International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 14s, 2025
https://www.theaspd.com/ijes.php

Study Of Calcium To Creatinine Ratio In A Spot Sample Of Urine For Early Prediction Of Pre-Eclampsia

Dr. G. Nithya[1], Dr. Ananya Girish (Corresponding Author)[2], Dr. S. Swathi[3], Dr. Akshay Ganeshkumar[4]

[1]Junior Resident Department of Obstetrics and Gynaecology Government Medical College, Tiruppur.
[2]Junior Resident Department of Obstetrics and Gynecology. Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals, Vinayaka Mission's Research Foundation, VMRF (DU), Salem, Tamil Nadu, India. Email:anigirish24@gmail.com
[3]Assistant professor Department of Obstetrics and Gynaecology Government Medical College, Tiruppur.
[4]Senior Resident Department of Neurosurgery All India Institute of Medical Sciences (AIIMS), New Delhi.

INTRODUCTION

Hypertension is one of the commonest medical complication during pregnancy.[1] Despite so much research, Pre-eclampsia is one of the leading cause of maternal morbidity and mortality in India and worldwide. Incidence is 5-15% in pregnancy. High blood pressure is a sign, not a disease. About 5-15% of the pregnancy are affected by hypertensive disorder and pre-eclampsia, of which pre-eclampsia constitute of about 70% and chronic hypertension of about 30%. Its incidence in primi gravida is about 10-15% and in multi gravida is 5%.[2]

Pre-eclampsia is one of the leading causes of maternal morbidity and mortality. It accounts for more than 40% premature deliveries and 18% maternal mortality.[2] Pre-eclampsia is a multi-system disorder, pathology behind is reduced perfusion to organs due to vasospasm. It is usually associated with proteinuria or oedema or both. Edema in pregnancy is no longer used as diagnostic criteria, because it is common accompaniment of normal pregnant women and the presence of isolated oedema doesn't indicate the risk of developing hypertension. Pre-eclampsia is a progressive and multi organ disorder ,it can progress to eclampsia leading to seizures and HELLP syndrome if left untreated.[1]

Various predictors for pre-eclampsia have been proposed till date, but none of them proved ideal either because of high false positivity or complexity in study interpretation.[3] Therefore, many randomized control trails are to be conducted to prove the test which is both sensitive and specific to predict pre-eclampsia. A Calcium creatinine ratio in a spot sample of urine has been found that decreased excretion of calcium may be considered as a useful tool for early diagnosis of pre-eclampsia.[4] Therefore, the study was done to determine the relationship between the hypocalciuria, calcium to creatinine ration and pre-eclampsia for an early predictor of pre-eclampsia in a random urine sample.

MATERIALS AND METHODS

This study was conducted in the Department of obstetrics and gynaecology, Coimbatore medical college hospital, Coimbatore.

Study Design:

Prospective study

Study Population:

Women of gestational age <20 weeks attending Antenatal clinic in the obstetrics and gynaecology in Coimbatore medical college hospital.

Study period:

January 2018 to January 2019.

Sample size:

200

Inclusion criteria:

- Antenatal women of any age
- Singleton pregnancy
- Gestational age less than 20 weeks
- Any parity
- Normotensive patients
- Without proteinuria

Exclusion criteria:

- Blood pressure of 140/90 mmhg or more
- Proteinuria -tested with dipstick >1+ in random urine sample
- History of PIH in past pregnancy
- History of chronic hypertension
- Multiple pregnancy
- Diabetes mellitus complicating pregnancy
- Renal disease
- Vascular disease
- Immunological disease .

METHODOLOGY

All antenatal women who attended the out patient department at the Department of Obstetrics and Gynaecology, Coimbatore medical college hospital, Coimbatore based on selection criteria was enrolled in this study. Women with history of chronic hypertension, diabetes mellitus, renal disease were excluded from this study based on exclusion criteria. Women who had baseline blood pressure of more than or equal to 140/90 mm Hg and who had proteinuria by dipstick method at first visit were excluded from the study. Blood pressure was measured in semi recumbent posture with lateral tilt in right arm at the level of heart and proteinuria was measured by dipstick method in a spot sample of urine for albumin.

1.Informed written consent was obtained from all patients for spot urinary calcium creatinine ratio estimation.

2.Participation in the study was voluntary.

3.All subjects were informed about the aims and objectives of the study, the test to be done and the nature of their population.

