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Original Research Article

Evaluation of urinary calcium to creatinine ratio as a predictor of preeclampsia

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ABSTRACT

Background: Hypertension in pregnancy is a big threat to the mother as well as the fetus. Prediction of preeclampsia with reasonable accuracy is one of the essential prerequisites for its prevention. Various biological markers are available for the prediction of preeclampsia but none of those is reasonably reliable, valid and economical. In this present study, the predictive value of the urinary calcium-creatinine ratio (CCR) for the prediction of preeclampsia was studied.

Methods: This Prospective, observational study was conducted in the department of obstetrics and gynecology, Jawaharlal Nehru Hospital, Bhilai, Chhattisgarh, India. The study population was comprised of consecutive 174 pregnant women with gestational age between 20-28 weeks attending antenatal OPD. Calcium and creatinine levels were estimated in the midstream clean catch urine sample. After initial workup, all patients were followed in the antenatal clinic till the time of delivery. The number of patients who develop the hypertensive disorder in pregnancy was noted and the correlation studied.

Results: On statistical analysis, CCR at ≤ 0.04 had a sensitivity of 71.43%, specificity of 98.75%, and the positive predictive value of 83.33% and negative predictive value of 97.53%. The accuracy of the test was 96.55%.

Conclusions: A single estimation of calcium to creatinine ratio in asymptomatic pregnant women between 20-28 week 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: Calcium creatinine ratio, Gestational hypertension, Preeclampsia, Preeclampsia prediction

INTRODUCTION

Hypertension in pregnancy is a big threat to mother as well as treating obstetrician which not only affects the general physiology of mother, placenta and fetus but also brings changes in many other organs and many times may lead to organ dysfunction and may prove to be detrimental to both mother and fetus. Hypertension in pregnancy, when associated with proteinuria, leads to further worsening of prognosis and such situation is termed as preeclampsia, which is a pregnancy specific clinical condition that can affect virtually any organ system. Preeclampsia is much more than simply

hypertension with proteinuria, the appearance of proteinuria remains an important diagnostic criterion to differentiate preeclampsia from gestational hypertension.¹ Hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics. These disorders complicate 5 to 10 per cent of all pregnancies, and together they are one of the deadly triad along with haemorrhage and infection that contributes greatly to maternal morbidity and mortality rates.¹ Hypertensive disorders complicate between 5% and 10% of all pregnancies. Hypertension may be present prior to pregnancy (chronic essential hypertension) or may be diagnosed for the first-time during pregnancy

(gestational hypertension, preeclampsia, eclampsia). These disorders are a major cause of maternal and perinatal mortality. The aetiology of preeclampsia remains elusive although it is well accepted that the process improves following delivery. Prompt recognition of preeclampsia and proper management can reduce serious complications of this disorder.²

In the Indian scenario, the women with preeclampsia account for around 44.4% of all cases of hypertensive disorders. Despite its prevalence and severity, the pathophysiology of this multisystem disease is still poorly understood. If preeclampsia is predicted timely the life threatening complications of preeclampsia can be preventable. The currently available predictive tests such as Doppler USG, Doppler velocimetry in uterine artery, mid trimester microalbuminuria and HCG levels etc. are expensive, involve complex procedures and require trained personnel to perform these tests and these may be nonspecific to the condition.³

Several researches have reported that hypocalciuria is associated with preeclampsia due to derangement of calcium metabolism. Also, hypocalciuria could be preceded by the development of preeclampsia. A decrease in serum calcium levels causes high blood pressure by stimulating the release of parathormone hormone and renin and also by inducing vasoconstriction by increasing its levels in vascular smooth muscles. There is also a decrease in urinary creatinine excretion.⁴

Hence the decrease in urinary calcium to creatinine ratio can be considered as a risk factor for the development of preeclampsia. This ratio is easily measurable, more effective even with spot urinary sample and is less expensive.

METHODS

This study was done to assess the efficacy of urinary Calcium/Creatinine ratio (CCR) as a predictor of preeclampsia & to assess the incidence of preeclampsia in general and in patients with abnormal CCR in the study population.

A prospective, observational study was done from September 2016 to October 2017. A consecutive series of 174 pregnant women seeking antenatal care and comes under the inclusion criteria was taken.

