

International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622
© Gynaecology Journal
www.gynaecologyjournal.com
2019; 3(6): 290-293
Received: 14-09-2019
Accepted: 18-10-2019

Rupali Modak

Assistant Professor, Department of
Gyne and Obst, R.G. Kar Medical
College, Kolkata, West Bengal,
India

Arghyapratim Das

Arghya Pratim Das, Resident,
Dept of Gyn & Obst, Burdwan
Medical College, Burdwan, West
Bengal, India

Amitava Pal

Professor, Department of Gyne and
Obst, Burdwan Medical College,
Burdwan, West Bengal, India

Deb Kumar Ray

Associate Prof. Department of
Biochemistry, Burdwan Medical
College, Burdwan, West Bengal,
India

Amitrajit Pal

Junior Resident, Department of
Pharmacology, Grant Medical
College, Mumbai, Maharashtra,
India

Corresponding Author:

Arghyapratim Das

Arghya Pratim Das, Resident,
Dept of Gyn & Obst, Burdwan
Medical College, Burdwan, West
Bengal, India

Evaluation of spot urinary protein-creatinine ratio as a predictor of preeclampsia

Rupali Modak, Arghyapratim Das, Amitava Pal, Deb Kumar Ray and
Amitrajit Pal

DOI: <https://doi.org/10.33545/gynae.2019.v3.i6e.428>

Abstract

Background and Objectives: Hypertensive disorders are the most common medical complications of pregnancy with an incidence of 12-22% and are rampant globally. The aim of the study was to establish whether a spot urinary protein –creatinine ratio (UPCR) measured between 20-24 weeks of gestation can predict subsequent development of preeclampsia

Methods: The prospective observational study included 120 pregnant mothers with singleton pregnancy with normal renal function having no proteinuria, attending antenatal clinics between 20-24 weeks of gestational age in two tertiary care teaching hospitals. Spot UPCR test was done in a mid- stream urine sample and protein was estimated by immunoturbidimetric microalbumin method and creatinine by modified Jaffe's method. Data was expressed as urine protein (mg/dl)/ urine creatinine (g/dl) = UPCR in mg/g or mg/mmol multiplying by 0.113.

Results: Prevalence of preeclampsia was 12.93%. The mean UPCR (mg//mmol) in unaffected group and preeclampsia groups was 26.84 ± 4.69 and 44.12 ± 9.43 respectively. The optimal cut-off value of spot UPCR was considered 35.5 mg/mmol. The relative risk (RR) of developing preeclampsia in women with $UPCR \geq 35.5$ mg/mmol was 21.78 (95% CI, 6.82- 69.54, $p=0.0001$). The sensitivity, specificity, PPV and NPV are of 80% and 94.06%, 66.67% and 96.94% respectively at or above UPCR cut-off value of 35.5 mg/mmol. The area under curve (AUC) of spot UPCR in ROC curve was 0.949 (95% CI, 0.891- 1.000).

Conclusions: A Spot UPCR ≥ 35.5 mg/mmol in the early part of mid trimester with high sensitivity and specificity is an accurate, reliable and steady fast time saving test that can predict the development of preeclampsia in later part of pregnancy.

Keywords: preeclampsia, cut-off points, urinary protein-creatinine ratio, pregnancy

Introduction

Preeclampsia (PE) is defined as a pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial dysfunction and it is the second highest cause of maternal mortality, constituting 12-18% of pregnancy related deaths [1]. Therefore a rapid and reliable diagnosis is mandatory. In addition to hypertension, proteinuria of at least 0.3gm/24 hour is required for diagnosis of preeclampsia [2]. The pathophysiology resulting preeclampsia begins early in pregnancy and precedes the onset of clinical features [3].

Prediction of Preeclampsia in early pregnancy can be of very much helpful in preventing the disorder or in decreasing the severity. Microalbuminuria is the marker of endothelial dysfunction and can be used as an early marker of preeclampsia, before the onset of overt syndrome, as it is likely that overt proteinuria is preceded by microalbuminuric phase. Although 24 h collection of urine is the gold standard for quantifying urine albumin excretion, the collection is cumbersome, time consuming, inconvenient to(patients as well as hospital staffs) and subject to errors such as incomplete collection leading to inaccuracies in 13-68% of collections [4]. Therefore the spot urinary protein to creatinine ratio (UPCR) has been advocated as an easy alternative method [5, 6]. Sufficient evidence from studies show a strong association between random protein to creatinine ratio and 24 hour protein excretion and the International society for the study of hypertension in pregnancy has accepted this test as a method for identification of significant proteinuria [7].

