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Original Research Article

Urinary Abumin - Creatinine Ratio as a Predictor of Severity of Pre-Eclampsia.

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Abstract:

Objectives: The present study was to investigate urinary albumin : creatinine ratio as a predictor of severity of pre-eclampsia and also assess the use of spot urinary albumin: creatinine ratio as an alternative method for assessing the prognosis of preeclampsia in comparison to 24 hr urinary protein estimation to the severity of pre-eclampsia.

Methods: A total of 100 pregnant women with age 18-35 years were enrolled. All the subjects were divided in two groups. 50 pregnant women who had been clinically diagnosed with pre-eclampsia were included in case group and 50 pregnant healthy women were included in control group. Urine sample was collected in a dry, clean container with a tight-fitting lid. A midstream sample of urine was done to avoid contamination. And cloudy or particulate sample was centrifuged prior to analysis. Proper precautions were taken while collecting blood samples to ensure safety of self and to the patient. Standard procedures were used to obtain accurate result at every step. Quantitative estimation of Microalbumin (MAL) of urine was done by turbidimetric immunoassay. The calculation of ACR was automatically performed by semi autoanalyzer.

Results: Maximum incidence of Preeclampsia in age group 20-24 years. Mean age of Preeclamptic woman was 21.24 years and normal pregnant woman was 23.75 years. Maximum incidence of Preeclampsia (70%) was in first gravida. Mean urinary albumin of preeclamptic women was 45.21mg/L. In normal pregnancy, mean urinary albumin was 14.12mg/L. And it was statistically significant differences (P<0.001). Mean urinary creatinine in preeclamptic women was 110.91mg/dl. In normal pregnancy, mean urinary creatinine was 161.92mg/dl. And it was significantly differences (P<0.001). Mean ACR of preeclamptic women was 41.97mg/g. Mean ACR of normal healthy pregnant women was 9.71. And it was statistically significant differences (p<0.001).

Conclusions: Pre-eclampsia remains a significant cause of maternal mortality and morbidity. There is a need of a biochemical marker, which can assess the disease and its severity earlier, to reducing the undesired outcome in pregnancy. Hence, Urinary albumin-creatinine ratio can be used as an early diagnostic as well as prognostic marker in pre-eclampsia.

Key words: Pregnancy, Pre-eclampsia, Albumin- creatinine ratio

Introduction

Pre-eclampsia is a multisystem disorder characterized by hypertension and proteinuria with onset after 20 weeks of gestation [1].

Ten million women develop PE each year around the world. In India the incidence of PE is reported to be 8-10% among the pregnant women. Worldwide about 76,000 pregnant women die each year from PE and hypertensive related disorder [2].

Preeclampsia results in an increased risk for intrauterine growth restriction, prematurity and death. PE is also recognized as a major risk factor for cardiovascular disease later in life for both the women and her child [3]. Unfortunately, there is no effective therapy for the management of pre-eclampsia and the only "cure'' is to deliver the infant [4]. Although the pathophysiology of pre-eclampsia remains unknown, recent studies show that PE is a two-stage disease, Placental stage (or stage 1) and a peripheral stage (stage 2). During stage 1, inadequate development of maternal spiral arteries results in a deficient maternal blood supply to the placenta, bringing about placental ischemia and hypoxia. This is followed by Stage 2, consisting of

the classical manifestation of widespread endothelial dysfunction, proteinuria, and edema.

Urinary Albumin - Creatinine Ratio:

The kidney undergoes a number of changes in internal structure and function during pregnancy. During normal pregnancy, the placenta and mother produce large amounts of hormones including human chorionic gonadotropin (HCG), human placental lactogen (h-PL), steroid hormones and estrogen [5]. Such changes in hormone levels can lead to changes in angiotensin level and increase water-sodium retention and the volume load, resulting in changes of maternal hemodynamic and kidney structure and function [6,7]. Protein measurement in 24-h urine sample is the traditional and gold standard method for the detection of proteinuria. 24- hour urine collection is time consuming and result may be inaccurate when the collection of urine is missed, depending upon the individual. The management of patient may be delayed during the urine collection. So, there is a need of an alternative method which is rapid, simple as well as valid and accurate, to identify significant urinary proteinuria. Sufficientevidence from studies shows a strong association between ACR and 24-hour protein excreation [8,9].

