Correlation of Random Urinary Protein to Creatinine Ratio in 24-Hour Urine Samples of Pregnant Women with Preeclampsia

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Abstract

Objective: To determine the value of random urinary protein to creatinine ratio (UPCR) for diagnosis of proteinuria in pregnant women with preeclampsia. Preeclampsia is the most common complication of pregnancy and one of the main causes of maternal mortality .So, early diagnosis of preeclampsia is very important.

Materials and methods: In this cross-sectional study 66 pregnant women suspected preeclampsia at ≥24 week of gestational age and BP≥140/90 mm/Hg were checked by two urine samples of 10am and 4pm to determine random UPCR, as well as a 24-hour urine sample to evaluate 24-hour protein excretion.

Results: The result revealed that 74.2% of the studied population had significant proteinuria. There was a correlation between UPCR and 24-hour urine protein excretion. Pearson's correlation coefficient was 0.502 at 10am and 0.428 at 4pm. The best cutoff for the random urine protein to creatinine ratio at 10am was 0.470 with sensitivity and specificity equal to 87.5% and 84.2%, respectively. The best cutoff for the random UPCR at 4pm was 0.595 with sensitivity and specificity equal to 91.7% and 94.7%, respectively.

Conclusion: Result of 24-hour urine collection showing random UPCR is considered as an appropriate situated method for emergency time.

Keywords: Preeclampsia, Pregnancy, Protein to creatinine ratio, Proteinuria

Introduction

Preeclampsia is one of the leading causes of maternal death, along with hemorrhage and infection (1). Preeclampsia causes a variety of fetal and maternal complications, including acute and chronic placental insufficiency, fetal distress, still birth, pulmonary edema, HELLP (H=hemolysis; El=elevated liver enzyme; LP=low platelets counts) syndrome, eclampsia, disseminated intravascular coagulation (DIC), and renal cortical necrosis (2). Early diagnosis and management of preeclampsia are very important due to severity of such complications. Diagnostic criteria for preeclampsia include increase in blood pressure (systolic ≥140 and diastolic ≥90) after the 20th week of pregnancy, also observation of either proteinuria ≥300 mg in a 24-hour urine sample, or 100mg/dl in two random urine samples with at least 6 hours interval (3,4). While 24 hour urine collection is the gold standard method for diagnosing proteinuria (1, 5), this significant procedure has high price and time limit for diagnosis.

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The test result can be cumbersome if it is done inaccurately. Proteinuria can also be measured using albumin instead of total protein level in a 24-hour urine collection. A simple replacement diagnostic tool, applying effectively for 24-hour urine collection, is the detection of protein with a dipstick in random sample, or a random urinary protein to creatinine ratio (UPCR). The data is inconclusive; however, some study has showed random UPCR as a valid correlation with 24 hour urine collection (6-13). Other studied have also showed the random urinary protein to creatinine ratio as an unreliable method, so they have suggested not to be replaced with 24- hour urine collection (14-17). The aim of this study was to determine the value of random urinary protein to creatinine ratio (UPCR) for diagnosis of proteinuria in pregnant women with preeclampsia.

Materials and methods

This cross-sectional study was performed in Shahed University Hospital in Tehran, Iran from May 2006 to May 2008. We included 66 pregnant women with a gestational age of 24 weeks or more. All participants were diagnosed with increase in blood pressure after 20th week of pregnancy to≥140/90 mm Hg, and subjected to a 24-hour urine protein assay. The exclusion criteria were chronic hypertension, diabetic mellitus, kidney disease and urinary infection. All cases were outpatients; also all tests were performed in a single laboratory. Approval for the study was obtained from the Institutional Review Board. Signed consent forms were also obtained from all participants before enrolling in the study. Demographic and general information such as age, number of pregnancy and gestational age were recorded. All patients underwent 24-hour urine collection as gold standard for diagnosis and two random samples (10am and 4pm) to determine level of protein to creatinine ratio. No samples were the first morning urine sample. Urine analysis was performed on all samples. Samples containing more than five red blood cells or white blood cells were excluded. Among 24-hour samples, the one with creatinine ≥10mg/ kg/ day was considered as an adequate sample for further analysis.