So, the aim of the study is to establish prospectively whether a spot urinary PCR (protein creatinine ratio) measured in early mid trimester can predict the development of preeclampsia in later part of pregnancy.

Materials and Methods

The prospective observational study was conducted between January 2018 to June 2019 on 120 pregnant mothers with singleton pregnancies attending at antenatal clinics of Burdwan Medical College, Burdwan and R G Kar Medical College, Kolkata at 20-24 weeks of gestation and followed-up till delivery. During follow-up only 4 cases did not turn-up and finally 116 pregnant mothers were selected in the study for data analysis. The study was approved by institutional ethics committee, and written informed consent was taken from all participating women.

Inclusion criteria

1. Age between 18 to 40 years
2. Gestational age at 20-24 weeks
3. Singleton pregnancy
4. Normotensive at the time of enrolment

Exclusion criteria

1. Multiple pregnancy
2. Chronic hypertension
3. Chronic renal disease
4. Molar pregnancy
5. Hypothyroidism, diabetes
6. Fetal congenital malformation
7. Fetal death

Pre-designed, pre-tested, semistructured schedule for interview was used for data collection regarding demographic profile, blood pressure, and body mass index (BMI) measurement. Obstetric history was documented regarding gravida, parity, past h/o preeclampsia, SFD babies. After history taking clinical and obstetrical examinations was done to detect gestational age, fundal height, FHS. Routine blood and urine and random spot urine for protein and creatinine ratio were recorded. USG with Doppler study was also performed.

All the selected pregnant women were evaluated clinically or by investigations to rule out any risk factors for development of preeclampsia at the time of booking. Blood pressure was measured in sitting posture. Preeclampsia was defined as blood pressure of $\geq 140/90$ mm of Hg with proteinuria. Based on these criteria the woman was categorized as those who remained normotensive or unaffected (Group 1) and who developed preeclampsia (Group 2).

Spot midstream urine was collected for estimation of protein by immunoturbidimetric micro albumin method and creatinine by modified Jaffe's method in ERBA semiautomatic biochemistry analyzer with commercially available reagent. Data was expressed as urine protein (mg/dl)/ urine creatinine (g/dl) = UPCR in mg/g or mg/mmol multiplying by 0.113. The cut-off value of PCR was taken as 35.5 mg/mmol in the present study. Those with UPCR ratio equal to or more than 35.5 mg/mmol were considered as test positive and the ratio less than 35.5

mg/mmol was considered as test negative [8, 9].

Statistical analysis

All the relevant data were analyzed by appropriate statistical tests using statistical package for social science (SPSS) version 20.0. Continuous variables were expressed as mean, median standard deviation (SD) and compared across the group using Mann-Whitney U test. Categorical variables were expressed as number of patients and percentage and compared across the group using Fisher exact test. Sensitivity, specificity, PPV and NPV with ROC were analysed for prediction of PE. P-value less than 0.05 was considered as significant.

Results and analysis

After obtaining informed consent 120 women were enrolled during antenatal period of 20-24 weeks of gestation, 4 women were excluded because of lack of follow-up. So, finally 116 pregnant women were included in the study for final analysis.

Table 1 summarizes that mean maternal age was 23 ± 3.42 years and mean BMI was 24 ± 2.46 Kg/m² in unaffected groups. Eighty-eight (75.86%) were primigravida. At the time of booking the mean systolic and diastolic blood pressure were slightly lower in unaffected group. Mean spot UPCR value between unaffected and pre-eclamptic women was higher in later group and the difference is statistically significant.

Table 2 shows that out of 18(15.52%) UPCR positive cases 12(10.35%) women developed preeclampsia. Only 3 women in a total of 98 women of negative UPCR developed pre-eclampsia in later part of pregnancy.

Table 3 depicts that majority (68%) of spot UPCR positive patients having UPCR cut-off value of > 35.5 mg/ mmol developed preeclampsia after 34 weeks and only 13% of women developed preeclampsia before 34 weeks. Three cases (20%) developed late PE (≥ 34 weeks) in spot UPCR negative women (cut-off value ≤ 35.5 mg/mmol).