The international society for the study of hypertension in pregnancy has accepted ACR test as a method for identification of significant proteinuria [8, 9]. Objectives of our study was to investigate urinary albumin : creatinine ratio as a predictor of severity of pre-eclampsia and also assess the use of Spot urinary albumin: creatinine ratio as an alternative method for assessing the prognosis of preeclampsia, in comparison to 24 hr urinary protein estimation to the severity of pre-eclampsia.

Material & methods

The present Study was carried out in Department of Biochemistry, Nalanda Medical college, Patna during a period from March 2016 to January 2017. The study was carried out on 100 pregnant women with gestational age ≥20 weeks coming for antenatal assessment in the OPD or admitted under department of Gynae. and obs., Nalanda Medical College and Hospital, Patna. The work was carried out after due clearance and approval from institutional ethical committee. The women were between 18-35 years of age and were selected according to inclusion and exclusion criteria of pre-eclampsia.

Inclusion criteria: Based on diagnostic criteria as per Williams obstetrics [10].

Diagnostic criteria for pre-eclampsia:

Minimum criteria:

- Blood pressure ≥ 140/90 mm Hg
- Proteinuria ≥ 300mg/24 hr or ≥ 1+ dipstick

Criteria for severs pre-eclampsia:

- Blood pressure ≥ 160/110 mm Hg after 20 weeks of gestation
- Proteinuria ≥2 gm/24 hours or ≥ 2+ dipstick
- Serum creatinine >1.2 mg/dl unless known to be previously elevated
- Platelets < 100,000/mm³
- Microangiopathic hemolysis
- Persistent headache or other cerebral or visual disturbances
- Persistent epigastric pain

Exclusion Criteria:

1) Presence of UTI

2) History of hypertension, diabetes mellitus and drug intake, alcoholism, liver disorder, cardiac disorder, renal disorder and any other major illness.

All the subjects were divided in two groups.

GROUP 1 (CASE: Preeclampsia):

50 pregnant women who had been clinically diagnosed with pre-eclampsia (both primigravida and multigravida) according to inclusion criteria were enrolled.

GROUP 2 (CONTROL: Healthy pregnant women):

50 Healthy normotensive pregnant women were included in control group.

The following scheme of study was adopted:

1**. General interrogation:** Name, Age, Address, Husband's occupation, Registration no., if indoor or outdoor.

2. Symptoms:

Headache, giddiness, abdominal pain, rapid weight gain, swelling of the body, vision changes etc. LMP, past medical and surgical history, family history, personal history was noted.

3. Physical examination: Pulse, Blood pressure, Build, Height, weight, Oedema of leg, chest, CVS, abdominal examination.

4. Investigations:

a) Estimation of urinary microalbumin and urinary creatinine

Biochemical investigations:

Method of collection of urine sample:

Specimen was collected in a dry, clean container with a tight-fitting lid. A midstream sample of urine was done to avoid contamination. And cloudy or particulate sample was centrifuged prior to analysis.

Method of collection of blood sample:

Proper precautions were taken while collecting blood samples to ensure safety of self and to the patient. Standard procedures were used to obtain accurate result at every step.

Estimation of urinary microalbumin (MAL) [11]:

Quantitative estimation of Microalbumin (MAL) of urine was done by turbidimetric immunoassay. Principle Undiluted sample of albumin was added to buffer containing antibody specific for human serum albumin. The absorbance (340 nm) of the resulting turbid solution was proportional to the concentration of albumin in the sample urine.

Reagent used:

- Reagent 1 contains – Buffer: Saline- 0.9% , Accelerator and Sodium azide- 0.09%
- Reagent 2 contains- Antiserum, Phosphate buffered saline, Polyclonal goat anti-human albumin and sodium azide - 0.09%
- Reagent 3 contains- Calibrator (dilution of pooled human serum contains 0.09% sodium azide. The Reagents were ready to use as provided by the manufacturer. They were stored in the lower compartment of the refrigerator at 2-8°c and protected from light to keep them stable till expiry date.

Procedure:

Table.1. procedure

Pipette into test tube	Standard	Test
Buffer	450µl	450µl
Antiserum	75µl	75µl
Standard	30µl	--
Sample	--	30µl

The above solution was mixed and reaction was started. First, we measured the absorbance of standard at 340nm. Semi autoanalyzer machine generated a factor. Absorbances of samples were read after 5 minutes against this factor. The calculation was automatically performed by semi autoanalyzer.

