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Research Article

Early Pregnancy Microalbuminuria as a Predictor of Pre-Eclampsia

Abou Senna HFA[1]* and Elraouf Abonar AEA[2]

[1]Department of Obstetrics and gynecology, Faculty of medicine, Al-Azhar University, Egypt
[2]Department of Clinical Pathology, Faculty of medicine, Al-Azhar University, Egypt

Abstract

Patients and methods: This study was done on 110 pregnant women attended the department of Obestatric and Gynecology, Sayed Galal University Hospital in the period from 4/2014 to 5/2015. From those 110 cases, 4 did not accept to be included in the study and another 6 cases were excluded due to history of significant liver disease, leaving one hundred cases to be included in the study. The laboratory investigations were done for all of the 100 cases in the department of Clinical Pathology, Sayed Galal University Hospital.

Results: Although microalbuminuria were more frequently seen among high risk group, the difference was non-significant. The cause may be the limited number of cases in the two groups. The mean age of cases was slightly higher than controls, but with a non-significant difference.

Taking into consideration that primigravida per se is a risk factor for preeclampsia, all of the 21 primigravida cases were considered as high risk. All of the low risk groups were in the full term, with three cases of the high risk group were preterm. The mean gestational age of the two groups showed non-significant difference. The mean blood pressure both at booking and at delivery showed non-significant differences between the cases and the control subjects. We found a mild rise of blood pressure by around 6-9 mm Hg. The difference between the blood pressure at booking and at delivery was highly significant, which means that this rise was seen in nearly all cases and controls. Slightly higher than one quarter of cases and control group delivered by CS, with the remaining delivered by normal vaginal delivery. There is no significant difference between the two groups as regards the mode of delivery. Birth weight was slightly lower in the cases group than in the control group, with a non-significant difference. The 24 h protein in urine was higher in the cases group than in the control group by around 35 mg. However, the difference between the two groups was non-significant. The non-significance here may be due to the high standard deviation in both groups. PIH was seen only in 7 subjects; 3 in the cases group and 4 in the control group, with a non-significant difference between the two groups. Preeclampsia was seen in 6 cases (12%) of the cases group, compared to 4 cases (8%) of the control groups. This difference was non-significant both because of the low difference between the two groups (only 2 cases) and the limited number of positive cases in both groups. No cases of eclampsia were diagnosed in our study patients or controls. Although age was directly related with the albuminuria, with maximum age among patients with macroalbuminuria and minimum age among patients with no albuminuria; the difference was non-significant. There was non-significant relation between parity and the albuminuria. The cause of this non significance is due to the limited number of micro and macro-albuminuria in our study groups. Blood pressure showed a steady increase between the normal and microalbuminuria and between micro and macroalbuminuria. However, the only significant difference was seen in the diastolic blood pressure at delivery. There was no significant relation between the gestational age and the occurrence of albuminuria. We found a non-significant relation between microalbuminuria and the mode of delivery. Although patients with albuminuria tended to give lower birth weighted babies, the difference was non-significant. There was non-significant relation between PIH and albuminuria. Among the 10 cases who developed preeclampsia, 5 had macroalbuminuria (41.7% of all macroalbuminuria cases), compared to 3 cased had microalbuminuria (14.3%) and only two cases having no albuminuria (3%). The difference was highly significant among the three groups. The most common risk in the high risk group was primigravia, seen in 42% of cases, followed by the maternal age>34 years, seen in 40% of cases (38% alone and 2% associated with twins). Previous history of preeclampsia was seen in 14% of cases and lastly twins were seen in 6% of cases. We found a non-significant relation between the occurrence of preeclampsia and the traditional risks for preeclampsia. The cause of this non significance may be due to the limited number of preeclampsia cases (only 6 cases in the high risk group). The predictive values of microalbuminuria in the pathogenesis of preeclampsia were as follows: sensitivity 80%, specificity 72.2%, positive likelihood ratio 288%, negative likelihood ratio 22.7%, positive predictive value 24.2%, negative predictive value 97%, Odd's ratio 10.4 and lastly accuracy 76.1%.

Conclusion: Microalbuminuria should be considered as an important risk factor for the development of preeclampsia, with high sensitivity and specificity values.

Keywords: Microalbuminuria; Preeclapmsia

Introduction

Pre-eclampsia remains a major cause of perinatal and maternal morbidities and mortality, and is one of the most common medical complications of pregnancy [1]. Preeclampsia and eclampsia occurs in up to 10% of all pregnancies [2]. Preeclampsia describes a common syndrome that occurs in the second half of pregnancy and often manifesting with hypertension and proteinuria. It is the second leading cause of maternal mortality worldwide, constituting 12-18% of pregnancy related maternal deaths [3].

