First 4-Hour Urinary Protein - Creatinine Ratio for Diagnosis of Significant Proteinuria in Preeclampsia

Sornpin Saikul MD*,
Budsaba Wiriyasirivaj MD*, Paiboon Charoenchinont MD*

** Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital*

Objective: *To evaluate the diagnostic accuracy of the first 4-hour urinary protein - creatinine ratio for prediction of the significant proteinuria in preeclampsia*
Study design: *Diagnostic test*
Subjects: *One hundred and sixty-four pregnant women who were initially diagnosed with hypertensive disorder and hospitalized in the obstetric ward and labor room at Bangkok Metropolitan Administration Medical Collage and Vajira Hospital between July 2005 and April 2006.*
Material and Method: *Urine samples were collected within 24 hours in two consecutive periods: the first 4 hours and the next 20 hours. The urine volume, urine protein and creatinine concentration were separately measured and the first 4-hour urinary protein - creatinine ratio were calculated. With the use of a protein level ≥ 300 mg in 24 hours urine collection as the gold standard, the sensitivity and specificity of the first 4-hour urinary protein-creatinine ratio for diagnosis of significant proteinuria were determined with cutoffs range.*
Results: *One hundred and sixty four patients were recruited for this study including 112 patients (68.3%) who had preeclampsia. The first 4-hour urinary protein-creatinine ratio was most accurate for diagnosis of preeclampsia is 0.30 with 81% sensitivity, 88% specificity, PPV of 93%, and NPV of 71%.*
Conclusion: *The first 4-hour urinary protein-creatinine ratio at 0.3 is the most accurate value for diagnosis of significant proteinuria in preeclampsia*

Keywords: *First 4-Hour urinary protein-creatinine ratio, Significant proteinuria, Preeclampsia*

J Med Assoc Thai 2006; 89 (Suppl 4): S42-6
Full text. e-Journal: *http://www.medassocthai.org/journal*

Hypertensive disorder complicating pregnancy is common with an incidence of 5% of pregnancies. It forms one of the deadly triad along with hemorrhage and infection and is associated with multisystemic disorders contributing greatly to maternal and neonatal morbidity and mortality[1].

Hypertensive disorder complicating pregnancy is classified into 5 groups; 1) Gestational hypertension defined as resting blood pressure ≥ 140/90 mmHg after 20 weeks' gestation without proteinuria; 2) Preeclampsia defined as gestational hypertension with a significant proteinuria and was subgroup into mild and severe forms. Severe preeclampsia defined as blood pressure ≥ 160/110 mmHg and proteinuria ≥ 2 g/day with or without multiorgan involvement i.e. pulmonary edema, oliguria, thrombocytopenia, abnormal liver enzymes in association with persistent epigastric or right upper quadrant pain, or persistent severe central nervous system symptoms (altered mental status, headache, blurred vision or blindness); 3) Chronic hypertension defined as resting blood pressure ≥ 140/90 mmHg before pregnant or diagnosed before 20 weeks' gestation not attributable to gestational trophoblastic disease. 4) Superimposed preeclampsia on chronic hypertension defined as significant proteinuria in hypertensive women without significant proteinuria before 20 weeks' gestation; and 5) Eclampsia is the occurrence of seizures in preeclamptic pregnant woman that cannot be contributed to other causes[1].

Correspondence to : Saikul S, Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, Samsen, Dusit, Bangkok 10330, Thailand.

As mandatory, the quantification of proteinuria in preeclampsia are necessary both for diagnosis of preeclampsia and classification of severity of the disease since it is a sign of worsening hypertensive disorder which resulted in poor pregnancy outcome. The gold standard for the diagnosis of significant proteinuria in preeclampsia is $\geq$ 300 mg per day[1]. However, the collection of urine within 24 hours was time-consuming and need strong cooperation from patients who required hospitalization, and thus could result in poor compliance, and delay in diagnosis and treatment. Therefore, a shorter period of urine collection would have clinical benefits for early diagnosis and treatment, thus, decrease maternal and perinatal morbidity and mortality. Patient compliance with testing may also improve if the test for proteinuria could be simplified or shortened.

