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Evaluation of Urinary Calcium–Creatinine Ratio for Early Prediction of Preeclampsia

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Abstract **Original Research Article**

Background: Preeclampsia (PE) is one of the most important hypertensive disorders in pregnancy. It is one of the fatal complications with significant mortality and morbidity. Incidence of preeclampsia is around 5-10% of all pregnancies, and in developing countries like Bangladesh it is around 4-18%. ***Objective*****:** The objective of this study was to determine the efficacy of urinary calcium-creatinine ratio in a spot urine sample for early prediction of preeclampsia in pregnant women. ***Methods***: It's a cross sectional type of analytical study, done in the department of Obstetrics & Gynaecology, Sir Salimuilah Medical College Mitford Hospital, Dhaka, Bangladesh. After fulfilling inclusion and exclusion criteria total 100 pregnant women with risk factors of preeclampsia were enrolled as the study population. ***Results*****:** Among different parameters serum calcium concentration of normal pregnancy and preeclampsia group varied significantly ($p<0.05$). Women with preeclampsia showed reduced excretion of calcium in comparison to normal pregnant women when spot urinary calcium concentration was evaluated. In this study comparison of spot urinary calcium-creatinine ratio in normal pregnant woman and in preeclamptic women was done and the result was highly significant ($p <0.001$). ***Conclusion*****:** This study is intended to identify at risk patients and put selection criteria for primary prevention to reduce morbidity and mortality in patients of preeclampsia. It showed lower urinary calcium excretion and calcium-creatinine ratio in preeclamptic women than normotensive pregnant women. Therefore, a single random urinary calcium-creatinine may be an effective tool for the early diagnosis of preeclampsia.

Keywords: Preeclampsia, Calcium-Creatinine Ratio, Urinary Calcium, Early Prediction.

INTRODUCTION

Hypertensive disorders of pregnancy, such as preeclampsia (PE) and pregnancy-induced hypertension (PIH) are major causes of maternal morbidity [1]. Preeclampsia (PE) is one of the fatal complications of pregnancy, It is a pregnancy induced auto-intoxication with multi-system disorder of unknown etiology which is associated with triad of oedema, hypertension and proteinuria occurs mostly in nullipara after 20th week of gestation and most frequently near term [2]. Further preeclampsia can progress to eclampsia leading to seizures and HELLP syndrome if left untreated [3]. It can also lead to haemorrhage and infection, resulting in significant maternal morbidity and mortality. The incidence of preeclampsia is around 5-10% in all pregnancies [4]. It is around 4-18% in developing countries. In Bangladesh it complicates about 10% of all deliveries [5]. It is the second most common obstetric cause of stillbirths and early or premature neonatal deaths. In this subcontinent the incidence of preeclampsia is 5.47% in primigravida and 2.8% in multigravida [6]. It accounts for about 44.44% of all cases of hypertensive disorders of pregnancy [7]. Despite of so much research and changes in management, preeclampsia is still a leading cause of maternal morbidity and mortality in worldwide. Preeclampsia is a "multisystem disorder". Pathology behind preeclampsia is reduced perfusion of organs due to vasospasm. It is usually associated with proteinuria or oedema or both [8]. In spite of extensive research,