Table 4 depicts the association of UPCR with pre-eclampsia. Out of total 18(15.52%) women, 12(10.34%) developed PE in later part of pregnancy and only 6 women (5.17%) shows false positivity i.e. the UPCR test is positive but do not produce the disease. Among 98(84.48%) UPCR test negative women, only 3 had false negative test i.e. they developed PE later on, but the test is negative. At the spot UPCR cut-off value of ≥ 35.5 mg /mmol, the sensitivity, specificity, PPV and NPV were 80%, 94.06%, 66.67%, 96.94% respectively.

Fig 1 shows the bar chart of severity of PE. Majority (53.33%) of spot UPCR positive mothers (cut-off value ≥ 35.5 mg/mmol) developed mild preeclampsia, whereas only 26.67% mother developed severe PE. None of the patient developed severe PE in UPCR negative test (cut-off value ≤ 35.5 mg/mmol).

Fig 2 explains the optimum spot UPCR to predict preeclampsia (cut-off value ≥ 35.5 mg/mmol) had a test sensitivity of 0.8, specificity of 0.95 and (1-specificity=0.05). The area under the curve (AUC) was 0.949 (95% CI 0.891-1.000; $p < 0.001$)

Table 1: Baseline anthropometric, clinical and spot UPCR parameters in study subjects

Parameters	Unaffected (Group 1) n=101	Preeclampsia (Group 2) n= 15	p-value
Age (Years)	22.73 (3.42)	26.4 (4.22)	0.001
BMI (Kg/m ²)	23.50 (2.46)	24.60 (2.75)	0.034
Gravida, n (%)			
Primi	80 (79.21)	8 (53.33)	0.045
G ₂	13 (12.87)	4 (26.67)	
G ₃	8 (7.92)	3 (20)	
SBP(mm Hg)	109.78 (11.55)	117.6 (8.01)	0.013
DBP(mm Hg)	68.93 (7.68)	72.4 (7.6)	0.095

GA (weeks)	21.59 (1.28)	21.67 (1.29)	0.819
Spot UPCR (mg/mmole)	26.84 (4.69), 26.6	44.12 (9.43), 44.8	0.001

Mean (Std. deviation), median

Table 2: Association of spot urinary PCR with Preeclampsia

	Unaffected (Group 1)	Preeclampsia (Group 2)	Total	p-value
Spot UPCR (mg/mmole)				
<35.5	95(81.90)	3(2.58)	98(84.48)	<0.001
≥35.5	6(5.17)	12(10.35)	18(15.52)	
Total	101(87.07)	15(12.93)	116(100)	

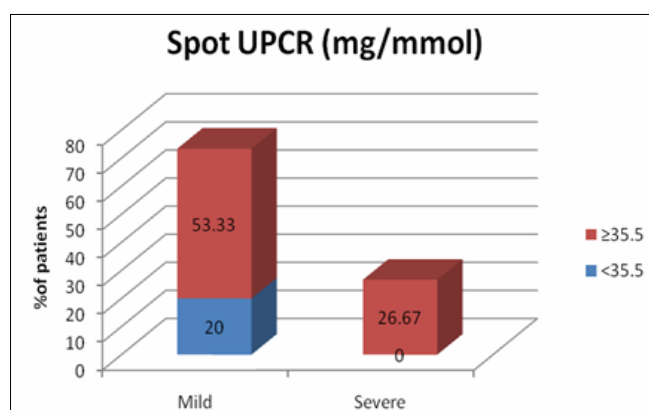
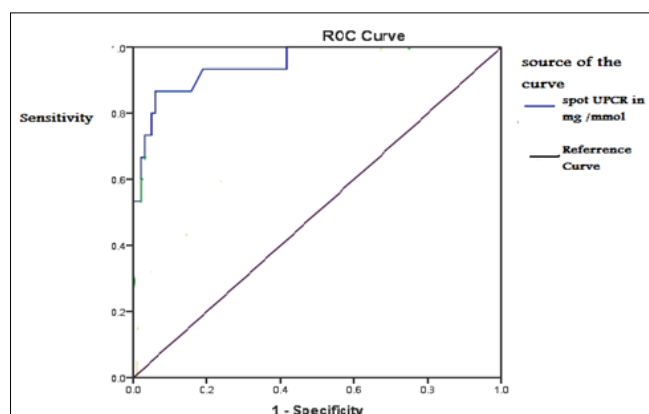
Table 3: Association of spot UPCR with onset of preeclampsia

