Thai Journal of Obstetrics and Gynaecology
January 2009, Vol. 17, pp. 30-36

OBSTETRICS

A Six-Hour Urinary Protein-Creatinine Ratio for Predicting Significant Proteinuria in Preeclampsia

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ABSTRACT

Objective: To determine an optimal cutoff level of urinary protein-creatinine ratio (PCR) obtaining from 6-hour urine collection specimens from women admitted with suspected preeclampsia for investigation of significant proteinuria.

Study design: Diagnostic test.

Subject: Pregnant women admitted for evaluation of preeclampsia were studied prospectively. They were instructed to collect a 24-hour urine in two separate containers: one for first six hours urine specimen, the other for following 18 hours urine specimen. Each sample was measured for volume, protein, and creatinine values. The first 6-hour urinary PCR and total 24-hour proteinuria were calculated. A receiver operating characteristic curve (ROC) of the 6-hour urinary PCR was constructed in order to determine the optimal cutoff level for estimate the degree of proteinuria.

Results: A total of 120 out of 126 women completed the study; 96 (80%) had significant proteinuria. This study had shown moderate correlation between 6-hour urine protein and 24-hour urine protein. By using a 6-hour urinary PCR, the optimal cutoff level to predict significant proteinuria was ≥ 0.20 which yielded sensitivity, specificity, PPV, NPV and area under the ROC curve of 93.7%, 64.0%, 90.8%,72.7% and 0.788 respectively. On the other hand, a cutoff level of ≥ 0.10 had shown a sensitivity of 100% and specificity of 20.8%, whil e the cutoff level of ≥ 0.75 offered 100% specificity, but poor sensitivity of 55.7%.

Conclusions: The 6-hour urinary PCR at ≥ 0.20 is the most appropriate value for diagnosis of significant proteinuria in preeclampsia.

Keywords: preeclampsia, significant proteinuria, urinary protein-creatinine ratio

Introduction

Preeclampsia affects 5-10% of all pregnancies and is one of the leading causes of maternal and fetal/neonatal morbidity and mortality.[1,2] Typically, it is manifested after 20 weeks of gestation; the diagnosis is made by the presence of hypertension in combination with significant proteinuria.[1,2] In clinical practice, identification of the disease in its early

stages would be helpful since an intensified monitoring, treatment, or delivery could be provided before life-threatening complications occur.

In addition to establishing the diagnosis, urine protein analysis is essential for the classification of severity of preeclampsia, i.e. mild or severe degree. Either single-voided urine sample or 24-hour urine collection is used for the determination of proteinuria. The latter is considered to be the gold standard;[1,2] however, this approach is inconvenient in that it requires sometimes hospitalization and good cooperation of the pregnant women in collecting urine samples. Besides, its time-consuming process could lead to a delayed diagnosis, which might result in delayed treatment or even poor pregnancy outcomes.

Aside from the 24-hour urine collection, the urinary dipstick, which is a method of assessing protein in single-voided urine samples, is commonly used in an obstetric practice.[1] This approach yields advantages in terms of rapidity and convenience. However, many studies found that the test is a poor predictor of 24-hour proteinuria because it detect only urine protein concentration, not a total amount of its excretion.[3-7] The random urinary protein-creatinine ratio (PCR) has been proposed as a more reliable method to evaluate the quantity of proteinuria.[8-11] This was based on the rationale that the PCR might represent variability in urine protein and creatinine excretion throughout the day.[8-10] Nevertheless, some authors found that the diagnostic performance of this technique was still influenced by the diurnal variations of protein and creatinine.[11,12] It is also questionable that the sample obtained immediately when a woman arrives at the clinic would be reliable, since ambulation is recognized as a contributing factor to increased protein excretion. [13]

It is not known whether an intermediate periodic duration of urine collection (i.e. 6-hour, 8-hour, or 12-hour interval) may improve the accuracy of PCR for the evaluation of proteinuria, given time for bed rest and quantifying urine. The aim of this study was to determine the optimal cutoff level of PCR from 6-hour urine collection and to evaluate its diagnostic performance for significant proteinuria in women with suspected preeclampsia.

