# Comparison of protein amount in 24-hour urine and protein/creatinine rate in spot urine of preeclamptic pregnant women

**Sevgi Gökdoğan[1], Berna Aslan Çetin[1], Pınar Yalçın Bahat[1], Alev Atış Aydın[2], Aysu Akça[1]**

[1]Gynecology and Obstetrics Clinic, Istanbul Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey
[2]Perinatology Clinic, Istanbul Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey

## Abstract

**Objective:** To compare protein amount in 24-hour urine and protein/creatinine rate in spot urine of preeclamptic pregnant women.

**Methods:** The study included 45 pregnant women with preeclampsia whose 24-hour urine protein and protein/creatinine rate in spot urine were checked in the Perinatology Clinic of Istanbul Kanuni Sultan Süleyman Training and Research Hospital between January 2015 and December 2015 and 45 pregnant women without preeclampsia as control group who were followed up in obstetrics polyclinics. Systolic and diastolic blood pressure values, protein amount in 24-hour urine, protein/creatinine rate in spot urine, delivery week, delivery type, birth weights and 1-minute and 5-minute APGAR scores of pregnant women in both groups were recorded and their correlation with protein/creatinine rate in spot urine were evaluated.

**Results:** When protein amounts in 24-hour urine and protein/creatinine rate in spot urine of patients were compared, significant correlation was found between 24-hour urine protein and protein/creatinine rate. It was also found that there was no significant correlation between protein/creatinine rates and blood pressure values, delivery week, birth weight and APGAR scores.

**Conclusion:** We found that there was a significant correlation between protein amount in 24-hour urine and protein/creatinine rates in spot urine. Therefore, in acute and emergency cases where proteinuria cannot be checked in 24-hour urine, protein/creatinine rate in spot urine can be useful to evaluate proteinuria.

**Keywords:** Preeclampsia, protein amount in 24-hour urine, protein/creatinine rate in spot urine.

## Özet: Preeklamptik gebelerde 24 saatlik idrarda protein miktarı ile spot idrarda protein/kreatinin oranının karşılaştırılması

**Amaç:** Preeklampsi tanılı hastalarda 24 saatlik idrarda protein miktarı ile spot idrarda protein/kreatinin oranının karşılaştırılması.

**Yöntem:** Çalışmaya, Ocak 2015–Aralık 2015 tarihleri arasında İstanbul Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Perinatoloji Servisi'nde 24 saatlik idrar proteini ile spot idrarda protein/kreatinin oranı bakılan preeklampsi tanılı 45 gebe ve kontrol grubu için de preeklampsi tanılı olmayan, gebe polikliniklerinde takip edilen 45 gebe dahil edildi. Her iki gruptaki gebelerin sistolik ve diyastolik tansiyon değerleri, 24 saatlik idrarda protein miktarı, spot idrarda protein/kreatinin oranı, doğum haftası, doğum şekli, doğum kiloları, 1. ve 5. dakikadaki APGAR skorları kaydedildi ve bunların spot idrardaki protein/kreatinin oranı ile korelasyonu incelendi.

**Bulgular:** Hastaların 24 saatlik idrarda protein miktarı ve spot idrarda protein/kreatinin oranları karşılaştırıldığında, 24 saatlik idrar proteini ile protein/kreatinin oranı arasında anlamlı korelasyon olduğu izlendi. Protein/kreatinin oranlarının ayrıca tansiyon değerleri, doğum haftası, doğum kilosu ve APGAR skorları ile yapılan karşılaştırılmasında bunlar arasında anlamlı bir korelasyon izlenmediği saptandı.

**Sonuç:** 24 saatlik idrarda protein miktarı ile spot idrarda protein/kreatinin oranları arasında anlamlı bir korelasyon olduğunu izledik. Bu nedenle 24 saatlik idrarda proteinürinin bakılamadığı akut, acil durumlarda spot idrarda protein/kreatinin oranının proteinüriyi değerlendirmede faydalı olduğunu bulduk.