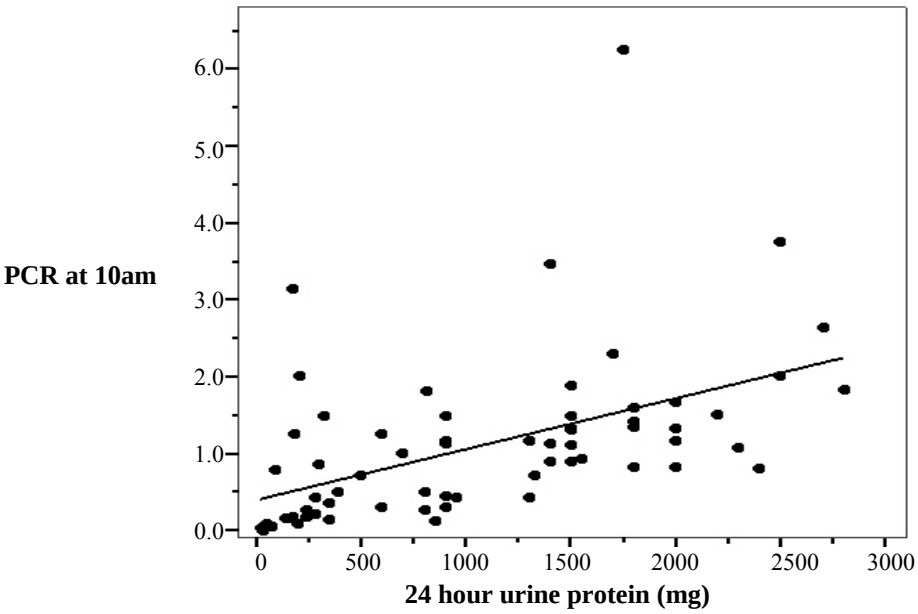
Proteinuria in the random samples was assayed using the Chem-Enzyme kit and Pyrogallol reagent. In acidic samples, the Pyrogallol reagent causes colored complexes with presence of proteins, which can be measured at a wavelength of 600 nm. Urine creatinine was assayed using Jaffe reaction and picric acid reagent.(Roche, Germany) In alkaline samples, picric acid forms orange colored complexes with presence of creatinine, measured at a wavelength of 492nm at 37°C. Proteinuria in the 24-hour urine collection was assayed using the turbidimetric test along with the Trichloro - acetic acid reagent. All reagents were prepared by the Roche, Germany Company.

Statistical analysis

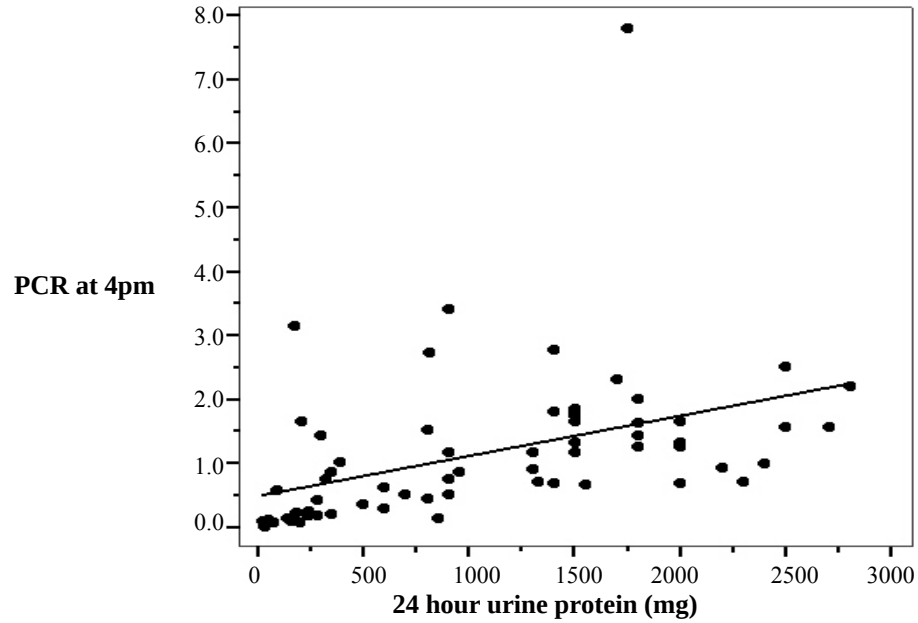
Data was collected and analyzed by SPSS software (SPSS Inc., Chicago, USA). The correlation between the random UPCR and the 24-hour urine protein assay was performed using Pearson's Correlation Coefficient and Linear Regression. Sensitivity, specificity, along with negative and positive predictive values for UPCR in every cut points for proteinuria prediction was also calculated. At last, a receiver operator characteristics (ROC) curve was drawn and area under curve was calculated.

