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Study on diagnostic value of spot protein creatinine ratio with 24 hours urine protein ratio in antenatal women with pre-eclampsia

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Abstract
Proteinuria is a major component of preeclampsia. Urine protein measurement after 24-hour urine collection is the traditional standard method for the detection of proteinuria. It is time-consuming. As an alternative, random spot sampling for a urine protein to creatinine (P/C) ratio has been investigated.
The aim of the study was to determine the diagnostic accuracy of the protein to creatinine ratio (P/C) compared with 24-hour urine collection for the detection of remarkable proteinuria and to evaluate the P/C ratio for different proteinuria ranges in patients with preeclampsia.

Keywords: Preeclampsia, proteinuria, urine protein-creatinine ratio

Introduction
According to the World Health Organisation, hypertensive disease during pregnancy is a major cause of material and perinatal mortality and morbidity. Preeclampsia occurring in 3% to 8% of pregnancy is major cause of material mortality, and it accounts for about 15% to 20% of iatrogenic preterm birth, Intrauterine growth retardation and perinatal morality. In pregnancy, preeclampsia is characterised by varying degrees of dysfunction of placenta and maternal response that shows features of systemic inflammation. Most consider hypertension and proteinuria to be the important hallmark of preeclampsia. As the severity of the proteinuria increases, there is also an equal increasing risk of maternal and foetal outcome. The principle objective in managing the preeclampsia is to predict proteinuria. Many of the Obstetrician depend up on the 24-hour time urine collection method for estimating the proteinuria. Since collection of 24-hour urine proteinuria is a time-consuming procedure and it is a cumbersome procedure for both the patient and also for the person handing the collection of urine. It is subjected to error because of inappropriate timing and incompleteness in its collection method. The other test that estimates the quantitative evaluation of proteinuria accurately, is the measurement of protein creatinine ratio in the spot a substitute of 24-hour urine protein excretion in quantifying proteinuria as shown by many investigators. But there are conflicting results and there is variation in the cut off values between these studies.
This present study was done know the efficacy of the spot urine protein creatinine ratio in assessing the severity of preeclampsia. Spot urine protein creatinine ration method is a very easy procedure in assessing the proteinuria. It is a simple procedure. It is as effective as 24-hour urine protein ratio.

Pre-eclampsia
Preeclampsia is a characteristic disease of pregnancy that is featured by a specific syndrome, characterised by variable degrees of dysfunction of placenta, and is associated with a maternal response, that has the features of systemic inflammation. Hypertension and proteinuria, are considered the hallmark of preeclampsia.
Proteinuria greater than 300mg/day in 24-hour urine collection or 1+ by qualitative method associated with hypertension that is blood pressure of systole, of more than or equal to 140-190 mmHg and blood pressure of diastole, of more than or equal to 90mmhg, developing after 20 weeks of gestation.

Pathogenesis

The pathogenesis of preeclampsia can be attributed to the below mentioned causes like.

1. Inflammatory responses
2. Activation of the Endothelial cells
3. Abnormal Invasion of cytotrophoblast of spiral arteries.
4. Placental pathology in preeclampsia.
5. Pro angiogenic and Anti angiogenic protein in preeclampsia antenatal women.

Classification of preeclampsia

Mild preeclampsia

Blood pressure of systole, of more than or equal to 140mmhg and, blood pressure of diastole of more than or equal to 90mmhg and associated with proteinuria of more than 300mg in 24-hour protein or 1+ urine proteinuria reading in a qualitative method.

Severe preeclampsia

Systolic blood pressure of more than 160mmhg and a diastolic blood pressure of more than or equal to 110 mmhg with proteinuria of more than 5gm in a 24-hour urine collection method or more than 3+ in a qualitative method.

Proteinuria

Proteinuria in one of the diagnostic criteria of preeclampsia. It has been suggested that proteinuria is a caused by two mechanisms.

1. The first cause is thought to be due to the abnormal trans glomerular passage of proteins because of increased permeability of the glomerular capillary wall and also due to the impaired reabsorption by the epithelial cells of the proximal tubules in kidney.
2. The kidney in Pregnancy: There are both anatomical and physiological changes in the urinary tract during pregnancy. The kidney during pregnancy enlarges, the pelvi-calyceal system, ureter dilates due to both humoral and also due to the obstructive causes. The estimated glomerular filtration rate and the estimated renal plasma flow is found to increase by 50%. Creatinine clearance is found to increase by 4th week and peaks at 9 to 11 weeks of gestation and then is sustained until the 36 weeks of gestation. In last four weeks of pregnancy, creatinine clearance is a reduced by 15 – 20%.

Significant proteinuria as defined by ISSHP is proteinuria of >300mg/dl in a 24-hour urine collection method or spot urine protein creatinine ratio as more than 0.3.

Recommended method of testing urine for protein

Dipstick method

All antenatal women are routinely screened for proteinuria during their first and regular antenatal visit by dipstick method or sulpho-salicylic method. If the test is found to be positive then further laboratory investigation is necessary.