***Corresponding author:** Hesham Fekry Ahmed Abou Senna, Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Egypt, Tel: +0201005231096; E-mail: mohammedelsokkary1@yahoo.com

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More than 100 clinical, biophysical and biochemical tests have been reported in the world literature to predict the development of preeclampsia [4-6]. Proteinuria has classically been an important finding in the diagnosis of preeclampsia and eclampsia. However, customary dip-stick methods for detecting proteinuria fail to detect minimal elevation in urinary excretion of albumin that may be present before other clinical signs and symptoms of preeclampsia with radioimmunoassay and other sensitive methodology for detection of microalbuminuria, it is now possible to detect minimal elevation in albumin excretion that have gone unnoticed in the past. Microalbuminuria refers to sub-clinical elevation of urinary albumin excretion [7]. It has been shown to precede the development of chronic renal failure in patients with insulin-dependent diabetes mellitus, and may be evidence of renal involvement in hypertension [8]. Although there is no established preventative therapy, there is potential gain in being able to identify the women and fetuses at risk, so that appropriate monitoring can ensue, as well as some evidence to support the prophylactic benefit of the early introduction of aspirin, calcium and/or heparin [9-11].

The pathophysiological events resulting in pre-eclampsia begin early in gestation, and precede the onset of the clinical features. One of the early pathophysiological hallmarks is endothelial cell damage [12,13]. Microalbuminuria is a marker of endothelial dysfunction and, in the general population, is associated with hypertension, obesity, diabetes, and overt renal disease, and also with an increased risk for myocardial infarction, stroke, and premature death [14]. The risk rises with the urinary albumin concentration, even within the so-called normal range [15]. Microalbuminuria might be used as an early marker of endothelial dysfunction in pre-eclampsia, before the onset of the overt syndrome, as it is likely that overt proteinuria is preceded by a microalbuminuric phase. Previous studies examining the effectiveness of such a screening procedure have had variable results. Although the 24 h collection of urine is the gold standard for quantifying urinary albumin excretion, it is cumbersome, and results in a delay of at least 24 h in diagnosis [16].

Urinary albumin is usually measured by an immunochemical method such as immunonephelometry, immunoturbidimetry, enzyme-linked immunosorbent assays (ELISA) or radioimmunodiffusion. Recently, a number of studies have used high-performance liquid chromatography (HPLC) for urinary albumin measurement in different populations, and demonstrated that the level of albumin detected in the urine by HPLC, when compared with conventional assays, is significantly greater because HPLC is able to measure both immunoreactive and immunounreactive intact albumin [17].

Aim of the Work

This thesis study is a trial to evaluate the role of early pregnancy microalbuminuria as a predictor for preeclampsia in low and high risk pregnancy.

Patients and Methods

Type of study

Controlled Prospective study.

Site of study

This study was done on 110 pregnant women attended the department of Obstetrics and Gynecology, Sayed Galal University Hospital in the period from 4/2014 to 5/2015. From those 110 cases, 4 did not accept to be included in the study and another 6 cases were excluded due to history of significant liver disease, leaving one hundred cases to be included in the study. The laboratory investigations were done for all of the 100 cases in the department of Clinical Pathology, Sayed Galal University Hospital.

These 100 patients were divided into 2 groups:

Group I: (50 patients): High risk patient for preeclampsia: has one or more of risk factors.

(1) Preeclampsia in a previous pregnancy.

(2) First pregnancy.

(3) Extremes of maternal age.

(4) Multifetal gestation.

(5) Family history of preeclampsia.

(6) Chronic hypertension, and/or renal disease.

(7) Pregestational diabetes mellitus.

(8) Obesity and insulin resistance.

Group II: (50 patients): Low risk patient for preeclampsia as control group.

Inclusion criteria

1. Equal to or less than 13 weeks of gestation at the time of recruitment.

Exclusion criteria

1. More than 13 weeks of gestation at the time of recruitment.

2. History of significant liver disease.

After well-informed verbal consent all patients were subjected to:

(1) At booking a complete clinical history was obtained from each patient with emphasis on her age, parity, last menstrual period, past obstetric and medical history as well as drug history. The family, social history and the history of the present pregnancy were also obtained. Patients were asked about symptoms of vaginal or urinary tract infection. This was then followed by a complete physical examination.

(2) 24 h urine collection. The collection was to start at 8 a.m the following day and complete 24 h after, using the clear white plastic 4 L container that was given to the patients and returned to the clinic immediately after collection. Subjects were asked to recapitulate this procedure. Patients with incomplete collection were made to repeat it.

All women were instructed to adhere to their normal diet and physical activity. The volume of urine was measured and two aliquots were stored for future assay. One was frozen at minus 20°C for creatinine and the other kept at 4°C for albumin assays respectively. All albumin assays were performed using the Turbidimetry method. All urine specimens were run in duplicate in the same assay with the mean value used for analysis.

Assessment of protein in urine/24 h

The method measures the shift in the absorption spectrum from 460 to 600 nm of the complex that occurs at acid PH between pyrogallol red-molibadate (PRM) and the basic amino groups of urine proteins.

The intensity of the colored complex formed is proportional to the concentration of protein in the urine sample

PRM+Urine protein (ph2.5) → PRM - Protein complex

Instrument

*Semi-Automated Photometer (Humalyzer3000) German.

*Automatic pipettes to measure reagent and sample volume.

Reagent Composition:

Pyrogallol red-molibadate (PRM): Succinate buffer 60 mmol/L pH 2.5

Pyrogallol red 0.06 mmol/L, sodium molibadate 0.04 mmol/L. Sodium dodecyl sulfate (SDS) 0.08 mmol/L.

