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Original Research Article

Microalbuminuria in early pregnancy as a Predictor of Preeclampsia

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Abstract

Background: Hypertensive disorders of pregnancy have been a challenge to the obstetricians and researchers since many centuries. Prediction of preeclampsia (PE) in the early pregnancy is of utmost help in preventing the disorder and minimizing its severity. ***Objective*:** To evaluate the predictive accuracy of microalbuminuria in early pregnancy for the development of preeclampsia. ***Methods:*** A prospective cohort study was carried out in the Obstetrics and Gynaecology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, over a period of one year. 133 pregnant women at 10 – 14 weeks of gestation were included in the study. The group of women with microalbumin excretion 20 – 300 mg/L in a spot sample of urine was designated as 'exposed' group and those with albumin excretion < 20 mg/L as 'unexposed' group. The outcome variable was development of either Preeclampsia or Eclampsia or Gestational Hypertension. ***Result:*** Among 133 study subjects, 13 developed adverse outcomes (PE/GHTN). The pregnant women were predominantly in their 2nd decades of life (20 – 30 years old) with mean ages of the adverse and normal outcome groups being 25.6 and 24.9 years respectively (p = 0.614). No significant association was found between adverse outcome and parity (p = 0.729). The past history of preeclampsia tends to be significantly associated with PE or GHTN (p = 0.048). Nearly half (46.2%) of those who developed preeclampsia/GHTN had microalbuminuria in early pregnancy compared to 23.3% of those who did not have microalbuminuria. The risk having preeclampsia/GHTN in the 'exposed' group is 2.5 (95% CI = 1.0 – 6.9) times higher than that in the 'unexposed' group (p = 0.037). The sensitivity of microalbuminuria was inappreciably low (46.2%). However, its specificity is optimum (76.7%). The positive and negative predictive values of the test were 17.6% and 92.9% respectively with high yield of false positive and low yield of false negative results. The overall predictive accuracy of the test was found to be 73.7%. ***Conclusion:*** The study concluded that presence of microalbuminuria in pregnant women in their 1st trimester significantly predicts PE/GHTN.

Keywords: Preeclampsia, Eclampsia, Microalbuminuria, Predictor.

INTRODUCTION

Pre-eclampsia and its complications are major causes of maternal and perinatal morbidity and mortality. The incidence of preeclampsia ranges between 2% and 10% of pregnancies, worldwide. Average incidence of preeclampsia in Bangladesh is 8.22% of pregnancies [1]. Preeclampsia is multi system disorder of pregnancy characterized by new onset of hypertension (systolic and diastolic blood pressure ≥ 140 and/or ≥ 90 mmHg, respectively on two occasions at least 4 hours apart) and new onset proteinuria (≥300 mg in 24 hours urine collection or dipstick test ≥1+) or in absence of proteinuria new onset end organ damage, usually after the 20th week of gestation [2]. Despite years of research, the exact etiology of the condition remains unclear even today. Pre-eclampsia is known as

'the disease of multiple theories'; among them genetic, immunological, circulatory factors, uterine vascular changes and endothelial dysfunction are important [3]. Recent progress in understanding the disease process along with the availability of better research tools have led to the development of some physical and biochemical tests to predict pre-eclampsia, such as mean arterial blood pressure in 2nd trimester, Roll over test, Angiotensin sensitivity test, Urinary calcium, plasma Fibronectin, Uterine artery Doppler velocimetry at 22-24 weeks, Inhibin A, PAPP-A, Fetal DNA in maternal blood etc. [4]. But still, none of these could conclusively predict the condition [5].

It has been postulated that abnormal placentation, believed to be due to failure of the second wave of trophoblastic invasion of the spiral arteries from the 20th week of pregnancy, is the primary insult [6]. The anatomic and physiologic disruption of normal placentation is thought to lead to the synthesis of products that affect angiogenesis and to abnormal lipid peroxidation. With the advance in gestation, these products will affect the endothelial system. The widespread endothelial damage may manifest in a pregnant woman as dysfunction of multiple organ systems including central nervous system, hepatic, renal and hematological system [7]. The distinctive renal lesion in pre-eclampsia has been called 'glomerular endotheliosis' [4] and proteinuria has classically been an important finding in the diagnosis of pre-eclampsia.

