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Study on Spot Urine Protein Creatinine Ratio in Preeclampsia as an Alternative for 24 Hour Urine Protein

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Abstract: ***Aim: Determination of diagnostic accuracy of spot protein creatinine ratio in comparison with 24hour urine proteinuria, evaluation of protein creatinine ratio for different proteinuria ranges in patients with preeclampsia and estimation of protein creatinine ratio for significant proteinuria in suspected preeclampsia. Design: observational study. Method: study was conducted on Department of Obstetrics and Gynaecology, SRN Hospital M. L. N. Medical College, Allahabad. Study was conducted on 150 pregnant women with >20 weeks of gestation with blood pressure more then 140/90 mm of mercury instructed to collect 24hour urine protein over 1 year from august 2017 to 2018.Protein creatinine ratio was evaluated in a random urinary sample. Relationship of spot urine protein creatinine and 24hour urinary protein, accuracy of the ratio against 24hour urinary protein and relationship of such ratio and adverse pregnancy outcome were studied. Result: The optimal cut off value of spot protein creatinine ratio for significant proteinuria was 0.27 at which sensitivity was 88.1% and specificity was 98.1% with positive predictive value of 97.36 % and negative predictive value of 91.37%. Conclusion: A definite correlation was found between 24hour urine protein and spot urine protein creatinine ratio which was statistically significant (r=0.9668. P value <0.)***

Keywords: preeclampsia, urine protein creatinine ratio, 24hour urine proteinuria

1. Introduction

Among hypertensive disorders of pregnancy preeclampsia is the leading cause & complicates 5-10% of pregnancy. Preeclampsia a pregnancy specific hypertensive disease with multisystem involvement. Most common form of high blood pressure that complicates pregnancy.

Defined as occurrence of new onset hypertension in the 2nd half of pregnancy.1) Blood pressure of≥140/90 mm of mercury after 20 weeks of gestation in a woman with previously normal blood pressure.2) proteinuria –greater than or equal to 300mg per 24hour urine collection or Protein creatinine ratio greater than or equal to 0.3. OR
Dipstic reading of 1+ (used only if other quantitative methods not available. 3) OR in absence of proteinuria new onset hypertension with the new onset of any of the following

a) Thrombocytopenia –platelet count less than 1lac /microlitre.
b) Renal insufficiency-serum creatinine concentration greater than 1.1 mg/dl or a doubling of serum concentration in the absence of other renal disease.
c) Impaired liver function –elevated serum concentration of liver transaminases to twice normal concentration
d) Cerebral symptoms –headache, visual disturbances, convulsions
e) Pulmonary edema.

Etiology

a) Placental implantation with abnormal trophoblastic implantation of uterine vessels (1).
b) Immunological maladaptive tolerance between maternal paternal(placenta), and fetal tissue (2)
c) Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy.
d) Genetic factors including inherited predisposing genes and epigenetic influences

Pathogenesis

Vasospasm

Endothelial cell injury

Increased pressure response –increased sensitivity to angiotension -2precedes the onset of gestational hypertension.

Proteinuria

Proteinuria sign of severity &value >5 gm in 24hour is one of the criteria to classify preeclamsia as severe.

Progressive proteinuria indicates worsening of the condition in hypertensive disorders of pregnancy &hence quantification guides clinician in decision making and treatment planning.

Proteinuria is recognized as an independent risk factor forcardiovascular and renal disease and as a predictor of end organ damage (3).

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The diurnal variation of specific gravity of urine due to changing glomerular filtration rate results in varying concentrations of urinary protein at different times of the day when this concentration divided by spot urine creatinine level results in constant ratio throughout the day, &hence is considered to be reliable indicator of proteinuria.

Urine protein creatinine ratio rapid method of estimation of proteinuria –a proteincreatinine ratio of >0.3 almost always indicates significant proteinuria.