Sampling

*Urine collected without preservatives.

*Turbid specimens should be centrifuged before testing.

Urinary albumin excretion (UAE): It is excretion of albumin in urine per day (24 h), expressed as (mg/24 h).

UAE (mg/24 h)=Albumin (mg/dl) × Volume of 24 h urine (dl)

(3)The patients were followed up till delivery, receiving routine antenatal care.

Normal albuminuria was defined as albumin excretion<30 mg/24 h, microalbuminuria as between 30-300 mg/24 h and macro albuminuria as>300 mg/24 h.

At each visit, the blood pressure was measured and urine tested for albumin.

The presence of preeclampsia was defined as the presence of blood pressure of 140/90 mm Hg or more, or a rise of 30 mm Hg in systolic pressure or of 15 mm Hg in diastolic pressure (measured twice, 6 h apart at bed rest) associated with proteinuria.

Statistical Analysis

Statistical package for social sciences (IBM-SPSS), version 22 IBM-Chicago, USA was used for statistical data analysis.

Data expressed as mean, standard deviation (SD), number and percentage. Mean and standard deviation were used as descriptive value for quantitative data.

Student t test was used to compare the means between two groups, and one-way analysis of variance (ANOVA) test was used to compare means of more than two groups. Paired t test was used to compare means in the same group at different times.

Sensitivity statistics were done for microalbuminuria as a risk factor for preeclampsia.

For all these tests, the level of significance (P-value) can be explained as:

No significance P>0.05

Significance P<0.05

High significance P<0.001

Results

Study groups

Our study included 100 pregnant women, half of them (50 cases) were in the (high risk) zone for the development of preeclampsia, and the other half were in the (low risk) zone. The high risk group were considered (cases) while the low risk group were considered (controls). Although microalbuminuria and macroalbuminuria were more frequently seen among high risk group, the difference was non-significant. The cause may be the limited number of cases in the two groups (Table 1).

The mean age of cases was slightly higher than controls, but with a non-significant difference (Table 2). Taking into consideration that primigravida per se is a risk factor for preeclampsia, all of the 21 primigravida cases were considered as high risk (Table 3). All of the low risk groups were in the full term, with three cases of the high risk group were preterm. The mean gestational age of the two groups showed non-significant difference (Table 4). The mean blood pressure both at booking and at delivery showed non-significant differences between the cases and the control subjects (Table 5). We found a mild rise of blood pressure by around 6-9 mm Hg. The difference between

	Albuminuria			Total
	Normal	Microalbuminuria	Macroalbuminuria	
High risk group for Pre-eclampsia (Cases)	31 (62%)	12 (24%)	7 (14%)	50
Low risk group for Pre-eclampsia (Controls)	36 (72%)	9 (18%)	5 (10%)	50
Total	67	21	12	100
Chi square=1.135, P value=0.567 (NS)				

Table 1: Microalbuminuria.

	Group	Mean	Std. Deviation	Std. Error Mean
Age	High risk group for Pre-eclampsia (Cases)	29.3	6.591	0.932
	Low risk group for Pre-eclampsia (Controls)	27.78	3.196	0.452
T test=1.467, P value=0.147 (NS)				

Table 2: Mean age between the two groups.

	High risk group for Pre-eclampsia (Cases)	Low risk group for Pre-eclampsia (Controls)	Total	
Parity	0	21	0	21
	1	2	21	23
	2	11	17	28
	3	4	7	11
	4	6	3	9
	5	2	1	3
	6	2	1	3
	7	1	0	1
	8	1	0	1
		Chi square=42.466, P value<0.001 (HS)		

Table 3: Parity difference between the two groups.

	Group	Mean	Std. Deviation	No. of preterm
Gestational age at delivery	High risk group for Pre-eclampsia (Cases)	37.08	1.7825	3 cases
	Low risk group for Pre-eclampsia (Controls)	37.2	1.1249	None
T test=0.403, P value=0.688 (NS)				

Table 4: Gestational age at delivery between the two groups.

the blood pressure at booking and at delivery was highly significant, which means that this rise was seen in nearly all cases and controls (Table 6).

Slightly higher than one quarter of cases and control group delivered by CS, with the remaining delivered by normal vaginal delivery. There is no significant difference between the two groups as regards the mode of delivery (Table 7). Birth weight was slightly lower in the cases group than in the control group, with a non-significant difference (Table 8). The 24 h protein in urine was higher in the cases group than in the control group by around 35 mg. However, the difference between the two groups was non-significant. The non-significance here may be due to the high standard deviation in both groups (Table 9). PIH was seen only in 7 subjects; 3 in the cases group and 4 in the control group, with a non-significant difference between the two groups (Table 10).

Preeclampsia was seen in 6 cases (12%) of the cases group, compared to 4 cases (8%) of the control groups. This difference was non-significant both because of the low difference between the two groups (only 2 cases) and the limited number of positive cases in both groups.

