

## **An Institutional Prospective Study of Clinical Correlation of Urinary Calcium Level and Development of Preeclampsia**

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**Type of Publication:** Original research Article

**Conflicts of Interest:** Nil

### **Abstract**

**Aims and objectives:** To assess efficacy of calcinuria as a selection criterion for primary prevention of pre-eclampsia. To develop calcinuria as a diagnostic test for prediction of Pre-eclampsia.

**Methods:** A prospective observational study was conducted over a period of 18 months on 100 women with 24-hour urinary calcium level at 16-20 weeks and 20-24 weeks of gestation

**Results:** 24-hour urinary calcium level decreases progressively from second trimester in women who developed pre-eclampsia, and this was statistically significant.

**Conclusion:** 24-hour urinary calcium level can be used as a diagnostic test for prediction of Pre-eclampsia. This will help in early diagnosis of the cases and enabling early treatment, which can improve the prognosis of both mothers and the newborn.

**Keywords:** PE, GHT, WHO.

### **Introduction**

Hypertension during pregnancy is a major health problem. Hypertensive disorder of pregnancy (Gestational Hypertension (GHT), Pre-eclampsia (PE) & Eclampsia (E) occurs in approximately 10-15% of all pregnancies [1]. Pre-eclampsia is a progressive, multisystemic and multifactorial pregnancy specific disorder. According to WHO, it is the leading cause of

maternal and fetal morbidity and mortality. All obstetricians dread preeclampsia (PE) for its potential maternal (12.6% of maternal deaths) and fetal complications.

Favorable maternal and perinatal outcomes for women with preeclampsia/ eclampsia depend on how soon the condition is identified and how quickly the woman has access to treatment. Urinary calcium levels is one such predictor used for early identification of females at risk of development of subsequent pre-eclampsia. Calcium homeostasis is altered in women with preeclampsia. In its clinical phase, preeclampsia is a hypocalciuric state and it has been reported that hypocalciuria predicts preeclampsia [2,3].

Urinary calcium is a very easily measurable marker and if proves to have a good diagnostic accuracy to predict pre-eclampsia, can be a boon for a resource limited country like ours. In present study, we thus aimed to assess the efficacy of calciuria as a criterion for primary prevention of pre- eclampsia and to test the validity of calciuria as a diagnostic test for prediction of Pre-eclampsia.

#### **Material And Methods**

**Study Area:** Department of Obstetrics and Gynecology, BJGMC Pune in collaboration with Biochemistry Department of BJGMC Pune.

**Study Population:** Pregnant females with singleton pregnancy attending ANC OPD of our hospital.

**Study Design:** A Prospective, observational Study

**Sample Size :**100

**Study Duration:** 18 months

**Inclusion Criteria:** All pregnant females with singleton pregnancy attending ANC OPD at tertiary care hospital between 16-28 weeks.

#### **Exclusion Criteria**

1. Patient who is not willing to give consent
2. Diagnosed cases of chronic hypertension
3. Multiple pregnancy
4. Gestational trophoblastic disease
5. Chronic renal disease
6. Autoimmune disorders
7. Known case of thyroid disorders
8. Psychiatric patients on lithium
9. Patients taking aspirin, steroids
10. Patients on Chronic diuretics

#### **Methodology**

- Study was commenced after approval from Institutional ethical committee.
- Informed written consent was taken after explaining the background of study and benefits and voluntary nature of participation.
- A thorough general physical examination and systemic examination was done followed by per speculum and per vaginal examination.
- Urine samples were sent for 24-hour urinary calcium-
  - 1<sup>st</sup> sample at 16 to 20 weeks of gestation
  - 2<sup>nd</sup> sample at 20 to 24 weeks of gestation
- All the cases were followed up till delivery for obstetric and neonatal outcome.