There Is a good correlation between urine protein creatinine ratio and 24 hour urine protein creatinine ratio >0.9 strongly predict significant proteinuria for 1 gm (4)protein creatinine ratio helpful in diagnosis of preeclampsia and can be used as a preadmission test in pregnancy induced hypertension cases (5) random protein creatinine ratio is a reliableindicator of significant proteinuria in preeclampsia and may be better at providing earlier diagnostic information than 24 hour urine proteinuria with more accuracy than urine dipstick test .The current gold standard, the 24hour urine protein is less ideal because it is cumbersome to collect and its processing is labour intensive and requires admission and time consuming and its usefulness is limited to collection errors, storage difficulties, specimen handling, and poor patient compliance. Not only there is a delay in diagnosis due to waiting time, but also this method proves pointless when urgent delivery is required due to worsening maternal and foetal condition. Considering these issues, alternative methods for diagnosis of proteinuria in pregnancy have been thought off, which include dipstick method and spot urinary protein: creatinine ratio. ;urine protein creatinine ratio has been considered important for predicting proteinuria in hypertensive patients .it compares the spot urine protein excretion to the spot urine creatinine excretion , thereby normalizing protein excretion to the glomerular filtration rate. Thus urine protein creatinine ratio is not subjected to diurnal variation or due to hydration status .In pregnant women the urine protein creatinine ratio & 24 hour urine are highly correlated .A rapid and accurate test may provide efficient inpatient and outpatient monitoring of proteinuria and may shorten the duration of hospitalization .Thus the study was conducted to determine the diagnostic accuracy of random urine protein creatinine ratio.

2. Material and Methods

The study was carried out in the department of obstetrics and gynecology at Swaroop Rani Hospital and Kamla Nehru Hospital in collaboration with the department of Pathology affiliated to MLN Medical College. Total 180 patients were enrolled for the study, out of which 20 had inadequate sample and 10 lost to follow up. So 150 cases included in the study.

Method of Collection of Data

Inclusion criteria
Pregnant women with gestational age >20 week with raised blood pressure.

Exclusion criteria
Women with overt diabetes
Preexisting chronic kidney disease
Multiple pregnancy
Urinary tract infection

Bed rest longer than 24hour24hour urinary protein creatinine ratio and spot urine protein creatinine ratio was recorded and maternal and fetal outcome was observed. A written and informed consent was obtained from all subjects prior to performance of any study related procedure. Thorough history, examination and investigation done.

1.Urine examination- routine and microscopy, 24hour urinary protein and protein creatinine ratio. All women included in the study irrespective of the severity of disease were asked to provide spot midstream urine sample and collect all the urine subsequently for 24 hours period.

Using the 24hour protein results as the gold standard, we calculated the test characteristics of the protein creatinine ratio to predict significant proteinuria (300mg/day) as arrange of values. Pearson's correlation coefficient expressed as"r"was used to correlate between spot urine protein creatinine ratio and 24 hour urine protein. Microsoft word and excel were used to generate tables, graphs.

Urine protein estimation; Urine total protein analysed using chlorimetric pyrogallol red. Tests were performed by automated analyser.

Methodology
Pyrogallol Red method

Reagents composition
Pyrogallol red 50 mmol
Sodium molybdate 0.04 mmol Protein calculation –albumin /globulin aqueous primary standard 1000 mg/l.

Test procedure	Blank	Standard	Sample
Reagent (ml)	1.0	1.0	1.0
Calibrator (µL)	-	20	-
Sample (µL)	-	-	20

Protein react in acid solution with pyrogallol red and molybdate to form a coloured complex. The intensity of the colour formed is proportional to the protein concentration in the sample. Read the absorbance of samples and standard, against the blank at 598 nm .colour is stable for atleast 30 minutes .
Absorbance of test ×concentration of standard
Absorbance of standard

Urinary Creatinine Estimation

Carried out in same random sample.

Method of Urine Creatinine Estimation - based on principle of modified jaffe's reaction, initial rate assay.