Calculation of Albumin : Creatinine Ratio (ACR):

ACR = Albumin/Creatinine: The values obtained albumin in mg/L and creatinine in mg/dl. For calculation, ACR= Albumin (mg/dl)/ Creatinine (g/dl) x100 So, ACR = Albumin : Creatinine Ratio (mg/g).

- ACR < 10 mg/g is considered normal.
- ACR 10-30 mg/g is considered high normal.
- ACR 30-300 mg/g is considered Microalbuminuria.
- ACR >300 mg/g is considered Macroalbuminuria.
- ACR > 2200 mg/g is considered nephrotic range.

Statistical Analysis

Data was analysed by using SPSS software. Mean and standard deviations were observed. P value was taken less than or equal to 0.05 for significant differences.

Observations & Results

In the present study, maximum incidence of Preeclampsia was seen in age group 20-24 years. Mean age of Preeclamptic woman was 21.24 years and normal pregnant woman was 23.75 years. The difference was significant (P<0.001). Maximum incidence of Preeclampsia (70%) was in first gravida.

Table.2. Age wise distributions

Age group (Years)	Normal Pregnant woman		Preeclampsia	
	No.	Percentage	No.	Percentage
15-19	3	6	1	2
20-24	21	42	25	50
25-29	22	44	17	34
30-34	4	**8**	7	14
Total	**50**	**100%**	**50**	**100%**

Table.3. Compared the mean age of the pregnant women.

Normal Pregnant woman (mean ± S.D.)	Preeclampsia (mean ± S.D.)	p-value
23.75±3.36	21.24±4.66	<0.001

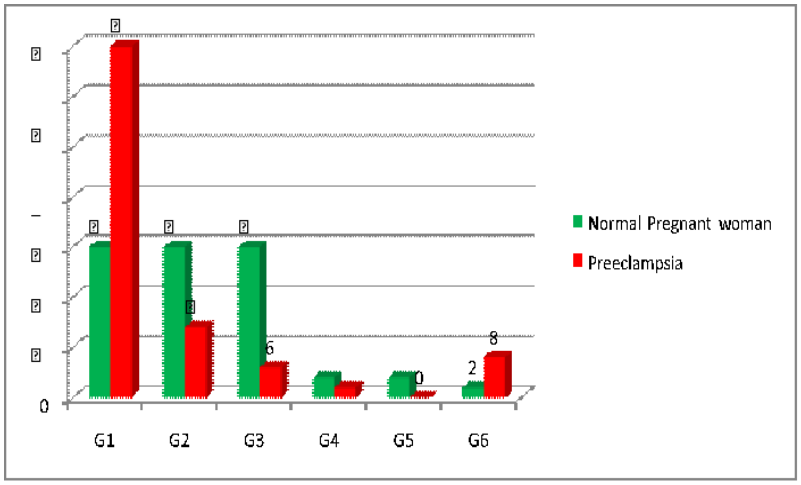

Figure.1. showing distribution of cases according to Parity inpreeclampsia and normal Pregnant woman.

Maximum incidence of Preeclampsia was seen in 32 and 36 weeks of gestational age. Mean gestational age in preeclampsia was 32.11 weeks and in normal pregnant woman was 27.34 weeks. It was significant differences (P<0.001).

Table.4. Showing distribution of cases according to gestational age (inweeks)

Gestational age (inweeks)	Normal Pregnant Woman		Preeclampsia	
	Cases	%	Cases	%
20	7	14	1	2
24	9	18	3	6
28	13	26	11	22
32	5	10	13	26
36	16	32	22	44
Mean±SD	27.34±5.12		32.11±3.01	

In the present study, maximum preeclamptic women (38%) had body weight in range of 60-64kg followed by 26% in range of 55-59 kg. Mean body weight in preeclamptic women was 57.46 kg and that in normal pregnant women was 50.96 kg. The difference in weight between two group was significant with P<0.001. In Preeclampsia 38%of women were average build, 46 % were obese and 16% were thin built. Pulse rate in preeclamptic women were in range of 60- 120 beats/min while in normal pregnancy the range is 60-90 beats/min. The difference of pulse rate was significant in two group with P<0.001. In Preeclampsia the range of systolic blood pressure was 130-210mm of Hg. Mean value was 142.01 mm of Hg. In normal pregnancy range of systolic blood pressure was 100-120 mm oh Hg. Mean value was 103.17 mm of Hg. The difference in systolic blood pressure in two group was significant with P<0.001. Diastolic blood pressure in preeclamptic women was in range of 90-120 mm of Hg. Mean value was 91.26 mm of Hg. In normal pregnancy the range was 60-80 mm of Hg with mean value of 70.07. The difference in diastolic blood pressure between two group was significant with P<0.001.