Hence, several investigators have previously reported a variety of rapid methods for a meticulous prediction of 24 hours urinary protein excretion. For example, there was a study reporting that dipstick urine protein seems to be inaccurate for diagnosis of preeclampsia as shown that 64-66 percent of the patients who had negative or traces of protein but had significant proteinuria[2,3]. Moreover, many studies have demonstrated a good correlation between the random urinary protein-creatinine ratio and 24 hour urine protein[4-7]. However, other studies have to the contrary reported a poor correlation of this value[8,9]. Therefore, this method is still controversial for clinically use. Other studies suggested that separated urine collection such as 4, 8 and 12 hours urine protein have a good correlation with 24 hours urine protein[10,11]. In particular, 4 hour urine protein has been reported as having the highest correlation ($r = 0.95$, $p < 0.001$)[11]. Nevertheless, the difference of protein excretion the day long, and the variation of protein excretion up to patient posture, resulted in the limitation of clinical use of this value[11,13].

This problem can be overcome by using creatinine as a denominator in order to stabilize the accuracy of protein value in difference time[9,16]. This study, therefore, aims to evaluate a diagnostic accuracy of the first 4-hour urine protein-creatinine ratio for prediction of significant proteinuria in preeclampsia.

Material and Method

The study was approved by the Ethics Committee of Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration (BMA) Medical College and Vajira Hospital, Bangkok, Thailand. One hundred and eighty nine women initially diagnosed as having hypertensive disorder in pregnancy were admitted for further investigation in the obstetric ward and labor room at BMA Medical College and Vajira Hospital from July 2005 to April 2006. All pregnant women had either resting blood pressure $\geq$ 140/90 mmHg after 20 weeks' gestation or had chronic hypertension before 20 weeks' gestation with new onset proteinuria. Those who had renal disease, liver disease, urinary tract infection or chronic hypertensions with prior proteinuria were excluded from this study.

After obtaining a written informed consent, all patients were asked to collect urine into two separated clearly labeled containers. The first container was for the first 4 hour urine collection and second container for the remaining 20 hour urine collection. Thus, total collecting period was 24 hours, which excluded the first void morning urine. The patients who could not completely collect 24 hours urine or had 24 hours urinary creatinine < 15 mg/kg[14] were excluded from the study (as it indicated an incomplete 24 hours urine collection).

Urine protein and creatinine concentration (mg/dl) were measured by the immunoturbidity assay, on the autoclave chemistry: Hitachi model 911. All tests were analyzed by well-trained technicians at laboratory service center of BMA Medical College and Vajira Hospital. If the urine samples could not be analyzed in the day time, they were stored at 4°C or used preservative solution until analysis. Urine protein level (mg) was calculated by urinary protein concentration multiplied with urine volume of each specimen. Urine creatinine level (mg) was also calculated by the same manner. Then the first 4-hour urinary protein-creatinine ratio was calculated. The total 24 hour urine protein (mg) and urine creatinine (mg) were calculated by summation of the first 4-hour and the consecutive 20-hour urine protein and creatinine.

Sample size of 143 patients was calculated based on a statistically significant level at 0.01. Statistical analysis was performed by the SPSS statistical package version 11.5 and STATA statistical software (Stata Corp. College Station, Texas). Descriptive statistics were used for baseline clinical data and were summarized as mean, median, or percentage as appropriate. With the use of the 24 hours protein as the gold standard, the sensitivity, specificity, positive predictive value, and negative predictive value of the first 4-hour urinary protein-creatinine ratio for prediction of significant proteinuria in preeclampsia were determined with a cutoffs range. Receiver Operating Characteristic (hereafter ROC) curves was then constructed and cal-

Table 1. Base-line clinical characteristics of all patients (n = 164)

	Mean (SD)	Range
Age (years)	29 (6.8)	15-44
Gestational age (weeks)	35 (4.3)	22-44
BMI (kg/m^2)	26.5 (6.1)	13.9-42.2
Resting systolic blood pressure (mmHg)	154 (17.1)	140-260
Resting diastolic blood pressure (mmHg)	100 (9.3)	90-130
Parity		
Nulliparous	78 (47.6%)	
Multiparous	86 (52.4%)	
Fetal number		
Singleton	158 (96.3%)	
Twins	6 (3.7%)	

culated area under the curves by using STATA statistical software (Stata Corp. College Station, Texas)

Results

From July 2005 to April 2006, there were 189 consecutive patients suspected as having a preeclampsia in which 25 patients had incomplete 24 hour urine collection, 15 patients had 24 hour urine creatinine < 15 mg/kg, and 10 patients delivered baby before complete urine collection. Thus there were 164 patients remained for analysis. Of this, 52 patients had gestational hypertension, 74 patients had mild preeclampsia, and 38 patients had severe preeclampsia. None of them had superimposed preeclampsia on chronic hypertension. Table 1 summarizes base-line clinical characteristics of all patients.

