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Study the Correlation of Urinary Calcium-Creatinine Ratio as a Predictor of Pre-Eclampsia

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Background
Aim: *To study the correlation of urinary calcium-creatinine ratio in predicting pre-eclampsia in pregnant women.*
Objectives
1. *To study the urinary calcium:creatinine ratio among all pregnant women.*
2. *To correlate the urinary calcium: creatinine ratio in normotensive and pre-eclamptic women.*

Methodology: *This Prospective, observational study was conducted in the department of obstetrics and gynecology, Sri Ram MurtiSmarak Institute of Medical Sciences, Bareilly, India. Urinary calcium creatinine ratio was determined in a random sample of urine in 50 patients of pre-eclampsia (Study group) and 50 normotensive pregnant (Control group) patients of age 20-35 years with gestational age 20 weeks onwards. Cut off value for CCR was taken as ≤ 0.04.*

Results: *Out of 50 pre-eclamptic cases, 26(52%) cases in the study group had CCR ≤0.04 while only 7(14%) cases in control group had CCR ≤0.04 with a statistically significant p value of 0.000. On statistical analysis, CCR at ≤0.04 had a sensitivity of 52%, specificity of 86%, positive predictive value of 79% and negative predictive value of 64%. The accuracy of the test was 69%.*

Conclusion: *A single estimation of urinary calcium to creatinine ratio in asymptomatic pregnant women after 20 weeks of gestation is a simple and cost-effective test. A value of less than or equal to 0.04, in a spot urine sample, has a good predictive value for preeclampsia.*

Keywords: *Preeclampsia, Urinary Calcium, Urinary Creatinine, Urinary Calcium Creatinine ratio.*

Introduction

Around the world, an estimated 529,000 women die during pregnancy or childbirth[1] of which 80% are directly related to pregnancy events such as haemorrhage and sepsis followed by hypertensive disorders of pregnancy and prolonged or obstructed labor while 20% of maternal deaths are due to indirect causes. Hypertensive disorders of pregnancy account for 3rd most common cause of maternal mortality after haemorrhage and sepsis. The incidence of maternal mortality due to pre-eclampsia in developed countries range from 2-5% while in developing countries range from 10-25%[2,3]. Preeclampsia is a disorder of the second half of pregnancy which regresses after delivery[4,5]. Preeclampsia is a syndrome characterized by the development of hypertension to the extent of 140/90 mm Hg or more with proteinuria during pregnancy after the 20th week of gestation.

As per the new **ACOG Practice Bulletin 2019**, although hypertension and proteinuria are the classical criteria for the diagnosis of pre-eclampsia, the presence of any one of the

following severe features in women with gestational hypertension without proteinuria should also be reclassified as pre-eclampsia. These features have been included in the diagnostic criteria of pre-eclampsia since they increase the risk of morbidity and mortality and require enhance surveillance- Thrombocytopenia (platelet count less than 100,000x109/L), Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes(to twice the upper limit of normal concentration), severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnosis, pulmonary edema, renal insufficiency (serum creatinine concentration greater than 1.1mg/dl or a doubling of serum creatinine concentration in the absence of other renal disease), new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnosis or with visual disturbances[6].

In addition it is recommended that women with gestational hypertension with severe range of BPs (systolic BP of 160mmHg or higher, or diastolic BP of 110mmHg or higher) should also be diagnosed as pre-eclampsia with severe features[6].

The various risk factors for pre-eclampsia include age <20 years and >35 years, primiparity, previous history of pre-eclampsia, family history of pre-eclampsia, pre-existing medical conditions like renal disease, diabetes[7]. Abnormal trophoblastic invasion of spiral arteries, exaggerated inflammatory response, inappropriate endothelial cell activation are key features in pathogenesis of pre-eclampsia. The predominant pathology is endothelial dysfunction which sets in early 8–18th weeks of gestation resulting in placental insufficiency which results in secondary symptomatic stage characterized by development of hypertension, renal impairment and proteinuria, liver disease and HELLP syndrome along with increased risk for eclampsia and pulmonary edema[8].