	Group	Mean	SD	SE	T test	P value
Systolic BP at booking	High risk group	118.58	8.4542	1.1956	0.795	0.428
	Low risk group	117.12	9.8471	1.3926		(NS)
Diastolic BP at booking	High risk group	74.96	5.3029	0.7499	0.225	0.822
	Low risk group	75.2	5.3452	0.7559		(NS)
Systolic BP at delivery	High risk group	127.2	11.2558	1.5918	1.254	0.213
	Low risk group	124.2	12.6314	1.7863		(NS)
Diastolic BP at delivery	High risk group	80.8	9.2229	1.3043	0.223	0.824
	Low risk group	81.2	8.7225	1.2335		(NS)

Table 5: Blood pressure.

Group		Mean	SD	SE	Paired t test	P value
High risk group	Systolic BP at booking	118.58	8.4542	1.1956	8.589	<0.001 (HS)
	Systolic BP at delivery	127.2	11.2558	1.5918		
	Diastolic BP at booking	74.96	5.3029	0.7499	6.187	<0.001 (HS)
	Diastolic BP at delivery	80.8	9.2229	1.3043		
Low risk group	Systolic BP at booking	117.12	9.8471	1.3926	6.671	<0.001 (HS)
	Systolic BP at delivery	124.2	12.6314	1.7863		
	Diastolic BP at booking	75.2	5.3452	0.7559	5.949	<0.001 (HS)
	Diastolic BP at delivery	81.2	8.7225	1.2335		

Table 6: Difference between BP at booking and at deliver of both groups.

		Mode of delivery		Total
		Normal	CS	
Group	High risk group for Pre-eclampsia (Cases)	37	13	50
	Low risk group for Pre-eclampsia (Controls)	34	16	50
Chi square=0.437, P value=0.509 (NS)				

Table 7: Mode of delivery between the two groups.

	Group	Mean	SD	SE
Birth weight (Kg)	High risk group for Pre-eclampsia (Cases)	2.797	0.67781	0.09586
	Low risk group for Pre-eclampsia (Controls)	2.925	0.66748	0.0944
T test=0.951, P value=0.344 (NS)				

Table 8: Birth weight between the babies of the two groups.

No cases of eclampsia were diagnosed in our study patients or controls (Table 11). Although age was directly related with the albuminuria, with maximum age among patients with macroalbuminuria and minimum age among patients with no albuminuria; the difference was non-significant (Table 12). There was non-significant relation between parity and the albuminuria. The cause of this non significance is due to the limited number of micro and macro-albuminuria in our study groups (Table 13).

Blood pressure showed a steady increase between the normal and microalbuminuria and between micro and macroalbuminuria. However, the only significant difference was seen in the diastolic blood

Group	Mean	Std. Deviation	Minimum	Maximum
High risk group for Pre-eclampsia (Cases)	108.26	138.5581	8	480
Low risk group for Pre-eclampsia (Controls)	75.56	116.4401	8	410
Total	91.91	128.3858	8	480
T test=1.278, P value=0.204 (NS)				

Table 9: 24 h urine protein collection.

		P I H		Total
		No	Yes	
Group	High risk group for Pre-eclampsia (Cases)	47	3	50
	Low risk group for Pre-eclampsia (Controls)	46	4	50
Total		93	7	100
Chi square=0.154, P value=0.695 (NS)				

Table 10: PIH between the two groups.

		Preeclampsia		Total
		No	Yes	
Group	High risk group for Pre-eclampsia (Cases)	44	6	50
	Low risk group for Pre-eclampsia (Controls)	46	4	50
Total		90	10	100
Chi square=0.444, P value=0.505 (NS)				

Table 11: Preeclampsia between the two groups of patients.

Albuminuria	Mean	Std. Deviation
Normal	28.31	5.076
Microalbuminuria	28.48	5.715
Macroalbuminuria	29.92	5.282
Total	28.54	5.21
Anova=0.479, P value=0.621 (NS)		

Table 12: Relation between age and microalbuminuria.

		Albuminuria			
		Normal	Microalbuminuria	Macroalbuminuria	Total
Parity	0	10	8	3	21
	1	15	5	3	23
	2	22	3	3	28
	3	8	2	1	11
	4	5	3	1	9
	5	2	0	1	3
	6	3	0	0	3
	7	1	0	0	1
	8	1	0	0	1
Total		67	21	12	100
Chi square=11.475, P value=0.779 (NS)					

Table 13: Parity in relation to albuminuria.

pressure at delivery (Table 14). There was no significant relation between the gestational age and the occurrence of albuminuria (Table 15). We found a non-significant relation between microalbuminuria and the mode of delivery (Table 16). Although patients with albuminuria tended to give lower birth weighted babies, the difference was non-significant (Tables 17 and 18).

There was non-significant relation between PIH and albuminuria (Table 19). Among the 10 cases who developed preeclampsia, 5 had macroalbuminuria (41.7% of all macroalbuminuria cases), compared to 3 cased had microalbuminuria (14.3%) and only two cases having no albuminuria (3%). The difference was highly significant among the three groups (Table 20). The most common risk in the high risk group was primigravia, seen in 42% of cases, followed by the maternal age>34 years, seen in 40% of cases (38% alone and 2% associated with twins). Previous history of preeclampsia was seen in 14% of cases and lastly twins were seen in 6% of cases (Table 21). We found a non-significant relation between the occurrence of preeclampsia and the traditional risks for preeclampsia. The cause of this non significance may be due to the limited number of preeclampsia cases (only 6 cases in the high risk group) (Tables 22 and 23).