**Anahtar sözcükler:** Preeklampsi, 24 saatlik idrarda protein miktarı, spot idrarda protein/kreatinin oranı.

deomed®

## Introduction

Preeclampsia is defined as the hypertension beginning with end organ dysfunction or proteinuria after 20 weeks of gestation in a normotensive woman. Signs and symptoms of severe hypertension and end organ damage are characterized as the serious spectrum of the disease. In the absence of proteinuria, preeclampsia is characterized with thrombocytopenia (thrombocytes number below 100,000/microliter), impaired hepatic function (hepatic transaminase concentration doubling up the normal level), onset of renal impairment (serum creatinine level rising above 1.1 mg/dl or serum creatinine doubling up in the absence of renal disorder), and the indications of end organ damage including recent onset of cerebral or visual impairment.[1]

In 2013, the American Congress of Obstetricians and Gynecologists (ACOG) removed proteinuria from the criteria necessary for the diagnosis of preeclampsia. Proteinuria is an independent risk factor for renal and cardiovascular disorders and it is considered as a marker indicating end organ damage.[2]

Although proteinuria is not a requirement for preeclampsia diagnosis, it is a significant laboratory finding identified in preeclamptic patients. In our study, we aimed to compare protein/creatinine (P/C) rates with protein measurement in 24-hour urine in preeclamptic pregnant women hospitalized in the Perinatology Clinic of İstanbul Kanuni Sultan Süleyman Training and Research Hospital.

## Methods

This study was planned prospectively by recording demographic and obstetric data of 45 preeclamptic pregnant women who were hospitalized in the Perinatology Clinic of İstanbul Kanuni Sultan Süleyman Training and Research Hospital between January 2015 and December 2015, diagnosed according to 2013 criteria of the American Congress of Obstetricians and Gynecologists (ACOG) and had no severe preeclampsia findings, and 45 non-preeclamptic pregnant women who were on the weeks of pregnancy similar to the study group and followed up in obstetrics polyclinics. The study was initiated with the approval no 15,933 obtained from the ethics board of the hospital in 2015. The principles stated in the Declaration of Helsinki were followed during the study.

Multiple pregnancies, and pregnant women with preeclampsia diagnosis under 24 weeks, premature rupture of membrane, diabetes, urinary tract infection or acute-chronic renal disorder were excluded from the study. The ages, obstetric anamneses, and CRL-based gestational ages of all pregnant women included in the study were recorded.

24-hour urine and clean-catch spot urines were asked from all preeclamptic patients in the study group. These procedures were explained to all patients in detail. Since checking P/C rate in the clean-catch urine yields more reliable results, the patients were asked for clean-catch urine sample and this procedure was also explained in detail. Same procedures were also repeated for the control group.

Clean-catch urine samples of these patients were transferred to the laboratory immediately. After the samples were centrifuged in sealed tubes at 8 min/3000 rpm, the tubes were analyzed in COBAS 6000 device (Roche Diagnostics Ltd., Rotkreuz, Switzerland) and the values were recorded quantitatively.

### Statistical analysis

IBM SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. In addition to descriptive statistical methods (mean, standard deviation) for the analysis of data, independent t-test was also used for pairwise comparison. Analysis of Pearson's correlation coefficient was used to compare protein/creatinine rate in spot urine and protein level in 24-hour urine. For different P/C rates, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. The relationship between P/C rate in spot urine and fetal obstetric outcomes were evaluated by ROC analysis. Level of significance at $p < 0.05$ was considered as positive.

## Results

The weeks of gestation for preeclamptic cases in the study ranged between 26 and 36 weeks and the mean week was calculated 31.02±0.49. The weeks of gestation for cases in the control group ranged between 26 and 38 weeks and the mean week was calculated 33.37±0.49 (**Table 1**).

There was no significant difference between study and control groups in terms of gravida, parity, week of gestation, systolic and diastolic blood pressure values. Statistically significant difference was identified between two groups for protein amount in 24-hour urine, P/C

**Table 1.** Comparison of demographic data and obstetric outcomes of preeclampsia and control groups.

|  | Preeclampsia group (n=45) | Control group (n=45) | p |
|---|---|---|---|
| Age | 31.48±0.87 | 29.00±0.76 | 0.488 |
| Gravida | 2.26±0.24 | 2.40±0.17 | 0.081 |
| Parity | 0.95±0.14 | 1.06±0.14 | 0.212 |
| Systolic blood pressure (mmHg) | 139.33±22.33 | 117.11±20.00 | 0.398 |
| Diastolic blood pressure (mmHg) | 87.11±14.43 | 73.77±15.00 | 0.482 |
| Delivery week | 33.08±0.47 | 37.37±0.30 | **<0.001** |
| Birth weight (g) | 1685.80±120.09 | 2868.70±77.27 | **0.001** |
| Protein (mg/day) | 2000.81±248.49 | 175.69±8.56 | **<0.001** |
| Protein/creatinine rate | 1.67±0.24 | 0.21±0.02 | **<0.001** |
| Volume of 24-hour urine (ml) | 2484.08±538.42 | 2170.45±434.92 | 0.386 |
| Week of gestation | 31.02±0.49 | 33.37±0.49 | 0.695 |
| 1-minute APGAR | 7.11±0.29 | 8.13±0.20 | **0.017** |
| 5-minute APGAR | 8.71±0.22 | 9.48±0.11 | **0.017** |

rate, delivery week, birth weight, and 1-minute and 5-minute APGAR scores.

In the preeclampsia group, mean delivery week was 33.08±0.47 and mean birth weight was 1685.80±120.09 g. In the same group, mean 1-minute APGAR score was 7.11±0.29 and mean 5-minute APGAR score was 8.71±0.22. For the cases in the preeclamptic group, the mean protein amount in 24-hour urine was 00.81±248.49

mg/day and mean P/C rate was 1.67±0.24 mg/mg. Of the cases in the control group of the study, the mean delivery week was 37.37±0.30, and mean birth weight was 2868.70±77.27 g. We found that mean 1-minute APGAR score of the cases in the control group was 8.13±0.20 and 5-minute APGAR score was 9.48±0.11. In the same cases, mean protein amount in 24-hour urine was 175.69±8.56 mg/day and mean P/C rate was 0.21±0.02 mg/mg (**Table 1**).

In the ROC analysis performed on P/C rate in the spot urine and the presence of preeclampsia, the area under curve (AUC) was 0.919 (**Fig. 1**).

In our study, we found that the sensitivity of the test was 86% and the specificity was 91% to detect the presence of preeclampsia when the threshold for P/C rate was 0.3 according to ACOG Guideline and the sensitivity was 60% and the specificity was 100% when the threshold for P/C rate was 1 (**Table 2**).
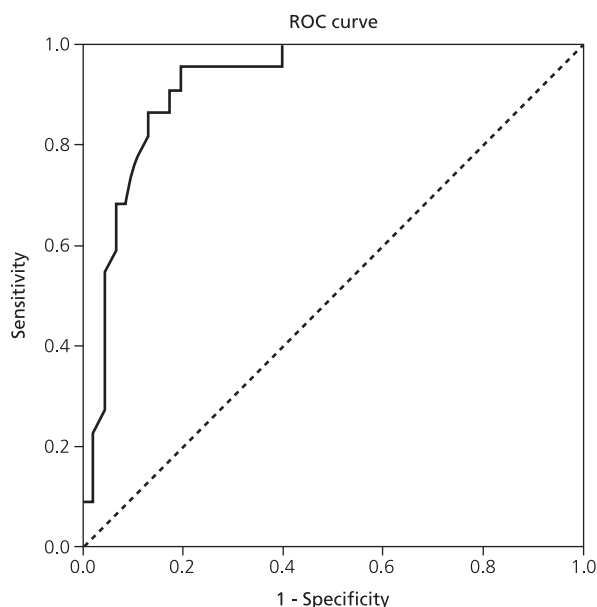


**Fig. 1.** ROC analysis performed between protein/creatinine rate and the presence of preeclampsia.

**Table 2.** Predictive values in different cut-off values of protein/creatinine rate.

| Cut-off value of P/C rate | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| 0.27 | 86.6 | 84.4 | 84.7 | 86.3 |
| 0.30 | 86.6 | 91.1 | 90.6 | 87.2 |
| 0.50 | 77.7 | 97.7 | 97.2 | 81.4 |
| 0.75 | 71.1 | 97.7 | 96.9 | 77.1 |
| 1 | 60 | 100 | 100 | 71.4 |

**NPV:** Negative predictive value, **PPV:** Positive predictive value

We found a high level of correlation between P/C rate in spot urine and protein amount in 24-hour urine (r=0.707).

