

CALCIUM/CREATININE RATIO IN SPOT URINE SAMPLE FOR EARLY DETECTION OF PREECLAMPSIAMittal Shilpa¹, Shaikh M.K.S², Thakur Ratna³, Jain Darshana⁴**HOW TO CITE THIS ARTICLE:**

Mittal Shilpa, Shaikh M.K.S, Thakur Ratna, Jain Darshana. "Calcium/Creatinine ratio in Spot Urine Sample for Early Detection of Preeclampsia". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 04, January 27; Page: 966-971, DOI: 10.14260/jemds/2014/1933

ABSTRACT: OBJECTIVE: The objective of the study is to detect predictive value of Calcium/Creatinine Ratio in spot urine sample in Preeclampsia and to introduce spot urine test in ANC profile. **MATERIALS AND METHODS:** The present study was conducted in the Departments of Biochemistry and Obstetrics & Gynecology, Sri Aurobindo Medical College & P. G. Institute, Indore. The study included total 100 asymptomatic pregnant women at 20-28 weeks of gestation and aged between 21-35 years. **RESULTS:** Eighty seven women remained normotensive and thirteen women developed Preeclampsia. The incidence of Preeclampsia was 13% out of which 11% were mild Preeclamptic and 2% were moderately Preeclamptic. Mean Urinary Calcium concentration was 9.23 ± 3.49 mg/dl in Normotensive women vs. 4.56 ± 1.19 mg/dl in Preeclamptic women. Mean Urinary Calcium was lower in Preeclamptic women. Mean Urinary Calcium/Creatinine Ratio was lower in Preeclamptic women (p -value <0.0001). **CONCLUSION:** This study evaluates that a Spot Urinary Calcium/Creatinine Ratio may be an effective parameter for detecting women at greater risk.

KEYWORDS: Preeclampsia, Urine Calcium, Urine Creatinine, Urinary Calcium/Creatinine Ratio.

INTRODUCTION: Preeclampsia is an idiopathic multisystem disorder causes maternal and fetal morbidity and mortality. Preeclampsia is an unpredictable multi-organ disorder unique to human pregnancy. It is one of the commonest medical disorders diagnosed by obstetrician in clinical practice¹. It is said that Preeclampsia and Eclampsia contribute to death of a woman every 3 minutes world-wide². Majorities of these conditions are preventable. In India, its incidence is 8-10% of pregnancies. The cardinal clinical features of preeclampsia are Hypertension & Proteinuria occurring after 20 weeks of gestation in women who were not previously known to be Hypertensive. Other signs and symptoms may include Headache & Edema. These disorders are also associated with adverse perinatal outcomes such as stillbirth, preterm and small for gestational age babies³⁻⁵.

Maternal calcium loss during pregnancy and lactation is a normal part of fetal and neonatal development. During pregnancy, the woman's body physiologically compensates by increasing intestinal absorption, decreasing renal calcium loss, and reabsorbing some calcium from the maternal skeleton. Renal function changes are seen in symptom free women in whom Preeclampsia will eventually develop. Hypo-calciuria during pregnancy is known as a risk factor for Preeclampsia⁶⁻⁸. Low calcium intake has been hypothesized to cause increase in blood pressure by stimulating the release of parathyroid hormone and/or renin which leads to increased intracellular calcium concentration in vascular smooth muscle cells and causes vasoconstriction⁹. Urine Creatinine is a known marker of renal function. Excretion of Calcium & Creatinine is affected by the factors which influence functions of the kidneys. Normal Urinary Calcium concentration is 100 to 300 mg/24 hours. Normal Urinary Creatinine concentration is 1500 to 3000 mg/24 hours. Although a 24-hour

ORIGINAL ARTICLE

collection is best, Random Urine Calcium measurement can be performed and is expressed in relation to Creatinine. A normal reference interval for the Urinary Calcium/Creatinine Ratio¹⁰ is <0.14.