Principe of method
In alkaline pH creatinine reacts with picric acid to form an orange colour complex (creatinine alkaline picrate) .The rate of formation of this complex is measured by reading the change in absorbance at wavelength of 505 nm in selected

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interval of time time and proportional to the concentration of creatinine . (inbuilt in autoanalyzer).

$$\text{creatinine} + \text{picric acid} \rightarrow \text{orange coloured complex}$$

reagents composition

Reagent no.	Reagent	Composition	Concentration
1	Picrate reagent	Picric acid preservative	40 Mm/L
2	Sodium hydroxide	Sodium hydroxide	200mM/L
3	Creatinine standard	Creatinine stabiliser	2 mg/dl

Working reagent preparation

Prepare working reagent by mixing equal volume of reagent 1 and reagent 2 to make up the desired volume.Mix gently for 2 minutes . Reagent 3 is ready to use.

Procedure

Pipette into tubes marked	Standard	Test
Urine	-	100µ
Reagent 3	100µ	-
Working creatinine reagent	1000µ	1000µ

Measure initial absorbance of the standard after 30 minutes and final absorbance after an interval of another 120 seconds.

Calculation

Urine creatinine (mg/dl)=

Final O.D. of Test –initial O.D. of test

Final O.D. of standard –initial O.D. of standard

Conversion factor

Creatinine concentration in µmol/L=Creatinine conc. in mg /dl×88.4

Spot Urinary Protein Creatinine Ratio

After obtaining theurine protein and creatinine concentration in mg per 100 ml.'ratio calculated by simply dividing protein concentration by creatinine concentration .24 hour urine protein calculation

Statistical analysis - Chi square test applied for statistical analysis. p value <0.5 was considered significant.

Table 1: Distribution of pregnant Patients according to 24 Hour Urine Protein

24 hr urine protein (gm/24 hr)	Number of cases	Percentage (%)
<0.3	55	36.6
0.3	3	2
0.3-1	67	44.6
1.1-3	21	14
>3	4	2.6

From above mentioned table 55(36.6%) pregnant women had less than 0.3 gm/ 24hour protein excretion. 95 (63.33%) patient had equal to or more than 0.3 gm /24hour protein excretion which was significant. Out of 95 pregnant women 3(2%) had 0.3 gm/24hour proteinuria, 67(44.6%) patient had 0.3 - 1 gm/24hour protein excretion, 21(14%) patient had 1.1to 3 gm/24hour and only 4 (2.6 %) patient had more than 3 gm/24hour urinary protein.

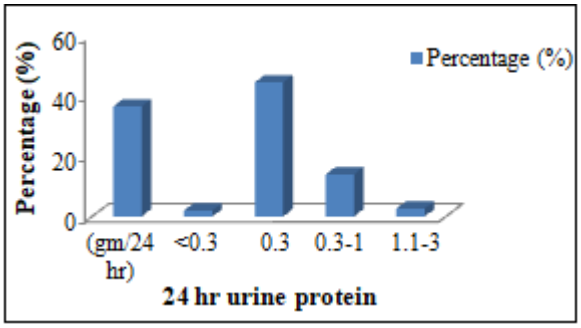


Figure 1

Table 2: Protein: creatinine ratio in spot urine

Protein: creatinine ratio in spot urine sample	Number of cases	Percentage (%)
<0.1	26	17.33%
0.1-0.27	29	19.33%
0.28-0.35	20	13.33%
0.36-0.5	11	7.33%
>0.5	64	42.66%
Total	150	100%

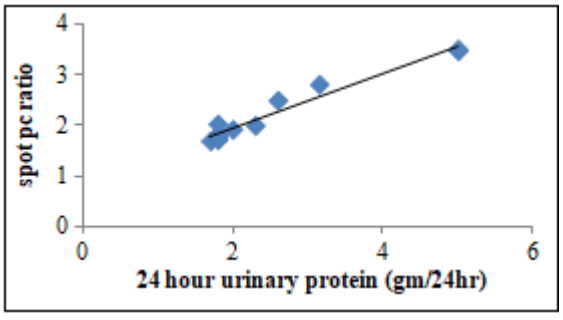
As shown in above table among 150 patients maximum patient 64(42.66%) had protein creatinine ratio more then 0.5, 26(17.33%) patient had less than 0.1, 29 (19.33%) patient in the range of 0.1-0.27, 20 (13.33%) patient had 0.28-0.35, and only 11 (7.33%) patient had between 0.36-0.5.

