4). Therefore, since 2014, the International Society for the Study of

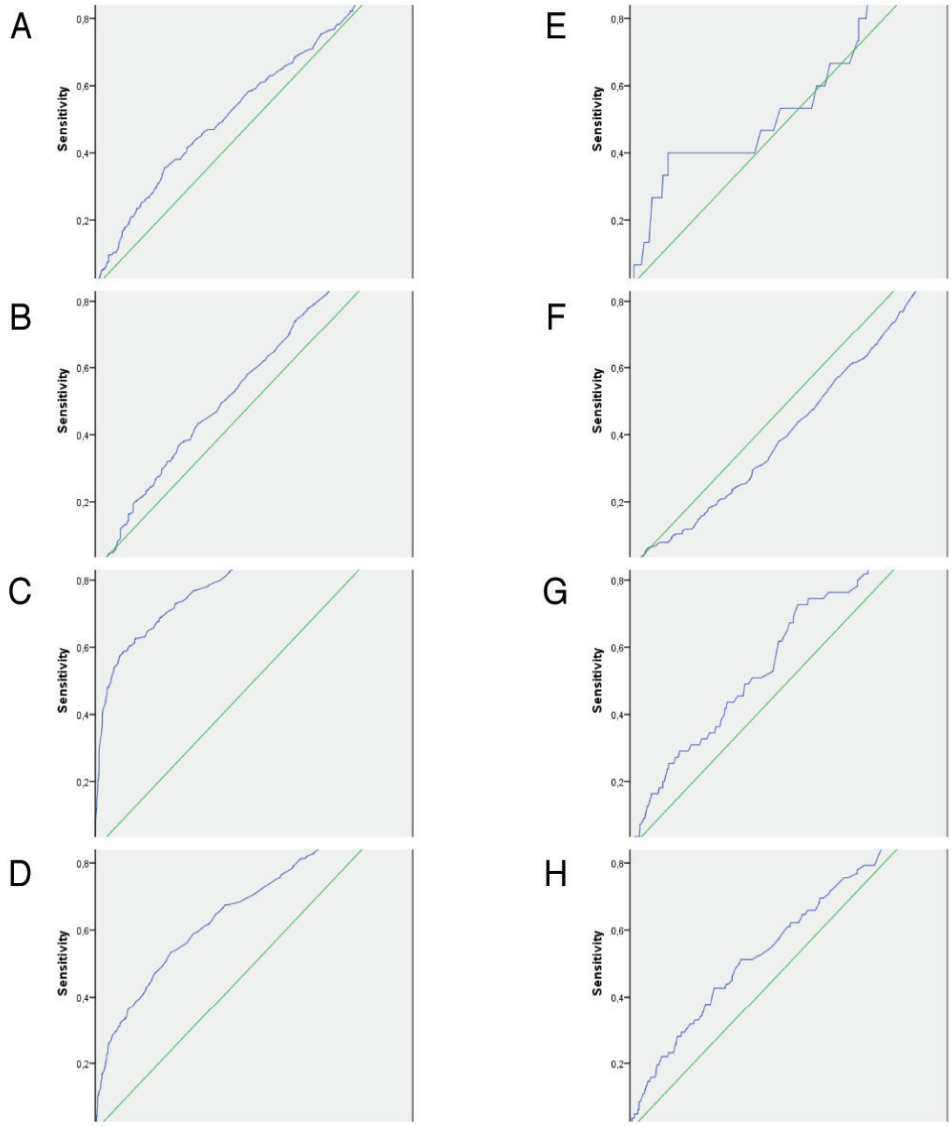

Figure 1. ROC curve analysis for maternal outcomes. A) oligohydramnios; B) caesarean delivery; C) magnesium sulfate therapy; D) preterm delivery; E) eclampsia; F) vaginal delivery; G) placental abruption; H) HELLP syndrome

ROC: Receiver operating characteristic, HELLP: Haemolysis, elevated liver enzymes and low platelets

Hypertension in Pregnancy and ACOG have not recommended the use of proteinuria as a criterion to diagnose PE (17,18). Although proteinuria is not recommended as a criterion in the diagnosis of PE, clinicians often use proteinuria levels in the decision-making process for delivery of PE cases (19). As many studies have shown that an increasing amount of proteinuria is associated with poor progression of the disease and poor perinatal outcomes (10,15,20), such as perinatal mortality (21) and preterm delivery (22). Guida et al. (3) reported that proteinuria, especially massive proteinuria, adversely affected fetal, maternal and neonatal outcomes, and poor maternal outcomes were also associated with the severity of proteinuria in their study (3). On the other hand, Thornton et al. (23) found the perinatal mortality rate significantly higher in the non-proteinuria group and did not detect any difference between the two groups in terms of maternal mortality.

Since this study was performed in a tertiary referral hospital, we found that almost all of the patients who were referred to our clinic with a pre-diagnosis of PE were examined for 24 h protein levels. No significant difference was observed among groups in terms of eclampsia and placental abruption, which significantly affect maternal mortality. Prematurity, an important cause of neonatal mortality, was observed to be high in the massive proteinuria group. We would like to draw attention to the correlation between prematurity and massive proteinuria in this study. Therefore, PE appears to be an isolated risk factor

Table 3. Obstetric outcomes between the groups

Variables		Group 1 0-300 24 h/mg (n=315)	Group 2 300-2000 24 h/mg (n=704)	Group 3 2000-5000 24 h/mg (n=234)	Group 4 ≥ 5000 24 h/mg (n=126)	p
Age (years)		32±6	31±6	31±6	31±6	0.222
BMI (kg/m²)		27.62±6.57	23.07±0.86	22.28±1.22	24.12±2.25	0.125
AST (U/L)		32±41	35±72	40±83	49±75	0.001
ALT (U/L)		27±46	27±67	33±82	41±77	0.001
LDH (U/L)		300±124	310±169	320±135	375±275	0.001
Creatinine (mg/dL)		0.55±0.15	0.57±0.24	2.13±22.76	0.64±0.29	0.001
Platelet (μL)		227,000±82,000	222,000±81,000	221,000±77,000	207,000±85,000	0.052
Systolic blood pressure (mmHg)		143±14	145±14	149±14	155±20	0.001
Diastolic blood pressure (mmHg)		90±10	90±9	93±9	95±11	0.001
Primigravida		78 (0.25)[a,b]	148 (0.21)[b]	66 (0.28)[a,b]	43 (0.34)[a]	0.005
Multigravida		238 (0.76)[a,b]	556 (0.79)[b]	168 (0.72)[a,b]	83 (0.66)[a]	0.005
Proteinuria in spot urine	0	177 (0.57)	318 (0.45)	83 (0.35)	36 (0.29)	-
	+1	81 (0.26)	184 (0.26)	40 (0.17)	23 (0.18)	-
	+2	32 (0.10)	121 (0.17)	45 (0.19)	16 (0.13)	-
	+3	21 (0.07)	69 (0.10)	65 (0.28)	44 (0.35)	-
	+4	1 (0.00)	8 (0.01)	1 (0.00)	6 (0.05)	-
Epigastric pain		17 (0.05)	45 (0.06)	22 (0.09)	15 (0.12)	0.044
Neurological symptoms		16 (0.05)[a,b]	23 (0.03)[b]	14 (0.06)[a,b]	13 (0.10)[a]	0.005
Eclampsia		2 (0.01)	7 (0.01)	2 (0.01)	4 (0.03)	0.060
HELLP syndrome		17 (0.05)[a,b]	34 (0.05)[b]	15 (0.06)[a,b]	16 (0.13)[a]	0.007
Placental abruption		9 (0.03)	27 (0.04)	10 (0.04)	9 (0.07)	0.220
Magnesium sulfate therapy		21 (0.07)[a]	93 (0.13)[b]	89 (0.38)[c]	105 (0.83)[d]	**<0.001**
Oligohydramnios		61 (0.19)[a,b]	117 (0.17)[b]	63 (0.27)[a,c]	40 (0.32)[c]	**<0.001**
Preterm delivery		138 (0.44)[a]	376 (0.53)[b]	182 (0.78)[c]	116 (0.92)[d]	**<0.001**
Premature membrane rupture		37 (0.12)	60 (0.09)	21 (0.09)	11 (0.09)	0.434
Vaginal delivery		86 (0.27)[a]	136 (0.19)[b]	34 (0.15)[b]	22 (0.17)[a,b]	**0.001**
Caesarean delivery		229 (0.73)[a]	569 (0.81)[b]	200 (0.85)[b]	104 (0.83)[a,b]	**0.001**
IUGR		58 (18%)[a]	159 (23%)[a,b]	66 (28%)[b]	39 (31%)[b]	0.008

[a,b,c,d]: Bonferroni correction was used for post-hoc tests after categorical comparisons; the letters symbolize the difference of the groups with each other. BMI: Body mass index (kg/m²), AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, HELLP: Haemolysis, elevated liver enzymes and low platelets, IUGR: Intrauterine growth restriction

for prematurity, as has been previously reported (24). There is a scarcity of evidence concerning how to identify the optimal delivery time in PE (25). However, it was shown, both in the present study and in the literature, that the decision to undertake preterm delivery prevented serious complications that might occur (3). Although the prematurity rate was high, no maternal mortality was observed in our study group. Furthermore, our cesarean delivery rates were found to be high in all groups due to the delivery protocol management in our clinic.

Newman et al. (4) detected no increased risk of maternal and neonatal morbidity, even in pregnancies with proteinuria >10 g/L in their study investigating the effects of massive proteinuria. They argued that massive proteinuria appeared to be a marker for early-onset PE and prognosis, and neonatal mortality was a

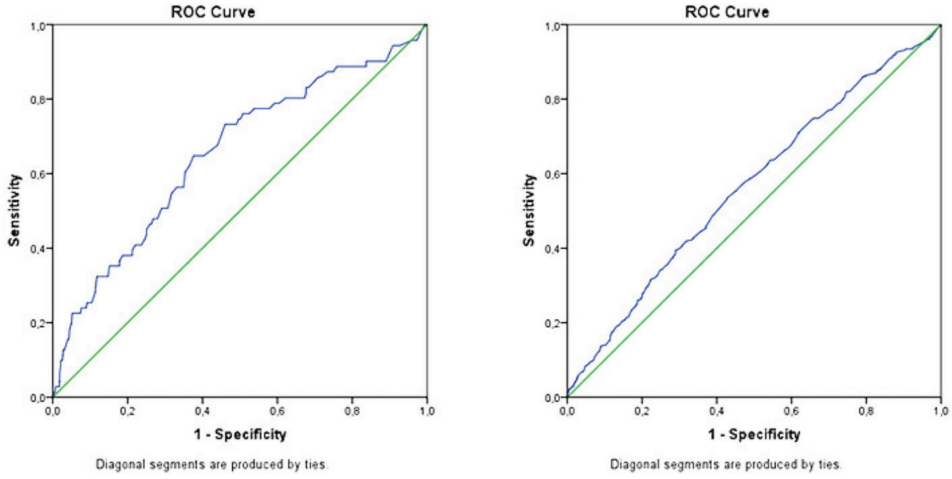

Figure 2. ROC curve analysis for perinatal outcomes. Neonatal death and IUGR

ROC: Receiver operating characteristic, IUGR: Intrauterine growth restriction

Table 4. Neonatal outcomes between the groups

Variables	Group 1 0-300 24 h/mg (n=315)	Group 2 300-2000 24 h/mg (n=704)	Group 3 2000-5000 24 h/mg (n=234)	Group 4 ≥ 5000 24 h/mg (n=126)	p
Apgar score	8.07±1.69	7.82±1.98	7.42±2.25	6.43±2.87	<0.001
Umbilical cord pH	7.30±0.07	7.30±0.07	7.30±0.08	7.29±0.07	0.511
Birth weight (g)	2626±805	2506±832	1957±858	1575±757	<0.001
Gestational week	36.1±3.3	35.4±3.4	32.7±4.1	30.7±3.9	<0.001

Table 5. Likelihood ratio tests

Effect	-2 log likelihood of reduced model	Chi-square	p
AST	3181,725	1,192	0.755
ALT	3182,411	1,877	0.598
Kreatinin	3199,974	19,441	**<0.001**
PLT	3183,960	3,426	0.330
SBP	3207,172	26,639	**0.001**
DBP	3182,492	1,959	0.581
Epigastric pain	3186,817	6,284	0.099
Neurological symptom	3190,410	9,877	0.020
Eclampsi	3182,043	1,510	0.680
Decolman	3180,812	0.279	0.964

The chi-square statistic is the difference in -2 log likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PLT: Platelet count, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

consequence of prematurity, rather than massive proteinuria (4). Dong et al. (15) demonstrated that severe proteinuria was associated with the onset week of PE, incidence of FGR and earlier delivery than GA. Kim et al. (22) concluded that massive proteinuria might be associated with early-onset PE and preterm delivery in their retrospective study (22). Many studies have shown that maternal and perinatal outcomes deteriorate with increasing proteinuria levels, and PE severity is directly related to proteinuria severity (5). However, there are also studies showing the opposite. In a systematic review of selected studies with a proteinuria cut-off value of 5 g/L of 24 h urine collection, the authors argued that proteinuria should not be used for clinical decisions (15). Again, Schiff et al. (26) stated that there was no difference among pregnancies with a marked, minimal or no increase in proteinuria in terms of maternal or fetal outcomes in their retrospective study.

Despite all the advances in medicine, the treatment of PE, which is both difficult to manage and related to poor outcomes, is still unclear in obstetric practice. Currently, the most effective treatment for PE is to terminate pregnancy. However, there is no consensus on optimal timing for delivery (27). The desire to prevent maternal organ damage contrasts with the desire to avoid prematurity and related complications. Clinical conditions that may lead to prematurity, intrauterine growth restriction or even death may occur (4). Although PE *per se* is an isolated risk factor for prematurity, the amount of proteinuria is associated with the earlier occurrence of the disease. In our study, prematurity and intrauterine growth restriction were significantly more common in the massive proteinuria group compared to the other groups.

Study Limitations

This study has some limitations. The first is the retrospective nature of the study. In addition, serious losses were observed in the follow-up of the patients in the postpartum period because of the tertiary nature of the study center, and therefore, the duration or normalization of proteinuria and hypertension could not be monitored. However, the high number of patients, being the largest tertiary health center of the region, and application of the treatment protocol of our clinic by the same physician group are among the strengths of this study.

Conclusion

We want to highlight that proteinuria in pregnancies affected by PE and which can be easily evaluated in almost every laboratory, should not be ignored. We believe that proteinuria is a valuable marker in PE management. We advocate the use of assessing proteinuria when evaluating the severity of PE. We further believe that proteinuria should be taken into consideration until new factors are found that enable more reliable estimation of obstetric outcomes in all preeclamptic women with massive proteinuria. Although clear conclusions cannot be drawn from the current literature, massive proteinuria seems to be especially closely correlated with significant maternal and neonatal adverse events. As clinicians we suggest considering this situation as a secondary but a valuable variable throughout management of pregnant women with PE.

Ethical Committee Approval: *The study was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (approval number: B.30.2.ATA.0.01.00/368).*

Informed Consent: *Retrospective study.*

Peer-review: *Externally peer-reviewed.*

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