The most commonly used test for quantifying urine proteinuria is the urine dipstick testing. The dipstick usually carried a reagent strip that is impregnated with a Ph indicator. Usually the chemical dye, the tetra bromophenol and a buffer to maintain a Ph of 3.0. Proteins, usually, the albumin binds to the Ph indicator dye that will produce a change of the colour. This change is independent of urine Ph.

Urine Protein

Trace	-	0.1 gm/I
1+	-	0.2 gm/I
2+	-	1 gm/I
3+	-	3 gm/I
4+	-	10 gm/I

Quantitative assessment of proteinuria

Dipstick to 24 hour urine proteinuria

The main factors for the usage of the dipstick test is that the test can be done easily and the low cost of the test. Proteinuria of 1+ by dipstick analysis method is believed widely to correspond to 300mg/24-hour urine protein collection method by. Dipstick testing is associated with false positive results which is mainly due to concentrated urine i.e., specific gravity of more than 1.030, alkaline urine contaminated with vaginal discharge. Brown *et al* in his study has reported 8 – 18% of false positive and a 67% of false positive cases with 1+.

Spot urine protein creatinine ratio with 24 hour urine collection method

In a study done and analysed by Shabazian *et al*, the cut off ratio of spot protein creatinine to 24-hour ratio is 0.3 for 300mg/24 hour with a positive predictive value of 94.45, negative predictive value of 96.8% sensitivity of 91.2% specificity of 87.8%. The value of less than 0.29 yield a sensitivity of exclusion of preeclampsia by 100%.

Eigbeoh and *et al* conducted another study and observed that cut off for positive spot protein creatinine ratio have been standardised by the International Society for the Study of Hypertension (ISSHP) as 0.3 in 2001 and a systematic review and a meta-analysis of articles from 1997 through 2008 confirmed this cut off for adequate sensitivity and specifying and described the use of the spot PCR as promising.

They concluded that the spot urine creatinine ratio is a reliable indicator of significant proteinuria >300mg/24 hour. The spot PCR may be used as an alternatively to the 24-hour urine collection method. Detecting significant proteinuria by using spot PCR as a substitute to 24-hour excretion remains unclear. Many investigators have proposed the use of spot urine protein creatinine ratio, but still there are conflicting results.

Aim of the study

The correlation between the 24-hour urinary collection to

1. To compare and correlate between the spot urine protein creatinine ratio in a single voided urine sample with the 24-hour urine protein ratio for estimation of proteinuria in patients with preeclampsia.
2. To know if the spot protein creatinine ratio can be used to quantify the proteinuria accurately and rapidly and at the time can overcome limitation of the routinely performed test.

Objectives of the study

To compare spot urine protein creatinine ratio in a single voided sample with 24-hour urine protein ratio for estimation of proteinuria in preeclampsia.

Materials and Methods

1. Study period: 1 Year
2. Sample size: 150 Cases
3. 3. Study design: Prospective study
4. Source of Data: This study was done at the department of Obstetrics and Gynaecology at the Institute of Social Obstetrics, Government Kasturba Gandhi Hospital attached to the Madras Medical College after getting Ethical clearance from the Hospital Ethical Clearance.

5. This study was done in 150 antenatal patients who has been admitted for evaluation of preeclampsia prospectively after explaining the nature of study and getting informed written consent.

Selection criteria

Antenatal women with preeclampsia of blood pressure of equal or more than 140/90 mmhg recorded on two occasions at least 6 hours apart, after 20 weeks of gestational age with previously normal blood pressure with proteinuria defined as urinary excretion of > 300mg/day protein or higher in a 24-hour urine specimen.

Patients were categorised as severe preeclampsia as mentioned earlier in the classification of the preeclampsia.

Inclusion criteria

- Patients with BP ≥ 140/90mmhg
- Patients with > 1+ proteinuria
- Singleton pregnancy.
- Gestational age > 20 weeks.
- No. H/O renal disease.
- No. H/O hypertension.

Exclusion criteria

- Case with gestational age < 20 weeks.
- Known hypertensives.
- Known renal diseases.
- Known epileptics.
- Multiple pregnancy.
- Gestational diabetes.
- UTI

Procedure

Study was undertaken in one hundred and fifty patients who satisfied the above criteria. After explaining the procedure and purpose of study informed consent was obtained from all the patients. All the antenatal women with the elevated blood pressure and proteinuria were admitted after excluding the above-mentioned excluding criteria and the admission blood pressure was recorded for all the patients in the right upper limb in sitting posture at level of the heart. Diastolic BP was determined as the disappearance of Korotkoff sound V.A detailed obstetric history was elicited. General examination and systemic examination were done for all the patients. Complete obstetric examination was done.

Admission blood pressure was checked again after 6 hours. One hundred and fifty patients with elevated blood pressure and elevated proteinuria were included in this study.

