Comparison of Spot urine Protein Creatinine ratio and the` Gold Standard 24 hr urine for proteinuria in all admitted patients of Pre-eclampsia

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Background: It is well known that estimation of 24-h urine protein and spot urine protein/creatinine (P/C) ratios are commonly performed investigations to assess proteinuria in pre-eclampsia pregnant women with pre eclampsia. **Aim and objective:** In this study, we aimed to compare the spot urine P/C ratio and 24-hour urine protein excretion in pregnant women with pre eclampsia. **Materials and Methods:** A total of 24-h urine protein estimation, spot urine P/C ratio, and serum uric acid measurements were carried out in241 pregnant preeclamptic women, and the correlation between these investigations,as well as their correlation with proteinuria was carried out. **Results:** Pearson's correlation testshowed a positive correlation between 24-h urine protein and spot P/C ratio and was statistically significant. **Conclusion:** We found a strong correlationbetween spot urinary P/C and 24-hour urinary protein. The spot urinary protein/creatinine ratio is a good predictor of proteinuria in preeclampsia.
Keywords: Urine, Preganacy, Pre-eclampisa, protein, Cretanine

Introduction
Hypertensive disorders of pregnancy (HDPs) complicate about 3–10% of pregnancies and form part of the deadly triad, along with hemorrhage and infection, causing maternal mortality. Approximately 30,000 maternal and 500,000 perinatal deaths are attributed to the HDPs annually. [1,2] Maternal complications conclude the sequelae of HDPs, including pre-eclampsia, eclampsia, stroke, and end organ dysfunctions of the hepatic and renal organs. [3] Preeclampsia is best described as a pregnancy- specific syndrome that can affect virtually every organ system. It is the most common and most serious multisystem disease that can only be cured by delivery [4]. The incidence of pre-eclampsia ranges from 8–10% in the nulliparous population.

It is a significant public health threat globally, contributing greatly to maternal and perinatal mortality and morbidity, and accounts for about 24% of maternal deaths in

India. Pre-eclampsia is defined as hypertension after 20 weeks of gestation in previously normotensive women. Hypertension is defined as systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg measured on two occasions 4 hours apart. Proteinuria is defined as protein in urine with an amount exceeding 0.3g/L or more in 24 hours of urine collection or a urine protein-creatinine ratioof >=30 mg/mmol. This usually correlates with >=30mg/dL (>= 1+ by quantitative estimation using reagent strip or dipstick urine analysis) in two random samples that are collected at least 4-6 hours apart with no evidence of urinary tract infections. [5,6,7]

Although pre-eclampsia is much more than simply gestational hypertension with proteinuria, the appearance of proteinuria remains an important diagnostic criterion. In the absence of proteinuria, Pre-Eclampsia is characterized by thrombocytopenia (thrombocytes > 1,00,00/microliter), impaired hepatic function (hepatic transaminase concentration doubling up the normal level), the onset of renal impairment (Serum creatinine doubling up in the absence of renal disorder), and the indication of end organ damage, including the recent onset of cerebral or visual impairment [8].

In this context, we aim to compare the diagnostic value of the P/C ratio in a spot voided urine sample for detection of proteinuria with that of 24-hour urine in pre-eclamptic pregnant women hospitalized in the ANC ward.

Materials and methods

This prospective study was done at the Department of Obstetrics and Gynecology at Dr. Baba Saheb Ambedkar Medical College and Hospital. All pregnant women who were admitted with the diagnosis of preeclampsia after 20 weeks of gestation were included.

Inclusion Criteria:

- Gestation age > 24 week calculated from first day of last menstrual period or from first trimester USG scan with pre-eclampsia.
- All patients diagnosed to have BP=> 140/90 with proteinuria (with a positive urine Dipstick test).

Exclusion Criteria:
- H/o chronic hypertension, proteinuria before conception or before 20 week of gestation.
- Patients with chronic renal disease, pathological vaginal discharge and recurrent UTI.
- Molar pregnancy
- Multiple pregnancies
- Associated co-morbid conditions like diabetes and known case of collagen vascular disease.
- Those who require delivery before completion of 24-hour urine protein.

Urine analysis

Once the diagnosis of PE was made, women were admitted for 24 h for in ANC ward. A spot urine sample was obtained for protein/creatinine ratio, followed by

24 h urine collection from 2ⁿᵈ morning voided urine till next day morning (24 h duration).