Table 5: Showing mean levels of Urinary Albumin(mg/L) inpreeclampsia and normal pregnant women.

Group	Range	Mean	SD	t-value	P-value	Sig
Normal Pregnancy	4-20	14.12	4.71			
Pre- Clampsia	27-72	45.21	13.12	14.9	<0.001	***

In the present study, Urinary Albumin in preeclamptic women was in range of 27-72 mg/L. Mean value was 45.21mg/L. In normal pregnancy the range was 4-20mg/L with mean value of 14.12mg/L. The difference in two group was significant with P<0.001.

Table.6: showing level of Urinary creatinine (mg/dl) in preeclampsia and normal pregnant women.

Group	Range	Mean	SD	t-value	P-value	Sig
Normal Pregnancy	48-267	161.92	54.19			
Pre- Clampsia	72.145	110.91	20.54	6.50	<0.001	***

In the present study, Urinary creatinine in preeclamptic women was in range of 72-145 mg/dl . Mean value was 110.91mg/dl. In normal pregnancy the range was 48-267mg/dl with mean value of 161.92mg/dl. And it was significantly differences (P<0.001).

Table 7: Showing mean levels of ACR (mg/g) in Preeclampsia and normal pregnant women.

Group	Range	Mean	SD	t-value	P-value	Sig
Normal Pregnancy	3-20	9.71	4.52	**1**4.12	<0.001	***
Pre- Clampsia	25-97	41.97	14.81			

In the present study, ACR in preeclamptic women was in range of 25-97mg/g. Mean value was 41.97mg/g. In normal pregnancy the range was 3-20 mg/g with mean value of 9.71. And it was significantly differences (p<0.001).

Table 8: Showing comparison of mean levels of ACR between the two groups in each age interval.

Age Interval	Group	N	Mean	SD	t-value	P-value	Sig
15-19	N	3	7.69	3.34	3.97	<0.001	***
	P	1	33.55	9.2			
20-24	N	21	9.58	3.38	11.653	<0.001	***
	P	25	38.62	12.57			
25-29	N	22	9.84	4.91	9.844	<0.001	***
	P	17	39.77	9.76			
30-34	N	4	11.16	4.16	3.198	<0.001	***
	P	7	60.87	20.48			

Discussions

Despite advancement in health care system, Pre-eclampsia remains as a subject of concern for gynecologist and health care policy maker. It is a great challenge for gynecologist to culminate pre-eclamptic pregnancy uneventfully as there is high risk of patient going into Eclampsia [12]. Here biochemist can play an important role by estimating Urinary albumin creatinine ratio [13,14,15], which can serve as diagnostic as well as prognostic marker in PE.

In the present study, total 100 patients were studied and were divided into two groups, Group N and Group P. Group N included 50 normal pregnant women and Group P included 50 pre-eclamptic women. All the subjects were in age group of 15-35 years.

Pre-eclampsia and age

In the present study, all subjects were in the age group of 15-35 years. Most of the pre-eclamptic women were in age group of 20-30 years with maximum percentage (50%) in age group 20-24 years. The mean age was 21.24± 4.66 (21±5) years. This age incidence of pre-eclamptic women was in conformity of other research workers like S.P.Jaiswar (2011), Sonagra et al (2012), Sarkar P.D et al (2013), N.R.Hazari et al (2014), Sreelatha et al (2015), Dr. Mohd Sabiullah et al (2015).

Pre-eclampsia and parity

Out of 50 pre-eclamptic women, 35 cases (70%) were primigravida while 15 cases (30%) were multigravida. In normal pregnant women, 15 cases (30%) were primigravida while 35 cases (70%) were multigravida. This comparative study shows pre-eclampsia was common in primigravida. This result wa also supported by Z. N.Wasu, M Omabe (2009) [16], Ferha Saeed et al (2011) [17], Manjusha Sajith et al (2014) [18].

Pre-eclampsia and gestational age

Out of 50 pre-eclamptic women, 22% of the patients had gestational age 28 weeks, 26% had gestational age of 32 weeks. Maximum numbers of patients (44%) had gestational age of 36 weeks. The mean gestational age was 32.11±3.01 (32±3) weeks. This study concluded that pre-eclampsia was common in third trimester of pregnancy. This result is supported by I. Massarenti (2005) [19], E. Del Zolto (2011) [20].