Urine for urine routine analysis and urine culture sensitivity was sent to the lab to rule out infection. A random sample of urine proteinuria was assessed by the dipstick method grading of proteinuria by dipstick is as follow

Trace	-	0.1 gm/I
1+	-	0.2 gm/I
2+	-	1 gm/I
3+	-	3 gm/I
4+	-	10 gm/I

Patients urine which shows proteinuria of 1+ by dipstick were analysed for the spot urine protein creatinine ratio and 24-hour urine protein ratio. A spot mid-stream sample of urine as collected from all the patient before the collection of 24-hour urine protein collection estimation was done. Modified Jaffes method was used to estimate the urine creatinine and calorimetry method was used to estimate the urine protein. The spot urine protein creatinine ratio was obtained by dividing the urine protein concentration in mg/dl by the urine creatinine concentration in mg/dl.24-hour urine samples were collected after collecting the specimen for the spot test and the 24-hour urine estimation was done.

Normal values of proteinuria in preeclampsia

In 24-hour, urine proteinuria

Significant proteinuria > 300mg/day

Proteinuria of severe range > 500mg/day

Spot urine protein creatinine ratio:

Insignificant > 0.3

Significant > 0.3

Complete blood count, which included haemoglobin in mg/dl, platelet count, Renal function test that included blood urea, serum creatinine, and Liver function test which included serum bilirubin, SGOT, SGPT Serum proteins like serum albumin, serum globulin

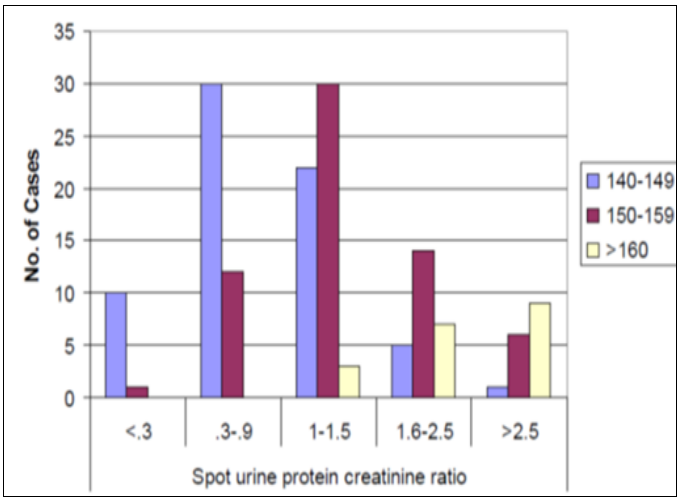
Examination of the fundus of the eye was carried out to all patients.

For cases which had suspicion of IUGR, ultrasonogram and Doppler study was done wherever indicated to confirm the same.

Results and Analysis

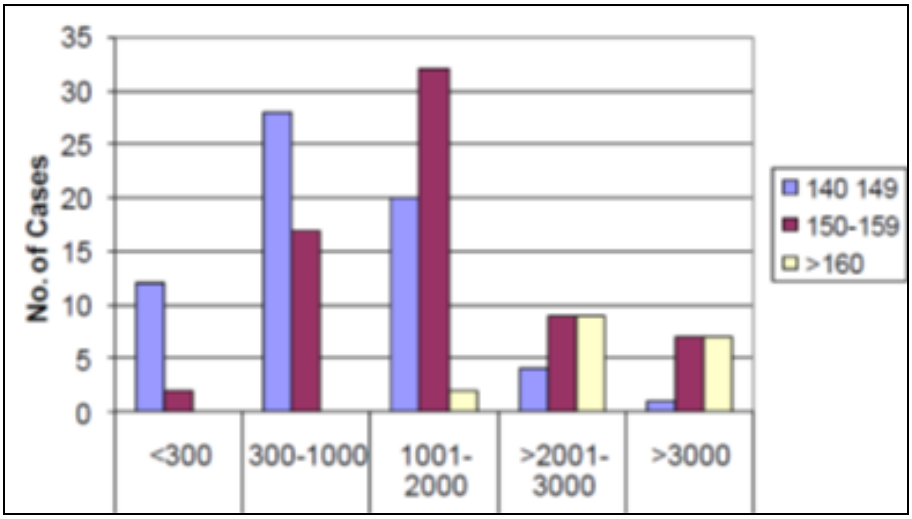
Case distribution in relation to systolic blood pressure and with spot urine PCR

		Spot urine protein creatinine ratio					
S. No.	Systolic BP (MMHG)	<0.3	.3-.09	1-1.5	1.6-2.5	>2.5	Percentage
1	140 -149	10	30	22	5	1	68
2	150 – 159	1	12	30	14	6	63
3	> 60	0	0	3	7	9	19
	Total	11	42	55	26	16	150