#### **Operational Definitions**

A pregnant woman having an average reading of systolic blood pressure (SBP) of more than/equal to 140 mmHg and/or diastolic blood pressure (DBP) of more than/equal to 90 mmHg was considered as hypertensive (DBP  $\geq$ 90 mmHg and/or SBP  $\geq$ 140 mmHg). Hypertension was classified as follows [19]:

1. Preeclampsia – eclampsia
2. Gestational hypertension

- 3. Chronic hypertension
- 4. Preeclampsia superimposed on chronic hypertension

**Statistical Analysis**

All the data was noted down in a pre-designed study proforma. Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-Square test. Quantitative data was represented using Mean ± SD. Analysis of Quantitative data between the two groups was done using unpaired t-test if data passed ‘Normality test’ and by Mann-Whitney Test if data failed ‘Normality test’. A p-value < 0.05 was taken as level of significance. Results were graphically represented where deemed necessary. SPSS Version 26.0 was used for most analysis and Microsoft Excel 2021 for graphical representation.

**Results**

Table 1. Distribution of study groups as per development of pre-eclampsia

Development of Pre-eclampsia	N	%
No	85	85.0%
Yes	15	15.0%
Total	100	100.0%

Incidence of pre-eclampsia was seen in 15% among study cases in present study.

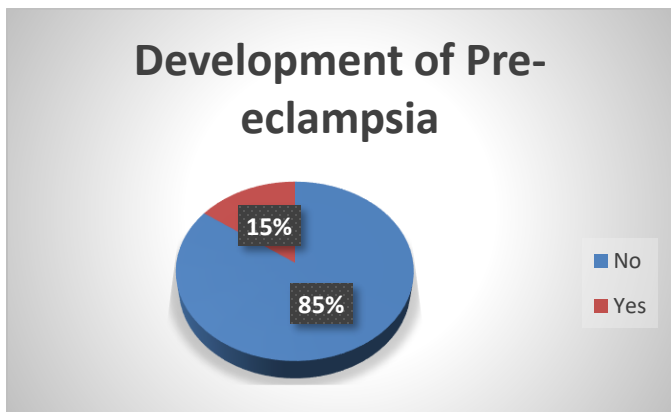


Table 2: Mean urinary calcium levels comparison among cases with and without pre-eclampsia

Urinary Calcium levels (mg/24 hrs)	PE	N	Mean	SD	p-value
16-20 weeks	No	85	174.01	26.61	<0.01
	Yes	15	107.04	18.68	
20-24 weeks	No	85	173.65	26.48	<0.01
	Yes	15	95.83	12.45	

Mean levels of urinary calcium was significantly lower in cases developing pre-eclampsia as compared to cases without pre-eclampsia, both at 16-20 weeks (107.04 vs 174.01; p<0.01) and at 20 to 24 weeks (95.83 vs 173.65; p<0.01). The urinary calcium levels decreased significantly with increasing duration of gestation (p<0.01).

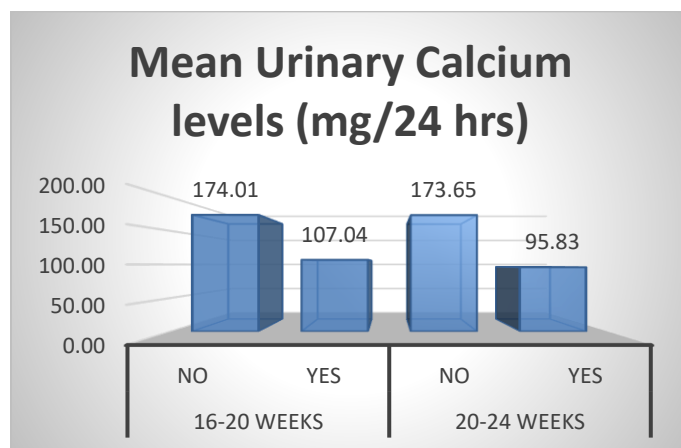
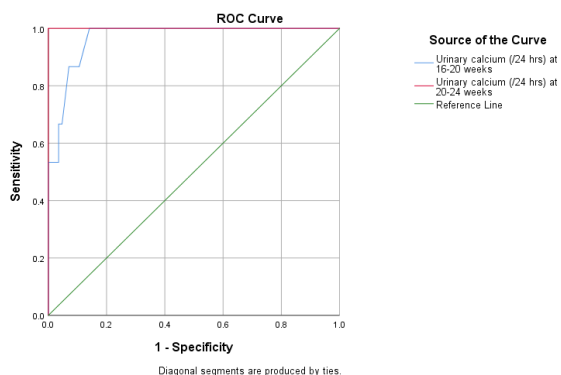