Table 3: Distribution of Patients showing correlation between P/C ratio and 24 hr urine protein excretion

Number of Cases	24 hr proteinuria (gm/24 hr)	Spot P/C ratio
55	<0.3	0.034-.234
3	0.3	0.27
67	0.3-1	0.29-1
21	1.1-3	1 -2.48
4	>3	2.8-3.5

According to above table cut off for 0.3 gm/24 hour was 0.27 .There was linear correlation between PCR and 24 hr urinary protein excretion and it was significant (correlation coefficient (r) =0.9668) P value<.001.senstivity -88.1%, specificity- 98.1% and positive predictive value was 97.36%, negative predictive value 91.37%.

Figure 2:



r=0.9668 , P<.001

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Table 4: Comparision of 24 hr urine protein to protein: creatinine ratio in a spot sample

Type	Number of cases	24 hr Proteinuria gm/24hr	Number of cases	Spot P/C Ratio
Preeclampsia	95	≥0.3	95	≥0.27
Pregnancy with hypertension	55	<0.3	55	<0.27

In above mentioned table. Out of 150 patient 95(63.33%) patients had significant proteinuria and had 24 hour urine protein excretion equal to or more then 0. 3gm/24 hour and thesepatients had 0.27 as protein creatinine ratio.

Table 5: Distribution of Patients according to mode of Delivery

Mode of delivery	Group 1	Percentage	Group 2	Percentage
Vaginal	60	63.15	31	56.36
Caesarean	35	36.84	24	43.63
	Total=95	100%	55	100%

From above table maximum patients delivered vaginally in both groups, 60(63.15%) in group 1 and 31(56.36%) in group 2.In group 1 only 35(36.84%) delivered by caeserian section and in group 2 only24 (43.63%) delivered by caeserian section.

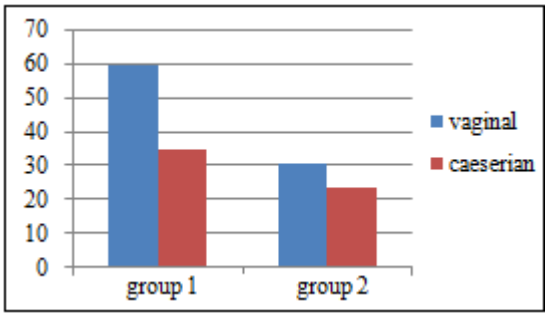

Table 6: Maternal outcome

No. of cases	24 hr Proteinuria in gm/24 hr	Protein: Creatinine ratio	Meternal complications			
			Plecental abruption	Liver dysfunction	ECLAMPSIA	PPH
3	0.3	0.27	0	0	0	0
67	0.3-1	0.29-1	9	1	1	1
21	1.1-3	1 -2.48	7	0	0	1
4	>3	2.8-3.5	0	1	1	1

Maternal outcome 95 singleton preeclampsia patients , in between 0.29-1 protein creatinine ratio there was 9(13.43%) cases of placental abruption, 1(1.49%)developed HELLP SYNDRME, 1(1.49%) developed eclamptic seizure and 1(1.49%) went into postpartum haemorrhage. Between 1 - 2.48 , there was 7(33.33%) had placental abruption only 1(4.76%) went into postpartum haemorrhage. And in case of >2.8 there was 1 (25%) HELLP SYNDROME, 1(25%) had eclamptic seizure 1(25%) went into postpartum haemorrhage.

Table 7: Fetal outcome

No. of cases	24 hr proteinuria in gm/24 hr	Protein: Creatinine ratio	Fetal outcome			
			Preterm	Low birth weight	Still birth	NICU admission
3	0.3	0.27	1	1	0	0
67	0.3-1	0.29-1	9	10	6	1
21	1.1-3	1 -2.48	45	39	13	7
4	>3	2.8-3.5	1	1	1	1

For neonatal outcome of all single tone preeclampsia patients, 59% were preterm, 54%low birth weight, 21%were still birth & 11.5% were admitted in NICU.