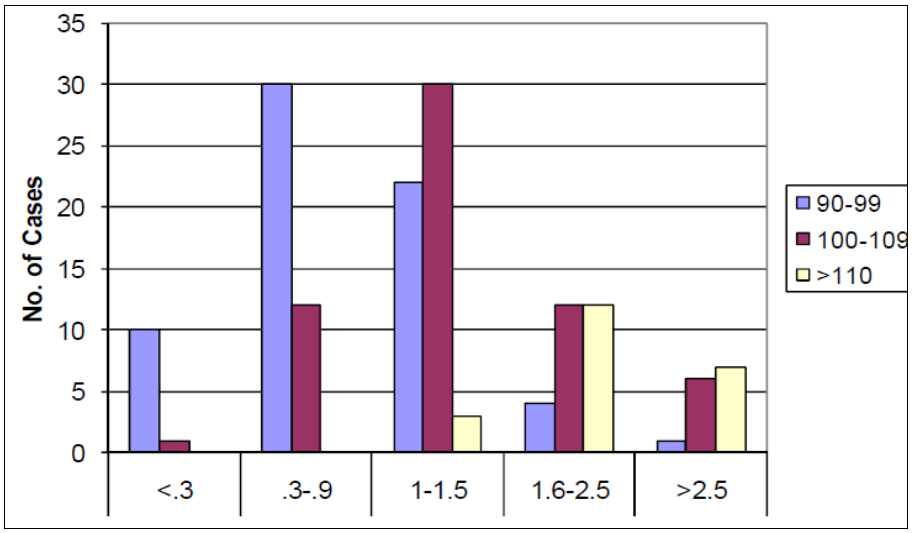
Case distribution of systolic blood pressure in relation with the 24-hour urine protein ratio

24 Hour Urine Proteinuria In mg/day							
S. No.	**Systolic BP in mmHg**	**<300**	**300-1000**	**1001-2000**	**>2001-3000**	**>3000**	**%**
1	140 149	12	28	20	4	1	43.3
2	150159	2	17	32	9	7	44.60
3	> 60	0	0	2	9	7	12
	Total	14	44	56	22	15	100



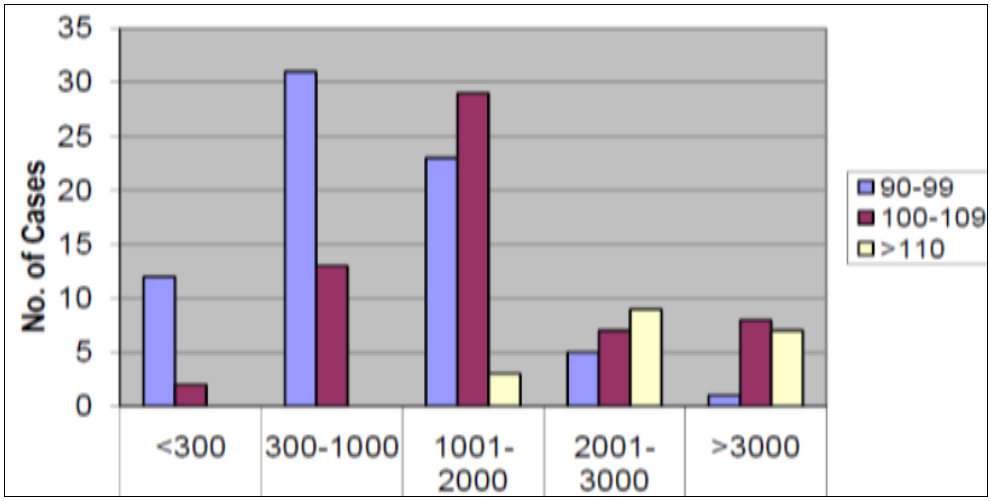
Case distribution in relation to diastolic blood pressure with Spot PCR

Spot PCR in gm/mmol							
S. No.	**Diastolic BP mmhg**	**<.3**	**.3-.9**	**1-1.5**	**1.6-2.5**	**>2.5**	**%**
1	90-99	10	30	22	4	1	44.60
2	100-109	1	12	30	12	6	4.60
3	>110	0	0	3	12	7	14.6
	Total	11	42	55	28	14	100



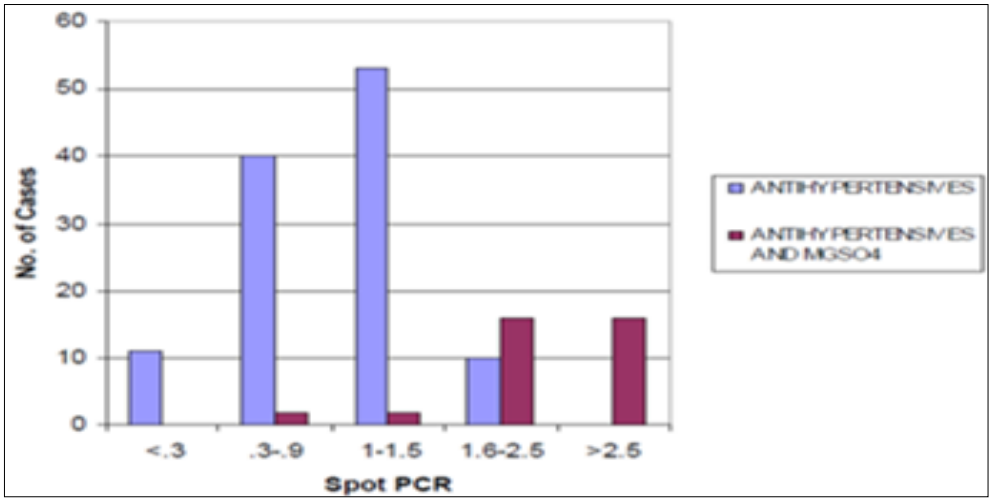
Case distribution in relation to diastolic blood pressure with the 24-Hour urine protein ratio