It is a multisystem disorder affecting all the organs due to imbalance between vasoconstrictors and vasodilators leading to increased vascular resistance. Renal impairment is one of the earliest manifestations of end organ damage. Women with pre-eclampsia have diminished renal perfusion and glomerular filtration due to damage caused by pre-eclamptic changes leading to decrease in creatinine clearance with corresponding elevated plasma creatinine level. Slightly increased serum creatinine and significantly increased urinary creatinine but decreased amount of urine is due to decreased glomerular filtration rate in pre-eclampsia. Urinary calcium excretion in normal pregnancy is 350-650 mg/day, compared with 100-250 mg/day in non-pregnant women. Hypocalciuria in women with preeclampsia may be due to decreased fractional excretion of calcium secondary to its increased tubular reabsorption[9]. In patients with pre-eclampsia a decrease in urinary calcium excretion results in decreased calcium/creatinine ratio which can be used as a marker for early diagnosis of pre-eclampsia.

In the light of above facts the present study was conducted with the aim to assess the role of urinary calcium to urinary creatinine ratio (CCR) in diagnosing pre-eclampsia in pregnancy for proper patient care.

Material and Methods

This prospective study was carried out at the Department of Obstetrics and Gynaecology at Sri Ram Murti Smarak Institute of Medical Sciences, Bareilly, for 1 ½ years from November 2017-May 2019. Pregnant women between age group of 20-35 years with gestational age 20 weeks onwards attending the antenatal clinic (outdoor), or admitted in the ward or in labour room were included in the study. A total of 100 pregnant women were divided into 2 groups: GROUP A-50 Pre-eclamptic women (cases) and GROUP B-50 Normotensive women (control).

Patients were explained about the study, consent was taken and their details regarding age, blood group and medical history was obtained.

Inclusion Criteria: All women with singleton pregnancy with gestational age more than 20 weeks.

Exclusion Criteria

1. Chronic hypertension
2. Previous history of pre-eclampsia
3. Chronic renal disease
4. Immunological or vascular disorders
5. UTI
6. High risk female- multiple gestation, polyhydramnios, diabetes mellitus

Sample collection: Patient was asked to submit random midstream urine sample in a 50 mL urine container for laboratory analysis for random urine dipstick test, calcium and creatinine. The dipstick analysis was done using the uriplus 900 urinalysis stip.

Sample analysis: Urinary Calcium was estimated by OCPC (0-Cresolpthalein Comsplexone) method calorimetrically. Urinary Creatinine was estimated by Jaffe's reaction (alkaline picrate). All the collected data was reviewed and analysed for urinary calcium-creatinine ratio (CCR) in both the study and control group.

Ratio – $\dfrac{\text{Urinary Calcium (mg/dl)}}{\text{Urinary Creatinine (mg/dl)}}$

Cut off for CCR was taken as ≤0.04

Statistical analysi: All findings were recorded in a predesigned format. Compiled data was presented in form of frequency and percentage and subsequently analysed by appropriate statistical tests (chi-square test andFischer exact test) using the SPSS (Statistical Package for the Social Science) Version 20.0 for the window. A probability value of 0.05 was accepted as the level of statistical significance.

Results

In this prospective clinical study comprising of 100 women over 20weeks of gestation, 48% were in the age group of 20-25 years, and only 14% were more than 30 years of age. The mean age in the study group was 26.18 years and in the control group was 25.24 years. Of the 50 subjects only 22% were booked while 78% were unbooked. The incidence of pre-eclampsia was higher in primigravidae (62%) while the rest were multigravida. Out of 50 cases of pre-eclampsia, 54% had mild pre-eclampsia while rest 46% had severe pre-eclampsia. The demographic and obstetric parameters were comparable in both the groups (Table-1)

Table-2 depicts the Systolic and Diastolic BP in study and control group. The mean systolic BP among mild pre-eclampsia was 145.18±8.42 and in severe pre-elampsia was 166.45±10.94 whereas in normotensive patients the mean systolic BP was 117.12±11.10. The mean diastolic BP in normotensive patients was 77.48±9.23, whereas in mild and severe pre-eclampsia it was 93.03±5.62 and 119.6±7.73 respectively.