3. Discussion

Maximum number of patients seen in the age group >35 years. The second largest number of cases were between 21-25 years of age group and there was 10.5% patients in the age of <20 years, least patients in between 31-35 years. Mean age of preeclampsia patients of our study was 29.4 years, which is comparable with the study of Catherine marnoch et al (2008)(8) was 28.8±6.9 years.

Most of the patients of both the groups were primigravida (1st time exposure to chorionic villi), (76.84%) in group 1 and (78.18%) in group 2, multiparity not an exception some cases had history of preeclampsia in previous pregnancies. Odegard et al (2000) (6) study had similar result- nulliparity increases the risk of preeclampsia. Similar study done by juhi et al (2015) (7). - 71% of patients were primigravida.

Maximum patient of group 1 admitted in 33-36 weeks of gestation (63.15%), 22% were between 24-32 weeks .In group 2 maximum patients belonged to 33-36 weeks and 37-40 weeks Mean gestational age of group 1 was 33.4 weeks which was comparable with the study of Oyademirci et al(2015)(4). (33.01±4 weeks and in CathrineAmarnoch et al (2008)(8) was (32.8±5, 6). Mean gestational age of group 2was 36.4 weeks.

In our study maximum patients came from rural area in both groups. in present study, most of the patients were illiterate. 73.68% cases seen in group 1 and 78.18% in group 2.

According to kuppuswami scale of socioeconomic status, maximum number of cases were from lower class (60%) in group 1and upper class (76.36%) in group 2. Low socioeconomic factors act asmultiple risk factors for preeclampsia because low socio economic statusare associated with nutritional issues, less antental care. Ceronmirelesetal (2001) (9) studied in maxico city that low socio- economic status ofwomen doubles the risk of preeclampsia and eclampsia. Our study similarto a study done in a semiurban setting Silma et al (2008)(10). Showed significant association between maternal education, income and preeclampsia.
Maximum patients in both the groups were unbooked, this high incidence of preeclampsia and hypertensive disease of pregnancy is due to illiteracy and unawareness of antenatal services provided in hospital. One of the criteria for severity of preeclampsia is blood pressure, more then 160/110 mm of mercury. In our study only 36 patient (24%) had blood pressure more then 160/110 mm of mercury and rest 114(76%) patients had blood pressure <160/110 mm of mercury.Most of the patient in both the groups had haemoglobin less then 11 gm%. In group 1, 84(88.42%) out of 95 had haemoglobin between 8.5-11 gm% it reflects poor nutrition both in terms of quality and quantity which increases morbidity and mortality during pregnancy. It may be due to poor socioeconomic status, illiteracy and various myth .95 pregnant women out of 150 (63.33%) had proteinuria equal to or more then 0.3 gm/24hour and they

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were classified as preeclampsia. Out of 95 preeclampsia maximum 92(96.8%) had > 0.3 -1 gm/24 hour protein excretion and rest 55 (36.66%) patient had less than 0.3 gm/24 hour protein excretion.

According to protein creatinine ratio we had taken mean 0.27 as a cut off for 0.3 gm /day proteinuria. 95 (63.33%) patient had protein creatinine ratio more the 0.27 and considered as significant proteinuria. And most of the patient 42.66% out of 95 had protein creatinine ratio >0.5. 55(36.66%) had protein creatinine ratio less then 0.27 and they were considered non-significant proteinuria.

