A PROSPECTIVE OBSERVATIONAL STUDY ON PREDICTION OF PREECLAMPSIA IN EARLY PREGNANCY BY SPOT URINE PROTEIN-CREATININE RATIO

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ABSTRACT

BACKGROUND
Hypertension and proteinuria are minimum criteria to diagnose preeclampsia. Proteinuria is called significant when there is excretion of more than or equal to 300 mg of urinary protein in 24 hrs. period. Even though 24 hrs. urine collection is the Gold standard for the diagnosis of significant proteinuria. Spot urine protein-creatinine ratio is a more rapid and convenient method to detect protein excretion.[1] Therefore, prediction of preeclampsia in early gestation is of utmost importance to detect and to intervene in the management of high-risk pregnancies much earlier to reduce the maternal death and foetal mortality and neonatal morbidity.[2]

MATERIALS AND METHODS
A prospective observational study was conducted during the period of January 2013 to November 2013. Women with 16 to 20 wks of gestation with singleton pregnancy, both Primi and Multigravida were included. A total number of 300 antenatal women who attended the antenatal clinic in the Department of Obstetrics and Gynaecology at Kilpauk Medical College. They were selected according to inclusion and exclusion criteria. Patient's urine sample was collected and protein-creatinine ratio was estimated. Protein estimation was done using pyrogallol method. Creatinine estimation was done by modified Jaffe's method and the ratio was obtained between the two. Patients were advised to attend the antenatal clinic every two weeks. In her follow-up visit she was examined thoroughly, especially her blood pressure and urine albumin was checked. Foetal well-being was assessed at each visit.

RESULTS
When age group was taken into consideration, about 42.9% developed preeclampsia and 5% did not develop preeclampsia in the age group <20 years. In the age group >30 years, 38.1% developed preeclampsia and 7.9% did not develop preeclampsia. There was statistical significance between normal cohort and preeclamptic cohort. In my study, about 81% preeclampsia occurred in primigravida and only 4.8% occurred in gravida 2 and gravida 3. About 9.5% of preeclamptic cohort and 2.2% of normal cohort were present among gravida 4. Among the people belonging to SE class 5, about 76.2% developed preeclampsia and 23.8% belonged to preeclamptic cohort in women belonging to SE class 4. There is no statistical significance with regard to SE class. About 47.6% of preeclamptic cohort were moderately obese patients. In my study group, preeclampsia did not occur in underweight persons. Only 9.5% of preeclampsia occurred in women with normal BMI and 33.3% in overweight individual. The variable BMI is also statistically significant. The cut-off value for urine PCR was taken as >0.45, to predict preeclampsia with 85.71% sensitivity and 99.64% specificity. When the cut-off value is reduced, the sensitivity increases. The area under the ROC curve for urine PCR is 0.964.

CONCLUSION
After analysing the study, it was found that urine spot PCR is a simple method and rapid test to predict preeclampsia. From this study, it was found that when the cut-off value for urine spot PCR was >0.45, the sensitivity was 85.71% and specificity was 99.64%. When the cut-off value is more, the specificity increases. It was also found that more number of preeclampsia occurred in women with increased pre-pregnant weight with increased BMI. Therefore, proper weight reduction will reduce the risk of developing preeclampsia. Urine spot PCR can be used to predict preeclampsia with a single random midstream urine sample when compared to 24 hrs. urine-protein estimation and routine dipstick method. Urine spot PCR can be used to predict preeclampsia in early gestation itself, so that the patient can be kept under proper surveillance with more frequent antenatal check-up and to detect the complications earlier to prevent maternal and foetal morbidity and mortality.

KEY WORDS
Hypertension, Preeclampsia, Spot Test.

BACKGROUND
Hypertensive disorders complicates about 5% - 10% of pregnancies. It is the third most common causes for maternal and foetal morbidity and mortality.[3] It is one among the triads, which causes maternal mortality like that of haemorrhage and infection. Hypertension and proteinuria are minimum criteria to diagnose preeclampsia. Proteinuria is called significant when there is excretion of more than or equal to 300 mg of urinary protein in 24 hrs. period.[3]

Proteinuria is a marker that indicates system wide endothelial leaks. Abnormalities in the angiogenic balance play an important role in the cascade of events leading to protein excretion, hypertension and endothelial dysfunction.[4]