Table 3: ROC Curve analysis for efficacy of urinary calcium levels for prediction of pre-eclampsia

Area Under the Curve					
Test Result Variable(s)	Area	SE	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Urinary Ca at 16-20 weeks	0.967	0.016	<0.01	0.936	0.998
Urinary Ca at 20-24 weeks	0.989	.0012	<0.01	0.976	0.99

Ideal Cut-off	Sensitivity	Specificity	Accuracy
< 140 mg/ 24 hrs at 16-20 weeks	100.0%	85.9%	93.0%
<120 mg/ 24 hrs at 20-24 weeks	100.0%	96.5%	98.3%

On ROC curve analysis, both urinary calcium levels taken at 16 to 20 and 20 to 24 weeks were observed to be significant predictors of development of pre-eclampsia in pregnancy. At 16 to 20 weeks, urinary calcium levels < 140 mg/ 24 hours had a sensitivity and specificity of 100% and 85.9% with overall accuracy of 93%. At 20 to 24 weeks, urinary calcium levels < 120 mg/ 24 hours had a sensitivity and specificity of 100% and 96.5% with overall accuracy of 98.3%.



## Discussion

All obstetricians dread preeclampsia for its potential maternal (12.6% of maternal deaths) and fetal complications. Favourable maternal and perinatal outcomes for women with preeclampsia or eclampsia depend on how soon the condition is identified and how quickly the woman has access to treatment. In order to arrest the disease process in the initial stages or to prevent complications especially in women predisposed

to PE, various predictors have been proposed from time to time [4].

Urinary calcium levels is one such predictor used for early identification of females at risk of development of subsequent pre-eclampsia. In present study, we thus aimed to assess the efficacy of calciuria as a criterion for primary prevention of pre- eclampsia and to test the validity of calciuria as a diagnostic test for prediction of Pre-eclampsia.

Study included 100 pregnant females with singleton pregnancy attending ANC OPD at tertiary care hospital between 16-28 weeks. Urine samples were sent for 24 hour urinary calcium: first sample at 16 to 20 weeks of gestation and second sample at 20 to 24 weeks of gestation. All the cases were followed up till delivery to see the development of pre-eclampsia and obstetric and neonatal outcome.

## Incidence of Pre-eclampsia

Preeclampsia occurs in 10-15% of pregnancies and is the second leading cause of direct maternal and fetal deaths [5]. In a meta-analysis of Indian data, Dhinwa M et al. [6] shows the pooled prevalence of hypertensive disorder of pregnancy in India as 11% (95% CI, 5%–17%), which was found significantly higher than the global prevalence. The overall pooled estimate shows high prevalence i.e 1 out of 11 women suffers from pregnancy induced hypertension. Mehta B et al. [7] in a hospital-based study, observed a total of 931 pregnant women. Prevalence of hypertension in pregnancy was found to be 6.9%. Hypertensive disorders of pregnancy were reported to be 7.49%, 15.5%, 5.4%, and 8.96%, respectively, in other various hospital-based studies in India [8-11].

Incidence of pre-eclampsia was observed as 15% in present study. This percentage is relatively higher as

compared to other studies which may be because of the fact that it was a hospital-based study which is a tertiary care center and referral unit for complicated cases.

### **Role of Urinary calcium levels**

In our study Mean levels of urinary calcium was significantly lower in cases developing pre-eclampsia as compared to cases without pre-eclampsia, both at 16-20 weeks (107.04 vs 174.01;  $p < 0.01$ ) and at 20 to 24 weeks (95.83 vs 173.65;  $p < 0.01$ ). On ROC curve analysis, both urinary calcium levels taken at 16 to 20 and 20 to 24 weeks were observed to be significant predictors of development of pre-eclampsia in pregnancy. At 16 to 20 weeks, urinary calcium levels  $< 140$  mg/ 24 hours had a sensitivity and specificity of 100% and 85.9% with overall accuracy of 93%. At 20 to 24 weeks, urinary calcium levels  $< 120$  mg/ 24 hours had a sensitivity and specificity of 100% and 96.5% with overall accuracy of 98.3%.