In the previous study done the incidence of preeclampsia was 13%.⁵

$P =$ Proportion of pregnant women developing pre-eclampsia $= 13 = 0.13$

$1-P = 1 - 0.13 = 0.87$

1.96 = Z value for 95% confidence level (standard normal deviate set at 1.96 at 95% confidence level)

$e =$ precision $= 0.05$ $N =$ minimal sample size

The sample size is calculated by COCHRAN FORMULA for descriptive analysis.

$N = \{Z^2 \times P \times (1-P)\} / e^2 = \{1.96^2 \times 0.13 \times 0.87\} / 0.05^2$
 $= 173.79 = 174.$

Inclusion criteria

- Antenatal women with gestational age between 20-28 weeks,
- Women who were willing for follow up with their regular antenatal checkups till delivery,
- Women who have not received any antihypertensive medication until enrolment into the study.

Exclusion criteria

- Women with H/o chronic hypertension, history of gestational hypertension in a previous pregnancy, diabetes mellitus, renal disease and other chronic illness.

Mid-stream clean catch sample was collected in a clean sterile universal bottle without any preservative. Calcium and creatinine levels were estimated in the collected samples. All the collected data were reviewed and analysed for the urinary calcium-creatinine ratio (CCR). After initial workup, all patients were followed thereafter in the antenatal clinic till the time of delivery. The number of patients who develop the hypertensive disorder in pregnancy was noted and correlation studied. So, the ratio is given as urinary calcium (mg/dl) /urinary creatinine (mg/dl).

Statistical analysis

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 (Unpaired t-test, chi-square test etc.) using the SPSS (Statistical Package for the Social Science) Version 21 for the window. A probability value of 0.05 was accepted as the level of statistical significance.

RESULTS

In the present study out of 174 pregnant women 10 (5.7%) women developed mild preeclampsia, 4 (2.3%) women developed severe preeclampsia, 5 (2.9%) women developed GHTN, and rest 155 (89.1%) women remained normotensive (Figure 1).

The study showed that out of 14 women who developed preeclampsia 10 women (71.4%) had $CCR \leq 0.04$ (true positive). On statistical analysis, it was found that when CCR alone was taken as a high risk factor for the early prediction of preeclampsia, it was highly significant ($p < 0.001$) (Table 1, Figure 2).

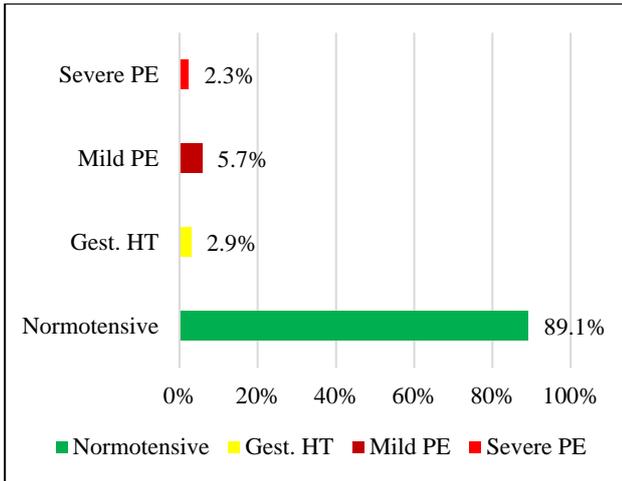


Figure 1: Incidence of hypertensive disorders.

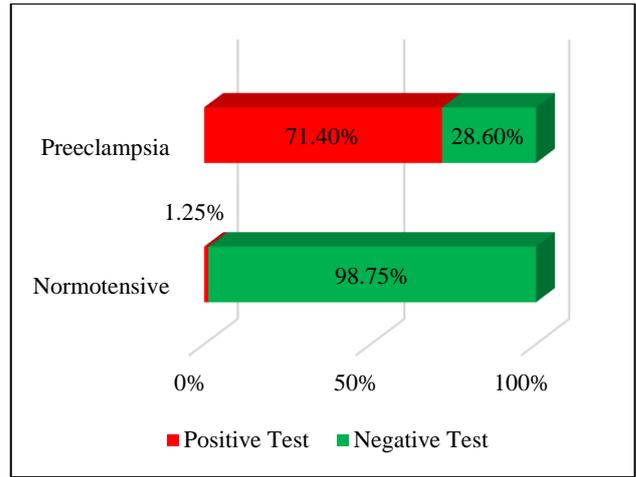


Figure 2: CCR result in preeclampsia and normotensive subjects.

Table 1: Statistical hypothesis testing.