Materials and Methods

This prospective descriptive study obtained approval from the Bangkok Metropolitan Administration Ethics Committee for Researches Involving Human Subjects. All consecutive pregnant women with gestational age (GA) of ≥ 20 weeks and resting blood pressure ≥ 140/90 mmHg (after laying down for at least 15 minutes), who were admitted to the obstetric ward at our institution between May 2007 and June 2008 for evaluation of preeclampsia were recruited. Exclusion criteria were the women who had clinical of urinary tract infection, history of renal disease, overt diabetes, chronic hypertension, or incomplete collection of urine sample (a 24-hour urine sample which contained creatinine amount less than10 mg/kg of body weight).[12]

After hospitalization, the patients were adviced to have bed rest. Each of the eligible women was informed about the study and signed consent form. All participants were instructed to collect their urine in two, clean separate, clearly marked containers. Each container was labeled with the patient's name, hospital number, number of the container, and collection time interval. The first container was for the first six hours of urine while the second one was for the remaining 18-hour urine sample. Total collection time was 24 hours. Each container was refrigerated at 2-8 ^{o}C in the refrigerator for urine preservation. All women who were diagnosed with mild or severe preeclampsia were treated according to the clinical practice guidelines of the department.

Laboratory tests were done at the Clinical Pathology Laboratory of the institution. Urinary protein quantification was determined by the biuret reaction using the automated colorimetric method model Olympus AU series (E For L Inc., Tokyo, Japan). Urinary creatinine was determined by the modified Jaffé reaction (E For L Inc., Tokyo, Japan) using the autoanalyzer Olympus AU series. The Randox control (Randox Laboratory Inc., United

Kingdom) was used to calibrate the machine each morning for a daily quality assurance. The first 6-hour urinary PCR was calculated by dividing whole amount of protein (mg) by whole amount of creatinine (mg), in the first 6-hour urine collection. The total 24-hour urinary volume, protein, and creatinine were calculated by summation of the 6-hour and 18-hour urine volume, protein, and creatinine respectively. A 24-hour urine sample which contained creatinine amount less than 10 mg/kg of body weight was considered inadequate urine collection.[12]

Sample size was calculated based on a pilot study of 20 pregnant women.

Data collection included: maternal age, parity, body mass index (BMI), highest systolic and diastolic blood pressures, serum creatinine and uric acid levels, GA at- and method of urine collection, total 24-hour urinary protein and creatinine, and 6-hour urinary PCR. Body mass index (BMI) was calculated from the height and weight measured on admission. We calculated GA based on the last menstrual period or ultrasound examination whatever was corresponse with clinical findings.

Statistical analysis was performed with the SPSS software package version 11.5 (SPSS Inc., Chicago, IL, USA). The STATA 7.0 (Stata Corp., College station, TX, USA) was additionally used to generate confidence interval (CI). Baseline characteristics were presented as mean with standard deviation (SD) for continuous variables, and as number with percentage for categorical variables. The Student t-test was used to compare continuous variables, and χ^2 test was used to compare categoric al variables. P-value of < 0.05 was considered statistically significant. Based on the 24-hour proteinuria of ≥ 300 mg as the gold standard for dia gnosing significant proteinuria in preeclampsia,[14] the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with associated 95% CIs of the first 6-hour urinary PCR at various cutoff levels were calculated. A receiver operating characteristic (ROC) curve was constructed and evaluated for the area under the curve (AUC) to find the appropriate cutoff level to predict significant proteinuria.

Results

One hundred and twenty out of 126 women (95.2%) had completed the 24-hour urine collection during the study period. Their mean age (± SD) was 28.4 ± 6.9 years; 77 (63.1%) were nulliparous. Mean gestational age on admission was 35.1 ± 4.6 weeks. Details of characteristics and laboratory data of the study population were presented in Table 1.

Ninety six out of one hundred and twenty (80%) had significant proteinuria (≥ 300 mg on 24-urine collection while the remaining (20%) had insignificant proteinuria(< 300 mg). The mean and standard deviation of significant and insignificant proteinuria were 2196.3 ± 5617.5 mg and 159.2 ± 21 2.1 mg respectively. Amongst the 96 women who had significant proteinuria in 24-hour urine protein collection, 35 (36.5%) had protein excretion between ≥ 2 and <5 g and 12 (12.5%) had protein excretion ≥ 5 g.