There was a linear correlation between 24 hour proteinuria and protein creatinine ratio with correlation coefficient of 0.9668 and p value of 0.001 which was highly significant. The optimal protein creatinine ratio for detection of significant proteinuria of 300mg/day was identified as 0.27 with sensitivity and specificity of 88% and 98% respectively, and positive predictive value and negative predictive value of 97.36% and 91.37% respectively. In U.K. morris et al(2012)(11) concluded optimal threshold of spot protein creatinine ratio to detect significant proteinuria is between 0.30 and 0.35, relating to sensitivity and specificity value above 75 %. Wheeler et al (2007) (12) conducted a study among 126 patients and reported a strong correlation of random spot protein creatinine ratio with 24 -hour urine protein levels (pearson´s r =0.88). Aggrawal et al (2008)(13) reported a significant association between the two test with a correlation coefficient of r=0.596(P<0.01). Nischintha et al(2014)(14) found a moderate correlation between 24 –hour urine protein and spot P/C ratio which was statistically significant (r=0.373, P< 0.001).

Maximum patients were delivered vaginally in both group 63.15% in group 1 and56.36% in group 2, only 36.84% in group 1 and 43.63% in group 2 delivered by caeserian section. Hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality and morbidity worldwide, in India, they account for the third most important cause of maternal mortality (International journal of reproduction, contraception, Obstetrics and Gynaecology 2017). The severity of proteinuria has been regarded as a predictor for adverse maternal and fetal outcome. In our study incidence of low birth weight, preterm and stillbirth increased as protein creatinine ratio exceeds >0.27. Costa et al (2011)(15) reported that at random spot protein creatinine ratio >0.3, there was a high probability of having unfavourable maternal and fetal outcomes.

Maternal outcome of study 24% developed severe hypertension (blood pressure >160/110 mm of mercury). Out of 95 preeclampsia patients, In between 0.29 -1 protein creatinine ratio there was 9(13.43%) cases of placental abruption, 1(1.49%) developed HELLP Syndrome, 1(1.49%) developed eclamptic seizure and 1(1.49%) went into postpartum haemorrhage. Between 1-2.48 protein creatinine ratio, there was 7(33.33%) had placental abruption only 1(4.76%) went into postpartum haemorrhage. And in case of > 2.8 protein creatinine ratio there was 1 (25%) HELLP Syndrome, 1(25%) had eclamptic seizure 1(25%) went into postpartum haemorrhage.

In all cases fetal outcome was observed in the form of prematurity, low birth weight, stillbirth and neonatal intensive care unit admission and perinatal mortality. For neonatal outcome of all singletone preeclampsia, 59% of the cases had a preterm delivery, 54%low birth weight, there were 21% stillbirth & 11.5% were admitted in NICU. Accessible healthcare and health education and awareness regarding antenatal check-ups for all women will lead to early detection of diagnosis of preeclampsia and recognition of severe preeclampsia. Immediate treatment and management of its complication will certainly improve the maternal and perinatal outcome.

4. Conclusion

Preeclampsia were more common in females more than 35 years of age and <20 years of age. Antenatal checkup was found to be rare as they were unaware of sequally of such condition. Nutrional updates were not known to these patients and their relatives, therefore anaemia and deficiency of micronutrients is very common. Mean gestational age of preeclampsiapatients of study was 33.4 weeks. Fetomaternal complications increases as protein creatinine ratio increases.

The optimal cut off value of spot protein creatinine ratio for significant proteinuria was 0.27 at which sensitivity was 88.1% and specificity was 98.1% with positive predictive value of 97.36 % and negative predictive value of 91.37%. A cut off value of 0.27 has been suggested as a reasonable “rule out test” for proteinuria above 0.3 gram/24 hour.

In the present study, we found a definite correlation between 24 hour urine protein and spot urine protein creatinine ratio which was statistically significant (r=0.9668, P value <0.001). Spot protein creatinine ratio test evaluate the severity of existing disease is as good as that of 24 hour protein estimation and is faster, better, simpler and more convenient to handle this test so that spot protein creatinine ratio test in comparision to 24 hour urinary protein becomes the first choice automatic.

Compliance with Ethical Standards

Conflict of interest – Dr**.** Ramona Perhar, Dr Meenakshi Devi, Dr. Rita Shukla declare that they have no conflict of interest.

Informed Consent–Informed consent was obtained from all individual participants included in the study.

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