24-hour urine protein ratio							
S. No.	**Diastolic BP mmhg**	**<300**	**300-1000**	**1001-2000**	**>2001-3000**	**>3000**	**%**
1	90-99	12	31	23	5	1	48
2	100-109	2	13	29	7	8	39.3
3	>110	0	0	3	9	7	12.7
	Total	14	44	55	22	15	100



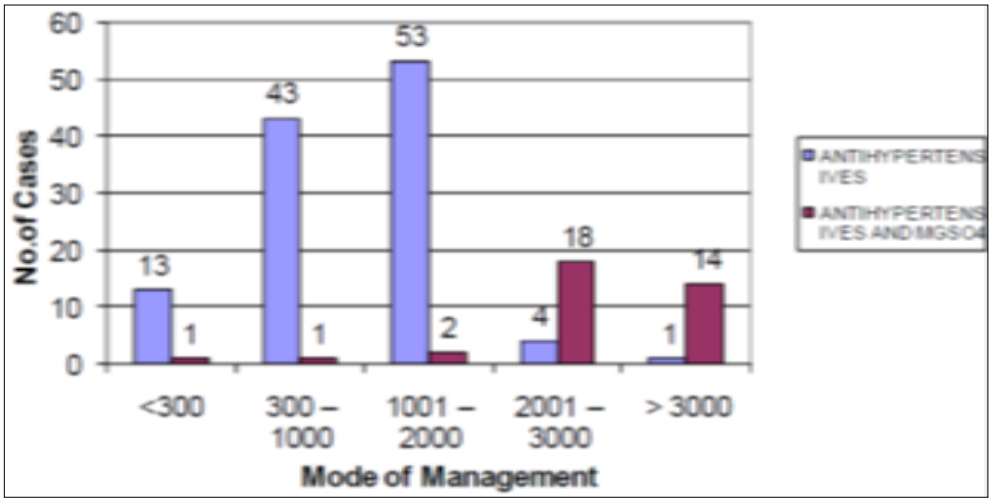
Distribution of management with Spot PCR

SPOT PCR							
S. No.	**Management**	**<.3**	**.3-.9**	**1-1.5**	**1.6-2.5**	**>2.5**	**TOTAL**
1	Anthypertensives	11	40	53	10	0	76
2	Anthypertensives and mgso4	0	2	2	16	16	24
	Total	11	42	55	26	16	100



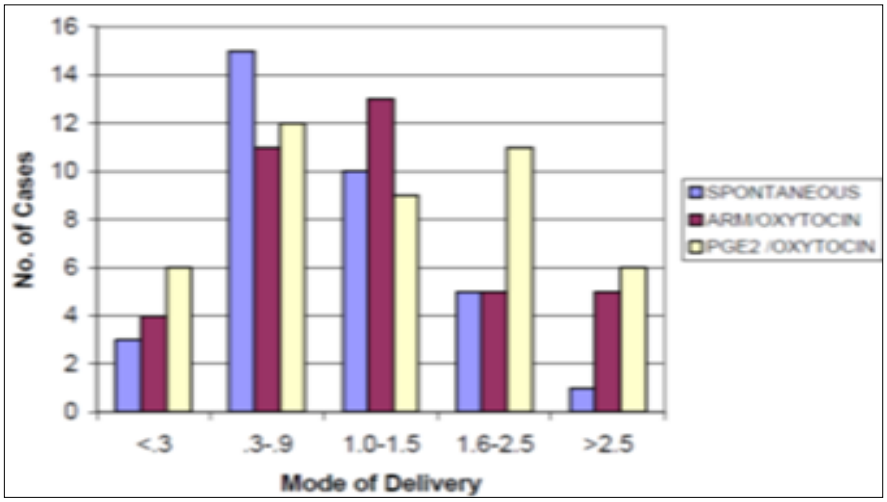
Distribution of management with 24 hour urine proteinuria

24 hour urine protein ratio in mg/day							
S. No.	**Management**	**<300**	**300-1000**	**1001-2000**	**>2001-3000**	**>3000**	**Total**
1	Anti hypertensives	13	43	53	4	1	76
2	Anti hypertensives and mgso4	1	1	2	18	14	24
	Total	14	44	55	22	15	100