Microalbuminuria is a marker of endothelial dysfunction [8]. It refers to the subclinical elevation of urinary albumin excretion. It has been shown to precede the development of nephropathy in insulin dependent diabetes mellitus (IDDM) [9], and might be the evidence of renal involvement in hypertension. However, customary dipstick methods for detecting proteinuria fail to detect minimal elevation in urinary excretion of albumin that may be present before other clinical manifestations of pre-eclampsia. With radioimmunoassay and other sensitive methodology for detection of microalbuminuria, it is now possible to detect minimal elevations in albumin excretion that have gone unnoticed in the past [10]. Although the 24-hour collection of urine is the gold standard for quantifying urinary albumin excretion, it is cumbersome and results in delay of at least 24 hours in diagnosis [11]. Therefore the 'spot' urinary microalbumin has been advocated as an alternative [12]. Healthy pregnant women may not excrete albumin in amounts detectable by the conventional dipstick screening test. So, the presence of microalbuminuria in early pregnancy may be an important clinical finding. The present study is, therefore intended to determine whether a 'spot' urinary microalbumin measured before 14 weeks of gestation can predict the development of pre-eclampsia.

MATERIALS & METHODS

This prospective cohort study was carried out in the Department of Obstetrics and Gynaecology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, over a period of one year from September 2016 to August 2017. Ethical clearance for the study was obtained from Institutional Review Board of BSMMU. Total 141 cases were enrolled in the study. As 8 cases were lost to follow up, the final analysis was done on 133 cases. Women who already have a chance of getting proteinuria like those with ongoing urinary tract infection or have a history chronic hypertension, diabetes mellitus, and chronic kidney disease were excluded from the study. Also, those with a baseline blood pressure ≥ 140/90 mm of Hg or with dipstick positive proteinuria at booking were excluded. Finally, women with a singleton pregnancy, attending at the antenatal clinic at their 10-14th weeks of gestation, were recruited. After obtaining informed consent, the women were interviewed by the researcher herself for the purpose of collecting data. Data regarding demographic characteristics, medical and family history (history of chronic hypertension, diabetes mellitus, and/or CKD) were recorded. Obstetric history documented was gravidity, parity, past history or family history of pre-eclampsia. They were asked about symptoms of urinary tract infection. A complete physical examination of the subjects was carried out accordingly. Blood pressure was measured with an appropriately sized cuff (encircling and covering two-thirds of the length of the arm) with the patient in an upright position with their right arm supported in horizontal position at the level of the heart, after a 5 to 10 minutes rest period. Systolic blood pressure was determined by Korotkoff phase I and Diastolic blood pressure by Korotkoff phase V (disappearance of sound). If the sound persists after deflation, then Korotkoff IV (muffling of the sound) was accepted. Then a sterile urine container was given to each of them with proper instructions to collect clean catch midstream urine for the study. An immediate dipstick test was performed using multistix reagent strips, which had a detection limit of ≥ 0.1 g/dl (Trace) as office procedure. Samples negative for proteinuria, were sent to the Department of Biochemistry for quantitative assessment of microalbumin within 2 hours of collection by Particle-Enhanced Turbidimetric Inhibition Immunoassay (PETINIA). Presence of microalbuminuria was considered if a spot sample of urine contains 20 – 300 mg/L of albumin. All the information obtained through interview, observation, clinical examination and investigations were recorded in a semi-structured data sheet. Then the participants were followed up once monthly up to 28 weeks, once twoweeklies up to 36 weeks, once weekly till delivery and up to 6weeks postpartum. At each visit they were clinically evaluated by measuring blood pressure and testing urine for protein by dipstick method. Pre-eclampsia were diagnosed if blood pressure found to be more than or equal 140/90 mmHg and dipstick proteinuria ≥ 2+. If proteinuria was less than 2+ value,