Mean urinary calcium among mild pre-eclamptic group was 4.73±6.9 whereas in severe pre-eclampsia was 3.22±4.1. However mean urinary calcium among pre-eclamptic and normotensive women it was 4.032±5.73 and 8.004±5.95 respectively with a p value of 0.001. The mean urinary creatinine in the study group was 83.406±58.605 and the in the control group was 63.22±48.262 which was statistically not significant.

Out of 50 pre-eclamptic cases, 26(52%) cases had CCR ≤0.04 with a mean value of 0.008±0.011 against 7(14%) cases in control group with a mean value of and 0.018±0.002 with a statistically significant p value of 0.000(Table-3).

Of the 100 women studied, 26(52%) were true positive with CCR ≤0.04 and only 7(14%) had false positive result(Table-4).

The results of diagnostic accuracy tests involving sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for calcium:creatinine ratio is depicted in Table-5.

Table-1: Demographic and obstetric profile of patients

Parameter	Study (n=50)	Control (n=50)
Age(years)	26.18	25.24
Parity		
Primigravida	31(62%)	26(525)
Multigravida	19(18%)	24(48%)
Antenatal status		
Booked	11(22%)	21(42%)
Unbooked	39(78%)	29(58%)
Family h/o Hypertention		
Yes	12(24%)	4(8%)
No	38(76%)	46(92%)
BMI (mean)	27.43	25.53

Table-2: Systolic and Diastolic BP in study and control group

	Cases(n=50)				Control (n=50)	
	Mild PE (27)		Severe PE(23)			
	mean	sd	mean	sd	mean	sd
Systolic BP	145.18	±8.42	166.45	±10.94		
Total mean	155.81				117.12	±11.10
Sd	±10.63					
Diastolic BP	mean	sd	mean	sd	mean	sd
	93.03	±5.62	119.6	±7.73		
Total mean Sd	106.3				77.48	±9.23
	±7.35					
Mean urinary calcium (mg/dl)	4.032	±5.738			8.004	±5.953
Mean urinary creatinine (mg/dl)	83.406	±58.605			63.22	±48.262

Table-3: Calcium to creatinine ratio (CCR) in cases and control group

CCR		Cases(n=50)	Control(n=50)	p value
≤0.04	no of patients	26(52%)	7(14%)	
	mean	0.008±0.011	0.018±0.002	0.000
>0.04	no of patients	24(48%)	43(86%)	
	mean	0.299±0.393	0.417±0.643	0.421

Table-4: Association of calcium-creatinine ratio with pre-eclampsia

CCR	Cases(n=50)	Control(n=50)	Total
≤0.04 (Test positive)	26(52%) (True positive)	7(14%) (False positive)	33
>0.04 (Test negative)	24(48%) (False negative)	43(86%) (True negative)	67

Table-5: Statistical analysis

	Sensitivity	Specificity	PPV	NPV	Statistical accuracy	P value
CCR	52%	86%	79%	64%	69%	0.000

Discussion

Pre-eclampsia is a multiorgan, heterogenous disorder of pregnancy associated with significant maternal and neonatal morbidity and mortality. A major challenge in modern obstetrics is early identification of pregnancies at high risk of pre-eclampsia and undertaking the necessary measures to reduce the prevalence of the disease and its complications. In this study an attempt was made to show the relationship between low urinary calcium creatinine ratio (CCR) and pre-eclampsia. A urine Calcium:Creatinine ratio threshold value of 0.04 was taken as cut off for prediction of preeclampsia.

In our study, the mean age in the study group (pre-eclamptic) was 26.18 years and in the control group (normotensive) was 25.24 years which was in accordance to the study conducted by Abdelmarouf H et al (2007) and Patrick J. Saudan[10,11]. The incidence of pre-eclampsia was higher in primigravidae i.e. 62% which was in accordance to the study conducted by Long PA et al (1979) who observed a significant higher incidence of pre-eclampsia in primigravidae rather than multigravidae[12]. The mean Systolic blood pressure was 155.81±10.94 and mean diastolic blood pressure 106.3±7.35. These findings were similar to the study conducted by Pal et al (2012) where the mean Systolic blood pressure among the study group was 156.8 ± 4.34 and mean Diastolic blood pressure was 102 ± 4.89[13].

In our study, mean urinary calcium among mild pre-eclamptic group was 4.73±6.9 whereas in severe pre-eclampsia was 3.22±4.1. Study conducted by Pal et al (2012) correlates with the results of our present study that showed hypocalciuria was associated with pre-eclampsia[13].Hypocalciuria in pregnancy is due to a decrease in distal tubular reabsorption of calcium and a decrease in the glomerular filtration rate due to glomerular endotheliosis.

The mean urinary creatinine in the study group was 83.406±58.605 whereas in the control group the mean urinary creatinine value was 63.22±48.262 which is statistically not significant. Our findings were in concordance with the study conducted by Amandeep K (2015) and showed that mean Urinary creatinine levels in normal pregnant females was 179.6 ±8.466 mg% while in pre-eclamptic pregnant females, the mean urinary creatinine excretion was 249.8 ± 14.4 mg%, with statistically significant p value of <0.001[14]. There is significantly increased excretion of creatinine in pre-eclamptic females as compared to normal pregnant females due to less amount of urine formed in pre-eclamptics. Slightly increased serum creatinine and significantly increased urinary creatinine but decreased amount of urine is due to decreased glomerular filtration rate in pre-eclampsia.

Hypocalciuria accompanied by hypercreatinurea are the features responsible for decreased urinary calcium;creatinine ratio in pre-eclamptic females < 0.04. Thus the ratio can be considered as a predictor of pre-eclampsia. In our study 26(52%) patients in the study group had calcium:creatinine ratio (CCR) ≤0.04 with a mean value of 0.008±0.002 against 14% in control group with a mean value of 0.018±0.011 with a statistically significant p value of 0.000. In our study of the 100 women studied, 26(52%) were true positive with CCR ≤0.04 and only 7(14%) had false positive result. Thus the sensitivity of the test was 52% while the specificity was 86%. The positive predictive value (PPV) was 79% while negative predictive value (NPV) was 64%. Similar findings were observed by Sheela CN (2011)on 200 women and showed that 21(11%) patients were test positive (CCR≤0.04) while 24(12%) were false positive which were in concordance with our findings and correlates that the sensitivity of CCR ≤0.04 was 69.2% with a specificity of 98.2%, PPV of 85.7% and NPV of 87% with a statistical accuracy of 87%, p value of <0.001 which is strongly significant[15].

S.no	Study	Cut off	Sensitivity	Specificity	PPV	NPV	p value
1.	Sheela CN et al (2011)[72]	≤0.04	69%	98%	85%	95%	<0.001
2.	Lakshami et al (2013)[73]	≤0.04	68%	95%	75%	93%	<0.001
3.	Solanki et al (2019)[103]	≤0.04	71%	98%	83%	97%	<0.001
4.	Present	≤0.04	52%	86%	79%	64%	0.000

Conclusion

Hypertensive disorders of pregnancy are a major contributing factor leading to maternal mortality. So prediction of pre-eclampsia in pregnancy may reduce maternal and fetal complications by timely management. The present study supports that there is a definite relationship between low urinary calcium to creatinine ratio and the development of preeclampsia. Estimation of Calcium -Creatinine ratio in a spot urine sample is a simple test, easily performed hence assures patient compliance. It has a good predictive value and justifies the cost and is suited to be adopted as a screening tool for preeclampsia. However this is a very small study and therefore larger randomized trials are needed for using urinary calcium creatinine ratio as a predictor of pre-eclampsia.

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