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Original Article

Obstetrics and Gynaecology Section

Trends of Urinary Calcium-creatinine Ratio during Pregnancy as an Early Predictor of Pre-eclampsia: A Prospective Cohort Study

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ABSTRACT

Introduction: Hypertensive disorder in pregnancy is a major cause of maternal and perinatal morbidity and mortality worldwide. Urinary Calcium:Creatinine Ratio (CCR) has been reported as a potentially useful biomarker for predicting Pre-eclampsia (PE).

Aim: To assess the trend of urinary CCR during pregnancy and to evaluate its association with the development of PE among antenatal women.

Materials and Methods: A prospective cohort study was conducted at the Department of Obstetrics and Gynaecology, Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR) Burla, Odisha, India, from February 2024 to February 2025 among pregnant women attending before the 20th week of pregnancy for antenatal check-ups. A total of 245 cases were finally selected and their urinary calcium and creatinine estimation were performed to find out CCR. Pregnancy-induced hypertension was detected in the patients as per guideline laid by the American College of Obstetricians and Gynaecologists (ACOG). Comparison of mean urinary CCR between the PE and non PE groups was done using an Independent t-test.

Results: Out of a total of 245 study participants, 35 (14.3%) developed PE. A progressive decline in urinary CCR was observed in women who developed PE compared to normotensive women. From 32 weeks of gestation onwards, mean CCR values were significantly lower in the PE group ($p<0.001$). Declining trend of urinary CCR demonstrated a sensitivity of 85.7%, specificity of 95.7%, for detecting PE. Receiver Operating Characteristic (ROC) curve analysis showed excellent discriminatory ability with an approximate Area Under the Curve (AUC) of 0.94.

Conclusion: Decreasing trends of CCR can be used as an effective marker in the early predictive marker for PE.

Keywords: Anaemia, Hypertensive disorders of pregnancy, Maternal morbidity, Predictor of pre-eclampsia

INTRODUCTION

Hypertensive disorders are among the most common medical disorders in pregnancy and continue to be a major cause of maternal and perinatal morbidity and mortality worldwide [1]. In developing countries, hypertension in pregnancy ranks second only to anaemia [2]. Owing to high maternal and perinatal mortality and morbidity associated with PE [3], it has been the long-standing goal of the obstetricians to identify the disease before it has the opportunity to cause substantial damage to the mother and foetus. Urinary CCR reflects calcium excretion independent of Glomerular Filtration Rate (GFR) and has been reported as a useful biochemical marker for predicting PE [4-9]. Though literature related to CCR was robust, most existing studies have focused primarily on defining single cut-off or threshold values of CCR for the prediction of PE [4-9]. However, pregnancy is a dynamic physiological state, and reliance on a single measurement may not adequately reflect evolving pathophysiological changes. Therefore, the present study aimed to assess the trend of urinary CCR during pregnancy and to evaluate its association with the development of PE among antenatal women.

MATERIALS AND METHODS

A prospective analytical cohort study was conducted in the Department of Obstetrics and Gynaecology (O&G), VIMSAR Burla, Odisha, India, from February 2024 to February 2025. Ethical approval for the study was obtained from the Institutional Ethics Committee, VIMSAR Burla (IEC. No. 1/28.4.10).

Inclusion criteria: Pregnant women attending the antenatal clinic of the O&G department before 20 weeks of gestation, normotensive at first antenatal visit (BP <140/90 mmHg), willing to provide consent for the study and comply with follow-up schedule were included in the study.

Exclusion criteria: Patients with a history of hypertension, diabetes mellitus, chronic kidney disease, immunological disorders, or any systemic illness likely to affect calcium metabolism were excluded.

Sample size: A total of 272 antenatal women attending the antenatal clinic at ≤20 weeks of gestation were assessed for eligibility based on its criteria. Of these, 13 patients had pre-existing hypertension, diabetes and other systemic illnesses, while 8 patients did not give consent. Consequently, 251 pregnant women were enrolled using consecutive non random sampling.