then the diagnosis was confirmed by measuring 24-hour urinary protein. A value of ≥ 300 mg protein in a 24-hour urine collection was diagnostic. Data were processed and analyzed using computerize software base SPSS (Statistical Package for Social Sciences) method. The test statistics used to analyze the data were descriptive statistics; Chi-square (χ^2) Test and Unpaired t-Test were employed to carry out the statistical analyses. Chi-square testwas used to find significant association between microalbuminuria and pre-eclampsia. Results were presented asmean ± SD. A p-value of < 0.05 was considered as statistically significant (considering a 95% confidence interval).

RESULT

The present study included a total of 133 pregnant women between 10 – 14 weeks of gestation. The group of women with albumin excretion 20 – 300 mg/L in a spot sample of urine at booking was designated as 'exposed' group (n = 34) and those with albumin excretion < 20 mg/L as 'unexposed' group (n = 99). The adverse outcome of interest was preeclampsia, eclampsia or gestational hypertension (GHTN), developed in the latter half of pregnancy. Of the 133 women, 13 developed preeclampsia/GHTN (6 in the 'exposed' group and 7 in the 'unexposed' group), designated as 'adverse outcome group'. None developed eclampsia. The rest 120 pregnant women remain normotensive, hence designated as 'normal outcome group'. The findings obtained from data analyses are presented here.

The age distribution shows that the pregnant women in both outcome groups were predominantly in their 2nd decades of life (20 – 30 years old) with mean ages of the adverse and normal outcome groups being 25.6 and 24.9 years respectively (p = 0.614). No significant association was found between adverse outcome and parity (p = 0.729) (Table I).

Table I: Comparison of Demographic & obstetric characteristics between the outcome groups

Variables of interest	Preeclampsia/GHTN		p-value
	Developed (n = 13)	Not developed (n = 120)	
Age (yrs)#			
< 20	2(15.5)	20(16.7)	
20 – 30	9(69.2)	79(65.8)	
≥ 30	2(15.4)	21(17.5)	
Mean ± SD#	25.6 ± 4.6	24.9 ± 4.5	0.614
Parity*			
Primi	6(46.2)	60(50.0)	0.792
Multi	7(53.8)	60(50.0)	

Figures in the parentheses indicate corresponding **%;**

#Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD**.

***Chi-squared Test (χ^2) was done to analyze the data.**

BMI distribution showed in Fig-1 describes, approximately 46% of the adverse outcome (PE/GHTN) group and 21% of the normal outcome group were overweight. The presence of obese pregnant women was also higher in the adverse outcome group than that in the normal outcome group. However, the difference between the groups in terms of BMI was not significant (p = 0.060).

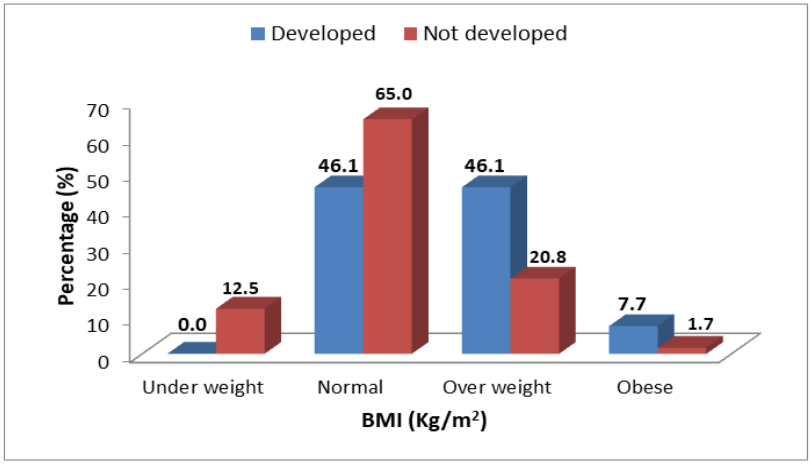

Fig 1: Comparison of BMI between the outcome groups

Table II shows Risk factors distribution.The past history of preeclampsia tends to be significantly associated with preeclampsia/GHTN (p = 0.048). However, family history of hypertension was not found to be associated with the development of preeclampsia/GHTN (p = 0.456).

