POSTPARTUM RESOLUTION TIME OF PROTEINURIA IS A GOOD PREDICTOR FOR POOR MATERNAL OUTCOMES IN PREECLAMPSIA

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ABSTRACT

Objective: *In this study, we aimed to define the mean resolution time of proteinuria in postpartum pregnant women with preeclampsia and to investigate the relationship between resolution time and the poor obstetric outcomes.*

Material and Method: *The research was conducted as a retrospective, descriptive, cross-sectional study by evaluation of the medical records. Women with preeclampsia were divided into two subgroups: Severe preeclampsia (SPE) and non severe preeclampsia (NSPE).*

Results: *The mean resolution time of proteinuria was 3 days; 3.5 days in the SPE group and 2.1 days in the NSPE group (p=0.002). The resolution time of proteinuria had a good predictive value for poor maternal outcome with an ROC-AUC of 0.73 (95% CI 0.59–0.88; p=0.002), the sensitivity and specificity were 62.5% and 80.2%, respectively. Proteinuria lasted longer than 3 days related with a higher risk of poor maternal outcomes. The ROC-AUC value of the resolution time of proteinuria for severe preeclampsia was found to be 0.70 (95% CI 0.61–0.80; p = 0.001). The sensitivity and specificity were 72.1% and 63.5%, respectively. Amount of proteinuria at diagnosis had a statistically significant relationship with the presence of proteinuria at discharge (OR 2.70; 97.5% CI 1.32–6.02; p = 0.0096).*

Conclusion: *Our results, show that the resolution time of proteinuria at the puerperal period has a predictive value for poor maternal outcomes.*

Keywords: *Preeclampsia, proteinuria, poor maternal outcomes.* **Nobel Med 2017; 13(2): 57-62**

PROTEİNÜRİNİN ÇÖZÜLME SÜRESİ PREEKLAMPSİDE KÖTÜ MATERNAL SONUÇLAR İÇİN İYİ BİR GÖSTERGEDİR

ÖZET

Amaç: Bu çalışmada, preeklampsili gebelerde proteinürinin ortalama rezolüsyon süresini belirlemeyi, rezolüsyon süresi ile kötü obstetrik sonuçlar arasındaki ilişkiyi araştırmayı hedefledik.

Materyal ve Metot: Araştırma tıbbi kayıtların değerlendirilmesi ile retrospektif bir çalışma olarak gerçekleştirildi. Preeklampsili kadınlar iki alt gruba ayrıldı: Şiddetli preeklampsi ve şiddetli olmayan preeklampsi.

Bulgular: Proteinürinin ortalama rezolüsyon süresi 3 gündü; şiddetli preeklampside 3,5 gün ve şiddetli olmayan preeklampside 2,1 gün (p=0,002). Proteinürinin rezolüsyon süresi 0,73 ROC-AUC ile kötü maternal sonuçlar için iyi bir belirleyici değere sahipti (%95 CI 0,59-0,88; p=0,002) (sensitivite ve spesifite sırası ile %62,5 ve %80,2). Proteinürinin 3 günden daha uzun sürmesi daha yüksek kötü maternal sonuç ile ilişkiliydi. Proteinürinin rezolüsyon süresinin şiddetli preeklampsi için ROC-AUC değeri 0,70 olarak bulundu (%95 CI 0,61-0,80; p=0,001) (sensitivite ve spesifite sırası ile %72,1 ve %63,5). Tanı sırasında proteiürinin miktarı hastaneden çıkışta proteinürinin varlığı ile istatistiksel olarak anlamlı bir ilişkiye sahipti (OR 2,70; %97,5 CI 1,32–6,02; p=0,0096).

Sonuç: Sonuçlarımız, proteinürinin lohusalık dönemindeki rezolüsyon süresinin kötü maternal sonuçlar için iyi bir belirleyici değere sahip olduğunu göstermektedir.