Even though 24 hrs. urine collection is the Gold standard for the diagnosis of significant proteinuria. Spot urine protein-creatinine ratio is a more rapid and convenient method to detect protein excretion.[1] It avoids the influence of variations in urinary solute concentration. Therefore, it is an accurate test and provides efficient in-patient and out-patient monitoring.[5]

Berg and Colleagues (2003) reported that about 16% of maternal deaths are due to complications related to preeclampsia and more than half of it are preventable.[6]

Therefore, prediction of preeclampsia in early gestation is of utmost importance to detect and to intervene in the management of high-risk pregnancies much earlier to reduce the maternal death and foetal mortality and neonatal morbidity.[7]

Prediction of preeclampsia by spot urinary Protein-Creatinine ratio in early pregnancy [Before 20 weeks of pregnancy]. In this study, we find the maternal outcome in developing Preeclampsia and Eclampsia.

MATERIALS AND METHODS
This prospective observational study was done during the period of January 2013 to November 2013. Our study included a total number of 300 antenatal women who attended the antenatal clinic in the Department of Obstetrics and Gynaecology at Kilpauk Medical College. They were selected according to inclusion and exclusion criteria.

Inclusion Criteria
Women with 16 to 20 wks of gestation with singleton pregnancy, both Primi and Multigravida.

Exclusion Criteria
- Patients with chronic hypertension.
- Known case of renal disease.
- Diabetes mellitus complicating pregnancy.
- Heart disease complicating pregnancy.
- Jaundice complicating pregnancy.
- Patients with urinary tract infection.
- Previous history of preeclampsia.

Sample Size for Frequency in a Population
Population size (For Finite Population Correction Factor or FPC) (N): 600 Hypothesized % frequency of outcome factor in the population (p): 25% +/- 5 Confidence limits as % of 100 (absolute +/- %) (d) : 5%
Design Effect (For Cluster Surveys- DEFF): 1 Sample Size:
- N= (Z)2[P] [l-P]/d2
- Proportion of Preeclampsia- 0.25[25%]
- (1.96) 2 [0.25] [0.75]/[0.05]2= 288 [300]
- Total no. of samples= 300

Sampling Method
Purposive sampling.

Informed consent was obtained from each patient after explaining about my study. A detailed history was obtained regarding her name, age, height, pre-pregnancy weight, obstetric score, place of residence, socioeconomic class, past history of preeclampsia, family history suggestive of preeclampsia and associated comorbid conditions.

Her vitals were checked and basic investigations were done.

Patient's urine sample was collected and protein-creatinine ratio was estimated. Protein estimation was done using pyrogallol method, creatinine estimation was done by modified Jaffe's method and the ratio was obtained between the two.

Patients were advised to attend the antenatal clinic every two weeks. In her follow-up visit, she was examined thoroughly, especially her blood pressure and urine albumin was checked. Foetal well-being was assessed on each visit.

Statistical Analysis
For each variable, Mean + SD of all variables of interest were determined for preeclampsia cohort and for normal cohort separately and difference was tested by chi-square test.

The predictive values of urine protein-creatinine ratio was analysed using Pearson's ROC curve. Analysis was done by SPSS version 15. Comparison of variables was done using chi-square test.

RESULTS
The study group was grouped into two depending upon the development of preeclampsia as normal cohort and preeclamptic cohort.

The variables taken into consideration in this study are age group, obstetric score, socioeconomic class, prepregnancy weight, body mass index, urine spot protein-creatinine ratio value.

	Cases					
	Valid		Missing		Total	
	No.	%	No.	%	No.	%
Age group *occurrence of preeclampsia	300	100.0%	0	.0%	300	100.0%
Obstetric score* occurrence of preeclampsia	300	100.0%	0	.0%	300	100.0%
Comorbid conditions *occurrence of preeclampsia	300	100.0%	0	.0%	300	100.0%
Se class *occurrence of preeclampsia	300	100.0%	0	.0%	300	100.0%

Table 1. Risk Factors associated with occurrence of Preeclampsia

Age Group (yrs.)	Preeclamptic Cohort		Normal Cohort	
	No. of Cases	%	No. of Cases	%
<20	9	42.9%	14	5%
21-25	4	19.0%	176	63.1%
26-30	0	0.0%	67	24.0%
31 and above	8	38.1%	22	7.9%