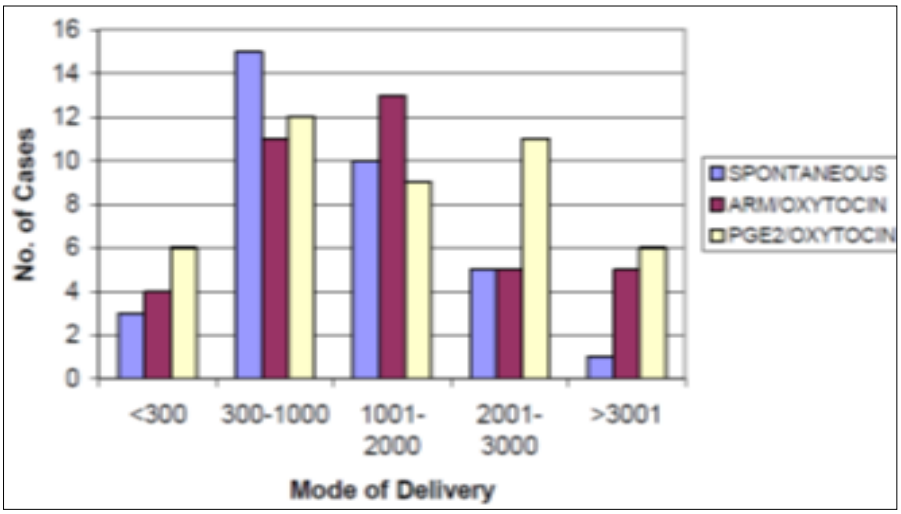
Mode of delivery with spot PCR

Spot PCR							
S. No.	**Mode of delivery**	**<.3**	**.3-.9**	**1-1.5**	**1.6-2.5**	**>2.5**	**Total**
1	Spontaneous	2	11	20	3	1	37
2	Arm/oxytocin	3	16	11	3	3	38
3	Pge2 / oxytocin	6	9	13	8	5	41



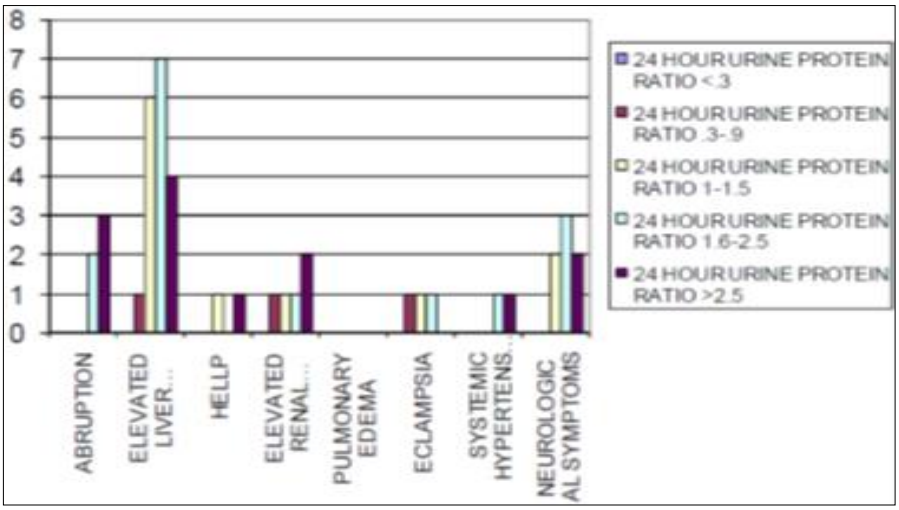
Mode of delivery with 24 hour urine protein ratio

24 Hour Urine Protein Ratio							
S. No.	**Mode of delivery**	**<300**	**300-1000**	**1001-2000**	**>2001-3000**	**>3000**	**Total**
1	Spontaneous	1	15	18	2	1	37
2	Arm/oxytocin	9	12	14	3	4	36
3	Pge2 / oxytocin	4	13	14	7	5	43



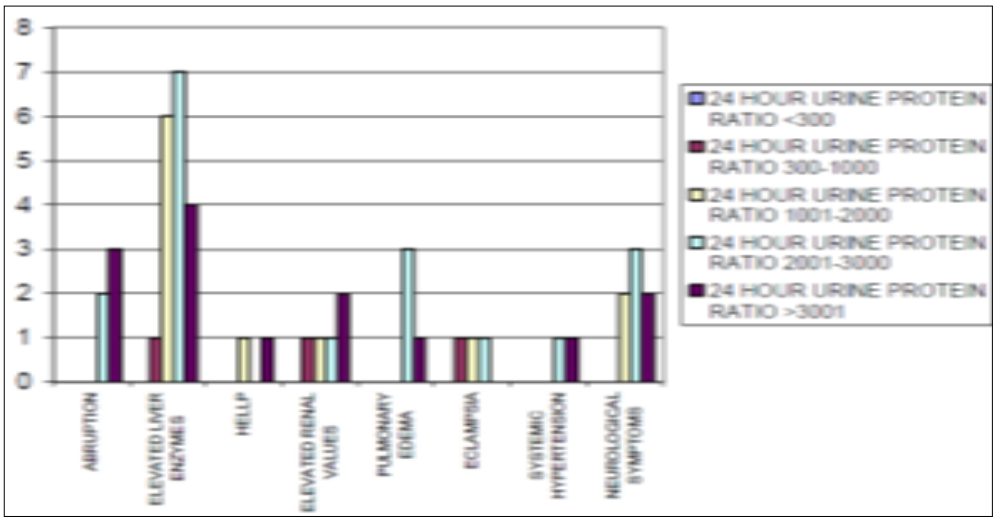
Distribution of maternal outcome with spot PCR

