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Original Article

Role of Urinary Albumin in the Prediction of Preeclampsia

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Abstract

The prospective study was conducted at the Department of Obstetrics & Gynecology of Sir Salimullah Medical College & Mitford Hospital and at the Department of Cell & Molecular Biology, Research Division, BIRDEM, during the period of Jan 2003 to July 2004. To explore a suitable biochemical marker to predict the future development of preeclampsia (PE), total 119 pregnant women at their 10-14 weeks of pregnancy were selected. Urinary albumin was measured in these subjects and they were followed up to the term for the possible development of PE. The data were analyzed by grouping the subjects into the PE group and control group. Out of 119 subjects 56 were primigravida and 63 were multigravida. From the total subjects 10 developed PE (04 primigravida and 06 multigravida), which shows a prevalence of about 8.4%. The PE group showed a relatively higher value of Albumin Creatinine Ratio (ACR) as compared to control. 63 subjects had microalbuminuria out of which 8 developed PE. The sensitivity of ACR in predicting the development of PE was 80%, specificity 49.54%, Positive pridictive value (PPV) 12.69% and Negitive pridictive value (NPV) 96.42%. It may be concluded that early pregnancy levels of microalbuminuria can be used as predictors of preeclampsia with high negative predictive value.

Key Words: Preeclampsia, Microalbuminuria

Introduction

Hypertension is a common medical complication occurring in about 6-8% of all pregnancies[1]. Preeclampsia (PE) is the causes of 50-70% cases of hypertension in pregnancy[2]. Preeclampsia is diagnosed when the blood pressure at or above 140/90 mmHg occurring on two occasions at least 6 hours apart, associated with proteinuria greater than 300mg/24 hours or greater than 1 gm/l in a random sample, after 20 weeks of gestation[3].

PE occurs in about 6% of the general population; the incidence varies with geographic location[2]. Imperfect documentation and lack of uniformity in the diagnostic criteria are the responsible factors in variation of its frequency. In the developing countries like Bangladesh, the incidence is expected to be higher. Predisposing factors are nulliparity, black race, maternal age below 20 or over 35 years, low socioeconomic status, multiple gestation, hydatidiform mole, polyhydramnios, nonimmune fetal hydrops, twins, obesity, diabetes, chronic hypertension and underlying renal disease[2].

Preeclampsia is not only common and dangerous for both mother and baby, but also unpredictable in onset and progression, and is incurable until termination of the pregnancy. PE is the second leading cause of maternal mortality constituting 12% to 18% of pregnancy related maternal deaths[4]. PE is known as 'the disease of multiple theories'. Among them genetic, immunological, circulatory factors, uterine vascular changes and endothelial dysfunction are important[2].

Many researches have been done to identify screening test that would predict the risk of developing PE before the classical triad of symptoms appear[5]. But the predictive ability of individual test has varied widely and many simply detect early disease. It is clear that no test reliably predicts PE[6]. Further studies are going on to detect an effective and practical early predictor of PE which will be of 'gold standard'[7].

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Previously many studies have been carried out using the same biochemical marker in both diabetes and PE to detect nephropathy. As microalbuminuria is thought to be the earliest sign of nephropathy in diabetes mellitus, some studies have been done to evaluate the predictive value of microalbuminuria for PE also. Persistent microalbuminuria indicates a high probability of damage of the glomerular filtration capacity of the kidney and is of great diagnostic relevance in pregnancy as a possible predictor of developing PE. So, here my attempt was to detect the predictive value of urinary albumin levels in pregnant women who are free from symptoms of PE.

Materials & Methods

A total number of 119 pregnant women at 10-14 weeks of pregnancy were selected randomly on the basis of availability, having no other complications or associated disease. Any pregnant woman having history of chronic hypertension, diabetes, renal disease, multiple pregnancies, any acute or chronic illness and women with symptoms of urinary tract infection were temporarily excluded from the study. Informed written consent was taken from all subjects.

At the time of registration, a detailed obstetric and medical history was taken by following a pre-designed data sheet. General, systemic and obstetric examinations were carried out on the same day. These patients were under regular follow up until delivery. Specific note was made of the development of preeclampsia/eclampsia during antenatal period and/or at the time of delivery.