	Value (CCR)	Count/%	Normotensive	Preeclampsia	Total
Positive	≤ 0.04	Count	2 (1.25%) (False positive)	10 (71.4%) (True positive)	12 (6.9%)
Negative	> 0.04	Count	158 (98.75%) (True negative)	4 (28.6%) (False negative)	162 (93.1%)
Total		Count	160 (100.0%)	14 (100.0%)	174 (100.0%)

Table 2: Comparison of urinary calcium, creatinine and CCR between women who developed PIH and who remained normotensive.

	Urinary calcium (mg/dl)	Urinary creatinine (mg/dl)	Urinary calcium to creatinine ratio
Normotensive (n=155)	21.22±7.77	98.99±12.49	0.199±0.074
Gestational hypertensive (n=5)	12.86±8.09	95.18±5.6	0.13±0.076
Mild preeclampsia (n=10)	7.28±6.41	90.77±30.01	0.07±0.068
Severe preeclampsia (n=4)	3.5±0.93	86.0±13.78	0.03±0.005

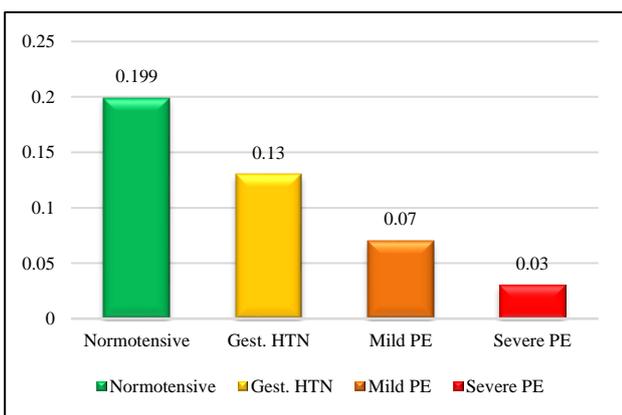


Figure 3: Comparison of CCR between women who developed PIH and who remained normotensive.

In the present study, we compared the values of mean urinary calcium, urinary creatinine and calcium to creatinine ratio and we found that urinary excretion of

calcium and creatinine decreases as the severity of hypertensive disorder of pregnancy increases (Table 2).

Similarly, the CCR also decreases as the severity of hypertensive disorder of pregnancy increases (Table 2, Figure 3).

Table 3: Statistical analysis of the CCR in preeclampsia.

Parameters	Value	95% CI
Sensitivity	71.43%	41.90% - 91.61%
Specificity	98.75%	95.56% - 99.85%
Positive predictive value	83.33%	54.81% - 95.31%
Negative predictive value	97.53%	94.5% - 98.91%
Accuracy	96.55%	92.65% - 98.72%
Disease prevalence	8.05%	4.47% - 13.13%

On statistical analysis, CCR at ≤ 0.04 had a sensitivity of 71.43%, specificity of 98.75%, the positive predictive

value of 83.33% and negative predictive value of 97.53%. The accuracy of the test was 96.55% (Table 3).

DISCUSSION

Preeclampsia is a syndrome of signs. Symptoms if any, are nonspecific and appears very late in the course of the disease. This makes the prediction and prevention of this disease very important. The age old method of detecting hypertension and proteinuria may be a criterion for diagnosis, but when the prediction is a concern it is having no value. Preexisting hypertension and/or proteinuria makes it less reliable for diagnosis also.

A variety of biochemical and biophysical tests are available which are primarily based on the pathology and pathophysiology of hypertensive disorders of the pregnancy.⁶ These tests are used with an intention of predicting the development of preeclampsia early in the pregnancy. But there is no simple method for predicting those patients who will develop preeclampsia (Sibai BM).⁷ Investigators have attempted to identify early markers of faulty placentation, reduced placental perfusion and endothelial cell activation (Redman CW).⁸ But none of them has been proved ideal either because of the high incidence of false positivity, high cost, feasibility or their complexity in result interpretation. Our present study was to evaluate the efficacy and predictive value of calcium creatinine ratio for the prediction of preeclampsia.

The incidence of preeclampsia in our study population was 8.01%. In the study done by Sheela CN et al, incidence of preeclampsia was 13% of which 11% had mild and 1.5% had severe disease and 0.5% had eclampsia.⁵

From a previous study done by Sheela et al, we took the cut off value for urinary calcium to creatinine ratio as 0.04. Out of 174 patients, 6.9% of patients tested positive ($CCR \leq 0.04$) and 93.1% tested negative ($CCR > 0.04$).⁵ Out of 12 test positive patients, 83.3% of patients had true positive, 16.7% had a false positive result. Out of 162 test negative patients, 2.4% of patients had false negative and rest 97.6% of patients had a true negative result. These findings were comparable to the previous study conducted by Sheela et al, and Patil N et al.^{5,9}

Women with established preeclampsia have been reported to have lower urinary calcium excretion, lower 1, 25 dihydroxycholecalciferol levels, ionized calcium levels, and higher PTH levels than normotensive controls.¹⁰ Because the placenta contributes approximately 50% of the circulating 1,25dihydroxycholecalciferol level in pregnancy, it was postulated that, in preeclampsia, the defective placenta is unable to produce sufficient levels of 1,25dihydroxycholecalciferol, resulting in inadequate gastrointestinal calcium absorption, low ionized calcium levels, and a secondary rise in PTH. How low circulating

calcium levels and elevated PTH levels cause hypertension remains unclear. Although acute infusions of PTH are associated with a fall in blood pressure, chronic elevations have been reported to cause vasoconstriction and hypertension. Low calcium levels may also contribute to hypertension via stimulation of renin release from the kidney Seely EW et al.¹¹

In the present study we found that mean value of urinary calcium in women who developed preeclampsia were significantly decreased (Ca 6.2 ± 5.6 mg/dl) p -value < 0.001 , as compared to urinary excretion of calcium in women who did not develop preeclampsia (Ca 20.10 ± 6.2). Taufield et al, observed marked hypocalciuria in patients with hypertensive disorders of pregnancy and suggested increased distal tubular reabsorption of calcium as a possible mechanism.¹²

Pedersen et al, in a longitudinal study reported that urinary calcium excretion was considerably lower in the third trimester of preeclamptic pregnant women than in both normotensive pregnant subjects and non-pregnant controls.¹³ They suggested that these changes could partly be related to a decrease in the glomerular filtration in preeclampsia.

The authors also found reduced tubular reabsorption in preeclamptic women because the fractional excretion was decreased. The increase in renal calcium excretion in normal pregnancy and decrease in renal calcium excretion in pre-eclampsia may be attributed to changes in kidney function¹³

In this study, excretion of creatinine was also decreased (p -value = 0.008) in women who developed preeclampsia (Cr 89.4 ± 15) as compared to women who did not develop preeclampsia (Cr 98.8 ± 12.4). While others noted a decrease of urinary creatinine in pre-eclampsia, Kazemi AFN et al, Mittal S et al, and Amandeep K, observed an increase in urinary creatinine in preeclamptic patients.¹⁴⁻¹⁶

In this study, the value of CCR is significantly lower ($CCR = 0.06 \pm 0.05$) in women who developed preeclampsia as compared to women who did not develop preeclampsia. The findings of Dasgupta M et al, were similar to our study.¹⁷ They concluded that Calcium: Creatinine ratio and calcium excretion index are better than only calcium measurement. McGrowder et al, also found that urinary calcium to creatinine ratio may be a useful potential screening test for pre-eclampsia.¹⁸

After the statistical analysis of results of our study CCR value ≤ 0.04 had the sensitivity of 71.43% (95% CI= 41.90%-91.61%), specificity of 98.75% (95% CI= 95.56%-99.85%), positive predictive value 83.33% (95% CI= 54.81%-95.31%), negative predictive value of 97.53% (95% CI= 94.5% - 98.91%) and accuracy of the test is 96.55% (95% CI= 92.65% - 98.72%). The result was similar to the studies of David A et al, and Aherwar R.^{19,20}

CONCLUSION

In developing countries like ours, significant numbers of pregnancies are complicated by preeclampsia. By predicting early we can prevent this complication by using low dose aspirin. The present study confirms that there is a definite relationship between low urinary calcium to creatinine ratio and the development of preeclampsia. A single estimation of calcium to creatinine ratio at less than or equal to 0.04, in a spot urine sample, in asymptomatic pregnant women between 20-28 week of gestation has a good predictive value. Moreover, it is a simple test, can be performed easily, and justifies the cost, hence ensuring patients' compliance. It can, therefore, be recommended as a screening tool to predict pre-eclampsia and may identify a population at risk, hence can be included in a primary prevention programme.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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