Statistical Analysis

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0. For statistical significance, p-value of less than 0.05 was considered statistically significant.

Observation and Results

Table 1:-Distribution of age(years) of study subjects.

Age(years)	Frequency	Percentage
<25 years	109	45.23%
26-30 years	76	31.54%
>30 years	56	23.24%
Mean ± SD	26.3 ± 4.2	
Median(25th-75th percentile)	26(22-30)	
Range	20-35	

In the table 1 shown below, Age group distribution showed that mean age of women is 26.3+_4.2 years and maximum no. of women 109 (45.23%) belonged to <25 years of age group. This indicates that preeclampsia is more common among young age patient and elderly gravida.

Table 2:-Distribution of vitals of study subjects.

Vitals	Frequency	Percentage	Mean ± SD	Median(25th-75th percentile)	Range
Systolic blood pressure(mmHg)					
140-149	95	39.42%	153.55 ± 11.63	150(140-160)	140-180
150-159	52	21.58%			
160-169	58	24.07%			
170-179	24	9.96%			
>=180	12	4.98%			
Diastolic blood pressure(mmHg)					
90-99	116	48.13%	99.15 ± 8.61	100(92-102)	90-120
100-109	76	31.54%			
110-119	47	19.50%			
120-129	2	0.83%			

Table 2 shows the distribution of vitals of study subjects. Among the stud population, 147 were having systolic blood pressure <160mmhg making it 61% of the whole study population and 94 were having systolic blood pressure >=160mmhg making it 39%. 192 were having diastolic blood pressure <110mmhg making it 79.67% of the study population and 49 were having diastolic blood pressure >=110mmhgmaking it 20.33%.

Table 3:-Distribution of 24 hours urine protein(mg) of study subjects.

24 hours urine protein(mg)	Frequency	Percentage	Mean ± SD	Median(25th-75th percentile)	Range
At admission					
>=300	241	100.00%	1628.29 ± 797.09	1180(983-2100)	800-4600
At discharge					
<300	29	12.03%	840.57 ± 462.33	890(546-985)	116-2130
>=300	212	87.97%			
At 3 weeks postpartum(n=151)					
<300	35	23.18%	549.04 ± 265.09	432(320.5-860)	120-880
>=300	116	76.82%			

Table 3 below shows the distribution of 24 hours urine protein(mg) among the study subjects. 24hr urine protein was performed in all 241 preeclamptic patient at admission and at discharge and at 3 weeks postpartum only 151 patient could attend the visit because of the COVID-19 disease. At admission the mean 24hr protein was 1628.29+_797.09(Range-800-4600) while at discharge, the mean was 840.57+_462.33(Range-116-2130) and at 3 weeks postpartum the mean was 549.04+_265.09(Range-120-880).

Table 4:-Distribution of spot protein creatinine ratio of study subjects.

Spot protein creatinine ratio	Frequency	Percentage	Mean ± SD	Median(25th-75th percentile)	Range
At admission					
>=0.3	241	100.00%	1.01 ± 0.26	0.96(0.802-1.15)	0.65-2.28
At discharge					
<0.3	52	21.58%	0.56 ± 0.28	0.63(0.434-0.658)	0.05-1.15
>=0.3	189	78.42%			
At 3 weeks postpartum(n=151)					
<0.3	36	23.84%	0.58 ± 0.32	0.41(0.303-0.96)	0.11-0.98
>=0.3	115	76.16%			

Table 4 shown below shows distribution of spot protein creatinine ratio among study subjects. At admission and discharge, spot protein creatinine ratio was performed in

241 patient and at 3 weeks postpartum spot protein creatinine ratio was done in only 151 patients. It was found that at admission the mean was 1.01+_0.26(Range-0.65-2.28), at discharge it was 0.56+_0.28(Range-0.05-1.15) and at 3 weeks postpartum the mean was 0.58+_0.32(Range-0.11-0.98). The same is shown in bar chart in figure 11. It suggested that mean of spot protein creatinine ratio decreased once the patient delivered.

Table 5:-Correlation of 24 hr urine protein (mg) and Spot Protein Creatinine Ratio in total study subjects.