Albuminuria		Systolic BP at booking	Diastolic BP at booking	Systolic BP at delivery	Diastolic BP at delivery
Normal	Mean	117.015	74.582	124.03	79.403
	SD	8.7896	5.2488	10.4533	7.361
Microalbuminuria	Mean	119.714	76.143	128.571	82.857
	SD	7.7727	5.0625	13.8873	11.0195
Macroalbuminuria	Mean	119.25	76	130	86.667
	SD	12.9904	6.0151	15.3741	10.7309
Total	Mean	117.85	75.08	125.7	81
	SD	9.1601	5.2985	11.9979	8.933
ANOVA test		0.851	0.897	2.065	4.193
P value		0.430 (NS)	0.411 (NS)	0.132 (NS)	0.018 (S)

Table 14: Blood pressure versus albuminuria.

Albuminuria	Mean	Std. Deviation
Normal	37.119	1.629
Microalbuminuria	37.429	1.121
Macroalbuminuria	36.75	1.138
Total	37.14	1.148
	ANOVA=0.815, P value=0.446 (NS)	

Table 15: Gestational age and risk for albuminuria.

		Albuminuria			Total
		Normal	Microalbuminuria	Macroalbuminuria	
Mode of delivery	Normal	49	15	7	71
	CS	18	6	5	29
Total		67	21	12	100
Chi square=1.085, P value 0.581 (NS)					

Table 16: Mode of delivery in relation to albuminuria.

Albuminuria	Mean	Std. Deviation
Normal	2.9522	0.71268
Microalbuminuria	2.7333	0.57213
Macroalbuminuria	2.575	0.50475
Total	2.861	0.67235
ANOVA=2.129, P value=0.125 (NS)		

Table 17: Birthweight relation to albuminuria.

Albuminuria	Mean	Std. Deviation
Normal	17.254	6.0361
Microalbuminuria	164.048	72.7183
Macroalbuminuria	382.5	50.1135
Total	91.91	128.3858
ANOVA=534.337, P value<0.001 (HS)		

Table 18: 24 h urinary protein and albuminuria.

		Albuminuria			Total
		Normal	Microalbuminuria	Macroalbuminuria	
PIH	No	63	18	12	93
	Yes	4	3	0	7
Total		67	21	12	100
Chi square=2.725, P value=0.256 (NS)					

Table 19: PIH and albuminuria.

		Albuminuria			Total
		Normal	Microalbuminuria	Macroalbuminuria	
Preeclampsia	No	65	18	7	90
	Yes	2	3	5	10
Total		67	21	12	100
Chi square=17.462, P value<0.001 (HS)					

Table 20: Preeclampsia in relation to albuminuria.

	Frequency	Percent
Twins	2	4
History of Pre-eclampsia	7	14
Age>34 years	19	38
Primigravida	21	42
Age>34 years + Twins	1	2
Total	50	100

Table 21: Risks seen among the high risk group.

		Preeclampsia		Total
		No	Yes	
Risk	Twins	2	0	2
	History of Pre-eclampsia	7	0	7
	Age>34 years	16	3	19
	Primigravida	18	3	21
	Age>34 years + Twins	1	0	1
Total		44	6	50
Chi square=1.726, P value=0.786 (NS)				

Table 22: Relation between risk of preeclampsia and the occurrence of preeclampsia among high risk group only.

Item	Value
Number of preeclampsia cases	10
Number of albuminuria among preeclampsia cases	08-Oct
Number of albuminuria among non-preeclampsia cases	25/90
True positive	8
True negative	65
False positive	25
False negative	2
Sensitivity	80%
Specificity	72.20%
Positive predictive value	2.88
Negative predictive value	0.227
Odd's ratio	10.4

Table 23: Predictive values.

Discussion

Hypertension is a common medical complication occurring in about 6-8% of all pregnancies. Preeclampsia (PE) is the causes of 50-70% cases of hypertension in pregnancy. Preeclampsia is diagnosed when the blood pressure at or above 140/90 mm Hg occurring on two occasions at least 6 h apart, associated with proteinuria greater than 300 mg/24 h or greater than 1 g/L in a random sample, after 20 weeks of gestation [1]. Preeclampsia is the most frequently encountered medical complications during pregnancy, affecting 3–5% of pregnant women worldwide [1].

In developing countries where access to health care is limited, preeclampsia is a leading cause of maternal mortality, with estimates of>60,000 maternal deaths/year [1]. In the developed world, the burden of this disease falls on the neonate because of premature deliveries performed to preserve the health of the mother. Worldwide, preeclampsia is associated with a perinatal and neonatal mortality rate of 10% [18-20]. 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. PE is known as 'the disease of multiple theories'. Among them genetic, immunological, circulatory factors, uterine vascular changes and endothelial dysfunction are important [18-20].