Spot UPCR (mg/mmole)	Preeclampsia		Total	p-value
	<34 weeks	≥ 34 weeks		
<35.5	0(0)	3(20.00)	3(20)	0.629
≥ 35.5	2(13.33)	10(67.67)	12(80)	
Total	2(13.33)	13(86.67)	15(100)	

Table 4: Association of UPCR with preeclampsia

UPCR (mg/mmole)	Pre-eclampsia (D+)	Unaffected (D -)	Total
Test positive(T+)	12(10.34)	6 (5.17)	18(15.52)
Test negative(T-)	3(2.59)	95 (81.90)	98(84.48)
Total	15(12.93)	101(87.07)	116(100)

UPCR, urinary protein creatinine ratio; sensitivity-80%, Specificity-94.06%, Positive predictive value (PPV) - 66.67%, Negative predictive value (NPV) - 96.94%, Positive likelihood ratio (LR+):13.467 (95% CI, 12.8-14.14), Negative likelihood ratio (LR-): 0.213(95% CI, 0.12-0.3) Predictive accuracy – 92.24%

**Fig 1:** Spot UPCR with severity of PE**Fig 2:** ROC curve to predict preeclampsia. The ROC curve obtained by a plot of spot UPCR in mg/mmole (AUC=0.949)

Discussion

Preeclampsia is a leading cause of maternal and fetal morbidity and mortality. Prediction of preeclampsia in early part of pregnancy can be of very much helpful in preventing the disorder or in decreasing the severity.

Out of total 116 women, 15 (12.93%) individuals developed preeclampsia in later months of pregnancy which is comparable with the findings of Mishra *et al.* [8]. PE was more common in primigravida (53.33%) in our study, whereas in the study by Baweja *et al.* [9] it was 66.7%. The present study also shows development of PE was more likely in mother with high BMI.

Baweja *et al.* [9] noted in their study that higher mean SBP in PE in contrast to unaffected group (SBP, 116 vs 109 mm of Hg) was statistically significant ($p=0.001$). Similar result was also observed in the present study (SBP of unaffected vs. preeclampsia was 117 vs 109 mm of Hg, $p=0.013$). The present study in relation to SBP also correlates well with other different studies [10, 11]. Mean DBP of both PE and unaffected groups in our study corroborates well with the study by Gupta *et al.* [12].

The median value of spot UPCR (44.8 mg/mmole) in our study was significantly higher in women who subsequently developed preeclampsia than those who are unaffected (median value 26.6 mg/mmole) and our findings correlate well with Baweja *et al.* [9] as the cut-off value of UPCR in both the cases was same (≥ 35.5 mg/mmole), but differ from other studies due to the difference in spot UPCR cut-off values which were ≥ 32.2 mg/g and ≥ 9.85 mg/g respectively [10, 12].

The sensitivity of spot UPCR at the cut-off value of ≥ 35.5 mg/mmole as a screening test to predict preeclampsia in the present study was found to be 80% which is comparable to the studies by Baweja *et al.* [9] (83.3%), Fatema *et al.* [10] (80%) and Mishra *et al.* [8] (87.5%).

Despite marked heterogeneity in terms of study design, sample size and different cut-off values of spot UPCR studied by Devi *et al.* [11], Nisell *et al.* [13] and Sethuram *et al.* [14] who showed high specificity and NPV for prediction of preeclampsia which were in line with our observations, but differ from other studies as the gestational hypertension were included with PE [10, 12]. The specificity and NPV were also high in our study and which were 94.06% and 96.94% respectively.

The protein-creatinine ratio has been questioned as an alternative to measuring 24h protein excretion, as the ratio may vary throughout the day. Recently it was clearly shown that in pregnant subjects with hypertension the PCR from single void urine sample does not vary significantly throughout the day and may be determined at any time [15]. Previous studies have demonstrated that maternal age, body size, renal function, gestational age, and parity are not the confounding factors with regard to the protein / creatinine ratio [16, 17]. With this fact in mind, we believe that our results justify the introduction of spot UPCR into clinical practice.