The relationship between 6-hour urinary PCR and 24-hour proteinuria is shown in Fig. 1, with a moderate correlation coefficient of 0.421 ($p < 0.001$). The correlation was enhanced ($r = 0.656$; $p < 0.001$) when including only the patients whose total urinary protein ranged from ≥ 300 mg to ≤ 2 g .

The ROC curve of 6-hour urinary PCR to predict significant proteinuria is presented in Figure 2. As shown in Table 2, a cutoff level of ≥ 0.10 yielded a sensitivity of 100% but poor specificity of 20.8 %, while a ratio of ≥ 0.75 yielded a specificity of 100% and sensitivity of 55.7%.

At the cutoff level of ≥ 0.20 revealed the sensitivity, specificity, PPV, and NPV of 93.7%, 64.0%, 90.8%, and 72.7% respectively with the AUC of 0.788 (95% CI 0.69-0.89; $p < 0.05$). At this cutoff level,we found false negative of 6.3%. These were mild preeclampsia patients and deliveried without any complication. So the cutoff level of ≥ 0.20 was selected as the most appropriate.

We further selected if any other cutoff value of the 6-hour urinary PCR could predict severe

proteinuria (24-hour urine protein ≥ 2 g). Setting a high cutoff point of ≥ 4.4, the results showed 100% specificity while the sensitivity was decreased to be only 14.7%.

Table 1. Characteristics of the study population (n = 120)

Characteristics	Proteinuria		P-value
	Significant (≥ 300 mg) (n = 96)	Insignificant (< 300 mg) (n = 24)	
Age (years), mean (SD)	28.2 (7.0)	29.3 (6.3)	0.48
Nullipara, n (%)	64 (66.7)	13 (54.2)	0.20
BMI (kg/m^2), mean (SD)	31.3 (6.6)	28.1 (7.2)	0.04*
Highest systolic blood pressure (mmHg), mean (SD)	163.4 (22.3)	153.4 (18.5)	0.04*
Highest diastolic blood pressure (mmHg), mean (SD)	108.0 (15.8)	99.0 (10.4)	< 0.01*
Serum creatinine (mg/dl), mean (SD)	0.8 (0.2)	0.7 (0.1)	0.09
Serum uric acid (mg/dl), mean (SD)	6.1 (1.7)	5.0 (1.2)	< 0.01*
GA at urine collection (weeks), mean (SD)	35.4 (4.6)	35.3 (4.7)	0.88
24-hour urine protein (mg), mean (SD)	2196.3 (5617.5)	159.2 (212.1)	< 0.01*
24-hour urine creatinine (mg), mean (SD)	1028.5 (513.9)	1000.2 (463.5)	0.79
6-hour PCR, mean (SD)	2.76 (0.24)	4.67 (0.21)	< 0.01*

BMI = body mass index; GA = gestational age; PCR = protein-creatinine ratio;
SD = standard deviation.
P < 0.05 = significant*

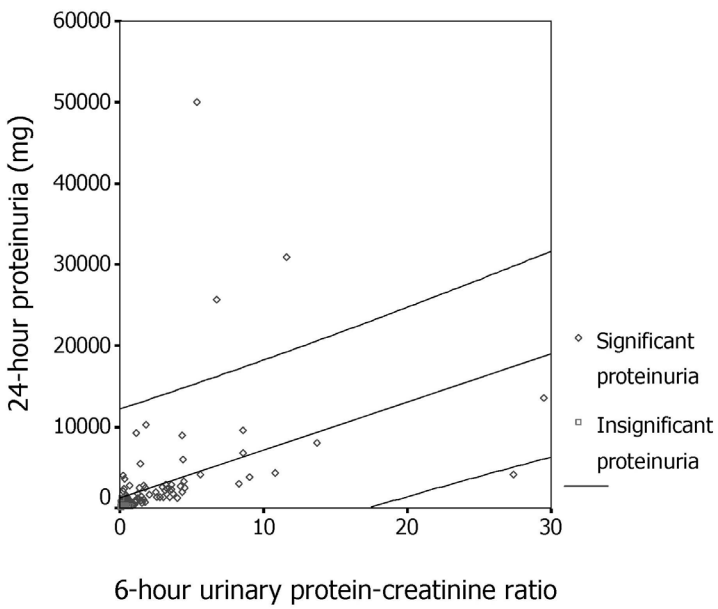

Fig. 1 The relationship between 6-hour urinary protein-creatinine ratio and 24-hour proteinuria (r = 0.421; p < 0.001)