Table 2. Occurrence of Preeclampsia among various Age Groups

- Chi-square= 65.652, p= 0.000.
- Age group distribution showed 42.9% of preeclamptic cohort and 5% of normal cohort belonged to age group less than 20 years.
- In the age group of 31 and above, 38.1% developed preeclampsia-
  - It indicates that preeclampsia is distributed and more common among teenage pregnancy and elderly gravida.
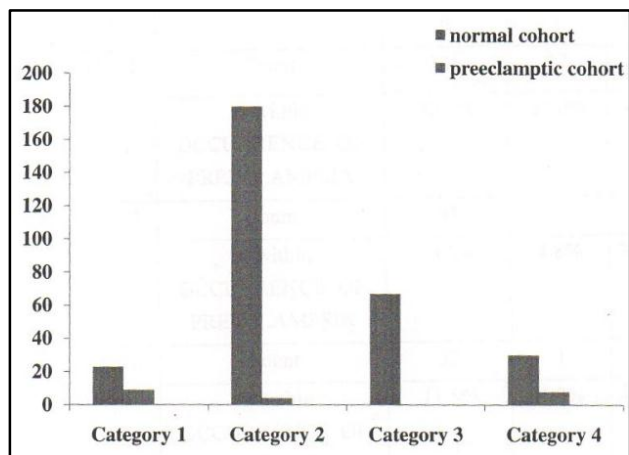

Figure 1. Age Group– Distribution among Study Population

Inference

As 'p' value is 0.000, there is statistically significant difference between preeclamptic cohort and normal cohort with regard to age group.

			Occurrence of Preeclampsia		
			0	1	Total
Obstetric Score	1	Count	146	17	163
		% within occurrence of preeclampsia	52.3%	81.0%	54.3%
	2	Count	3	1	94
		% within occurrence of preeclampsia	33.3%	4.8%	31.3%
	3	Count	32	1	33
		% within occurrence of preeclampsia	11.5%	4.8%	11.0%
	4	Count	6	2	8
		% within occurrence of preeclampsia	2.2%	9.5%	2.7%
	5	Count	2	0	2
		% within occurrence of preeclampsia	.7%	.0%	.7%
Total		Count	279	21	300
		% within occurrence of preeclampsia	100.0%	100.0%	100.0%

Table 3. Obstetric Score- Occurrence of Preeclampsia

Chi-square= 12.964, p= 0.011.

Parity	Preeclamptic Cohort		Normal Cohort	
	No. of Cases	%	No. of Cases	%
Primi	17	81%	146	52.3%
Gravida 2	1	4.8%	93	33.3%
Gravida 3	1	4.8%	32	1 1.5%
Gravida 4	2	9.5%	6	2.2%
Gravida 5	0	0.0%	2	0.7%

Table 4. Percentage distribution of Preeclampsia among Primigravida and Multigravida

This study indicates statistical significance between normal cohort and preeclamptic cohort.

Regarding parity, 81% of preeclampsia occurred in primigravida.

About 9.5% of preeclampsia occurred in fourth gravida, but it affected only 4.8% of gravida 2 and gravida 3.
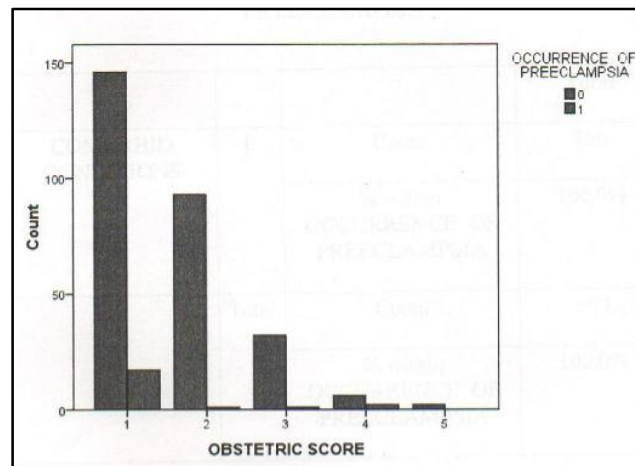

Figure 2. Obstetric Score- Distribution of Preeclampsia among Study Group

- 0= normal cohort, 1= preeclamptic cohort

Inference

Comorbid Conditions	0		Total
		Count	300
		% within occurrence of preeclampsia	100.0%
	Total	Count	300
		% within occurrence of preeclampsia	100.0%

Table 5. Comorbid Conditions– Occurrence of Preeclampsia

Patients in the study group were selected without any comorbid conditions like chronic hypertension, renal disease, heart disease etc.