24 Hour Urine Protein Ratio							
S. No.	**Maternal outcome**	**<.3**	**.3-.9**	**1-1.5**	**1.6-2.5**	**>2.5**	**TOTAL**
1	Abruption	0	0	0	2	3	5
2	Elevated liver enzymes	0	1	6	7	4	18
3	Hellp	0	0	1	0	1	2
4	Elevated renal values	0	1	1	1	2	3
5	Pulmonary edema	0	0	0	2	3	5
6	Eclampsia	0	1	1	1	0	3
7	Systemic hypertension	0	0	0	1	1	2
8	Neurological symptoms	0	0	2	3	2	7



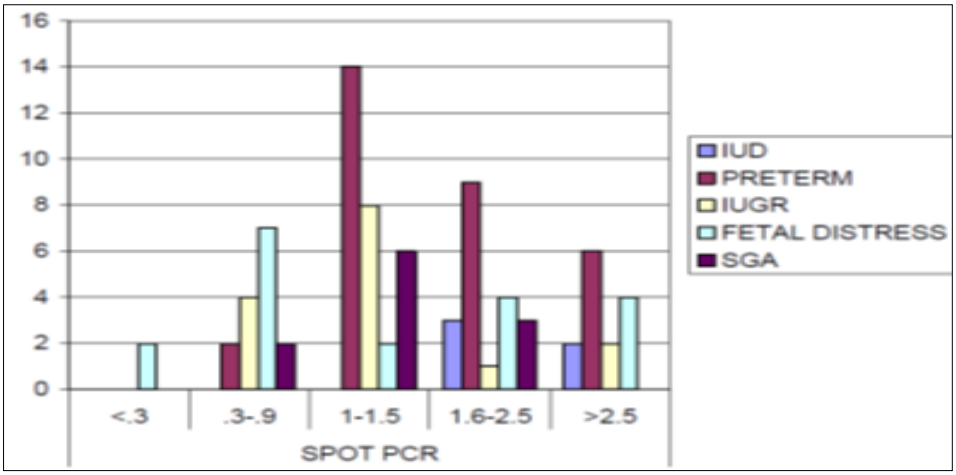
Distribution of maternal outcome with 24 hour urine protein ratio

24 Hour Urine Protein Ratio							
S. No.	**Maternal outcome**	**<300**	**300-1000**	**1001-2000**	**>2001-3000**	**>3000**	**TOTAL**
1	Abruption	0	0	0	2	3	5
2	Elevated liver enzymes	0	1	6	7	4	16
3	Hellp	0	0	1	0	1	2
4	Elevated renal values	0	1	1	1	2	3
5	Pulmonary edema	0	0	0	3	1	4
6	Eclampsia	0	1	1	1	0	3
7	Systemic hypertension	0	0	0	1	1	2
8	Neurological symptoms	0	0	2	3	2	7



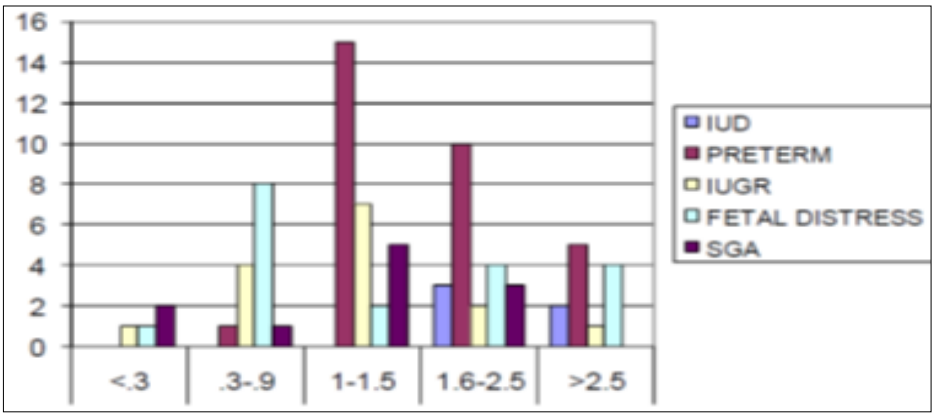
Distribution of fetal outcome with spot PCR

Spot Pcr							
S. No.	**Fetal outcome**	**<.3**	**.3-.9**	**1-1.5**	**1.6-2.5**	**>2.5**	**TOTAL**
1	IUD	0	0	0	3	2	5
2	Preterm	0	2	14	9	6	31
3	IUGR	0	4	8	1	2	15
4	Fetal distress	2	7	2	4	4	9
5	SGA	0	2	6	3	0	11