24 hr urine protein (mg) and Spot Protein Creatinine Ratio	At admission	At discharge (post delivery)	At 3 weeks postpartum
Correlation coefficient	0.999	0.977	1.000
P -value	<0.0001	<0.0001	<0.0001

Table 5 shows correlation of 24 hr urine protein (mg) and Spot Protein Creatinine Ratio in total study subjects. A good correlation of r=0.999 at admission, r=0.997 at discharge and r=1.0 at 3 weeks postpartum was observed between the 24hr urine protein and spot urine protein creatinine ratio among 241 study subjects which was significant with a P value of <0.0001.

Table 6:-Correlation of 24 hr urine protein (mg) and Spot Protein/Creatinine Ratio in 30 to <34 weeks.

24 hr urine protein (mg) and Spot Protein/Creatinine Ratio	At admission	At discharge (post delivery)	At 3 weeks postpartum
Correlation coefficient	1.000	0.674	1.000
P- value	<0.0001	<0.0001	<0.0001

Table 6 shows the correlation of 24 hr urine protein (mg) and Spot Protein Creatinine Ratio in 30 to <34 weeks of period of gestations. The correlation of 24hr urine protein with spot protein creatinine ratio was studied at different gestational age at admission, at discharge and at 3 weeks postpartum. Between 30 to <34weeks of period of gestation, it was found that there was a good correlation between these two test with value of r=1.0 at admission, r=0.674 at discharge and r=1.0 at 3 weeks postpartum. P value of <0.0001 was observed which is statistically significant.

Table 7:- Correlation of 24 hr urine protein (mg) and Spot Protein Creatinine Ratio in 34 to <36 weeks.

24 hr urine protein (mg) and Spot Protein Creatinine Ratio	At admission	At discharge (post delivery)	At 3 weeks postpartum
Correlation coefficient	0.997	0.983	1.000
P-value	<0.0001	<0.0001	<0.0001

Table 7 shown below shows the correlation of 24 hr urine protein (mg) and Spot Protein Creatinine Ratio in 34 to <36 weeks of period of gestations. This correlation of 24hr urine protein with spot protein creatinine ratio was studied at 34-36weeks POG at admission, at discharge and at 3 weeks postpartum. It was observed that there was a good correlation with value of r=0.997 at admission, r=0.983 at discharge and r=1.0 at 3 weeks postpartum. The P-value was <0.0001 which is statistically significant.

Table 8:-Correlation of 24 hr urine protein (mg) and Spot Protein Creatinine Ratio in >=36 weeks.

24 hr urine protein (mg) and Spot Protein Creatinine Ratio	At admission	At discharge (post delivery)	At 3 weeks postpartum
Correlation coefficient	0.999	0.987	1.000
P-value	<0.0001	<0.0001	<0.0001

Table 9:- Inter rater kappa agreement of 24hr urine protein(At Discharge) and Spot Protein Creatinine Ratio(At Discharge) in total study subjects.

24hr urine protein(At Discharge)	Spot Protein Creatinine Ratio(At Discharge)		Total	P-value	Kappa
	<0.3(n=52)	>=0.3(n=189)			
<300	29 (12.03%)	0 (0.00%)	29 (12.03%)		
>=300	23 (9.54%)	189 (78.42%)	212 (87.97%)	<.0001	0.664
Total	52 (21.58%)	189 (78.42%)	241 (100.00%)		

Table 10:- Inter rater kappa agreement of 24hr urine protein(At 3 week postpartum) and Spot Protein Creatinine Ratio(At 3 week postpartum) in total study subjects.

24hr urine protein(At 3 week postpartum)	Spot Protein Creatinine Ratio(At 3 week postpartum)		Total	P-value	Kappa
	<0.3(n=36)	>=0.3(n=115)			
<300	35 (23.18%)	0 (0.00%)	35 (23.18%)		
>=300	1 (0.66%)	115 (76.16%)	116 (76.82%)	<.0001	0.982
Total	36 (23.84%)	115 (76.16%)	151 (100.00%)		

Inter rater kappa agreement of 24hr urine protein(At Discharge) and Spot Protein Creatinine Ratio(At Discharge) in total 251 study subjects was studied at 30-34weeks period of gestation and was observed that kappa value was 1.000 which is significant.

Discussion

In our study, 241 admitted antenatal cases of preeclampsia with a urinary dipstick value 1+ were selected as study subjects. Proper history-taking and general physical and obstetric examinations were done for all. A random midstream urine sample for estimation of spot urine Protein creatinine ratio and the 24-hr urine starting from the second urine sample in the morning till the first urine sample of the next morning for 24-hr urine protein estimation was done in all patients at admission, at discharge, and at 3 weeks postpartum. The 24-hour urinary protein and spot protein creatinine ratios were determined and documented.