Ozcan et al (1995) investigated the predictive value of decreasing Calcium/Creatinine Ratio in a spot urine sample and reported that it might be an effective marker for preeclampsia¹¹. So, prediction and early detection are the important measures to prevent the severity of disease and its complications. This can be achieved by regular antenatal check-ups, investigations and early treatment of Preeclampsia.

MATERIAL AND METHODS: The present study was conducted in the Departments of Biochemistry and Obstetrics & Gynecology, Sri Aurobindo Medical College & P. G. Institute, Indore. The Institutional ethical committee has approved this research work. This observational and prospective study included total 100 asymptomatic pregnant women at 20-28 weeks of gestation and aged between 21-35 years.

Inclusion criteria were asymptomatic normotensive pregnant women aged between 21-35 years with 20-28 weeks of gestation with Blood pressure less than and equal to 130/80 mm Hg & no traces of Protein in urine.

Exclusion criteria were women with past history of Preeclampsia/Eclampsia, Diabetes mellitus, Chronic Hypertension, Renal diseases, any other chronic illnesses and multiple pregnancies. Women Under treatment of Anti-epileptic Drugs and Calcium supplements in any form and Family history of Diabetes mellitus or Hypertension.

Blood pressure was measured in semi-recumbent position with tilt in the right arm. Proteinuria was excluded by testing Spot urine sample by Dip-stick method. Pre-test and post-test counseling were given to the subjects. After taking written consent from subjects, Spot urine sample was collected and centrifuged and assessed in the Biochemistry laboratory.

Urine Calcium was estimated by commercially available standard enzymatic kits by Arsenazo III method¹² with VITROS 5, 1 FS (dry chemistry) analyzer. And Urine Creatinine was estimated by commercially available standard enzymatic kits by Creatininase method¹³ with VITROS 5, 1 FS (dry chemistry) analyzer. Calcium/Creatinine Ratio was calculated. All the women were followed-up till the delivery. Women who developed Hypertension (B.P. equal or more than 140/90 mm Hg) with or without edema associated with Proteinuria were labelled Preeclamptic (Group-B subjects). Those who remain normotensive till delivery served as controls (Group-A subjects). The two groups did not differ in respect to age and socio-economic strata.

RESULTS: Out of 100 women, who were followed from 20-28 weeks of gestation till delivery, 13 women (13%) Group-B developed Preeclampsia; whereas 87 women (87%) Group-A remained normotensive. In our study, the incidence of Preeclampsia was 13%; of which 11% subjects were having mild Preeclampsia & 2% moderate Preeclampsia.

The mean Urinary Calcium level was significantly lower in Preeclamptic women, group-B (4.56±1.19 mg/dl) than normotensive women, group-A (9.23±3.49 mg/dl) (p-value<0.0001). Women destined to develop Preeclampsia group-B had significant higher mean Urinary Creatinine levels (98.45±29.72mg/dl) as compared to women who remained normotensive group-A (78.14±25.60 mg/dl) (p-value=0.0104). The mean of Urinary Calcium/Creatinine Ratio was significantly lower in

ORIGINAL ARTICLE

Preeclamptic women group-B ($0.04+0.02\text{mg/dl}$) than normotensive group-A ($0.12+0.05\text{ mg/dl}$) ($p\text{-value}=0.0001$). [Table: 1]

Quantitative or continuous variables were presented as mean+SD and compared using student 't' test. $p\text{-value} < 0.05$ was considered as statistically significant.

DISCUSSION: The present study and its objectives point towards the fact that a single estimation of Urinary Calcium/Creatinine Ratio in spot urine sample and its statistical analysis shows that the mean of Urinary Calcium/Creatinine Ratio was significantly lower in Preeclampsia i.e. Group-B ($0.04+0.02\text{ mg/dl}$) than the normotensive group i.e. Group-A ($0.12+ 0.05\text{ mg/dl}$) ($p\text{-value}=0.0001$).

