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Role of urinary calcium-creatinine ratio in predicting pregnancy-induced hypertension: A prospective observational study

Dr. Virendra Yadav[1], Dr. Nitika Banwal[1*], Dr. Sunil Baroopal[2]
[1] Senior Resident, Department of Obstetrics & Gynecology, Government Medical College, Sirohi, Rajasthan, India
[2] Assistant Professor, Department of General Medicine, Government Medical College, Sirohi, Rajasthan, India
Corresponding Author: Dr. Nitika Banwal
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Abstract

Background: Hypertensive disorders of pregnancy are important causes of maternal and perinatal morbidity and mortality. Early identification of women at risk of pregnancy-induced hypertension (PIH) may facilitate closer surveillance and timely intervention. Reduced urinary calcium excretion and a low urinary calcium-creatinine ratio (UCa/Cr) have been proposed as potential early markers of preeclampsia.

Aim: To evaluate the urinary calcium-creatinine ratio in a spot urine sample obtained before 20 weeks of gestation and assess its utility in predicting pregnancy-induced hypertension.

Methods: This prospective observational study was conducted in the Department of Obstetrics and Gynecology, Rajkiya Mahila Chikitsalaya, JLN Medical College, Ajmer, from June 2023 to May 2024. A total of 270 normotensive pregnant women with singleton pregnancies and gestational age <20 weeks were enrolled. Women with hypertension, proteinuria, previous PIH, chronic hypertension, multiple pregnancy, diabetes mellitus, renal, vascular or immunological disease were excluded. A spot urine sample was analyzed for calcium and creatinine, and the urinary calcium-creatinine ratio was calculated. Participants were followed throughout pregnancy for development of PIH.

Results: Of 270 women, 60 (22.22%) developed PIH and 210 (77.78%) remained normotensive. The most common age group was 26–30 years in both groups. Age, parity, socioeconomic status, gestational age at enrollment and family history of hypertension were not significantly associated with PIH. Cesarean delivery was more frequent among women with PIH (35.0% vs. 20.95%; p=0.024). BMI was significantly associated with PIH (p<0.0001), with overweight women constituting 55.0% of the PIH group. Mean urinary calcium-creatinine ratio was significantly lower among women who developed PIH (0.04±0.02) than among normotensive women (0.18±0.06; p<0.0001). A UCa/Cr ≤0.04 was present in 91.67% of PIH women compared with 1.90% of normotensive women (p<0.0001). The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 91.67%, 98.10%, 93.22%, 97.63% and 96.67%, respectively.

Conclusion: A low urinary calcium-creatinine ratio, particularly a value ≤0.04, was strongly associated with subsequent pregnancy-induced hypertension. Spot urinary UCa/Cr is a simple, non-invasive and inexpensive biomarker that may have potential utility in early risk stratification of pregnant women.

Keywords: Urinary calcium creatinine ratio, pregnancyinduced hypertension, preeclampsia, hypocalciuria, pregnancy, screeng

Introduction

Hypertensive disorders of pregnancy (HDP) are among the major causes of maternal and perinatal morbidity and mortality. They complicate approximately 5–10% of pregnancies and include gestational hypertension, preeclampsia, eclampsia, chronic hypertension and preeclampsia superimposed on chronic hypertension. [1, 2, 3, 4, 5, 6] Preeclampsia is a multisystem disorder characterized by new-onset hypertension after 20 weeks of gestation with proteinuria and/or evidence of maternal organ dysfunction. The disease is associated with placental dysfunction, endothelial injury and multisystem involvement [7, 8, 9, 10].

Despite improvements in antenatal surveillance and management, early identification of women who are likely to develop hypertensive disorders remains challenging. Established risk factors include obesity, nulliparity, previous hypertensive disorders of pregnancy, chronic hypertension, diabetes, renal disease and other maternal comorbidities [11, 12, 13, 14, 15]. therefore, identification of a simple biochemical marker that could be obtained during routine antenatal care would be clinically valuable.

Hypocalciuria has been described in women with preeclampsia. Taufield *et al*. demonstrated reduced urinary calcium excretion in preeclampsia and suggested altered renal calcium handling as a possible component of the disease process [16]. The urinary calcium-creatinine ratio (UCa/Cr) provides a convenient assessment of urinary calcium excretion from a spot urine sample and avoids the practical difficulties associated with 24-hour urine collection [17, 18].