Anahtar kelimeler: Preeklampsi, proteinüri, kötü maternal sonuçlar. **Nobel Med 2017; 13(2): 57-62**

INTRODUCTION

Preeclampsia and eclampsia affect approximately 3-10% of all pregnancies and cause 12% of maternal deaths.[1] Preeclampsia is a multisystemic disorder of human pregnancy. Although the pathogenesis of preeclampsia is not exactly known, abnormal vascular response to placentation resulting in placental hypoperfusion and ischemia are accepted as the main triggering mechanisms for preeclampsia. The endothelium of the maternal kidney and the vascular system seem to be the two most affected sites in preeclampsia.[2,3] Inappropriate placentation causes the release of several serum anti-angiogenic factors, particularly soluble fms-like tyrosine kinase 1 (sFlt1), from the placental bed into the maternal bloodstream. The normal function of the glomerular and vascular endothelium is damaged by elevated sFlt1 levels through the antagonism of vascular endothelial growth factor. In the kidney, glomerular endothelial damage and disruption of the normal function of the glomerular podocytes result in proteinuria.[4] Although the changes related to preeclampsia are accepted to resolve completely postpartum, several studies have shown that women who had a pre-eclamptic pregnancy had a significantly increased risk of future cardiovascular and renal disease.[5,6] Thus, even if the acute symptoms of preeclampsia ended, there was still an increased risk of indirect cardiovascular disease and end-stage renal disease.[6,7]

Proteinuria is no longer required in the new definition of preeclampsia that was changed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2014.[8] In recent studies, it has been emphasized that the level of proteinuria is not an indicator of maternal morbidity or perinatal mortality.[9-11] However, it has been emphasized that the resolution time of proteinuria in the long-term after preeclampsia could be related with poor obstetric outcomes in several studies, but the relationship between the resolution time of proteinuria and adverse maternal obstetric outcomes has not been fully examined in the literature.[12,13]

We aimed to determine the short-term resolution time trend of proteinuria postpartum in women with preeclampsia and to investigate the relationship between this time and the poor obstetric outcomes.

MATERIAL AND METHOD

The investigation was conducted as a retrospective, descriptive, cross-sectional study by evaluation of the medical records. Patients with preeclampsia, admitted to Istanbul Medeniyet University Göztepe Teaching and Research Hospital, Department of Obstetrics and Gynaecology between January 2012 and December 2014, were enrolled in our study. The approval of the Local Ethics Committee was obtained for this study (2014/0183).

Women who had diabetes mellitus, gestational diabetes, coagulation disorders, renal diseases, chronic hypertension, vascular complications and any foetal malformations were excluded from this study. Information regarding maternal demographic characteristics, laboratory results and maternal and neonatal clinical findings was obtained from the patients' medical records. Ongoing hypertension

and the use of antihypertensive medication were assessed through telephone interviews 6 months postpartum.

The definition of preeclampsia was established as Systolic Blood Pressure (SBP)≥140 mmHg or Diastolic Blood Pressure (DBP)≥90 mmHg after 20 weeks of pregnancy in previously normotensive pregnant women, adding new-onset proteinuria or any severe features of preeclampsia such as 'thrombocytopenia (platelet count less than 100.000/microliter)', 'renal insufficiency (serum creatinin concentration greater than 1.1 mg/dL)', 'impaired liver function(elevated liver enzymes to twice normal concentration, associated with epigastric or right upper-quadrant pain)', 'pulmonary oedema, new-onset cerebral or visual disturbance' according to the guidelines of The American Congress of Obstetricians and Gynaecologists.[14]

Severe preeclampsia was established as SBP≥160 mmHg or DBP ≥110 mmHg along with the presence of other severe features of preeclampsia. Women with preeclampsia were divided into two subgroups according to presence of the severe symptoms on admission to the hospital: severe preeclampsia (SPE) and preeclampsia without severe pre-eclamptic features (Non Severe PE).

Poor maternal outcome was defined as the presence of one or more complications such as maternal mortality, hepatic or renal dysfunction, eclampsia, neurologic deficit, abruption of placenta, disseminated coagulopathy and blood transfusion due to obstetric haemorrhage.

Poor neonatal outcome was defined as the need for neonatal intensive care unit and the presence of one of the adverse neonatal outcomes presented hereafter. Small for gestational age (SGA) is defined as a weight below the 10th percentile for gestational age at birth. Neonatal mortality is defined as death within the first 28 days of life. In addition, the neonatal birth weights and Apgar scores at 5 min were recorded.

Poor obstetric outcome was defined as the presence of poor maternal and/or poor neonatal outcomes.

Patients with high BP (BP≥150/90 mmHg) on discharge were prescribed antihypertensive drugs such as methyldopa, nifedipine, metoprolol or a combination of drugs. In addition, these patients were classified as having hypertension at discharge.

The mean resolution time of proteinuria was calculated after excluding the cases that had proteinuria at discharge.

The ongoing effects of preeclampsia were defined as the presence of proteinuria at discharge, being on antihypertensive treatment at discharge and antihypertensive medication use 6 months postpartum.

Laboratory Assay of Proteinuria

Proteinuria was defined as a dipstick reading ≥1+ (1+ = 30 mg/dL; 2+ = 100 mg/dL; 3+ = 300 mg/dL; 4+ = 500–1000 mg/dL). Due to the ease of accessibility and the quick results obtained from the dipstick method, we preferred to use the dipstick method for the laboratory measurement of proteinuria. Furthermore, it was confirmed that the dipstick method could be used to predict adverse obstetric events and performed as well as other methods in determining proteinuria in pre-eclamptic women.[9]

Statistical Analysis

The subjects' demographic, clinical and biochemical variables are expressed as the mean ± standard deviation (SD) or percentage (n). The chi-square test was used for categorical variables and the independent t-test was used for continuous variables. These were conducted to investigate the differences between characteristics in each subgroup. Logistic regression analysis was used to select the determinants for dependent variables (i.e. proteinuria and hypertension at discharge and hypertension at 6 months postpartum). The effectiveness of the resolution time of proteinuria in predicting the adverse outcomes was assessed by using receiver operating characteristic (ROC) curves and by comparing the Area under the ROC curves (AUC). Statistical analysis was performed using the NPAR1WAY procedure (SAS System 9.1, SAS Institute Inc., Cary, NC, USA).

RESULTS

The study population included 116 pregnant women with preeclampsia admitted to the obstetrics ward. Of 116 women, 43 (37%) had severe clinical findings of preeclampsia while 73 (62%) did not. The clinical properties and obstetrics outcomes of the study population are presented in Table. Resolution time of proteinuria was 3.51±2.14 days in the SPE group and was 2.15±1.71 days in the NSPE group (p=0.002). The presence of proteinuria at discharge was 27% (32/116) in all cases. This was found to be higher in the SPE group than in the NSPE group, and the results are also shown in Table. The rate of antihypertensive drug prescription at discharge was 35% (41/116) in all cases. There was no statistically significant difference between the two groups. The rate of hypertension 6 months postpartum was 12% (15/116), and there was no statistically significant difference between the SPE and NSPE subgroups.

Table. The laboratory findings and perinatal outcomes.