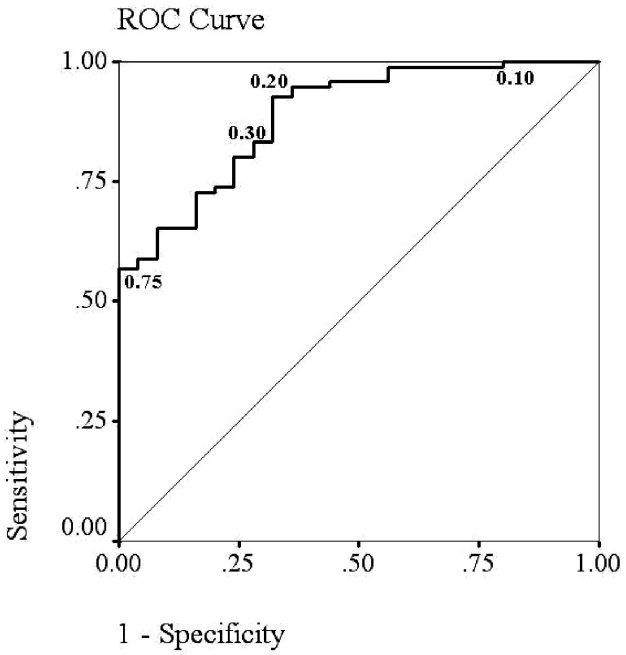

Fig. 2 The receiver operating characteristic curve of 6-hour urinary protein-creatinine ratio for predicting significant proteinuria (at cutoff level 0.20,AUC= 0.788 ; 95% CI 0.69-0.89; $p < 0.05$)

Table 2. Accuracy of protein-creatinine ratio at difference cutoff level for predicting of significant proteinuria

cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 0.10	100	20.0	82.6	100
≥ 0.20	93.7	64.0	90.8	72.7
≥ 0.30	82.1	72.0	91.7	51.4
≥ 0.75	56.8	100	100	37.9

PPV = positive predictive value; NPV = negative predictive value

Disscusion

Measurement of urine protein amount is the crucial laboratory investigation for evaluating preeclampsia. During the past decades, several quick approaches to determining proteinuria have been proposed as alternatives to the gold standard 24-hour urine measurement.[1,2] One of those is random urinary PCR which have been demonstrated by many authors that it yielded good ability to predict significant proteinuria with the sensitivities and specificities at various cutoff levels (ranged from 0.17 to 0.40) were 69–96% and 41–97% respectively.[15] Nevertheless, some authors found that this test could provide an accurate estimation of total 24-hour protein excretion only when glomerular infiltration was stable.[17]

Because of the diurnal variation of urine protein excretion in preeclampsia might lead to an inaccurate spot urine measurement[11,12], Saikul et al studied their diagnostic performance of significant proteinuria from the first 4-hour urine collection.[16] In their study, no data on the correlation of 4-hour

PCR with 24-hour proteinuria were presented. At the appropriate cutoff value of the 4-hour PCR of > 0.30, a good specificity of 88% was demonstrated; however, the false negative rate was as high as 19%. Thus, we decided to use 6-hour urine sample instead of 4-hour urine collection. We expected to gain more precise level of proteinuria, closer to the gold standard, the 24-hour collection. Our study revealed moderate correlation between the first 6-hour PCR with 24 hours urine protein excretion. Because of the purpose to rule in women for further investigation of significant proteinuria, we selected the appropriate cutoff level of 6-hour PCR by giving higher priority to the sensitivity than the specificity. Thus, we selected the value of > 0.20 as the appropriate ratio. At this value, the specificity, PPV, and NPV were high while the false negative rate (6.3%) was much lower than that in the study of Saikul et al. Comparing to previous studies of random urinary PCR[8,11], our 6-hour PCR had lesser correlation with 24-hour proteinuria. Nevertheless, we could not conclude that the 6-hour PCR was less effective for the prediction of significant proteinuria, since the sample sizes and backgrounds of the study population were different. The study which measures both random and 6-hour urinary PCR is justified to compare the predictive ability of both methods.