Results

For this study, 66 patients were enrolled. The mean maternal age was 24.45±7.60 years (range of 14-46 years old) and the mean gestational age was 28.18±2.75 weeks (range of 24-35weeks). Gestational age of 13 (19.7%) women was lower than 25 weeks, 43 (65.2%) women were between 26 to 30 weeks, and 10 (15.2%) women were more than 31 weeks. Parity range was 1-5. Of these cases, 49 patients (74.2%) had obvious proteinuria, while 17 (25.8%) participants had proteinuria less than 300mg based on their 24-hour urine samples. The result of 24-hour urine samples also showed mean protein of 1062.27mg and (mean 24-hour of 844.50 mg/dl). The mean volume of 24-hour urine collected was 1165.76 ml. Mean blood nitrogen was 10.04±4.15 mg/dl (Range of 5-18 mg/dl) and mean blood creatinine was 0.73±0.20 Unit?? (Range of 0.4-1.3 mg/dl). The result of Pearson correlation coefficient, regarding random UPCR and 24-hour urine protein, showed significant correlation of 0.502 and 0.428 belonging to 10am and 4pm, respectively ($p<0.001$ for bout; plot 1,2).



Plot 1: Correlation between 24-hour urine protein and UPCR from a 10am urine sample

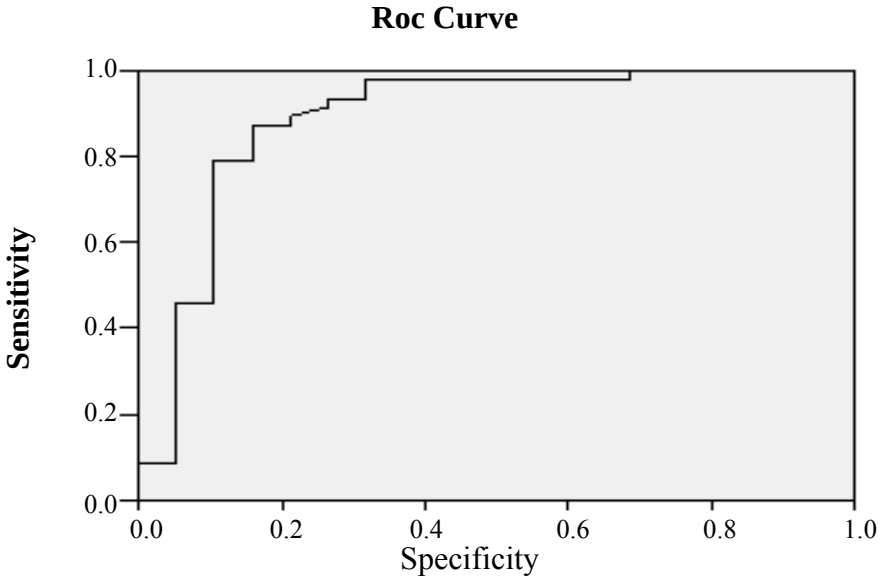


Plot 2: Correlation between 24-hour urine protein and protein to creatinine ratio from a 4pm urine sample

To establish the most efficient predictive test, cutoff points in random urinary protein to creatinine ratio at 10am and 4pm were used to establish ROC curves (plot 3, 4).