4. A detailed history ,a complete physical general examination and obstetric examination was performed. All women were examined in detail and history obtained in detail about the present and past medical and surgical illness. Anyone antenatal women with the history suggestive of illness ,mentioned in the exclusion criteria was not involved in the trail and detailed obstetric examination was also done. Blood pressure was measured, those women with higher blood pressure of more than 140/90 mm Hg on two successive measurements of 4-6 hours apart and proteinuria of >1+ dipstick were excluded in this study.

5.A spot urine sample was collected for estimation for calcium and creatinine in the laboratory. Calcium was determined by orthocresolphthalein complex method and urinary creatinine by Jaffee's method.

6.Calcium creatinine ratio was calculated those with ration of <0.04 were considered Positive, those with ratio of >0.04 were considered as test Negative.

7.Cutoff for CCR is taken as less than or equal to 0.04.

8.Patient are then followed every 4 weeks to predict how many of them developed pre-eclampsia. The doctors and patients were blinded from the CCR values and they were observed and followed up regularly once in 4 weeks up to delivery. Each and every patients involved in the study was closely observed for symptoms and signs of pre-eclampsia, like headache, vomiting, epigastric pain, reduced urine output, pedal oedema, increased weight, pain, raised blood pressure and proteinuria. The data was collected at the end of the study and entered in the excel spread sheet and statistical analysis was done.

STATISTICAL ANALYSIS:

The results obtained were further analysed for Standard Deviation ,t test, SEM and p value.The p value of <0.001 was considered significant. Comparative study was done using chi square test.

Gestational Hypertension:

Defined as blood pressure of more than or equal to 140/90mmhg without proteinuria after 20 weeks of gestation.

Preeclampsia:

Defined as blood pressure of more than or equal to 140/90 mmHg with associated proteinuria. Calcium Creatinine Ratio were estimated and the value less than or equal to 0.04 were positive .(i.e low calcium excretion). Those with calcium creatinine ratio more than 0.04 were considered Negative.(i.e normal calcium excretion). The SD, t test, SEM and p value is determined by statistical analysis, Chi square test is done for comparative study between the normal group and the group who developed pre-eclampsia.

Outcome Measures:

The outcome of this study is measured based on

- Gestational age of collection of spot urine sample for CCR.
- Number of CCR positive women.
- Number of antenatal women with CCR positive developed Pre-eclampsia.
- Gestational age of development of Pre-eclampsia.
- Gestational age at delivery.
- Mode of delivery.

RESULTS

During the study period , a total of 200 antenatal asymptomatic low risk women were included in the study. 19 patients(9.5%) had CCR ratio less than or equal to 0.04 while 181 patients(90.5%) had CCR ratio more than 0.05. 40% of women belongs to the age group between 17-20 years ,40.5% between 21-25 years ,17.5% between 26-30 years while remaining 2% of patients aged above 31 years. There are 127(63.5%) primigravida patients and 73(26.5%) multigravida patients.

Mean age of patients with a positive CCR is 23.16 years with SD of 5.480; mean age of patients with negative CCR is 22.46 years with SD of 3.304, p=0.416. Among those with a positive CCR, 15(78.9%) were primigravida and 4(21.1%) were multigravida, while in those with a negative CCR, 112(61.9%) were primigravida and 69(38.1%) were multigravida.