the mechanism how pregnancy initiates or aggravates hypertension remains unknown. It is amongst the most significant unsolved problems in obstetrics. This is the disorder of widespread vascular endothelial malfunction and vasospasm which occurs later part of gestation and presents till 4-6 weeks postpartum [9]. Although de novo preeclampsia and preeclampsia superimposed on chronic hypertension are leading causes of maternal and fetal morbidity, gestational, hypertension which is isolated de novo hypertension in the second half of pregnancy and treated essential hypertension carry a good prognosis for both mother and fetus. Gestational hypertension often precedes preeclampsia, which is characterized physiologically by associated maternal organ dysfunction (liver disease, proteinuria, etc.), but prompt identification of preeclampsia may be difficult in hypertensive pregnancies at first clinical presentation. Here hypertension is diagnosed when systolic blood pressure is greater than 140 mmHg and diastolic blood pressure greater than 90 mmHg on two successive measurements done 4-6 hours apart or when systolic blood pressure is increased by 30 mmHg and diastolic blood pressure by 15 mmHg. Proteinuria is defined as excretion of 300 mg or more of protein in 24 hour urine sample or > 1+ dipstick in a random sample of urine. Identifying women with gestational hypertension who are likely to progress to preeclampsia would allow better counseling, even closer monitoring, and, perhaps one day, initiation of preventative therapeutic intervention in these women. Prediction of preeclampsia in patients is extremely essential so that early detection, timely intervention and treatment will prevent the devastating complications. A variety of biochemical and biophysical markers, based primarily on rationales implicated in the pathology and pathophysiology of hypertensive disorders due to pregnancy have been proposed for the purpose of predicting the development of preeclampsia later in pregnancy. There is no test that fulfils all criteria established to be a good predictor of preeclampsia [10]. Early test for prediction of preeclampsia as previously reported are platelet count, hematocrit and serum uric micro albuminuria [11]. These are poor predictor of preeclampsia. Fibronectin, urinary calcium excretion, roll over test are also used. Doppler ultrasound test is found contradictory and non-conclusive. Angiotensin II sensitivity test shows best predictive value but clinically not practiced. Many of these tests are expensive, require proper equipment to perform, and may be nonspecific. But none of them have been proved ideal either because of high incidence of false positivity or their complexity in result interpretation. In this regard it has been found that decreased urinary excretion of calcium may be considered as a useful tool for the early diagnosis of preeclampsia. Reduction in urinary calcium excretion is observed at 10-24 weeks of gestation in patients who later developed preeclampsia and persisted throughout pregnancy. It is reported that 24 hrs. urine samples can be replaced by single voided urine [12]. So determination of calcium-creatinine ratio in a spot sample may easily predict the case of preeclampsia. When used as a single test, the urinary calcium-creatinine ratio is a better predictor of preeclampsia than the urinary microalbuminuria concentration [13]. It is cheap, can be performed on spot urine sample, with a modest early predictive value. Many studies from different corners of the world suggest that evaluation of urinary calcium-creatinine ratio after 20wks of gestation may be an effective screening method for impending preeclampsia and may identify population at risk.14 This disorder is highly prevalent in our country in spite of great advances in the field of obstetrics. Few studies are available in this regard. The present work is focused on prevention of the disease rather than treatment. This study is to estimate the urinary calcium-creatinine ratio in prediction of preeclampsia. It is a simple and noninvasive screening test which is also cost effective. The aims of this study were to investigate whether hypocalciuria precedes preeclampsia in pregnant women and whether the urinary calcium-creatinine ratio is a reliable predictor of emerging preeclampsia in such group. In this study an endeavor will be made to identify at risk patients by calcium-creatinine ratio in spot urine sample which might help the primary prevention program on preeclampsia.

MATERIALS AND METHODS

Study design: It's a cross sectional type of analytical study to evaluate urinary calcium-creatinine ratio as an early predictor of preeclampsia.

Place of study: Department of Obstetrics & Gynaecology, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh.

Period of study: This study was carried out from 1st July, 2019 to 31st December, 2019.

Population of the study: Pregnant woman between 20-45 years, gestational age of 20 weeks or more with risk factors of preeclampsia (like HTN, DM, Nullparity, Previous H/O PET etc) admitted in Obstetrics ward of Sir Salimullah Medical College Mitford Hospital were the study population.

Sample size: The sample size will be determined by using the following formula-

$n=(Z^2xpxq)/d^2$

Due to lack of time, resources, accessibility and availability a total of 100 pregnant women with risk factors preeclampsia will be taken for the study.

Inclusion Criteria:

- Pregnant woman, between 20-45 years, gestational age of 20 weeks or more, with risk factors of preeclampsia (like HTN, DM, Nulliparity, Previous H/O PET etc).

- Who wanted to participate in this study with informed written consent.

Exclusion Criteria:

- Pregnancy complicated by uncontrolled HTN, DM, renal disease, etc.
- Not willing to participate in this study.

Data collection plan: Data was collected purposively on the basis of inclusion and exclusion criteria. Total 100 pregnant women, between 20-45 years with gestational age 20 weeks or more with risk factors of preeclampsia were enrolled in this study Informed written consent was taken from each participant who fulfilled the criteria. Initial evaluation of the patients was performed by history, physical examination and necessary investigations were sent. Data was collected personally by the researcher using self-made semi-structured questionnaire. All relevant information from history, examination and investigation results was recorded in data collecting sheet. Each data sheet was assigned a case ID and information was recorded in computer. Further preparation and organization of data was done using SPSS version 23.0.

Data processing and analysis: Data was recorded systematically in preformed data collecting sheet and collected data were sorted and screened for any discrepancy. Quantitative data was expressed as mean and standard deviation; qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using windows based computer software SPSS®-23. p value less than 0.05 or 95% confidence interval (Cl) was regarded as statistically significant.