The selected subjects were on normal diet and requested to fast overnight (10-12 hours) then they reported at around 8:00 am in the Research Division, BIRDEM. From all these subjects during their 10 to 14 weeks of pregnancy clean catch fasting morning urine sample (5 ml) were collected in a clean container first and was preserved at -70^{0}C until biochemical analysis was performed.

10 ml of venous blood was collected into a test tube. Serum was separated rapidly after centrifuging for 10 minutes at a rate of 3000 rpm at 4^0 C and then preserved at -70^0 C until biochemical analysis was done. Serum was not allowed to thaw until the assay was performed.

Relevant investigations were done with blood to exclude diabetes mellitus, any renal disease and hyperlipidemia. Serum glucose was estimated by enzymatic Glucose Oxidase (GOD-PAP) method in autoanalyzer, Autolab of AMS (Analyzer Medical System, Rome, Italy) using reagents of Randox Laboratories, UK. Serum triglyceride was estimated by enzymatic colorimetric (CPO-PAP) method[8] in autoanalyzer (Analyzer Medical System, Rome, Italy) using reagents of Randox Laboratories, UK. Total cholesterol was measured by enzymatic endpoint (cholesterol oxidase / peroxidase) method[9] in autoanalyzer (Analyzer Medical System, Rome, Italy) using reagents of Randox Laboratories, UK. Serum High Density Lipoprotein (HDL) was measured by enzymatic colorimetric (Cholesterol CHOD-PAP) method[10] in autoanalyzer (Analyzer Medical System, Rome, Italy) using reagents of Randox Laboratories, UK. The LDL-Cholesterol level in serum was calculated by using Friedewald formula[10]. Esimation of serum/urinary creatinine was done by alkaline-picrate method using reagents of Randox Laboratories, UK. The urinary microalbumin concentration was determined by immunoturbidimetry assay[11]. The cut-off value of Albumin Creatinine Ratio (ACR) for microalbuminuria was taken as 32mg/g creatinine from McCormik[12].

By statistical analysis, data were expressed as mean±SD. The statistical significance of differences between mean values was assessed by Student's unpaired t-test, Mann Whitney U-test and Chi square test, where appropriate. The difference between groups were evaluated with the "p" value <0.05.

Results

In this study, 119 pregnant women were included at their 10-14 weeks of without any complication or any known risk factors for developing preeclampsia. Among them PE developed in 10 patients, of which 4 were primigravida and 6 were multigravida. The rest 109 patients remained normotensive (Controls). The prevalence of PE among the study group was 8.4%. in

Table I, the age and BMI showed no significant difference between the two groups. The SBP (mean±SD, mmHg) were 105±11 vs 134±11, DBP (mean±SD, mmHg) 67±9 vs 92±10 and MAP (>80 mmHg) 80±8 vs 106±9 respectively in Control and PE subjects. The entire BPs was higher in PE cases and the differences with the Control were highly significant (p<0.001).

Table I: Anthropometric and Clinical Parameters of the Study Subjects

Group	Age Years	BMI kg/m²	SBP mmHg	DBP mmHg	MAP MmHg
Control n=109	25±4	22.68±3.49	105±11	67±9	80±8
PE n=10	26±5	24.54±4.35	134±11	92±10	106±9
t/p value					
Control vs. PE	0.68/0.49	1.58/0.11	7.7/0.001	8.80/0.001	9.30/0.001

BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; n, number of subjects. Results are expressed as mean ± SD, t/p value was calculated using by Student's unpaired t-test.

Table II: Serum Biochemical Parameters of the Study Subjects

Group	S Glu mmol/l	S Chol mg/dl	S TG mg/dl	S HDL mg/dl	S LDL mg/dl
Control n=109	4.28±0.64	167±29	118±43	50.32±10.63	93.34±24.81
PE n=10	4.6±0.62	180±35	137±30	49.9±6.5	103.50±32.59
t/p value					
Control vs. PE	1.46/0.146	1.39/0.164	1.38/0.168	-0.12/0.90	1.20/0.23

S Glu, Serum Glucose; S TG, Serum Triglycerides; S Chol, Serum Cholesterol; S HDL, Serum High Density Lipoprotein; S LDL, Serum Low Density Lipoprotein. Results are expressed as mean ± SD, t/p value was calculated using by Student's unpaired t-test.