Aside from the cutoff point of > 0.20, we sought to determine if any cutoff level of the 6-hour PCR could predict 24-hour urine protein excretion > 2 g (for determining severe preeclampsia). In this circumstance, with the aim to detect specific amount of proteinuria, the selected cutoff value was determined by giving higher priority to the specificity than the sensitivity. We found that the cutoff point of > 4.40 revealed 100% specificity and PPV. In clinical application, this ratio might be helpful in evaluating severe proteinuria (> 2 g) to make a diagnosis of severe preeclampsia in a shorter time than 24-hour urine protein measurement. However, since the number of women whose 24-hour proteinuria > 2 g in our study was limited (n = 35), further study with larger sample size is warranted to verify our result.

In conclusion, we propose that 6-hour PCR with cutoff level of > 0.20 is appropriate for assessment of significant proteinuria which has shown moderate correlation with 24-hour urine protein. It is interesting to employ this 6-hour PCR measurement in the out-patient settings. Since our enrolled subjects were hospitalized and at bed rest, future research is required to prove the accuracy of 6-hour PCR > 0.20 in predicting significant proteinuria in ambulatory women.

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อัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะจากการเก็บปัสสาวะที่ 6 ชั่วโมง เพื่อวิเคราะห์ระดับโปรตีนในปัสสาวะที่มีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ

สุรศักดิ์ ศิลประเสริฐ, ชาดากานต์ ผโลประการ, สุมนมาลย์ มนัสศิริวิทยา, บุษบา วิริยะสิริเวช

วัตถุประสงค์ *: เพื่อหาอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะจากการเก็บปัสสาวะที่ 6 ชั่วโมงที่เหมาะสมที่สุด ในการวิเคราะห์ระดับโปรตีนในปัสสาวะที่มีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ*

รูปแบบการวิจัย *: การวิจัยแบบการตรวจเพื่อวินิจฉัยโรค (diagnostic test)*

กลุ่มตัวอย่าง *: สตรีที่มีภาวะความดันโลหิตสูงขณะตั้งครรภ์ และอายุครรภ์มากกว่า 20 สัปดาห์ที่เข้ารับการรักษาแบบผู้ป่วยในที่วิทยาลัยแพทยศาสตร์ กรุงเทพมหานครและวชิรพยาบาล สำนักการแพทย์ กรุงเทพมหานคร จำนวน 120 คน*

วิธีดำเนินการวิจัย *: สตรีที่มีความดันโลหิตสูงขณะตั้งครรภ์ที่เข้ารับการรักษาแบบผู้ป่วยในจะได้รับการเก็บปัสสาวะใน 6 ชั่วโมงแรกและอีก 18 ชั่วโมงถัดมาเพื่อหาปริมาณปัสสาวะ ปริมาณโปรตีนและปริมาณครีเอทินีน นำมาคำนวณเป็นค่าของอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่ 6 ชั่วโมงและ 24 ชั่วโมงตามลำดับ จากนั้นนำไปทดสอบทางสถิติหาค่าอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่ 6 ชั่วโมงที่เหมาะสมที่สุดในการวินิจฉัยผู้ป่วยครรภ์เป็นพิษ*

ตัววัดที่สำคัญ *: อัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่ 6 ชั่วโมง*

ผลการวิจัย *: จากผู้ป่วย 120 ราย มีโปรตีนในปัสสาวะอย่างมีนัยสำคัญร้อยละ 80 พบว่าอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่ 6 ชั่วโมงที่เหมาะสมที่สุดในการวินิจฉัยผู้ป่วยครรภ์เป็นพิษคือ 0.20 โดยมีค่าความไวร้อยละ 93.7 ความจำเพาะร้อยละ 64.0 ค่าพยากรณ์ผลบวกร้อยละ 90.8 ค่าพยากรณ์ผลลบร้อยละ 72.7 นอกจากนี้ค่าที่มากกว่า 0.1 ขึ้นไปมีค่าความไวร้อยละ 100 และค่าที่มากกว่า 0.75 ขึ้นไปมีความจำเพาะร้อยละ 100*

สรุป *: อัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะ 6 ชั่วโมงแรกที่ 0.20 มีความเหมาะสมในการวิเคราะห์ระดับโปรตีนในปัสสาวะที่มีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ*