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A study of the correlation of spot urinary protein – creatinine ratio in antenatal patients with hypertensive disorders on severity of preeclampsia, maternal organ dysfunction and its implication on perinatal outcomes

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Abstract
Aim: To evaluate the correlation of spot urinary protein – creatinine ratio in single voided urine sample in antenatal patients with hypertensive disorders for assessing the severity of preeclampsia, maternal organ dysfunction and its implication in perinatal outcomes.
Material and Methods: 150 cases of Pregnancy Induced Hypertension admitted in ward/Labour room of Department of Obstetrics & Gynaecology, SRMSIMS were studied and grouped into mild and severe pre-eclampsia depending upon blood pressure and clinical parameters. Midstream urine sample estimation for protein-creatinine ratio was done along with the biochemical parameters for renal and liver function tests.
The correlation of spot urinary protein-creatinine ratio with severity of preeclampsia along with the derangements in fundoscopy, liver function and renal function tests with increasing severity of proteinuria using optimal protein–creatinine ratio of 0.3 and effects of Pre-eclampsia on perinatal outcomes were evaluated.
Results: Protein-Creatinine ratio of 0.3 can be used as an optimal cutoff to detect the severity of preeclampsia. On evaluation of organ dysfunction in relation to Protein-creatinine ratio, a statistically significant p value was observed between increasing grades of pre- eclampsia with abnormal fundoscopy, abnormal renal function tests and abnormal liver function tests. While studying the fetal parameter in terms of IUFD, prematurity, low birth weight, APGAR < 7 at 5 minutes, NICU admission no statistically significant result was found with respect to the value of protein-creatinine ratio but still it was seen that protein creatinine ratio could be used as a single parameter for early detection of maternal organ dysfunction and perinatal outcome and thereby helps in management and improve prognosis.
Conclusion: The optimal spot Protein-creatinine ratio cut off point of 0.3 can be used to assess the disease severity in hypertensive disorders of pregnancy and early detection of maternal organ involvement, maternal and perinatal outcomes.
Clinical significance: Determination of protein/creatinine ratio is a valuable tool to determine the severity of disease and adverse maternal and perinatal outcomes.

Keywords: Pre-eclampsia, protein-creatinine ratio, maternal outcome, perinatal outcome

Introduction
Hypertension is one of the common medical problem that complicates 12-22% of pregnancies [1]. Of all the hypertensive disorders of pregnancy, pre-eclampsia remains the leading cause of maternal and perinatal morbidity and mortality that complicates 2-8% of all pregnancies [2].
The basic underlying pathology remains endothelial dysfunction and vasospasm resulting from increased circulating pressor substances, increased sensitivity of the vascular system to normally circulating pressor substances [3]. It is a multisystem disorder leading to widespread endothelial disease affecting almost all the vessels.
Though it is a disease of unknown etiology yet it can be predicted and its progression and multisystem dysfunction can be diagnosed early to decrease maternal morbidity. Renal system is primarily affected by the disease. Though there are various available tests to predict the disease progression but each test has its own limitations.
Kidneys are the most commonly affected organ and 'glomerular endothelosis' is the characteristic lesion seen in patients of preeclampsia [4]. The chain of events follows: Spasm of the afferent glomerular arterioles → anoxic change to the endothelium of the glomerular tuft → glomerular endotheliosis → increased capillary permeability → increased leakage of proteins.

In a non-pregnant women without kidney disease, urinary protein excretion is less than 150 mg daily but in pregnancy urinary protein excretion increases substantially due to increased glomerular permeability and when exceeds 300 mg/24 hours is considered abnormal [5].

24-hour urinary protein remains 'Gold Standard' test for proteinuria and patients with hypertension have only < 300 mg, those with mild preeclampsia have 300 mg to 5000 mg, and those with severe preeclampsia have > 5000 mg of protein [6] but cumbersome, time consuming, delay in diagnosis and treatment, subject to errors (inaccuracies in 13-68% of collections) [1]. The Protein Creatinine Ratio in a single urine specimen rapid and accurate and avoids collection errors. A protein-creatinine ratio of 0.3 was taken as cut-off for prediction of pre- eclampsia and assessing severity among patients with pregnancy induced hypertension. Also, Protein-Creatinine ratio can be used as a single parameter for early detection of maternal organ dysfunction and perinatal outcome and thereby helping in management and improve prognosis. In the present study, investigated the correlation between spot urinary protein-creatinine ratio and its effects on various maternal and fetal parameters in patients with hypertensive disorders of pregnancy in order to find out its usefulness in predicting the severity of preeclampsia.

Aim

To evaluate the correlation of spot urinary protein – creatinine ratio in single voided urine sample in antenatal patients with hypertensive disorders for assessing the severity of preeclampsia, maternal organ dysfunction and its implication in perinatal outcomes.

Material and Methods

This was a prospective case study conducted in the Department of Obstetrics and Gynaecology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly on 150 women diagnosed with hypertension department and those admitted in the ward and labor room from November 2018-May 2020.

Inclusion criteria

Previously normotensive and normo-proteinuric women with gestational age > 20 weeks calculated from the first day of last menstrual period with singleton pregnancy and Systolic blood pressure of ≥ 140 mm Hg and/ or diastolic blood pressure of ≥ 90 mm Hg on two occasions at least 4 hours apart.

Exclusion criteria

1. History of chronic hypertension and proteinuria before conception or development of hypertension before 20 weeks of gestation.
2. Patients with chronic renal disease.
3. Patients with history of recurrent urinary tract infection.
4. Molar pregnancy.
5. Multiple pregnancies.
6. Patients with associated liver dysfunction.
7. Patients who require delivery before completion of collection of 24-hour urine sample.

Cases were recruited according to inclusion criteria and grouped into mild (72) and severe pre- eclampsia (78) depending upon blood pressure and clinical parameters. Midstream urine sample estimation for protein-creatinine ratio was done along with the biochemical parameters for renal and liver function tests.

Urine protein estimation was done by Pyrogollol red method and creatinine estimation was done by Jafee's method.

A protein-creatinine ratio of 0.3 was considered as a significant observation in patients of mild and severe preeclampsia to predict the severity of pre-eclampsia based upon blood pressure and clinical parameters.

The correlation of abnormal fundoscopy, liver and renal function tests and perinatal outcomes parameter in terms of IUFD, prematurity, low birth weight, APGAR < 7 at 5 minutes, NICU admission with spot protein-creatinine ratio was done and the results were analysed on software IBM SPSS version 20.0.

Observations

Table 1: Demographic and clinical parameters of study population

Parameters	Mild PE (n = 72)	Severe PE (n = 78)
Age (years)	24.71 ± 4.76	24.97 ± 4.36
Body Mass Index (kg/m2)	25.73 ± 3.81	26.06 ± 3.57
Parity	Primi (55.56%)	Primi (58.97%)
Socioeconomic status	Low (44.44%)	Low (56.41%)
Mean Systolic BP (mm Hg)	143.94 ± 14.1	167.26 ± 17.6
Mean Diastolic BP (mm Hg)	93.67 ± 10.2	105.74 ± 99.9
Mean Spot Urinary Proteins (mg/dl)	47.3 ± 33.6	128.6 ± 105.5
Mean Spot Urinary Creatinine (mg/dl)	111.2 ± 73.1	60.2 ± 35.6

53.3% cases were between 20-25 years of age and the mean age among 72 cases of mild preeclampsia was 24.71 ± 4.76 years while among severe preeclampsia was 24.97 ± 4.36 years. Majority of cases i.e. 55.56% among mild preeclampsia and 58.97% among severe preeclampsia were primigravidae with mean BMI of 25.73 ± 3.81 kg/m2 and 26.06 ± 3.57 kg/m2 but belonging to lower socio-economic status.

The mean systolic BP among mild preeclampsia was 143.94 ± 14.1 mm Hg, whereas in severe preeclampsia was 167.26 ± 17.6 mm Hg and the mean diastolic BP among mild pre-eclampsia and severe preeclampsia was 93.67 ± 10.2 mm Hg and 105.74 ± 99.9 mm Hg respectively. The mean value of spot urinary proteins in cases of mild and severe preeclampsia is 47.3 ± 33.6 mg/dl and 128.6 ± 105.5 mg/dl respectively while for spot urinary creatinine is 111.2 ± 73.1 mg/dl and 60.2 ± 35.6 mg/dl respectively.

Table 2: Comparison of spot urinary protein – creatinine with severity of pre-eclampsia

PCR		Mild PE (n = 72)	Severe PE (n = 78)	P Value
< 0.3 (n = 43)	No. of pt (n = 43)	37 (51.38%)	6 (7.69%)	< 0.001
	Mean ± SD	0.19 ± 0.06	0.25 ± 0.07	
	Total mean ± SD	0.22 ± 0.007		
≥ 0.3 (n = 107)	No of pt (n = 107)	35 (48.61%)	72 (92.30%)	
	Mean ± SD	1.00 ± 0.79	1.5 ± 2.2	
	Total mean ± SD	1.95 ± 1.87		

Out of 150 patients of Pregnancy Induced Hypertension, 43 (28.67%) patients had protein creatinine ratio < 0.3 and rest 107 (71.33%) patients had protein creatinine ratio ≥ 0.3. 51.38% in mild pre-eclampsia and 7.69% among severe pre-eclampsia had protein creatinine ratio < 0.3, the mean value being 0.19 ± 0.06 and 0.25 ± 0.07 respectively whereas 48.61% in mild preeclampsia and 92.30% of severe preeclamptic patients had protein-creatinine ratio ≥ 0.3, with the mean value being 1.00 ± 0.79 and 2.5 ± 2.2 respectively.

Organ affection was seen more in cases of severe preeclampsia as compared to mild preeclampsia. Abnormal fundoscopy was seen in 29.45% cases of severe pre-eclampsia whereas only 5.56% of mild preeclampsia had abnormal fundal changes (p value 0.000138). Similarly, liver function tests and renal function tests were deranged in 92.30% and 97.43% respectively in severe preeclampsia (p value 0.0000 and 0.000018 respectively). Mild preeclampsia group had increase percentages of renal function derangements i.e. 70.83% compared to derangement of liver function tests i.e. 33.33%.

Out of 27 cases with abnormal fundoscopic findings, only 4 cases (14.81%) had protein-creatinine ratio < 0.3 whereas 23 (85.18%) cases had protein-creatinine ratio ≥ 0.3. Among 127 cases of abnormal renal function, 96 cases (75.60%) had protein-creatinine ratio ≥ 0.3. Similarly, out of 96 cases of with deranged liver function test, 78 cases (81.25%) had protein–creatinine ratio ≥ 0.3.

A significant p value of 0.0078, 0.0067 and 0.0003 was observed among patients with abnormal fundoscopy, deranged renal function test and deranged liver function test with protein creatinine ratio ≥ 0.3 respectively.

Table 3: Comparison of spot urinary protein – creatinine with organ dysfunction

PCR	Abnormal Fundoscopy		Deranged RFT		Deranged LFT		P Value
	Mild PE (n = 4)	Severe PE (n = 23)	Mild PE (n = 51)	Severe PE (n = 76)	Mild PE (n = 24)	Severe PE (n = 72)	
< 0.3 (n = 43)	3 (75%)	1 (4.34%)	21 (41.18%)	10 (13.16%)	12 (50%)	6 (8.33%)	0.949
	4 (14.81%)		31 (24.40%)		18 (18.75%)		
≥ 0.3 (n = 107)	1 (25%)	22 (95.65%)	30 (58.82%)	66 (86.84%)	12 (50%)	66 (91.67%)	0.004
	23 (85.18%)		96 (75.60%)		78 (81.25%)		

Abnormal fundoscopy was associated with 95.65% cases of severe preeclampsia against 25% cases of mild preeclampsia with PCR ≥ 0.3. When abnormal renal function tests was studied, it was computed that PCR ≥ 0.3 was associated with 58.82% cases of mild preeclampsia and 86.84% cases of severe preeclampsia and abnormal liver function tests was associated with 50% and 91.67% cases of mild and severe preeclampsia respectively. The p value were statistically significant in cases with protein-creatinine ratio ≥ 0.3.

Out of total 150 cases, 143 women delivered, and 7 patients among mild pre-eclampsia were discharged antenatally. All cases of severe preeclampsia were delivered. Among the total deliveries, 65 cases belonged to mild preeclampsia and 78 cases belonged to severe preeclamptic women.

125 were live birth out of total 143 deliveries, 58 of which belonged to mild preeclampsia while 67 were cases of severe preeclampsia and NICU care was required in 3% and 7% cases of mild and severe preeclampsia respectively. Stillbirth occurred in 5% and 8% cases of mild and severe preeclampsia respectively.