Fig. 1 is the ROC curve for the first 4-hour urinary protein-creatinine ratio. The best cut off which give the maximum area under the curve is 0.3 (area under the curve 0.845; 95%CI 0.79- 0.9, p < 0.001). The first 4-hour protein-creatinine ratio cut off at 0.3 for detection of significant proteinuria has 81% sensitivity, 88% specificity, PPV of 93%, and NPV of 71%.

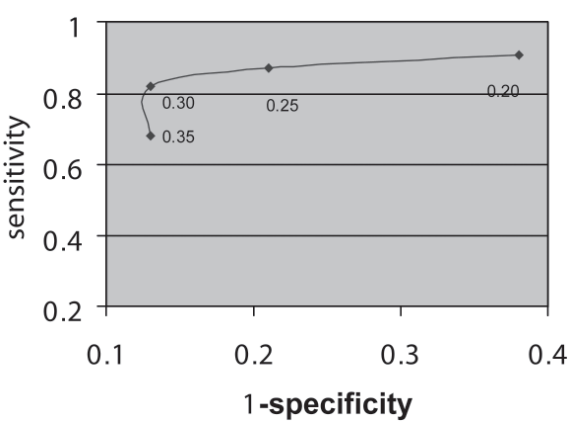

Fig. 1 ROC curve for various cutoffs for the first 4-hour urinary protein-creatinine

Discussion

This is the first study that uses the first 4-hour protein-creatinine ratio instead of protein value alone for diagnosis of significant proteinuria in preeclampsia. The results of this study has revealed that the first 4-hour urinary protein - creatinine ratio ≥ 0.30 had highest accuracy for predictive of significant proteinuria in this study population. Thus, the variation in urine protein and creatinine excretion throughout the day and posture[8] were controlled, therefore, the diagnosis is more precise than 4-hour proteinuria alone[11].

In conclusion, we propose that the first 4-hour urinary protein-creatinine ratio can represent and be used as an alternative to the 24 hour urine protein to diagnose significant proteinuria in preeclampsia. However, this study was carried out in a hospital with non ambulatory patient. A future study should be aimed at evaluating the first 4-hour urinary protein-creatinine ratio in an ambulatory setting for prediction of significant proteinuria in preeclampsia.

References

1. Cunning-ham FG, Leveno KJ, Hauth JC, Gilstrap LC III, Wenstrom KD. Hypertensive disorders in pregnancy. Williams Obstetrics. 22 nd ed. New York: McGraw-Hill ; 2005: 761-808.
2. Meyer NL, Mercer BM, Fredman SA, Sibai BM. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. Am J Obstet Gynecol 1994 ; 170: 137-41.
3. Kieler H, Zettergren T, Svensson H, Dickman PW,

