Zeynep Kamil Med J 2023;54(2):62–67
DOI: 10.14744/zkmj.2022.57873

ORIGINAL ARTICLE

The relationship between proteinuria and fetal-maternal complications: A retrospective analysis

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ABSTRACT

Objective: This is retrospective research aimed at investigating the relationship between preeclampsia indicators and fetal-maternal results. Two hundred six women were enrolled in the study who were 25–42 weeks pregnant: 103 with preeclampsia and 103 in the control group. Control patients presented to Antalya Education and Training Hospital Obstetrics and Gynecology Clinics between January 2012 and 2015.

Material and Methods: The pregnant women enrolled in the study were asked about their demographic features. Blood pressure is measured. Time of hospitalization, hematologic and biochemical parameters, type of delivery, cesarean indication if done, and maternal-fetal complıcations were recorded. Furthermore, the characteristics of newborns were recorded. The relationship between categorical variables was analyzed using Fisher's exact test or Pearson's Chi-square test. If the number of samples was <50, the Shapiro–Wilk test was used, and if it was more than 50, the Kolmogorov–Smirnov test was used. The groups were analyzed for statistically significant differences using the Mann-Whitney U-test or Student's t-test. The relationship between continuous variables not correlated with normal distribution and ordinal variables was examined using Spearman's correlation test, and continuous variables correlated with normal distribution were analyzed using Pearson's correlation test.

Results: The delivery type of patients with +2 and +3 positive proteinuria was cesarean section, and 65% had antihypertensive therapy. One-quarter (26.3%) of patients with fetal IUGR and 55.2% needed a blood transfusion, and the difference between the +1 and no proteinuria groups was significant ($p<0.05$). The best predictor of the duration of maternal hospitalization was proteinuria, followed by diastolic blood pressure, and the difference was significant ($p<0.05$). Systolic blood pressure, SGOT, LDH, BUN, and uric acid values were positively and significantly correlated ($p<0.05$). The best predictor of neonatal birth weight was proteinuria, which was significant ($p<0.05$).

Conclusion: The results of this trial show that proteinuria is an indicator that correlates with maternal and neonatal outcomes.

Keywords: Maternal-fetal outcomes, preeclampsia, proteinuria.

Cite this article as: Alcı A, Purut YE, Babayeva G, İsenlik BS. The relationship between proteinuria and fetal-maternal complications: A retrospective analysis. Zeynep Kamil Med J 2023;54(2):62–67.

Received: August 08, 2022 **Revised:** October 25, 2022 **Accepted:** November 15, 2022 **Online:** June 08, 2023
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INTRODUCTION

Hypertensive diseases of pregnancy are one of the most important causes of maternal and perinatal mortality and morbidity. Hypertension is the most common complication of pregnancy, and its incidence is between 5 and 8%.[1,2] In 2013, the American College of Obstetricians and Gynecologists (ACOG) grouped hypertensive diseases in pregnancy and determined the criteria for preeclampsia in a report to improve the diagnosis, management, and maternal and neonatal outcomes of hypertension. In the bulletin published by ACOG in 2013, hypertension was required for the diagnosis of preeclampsia, and proteinuria was described as a criterion that could accompany but not be obligatory. In new-onset hypertensive patients without proteinuria, it was stated that in addition to hypertension, one of those criteria was required for the diagnosis of preeclampsia: high creatinine level (above 1.1 mg/dL without known renal pathology), platelet count <100000/mL, cerebral visual symptoms, pulmonary edema, or liver transaminase levels doubling their normal levels.[3] Severe preeclampsia was defined as a blood pressure value above 160/110 mm-Hg (without the use of antihypertensives) in at least 2 measurements with an interval of 4 h in the presence of one of the same conditions. Although the pathophysiology of preeclampsia remains mysterious, hypoxia and perhaps more importantly, ischemia-reperfusion-type damage occurring in the intervillous space due to problems in spiral artery structuring may cause the formation of preeclampsia by causing oxidative stress and free radicals in the placenta, disruption in the release of cytokines and growth factors, and leukocyte and macrophage activation.[4,5] Increased oxidative stress products and decreased antioxidant activity have been found in maternal blood in preeclampsia.[6,7] Widespread endothelial damage is also thought to cause preeclampsia.[8]

While maternal risks in preeclampsia are disseminated intravascular coagulopathy (DIC), acute kidney failure (AKF), pulmonary edema, ablatio placenta, hemolysis, elevated liver enzymes, low platelets (HELLP), subcapsular liver hematoma, intracerebral hemorrhage, and death; fetal complications can be grouped as early and late period complications. Early complications include preterm birth and prematurity, low birth weight, intrauterine/perinatal fetal death, respiratory distress syndrome, bronchopulmonary dysplasia, thrombocytopenia, neutropenia, necrotizing enterocolitis, intraventricular hemorrhage, and periventricular leukomalacia, while late complications include hypertension, coronary artery disease, non-insulin-dependent diabetes, and mental retardation.[8,9] This study aimed to investigate the relationship between preeclampsia markers, their levels, and perinatal and neonatal outcomes.

MATERIAL AND METHODS

The sample of the study consisted of 206 pregnant women with 25–42 weeks of pregnancy who were admitted to Antalya Training and Research Hospital Gynecology and Obstetrics Clinics between January 2012 and January 2015. Exclusion criteria were defined as patients with chronic hypertension, diabetes mellitus, kidney disease, liver disease, thromboembolic diseases, and known thrombophilia, malformations in pregnancy, or multiple pregnancies. After getting approval from the Antalya Training and Research Hospital Scientific Researche Evaluation Committee (39/4, 10.04.2014), the data collection phase was started. Study protocol conforms to the "Declaration of Helsinki- cs Principles for Medical Research Involving Human Subjects". While 103 randomly selected pregnant women with a diagnosis of preeclampsia were included in the study group, 103 healthy pregnant women without any medical or obstetric complications constituted the control group. Age, gestational week, gravida, parity, abortion, and blood pressure, maternal hospital stay, hematological and biochemical parameters, mode of delivery, indication for cesarean section, ablatio placentae, DIC, AKF, pulmonary embolism, fetal intracranial hemorrhage, fetal subcapsular hematoma, maternal transfusion requirement, need for dialysis, first examination notes of the newborn, fetal growth restriction, neonatal intensive care unit (NICU) need and length of stay, respiratory distress syndrome, transient neonatal tachypnea, sepsis, necrotizing enterocolitis, and perinatal mortality complications were screened retrospectively. Laboratory values for the patients were also obtained.

Descriptive statistics are presented with frequency, percentage, mean, standard deviation (SD), median, minimum (min), and maximum (max) values. Fisher's exact test or Pearson's chi-square test was used to analyze the relationships between categorical variables. In the normality test, the Shapiro–Wilks test was used when the sample size in the group was <50, and the Kolmogorov–Smirnov test was used when it was larger. In the analysis of the difference between the measurement values of the two groups, the assumption of normality was checked with the Shapiro–Wilk test. The Mann–Whitney U-test was used when it did not fit the normal distribution, and the Student's t-test was used when it did. The spearman correlation test was used for the relationships between ordinal or non-normally distributed continuous variables, and the Pearson correlation test was used for normal-distributed continuous variables. $p<0.05$ was considered statistically significant. Analyzes were made with the SPSS 18.0 package program.

RESULTS

The files of the patients who gave birth in our hospital between 2012 and 2015 were examined, and 206 patients were included in the study. The age range of the patients in the study was 16–42 years. The mean age in the preeclamptic group was 28.1±6.24 years, and it was 27.65±6.04 years in the control group. In general, the correlation of all measurements with the amount of proteinuria was analyzed by the Spearman correlation test, both in all patients and in the preeclampsia group. In the group in which all patients were examined, as the amount of proteinuria increased, the gestational week decreased, the number of pregnancies decreased, the systolic-diastolic blood pressure increased, the platelet count decreased, AST, ALT, LDH, uric acid, BUN, creatinine levels increased, aPTT increased, the maternal length of stay at the hospital was prolonged, the length of stay in the NICU was prolonged, and the newborn height, weight, and Apgar score decreased ($p<0.05$). Among all measurements, the highest correlation was observed between systolic-diastolic blood pressure, maternal length of stay at the hospital, uric acid level, and proteinuria ($r>0.5$), (Table 1).

In the preeclamptic group, proteinuria was negatively correlated with newborn height ($r=-0.390$), newborn weight ($r=-0.421$), Apgar score ($r=-0.353$), and was negatively correlated with neonatal hospitalization time ($r=0.408$), ($p<0.05$), (Table 2).

Table 1: Correlation between preeclampsia and proteinuria in all groups and demographic characteristics

	All patients n=206	Preeclampsia n=103
Age	r=0.005 p=0.948	r=-0.149 p=0.132
Gestational week	r=-0.376 p<**0.001**	r=-**0.294**** p=0.003
Number of pregnancies	r=-**0.148*** p=0.034	r=-0.120 p=0.226
Number of births	r=-0.113 p=0.105	r=-0.130 p=0.191
Number of abortions	r=-0.075 p=0.282	r=0.023 p=0.816
Number of living births	r=-0.090 p=0.199	r=-0.147 p=0.138

*: P<0.05; **: P<0.01; Spearman correlation.

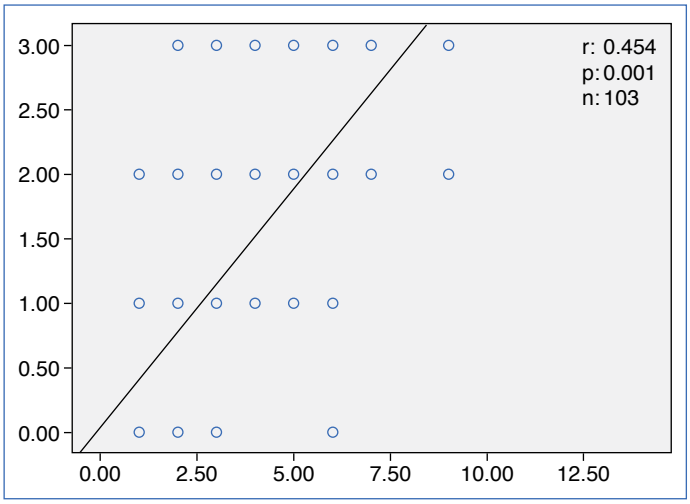

Figure 1: Positive correlation between proteinuria and maternal length of stay at the hospital in the preeclamptic group.

The mode of delivery was the cesarean section in 81.9% of patients with proteinuria levels +2 and +3, and in 55.9% of patients without proteinuria or with a proteinuria level +1, and the difference between them was statistically significant (p<0.001). Antihypertensive treatment was needed in 65% of patients with proteinuria levels +2 and +3, and in 6.72% of patients without proteinuria or with proteinuria level +1 (p<0.001). FGR (fetal growth restriction) was observed in 26.3% of patients with proteinuria levels +2 and +3, and in 0.75% of patients without proteinuria or with +1 proteinuria (p<0.001). Blood or blood product replacement was needed in 55.2% of patients with proteinuria levels +2 and +3, and in 3.26% of patients without proteinuria or with +1 proteinuria (p<0.01). Although there is no statistically significant relationship between proteinuria level and eclampsia, it is noteworthy that all three eclamptic cases were found in the +2/+3 proteinuria group (Table 3).

The relationship between the parameters used to evaluate the severity of preeclampsia and maternal and neonatal outcomes was analyzed. The best correlation was observed between the maternal length of stay at the hospital and proteinuria (r=0.657, p<0.001, n=206), and second between the maternal length of stay at the hospital and diastolic blood pressure (r=0.554, p<0.001, n=206), (p<0.05) (Fig. 1).

Table 2: Correlation between proteinuria and maternal and neonatal outcomes

	Amount of proteinuria all patients n=206	Amount of proteinuria preeclampsia n=103
Maternal hospitalization (days)	r=0.657* p<0.001	R=0.454* p<0.001
Newborn height cm	r=-0.362* p<0.001	r=-0.390* p<0.001
Newborn weight g	r=-0.428* p<0.001	r=-0.421* p<0.001
Apgar score	r=-0.283* p<0.001	r=-0.353* p<0.001
Newborn hospitalization (days)	r=0.490* p<0.001	r=0.408* p<0.001

P<0.05; *: P<0.01; Spearman correlation; BUN: Blood urine nitrogen.

Table 3: Relationship between proteinuria levels and maternal morbidity

	Proteinuria				p
	0–1		2–3		
	n	%	n	%	
Group					
Control	103	76.87	0	0	<**0.001***
Preeclampsia	31	23.13	72	100	
Mode of delivery#					
Normal vaginal birth	59	44.03	13	18.06	<**0.001***
Cesarean section	75	55.97	59	81.94	
Antihypertensıve treatment#					
No	125	93.28	25	34.72	<**0.001***
Yes	9	6.72	47	65.28	
FGR+					
No	133	99.25	53	73.61	<**0.001***
Yes	1	0.75	19	26.39	
Eclampsia+					
No	134	100.00	69	95.83	0.042*
Yes	0	0.00	3	4.17	
Transfusion of blood products+					
No	89	96.74	17	44.74	<**0.001***
Yes	3	3.26	21	55.26	

#: Analyzed with Pearson Chi-square test; +: Analyzed with Fisher's exact test; *: P<0.05 the difference is statistically significant; FGR: Fetal growth restriction.

Table 4: Correlations of the parameters used to evaluate the severity of preeclampsia with maternal and neonatal outcomes

General n=206	Systolic	Diastolic	Hgb (g/dL)	Hct (%)	PLT (mm^3)	AST (U/L)	ALT (U/L)	LDH (U/L)	Uric acid (mg/dL)	BUN mg/dL	Cr mg/dL
Amount of proteinuria											
r	0.836**	0.36**	0.018	-0.067	-0.158*	0.412**	0.227**	0.485**	0.637**	0.369**	0.213**
p	<0.001	<0.001	0.792	0.336	0.023	<0.001	0.001	<0.001	<0.001	<0.001	0.002
Maternal hospitalization (days)											
r	0.550**	0.554**	-0.052	-0.071	-0.207**	0.425**	0.253**	0.480**	0.542**	0.258**	0.142*
p	<0.001	<0.001	0.462	0.308	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	0.042
Newborn height cm											
r	-0.363**	-0.295**	-0.168*	-0.13	0.028	-0.196**	-0.1	-0.262**	-0.239**	-0.305**	-0.224**
p	<0.001	<0.001	0.016	0.062	0.694	0.005	0.153	<0.001	0.001	<0.001	0.001
Newborn weight g											
r	-0.408**	-0.376**	-0.183**	-0.116	0.004	-0.320**	-0.230**	-0.289**	-0.320**	-0.307**	-0.156*
p	<0.001	<0.001	0.008	0.096	0.951	<0.001	0.001	<0.001	<0.001	<0.001	0.026
Apgar score											
r	-0.274**	-0.253**	0.061	0.052	0.116	-0.219**	-0.150*	-0.180**	-0.160*	-0.250**	-0.238**
p	<0.001	<0.001	0.383	0.457	0.097	0.002	0.031	0.01	0.022	<0.001	0.001
Newborn hospitalization (days)											
r	0.466**	0.431**	0.003	-0.01	-0.113	0.319**	0.274**	0.371**	0.400**	0.362**	0.208**
p	<0.001	<0.001	0.97	0.883	0.105	<0.001	<0.001	<0.001	<0.001	<0.001	0.003

*: P<0.05; **: P<0.01; HGB: Hemoglobin; HCT: Hematocrit; PLT: Platelet; AST: Aspartate transaminase; ALT: Alanine transaminase; BUN: Blood urea nitrogen.