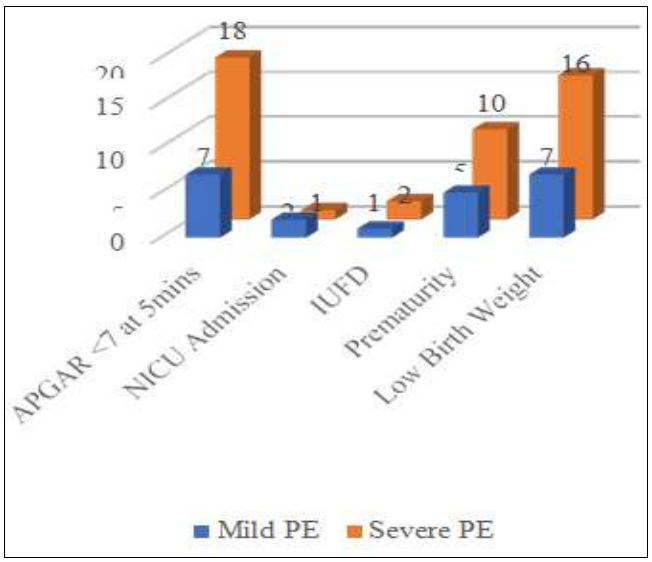

Fig 1: Protein-creatinine ratio < 0.3

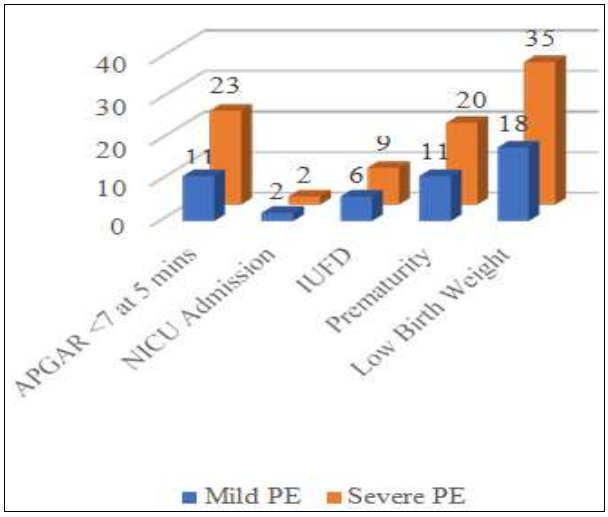

Fig 2: Protein-creatinine ratio ≥ 0.3

Fig 1 and 2: Comparison of spot urinary protein – creatinine with perinatal outcomes

57 and 28 cases among severe and mild pre-eclamptic mothers respectively, out of 125 live births had PCR ≥ 0.3 among which 2.56% and 3.08% among severe and mild preeclampsia required NICU admission. Stillbirth occurred in 2.56% and 11.54% cases with PCR < 0.3 and ≥ 0.3 respectively among severely pre-eclamptic women.

Out of 143 deliveries, 44.87% cases among severe preeclampsia and 27.69% cases of mild preeclampsia with protein creatinine ratio ≥ 0.3 had birth weight < 2.5 kg, 25.64% babies among severe preeclamptic group and 16.92% of mild pre-eclampsia were premature. APGAR < 7 at 5 minutes was observed among 29.48% cases of severe preeclampsia and 16.92% cases of mild preeclampsia with protein-creatinine ratio ≥ 0.3. However, the correlation of spot protein-creatinine ratio < 0.3 and PCR ≥ 0.3 with poor perinatal outcome was not statistically significant (p value 0.757 and 0.089 respectively).

Discussion

It was observed that with increasing severity of pre-eclampsia, frequency of organ involvement increases.7 The derangement of organ dysfunction is more closely related with protein-creatinine ratio > 0.3.8 A couple of studies have also been done to find out association between the amount of proteinuria and maternal-fetal outcome in patients with preeclampsia but the results have been variable.

Gangaram *et al*. (2009) [7], studied 155 women and found that spot urinary protein-creatinine cutoff value of ≥ 300 mg/g was associated with 55% and 57% sensitivity and specificity respectively to detect maternal morbidity and 71% and 51% sensitivity and specificity respectively to detect stillbirth.