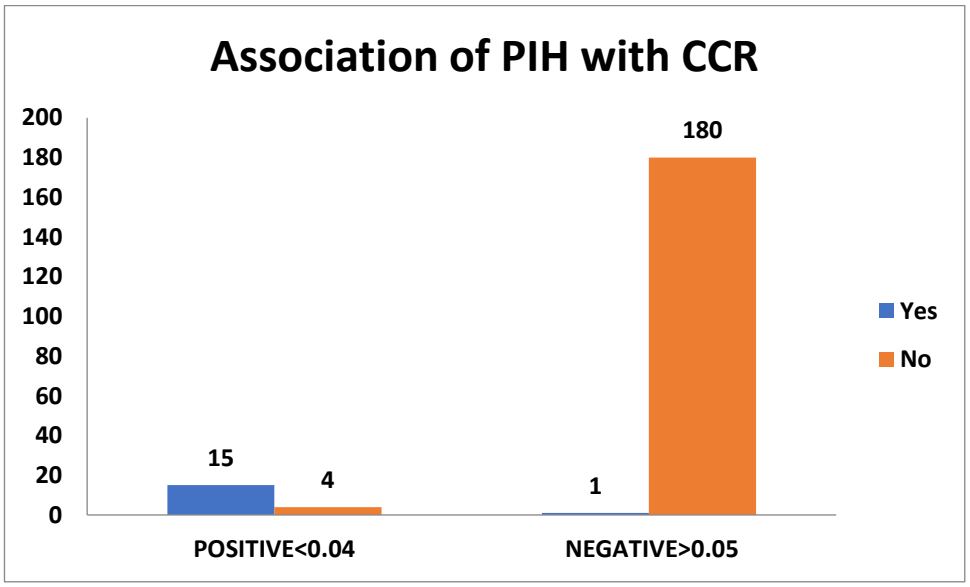
Table 1: Association of PIH with CCR

CCR	Pregnancy induced hypertension		P Value
	Yes	No	
POSITIVE<0.04	15(78.9%)	4(21.1%)	.000*
NEGATIVE>0.05	1(0.6%)	180(99.4%)	

*P- Value is <0.05 and it is statistically significant

Among the 19 patients with positive CCR, 15 developed PIH while 4 remained normotensive, while only 1 patient developed PIH among the181patients with a negative CCR, p=0.001

Figure 1: Association of PIH with CCR



Among 200 women involved in this study ,19 had positive CCR of which 6 developed severe pre-eclampsia,5 developed non severe pre-eclampsia and 4 developed GHT , remaining 4 didn't developed hypertension of pregnancy. While 181 patients had negative CCR among that one patient developed GHT in spite of negative CCR and 180 patients didn't developed hypertension of pregnancy. The type of PIH not being significantly associated with CCR.

Table 2: Association of Gestational age at delivery with CCR

CCR	Gestational age		P Value
	PRETERM	TERM	
POSITIVE<0.04	5(26.3%)	14(73.7%)	.000*
NEGATIVE>0.05	10(5.5%)	171(94.5%)	

*P- Value is <0.05 and it is statistically significant
In among 19 positive CCR women,5 had preterm birth and 12 had term deliveries, while in 181 negative CCR women,10 had preterm birth and 171 had term deliveries, p=0.001

Figure 2: Association of Gestational age at delivery with CCR

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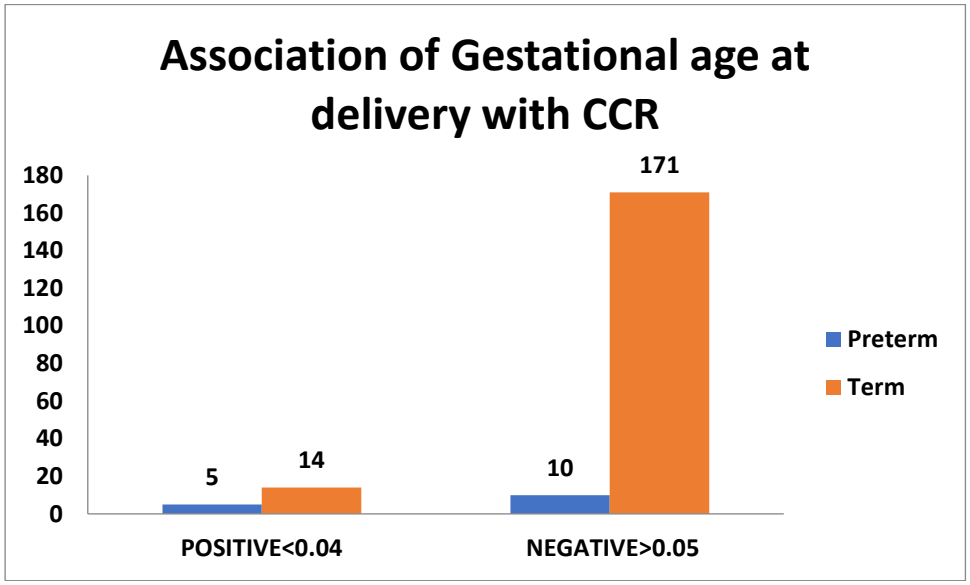