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 [18-20]. Serum proteins play major roles in the body including transporting essential molecules such as hormones, vitamins, lipids, minerals and exogenous substance such as drugs [21,22]. The most abundant serum protein is albumin, accounting for 60% of serum protein and with a concentration of 3.4-5.4 g/dL. Normally, the kidneys reabsorb almost all the filtered albumin. A very low amount of albumin is present in the urine. However, certain illnesses such as diabetes, CKD and hypertension may mediate physiological changes that lead to excretion of larger amounts of albumin into the urine, albuminuria [23]. Albumin in the urine at levels exceeding 300 mg/day is regarded as macroalbuminuria. Low amount of albumin in the urine that cannot be detected by conventional dipsticks (micro-albuminuria] was firstly reported in 1969 by who studied the increased level of albuminuria in type 2 diabetes. Microalbuminuria is defined as levels of albumin between 30-300 mg per day [24].

One important advancement in the recent years is the accumulation of substantial evidence that PE is associated with widespread vascular dysfunction both in placenta and the mother. 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 this 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 [25]. The aim of our study was to evaluate the role of early pregnancy microalbuminuria as a predictor for preeclampsia in low and high risk pregnancy. Our study included 100 pregnant women; half of them (50 cases) were in the (high risk) zone for the development of preeclampsia, and the other half were in the (low risk) zone. The high risk group were considered (cases) while the low risk group were considered (controls).

Although microalbuminuria and macroalbuminuria were more frequently seen among high risk group, the difference was non-significant. The cause may be the limited number of cases in the two groups.

The mean age of cases was slightly higher than controls, being 29.3 years among cases and 27.78 years among controls, but with a non-significant difference. These figures were similar to those seen by whose median ages were 27 years for microalbuminuria group and 28 years for non-microalbuminuria group [26]. On the other hand, our study population were much younger than those seen by Sandvik et al. whose patients' mean age was 37.9 years among cases with preeclampsia and 39 years among cases without preeclampsia [27].

Taking into consideration that primigravida per se is a risk factor for preeclampsia, all of the 21 primigravida cases were considered as high risk. This caused the highly significant difference between cases and controls regarding parity. Jensen found that micro-albuminuria was more frequently seen among nulliparous versus multiparous women, but with a non-significant difference. On the other hand, Bar et al. found a non-significant correlation between parity and preeclampsia [28]. In our study, the mean blood pressure both at booking and at delivery showed non-significant differences between the cases and the control subjects. The mean blood pressure at booking was 118.5/75 mm Hg for high risk group and 117/75.2 mm Hg for low risk group. Sandvik et al. found a slight and non-significant difference between cases with preeclampsia and those with non-preeclampsia [27]. Blood pressure rose at delivery by around 6-9 mm Hg to be 127.2/80.8 mm Hg for high risk group and 124.2/81.2 mm Hg for low risk group. The difference between the blood pressure at booking and at delivery was highly significant, which means that this rise was seen in nearly all cases and controls. Both groups were in the full term, with the exception of only three cases among the high risk group were preterm. The mean gestational age of the two groups was 37.08 weeks for cases and 37.2 weeks for controls, with non-significant difference. This was similar to that seen by Jensen whose population study median gestational age was 37 weeks for both micro-albuminuria and non-micro-albuminuria groups. Bar found that preterm delivery was much higher among preeclampsia group (62.5%) compared to only 4.5% among non-preeclampsia group, with a highly significant difference [26,28].

Slightly higher than one quarter of our cases and controlled delivered by CS, with the remaining delivered by normal vaginal delivery. There is no significant difference between the two groups as regards the mode of delivery. Birth weight was slightly lower in the cases group than in the control group, with a non-significant difference. Jensen found that birth weight was lower among patients with microalbuminuria than those with non microalbuminuria, with a highly significant difference [26,28]. Jensen et al. found that IUGR was seen much frequent among preeclampsia group (56%) compared to only 2.2% among patients with non-preeclampsia group [26]. The 24 h protein in urine was higher in the cases group than in the control group by around 35 mg. However, the difference between the two groups was non-significant. The non-significance here may be due to the high standard deviation in both groups.

PIH was seen only in 7 subjects; 3 in the cases group and 4 in the control group, with a non-significant difference between the two groups. Definition of gestational hypertension was given by working group of National High Blood Pressure Education Programme (NHBPEP 2000). According to it, any pregnant female of ≥ 20 weeks of gestation with blood pressure ≥ 140/90 mm Hg noted first time during pregnancy on ≥ 2 occasions at least 6 h apart without any visible proteinuria was considered as having gestational hypertension. It is also

known as pregnancy induced hypertension (PIH). Here blood pressure returns to normal pre-pregnant level within 12 weeks of delivery so it is also known as transient hypertension. Overall incidence of PIH is 6-7% of all pregnancies. The risk of its progression to preeclampsia is 15-26%. When PIH develops after 36 weeks of gestation, the risk of its progression to preeclampsia falls to 10% [29]. Preeclampsia was seen in 6 cases (12%) of the cases group, compared to 4 cases (8%) of the control groups. This difference was non-significant both because of the low difference between the two groups (only 2 cases) and the limited number of positive cases in both groups. No cases of eclampsia were diagnosed in our study patients or controls. The incidence of preeclmpsia was much higher than that seen by Jensen which was only 2.6% [26].