In Table II, the fasting serum glucose level and serum lipid profile showed no significant difference among the study groups. Table III shows that the serum creatinine levels (mean ± SD, mg/dl) were 0.8±0.10 vs 0.80±0.08 in control and PE subjects. No significant difference was seen in between the groups.

The value of median ACR [mg of albumin/g of creatinine] was 33.33 (6.7-98.5) in control subjects whereas the corresponding value was 42.38 (28.8-63.05) in PE subjects. The ACR value of PE subjects was relatively higher than that of the controls. The cut-off value of ACR for microalbuminuria was taken as 32mg/g creatinine from McCormik[12].

Table IV & V shows that, among total ACR positive 63 subjects, 8 developed PE later pregnancy, that is 87.30% were

Table III: Serum Creatinine and ACR in the Study Subjects

Group	S Creat (mg/dl)	ACR (mg/g)
Control (n=109)	0.80±0.10	33.33 (6.7-98.5)
PE (n=10)	0.80±0.08	42.38 (28.8-63.05)
t/p or U/p value		
Control vs. PE	-0.01/0.98	384.0/0.074

PE, Preeclampsia; S creat, Serum creatinine; ACR, Albumin Creatinine Ratio; Data are expressed as Mean±SD for serum creatinine and in Median (range) for ACR. t/p value was calculated using by Student's unpaired t-test; U/p value was calculated using Mann-Whitney U test.

Table IV: Percentage of PE among ACR positive cases

	Total	Control (%)	PE	PE (%)
ACR+	63	87.30	8	12.69

PE, Preeclampsia; ACR, Albumin Creatinine Ratio

Table V: The sensitivity, specificity and predictive values of ACR for PE

	PE		
ACR	+	-	Total
+	8	55	63
-	2	54	56
Total	10	109	119

PE, Preeclampsia; ACR, Albumin Creatinine Ratio. Sensitivity=80%; Specificity=49.54%; PPV= 12.69%; NPV =96.42%

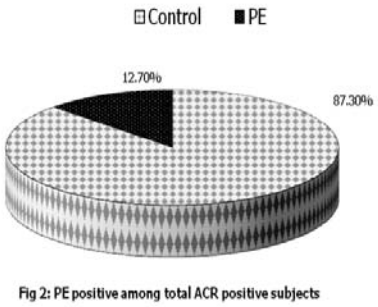

Fig 2: PE positive among total ACR positive subjects

Figure 1: PE positive among total ACR positive subjects

Discussion

Prediction of PE in the early stages of pregnancy can be very helpful in preventing the disorder or in decreasing its severity. It has, thus, become a major focus of research in PE. However, expected progress could not be made in this area due to the deficiency in the understanding of the pathophysiology of the disorder.

One important advancement in the recent year is the accumulation of substantial evidence that PE is associated with widespread vascular dysfunction both in placenta and the mother[13]. It seems that the abnormality starts in placenta and then maternal circulation is involved. Realizing this association attention has been drawn to the biochemical markers of microvascular damage and among these microalbuminuria got special priority as it is now widely used in different clinical situations. An albumin excretion between 25 and 250 mg/day is defined as microalbuminuria and its presence indicates glomerular dysfunction resulting from generalized microvascular damage. So far the attempts to use microalbumin as a predictor of PE have yielded variable results.

The sensitivity of predicting PE by measuring microalbumin in early pregnancy varied between 50% to 68%, the specificity varied between 58 to 97%, PPV varied between 26 to 61% and the NPV varied between 87-94%[14]. One of the reasons of this variability is the lack of strict criteria regarding the selection of the PE subjects and in most of the cases the PE and Gestational Hypertension (the nonproteinuric type of Pregnancy Induced Hypertension) were mixed up in different proportions. Out of 119 pregnant subjects 10 developed PE in later stages; thus, the prevalence is about 8.4% which is little lower than the usual values in the developing world, but seems to be reasonable is an urban setting. The present data (Table-III) shows that the group of pregnant subjects who developed PE in later stages had significantly higher values of ACR as compared to cases who did not develop PE

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In the absence of reference range of ACR in early pregnancy the ACR cut-off point for normal subjects (32 mg/g)[12] was taken as the cut-off point in our subjects. Using these criterion 63 patients had microalbuminuria, among whom 8 developed PE in later pregnancy and 56 did not develop PE.