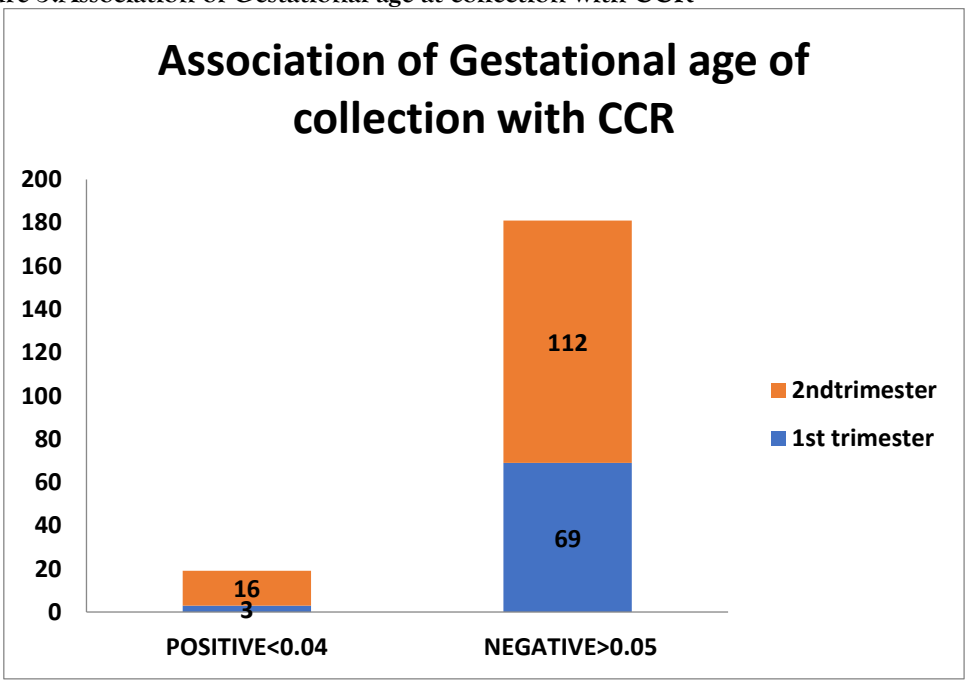
Table 3: Association of Gestational age at sample collection with CCR

CCR	Gestational age at sample collection		P Value
	1st trimester	2ndtrimester	
POSITIVE<0.04	3(15.8%)	16(84.2%)	.046*
NEGATIVE>0.05	69(38.1%)	112(61.9%)	

*P- Value is <0.05 and it is statistically significant

Among the women with gestational age of less than 12 weeks ,69 women had negative CCR, 3 had positive CCR while between 12-20 weeks, 16 women had positive CCR and 112 had negative CCR with significant p value of 0.046. Estimation of CCR in second trimester is more ideal.

Figure 3:Association of Gestational age at collection with CCR



Among 19 women with positive CCR , 6 had LSCS remaining 13 delivered vaginally. while among 181 women with negative CCR , 54 had LSCS and the remaining 126 patients had normal vaginal delivery with p-value of 0.939 and it is not statistically significant.

Table 4: Association of PIH with CCR in primigravida

CCR	Pregnancy induced hypertension (n=127)		P Value
	Yes	No	
POSITIVE<0.04	12(80.0%)	3(20.0%)	.000*
NEGATIVE>0.05	0(0.0%)	112(100.0%)	

*P- Value is <0.05 and it is statistically significant

Among 15 primigravida patients with positive CCR, 12 had PIH while none of the 112 primigravida patients with negative CCR had PIH, p=0.001