Table II: Comparison of risk factors between the outcome groups

Risk factors	Preeclampsia/GHTN		p-value
	Developed (n = 13)	Not developed (n = 120)	
Past history of preeclampsia**	2(15.4)	2(1.7)	0.048
Family history of hypertension*	4(30.8)	26(21.7)	0.456

Figures in the parentheses indicate corresponding **%;**
***Chi-squared Test (χ^2) was done to analyze the data.**
****Fisher's Exact Test** was done to analyze the data**.**

Distribution of systolic and diastolic blood pressures at booking were almost similar between the outcome groups (p = 0.190 and p = 0.372 respectively). Level of haemoglobin was also almost identical between the groups (p = 0.920) (Table III).

Table III: Comparison of clinical & biochemical characteristics at booking between outcome groups

Variables#	Preeclampsia/GHTN		p-value
	Developed (n = 13)	Not developed (n = 120)	
Systolic BP (mmHg)	109.6 ± 13.6	104.3 ± 13.6	0.190
Diastolic BP (mmHg)	74.2 ± 8.1	71.9 ± 8.7	0.372
Level of Hb (gm/dl)	10.3 ± 0.7	10.3 ± 0.6	0.920

#Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Table IV shows, the mean gestational age at delivery was 38 weeks in pregnant women with adverse outcome and that in women with normal outcome was 38.6 weeks (p = 0.058). However, the mean systolic and diastolic blood pressures were significantly higher in the adverse outcome group than those in the normal outcome group (p < 0.001).

Table IV: Comparison of clinical characteristics at delivery between outcome groups

Clinical characteristics at delivery#	Preeclampsia/GHTN		p-value
	Developed (n = 13)	Not developed (n = 120)	
Gestational age (weeks)	38.0 ± 1.1	38.6 ± 1.1	0.058
Systolic BP (mmHg)	132.3 ± 37.7	112.0 ±17.1	< 0.001
Diastolic BP (mmHg)	89.6 ± 7.4	73.8 ± 7.1	< 0.001

#Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Nearly half (46.2%) of those who developed preeclampsia/GHTN had microalbuminuria in early pregnancy compared to 23.3% of those who did not have microalbuminuria. The risk having preeclampsia/GHTN in the 'exposed' group is 2.5 (95% CI = 1.0 – 6.9) times higher than that in the 'unexposed' group (p = 0.037) (Table V).

Table V: Association between exposure and outcome

Microalbuminuria	Preeclampsia/GHTN		Relative Risk (95% CI of RR)	p-value
	Developed (n = 13)	Not developed (n = 120)		
Present	6(46.2)	28(23.3)	2.5 (1.0 – 6.9)	0.037
Absent	7(53.8)	92(76.7)		

Figures in the parentheses indicate corresponding %.

The accuracy of microalbuminuria in predicting the development of preeclampsia is calculated according to the formulae for computation of the components of accuracy, using Table VI:

Table VI: Accuracy of microalbuminuria in predicting preeclampsia/GHTN

Microalbuminuria	Preeclampsia/GHTN		Total
	Developed	Not developed	
Present	6	28	**34**
Absent	7	92	**99**
Total	**13**	**120**	**133**

1 Sensitivity = 6 / (6 + 7) × 100 = 46.2%
2 Specificity = 92 / (28 + 92) × 100 = 76.7%
3 Positive predictive value of thetest (PPV) = 6 / (6 + 28) × 100 = 17.6%
4 Negative predictive valueof the test (NPV) = 92 / (7 + 92) × 100 = 92.9%
5 Percentage of false positive= 28 / (6 + 28) × 100 = 82.4%
6 Percentage of false negative = 7 / (7 + 92) × 100 = 7.1%
7 Diagnostic accuracy = (6 + 92) / (6 + 28 + 7 + 92) × 100 = 73.7%

DISCUSSION

Preeclampsia is unpredictable in onset and progression and is incurable until termination of the pregnancy. So prediction of PE in the early stages of pregnancy can be of immense help in preventing the disorder or in minimizing its severity. PE is associated with widespread vascular dysfunction both in placenta and in the maternal circulation. Realizing this association, attention has been drawn to the biochemical markers of microvascular damage and among this microalbuminuria got special priority.