In a similar study, Gasnier R et al. [12] compared calciuria among groups of normal, hypertensive and preeclamptic pregnant women, and assessed its correlation with the severity of the disease. There were statistically significant differences between the groups when comparing severe preeclampsia with chronic hypertension, and severe preeclampsia with the control group ( $P < 0.0001$ ). The calciuria medians were 81.5mg/ 24h for severe preeclampsia, 118mg/ 24h for mild preeclampsia, 226mg/ 24h for chronic hypertension, and 272mg/ 24h for the control group. In a ROC (receiver operating characteristic) curve analysis, the best cut-off point for preeclampsia diagnosis was 167mg/ 24h, with a sensitivity of 75% and a specificity of 85%. Study concluded that measurement of calciuria can differentiate between severe preeclampsia and chronic hypertension, and hypocalciuria is also a marker for

disease severity. Pal et al. [13] assessed the efficacy of calciuria as a diagnostic test for the prediction of preeclampsia. Preeclamptic women excreted significantly less total urine calcium ( $87.0 \pm 3.59$  mg/24 h) than normotensive women ( $303.68 \pm 17.699$  mg/24 h) ( $p < 0.0001$ ) at 40 weeks of gestation. Urinary calcium decreases progressively from 28 weeks to 40 weeks in the study group when compared to normotensive group. Study concluded that preeclamptic women excrete less calcium than normotensive women. Ramos et al. [14] aimed to determine urinary calcium excretion in pregnant patients with chronic arterial hypertension (CAH) and preeclampsia (PE), and in normotensive patients (N). Forty-four pregnant patients (gestational age, 20-42 weeks; 18 CAH, 17 PE, 9 N) were evaluated for calciuria, proteinuria, plasma uric acid and blood pressure. Patients with PE ( $82 \pm 15.1$  mg/24 h) showed significantly lower calciuria ( $P < 0.05$ ) than the group with CAH ( $147 \pm 24.9$  mg/24 h) and the N group ( $317 \pm 86.0$  mg/24 h) ( $P < 0.05$ , Student t-test). Calciuria was significantly lower in the group with preeclampsia than in the group with chronic arterial hypertension. Authors conclude that calciuria can be a further factor for identifying preeclampsia. Dasgupta et al. [15] have reported the changes in calcium excretion in pre-eclampsia, eclampsia and their role as predictor and concluded that hypocalciuria was a good tool for prediction of HDsP and was independent of renal function.

We also observed that urinary calcium levels decreased significantly with increasing duration of gestation in cases developing pre-eclampsia (107.04 at 16-20 weeks to 95.83 mg/ 24h at 20-24 weeks;  $p < 0.01$ ).

Urinary calcium and calcium creatinine levels in women destined to develop PE progressively diminished till

term is a finding which is also reported by several researchers [2,16,17]. Consistent with this study, another study done by Jafrin et al. [18] revealed significant progressive decrease in serum calcium in subjects with pre-eclampsia compared to normal pregnant women.

Thus, to summarize, our study revealed that, urinary calcium excretion was reduced in patients with pre-eclampsia. A cut-off of < 140 mg/ 24 hrs at 16 to 20 weeks and < 120 mg/ 24 hrs at 20-24 weeks can be used as a diagnostic test for prediction of Pre-eclampsia.

### Conclusion

The study revealed that, urinary calcium excretion was reduced in patients with pre-eclampsia. Lower urinary calcium levels were observed in cases during second trimester, which further decreased with the progression of the pregnancy. A cut-off of < 140 mg/ 24 hrs at 16 to 20 weeks and < 120 mg/ 24 hrs at 20-24 weeks can be used as a diagnostic test for prediction of Pre-eclampsia. This will help in early diagnosis of the cases and enabling early treatment, which can improve the prognosis of both mothers and the newborn.

### Abbreviations

- GHT-Gestational hypertension
- PE-Preeclampsia
- E-Eclampsia
- SD- Standard deviation
- HDP-Hypertensive disorder of pregnancy
- HDsP-Hypertensive disorders of pregnancy

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