Larsson A. Assessing urinary albumin excretion in pre-eclamptic women: which sample to use? BJOG 2003; 110: 12-7.
4. Young RA, Buchanan RJ, Kinch RA. Use of the protein-creatinine ratio of a single voided urine specimen in the evaluation of suspected preeclampsia. J Fam Pract 1996; 42: 385-7.
5. Robert M, Sepandj F, Liston RM, Dooley KC. Random protein-creatinine ratio for the quantitation of proteinuria in pregnancy. Obstet Gynecol 1997; 90: 893-5.
6. Thompson DR, Lieberman ES. Use of a random protein-to-creatinine ratio for the diagnosis of significant proteinuria during pregnancy. Am J Obstet Gynecol 2001; 185: 808-11.
7. Yamasmit W, Charoenvidhya D, Chaithongwongwattana S, Wongkitisophon K, Uerpairojkit B. Correlation between random urinary protein-to-creatinine ratio and quantitative of 24 hour proteinuria in preeclampsia. J Med Assoc Thai 2003; 86: 69-73.
8. Durnwald C, Mercer B. A prospective comparison of total protein/creatinine ratio versus 24 hour urine protein in women with suspected preeclampsia. Am J Obstet Gynecol 2003; 189: 848-52.
9. Ragip AA, Baykal C, Karacay O. Random urine protein-creatinine ratio to predict proteinuria in new onset mild hypertension in late pregnancy. Obstet Gynecol 2004; 104: 367-71.
10. Adelberg AM, Miller J, Doerzbacher M, Lambers DS. Correlation of quantitative protein measurements in 8, 12 and 24-hour urine samples for the diagnosis of preeclampsia. Am J Obstet Gynecol 2001; 185: 804-7.
11. Wongkitisophon K, Yamasamit W, Tannirandorn Y, Phupong V, Pansin P, Charoenvidhya D. Correlation of 4 and 24 hour urine protein in women with initially diagnosed hypertensive disorders in pregnancy. J Med Assoc Thai 2003; 86: 529-33.
12. Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. N Engl J Med 1983; 309: 1543-6.
13. Higby K, Suiter CR, Phelps JY, Siler-Khodr T, Langer O. Normal values of urinary albumin and total protein excretion during pregnancy. Am J Obstet Gynecol 1997; 171: 984-8.
14. Habermann TM, Rajkuman SV, Chutka DS, Edson RS, Litin SC, McCallum DK. Mayo clinic internal medicine board review 2002-2003. USA: Courier Kendalville ; 2002: 533-726.
15. National High Blood Pressure Education Program. Working Group Report on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183: S1-22.
16. Price CP, Newall RG, Boyd JC. Use of protein: creatinine ratio measurements on random urine samples for prediction of significant proteinuria:a systemic review. Clin Chem 2005 ; 51:1577-86.

อัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะ 4 ชั่วโมงแรก เพื่อการวินิจฉัยภาวะการมีโปรตีนในปัสสาวะอย่างมีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ

ศรพิณ ไทรกุล, บุษบา วิริยะสิริเวช, ไพบูลย์ เจริญชัยนนท์

วัตถุประสงค์: *เพื่อหาค่าอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะ 4 ชั่วโมงแรกที่แม่นยำที่สุดในการวินิจฉัยภาวะการมีโปรตีนในปัสสาวะอย่างมีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ*

รูปแบบการศึกษา: *การศึกษาแบบการตรวจเพื่อการวินิจฉัย*

วัสดุและวิธีการ: *สตรีตั้งครรภ์ที่มีความดันโลหิตสูง และเข้ารับการรักษาที่หอผู้ป่วยสูติกรรม และห้องคลอด วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ทำการเก็บปัสสาวะของผู้ป่วยที่เข้าร่วมการวิจัย โดยแบ่งปัสสาวะแยกขวดเป็น 2 ช่วงเวลา คือ ปัสสาวะที่ 4 ชั่วโมงแรกและที่ 20 ชั่วโมงถัดไป จากนั้นนำปัสสาวะทั้ง 2 ขวดไปตรวจหาปริมาณโปรตีน และ ครีเอทินิน แล้วนำมาคำนวณอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะที่ 4 ชั่วโมง และคำนวณค่าโปรตีนของปัสสาวะ 24 ชั่วโมง เพื่อนำไปทดสอบทางสถิติหาค่าอัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะ 4 ชั่วโมงแรกที่แม่นยำที่สุดในการวินิจฉัยภาวะครรภ์เป็นพิษ*

ผลการศึกษา: *มีสตรีตั้งครรภ์ที่มีความดันโลหิตสูงและมีคุณสมบัติตามเกณฑ์การคัดเลือกเข้าสู่การวิจัยทั้งสิ้น 164 คน อัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะ 4 ชั่วโมงแรก ที่แม่นยำที่สุดในการวินิจฉัยภาวะการมีโปรตีนในปัสสาวะอย่างมีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษคือ 0.3 โดยมีความไว 81% ความจำเพาะ 88% ค่าพยากรณ์ผลบวก 93% ค่าพยากรณ์ผลลบ 71%*

สรุป: *อัตราส่วนโปรตีนต่อครีเอทินินของปัสสาวะ 4 ชั่วโมงแรกที่ 0.3 มีความแม่นยำในการวินิจฉัยภาวะการมีโปรตีนในปัสสาวะอย่างมีนัยสำคัญในผู้ป่วยครรภ์เป็นพิษ*