The AUC value was 0.479 in the ROC analysis performed between P/C rate in spot urine and systolic blood pressure being >140 and it was 0.472 between P/C rate in spot urine and diastolic blood pressure being >90. In the ROC analysis performed for P/C rate in spot urine and premature delivery week (<34 week), low birth weight (below 2500 g), 1-minute APGAR score below 4 and 5-minute APGAR score below 4, AUC values were 0.496, 0.579, 0.398 and 0.484, respectively.

## Discussion

Preeclampsia is a multisystem condition characterized with the hypertension starting in the second part of the pregnancy together with proteinuria or dysfunction of any organ. Although the delivery rates at term or near term of pregnant women affected are high and their maternal and fetal outcomes are good, they have serious maternal and/or fetal mortality/morbidity rates.[3,4] The condition is characterized by systemic endothelial damage, vascular collapse and glomerular endotheliosis.

The method commonly exercised and considered as golden standard for determining the proteinuria is the protein amount checked in 24-hour urine. However, the differences in 24-hour urine accumulation due to lower or higher collection during urine accumulation of patients may result in incorrect results for protein levels.[5] Due to the difficulty of conformity in the step of collecting 24-hour urine tests, inconvenient and expensive process of collecting 24-hour urine, and convenience of checking spot urine, checking P/C rate in spot urine has been brought up into agenda.

According to the statistical results of our study, we found that P/C rate in spot urine was well correlated with protein value in 24-hour urine (r=0.707, p<0.001). Today, many international organizations consider that P/C rate in the spot urine being between 0.26 and 0.3 mg protein/mg creatinine is the indication of preeclampsia.[6,7]

Similar to our study, Shahbazian et al. compared P/C rate in spot urine and protein amount in 24-hour urine in their study conducted on 81 patients.[8] In this study, they found significant correlation between two tests (r=0.84, p<0.001).

In the study conducted on 75 cases in 2014, Nischintha et al. concluded that there was a positive correlation between P/C rate in spot urine and protein amount in 24-hour urine, and they reported that P/C rate could be used as an alternative test instead of protein amount in 24-hour urine.[9]

Demirci et al. compared P/C rate in spot urine and protein amount in 24-hour urine in their study performed in 2013 and they found a significant correlation (r=0.758) between two values similar to our study and other up-to-date studies.[10–12]

P/C rate is associated with proteinuria, but it does not have a certain cut-off value enough for diagnosis. Depending on different cut-off values, specificity and sensitivity rates change and specificity increases as cut-off value rises. In the retrospective study conducted between 2005 and 2007 on a series of 356 cases, Stout et al. evaluated the relationship between 24-hour urine and P/C rate in spot urine. According to the results of the study, AUC was found 0.82 in the ROC analysis performed on P/C rate and protein amount in 24-hour urine, but it was reported that it was difficult to find a certain cut-off value for P/C rate in spot urine.[13] In this study, the calculation was done by considering cut-off value as 0.08 and 1.19. P/C rate ruled out preeclampsia when cut-off value was <0.08 whereas preeclampsia was considered to be present when cut-off value >1.19. In P/C rates between these values, collecting 24-hour urine was reported necessary for diagnosis. In the study on a series of 54 cases, Nisell et al. reported the best cut-off value as 0.27 and the sensitivity was found 95% and specificity 100% at this value.[14] In our study, when we considered the threshold value for P/C rate as 0.27, the sensitivity was 86% and specificity was 84%; when the threshold value was 0.3 according to ACOG Guideline, the sensitivity was 86% and specificity was 91%, and they were 60% and 100%, respectively, when threshold was 1. In our study, sensitivity decreased and specificity increased as cut-off value increased. The P/K cut-off value we found in preeclampsia diagnosis is 0.3, same as the value of ACOG.