Several studies have evaluated UCa/Cr as a predictor of preeclampsia. Ozcan *et al*. reported significantly lower UCa/Cr among women who developed preeclampsia and identified a cutoff of 0.066 with 75% sensitivity and 86%

specificity [19]. Saudan *et al*. also found that a low UCa/Cr preceded the development of preeclampsia, although the diagnostic performance varied according to the cutoff used [20]. Subsequent studies have reported promising diagnostic performance for a cutoff around 0.04 [21, 22, 23, 24]. However, variations in study population, gestational age, sampling methods and diagnostic thresholds have resulted in inconsistent findings.

The present study was undertaken to evaluate the urinary calcium-creatinine ratio in low-risk pregnant women before 20 weeks of gestation and determine its association with subsequent development of pregnancy-induced hypertension.

Materials and Methods

Study design and setting

This prospective observational study was conducted in the Department of Obstetrics and Gynecology, Rajkiya Mahila Chikitsalaya, Jawaharlal Nehru Medical College, Ajmer, Rajasthan, from June 2023 to May 2024. The study enrolled 270 antenatal women with gestational age <20 weeks.

Participants

Women of any age and parity with singleton pregnancy, gestational age <20 weeks, normotension and absence of proteinuria were eligible for inclusion. Women were excluded if they had blood pressure ≥140/90 mmHg, proteinuria ≥1+ on dipstick examination, history of PIH in a previous pregnancy, chronic hypertension, multiple pregnancy, diabetes mellitus complicating pregnancy, renal disease, vascular disease or immunological disease.

Data collection

Baseline demographic and obstetric characteristics including age, parity, socioeconomic status, gestational age, BMI and family history of hypertension were recorded. Participants underwent routine antenatal assessment and were followed during pregnancy for the development of pregnancy-induced hypertension. Pregnancy and delivery outcomes were subsequently documented.

Urinary calcium-creatinine ratio

A spot urine sample, preferably a first-morning midstream sample, was collected from each participant. Urinary calcium and creatinine concentrations were estimated using standard biochemical methods. The urinary calcium-creatinine ratio was calculated from the urinary calcium and creatinine concentrations. A UCa/Cr value ≤0.04 was considered indicative of increased risk based on previously published studies [21, 22, 23, 24].

Outcome definition

The primary outcome was development of pregnancy-induced hypertension during follow-up. Participants who remained normotensive throughout pregnancy constituted the normotensive group, while those who developed PIH constituted the PIH group.

Statistical analysis

Data were compiled in Microsoft Excel and analyzed using SPSS. Continuous variables were expressed as mean±standard deviation and categorical variables as frequencies and percentages. Student's t-test or Mann-Whitney U test was used for comparison of continuous variables, while the Chi-square test was used for categorical variables. Diagnostic performance of UCa/Cr was assessed using sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristic

A total of 270 antenatal women were enrolled and followed throughout pregnancy. Sixty women (22.22%) developed pregnancy-induced hypertension, whereas 210 (77.78%) remained normotensive.

The majority of participants in both groups belonged to the 26–30-year age group. The association between age and development of PIH was not statistically significant (p=0.485). Nulliparity was more common in both groups, but parity was not significantly associated with PIH (p=0.119). Socioeconomic status also showed no significant association with PIH (p=0.369). Mean gestational age at enrollment was comparable between the groups (14.2±3.1 weeks vs. 14.5±3.0 weeks; p=0.524). Family history of hypertension was also not significantly associated with PIH (p=0.432).

BMI category

BMI demonstrated a significant association with PIH (p<0.0001). The PIH group contained a substantially greater proportion of overweight women, with 33 (55.0%) women classified as overweight compared with 49 (23.33%) in the normotensive group.

Mode of delivery

Normal vaginal delivery was the predominant mode of delivery in both groups. However, cesarean delivery was more frequent among women who developed PIH: 21 (35.0%) compared with 44 (20.95%) among normotensive women. This difference was statistically significant (p=0.024).

Urinary biochemical parameters

Urinary calcium concentration was markedly lower in the PIH group than in the normotensive group (72.73±34.02 vs. 195.24±42.38 mg/dL; p<0.0001). Urinary creatinine was higher in the PIH group (1648.37±27.43 vs. 1140.08±226.76 mg/dL; p<0.0001). Most importantly, the mean UCa/Cr ratio was substantially lower among women who developed PIH (0.04±0.02) compared with normotensive women (0.18±0.06; p<0.0001).