Although age was directly related with the albuminuria, with maximum age among patients with macroalbuminuria and minimum age among patients with no albuminuria; the difference was non-significant. There was non-significant relation between parity and the albuminuria. The cause of this non significance is due to the limited number of micro and macro-albuminuria in our study groups. Blood pressure showed a steady increase between the normal and microalbuminuria and between micro and macroalbuminuria. However, the only significant difference was seen in the diastolic blood pressure at delivery [26]. Jensen DM found a highly significant rise of blood pressure among patients with microalbuminuria compared to those with non microalbuminuria. They found that preeclampsia was seen in 41% of patients with microalbuminuria, compared to only 12% of patients with non microalbuminuria, with a highly significant difference. There was no significant relation between the gestational age and the occurrence of albuminuria. We found a non-significant relation between microalbuminuria and the mode of delivery. Although patients with albuminuria tended to give lower birth weighted babies, the difference was non-significant. There was non-significant relation between PIH and albuminuria.

Among the 10 cases who developed preeclampsia, 5 had macroalbuminuria (41.7% of all macroalbuminuria cases), compared to 3 cased had microalbuminuria (14.3%) and only two cases having no albuminuria (3%). The difference was highly significant among the three groups. The most common risk in the high risk group was primigravia, seen in 42% of cases, followed by the maternal age>34 years, seen in 40% of cases (38% alone and 2% associated with twins). Previous history of preeclampsia was seen in 14% of cases and lastly twins were seen in 6% of cases. Relation between risk of preeclampsia and the occurrence of preeclampsia among high risk group only: We found a non-significant relation between the occurrence of preeclampsia and the traditional risks for preeclampsia. The cause of this non significance may be due to the limited number of preeclampsia cases (only 6 cases in the high risk group).

The predictive values of microalbuminuria in the pathogenesis of preeclampsia were as follows: sensitivity 80%, specificity 72.2%, positive likelihood ratio 288%, negative likelihood ratio 22.7%, positive predictive value 24.2%, negative predictive value 97%, Odd's ratio 10.4 and lastly accuracy 76.1%. These figures were somewhat similar to that seen by Sheela et al. whose results were: sensitivity 53.8%, specificity 86%, positive predictive value 36%, negative predictive value 95%, accuracy 73.6% and area under curve (AUC) 0.7985 with a confidence interval of 0.72-0.88 [30]. Salako et al. [31,32] found significantly increase d incidence of preeclampsia with an increase in albumin excretion. Single urinary microalbumin excretion estimation at time of antenatal booking predicted occurrence of HDP with the sensitivity, specificity, positive and negative predictive values of 88.9%, 67.9%, 22.2% and 98.3%, respectively. Shaarawy et al. who have evaluated the clinical value of microtransfferrinuria and microalbuminuria in prediction of preeclampsia in asymptomatic women have concluded that microtransfferrinuria was a more sensitive marker than microalbuminuria [33]. However, Chhabra et al. have found that estimation of microalbuminuria around 18 weeks of gestation seemed useful, especially in primigravida [34,35].

However, there is a high variation among different studies regarding these figures. For example, Shaarawy stated that 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% [33]. 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 non-proteinuric type of Pregnancy Induced Hypertension) were mixed up in different proportions.

Conclusion

Microalbuminuria should be considered as an important risk factor for the development of preeclampsia, with high sensitivity and specificity values.

References

1. WHO (2005) Make every mother and child count. World Health Report, 2005. Geneva, Switzerland: World Health Organization.
2. Palma Gamiz JL (1998) Arterial hypertension and pregnancy: Diagnostic criteria and therapeutic approach. Rev Esp Cardiol 514: 50-58.
3. Hsu S, Euerle BD (2012) Ultrasound in pregnancy. Emerg Med Clin North Am 30: 849-867.
4. Sibai BM (1998) Prevention of preeclampsia: A big disappointment. Am J Obstet Gynecol 179: 1275-1278.
5. Caritis S, Sibai B, Hauth J, Lindheimer M, VanDorsten P, et al. (1998) Predictors of pre-eclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol 179: 946-951.
6. Sibai BM, Lindheimer M, Hauth J, Caritis S, VanDorsten P, et al. (1998) Risk factors for preeclampsia, abruptio placentae and adverse neonatal outcomes among women with chronic hypertension. N Engl J Med 339: 667-71.
7. Higby K, Suiter CR, Siler-Khodr T (1995) A comparison between two screening methods for detection of microproteinuria. Am J Obstet Gynecol 173: 1111-1114.
8. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, et al. (1982) Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1: 1430-1432.
9. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. (2010) Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: A meta-analysis. Obstet Gynecol 16: 402-414.
10. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L (2010) Calcium supple-mentation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. CD001059.
11. Vucic N, Frleta M, Petrovic D, Ostojic V (2009). Thrombophilia, preeclampsia and other pregnancy complications. Acta Med Croatica 63: 297-305.
12. Young BC1, Levine RJ, Karumanchi SA (2010) Pathogenesis of preeclampsia. Annu Rev Pathol 5: 173-192.
13. Karumanchi SA, Levine RJ (2010) How does smoking reduce the risk of preeclampsia? Hypertension 55: 1100-1101.
14. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, et al. (2004) Microalbuminuria independ-ently predicts all-cause and cardio-vascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. Int J Epidemiol 33: 189-198.
15. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, et al. (2004) Very low levels of microalbuminuria are associated with increased risk of

coronary heart disease and death independently of renal function, hypertension and diabetes. Circulation 110: 32-35.