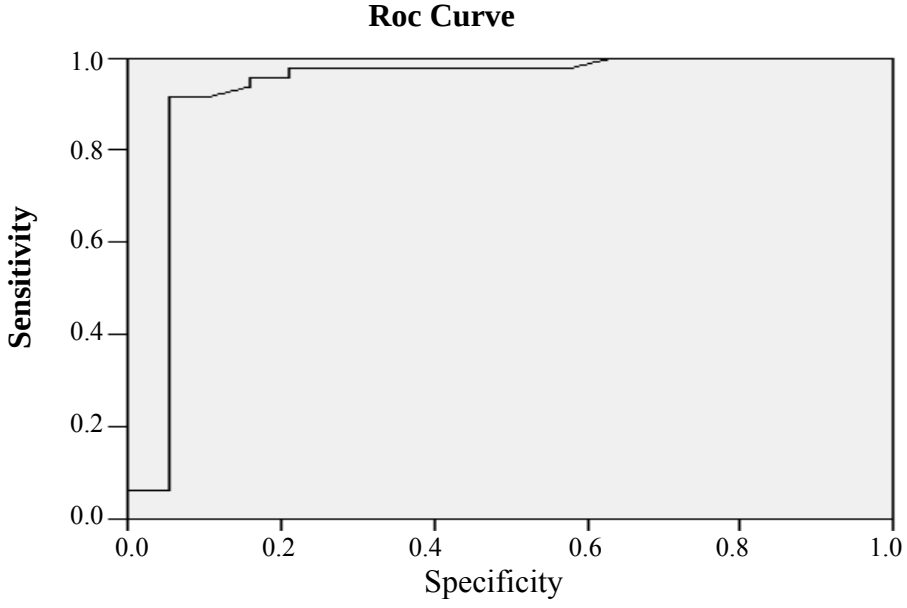
Maximum sensitivity and specificity in receiver operating characteristic PCR (protein creatinine ratio) curve for 10am was observed at 0.595 mg. At this cutoff, sensitivity was 91.67%, and specificity was 94.74%. Specificity and sensitivity at different cut points for random UPCR at 10am were shown in table 1

Maximum sensitivity and specificity for PCR at 4pm was observed at 0.470 mg. At this cutoff, sensitivity was 87.5%, and specificity was 84.21%. Specificity and sensitivity at different cut points for random UPCR at 4pm were shown in table 2.



Plot 3: Receiver operator characteristics (ROC) curve of protein to creatinine ratio from 10am urine samples of patients with preeclampsia

Measured protein from a 24-hour urine collection was chosen as the gold standard of preeclampsia diagnosis in this analysis. The area under the curve was 0.890 with a standard error of 0.055. This area is significantly different from 0.5 ($p<0.001$).



Plot 4: Receiver operator characteristics (ROC) curve of protein to creatinine ratio from 4pm urine samples of patients with preeclampsia

Measured protein from 24-hour urine collection was chosen as the gold standard of preeclampsia diagnosis in this analysis. The area under the curve was 0.932 with a standard error of 0.049. This area is significantly different from 0.5 ($p <0.001$)

Table1: Sensitivity and specificity of protein to creatinine ratio cutoff points of 10am urine samples

Cut point of PCR 10 am	TN	FN	FP	TP	Sensitivity TP/ (TP+FN)	Specificity TN/ (TN+FP)	PPV TP/ (TP+FP)	NPV TN/ (TN+FN)	Accuracy (TP+TN)/ (TN+TP+FN +FP)	S+S
0.299	13	2	6	46	95.83	68.42	88.46	86.67	88.06	164.25
0.349	14	3	5	45	93.75	73.68	90.00	82.35	88.06	167.43
0.399	14	4	5	44	91.67	73.68	89.80	77.78	86.57	165.35
0.449	16	6	3	42	87.50	84.21	93.33	72.73	86.57	171.71
0.499	16	6	3	42	87.50	84.21	93.33	72.73	86.57	171.71
0.549	16	8	3	40	83.33	84.21	93.02	66.67	83.58	167.54
0.599	16	8	3	40	83.33	84.21	93.02	66.67	83.58	167.54

Table 2: Sensitivity and specificity of protein to creatinine ratio cutoff points of 4pm urine samples

Cut point of PCR 4 pm	TN	FN	FP	TP	Sensitivity TP/ (TP+FN)	Specificity TN/ (TN+FP)	PPV TP/ (TP+FP)	NPV TN/ (TN+FN)	Accuracy (TP+TN)/ (TN+TP+FN +FP)	S+S
0.399	15	2	4	46	95.83	78.95	92.00	88.24	91.04	174.78
0.449	16	2	3	46	95.83	84.21	93.88	88.89	92.54	180.04
0.499	16	3	3	45	93.75	84.21	93.75	84.21	91.04	177.96
0.549	17	4	2	44	91.67	89.47	95.65	80.95	91.04	181.14
0.599	18	4	1	44	91.67	94.74	97.78	81.82	92.54	186.40
0.649	18	5	1	43	89.58	94.74	97.73	78.26	91.04	184.32
0.699	18	8	1	40	83.33	94.74	97.56	69.23	86.57	178.07
0.749	18	12	1	36	75.00	94.74	97.30	60.00	80.60	169.74
0.799	18	13	1	35	72.92	94.74	97.22	58.06	79.10	167.65