In the present study, we found that the mean Urinary Calcium levels in spot urine sample of control and preeclamptic groups were $9.23\pm 3.49\text{mg/dL}$ and $4.56\pm 1.19\text{mg/dL}$ respectively. It was lesser in preeclamptic group as compared to the control group. And in a same way; Taufield et al (1987) found a significantly lower mean Urinary Calcium level in women with Preeclampsia than in normotensive women¹⁴. The mean Urinary Calcium levels were reported lesser in preeclamptic women by Kazemi AFN et al (2010)¹⁵.

In the present study, we also found that the mean Urinary Creatinine levels in spot urine samples of control and preeclamptic groups were $78.14\pm 25.60\text{mg/dL}$ and $98.45\pm 29.72\text{mg/dL}$ respectively. It was higher in preeclamptic group as compared to the control group. And in the same way it was also reported higher in preeclamptic women (110.61 ± 11.53) as compared to the control group (109.15 ± 56.42) by Kazemi AFN et al (2010)¹⁵.

In the study of Rodriguez MH et al (1988), 83% pregnant women with low Calcium/Creatinine Ratio developed Preeclampsia¹⁶. In study of Kamra et al (1997) 71.4% pregnant women with low Calcium/Creatinine Ratio developed Preeclampsia¹⁷. In the study of J Kar et al (2002), 64.2% pregnant women with low Calcium/Creatinine Ratio developed Preeclampsia¹⁸. Huikeshoven FJM et al (1990) concluded that the measurement of Urinary Calcium excretion is of value for the study of pregnant women with Preeclampsia, both in terms of 24 hour excretion and in the Urinary Calcium/Creatinine Ratio of a single urine sample¹⁹. Raniolo E et al (1991) determined that the Urinary Calcium/Creatinine Ratio was not significantly different between the groups of normotensive pregnant women (0.52 ± 0.32) and women with Preeclampsia (0.49 ± 0.32). These findings don't correlate; what we have found during our study²⁰.

Readily accessible routine and other Biochemical screening tests for Preeclampsia would ideally reduce the incidence of Maternal & Neonatal complications. Hence there is a need to detect the predictive values of these tests and thereby their feasibility as screening tools to identify women at risk of developing preeclampsia.

This study is an attempt in this direction. An availability of a good screening test would initiate more research in this direction and would ultimately pave the way for implementation of measures for primary prevention. Estimation of Calcium and Creatinine in a spot urine sample is a simple & economic test, easily performed and hence assures patient compliance. It has a good predictive value and high sensitivity. It needs to be adopted as a screening tool for preeclampsia. It can therefore be recommended as a screening test for Preeclampsia and could be offered to all asymptomatic pregnant women between 20-28 weeks of gestation during their routine antenatal checkups.

CONCLUSION: Estimation of Urinary Calcium/Creatinine Ratio in a spot urine sample can be added as an effective and routine marker in ANC profile for predicting Preeclampsia which will reduce Maternal/Perinatal morbidity and mortality; and it also improve Maternal/Perinatal outcome.

REFERENCES:

1. Hypertension in pregnancy ACOG Technical Bulletin no. 219 1996, 1-8.
2. Jenny E. Mayer & Philip N. Baker-Current opinion in Obstet & Gynecol 2002, 14: 119-125.
3. Villar J, Belizan J, Fisher P. Epidemiological observation on the relationship between calcium intake and eclampsia. *Int J Gynaecol Obstet* 1983, 21:271.
4. Habli M, Levine RJ, Qian C, Sibai B. Neonatal outcomes in pregnancies with preeclampsia or gestational hypertension and in normotensive pregnancies that delivered at 35, 36, or 37 weeks of gestation. *Am J Obstet Gynecol* 2007, 197(4):406 e401-407.
5. Ananth CV, Basso O. Impact of pregnancy-induced hypertension on stillbirth and neonatal mortality. *Epidemiology* 2010, 21(1):118-123.
6. Halhali A, Diaz L, Avila E et al. Decreased fractional urinary calcium excretion and serum, 1, 25-dihydroxyvitamin D and IGF-I levels in preeclampsia. *J Steroid Biochem Mol Biol* 2007;103:803-6.
7. Szmidi-Adjide V, Vendittelli F, David S et al. Calciuria and preeclampsia: a case control study. *Eur J Obstet Gynecol Reprod Biol* 2006;125:193-8.
8. Segovia BL, Vega IT, Villarreal EC et al. Hypocalciuria during pregnancy as a risk factor of preeclampsia. *Gynecol Obstet Mex* 2004;72:570-4.
9. Belizan JM, Villar J, Repke J. The relationship between calcium intake and pregnancy-induced hypertension: up-to-date evidence. *Am J Obstet Gynecol* 1988, 158(4):898-902.
10. Foley KF, Boccuzzi L. Urine Calcium. Laboratory Measurement and Clinical Utility. *Lab medicine* 41(11) Nov 2010.
11. Ozcan T, Kaleli B and Ozeren M et al. Urinary calcium to creatinine ratio for predicting preeclampsia; *Am J Perinatol*. 1995 Sep;12(5):349-51.
12. Juha R, William EW, Michael K, Leila R. Bone and Mineral metabolism. In Burtis CA, Ashwood ER, Bruns DE. Editors. *Tietz text book of clinical chemistry and molecular diagnostics*, Philadelphia: W.B Saunders 5th edn. 2012; 1733-1801.
13. Lamb EJ and Price CP. Kidney Function Tests In. Burtis CA, Ashwood ER, Bruns DE. Editors. *Tietz text book of clinical chemistry and molecular diagnostics* 5th edn: Philadelphia: W.B Saunders 2012; 669-707.
14. Taufield P, Ales KL, Resnick LM, Druzin ML, Gestnar JM, Laraugh JH. Hypocalciuria in preeclampsia. *N Eng J Med*. 1987; 316:715-18.
15. Kazemi AFN, Sehhatie F, Sattarzade N and Mameghani ME. The Predictive Value of Urinary Calcium to Creatinine Ratio, Roll-Over Test and BMI in Early Diagnosis of Pre-Eclampsia. *Research Journal of Biological Sciences* 2010; 5(2):183-186.
16. Rodriguez MH, Masaki DI and Mestman J et al. Calcium/Creatinine Ratio and microalbuminuria in the prediction of preeclampsia. *Am J Obstet Gynecol* 1988 Dec; 159(6):1452-5.
17. Kamra R, Gupta HP, Das K, Natu SM. Role of urinary calcium / creatinine ratio in the prediction of pregnancy induced hypertension. *J Obstet Gynecol India*. 1994; 47(4):353-358.

ORIGINAL ARTICLE

18. Kar J, Srivastava K, Mishra RK, Sharma N, Pandey ON, Gupta S. Role of urinary calcium creatinine ratio in prediction of pregnancy induced hypertension. J Obstet Gynaecol. India 2002; 52(2):39-42.
19. Huikeshoven FJM and Zuiderhoudt FMJ. Hypocalciuria in hypertensive disorder of pregnancy and how to measure it. Eur J Obstet Gynecol Reprod Biol. 1990; 36:81-85.
20. Raniolo E, Phillippou G. Prediction of PIH by means of urinary calcium creatinine ratio. Med J Aus 1993; 1 58(2):98-100.