16. Gaspari F, Perico N, Remuzzi G (2006) Timed urine collections are not needed to measure urine protein excretion in clinical practice. Am J Kidney Dis 47: 1-7.
17. Comper WD, Osicka TM, Clark M, MacIsaac RJ, Jerums G (2004) Earlier detection of microalbuminuria in diabetic patients using a new urinary albumin assay. Kidney Int 65: 1850-1855.
18. Sibai BM (2013) What to expect from expectant management in severe preeclampsia at<34 weeks gestation: Pregnancy outcomes in developed vs. developing countries. Am J Obstet Gynecol 209: 400-401.
19. Zhang JJ, Grewal J, Roosen-Runge M, Lazaga AP, Souza JP, et al. (2012) Severe anemia, sickle cell disease and thalassemia as riskfactors for preeclampsia in developing countries. Pregnancy Hypertens 2: 191-192.
20. Osungbade KO, Ige OK (2011) Public health perspectives of preeclampsia in developing countries: Implication for health system strengthening. J Pregnancy 481095.
21. Jank A, Kratzsch J, Stepan H (2012). Effect of terminated fetal circulation on maternal angiogenic factors in severe early preeclampsia. Hypertens Pregnancy 31: 201-206.
22. Stepan H, Philipp A, Roth I, Kralisch S, Jank A, et al. (2012) Serum levels of the adipokine zinc-alpha2-glycoprotein are increased in preeclampsia. J Endocrinol Invest 35: 562-565.
23. Kadono M, Hasegawa G, Shigeta M, Nakazawa A, Ueda M, et al. (2010) Serum albumin levels predict vascular dysfunction with paradoxical pathogenesis in healthy individuals. Atherosclerosis 209: 266-270.
24. Mattix HJ, Hsu CY, Shaykevich S, Curhan G (2002) Use of the albumin/creatinine ratio to detect microalbuminuria: Implications of sex and race. J Am Soc Nephrol 13: 1034-1039.
25. Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RA (2001) Pathophysiology of hypertension during preeclampsia linking placental ischemia with endothelial dysfunction. Hypertension 38: 718-722.
26. Jensen DM, Damm P, Ovesen P, Molsted-Pedersen L, Beck-Nielsen H, et al. (2010) Micro-albuminuria, preeclampsia, and preterm delivery in pregnant women with type 1 diabetes: Results from a nationwide Danish study. Diabetes Care 33: 90-94.
27. Sandvik MK, Hallan S, Svarstad E, Vikse BE (2013) Preeclampsia and prevalence of microalbuminuria 10 years later. Clin J Am Soc Nephrol 8: 1126-1134.
28. Bar J, Kaplan B, Wittenberg C, Erman A, Boner G, et al. (1999) Microalbuminuria after pregnancy complicated by preeclampsia. Nephrol Dial Transplant 14: 1129-32.
29. Hromadnikova I, Kotlabova K, Hympanova L, Krofta L (2016) Gestational hypertension, preeclampsia and intrauterine growth restriction induce dysregulation of cardiovascular and cerebrovascular disease associated microRNAs in maternal whole peripheral blood. Thromb Res 137: 126-140.
30. Sheela CN, Beena SR, Mhaskar A (2011) Calcium-creatinine ratio and microalbuminuria in prediction of preeclampsia. J Obstet Gynaecol India 72: 76.
31. Salako BL, Olayemi O, Odukogbe AT, Adedapo KS, Aimakhu CO, et al. (2003) Microalbuminuria in pregnancy as a predictor of preeclampsia and eclampsia. West Afr J Med 22: 295-300.
32. Salako BL, Odukogbe AT, Olayemi O, Adedapo KS, Aimakhu CO, et al. (2003) Serum albumin, creatinine, uric acid and hypertensive disorders of pregnancy. East Afr Med J 80: 424-428.
33. Shaarawy M, Meleigy M, Rasheed K (2001) Maternal serum transforming growth factor beta-2 in preeclampsia and eclampsia, a potential biomarker for the assessment of disease severity and fetal outcome. J Soc Gynecol Investig 8: 27-31.
34. Chhabra S, Bhagwat N, Chakravorty A (2002) Reduction in the occurrence of uterine rupture in Central India. J Obstet Gynaecol 22: 39-42.
35. Chhabra S, Dhorey M (2002) Retained placenta continues to be fatal but frequency can be reduced. J Obstet Gynaecol 22: 630-633.