Our study found that abnormal fundoscopy was seen in 29.45% cases of severe pre-eclampsia whereas only 5.56% of mild preeclampsia had abnormal fundal changes. Similarly, liver function tests and renal function tests were deranged in 92.30% and 97.43% respectively in severe preeclampsia. Mild preeclampsia group had increase percentages of renal function derangements i.e. 70.83% compared to derangement of liver function tests i.e. 33.33%. Archana Kumari *et al*. (2014) [9], investigated association between maternal and fetal complications and the amount of proteinuria measured by spot urine protein creatinine ratio among 200 patients with preeclampsia and found that 44% developed severe hypertension, 21% developed raised liver enzymes, and 14% developed renal insufficiency, 26 (13%) were still birth and 74% of newborns were born with low birth weight; 58% of newborns had to shift to neonatal HDU after birth and the perinatal mortality in our study was 23%. It was hence concluded that the frequency of various maternal and fetal complications was between 14–53% and 22–92%, respectively and a statistically significant association was found between the frequencies of various complications in mother and newborn and spot Urinary Protein Creatinine Ratio.

On evaluating the organ dysfunction in relation to protein-creatinine ratio in our study, it was observed that 85.18% cases with abnormal fundoscopy has protein-creatinine ratio ≥ 0.3, similarly 75.60% cases of abnormal renal function tests and 81.25% cases of abnormal liver function tests had protein-creatinine ratio ≥ 0.3 and this was statistically significant. Coelho *et al.* (2004) [10], in his study with retrospective data of 334 pregnancies to determine the role of proteinuria on pregnancy outcome in hypertensive syndrome with singleon pregnancies concluded that the presence of proteinuria predicted adverse maternal outcome like renal insufficiency with 0.7% (1/131) with increase proportional to elevation in amount of proteinuria.

Coelho *et al.* (2004) [10], studied the perinatal effects and found that the worst perinatal outcome was observed among proteinuric group against non proteinuric group in terms of increase prematurely (62.2% vs 11.5%), newborn with weight < 2500g (6.5% vs 1.5%), newborn with Apgar < 7 in the 5th minute (30.4% vs 3.5%), stillborn (14.4% vs 1.4%), neonatal deaths (6.1% vs 0.98%). The Perinatal Mortality was greater with proteinúria (175 vs 19, 7) and, when = 2.0g (297.8 vs 19.6).10 In our study, a significant association was seen in terms of livebirths when a cutoff of 0.3 for spot urinary protein-creatinine ratio was taken, however, there was no significant relationship when the perinatal outcome was studied in terms of NICU Admission, low birth weight babies, prematurity, APGAR < 7 at 5 minutes, and intrauterine fetal demise. Xu X *et al* (2020) [11], evaluated 407 patients with preeclampsia and studied the association between proteinuria and maternal and neonatal outcomes in pregnant women with pre-eclampsia and found that the newborn 5-min Apgar scores were statistically lower in the proteinuria group versus the group without proteinuria (9.77 versus 9.95). Compared with patients without proteinuria, patients with proteinuria had a significantly higher rate of births before 37 weeks of gestation (50.80% versus 31.60%) [11].

In our study, 5 minutes APGAR score of < 7 was observed in

29.48% and 23.08% cases of severe preeclampsia with protein-creatine ratio ≥ 0.3 and < 0.3 respectively against 16.92% and 10.77% cases of mild preeclampsia with protein-creatine ratio ≥ 0.3 and < 0.3 respectively and prematurity was seen in 25.64% and 12.82% cases of severe preeclampsia with protein- creatine ratio ≥ 0.3 and < 0.3 respectively against 16.92% and 7.69% cases of mild preeclampsia with protein-creatine ratio ≥ 0.3 and < 0.3 respectively

Conclusion

24-hour urine collection has been considered as the standard method for quantitation of proteinuria in the management of women with pre-eclampsia. However, this method is inconvenient to patient and leads to incomplete collection causing delay in diagnosis. Our contention was, that the value of the protein/creatinine ratio in a single urine sample which may avoid collection error and give physiologically relevant information. Protein/creatinine ratio has been found to be useful in out-patient setting to monitor organ function. Protein/creatinine ratio in spot urinary sample provides valuable information for clinical purpose and with a cutoff point of 0.3 is found to be satisfactory used in predicting disease severity in form of organ involvement, like deranged liver and renal function tests and abnormal fundoscopy indicating retinal changes and hence can be used as a biochemical parameter for diagnosis of severe preeclampsia. It has also been found to be useful, though not statistically significant, in predicting the perinatal outcomes in terms of NICU Admission, low birth weight babies, prematurity, APGAR < 7 at 5 minutes, and intrauterine fetal demise. However, our being a very small study, a large randomized control trial are needed before establishing its diagnostic accuracy as a predictor of pre-eclampsia.

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