	Occurrence of Preeclampsia		
	0	1	Total
SE class 2 count	1	0	1
% within occurrence of preeclampsia	.4%	.0%	.3%
SE class 4 count	91	5	96
% within occurrence of preeclampsia	32.6%	23.8%	32.0%
SE class 5 count	187	16	203
% within occurrence of preeclampsia	67.0%	76.2%	67.7%
Count	279	21	300

Table 6. SE Class- Occurrence of Preeclampsia

About 67.7% of the pregnant women belonged to socioeconomic class 5. Out of which, 76.2% developed preeclampsia and 67% belonged to normal cohort

SE Class	Preeclamptic Cohort		Normal Cohort	
	No. of Cases	%	No. of Cases	%
2	0	0.0%	*1*	0.4%
4	5	24.x%	01	32.6%
5	*16*	76.2%	1x7	67.0%

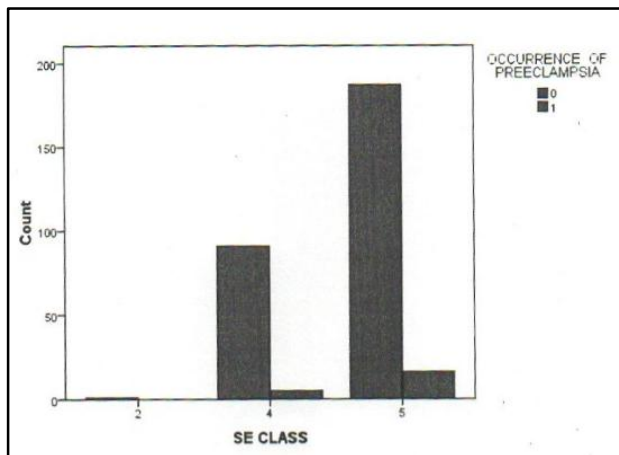*Table 7. SE Class- Occurrence of Preeclampsia*

Figure 3. SE Class- Distribution of Preeclampsia

When SE class was taken into consideration, 67% of normal cohort and 76.2% of preeclamptic cohort occurred in the class 5, whereas 32.6% of normal cohort and 23.8% of preeclamptic cohort belonged to class 4 SE class.

Inference
Since, the p-valve is 0.673, there is no statistical significance between preeclamptic cohort and normal cohort with regard to socioeconomic class.

			Occurrence of Preeclampsia		
			0	1	Total
BMI Group	1	Count	34	0	34
		% within occurrence of preeclampsia	12.2%	.0%	11.3%
	2	Count	128	2	130
		% within occurrence of preeclampsia	45.9%	9.5%	43.3%
	3	Count	96	7	103
		% within occurrence of preeclampsia	34.4%	33.3%	34.3%
	4	Count	16	10	26
		% within occurrence of preeclampsia	5.7%	47.6%	8.7%
	5	Count	5	*2*	*7*
		% within occurrence of preeclampsia	*1.8%*	*9.5%*	*2.3%*
Total		Count	*279*	*21*	*300*
		% within occurrence of preeclampsia	100.0%	100.0%	100.0%

Table 8. BMI Group- Occurrence of Preeclampsia

Chi-square= 53.058, p= 0.0

BMI	Preeclamptic Cohort		Normal Cohort	
	No. of Cases	%	No. of Cases	%
<18.5	0	0.0%	34	12.2%
18.5-24.9	2	9.5%	128	45.9%
25-29.9	7	33.3%	96	34.4%
30-35	10	47.6%	16	5.7%
35-40	2	9.5%	5	1.8%

Table 9. BMI- Occurrence of Preeclampsia

- BMI of the study population was calculated according to her pre-pregnant weight.
- Quetelet index was used to calculate the BMI.
- From the above table it is clear that about 47.6% of preeclampsia occurred in the moderately obese group.
- 33.3% of preeclamptic cohort and 34.4% of normal cohort were present in overweight group.
- In women with normal BMI, preeclampsia occurred in 9.5% and 45.9% comes under normal cohort. My study population also included severely obese women and about 9.5% developed preeclampsia and 1.8% comes under normal cohort.
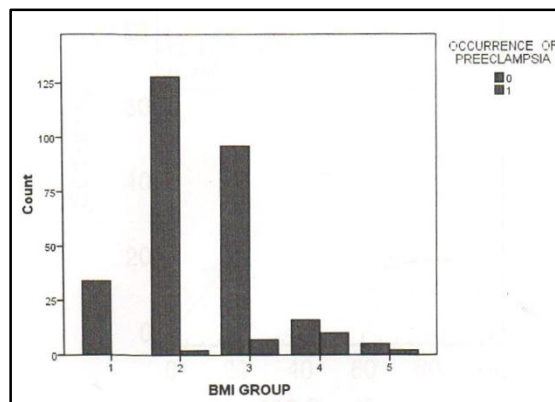