RESULTS

This study included 100 pregnant women with risk factors of preeclampsia from 1st July, 2019 to 31st December 2019. All patients were enrolled after meeting the inclusion and exclusion criteria of the research proposal. Patients from different corners of Bangladesh were enrolled. Preeclampsia was found in 12 patients among 100 pregnant women (12%) a rest 88 women had normal pregnancy outcome. Age of the respondents ranged from 18-43 years with mean age ± SD was 26.57 ± 2.88 years and mean gestational age ± sd was 31.96 ± 3.50 weeks. Maximum participants were from 25-29 years age group, which constitutes 32% of the total respondents. The youngest age group 18-24 years contributes 27% of the total study population. Only 6% was from the highest age group, 40-45 years, which is the least among age distribution of the respondents. Further evaluation of age group of preeclamptic women revealed that 2 cases were observed in 40-45 years age group (16.66%), 4 cases in 35-39 years of age group (33.33%), and 3 cases in 25-29 years age group (25%), 2 cases in 30-34 years age group (16.66%) and 1 case was found in 18-24 age group (8.33%). So mean age ± sd of preeclamptic women was 31.46 ± 2.15 years. Gestational age of most of the respondents was below 35 weeks of which 59 were primigravida and 41 were multiparity. Among those 12 cases of preeclampsia. primigravida was noted in 7 patients (58.33%) and multiparity in 5 patients (41.66%). Underlying co-morbidities were found in 4 cases (33.33%). Previous history of preeclampsia was found in 2 patients (16.66%) but family history was not evident in these cases. Among 100 respondents only 17% had tertiary education and 14% did not have any academic qualification. The highest number of respondents, 43% head only primary education, and 26% completed the boundary of secondary education. Almost half of the respondents, 48% were housewives, 25% were garments workers, 18% were industrial workers, and 9% were Job holders. Maximum respondents were from third trimester. In this diagram, 53% were from 30-34 weeks of gestation and 21% were from 35 weeks onwards. Only 7% women were in 20-24 weeks of gestational age group. Shows that more than half of the pregnant women, 59% were primigravida and rest 41% were multiparous women. Among the respondents, only 12% women developed preeclampsia 88% had normal pregnancy outcome (Table-1, 2).

Table-1: Demographic characteristics of the respondents (n=100)

Age	**Number**	**Percentage**
18-24 years	27	27
25-29 years	32	32
30-34 years	20	20
35-39 years	15	15
Education level		
No education	14	14
Primary	43	43
Secondary	26	26
Tertiary	17	17
Occupation		
House wife	48	48
Garments Worker	25	235
Industrial Worker	18	18
Job Holder	9	9
Gestational		
20-24 weeks	7	7
25-29 weeks	19	19
30-34 weeks	53	53
≥35	21	21
Parity		
Multiparity	41	41
Primigravida	59	59
Preeclampsia		
Preeclampsia	12	12
Normal Pregnancy	88	88

Table-2: Physical and clinical variables of the respondents (N=100)

Variables	Mean+ SD		Test Value t = t test $_x$2 = Chi-square test	P value (*Significant when p<0.05)
	Normal (n= 88)	PE (n=12)		
Age	26.57 ± 2.88	31.46 ± 2.15	1.97(0	*0.003
Mean gestational age (weeks)	28.49 ± 4.29	30.96 ± 3.50	3.05 (t)	*0.0001
Height (Cm)	150.12 ± 4.16	151.78 ± 3.55	2.63 (t)	0.057
Weight (Kg)	52.96 ± 5.29	63.1 3 ± 3.26	14.16(t)	*0.0001
BMI	23.57 ± 1.90	27.43 ± 1.54	13.63(t)	*0.0001
Pulse rate (BPM)	84.51 ± 4.50	84.48 ± 6.99	0.2 (t)	0.97
Systolic Blood				
Pressure (mm Hg)	106.00 ± 9.58	151.67 ± 9.01	30.05 (t)	*0.0001
Diastolic Blood				
Pressure (mm Hg)	69.60 ± 7.43	98.27 ± 6.80	24.63 (t)	*0.0001
Oedema	9	12	125.69 (x2)	*0.0001
Foetal Heart				
Rate (BPM)	126.42 ± 3.20	128.37 ± 4.37	1.68 (t)	0.85

Table-3: Biochemical variables among the study population (N=100)

Variables	Mean ± SD		t -1 test	P value (*Significant when p<0.05)
	Normal (n= 88)	PE (n= 12)		
Serum calcium (mg/dl)	8.42 ± .39	8.18 ± .42	2.08	*0.039
Serum creatinine (mg/d!)	1.05± .21	1.13± .27	1.92	0.056
Serum uric acid (mg/dl)	3.87 ±.75	6.76 ±1.99	11.74	*0.0001
Urinary calcium (mg/d!)	7.39 ± 2.80	3.45 ± 2.61	8.89	*0.0001
Urinary creatinine (mg/dl)	53.11 ±20.17	60.45 ±32.13	1.67	0.09
Urinary Protein (mg/day)	246.31 ±3.10	302.82±16.28	10.07	*0.0001
Urinary Ca/Cr	0.13 ±0.06	0.06 + 0.05	7.31	*0.0001