All participants were normotensive at recruitment and were followed longitudinally until delivery. During follow-up, 6 patients were lost to follow-up in the subsequent visits and they were excluded from the final analysis. Hence, a total number of 245 participants were considered for the final analysis of the study.

Study Procedure

A pre-designed questionnaire was used to collect data from each study participants. Baseline data including age, Socio-economic Status (SES), parity were recorded. SES was classified according to updated BG Prasad Socio-Economic Status (SES) scale [10]. General, systemic and obstetric examinations were performed at enrollment and during follow-up, with special emphasis on blood pressure, oedema and weight. Routine laboratory investigations were conducted to exclude other medical conditions. A random midstream urine sample was collected for estimation of urinary calcium and creatinine, and the CCR was calculated. Subsequent

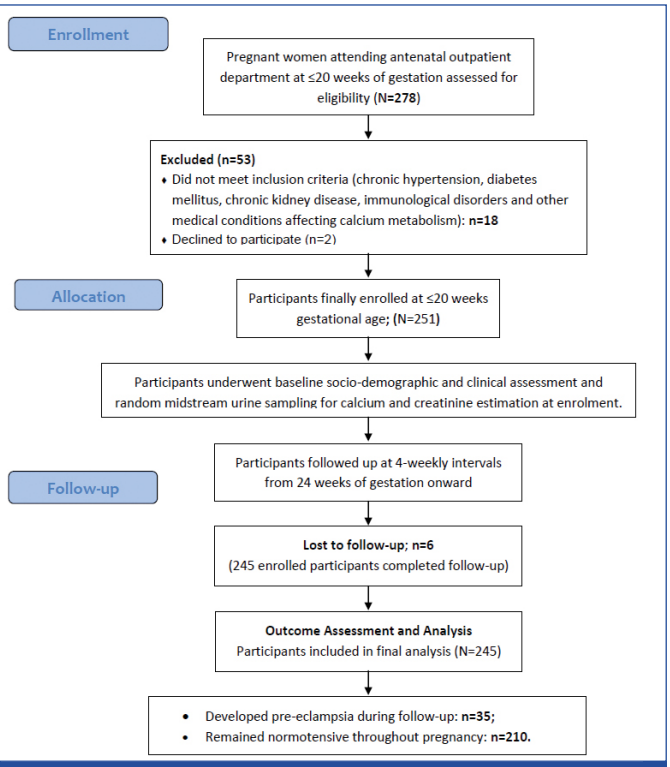
urine samples were collected at 4-weekly intervals from 24 weeks of gestation onward. Participants were followed-up clinically at regular antenatal visits as per the schedule. Participants who remained normotensive throughout pregnancy were included in the control (Non PE) group, while those who developed PE were included as the study (PE) group. PE was diagnosed according to the ACOG criteria [11,12].

Laboratory investigations: At the first antenatal visit, all enrolled participants underwent routine laboratory investigations, including ABO and Rh blood grouping, haemoglobin estimation, fasting blood glucose, Venereal Disease Research Laboratory (VDRL) sickling test, and complete urine examination for protein, sugar, pus cells, and epithelial cells. Quantitative estimation of urinary calcium and creatinine was performed using a single random voided urine sample at the initial visit. This investigation was repeated at each subsequent antenatal visit, scheduled at four-week intervals until 40 weeks of gestation or delivery, whichever occurred earlier. Participants who developed PE during follow-up underwent additional investigations, including liver function tests, renal function tests, serum creatinine estimation, and complete haemogram.

Urinary Calcium-Creatinine Ratio (CCR) Estimation: Random midstream urine samples were collected from participants and sent to the laboratory for analysis of urinary calcium and creatinine concentrations. Urinary calcium estimation was performed using the O-Cresolphthalein Complexone (OCPC) method at a wavelength of 575 nm, while urinary creatinine was measured using the Jaffe's alkaline picrate method at 512 nm. The urinary CCR was calculated for further analysis.