		Severe preeclampsia n: 43	Without severe features preeclampsia n:73	*p*-value
Age, year mean(±SD)		30.1±6.0	28.05±5.9	0.07
Nulliparity n(%)		25(22%)	39(33%)	0.7
At diagnosis of Preeclampsia	Gestational age, week (±SD)	33.84±4.15	36.27±3.44	0.001
	SBP mm Hg (±SD)	167.09±22.76	152.97±32.532	0.02
	DBP mm Hg(±SD)	104.77±14.31	98.85±11.15	0.03
	ALT Level U/L (±SD)	40.47±54.28	16.61±16.74	0.03
	AST U/L Level(±SD)	64.54±97.09	26.69±19.19	0.01
At discharg	SBP mm Hg (±SD)	135.4±15.7	129.1±13.5	0.04
	DBP mm Hg ±SD)	84.7±11.4	80.4±11.7	0.02
Clinical outcomes				
Resolution time of proteinuria,day (±SD)		3.51±2.14	2.15±1.71	0.002
Time from diagnosis to delivery, day (±SD)		1.30±3.73	0.65±1.27	0.81
Time to discharge from delivery, day (±SD)		4.39±2.01	3.55±1.36	0.007
Poor maternal outcome n(%)		11(9)	5(4)	0.008
Poor obstetric outcome n(%)		36(31)	44(38)	0.01
Neonatal outcomes				
APGAR 5th min (±SD)		6.8±3,2	8.6±2,3	<0.001
Birthweight g (±SD)		1935±814.13	2667.29±828.16	0.001
Need NICU n(%)		29(67)	30(40)	0.009
Death n(%)		9(24)	4(5)	0.01
Ongoing effects of preeclampsia				
Presence of proteinuria at discharge n(%)		17(15)	15(13)	0.03
Presence of hypertension at discharge n(%)		18(15)	23(20)	0.354
Hypertension at 6 months n(%)		5(4)	10(9)	0.972

SBP: Systolic blood pressure, **DBP:** diastolic blood pressure, **ALT:** alanine transaminase, **AST:** aspartate transaminase, **NICU:** neonatal intensive care unit

In this study, logistic regression analysis was used to select the risk factors for the presence of proteinuria and hypertension at discharge and hypertension 6 months postpartum. So, we researched the risk factors related with on going effect of preeclampsia. After we fitted the initial model with all the independent variables noted in Table, we used stepwise regression to select the best model, which had the lowest Akaike Information Criteria score. We found that in the reduced model, the amount of proteinuria at the diagnosis of preeclampsia had a statistically significant relationship with the presence of proteinuria at discharge (OR 2.70; 97.5% CI 1.32–6.02; p= 0.0096). In this model, a relationship was observed between the systolic BP on admission and the presence of hypertension on discharge (OR 1.05; 97.5% CI 1.02–1.09; p= 0.0045). This implies that keeping all other variables constant, an increase, on admission, of the systolic BP by 10 mmHg would increase the odds of having hypertension at discharge by 1.05 times (data not shown). In the regression analysis, hypertension 6 months postpartum had no statistical relationship with the independent variables. The results of regression analyses are not presented in a table.

In 84 cases, the mean resolution time of proteinuria was 3 days: 3.5 days in the SPE group and 2.1 days in the NSPE group (p=0.002). In this study, we researched the relationship between the resolution time of proteinuria and the following parameters: poor maternal outcome; poor neonatal outcome and the severity of preeclampsia. We investigated the effect of the increase of proteinuria resolution time by 1 day on the parameters noted above using ROC curves and by comparing AUC. The AUC of the ROC was computed for each analysis.[15] An AUC-ROC of >0.7 is considered the minimum to indicate an adequately discriminated test; 1.0 indicates perfect discrimination and 0.5 is non-discriminative. The performance associated with these parameters ranged from fair ($0.5 < AUC \leq 0.7$) to good ($0.7 < AUC \leq 0.9$).

The resolution time of proteinuria had a good predictive value for poor maternal outcome with an ROC-AUC of 0.73 (95% CI 0.59–0.88; p=0.002). The sensitivity and specificity were 62.5% and 80.2%, respectively (Figure 1). The maximum sensitivity and specificity cut-off point was 0.127 (pointed 3 days). It means that women with preeclampsia who had proteinuria, which lasted longer than 3 days, had a higher risk of poor maternal outcomes.

The resolution time of proteinuria had a fair predictive value for the presence of severe disease on admission to the hospital with an ROC-AUC of 0.70 (95% CI 0.61–0.80; p=0.001). The sensitivity and specificity were 72.1% and 63.5%, respectively (Figure 2). The maximum sensitivity and specificity cut-off point was 0.304 (pointed 2 days). If the proteinuria lasted longer than 2 days, the risk of severe preeclampsia was high.

DISCUSSION

We investigated the resolution time of proteinuria and hypertension during the postpartum period in women with preeclampsia. Our results showed that in the puerperal period, 35% of the women had hypertension. Moreover, in 12% of the women, hypertension was still present 6-months postpartum. The prevalence of persistent hypertension was 50%-78% in the puerperal period and 14.8%-18% at 6 months to 2 years postpartum.[12,13,16,17] In normal pregnancy, the renin–angiotensin–aldosterone system is activated by hemodynamic changes such as the reduction in systemic vascular resistance and systemic blood pressure, resulting in the increase

of water and sodium retention.[18] In preeclampsia, generalized vasoconstriction from enhanced responses to vasoactive substances leads to increased blood pressure and reduced intravascular volume.[3,11,16] The generalized vasoconstriction during preeclampsia could explain the persistence of hypertension following the postpartum period and could be relevant to the increased risk of long-term age-related hypertension. According to Kaze FF *et al.*, increasing age, low gestational age at delivery, low foetal birth weight, and increased proteinuria at delivery were reported as factors that are correlated with the persistence of proteinuria and hypertension.[13] In our study, the systolic BP on admission was found as the only factor correlated with the persistence of hypertension. There have also been controversial reports about the normalization time of hypertension and the factors associated with the persistence of hypertension.[12,19,20]

We investigated the persistence of proteinuria during the just postpartum period in women with preeclampsia and the determinants associated with it. We also assessed the effectiveness of the resolution time of proteinuria in predicting adverse outcomes. Our results showed that in the puerperal period, 27% of the women with preeclampsia had persistent proteinuria. In other studies, this was reported to be approximately 50%-67% .[12,16,21] According to Unverdi *et al.*, the persistence of proteinuria in Turkish women with preeclampsia at 3-months postpartum was reported to be 7.3% and was emphasized as the most important predictor of renal disease after delivery.[22] During pregnancy, urinary protein excretion increases because of increased glomerular filtration rate, increased permeability of the glomerular basement membrane, and reduction of the tubular reabsorption of filtered protein. In preeclampsia, the excess of soluble fms-like tyrosine kinase (sFlt-1) binds to the vascular endothelial growth factor (VEGF) and inhibits its receptors that are present on glomerular endothelial cells and podocytes. Dysregulation of the VEGF leads to glomerular barrier dysfunction and results in the proteinuria and podocyturia noted in preeclampsia.[23] The restoration of the normal balance of angiogenic factors in preeclampsia occurs after delivery of the placenta and promotes rapid endothelial cell healing. The healing of preeclamptic glomerular endothelial injury has been reported to occur over a period of 3–6 months and even in excess of 12 months in some cases. This explains the discrepancy in the results.[24,25]

At the recent studies, the determinants associated with the resolution time of proteinuria after delivery was investigated. Berks D *et al.*, reported that the resolution time of proteinuria was not significantly correlated with maximal systolic and diastolic BP

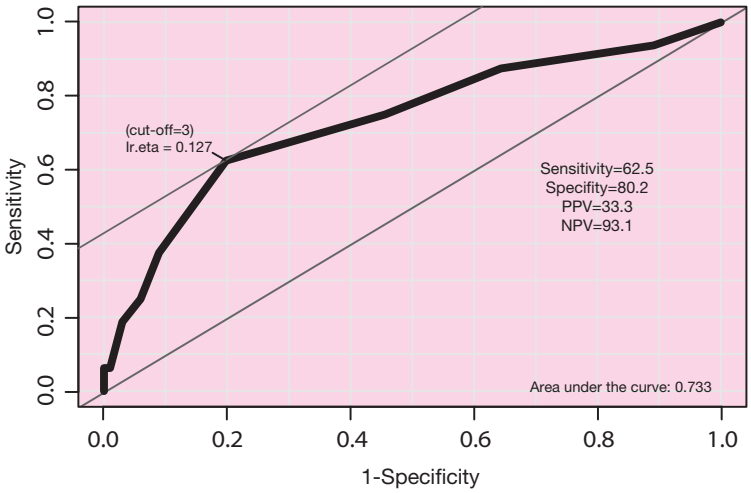

Figure 1. ROC-AUC analysis for prediction of maternal complications with the resolution time of proteinuria in women with preeclampsia.(p=0.05)

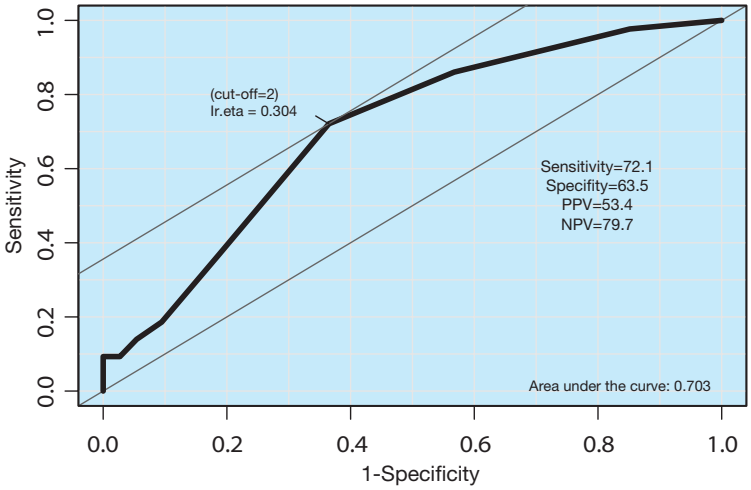

Figure 2. ROC-AUC analysis for prediction of severe preeclampsia at admission with the resolution time of proteinuria in women with preeclampsia.

during preeclampsia, gestational age at onset of preeclampsia, or the time interval between diagnosis and delivery.[12] Most of studies revealed a relationship between the degree of urinary protein excretion at diagnosis and the resolution time of proteinuria postpartum in women with preeclampsia.[12,13,26] As previously suggested, endothelial dysfunction plays a central role in the pathogenesis of preeclampsia and leads to hypertension and proteinuria. The level of proteinuria and blood pressure reflect the extent of renal and vascular endothelial cell injury during preeclampsia.[26] Consistent with other research findings, we found that the amount of proteinuria at diagnosis had a statistically significant relationship with the persistence of proteinuria at discharge. Also, we found a longer short-term resolution time in the SPE group than in the NSPE group. The proteinuria level at diagnosis and severity of disease had an important impact on the on going effect of preeclampsia.

In addition, we showed that the resolution time of proteinuria was predictive for poor maternal outcomes and the presence of severe disease on admission. The resolution time of hypertension and proteinuria could well-reflect endothelial cell recovery after preeclampsia or the ability of women with preeclampsia to recover from endothelial cell injury. The resolution time of proteinuria could be correlated with the magnitude of the damage that was caused by preeclampsia. The statistically significant relationship between this resolution time period, severity of preeclampsia, and poor maternal outcomes supported this hypothesis. However, the findings of this study should be investigated with prospective studies based on larger populations.

In this study, the amount of proteinuria on admission was the only determinant related to the presence of proteinuria at discharge. Due to the short follow-up period, we could not establish any relationship between the amount of proteinuria on admission, the long-term resolution of proteinuria, or later cardiovascular and/or renal disease. Moreover, it restricted our ability to compare our findings with others.[16,17,26]

CONCLUSION

Despite the limitations of this study, our findings showed that not previously documented in the literature, the severity of preeclampsia was significantly correlated with the resolution time and presence of proteinuria at discharge. In addition, our findings suggest that the postpartum resolution time of proteinuria is a good predictor for adverse maternal outcomes.

*The authors declare that there are no conflicts of interest.

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