Our study found that the sociodemographic variables show that the mean age of women is 26.3 + 4.2 years, and the maximum number of women, 109 (45.23%), belonged to the 25-year-old age group. The median age was 26 years old. The randomurine protein creatinine ratios and the 24 hour urine protein were correlated in the total study subjects; a good correlation was found with a correlation coefficient of r = 0.999 at admission, r = 0.997 at discharge, and r = 1.0 at 3 weeks postpartum, with a pvalue of 0.0001, which is highly significant when all the observations are considered. The same two tests were correlated at different gestational ages, and it was observed that between 30-34 weeks POG, there was a good correlation of r = 1.0 at admission, r = 0.674 at discharge, and r = 1.0 at 3 weeks postpartum, with a P value of < 0.0001, which is statistically significant. Between 34 and 36 weeks, there was a good correlation of r = 0.997 at admission, r = 0.983 at discharge, and r = 1.0 at 3 weeks postpartum, with a P value of < 0.0001, which is statistically significant. After >=36 weeks of POG, there was a good correlation of r = 0.999 at admission, r = 0.987 at discharge, and r = 1.0 at 3 weeks postpartum, with a P value of < 0.0001, which is statistically significant. Our study, also supported by Shankar R. and associates,analyzed the two parameters among 90 pregnant women from gestational age 20 to 40weeks, including 30 with preeclampsia and 30 with antepartum eclampsia, which were considered cases, and 30 normotensive pregnant women as controls, and found a

strong correlation at a p value <0.001 and also observed an association of raised values with severity of disease as well as with adverse feto maternal outcome.

Similarly, the Jaschevatzky study and associates on 70 healthy patients and 35 preeclamptic patients found a better correlation (r = 0.9278, p < 0.001) between 24 hour proteinuria and random urinary protein creatinine ratio. However, there is a decreased degree of correlation in patients with proteinuria. A random urinary protein:creatinine ratio has been proposed as an alternative to 24-h urinary collection for protein for the detection of significant proteinuria [9]. It has also been recommended by the National Kidney Foundation for the diagnosis of proteinuria in patients with chronic renal disease, diabetic nephropathy, without mentioning the pregnant state [10]. In a recent meta-analysis, 11 studies were identified that compared spot urinary P/C ratio with 24-hour urinary protein excretion [11]. The ROC curve was utilized in nine of 11 studies. The range of the area under the curve varied from 0.82 to 0.94. In our study, it was 0.90. Similarly, only nine studies identified the cut-off points for the spot urinary protein-creatinine ratio. The cut-off point identified by our study was 0.14 mg/dl. This value corresponded with the protein excretion rate of 300 mg/24 h. In a study from neighboring Iran, the cutoff value of 0.20 of the spot urinary P/C ratio identified urinary protein excretion of 300 mg/dl [12]. Similarly, in a study by Wheeler et al., the cutoff value of 0.21 for spot urinary P/C ratio identified urinary protein excretion of 300 mg/dl, and a P/C ratio of less than 3.0 (5000 mg per 24 h) was found to have a 100% NPV [13]. Dwyer et al. compared the spot urinary P/C ratio with urinalysis. In their study of 116 women at risk of PE, a cut-off of 0.24 was found to be equivalent to a P1+ urinalysis. The investigators found a sensitivity of 66% for spot urinary P/C ratio versus 41% for urinalysis [14]. Their study also found an AUC of 0.89 (95% CI 0.83–0.95). The authors concluded that urinary P/C ratio was a better screening test for proteinuria in patients at risk of PE. We found a strong correlation between spot urinary P/C and 24 h urinary protein (P < .000). This strong correlation has also been observed in other studies, with values ranging from 0.87 to 0.97. Aggarwal et al., in a study of 120 women diagnosed with hypertension during pregnancy, found a correlation between spot urinary P/C and 24-hour urinary protein. The authors concluded that with increased proteinuria, the correlation increased significantly [15].

Conclusion

Our study showed a strong correlation between the spot urinary P/C ratio and 24-hour urinary protein in pregnant women with pre-eclampsia. The spot urinary P/C ratio is a good predictor of proteinuria in pre-eclampsia. However, large-scale studies are required to determine the usefulness of the P/C ratio in clinical practice.

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Competing interests

The authors have declared that no competing interests exist.

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