STATISTICAL ANALYSIS

Data were entered into Microsoft excel and analysed using appropriate statistical tests by IBM Statistical Package for Social Sciences (SPSS) software version 26.0. Categorical variables were expressed as frequencies and percentages. Associations between categorical variables were assessed using the Chi-square test. Continuous variables were expressed as Mean±Standard Deviation (SD). Comparison between mean urinary CCR between the PE and non PE groups at different gestational ages was done using an Independent t-test. A p-value<0.05 was considered statistically significant. Diagnostic accuracy of declining CCR trends was assessed by calculating sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) and Receiver Operating Characteristics (ROC) curve.



[Table/Fig-1]: Flow diagram of study participants.

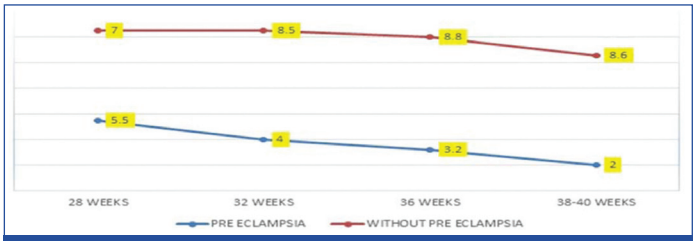
RESULTS

The overall prevalence of PE in the present study was 35 (14.28%). Prevalence of PE among age groups 15-19, 20-24, 25-29 and 30 years were 14.2%, 48.5%, 20%, 17.1%, respectively are depicted in [Table/Fig-2]. PE most frequently detected in primigravida (62.8%) followed by those with gravida 2 (20%) and multigravida with three or more (17.1%). Majority of cases developed PE were belong to low SES (i.e., 64.28%). Prevalence of PE among middle and high SES group were 28.57% and 7.14%, respectively.

Variables	Pre-eclampsia (PE) (n=35)	Normotensives (n=210)	Total (N=245)	p-value
Age (in years)				
15-19	5 (14.3)	28 (13.3)	33 (13.5)	0.58*
20-24	17 (48.6)	84 (40)	101 (41.2)	
25-29	7 (20)	62 (29.5)	69 (28.2)	
≥30	6 (17.1)	36 (17.1)	42 (17.1)	
Parity				
Primigravida	22 (62.9)	118 (56.2)	140 (57.1)	0.70*
Gravida- 2	7 (20.0)	56 (26.7)	63 (25.7)	
Gravida ≥3	6 (17.1)	36 (17.1)	42 (17.1)	
Socio-Economic Status (SES) (BG Prasad Scale)**				
Class-I (Upper)	2 (5.7)	16 (7.6)	18 (7.3)	0.40*
Class-II (Upper middle)	4 (11.4)	38 (18.1)	42 (17.1)	
Class-III (Middle)	7 (20)	57 (27.1)	64 (26.1)	
Class-IV (Lower middle)	11 (31.4)	60 (28.6)	71 (29)	
Class-V (Lower)	11 (31.4)	39 (18.6)	50 (20.4)	

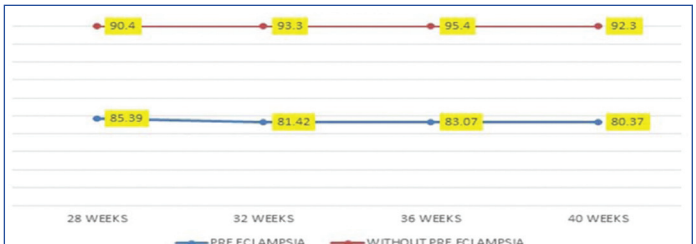
[Table/Fig-2]: Baseline characteristics of the study participants.
*Chi-square test; p-value<0.05 was considered as significant; **SES was classified according to updated BG Prasad SES scale

The mean urinary calcium excretion was 5.5 mg/dL, 4.0 mg/dL, 3.2 mg/dL, and 2.0 mg/dL at 28 weeks, 32 weeks, 36 weeks, and 38 - 40 weeks GA respectively in PE group and 7.0 mg/dL, 8.5 mg/dL, 8.8 mg/dL and 8.6 mg/dL at 28 weeks, 32 weeks, 36 weeks and 38-40 weeks, respectively in patients without PE [Table/Fig-3].