Discussion

In this study, two random urinary samples (once in morning and once in the afternoon) from pregnant women were analyzed. Both samples demonstrated a significant correlation between random urinary protein to creatinine ratio and protein in 24-hour urine collection; however, there are different cutoff values for different ratios of 10am and 4pm.

In a similar study of Wikstrom et al(2006)., looking at pregnant women with preeclampsia, has showed random UPCR is not reliable tool to predict 24-hour proteinuria because its level fluctuates throughout the day. Nevertheless, many studies strongly confirmed the correlation between 24-hour urine collection and random UPCR (6-13).

IN this study, a cutoff point was calculated for 10am and 4pm, separately; although, the 4pm sample demonstrated higher sensitivity and specificity. Numerous studies, investigated the specificity and sensitivity of random UPCR, have offered a variety of different cutoff values.

In a study by Chen et al. ,(2008) performed on 60 pregnant women with preeclampsia, level of random UPCR in cutoff points is greater than or equal to 0.3mg. Their results have also showed a correlation coefficient of 0.897, having a direct relation with 24-hour urine protein, as well as specificity of 95.2 and sensitivity of 97.4 (7). In another study performed by Dwyer on 116 pregnant women with preeclampsia, they have revealed a correlation with 24-hour urine protein; whereas, the level of random UPCR in cutoff points is greater than or equal to 0.28mg/mg (8). In Zadeh Modarres's study on 50 pregnant women with preeclampsia, she obtained significant correlation between 24-hour urine protein and random UPCR, while best cutoff point was 0.20mg/mg with sensitivity of 94% and specificity of 96% (9). Also, in a study by Nisell on 54 pregnant women with suspected preeclampsia, correlation between 24-hour urine protein and random

UPCR was evaluated and the best cutoff was 0.27 with sensitivity of 95% and specificity of 100%.

Differences in cutoff values could be due to the following items: variations in urine sample collections, participant demographics, sample size, prevalence of obvious proteinuria, inclusion and exclusion criteria, and other effective factors. Many studies also failed to exclude patients with chronic diseases affecting renal function and urinary protein excretion, like diabetics, chronic hypertension, nephropathies, and urinary tract infection (13). These diseases possibly alter the existence of urinary protein excretion. Some studies prepared random urine samples after 24-hour urine collections (18).

By excluding patients with underlying disease affecting urinary protein excretion, this study designed better tests to demonstrate the correlation between random urinary proteins to creatinine ratio. In addition, in order to reduce the effect of variable protein excretion in different hours throughout the day, two random urinary samples were taken at different times of a day (10am and 4pm). Sampling was also done in an outpatient setting, imitating the confounder factor of bed rest. Nevertheless, in this study, the lack of cases with massive proteinuria limits the scope of our finding.

Results of this study showed significant correlation between the random urinary proteins to creatinine ratio in 24-hour urine collection. As the result showed, Pearson correlation coefficients in 10am and 4pm were 0.502 and 0.425, respectively.) Despite the number of false negative cases, the average of both samples (10am and 4pm) showed that low false negatives were more likely in cases with lower levels of proteinuria. The simultaneous consideration of disease status and prognosis in these patients can be useful in the interpretation of this test. On the other hand, we documented a high mean of protein to creatinine ratio in random urine sample of false positive cases, regarding to the low number of false positive cases commenting about mean of false positive case needs more false positive cases. Based on the differences between cutoff values and mean level of protein of 10am and 4pm samples, it seems that protein excretion in the afternoon was greater than the ones in the morning. Previous studies have not compared different urine sample time point, so the observed difference cannot be justified by the number of samples.

It seems the ratio of protein to creatinin excretion is not constant throughout the day. Regardless, a high ratio definitively represents proteinuria.

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