Distribution of fetal outcome with 24 hour urine protein ratio

24 Hour Urine Protein Ratio							
S. No.	**Fetal outcome**	**<.3**	**.3-.9**	**1-1.5**	**1.6-2.5**	**>2.5**	**TOTAL**
1	Iud	0	0	0	3	2	5
2	Preterm	0	1	15	10	5	31
3	Iugr	1	4	7	2	1	15
4	Fetal distress	1	8	2	4	4	19
5	Sga	2	1	5	3	0	11



Discussion and Summary

This study was carried on a 150 selected admitted antenatal cases with the preeclampsia complicating pregnancy with gestational age >20 wks. Women with urinary tract infection, renal disorder were excluded.

In this study of 150 cases of preeclampsia, 77.3% of cases were grouped under mild preeclampsia and 12.6% of cases were grouped under severe preeclampsia, depending upon the systolic blood pressure.

Based on the diastolic blood pressure there were 78.4% cases of mild preeclampsia and 14.6% of cases were categorised under severe preeclampsia. Both the variables were compared, and the P value for the systolic and diastolic blood pressure for the spot PCR, and 24-hour urine protein ratio was calculated and it was found to <0.001 which was significant.

The varying degree of urine albuminuria by dipstick method, was compared with the spot PCR and 24-hour urine proteinuria and the P value was calculated, which was found to <0.001, which was significant. In this case study of 150 preeclampsia women there were 77.4% of cases with mild proteinuria and 22.6% of cases with severe proteinuria by the dipstick analysis.

In this case study of 150 patients with preeclampsia 114 patients were managed with antihypertensives, which contributed to 76% of the total cases and 24% of cases were managed with antihypertensives and MGSO4 regimen. The P value for the management of cases between the spot PCR and 24-hour urine protein ratio was calculated which was found to be <0.0001, which was significant.

When analysing the maternal outcome of the 150 cases of preeclampsia, there were 8 cases of Abruption, which was managed by stabilisation of the patients urgent investigation, immediate measure to control the hypertension and immediate termination of pregnancy and efficient postpartum management.

In this study there were 18 cases with elevated liver enzymes like raised alkaline phosphatase, there were 5 cases with raised serum uric acid values, and 3 cases with Eclampsia, 7 cases with neurological symptoms like blurring of vision, in the 150 case followed postpartum 2 cases were found to have persistent hypertension which was referred the medicine department and nephrology department and the patients are continuing antihypertensives. This shows that as the spot urine PCR increased the adverse maternal outcome also increased.

The P value for the maternal outcome, between the spot PCR and 24-hour urine protein was calculated and it was found to <0.001 which was significant.

The foetal outcome for 150 cases were analysed. There were 5 cases of IUD, 31 cases of preterm, 9 cases of foetal distress, 11 cases of small for gestational age.

The foetal outcome P value was calculated by comparing the foetal outcome with spot PCR and 24-hour urine protein ratio

which was significant, this P =0.001.
The birth weight of 150 cases were analysed and P value of birth weight variable between spot PCR and 24-hour protein ratio was calculated which was found to be significant that is 0.001.
Coefficient correlation was used to determine the correlation between the urine protein excretion and spot urine protein creatinine ratio.
In this study there was a significant correlation between 24-hour urine protein and spot protein creatinine ratio r=.869, p<0.001.
24-hour urine protein collection was often used during pregnancy to quantify proteinuria. For years this has been the standard for the diagnosis of and treatment of preeclampsia. However, 24-hour urine collection are cumbersome, subjective to collective error, requires patient's compliance and result in a greater than 24-hour delay in diagnosis from the start of collection. We found an excellent correlation between single voided urine protein creatinine ratio and 24-hour urine protein. Reliability on a single voided spot protein creatinine ratio decreases the need for patient's compliance minimizes collection and laboratory errors and saves almost a day in ascertaining the results.
This study has found close correlation r=.869, p<0.001, between spot urine protein creatinine ratio and 24-hour urine protein excretion.

Conclusion

Since the level of urinary protein excretion has considerable clinical implication in the course of pregnancy and on the maternal and perinatal outcome the early detection of even minor degrees of proteinuria is important. Dipstick analysis and sulfo salicylic acid method as a screening for proteinuria lacks reliability with high rate of false positives. For years 24-hour urine proteinuria has been standard for the quantification of proteinuria in the management in women with preeclampsia. However, this method is cumbersome, subjective to collection error, require good patients' compliance and results in delay in more than 24 hours from the start of collection. The present study indicates the value of protein creatinine ratio in the diagnosis than urine 24-hour urine protein ratio. Furthermore, spot urine creatinine ratio method had been found to be far more cost effective and increased the patient's compliance than a 24-hour urine protein excretion ratio. Therefore, the spot protein ratio can be used as an alternative to quantify the urine protein excretion in a 24-hour collection in preeclampsia complicating antenatal women.

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