Figure 4. BMI- Distribution of Preeclampsia among Study Group

Inference
As p= 0.000, there is statistical significance between preeclamptic cohort and normal cohort with regard to BMI.
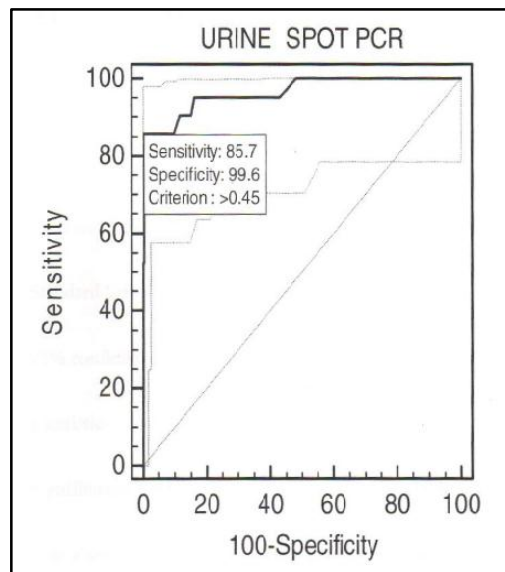

Figure 5. ROC Curve- Urine Spot Protein-Creatinine Ratio Urine Spot PCR

Urine Spot PCR	Total	Preeclamptic Cohort	Normal Cohort
>0.3	21	18	3
0.2-0.29	54	2	52
<0.2	225	1	224

Table 10. Urine Spot PCR- Occurrence of Preeclampsia

Area under the ROC curve (AUC)	0.964543
Standard Error[4]	0.0230
95% confidence interval[7]	0.936806 to 0.982438
Z statistic	20.192
Significance level P (Area= 0.5)	< 0.0001

The above table and ROC infer that there is a Good Fit in the prediction for the cut-off value >0.45 and the Area under the ROC curve (AUC) is 0.964543. Sensitivity is 87.5 and specificity is 99.6. It indicates spot PCR is the good indicator for prediction of preeclampsia.

Area under a Receiver Operating Characteristic Curve (ROC)

Total area under ROC curve is used as a single index for measuring the performance of a test, when the AUC is larger the better is overall performance of the medical test to correctly identify diseased and non-diseased subjects. When the AUCs of two tests are equal it represents similar overall performance of tests, but this does not necessarily mean that both the curves are identical. It indicates that they may cross each other.

- Regarding urine spot PCR values, when the cut-off value is >0.45, the sensitivity is 85.71%, specificity is 99.64%.
- When the cut-off value is >0.5, the sensitivity of urine spot PCR is 76.19% and the specificity is the same (99.64%).
- If the cut-off value is reduced to 0.2, the sensitivity of the test increases to 95.24%.

	Occurrence of Preeclampsia	N	Mean
Age (Yrs.)	1	21	24.71
	0	279	24.77
HT (CM)	1	21	152.48
	0	279	152.18
WT (KG)	1	21	69.14
	0	279	55.55
BMI	1	21	29.8481
	0	279	88.5271
Sample Taken GA (WKS)	1	21	18.00
	0	279	18.01
Urine Spot PCR	1	21	.73
	0	278	.12

Table 11. Mean distribution of Preeclampsia among Various Variables

	Occurrence of Preeclampsia	Std. Deviation	Std. Error Mean
Age (Yrs.)	1	5.596	1.221
	0	3.412	.204
HT (CM)	1	5.810	1.268
	0	6.175	.370
WT (KG)	1	8.873	1.936
	0	11.422	.684
BMI	1	4.11899	.89884
	0	1078.18279	64.54912
Sample Taken GA(WKS)	1	1.549	.338
	0	1.373	.082
Urine Spot PCR	1	.482	.105

Table 12. Occurrence of Preeclampsia- Standard Deviation among Various Factors

From this study, it was found that the following variables are statistically significant
- Age of the patient.
- Obstetric score.
- Socioeconomic class.
- Prepregnancy weight of the patient and BMI.
- Urine spot protein-creatinine ratio.