The present study was aimed at determining the role of microalbuminuria in early pregnancy as a predictor for preeclampsia or gestational hypertension found that about half (46.2%) of the pregnant women who developed preeclampsia/GHTN had microalbuminuria in the early pregnancy compared to 23.3% of those who did not develop any adverse outcome. The risk of having preeclampsia/GHTN in pregnant women (at 10-14 weeks of gestation) with microalbuminuria is 2.5-fold (95% CI = 1.0 – 6.9) higher than that in those without microalbuminuria (p = 0.037). Consistent with this finding, a study from China showed that pregnant women who developed gestational hypertension had an increased level of microalbuminuria 4-8 weeks before the onset of gestational hypertension as compared to patients who remained normotensive. This bears consistency with the findings of the present study [13]. Kour and Kour (2014) in a study at Srinagar, India also demonstrated that pregnant women with microalbuminuria between 24-34 weeks of gestation carry significantly higher risk of developing gestational hypertension on subsequent follow up [14].

The diagnostic accuracy analysis revealed that the sensitivity of microalbuminuria is inappreciably low (46.2%). This means that more than half (53.8%) of the pregnant women who may develop preeclampsia or GHTN could be escaped from 'high-risk' pregnancy if this test is used for screening them out. However, its specificity is optimum (76.7%) which can help screening out most of the pregnant women who would not develop preeclampsia. As the negative predictive value (NPV) of the test is commendably high (92.9%), the pregnant women who does not have microalbuminuria in their 1st trimester or otherwise normal pregnant women would rarely develop preeclampsia or GHTN. But the test cannot reliably be used to predict the development of preeclampsia, for its extremely low (17.6%) positive predictive value (PPV) which may yield a high percentage of false positive (82.4%). The overall diagnostic accuracy of the test was found to be 73.7%, which is mainly due to its high negative predictive value. These figures are quite similar to that seen by Sheela et al (2011) whose results were; sensitivity 53.8%, specificity 86%, positive predictive value 36%, negative predictive value 95%, accuracy 73.6% [15]. A similar study conducted recently in Egypt (Senna &Abonar 2017) reported a higher sensitivity of microalbuminuria (80%), but its specificity, positive and negative predictive values were more or less similar (72.2%, 24.2% and 97% respectively) to our findings [16]. A study conducted in Africa also reported that microalbuminuria at booking is good at predicting the subsequent development preeclampsia or eclampsia thus contrasting with findings of the present study [10]. There is a wide variation in the figures of sensitivity, specificity, PPV and NPV is evident. The sensitivity of predicting PE by measuring microalbumin in early pregnancy varies between 50 – 68%, the specificity varies between 58 – 97%, PPV varies between 26 – 61% and the NPV varies between 87 – 94% [17]. One of the reasons of this variability might be the lack of strict criteria regarding the definition of exposure and outcome variables (microalbuminuria and PE/GHTN respectively). As different laboratory uses different cut-off values of urine albumin to define microalbuminuria, it is difficult to compare the results of one study with those of others.

CONCLUSION

Though the presence of microalbuminuria in 1st trimester significantly predicts development of preeclampsia or gestational hypertension in the subsequent, its sensitivity and positive predictive values are unusually low. However, its negative predictive value is appreciably high and specificity is optimum. Thus, it can be concluded that the test could be used in screening out those pregnant women who will hardly develop preeclampsia or GHTN.

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