In the study of Nischintha et al., the authors also included newborn and fetal data in the study and they showed that the rate of newborns with very low birth weight increased from 9.8% to 17.6% in proteinuria values over 300 mg/day, which was the threshold. However, when P/C rate increased, they did not observe additional increase proportionately.[9] In our study, we

did not observe any significant relationship between decreasing P/C rate and newborns with low birth weight in patients with P/C rate >0.3 (ROC AUC: 0.579).

We compared proteinuria amount and gestational outcomes in our study. When we evaluated each parameter (delivery week, birth weight, APGAR score, blood pressure values of cases), we found that these parameters were not correlated with proteinuria. In other words, when proteinuria amount is high, gestational outcomes are not more complicated in parallel. ACOG's decision to remove proteinuria from the criteria for severe preeclampsia supports our finding.

Checking P/C rate in spot urine in order to establish emergency or acute preeclampsia diagnosis to patients saves time. On the other hand, collecting 24-hour urine is time-consuming during diagnosis process. In this case, maternal and fetal morbidity and mortality increase. Considering more recent studies, we believe that P/C rate in preeclamptic patients can be soon an alternative to the method of collecting 24-hour urine.

## Conclusion

In our study, we compared protein/creatinine rate in spot urine to the protein amount in 24-hour urine. We found that the protein amount in 24-hour urine was correlated to the protein/creatinine rate in spot urine of our patients. Based on the results of our study, we believe that P/C rate in spot urine can be an alternative test to the protein test on 24-hour urine, especially in emergency cases.

**Conflicts of Interest:** No conflicts declared.

## References

1. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.

2. Barnas U, Schmidt A, Haas M, Kaider A, Tillawi S, Wamser P, et al. Parameters associated with chronic renal transplant failure. Nephrol Dial Transplant 1997;12 Suppl 2:82–5.

3. Sibai BM, Caritis S, Hauth J; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What we have learned about preeclampsia. Semin Perinatol 2003;27:239–46.

4. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of preeclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 2011;25:391–403.

5. Saudan PJ, Brown MA, Farrell T, Shaw L. Improved methods of assessing proteinuria in hypertensive pregnancy. Br J Obstet Gynaecol 1997;104:1159–64.

6. Piccoli GB, Attini R, Parisi S, Vigotti FN, Daidola G, Deagostini MC, et al. Excessive urinary tract dilatation and proteinuria in pregnancy: a common and overlooked association? BMC Nephrol 2013;14:52.

7. Verlohren S, Galindo A, Schlembach D, Zeisler H, Herraiz I, Moertl MG, et al. An automated method for the determination of the sFlt-1/PlGF ratio in the assessment of preeclampsia. Am J Obstet Gynecol 2010;202(2): 161.e1–161.e11.

8. Shahbazian N, Hosseini-Asl F. A comparison of spot urine protein-creatinine ratio with 24-hour urine protein excretion in women with preeclampsia. Iran J Kidney Dis 2008;2: 127–31.

9. Nischintha S, Pallavee P, Ghose S. Correlation between 24-h urine protein, spot urine protein/creatinine ratio, and serum uric acid and their association with fetomaternal outcomes in preeclamptic women. J Nat Sci Biol Med 2014;5:255–60.

10. Demirci O, Kumru P, Arınkan A, Ardıç C, Arısoy R, Tozkır E, et al. Spot protein/creatinine ratio in preeclampsia as an alternative for 24-hour urine protein. Balkan Med J 2015;32:51–5.

11. Wheeler TL 2nd, Blackhurst DW, Dellinger EH, Ramsey PS. Usage of spot urine protein to creatinine ratios in the evaluation of preeclampsia. Am J Obstet Gynecol 2007;196:465.e1–4.

12. Eslamian L, Behnam F, Tehrani ZF, Jamal A, Marsoosi V. Randomurine protein creatinine ratio as a preadmission test in hypertensive pregnancies with urinary protein creatinine ratio. Acta Med Iran 2011;49:81–4.

13. Stout MJ, Scifres CM, Stamilio DM. Diagnostic utility of urine protein-to-creatinine ratio for identifying proteinuria in pregnancy J Matern Fetal Neonatal Med 2013;26:66–70.

14. Nisell H, Trygg M, Back R. Urine albumin/creatinine ratio for assessment of albuminuria in pregnancy hypertension. Acta Obstet Gynecol Scand 2006;85:1327–30.