Variable	Chi-square Value	P
Age Group	65.652	0.000
Parity	12.964	0.011
SE Class	0.791	0.673
BMI	53.058	0.000

Table 13. The Final Outcome of the Study

Urine spot PCR with significant 'P'= < 0.0001.

Summary

From this study, it is found that there is statistical significance between preeclamptic cohort and normal cohort with regard to following variables-
- Age group,
- Obstetric score.
- Socioeconomic class.
- BMI.
- Urine PCR.
    - When age group was taken into consideration, about 42.9% developed.
    - Preeclampsia and 5% did not develop preeclampsia in the age group < 20 years.

J. Evolution Med. Dent. Sci./eISSN- 2278-4802, pISSN- 2278-4748/ Vol. 7/ Issue 22/ May 28, 2018

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- In the age group >30 years, 38.1% developed preeclampsia and 7.9% did not develop preeclampsia. There was statistical significance between normal cohort and preeclamptic cohort.
- In my study, about 81% preeclampsia occurred in primigravida and only 4.8% occurred in gravida 2 and gravida 3.
- About 9.5% of preeclamptic cohort and 2.2% of normal cohort were present among gravida 4.
- Among the people belonging to SE class 5, about 76.2% developed preeclampsia and 23.8% belonged to preeclamptic cohort in women belonging to SE class 4.
- There is no statistical significance with regard to SE class.
- About 47.6% of preeclamptic cohort were moderately obese patients. In my study group, preeclampsia did not occur in underweight persons.
- Only 9.5% of preeclampsia occurred in women with normal BMI and 33.3% in overweight individual. The variable BMI is also statistically significant.
- The cut-off value for urine PCR was taken as >0.45 to predict preeclampsia with 85.71% sensitivity and 99.64% specificity. When the cut-off value is reduced, the sensitivity increases.
- The area under the ROC curve, for urine PCR is 0.964.

DISCUSSION
- Our study population included 300 antenatal women who attended antenatal outpatient department. Among them, urine spot PCR predicted preeclampsia in 21 patients.
- Out of 21 patients 18 women had urine spot PCR, cut-off value >0.45.
- Only 2 patients developed preeclampsia in the cut-off value between 0.2 and 0.29.
- In the cut-off value < 0.2, only one patient developed preeclampsia.
- It was also found that preeclampsia is more common among women with increased pre-pregnant weight and BMI >25.
- Our study also reported that primigravida and age group less than 20 years were more prone to develop preeclampsia.
- Our study is supported by the analysis done by Laleh Eslamian, Fariba Behnam, Zahra Foroohesh Tehrani, Ashraf Jamal and Vajiheh Marsoosil (26 Apr. 2009;). The study showed a cut-off value of 0.22 mg/mg for protein-creatinine ratio and it best predicted significant proteinuria with sensitivity, specificity, positive and negative predictive values of 87%, 92.6%, 90.6% and 89.3% respectively.[8]
- Amita Sharma, Pandey Kiran, Bhagoliwal Ajai (3 August 2013); Spot urine P/C ratio and the 24-hour urine protein was measured.[9]
- They found that there was a strong correlation between the spot P/C ratio and 24-hour urine-protein excretion (Pearson's correlation coefficient r= 0.71; P < 0.0001).
  ▪

- The optimal cut-off point of spot P/C ratio was 0.25, for 300 mg/24 h of protein excretion with sensitivity and specificity of 69% and 75% respectively.[9]

CONCLUSION
After Investigating and Analysing the Study, it was found that-
- Urine spot PCR is a simple method and rapid test to predict preeclampsia. When cut-off value is more, the specificity increases.
- From this study it is concluded that, when the cut-off value for urine spot PCR is >0.45, the sensitivity is 85.71% and specificity is 99.64%.
- Urine spot PCR can be used to predict preeclampsia in early gestation itself, so that the patient can be kept under proper surveillance with more frequent antenatal check-up and to detect the complications earlier to prevent maternal and foetal morbidity and mortality.
- Urine spot PCR can be used at the level of primary health centre, to detect the high-risk pregnancies and refer them to the tertiary care centre at the earliest.
- It was also found that more number of preeclampsia occurred in women with increased pre-pregnancy weight with raised BML overweight and obese women developed preeclampsia more than the normal individual; therefore, proper weight reduction will reduce the risk of developing preeclampsia.
- Urine spot PCR can be used to predict preeclampsia with a single random midstream urine sample when compared to 24 hrs. urine-protein estimation and routine dipstick method.

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