[Table/Fig-3]: Mean urinary calcium excretion (mg/dL) at different gestation age.

The mean creatinine excretion at 28 weeks, 32 weeks, 36 weeks and 38-40 weeks were 85.39 mg/dL, 81.42 mg/dL, 83.07 mg/dL and 80.37 mg/dL, respectively in PE patients and 90.4 mg/dL, 93.3 mg/dL, 95.4 mg/dL and 92.3 mg/dL, respectively in normotensive patients [Table/Fig-4].



[Table/Fig-4]: Mean creatinine excretion (mg/dL) at different gestational age.

A statistically significant decline of UCCR in the PE group was observed as compared to non PE group at different gestational ages [Table/Fig-5].

Sr No.	Gestational age (in weeks)	PE Group (n=35) (Mean±SD)	Non PE Group; (n=210) (Mean±SD)	t-value	p-value
1	28	0.064±0.018	0.070±0.020	1.80	0.079
2	32	0.053±0.015	0.089±0.027	11.44	<0.001*
3	36	0.036±0.010	0.085±0.025	20.29	<0.001*
4	38-40	0.018±0.006	0.090±0.028	32.99	<0.001*

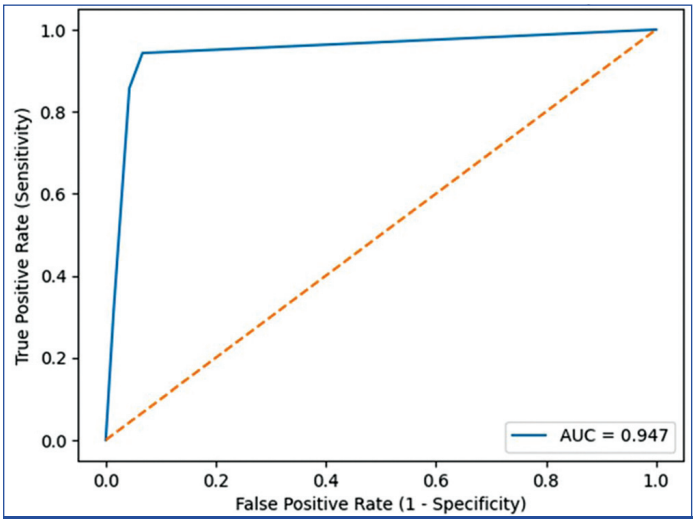
[Table/Fig-5]: Comparative analysis of mean urinary Calcium/Creatinine Ratio (CCR) at different gestational periods between cases (PE) and control (Non PE) group.
*Unpaired t-test; p-value<0.001 was considered as significant

Among 35 women, who developed PE, 30/35 (85.7%) demonstrated a decreasing trend of UCCR, while 5 (2.04%) showed an increasing or near static trend. Of the 210 normotensive women, 201 (82.0%) exhibited an increasing or nearly static trend, and only 9 (3.6%) showed a decreasing trend. A decreasing trend of UCCR predicted PE with a sensitivity of 85.7% and specificity of 95.7%, the PPV and NPVs were 77.2% and 97.5%, respectively [Table/Fig-6].

Trend of UCCR	Number of cases with PE n (%)	Number of cases without PE n (%)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Decreasing	30 (85.7 %) (TP)	9 (3.6%) (FP)	85.7%	95.7%	77.2%	97.5%	19.9	0.15
Increasing /static	5 (2.04%) (FN)	201 (82.0%) (TN)						

[Table/Fig-6]: Trend of UCCR and its association with development of PE.

The ROC analysis demonstrated excellent diagnostic accuracy of CCR for prediction of PE, with an AUC of 0.947. Youden index was calculated as 0.81 showing excellent diagnostic accuracy and cut-off value of CCR ≤0.05 was found, providing the best balance between sensitivity and specificity [Table/Fig-7].



[Table/Fig-7]: ROC curve for urinary CCR in prediction of PE.

DISCUSSION

In the present cohort of 245 antenatal women followed from early pregnancy until delivery, 14.3% developed PE, which is comparable to the prevalence reported in similar Indian hospital-based studies like Mou AD et al., where they found prevalence of PE was 14.28%, whereas studies conducted by Khan B et al., Shandilya V et al., noted the prevalence of PE to be 3% and 6.2% respectively [13-15]. This may be due to regional variation due to factors like SES, nutritional status, age at attaining pregnancy, and haemoglobinopathies.

In the present study, the majority of the PE cases (68.5%), belonged to the age group of 20-29 years, whereas 51.6% of the cases were reported from this age group in the study conducted by Shandilya V et al., [15]. Proportionately higher i.e., 79% of the cases were from age group of 19-25 years in a study conducted by Dasari A et al., in western Bihar [16]. In the present study, PE was observed in higher numbers in primigravida i.e., 62.9% versus 37.1% in multigravida; however, this was not statistically significant. Similar findings were observed in the study by Dasari A et al., i.e., 63% and 36.6% of the cases were associated with primigravida and multigravida, respectively [16].

The majority of the cases (i.e., 82.8%) were from the lower to middle SES group. Similar observations (i.e., 6%) from high SES and the rest patients found to have low to average SES were reported in a study by Bej P et al., [17].

Analysis of mean calcium excretion at different gestational ages, the trend was found to be decreasing in the study group, whereas a static trend was noticed in normotensive patients. In a Nigerian study, mean calcium excretion was found to be lower compared to normotensive patients, although they did not mention the trend of urinary calcium level over the period of gestation [18]. In a systematic review [19], urinary calcium excretion was found to decrease with increasing severity of pregnancy-induced hypertension, which could explain the findings in the current study. On the other hand, mean creatinine excretion in PE patients was also found to be less in comparison to normotensive patients, which might be due to reduced GFR because of renal artery vasospasm.

In the current study, the value of the CCR remained unchanged in normotensive pregnant women it showed a declining trend in the PE group. Declining UCCR trends demonstrated a sensitivity of 85.7% and specificity of 95.7%. Similar findings were reported in a prospective study conducted by Hagras AM et al., where the urinary CCR ≤0.04 had 79.3% sensitivity, 96.3% specificity, 91.5% PPV, 90.3% NPV, and 90.7% overall accuracy in predicting PE [20]. On the other hand, a study conducted by Solanki G et al., revealed that CCR at ≤0.04 had a sensitivity of 71.43%, specificity of 98.75%, and the PPV of 83.33% and NPV of 97.53% [6].

Compared to other biochemical markers proposed for the prediction of PE, UCCR estimation offers notable advantages. It is non invasive, inexpensive, technically simple, and feasible in routine antenatal settings, especially in resource-limited sites.

Limitation(s)

Being a single-centre hospital-based study, the findings may have limited generalisability. Additionally, dietary calcium intake and supplementation, which may influence urinary calcium excretion, were not quantitatively assessed. Larger multicentric studies with adjustment for dietary and biochemical confounders are warranted to further validate the predictive utility of UCCR trends.

CONCLUSION(S)

A progressive decline in urinary CCR during pregnancy is significantly associated with the development of PE. These findings suggest that serial assessment of UCCR may serve as a simple, cost-effective screening tool for early identification of pregnant women at risk of developing PE.

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