Serum calcium concentration of preeclampsia group (8.18±.42) and normal pregnancy (8.42 ±. 39) varied significantly (p<0.05). On the other hand serum creatinine concentration didn't show significant difference (1.13±.27 vs 1.05±.21, p> 0.05). Significantly higher serum Uric acid concentration was observed in preeclampsia patients (6.76±1.99 vs 3.86±.75, p <0.01). Regarding urinary biochemical study, urinary calcium concentration (mg/100ml), urinary creatinine concentration (mg/100ml) and calcium-creatinine ratio in spot sample was estimated. Women with preeclampsia didn't differ significantly from normal pregnant patients in respect of urinary creatinine concentration (60.45±32.13 vs 53.11±20.17, p> 0.05). But the results were significant in case of spot urinary calcium excretion. Women with preeclampsia showed reduced excretion of calcium in comparison to normal pregnant women when spot urinary calcium concentration was evaluated (3.45 ± 2.61 vs 7.39 ± 2.80, p <0.001). In this study comparison of spot urinary calcium-creatinine ratio in normal pregnant woman and in preeclamptic women was done, and the result was highly significant. The ratio reduced in preeclampsia patient in comparison to normal pregnant (.06+.05 vs .13+.06, p <0.001) (Table-3).

DISCUSSION

This cross sectional type of analytical study was conducted in department of obstetrics and Gynaecology, Sir Salimullah Medical College Mitford Hospital, Dhaka. It was conducted from 1st July, 2019 to 31st December, 2019 for six months. Total 100 pregnant women, from different parts of our country with risk factors of preeclampsia were enrolled in this study after satisfying the protocol criteria. Informed written consent was taken from each patient. Among them 12 patients were found to have preeclampsia which is consistent with the study of Khatoon *et al*., [5]. Rest 88 patients had normal pregnancy outcome. Different aspects or variables of the study population were assessed. Regarding demographic variables, mean age + SD of the preeclampsia and normal pregnant group were 31.46±2.15 yrs and 26.57 ± 2.88 yrs respectively. It showed statistically significant difference (p=0.003) which means that older women are more susceptible to develop preeclampsia than younger one. It reflects the research of Waterston M *et al*., [15]. When age group was evaluated maximum number of preeclampsia patients were observed in 35-39 year age group. Gestational age of most of the respondents was below 35 weeks. Gestational mean age ± SD of the preeclampsia and normal pregnant group were 30.96 ±