Association of urinary calcium-creatinine ratio cutoff with PIH

A UCa/Cr ≤0.04 was observed in 55 (91.67%) women who developed PIH compared with only 4 (1.90%) normotensive

women. Conversely, 206 (98.10%) normotensive women had a UCa/Cr >0.04 compared with only 5 (8.33%) women in the PIH group. The difference was highly statistically significant (p<0.0001).

Diagnostic performance of UCa/Cr ≤0.04 for PIH

Using ≤0.04 as the cutoff, UCa/Cr demonstrated sensitivity of 91.67% and specificity of 98.10%. The positive predictive value was 93.22%, negative predictive value was 97.63%, and overall diagnostic accuracy was 96.67%.

Discussion

Hypertensive disorders of pregnancy remain an important cause of maternal and perinatal morbidity and mortality. Early prediction of women at risk of PIH is therefore an important component of antenatal care [26, 27, 28, 29]. The present study evaluated the urinary calcium-creatinine ratio obtained from a spot urine sample before 20 weeks of gestation and assessed its association with subsequent development of PIH.

In the present study, 60 of 270 women developed PIH during follow-up. The largest proportion of participants in both groups belonged to the 26–30-year age group, and age was not significantly associated with development of PIH. This finding is comparable with the observations of Saudan *et al*., who reported relatively similar maternal ages across normotensive, gestational hypertensive and preeclamptic groups [20]. Sheela *et al*. similarly reported that most women in their study were 21–30 years of age [30].

Nulliparity was common in both groups, although the association between parity and PIH did not reach statistical significance in the present study. Saudan *et al*. reported a higher proportion of primiparous women among women with hypertensive disorders, particularly preeclampsia [20]. Differences in population characteristics and sample distribution may account for the lack of statistical significance in our cohort.

BMI demonstrated a strong association with PIH in the present study. More than half of the women in the PIH group were overweight, whereas normal BMI predominated among normotensive participants. The association was statistically significant (p<0.0001). This finding is biologically plausible because increased maternal adiposity is associated with inflammatory, metabolic and vascular abnormalities that may contribute to endothelial dysfunction and hypertensive disease. Previous literature has also demonstrated an association between increased BMI and preeclampsia [31].

The mode of delivery differed significantly between the groups. Cesarean delivery occurred in 35% of women with PIH compared with 20.95% of normotensive women. This may reflect the increased obstetric intervention commonly required in pregnancies complicated by hypertensive disorders, although mode of delivery itself should not be interpreted as a predictor of PIH.

The principal finding of the present study was the marked reduction in urinary calcium-creatinine ratio among women who subsequently developed PIH. The mean UCa/Cr was 0.04±0.02 in the PIH group compared with 0.18±0.06 in the normotensive group (p<0.0001). Hypocalciuria has previously been described in preeclampsia, with altered renal calcium handling proposed as one of the mechanisms contributing to reduced urinary calcium excretion [16].

Ozcan *et al*. demonstrated significantly lower urinary calcium-creatinine ratios among women who developed preeclampsia and reported a cutoff of 0.066 with 75% sensitivity and 86% specificity [19]. Saudan *et al*. found that women with gestational hypertension who subsequently developed preeclampsia had lower urinary calcium-creatinine ratios than women who remained gestational hypertensive; however, the sensitivity and specificity at their selected cutoff were more modest [20].

The present findings are particularly comparable with studies using a cutoff of 0.04. Munge *et al*. reported a sensitivity of 63.63% and specificity of 94.87% using UCa/Cr ≤0.04 [21]. Solanki *et al*. reported sensitivity of 71.43%, specificity of 98.75%, PPV of 83.33% and NPV of 97.53% at the same cutoff.[22] Tejaswi *et al*. also found significantly lower UCa/Cr among women who developed preeclampsia and reported useful predictive characteristics for a cutoff of 0.04 [23]. Hagras *et al*. reported sensitivity of 79.3%, specificity of 96.3% and overall accuracy of 90.7% using the same cutoff [24].