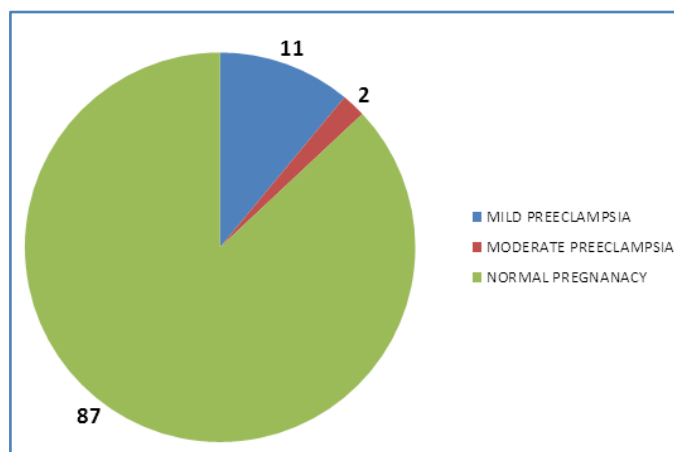


Fig. 1: INCIDENCE OF PREECLAMPSIA

S. No.	Characteristics (Mean±SD*)	Preeclamptic Women (N† = 13)	Normotensive Women (N† = 87)
1	Mean Maternal Age (in years)	24.77±3.19	24.91±2.56
2	Mean Gestational Age (in weeks) [at the time of joining the study]	25.08±2.40	25.15±2.63
3	Systolic B.P. (mm of Hg) [at the time of joining the study]	119.69±7.52	117.43±7.58
4.	Diastolic B.P. (mm of Hg) [at the time of joining the study]	78.31±3.73	77.24±4.74
5	Systolic B.P. (mm of Hg) [at the time delivery]	144.46±4.91	122.46±7.09
6	Diastolic B.P. (mm of Hg) [at the time of delivery]	96.00±4.47	78.46±3.97
7	Mean Urinary Calcium level (mg/dL)	4.56±1.19	9.23±3.49
8	Mean Urinary Creatinine level (mg/dL)	98.45±29.72	78.14±25.60
9	Mean Urinary Calcium/ Creatinine Ratio	0.04±0.02	0.12±0.05

Table 1: CLINICAL & LABORATORY CHARACTERISTICS OF STUDY GROUPS

*SD = Standard Deviation

†N = No. of cases

Calcium/ Creatinine Ratio	Preeclamptic women (N %)	Normotensive women (N %)	Test Result (N %)
Test positive (≤ 0.04)	10 (83.3%) (True positive)	2 (16.7%) (False positive)	12 (12%)
Test negative (> 0.04)	3 (3.4%) (False negative)	85 (96.6%) (True negative)	88 (88%)
Total cases	13	87	100

Table 2: ASSOCIATION OF CALCIUM CREATININE RATIO WITH PREECLAMPSIA

	Sensitivity	Specificity	PPV	NPV
Ca/Cr Ratio	76.90%	97.70%	83.33%	96.60%

Table 3: RESULTS OF STATISTICAL ANALYSIS

Ca/Cr Ratio – Calcium/Creatinine Ratio;

PPV - Positive Predictive Value;

NPV - Negative Predictive Value

AUTHORS:

1. Mittal Shilpa
2. Shaikh M.K.S.
3. Thakur Ratna
4. Jain Darshana

PARTICULARS OF CONTRIBUTORS:

1. Post Graduate Student, Department of Biochemistry, Sri Aurobindo Medical College & P.G. Institute, Indore (M.P.).
2. Professor & Head, Department of Biochemistry, Sri Aurobindo Medical College & P.G. Institute, Indore (M.P.)
3. Professor & Head, Department of Obstetrics & Gynaecology, Sri Aurobindo Medical College & P.G. Institute, Indore (M.P.)

4. Postgraduate Student, Department of Biochemistry, Sri Aurobindo Medical College & P.G. Institute, Indore (M.P.).

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Mittal Shilpa,
Department of Biochemistry,
Sri Aurobindo Medical College & P.G. Institute,
Indore (M.P.).
E-mail: shilpamittal75@rediffmail.com

Date of Submission: 01/01/2014.

Date of Peer Review: 02/01/2014.

Date of Acceptance: 16/01/2014.

Date of Publishing: 23/01/2014.