Conclusion

The present study concludes that a single spot UPCR in early mid trimester of pregnancy in asymptomatic pregnant women is very much effective for prediction of development of preeclampsia in later months of gestation. A spot UPCR cut-off value of ≥ 35.5 mg/mmole predicted preeclampsia well before the onset of clinical manifestations with high sensitivity of 80%, specificity of 94.06% and NPV of 96.94% and predictive

accuracy was 92.24%

Small sample size, shorter duration of study period is the limitations of the present study. Large multi-centric study groups with RCTs are required for reliable study outcome. Long term follow-up of patients is also required.

Funding: No funding source

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

References

1. Kliman HJ. Uteroplacental blood flow the story of decidualization, menstruation and trophoblast invasion. *Am J Pathol.* 2011; 157:1759-68.
2. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorder of pregnancy. *Am J Obstet Gynecol.* 1988; 158:892-8.
3. Torrado J, Farro I, Zocalo Y, Farro F, Sosa C, Scasso S *et al.* Preeclampsia is associated with increased central aortic pressure, elastic arteries stiffness and wave reflections, and resting and recruitable endothelial dysfunction. *Int Hypertens.* 2015; 2015:720683. doi10.1155/2015/720683
4. Cote AM, Firoz T, Mattman A, Lam EM, Von Dadelszen P, Magee LA. The 24 hour urine collection: gold standard or historical practice? *Am J Obst Gynecol.* 2008; 199(6):625.e1-6.
5. Fagerstrom P, Sallsten G, Akerstrom M, Haraldsson B, Barregard L. Urinary albumin excretion in healthy adults: a cross sectional study of 24 hour versus timed overnight samples and impact of GFR and other personal characteristics. *BMC Nephrol.* 2015; 16:8.
6. Huang Q, Gao Y, Yu Y, Wang W, Wang S, Zhong M. Urinary spot albumin: creatinine ratio for documenting proteinuria in women with preeclampsia. *Rev Obstet Gynecol.* 2012; 5(1):9-15.
7. Brown MA, Lindheimer MN, De Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregn.* 2001; 20(1):9-14.
8. Mishra VV, Goyal PA, Priyankur R, Choudhary S, Aggarwal RS, Gandhi K *et al.* Evaluation of spot urinary albumin –creatinine ratio as screening tool in prediction of preeclampsia in early pregnancy. *J Obstet Gynecol India.* 2017; 67(6):405-8.
9. Baweja S, Kent A, Masterson R, Roberts S, McMahon LP. Prediction of preeclampsia in early pregnancy by estimating the spot urinary albumin: creatinine ratio using high performance liquid chromatography. *BJOG.* 2011; 118(9):1126-32.
10. Fatema K, Khatun M, Akter S, Ali L. Role of urinary albumin in the prediction of preeclampsia. *Faridpur Med Coll J.* 2011; 6(1):14-18.
11. Devi LT, Nimonkar A. Spot urinary albumin creatinine ratio as a predictor of preeclampsia and dilemma in clinical interpretation. *Int J Reprod Contracept Obstet Gynecol.* 2018; 7(10):4086-92.
12. Gupta N, Gupta T, Asthana D. Prediction of preeclampsia in early pregnancy by estimating the spot urinary albumin/creatinine ratio. *J Obstet Gynecol Ind.* 2017; 67(4):258-62.
13. Nisell H, Trygg M, Back R. Urine albumin/creatinine ratio for the assessment of albuminuria in pregnancy hypertension. *Acta Obstet Gynecol.* 2006; 85(11):1327-30.
14. Sethuram R, Ushakiran TS, Weerakkody ANA. Is the spot urine/creatinine ratio a valid diagnostic test for preeclampsia? *J Obstet Gynecol.* 2011; 31(2):12-30.
15. Valerio EG, Ramos GL, Martins-Costa SH, Muller ALL. Variation in the urinary protein/creatinine ratio at four different periods of the day in hypertensive pregnant women. *Hypertens Pregnancy.* 2005; 24:213-21.
16. Neithardt AB, Dooley SL, Borensztajn J. Prediction of 24-hour protein excretion in pregnancy with a single voided urine protein-to-creatinine ratio. *Am J Obstet Gynecol.* 2002; 186:883-6.
17. Schwab SJ, Christensen RI, Dougherty K, Klahr S. Quantification of proteinuria with the use of protein-to-creatinine ratios in single urine samples. *Acta Intern Med.* 1987; 147:943-4.