In the present study, the diagnostic performance was even higher, with sensitivity of 91.67%, specificity of 98.10% and overall accuracy of 96.67%. The high negative predictive value of 97.63% is particularly relevant for a screening test because a UCa/Cr >0.04 was associated with a low probability of PIH in this study population.

However, variation in cutoff values and diagnostic performance across studies indicates that UCa/Cr should not be considered an independent diagnostic test for preeclampsia. Ibrahimi *et al*. reported that although urinary calcium-creatinine ratio had predictive value, proteinuria and uric acid performed better in their study [31]. Jagu *et al*. also found that the optimal cutoff in their cohort was higher than 0.04, emphasizing the influence of population characteristics and disease prevalence on predictive values [32].

The potential usefulness of UCa/Cr lies in its simplicity. A spot urine sample is inexpensive, non-invasive and easy to obtain during routine antenatal visits. This may be particularly valuable in resource-limited settings where sophisticated biochemical or angiogenic marker-based testing is not routinely available.

The present study has certain limitations. It was conducted at a single tertiary-care center, which may limit generalizability. The study population was restricted to women with gestational age <20 weeks and without major medical comorbidities. Dietary calcium intake, hydration status and other factors that can influence urinary calcium excretion were not extensively evaluated. Furthermore, the study assessed PIH as the principal outcome and did not provide detailed subgroup analysis according to severity of preeclampsia. Larger multicentric prospective studies are required to validate the optimal UCa/Cr cutoff in different populations.

Table 1: Baseline demographic and obstetric characteristics

Variable	Normotensive (n=210)	PIH (n=60)	p-value
Age group			
20–25 years	57	16	0.485
26–30 years	109	27	
31–35 years	31	10	
36–40 years	13	7	
Parity			
Nulliparous	173	44	0.119
Multiparous	37	16	
Socioeconomic status			
Lower socioeconomic class	123	29	0.369
Middle	64	23	
Upper	23	8	
Gestational age (weeks)	14.2±3.1	14.5±3.0	0.524
Family History			
Present	33	12	0.432
Absent	177	48	

Table 2: Distribution according to body mass index

BMI category	Normotensive (n=210)	PIH (n=60)	p-value
Underweight	33 (15.71%)	14 (23.33%)	<0.0001
Normal	113 (53.81%)	7 (11.67%)	
Overweight	49 (23.33%)	33 (55.00%)	
Obesity	15 (7.14%)	6 (10.00%)	

Table 3: Mode of delivery according to pregnancy hypertension status

Mode of delivery	Normotensive (n=210)	PIH (n=60)	p-value
Vaginal delivery	166 (79.05%)	39 (65.00%)	0.024
LSCS	44 (20.95%)	21 (35.00%)	

Table 4: Comparison of urinary biochemical parameters

Parameter	Normotensive (n=210)	PIH (n=60)	p-value
Urinary calcium (mg/dL)	195.24±42.38	72.73±34.02	<0.0001
Urinary creatinine (mg/dL)	1140.08±226.76	1648.37±27.43	<0.0001
Urinary calcium-creatinine ratio	0.18±0.06	0.04±0.02	<0.0001

Table 5: Association of urinary calcium-creatinine ratio cutoff with PIH

UCa/Cr	Normotensive (n=210)	PIH (n=60)	p-value
≤0.04	4 (1.90%)	55 (91.67%)	<0.0001
>0.04	206 (98.10%)	5 (8.33%)	

Table 6: Diagnostic performance of UCa/Cr ≤0.04 for PIH

Diagnostic parameter	Value
Sensitivity	91.67%
Specificity	98.10%
Positive predictive value	93.22%
Negative predictive value	97.63%
Diagnostic accuracy	96.67%

Conclusion

The urinary calcium-creatinine ratio was significantly lower among pregnant women who developed pregnancy-induced hypertension. A spot urine UCa/Cr cutoff of ≤0.04 demonstrated high sensitivity, specificity, predictive values and overall diagnostic accuracy in the present study.

UCa/Cr is a simple, inexpensive and non-invasive biochemical parameter that may be useful for early risk stratification of pregnant women. It may serve as an adjunct to conventional antenatal surveillance rather than a replacement for blood pressure measurement, proteinuria assessment and clinical evaluation.

Further multicentric studies with standardized gestational-age-specific cutoffs and adjustment for dietary and renal factors are recommended before routine implementation of UCa/Cr as a standalone screening test.

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