Systolic blood pressure also showed a significant and strong positive correlation with AST, ALT, LDH, uric acid, and BUN values. (p<0.05). The strongest negative correlation was found between newborn weight and proteinuria (r=0, –428) (p<0.001; n=206). Proteinuria showed weaker correlations with systolic blood pressure (r=–0.408, p<0.001, n=206), diastolic blood pressure (r=–0.376, p<0.001, n=206), AST (r=–0.320, p<0.001, n=206), uric acid (r=–0.320, p<0.001, n=206), BUN (r=–0.307, p<0.001, n=206), LDH (r=–0.289, p<0.001, n=206), and ALT (r=–0.230, p<0.001, n=206), (p<0.05). It was determined that proteinuria showed the strongest correlation with the newborn's 5th min Apgar score (r=–0.283, p<0.001, n=206). Apgar score showed significant negative correlations with systolic blood pressure (r=–0.274, p<0.001, n=206), diastolic blood pressure (r=–0.253, p<0.001, n=206), BUN (r=–0.250, p<0.001, n=206), and Cr (r=–0.238, p<0.001, n=206). Proteinuria showed the strongest positive correlation with neonatal length of stay at the hospital (r=0.490, p<0.001, n=206). Neonatal length of stay at the hospital showed correlations with systolic blood pressure (r=0.466, p<0.001, n=206), diastolic blood pressure (r=0.431, p<0.001, n=206), AST (r=0.319, p<0.001, n=206), ALT (r=0.274, p<0.001, n=206), LDH (r=0.371, p<0.001, n=206), uric acid (r=0.400, p<0.001, n=206), and BUN (r=0.362, p<0.001, n=206), (p<0.05) (Table 4).

Preeclampsia and systolic and diastolic blood pressures were correlated with proteinuria (Fig. 2).

DISCUSSION

In the bulletin published by ACOG in 2013, it was stated that proteinuria was not associated with maternal and perinatal outcomes, and it was recommended that massive proteinuria should not be a diagnostic criterion for severe preeclampsia.[3] Thus, proteinuria has become controversial as a marker for determining the severity of preeclampsia.

Liu et al.[7] compared preeclamptic pregnant women and pregnant women with gestational hypertension in Taiwan and reported that they observed a positive correlation between resistant hypertension and proteinuria in the preeclamptic group. This study is consistent with our results.

Kumari et al.[8] tried to reveal the relationship between proteinuria and maternal and perinatal outcomes of preeclamptic pregnant women and found a significant positive relationship between proteinuria and resistant hypertension in their study published in 2010. Our findings and current literature suggest that while systolic and diastolic blood pressures are used as markers to understand the severity of the disease, the amount of proteinuria, which is strongly correlated with these, also increases proportionally with the severity of the disease.

Madazlı et al.[9] grouped pregnant women as having mild preeclampsia, severe preeclampsia, and eclampsia in a study they conducted in our country. In the severe preeclampsia and eclampsia groups, they used a proteinuria criterion above 5 g/dL in 24-h urine.

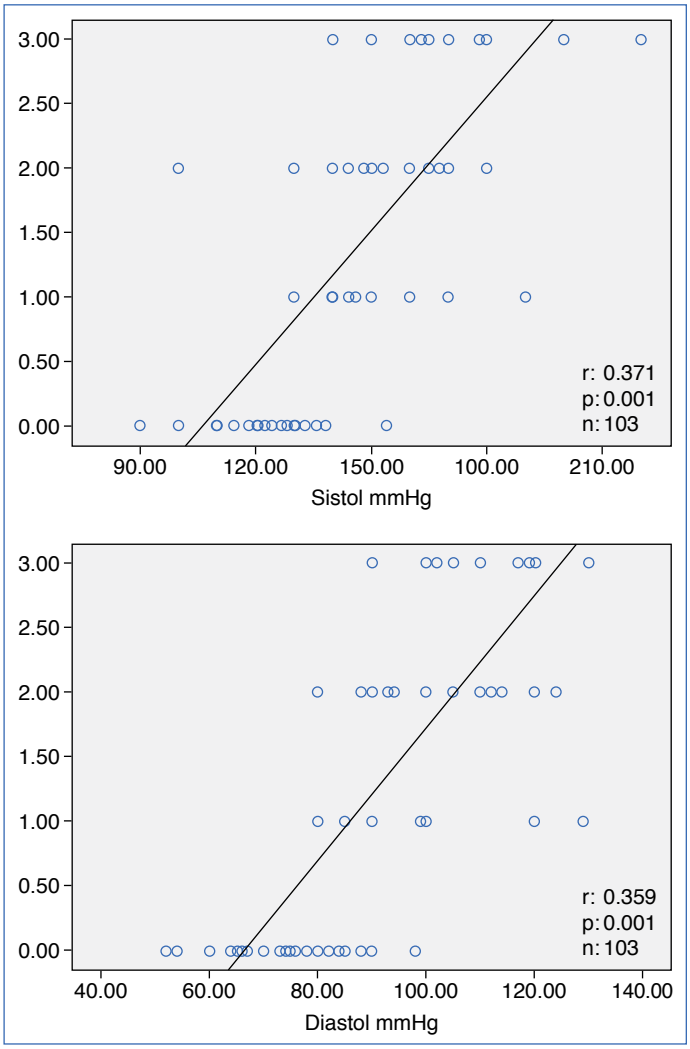

Figure 2: Positive correlation between proteinuria and systolic and diastolic blood pressure in the preeclamptic group.

They evaluated the need for a postpartum intensive care unit and high blood pressure as maternal morbidities. They observed a significant increase in maternal morbidity rates in the severe preeclampsia and eclampsia groups compared to the mild preeclampsia group. Again, Yücesoy et al.[10] showed that the frequency of maternal morbidity (abruptio placentae, acute renal failure, and DIC) increased in preeclamptic patients compared to hypertensive pregnant women without proteinuria. Our data is in agreement with these studies.

In a prospective study involving 340 patients in 2002, Hall et al.[11] followed the patients every 2 weeks with 24-h urine results and observed that the proteinuria level increased in 75% of the patients. They did not observe a significant difference between maternal outcomes. As a result, they argued that proteinuria and its increased levels were not associated with pregnancy outcomes. Contrary to this study, we found a positive correlation between the severity of proteinuria and the duration of the maternal hospital stay. The inconsistency between studies might be due to the fact that one group used 5 g/dL as the criterion for proteinuria, while the other group used 2 g/dL as the criterion.

In their study in 2008, Homer et al.[12] divided the patients into three groups: proteinuria positive preeclampsia, proteinuria negative preeclampsia, and gestational hypertension. They found that severe hypertension, preterm delivery, increased need for neonatal intensive care, and perinatal mortality rates were higher in the proteinuria positive preeclampsia group. In the same study, it was also reported that the proteinuria negative preeclampsia group had a significantly higher rate of severe hypertension and preterm delivery compared to the gestational hypertension group. Similarly, neonatal complications increased as soon as proteinuria was added to the clinical picture in our study, and proteinuria seemed to be associated with perinatal morbidity in preeclamptic pregnant women.

In a study involving 946 patients in the UK, Bramham et al.[13] compared the preeclamptic group with a proteinuria level of 300–500 mg/dL, the preeclamptic group with a proteinuria level >500 mg/dL, the gestational hypertensive group without proteinuria and, and the chronic hypertensive group in terms of maternal and neonatal outcomes. In the group with a proteinuria level >500 mg/dL, the rates of premature birth and <5th percentile newborn weight were significantly higher. When the group with a proteinuria level of 300–500 mg/dL was compared with the gestational hypertensive and chronic hypertensive groups, they found that low birth weight was significantly higher in the proteinuric group than the other groups. They reported that patients with a proteinuria level >300 mg/dL should be followed closely and that a proteinuria level >500 mg/dL was associated with increased pregnancy complications. When the relationship between preeclampsia markers and newborn weight was analyzed in our study, proteinuria showed a strong negative correlation with newborn weight.

There are studies in the literature investigating the relationship between neonatal outcomes and biochemical markers of preeclampsia. One of these was the study by Kocijancic et al.,[14] published in 2013. In that study, patients complicated with hypertensive diseases of pregnancy were examined in two groups: complications such as abruptio placentae, preeclampsia, eclampsia, HELLP syndrome, and intrauterine fetal demise were included in the first group, and hypertensive diseases of pregnancy without obstetric and neonatal complications were compared in the second group. It was aimed at investigating the correlation between biochemical parameters and neonatal outcomes and the existence of a specific biochemical marker that could influence a birth decision. As a result, they reported that they found a strong negative correlation between proteinuria in 24-h urine and Apgar score between groups. In our study, a negative correlation was found between Apgar score and systolic/diastolic blood pressure, BUN, and proteinuria. In their retrospective study including 690 patients, Akyol et al.[15] examined severe preeclamptic patients in two groups as having <2 g/dL and >2 g/dL according to proteinuria level and evaluated the patients in terms of perinatal and neonatal outcomes, but they did not find a statistically significant difference between the mean birth weights of newborns (151). In a study conducted on 307 preeclamptic patients in Norway, patients were divided into three groups as +1, +2, and +3, according to the proteinuria level. It was reported that a significant increase in FGR was observed in the group with +3 proteinuria compared to the other groups was observed.[16] In accordance with this study, when we compared the group with +2/+3 proteinuria and the group with 0/+1 proteinuria, we found a significant increase in FGR in the group with +2/+3 proteinuria.

We observed a cesarean section rate of 75% in the preeclamptic group and 54% in the control group, and fetal distress was observed in 43% of the patients with cesarean section in the preeclamptic group, while 57% of the patients in the control group had a previous history of cesarean section. In the preeclamptic group, it was observed that the cesarean section rate was 55% in patients without proteinuria and with +1 proteinuria, and it was 81% in patients with proteinuria 2 and above. The difference was statistically significant. Similarly, in another study involving 670 patients in a tertiary referral center in Australia, maternal and neonatal outcomes between pregnant women with proteinuric preeclampsia and non-proteinuric hypertensive diseases were analyzed, and more preterm and operative deliveries were observed in the preeclamptic group.[17] It was thought that the increased operative delivery rates in the proteinuric group were due to the excess of expected complications, prodromal findings, and the need for urgent delivery.

Antihypertensive treatment use was approximately 10 times higher in the group with high proteinuria. It was observed that the increased need for antihypertensives with resistant hypertension also increased with proteinuria, which correlated with the increase in systolic-diastolic blood pressure. Dadalszen et al.[18] analyzed the relationship between poor maternal outcomes and preeclamptic markers in 546 preeclamptic patients with at least one maternal complication. They found that the most common maternal bad outcomes were increased oxygen demand, antihypertensive need, and need for transfusion of blood and blood products over 10 units, and they reported a significant association between proteinuria and poor maternal outcomes in parallel with our thesis.

While the need for transfusion of blood and blood products was 3% in the control group, it was 38% in the preeclamptic group, and the difference was statistically significant. While the need for transfusion was 55% in the group with proteinuria levels +2 and above, this rate was found to be 3% in the group without proteinuria and with +1 proteinuria. Similarly, in two studies originating from Türkiye, the need for transfusion was found to be increased in the hypertensive group. In a study in which Turgut et al.[19] compared HELLP syndrome and preeclampsia, they found that the need for transfusion of blood and blood products in HELLP syndrome was significantly higher. In a study in which Kumru et al.[20] investigated the maternal and fetal outcomes of severe preeclampsia and HELLP syndrome, they found a significantly increased need for transfusion of blood and blood products in HELLP syndrome.

The results of our study reveal that proteinuria correlates with both maternal and neonatal morbidity. In addition, proteinuria is strongly correlated with the severe preeclampsia criteria recommended by the ACOG in 2013. Our findings suggest that the presence of proteinuria is an important marker in preeclamptic patients.

Statement

Ethics Committee Approval: The Antalya Training and Reserch Hospital Scientific Clinical Research Ethics Committee granted approval for this study (date: 10.04.2014, number: 39/4).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – AA; Design – AA; Supervision – GB; Data Collection and/or Processing – YEP; Analysis and/or Interpretation – GB; Literature Search – YEP; Writing – AA; Critical Reviews – BSİ.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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