Figure 4: Association of PIH with CCR in primigravida

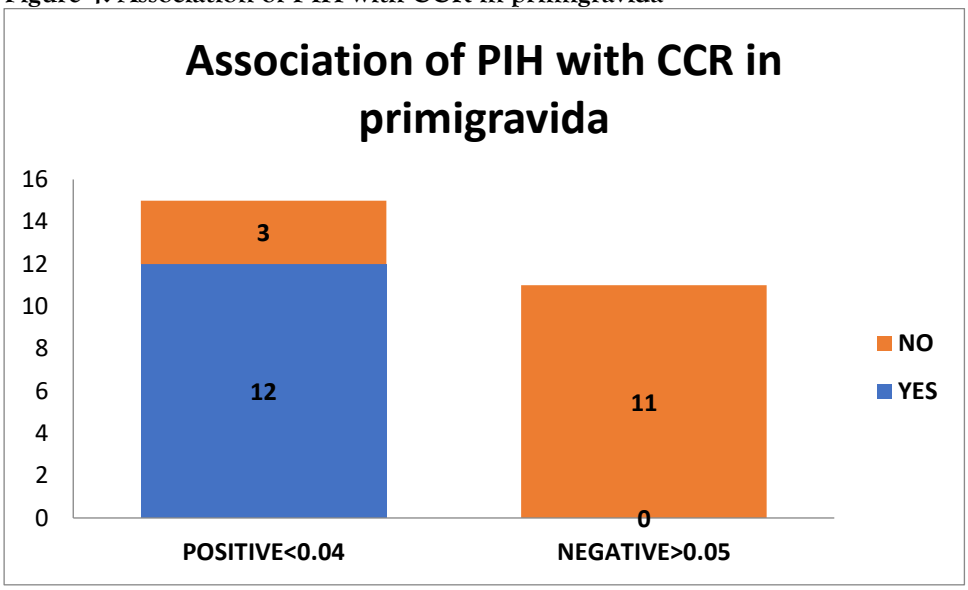


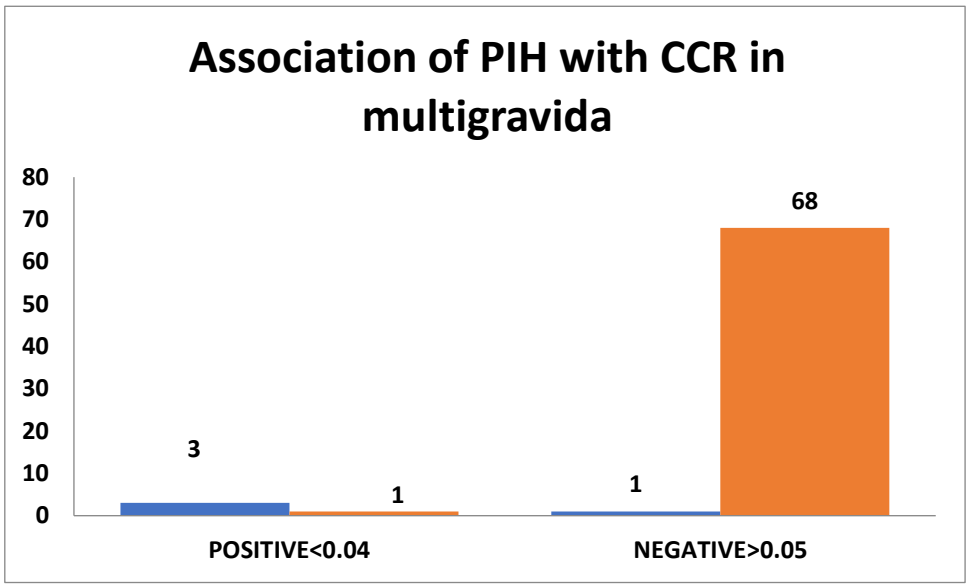
Table 5: Association of PIH with CCR in multigravida

CCR	Pregnancy induced hypertension		P Value
	Yes	No	
POSITIVE<0.04	3(75.0%)	1(25.0%)	.000*
NEGATIVE>0.05	1(1.4%)	68(98.6%)	

*P- Value is <0.05 and it is statistically significant

3 of the 4 multigravida patients with positive CCR developed PIH while only 1 of the 69 patients with a negative CCR developed PIH, p=0.001

Figure 5: Association of CCR with PIH in multigravida patients



DISCUSSION:

In the above study, 200 mothers with gestational age less than 20 weeks were enrolled in this study .They were assessed by determining the calcium to creatinine ratio in a spot sample of urine for the development of pre-eclampsia. CCR was calculated those with ratio less than or equal to 0.04 were considered positive and those with ratio of more than 0.04 were considered as test negative. Cut off for positive CCR is taken as less than or equal to 0.04.

All 200 Patients were then followed till delivery once in four weeks to predict how many of them developed pre-eclampsia and the results obtained were analysed for statistical significance and if pre-eclampsia developed managed as per local protocol. Out of 200 samples, 19 women had positive calcium creatinine ratio while 181 had negative calcium creatinine ratio.

Among the 19 positive CCR ratio-

- 15 developed hypertension i,e 6 developed severe pre-eclampsia,5 developed non severe pre-eclampsia and 4 developed gestational induced hypertension, while the remaining 4 women remains normotensive and No one developed eclampsia.

While among 181 negative CCR ratio ,one women developed gestational induced hypertension.

In our study we estimated the association between the CCR ratio and the development of hypertension in pregnancy and the p value obtained is 0.001 and it is considered as statistically significant.