3.50 weeks and 28.49 ± 4.29 weeks respectively and differed significantly (p<0.001). It means that preeclampsia may be more frequent in later gestational age which is an important risk factor. Among the respondents, primigravida (59%) outnumbered multiparity women (41%). In women with preeclampsia, 7 were primigravida and 5 were multiparous, which represents primigravida as one of the established factors of preeciampsia as found in the study of Qublan *et al*., [15]. Underlying co-morbidities were found in 4 cases (33.33%). Previous history of preeciampsia was found in 2 patients (16.66%) but family history was not evident in such cases. However, no significant difference was observed regarding occupation, socioeconomic status or education level of the respondents. But pregnant women with secondary and tertiary education were to some extent oriented with manifestations and complications of preeciampsia. It means that proper education regarding pregnancy and factors influencing it may provide better pregnancy outcome, which needs further research. Regarding clinical variables, no significant difference was observed in respect to pulse rate. Systolic (151 + 9.01 vs 106 ± 9.5, p<0.001) and diastolic blood pressure (98.27 ± 6.80 vs 69 ± 7.4, p<0.001) showed a great variation between the preeciampsia and normal pregnant groups. Oedema was profound in women with preeciampsia with significant statistical difference. Though height was almost similar in both groups, BMI was higher in preeclamptic group than in normal pregnant group and it may be due to increased weight gain in preeclampsia. Foetal heart rate and foetal movement did not show statistical difference. Exploration of biochemical variables reveals, serum calcium concentration of preeciampsia group (8.18±.42) and normal pregnancy (8.42±.39) varied significantly (p<0.05). It means that serum calcium level was lower in patients with preeciampsia. It goes with other studies like Saudan *et al*., [16]. On the other hand serum creatinine concentration didn't show significant difference (1.13±.27 vs 1.05+ .21, p>0.05). Significantly higher serum Uric acid concentration was observed in preeciampsia patients (6.76± 1.99 vs 3.86± .75, p<0.01). Previous Research works by Qublan *et al*., and Saudan *et al*., had similar results indicating possibilities of serum uric acid to be considered as an important factor for preeclampsia. Analysis of urinary biochemicals reveals that, women with preeclampsia did not differ significantly from normal pregnant patients in respect of urinary creatinine concentration (60.45 ± 32.13 vs 53.11 ± 20.17, p> 0.05). But the results were significant in case of spot urinary calcium and protein concentration. Women with preeclampsia showed reduced excretion of calcium in comparison to normal pregnant women when spot urinary calcium concentration was evaluated {3.45 ± 2.61 vs 7.39 ± 2.80, p 0.001). This is in accordance with the observations made by previous authors like Malas *et al*., [9], Ingec M *et al*., [11], Stars GV *et al*., [17]. It is probably due to increased tubular reabsorption of calcium and decrease in glomerular filtration rate. Sanches-Ramos *et al*., [18] confirmed previous finding of altered urinary calcium excretion in pregnant woman with preeclampsia. Vural *et al*., [19] conducted a case control study with 59 patients and concluded that hypocalciuria may be an important feature of preeclampsia. Bilgin *et al*., [20] from another study concluded that hypocalciuria is an important feature of preeclampsia and 24 hours urinary calcium excretion or calcium-creatinine ratio in random urine samples is a reliable index of preeclampsia. In this study calcium-creatrnine ratio in a spot urine sample is evaluated as a predictor of preeclampsia. Here spot urinary calcium-creatinine ratio in women with preeclampsia is compared with normal pregnant women and the result is highly significant. The ratio reduced in preeclampsia patient in comparison to normal pregnant (.06±.05 vs .13±.06, p<0.001). These results correlate very well with several previous studies done at different corners of the world. Kazerooni *et al*., [21] conducted a similar study with 102 patients and result was in favor of significantly lowered calcium-creatinine ratio in preeclampsia. Almost same outcome was found in research work by Szmidt-Adjide *et al*., [22]. It revealed results in favor of the present proposition in a case control study consisting of 47 preeclampsia women and 50 controls. Rodriguez *et al*., [23] suggested that calcium-creatinine ratio may be useful in predicting preeclampsia and evaluated the calcium-creatinine ratio in 88 normotensive pregnant women. So results of this present study are consistent with previously performed multiple studies.

CONCLUSION

Preeclampsia is a real challenge in obstetric field and an important cause of maternal mortality. Relevant tests to predict this hypertensive disorders in pregnancy are practiced and many are coming up. Among these, single urinary calcium-creatinine ratio in spot sample is an effective screening method for impending preeclampsia and may identify population at greater risk. Thus it helps to recruit them in primary prevention programs. It is noninvasive, cheap and convenient as a screening test. Even though it can be used in all pregnant women, it is usually recommend as a screening test in women with high risk of hypertensive disorders in pregnancy. The present study is intended to identify at risk patients and put selection criteria for primary prevention. This test forms a satisfactory basis for the early diagnosis of preeclampsia. This study has showed lower level of urinary calcium excretion and calcium-creatinine ratio in preeclamptic women than normotensive pregnant women. The findings of this study are consistent with other researches. Therefore, a single random urinary catcium-creatinine ratio may be an effective tool for early diagnosis of preeclampsia and can be considered as a valuable predictor in care and study of pregnant patients with preeclampsia. It also denotes that early

therapeutic use of calcium may reduce the morbidity and mortality in patients of preeclampsia.

Limitations of the study

This study has got some limitations, the means by which clinicians can intervene for further investigation.

1. Only 100 pregnant women with risk factor of preeclampsia have been purposively selected which constitute a little portion of the total patients
2. Patients have been purposively recruited from a tertiary level hospital that may not reflect the diversity of the disease presentation in our country.
3. The study does not compare spot urinary calcium-creatinine ratio with other screening tools of preeclampsia.
4. Calcium-creatinine ratio in spot sample may vary according to the etiological factors of preeclampsia, which needs further exploration.

RECOMMENDATION

Multiple tests are available for prediction and risk stratification of pregnant women with risk factors of preeclampsia. But none of them is highly sensitive and specific. So here lies the possibility to come up with non-invasive, cost effective, easy to perform method like calcium-creatinine ratio in spot urine sample for screening and risk categorization of preeclampsia.

Conflict of Interest: None.

Source of fund: None.

Abbreviations:

PE: Preeclampsia
GIH: Gestation Induced Hypertension
SPSS: Statistical Package Software System
SD: Standard Deviation

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