The sensitivity of microalbumin as a predictor of PE was found to be 80% which lies above the values reported by various authors. The specificity in the present study 49.54%, however, was slightly lower and the NPV in the present study was 96.42%. The substantial discrepancy between the earlier works and the present study regarding PPV may be explained by the fact that, in almost all the earlier studies, the gestational age of the subjects were higher and that increased the possibility of including already developed PE at a mild stage. Increasing the number of subjects may also increase PPV.

Conclusion

As proteinuria is one of the classic signs of preeclampsia, the presence of microalbuminuria in some otherwise symptom-free patient confirms that changes in renal function are present in whom preeclampsia as will eventually develop[15]. Early pregnancy levels of microalbuminuria can be used as predictors of PE with high negative predictive value.

References :

1. Berlin M, Washington AE. Screening for Preeclampsia. For the U.S. Preventive Services Task Force. Guide to Clinical Preventive Services - NCBI Bookshelf. Available from: URL: http://www.ncbi.nlm.nih.gov/books/NBK 15503.htm [acessed on 12-11-10]

2. Reynold C, Mabie WC, Sibai BM, DeCherny AH, Nathan L. Hypertensive States of Pregnancy. In DeCherney AH, Nathan L (eds) Current Obstetric & Gynecologic Diagnosis & Treatment 9th ed. New York: Mc Graw-Hill; 2003: 338-353

3. Arias F. Practical Guide to high risk pregnancy and delivery.2nd edition. India: Mosby;1992.

4. Warden M, Euerle B. Preeclampsia (Toxaemia of Pregnancy). Medicine [serial online] Retrieved: 2005 May 07 Available from: URL: http://www.emedicine.com/med/topic/1905.htm [acessed on 12-11-10]

5. Beaulieu MD. Prevention of preeclampsia. In: Canadian Task Force on the Periodic Health Examination. Canadian Guide to Clinical Preventive Health Care. Ottawa: Health Canada, 1994; 136-43Availablefrom: URL:http://www.phac.aspc.gc.ca/publicat/clinic-clinique/pdf/s1c13e.pdf [acessed on 12-11-10]

6. Robson SC, Edmond DK. Hypertensive and renal disease in pregnancy. Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates 6th ed. United Kingdom: Blackwell Science Ltd; 1999. p.166-185

7. Lijima T, Sujuki S, Sekijuka K, Hishika T, Yagme M, Jinde K et al. Follow-up study on urinary type IV collagen in patients with early stage diabetic nephropathy. J Clin Lab Anal 1998; 12: 378-382

8. Trinder P. Cholesterol Fluid Monoreagent. Ann Clin Biochem 1969;6:24-7.

9. Trinder P. Report of National Cholesterol Education Program Expert panel on detection, Evaluation and treatment of high blood cholesterol in Adults. Arch Intern Med 1988;148:36-9.

10. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparatory ultra centrifuge. Clin Chem 1972;18:499-502.

11. Fielding BA, Price DA, Houton CA. Enzyme immunoassay for urinary albumin. Clin Chem 1983;29(2):355-57.

12. McCormick CP, Konen JC, Shihabi ZK. Microtransferrinuria and microalbuminuria in the diabetic human. Clin Physiol Biochem 1990;8:538S.

13. Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RF. Pathophysiology of Hypertension During Preeclampsia Linking Placental Ischemia With Endothelial Dysfunction. Hypertension 2001;38: 718.

14. Shaarawy M, Salem ME. The Clinical value of microtransferrinuria and microalbuminuria in the prediction of pre-eclampsia. Clin Chem Lab Med 2001;39(1):29-34.

15. Rodriguez MH, Masaki DI, Mestman J, Kumar D, Rude R. Calcium/creatinine ratio and microalbuminuria in the prediction of pre-eclampsia. Am J Obstet Gynecol 1988;159:1452-5.