Narendra Patil et al, government medical college and cancer hospital ,Aurangabad ,Maharashtra conducted a study ,calcium to creatinine ratio and microalbuminuira in prediction of pre-eclampsia in a spot sample of urine between 20 and 34 weeks of gestation. They concluded that CCR ratio less than or equal to 0.04 is a good test for prediction of pre-eclampsia and can be recommended as screening test in asymptomatic low risk antenatal women, while microalbuminuria on the other hand is a weak test for prediction of pre-eclampsia.[5]

Whereas in our study we estimated only CCR ratio with less than 20 weeks of gestation with significant p value.

Ozcan conducted a trial,for determining the efficacy of hypocalciuria in urine sample for prediction of pre-eclampsia as early as 1990s and concluded hypocalciuria can be used as prediction of pre-eclampsia.[6]

And therefore from the above study shows that it can be used as screening test in low risk aymptomatic women for prediction of pre-eclampsia with p value 0f <0.001.

In our study we also compared the association of types of PIH with CCR ratio.Among the 19 positive CCR ratio patients, 6 developed severe pre-eclampsia,5 developed non severe pre-eclampsia, 4 developed gestational hypertension and 4 remains normotensive. One woman developed Gestational hypertension even though CCR ratio is more than 0.04.

On statistical analysis ,the association of types of PIH with CCR ratio had p value of 0.814 and it is statistically not significant.so in our study the CCR ratio has no influence on the types of PIH.

In our study we also the compared the mean age association with CCR.on analysis (table 2),

- 40%-belongs to age group 17-20 years
- 40.5%-belongs to age group 21-25 years
- 17%-belongs t0 age group 26-30 years
- 25-aged above 31 years

0n statistical analysis , the association of types of PIH with CCR shows p value of 0.416 and it is not statistically significant.

In comparing the association of parity with CCR,the incidence of positive CCR in primi is 78.9%,while in multi it is 21.1%. Among which 12 cases of primi and 4 cases of multi developed hypertension during pregnancy.The incidence of hypertension in pregnancy is 10% in primi and 5 % in multigravida.so in my study also interprets the incidence of PIH is more in primi than multi gravida.

On statistical analysis ,the association of parity with CCR shows p value of 0.142 and it is not statistically significant.

The incidence of preterm birth is more common than term birth in hypertension of pregnancy and it is about more than 40%. In our study also when comparing the association of gestational age at delivery with CCR, premature deliveries is more than term deliveries in women those who developed hypertension during pregnancy and it showed p value of 0.001 and it is statistically significant.

So there is more number of premature deliveries in hypertension of pregnancy than normotensive women might be due to early intervention and termination of pregnancy to prevent maternal mortality and morbidity.

Izumi had reported that CCR had reduced value as a screening method for pre-eclampsia , but the screening was done during initial period of pregnancy at equal or less than 12 weeks of gestation ,where as in above study the gestational age of less than 20 weeks is taken ,giving a wider range of prediction.[7]

In our study we compared the association of gestational age of collection with CCR ,

- First trimester (14 weeks)-69 had negative CCR and 3 of them had positive CCR.
- Second trimester(14-20 weeks)-112 had negative CCR and 16 had positive CCR.
  While comparing the association of gestational age of collection with CCR had p value of 0.046 and it is statistically aignificant. And the second trimester CCR(84%) is more ideal than first trimester(15%).

On comparing the association of mode of delivery with CCR ratio,

Among 19 positive CCR,6 delivered by LSCS and 13 delivered by NVD.

While among 181 negative CCR,54 delivered by LSCS and 126 delivered by NVD.

On statistical analysis,the association of mode of delivery with CCR had p value of 0.939 and it is not statistically significant.

On comparing the association of PIH with CCR in primigravida,among 127 women,15 had positive CCR with incidence of 15%,with significant P value of 0.000* and it is statistically significant.

While comparing the association of PIH with CCR in multigravida ,among 73 women 4 had positive CCR with incidence of 5% with significant p value and it is statistically significant .

CONCLUSION

From this study ,the following conclusion have been arrived,

The estimation of Calcium Creatinine Ratio in a spot sample of urine for prediction of pre-eclampsia had p value of < 0.001 and it is statistically significant and it can be used as a screening test for low risk asymptomatic antenatal women with less than 20 weeks of gestation for prediction of pre-eclampsia regardless of parity. Second trimester is the ideal time to collect the sample

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