Pre-eclampsia and Body weight

In the present study, maximum numbers of pre-eclamptic had body weight between 55-69 kgs. Majority of subjects (38%) had body weight between 60-64 kg. The second largest group (26%) had body weight between 55- 59 kg. 12% of subjects had body weight between 65-69 kg. The mean body weight was 57.46±6.51 (57±7) kg in pre-eclamptic while 50.96±6.68 (51±7) kgs in normal pregnant women. And it was significant with p value less than 0.001. This study showed that increased body weight was significantly associated with increased incidence of pre- eclampsia. This study was supported by Dantas E.M et al (2013) [21], P.M Catalano (2007) [22].

Build of women in pre-eclampsia

In the present study, Out of 50 patients of pre-eclampsia, 38% women had average build, 46% were obese and 16% women were thin. It was shown that pre- eclampsia had significant relation with

obesity. This study was supported by the work of Dantas E.M et al (2013), P.M Catalano (2007).

Pulse rate in pre-eclampsia

In the pre-eclamptic patient group, the range of pulse rate was in between 60-120 beats/minute with mean ±SD of 87.02±14.79 (87±15) beats/minute. Out of 50 normal pregnant women the range of pulse rate was 60-90 beats/minute with mean ±SD of 76.08±3.87 (76±4) beats/minute. It was shown that pre-eclamptic patients had comparatively higher pulse rate than normal pregnant women. This study was supported by E. Emeroth (1998) [23], Rober N.Taylor (2017) [24].

Pre-eclampsia and Blood pressure

In the present study, Systolic blood pressure in 50 pre-eclamptic women were in range of 130-210 mm of Hg with mean± SD of 142.01±9.21 (142±9) mm of Hg and diastolic blood pressure in range of 90-120 mm of Hg with mean± SD of 91.26±5.0(91±5) mm of Hg, while in normal pregnant women systolic blood pressure were in range of 100-120 mm Hg with mean± SD of 103.12±6.34 (103±6) mm of Hg and diastolic blood pressure were in range of 60-80 mm Hg with mean± SD of 70.03±7.12 (70±7) mm of Hg. This finding showed a significant difference in systolic and diastolic blood pressure in pre-eclamptic women and control group. This finding was in agreement with the works of S.P Jaiswar (2011), Sonagara AD et al (2012), Sarkar PD et al (2013), N.R Hazari et al (2014) and Dr.Sabiullah et al (2015).

Urinary Albumin: Creatinine ratio and Pre-eclampsia

The levels of urinary albumin in pre-eclamptic women were in the range of 27-72 mg/L with mean± SD of 45.21±13.12 (45±13) mg/L. In normal pregnant women urinary albumin were in range of 4-20 mg/L with mean± SD of 14.12±4.71 mg/L. The difference was significant with p value <0.001. This comparasion between the two groups showed that pre-eclamptic women had increased level of urinary albumin than normal pregnant women.

The level of Urinary creatinine in pre-eclamptic were in the range of 72-145 mg/dl with mean± SD of 110.9±20.54 (111±21) mg/dl. In normal pregnant women the range was 48-267 with mean± SD of 161.92±54.19 (162±54) mg/dl. The difference was significant with p value <0.001. This comparison showed that the pre-eclamptic women had decreased level of urinary creatinine than normal pregnant women.

The level of Urinary ACR in pre- eclamptic were in range of 25-97 mg/g with mean ± SD of 41.97±14.81 (42±15) mg/g. In normal pregnant women the range was 3-20 mg/g with mean±SD of 9.71±4.52 mg/g. The difference was significant with p-value <0.001. This comparison showed that the pre-eclamptic women had increased level of urinary ACR than normal pregnant women.

Age wise comparative study of Urinary ACR in between the two groups of women was shown that in the age group 15-19 years of, pre-eclamptic women had 33.55±9.2 mg/g compared to normal pregnant women in whom the level was 7.69±3.34 mg/g. In the 20-24 years age group mean level was 38.62±12.57 mg/g in pre-eclamptic women while in normal pregnant women level was 9.58±3.38 mg/g. In the 25-29 years of age of pre-eclampticwomen was 39.77±9.76 mg/g and in normal pregnant women 9.84±4.91 mg/g. Likewise in 30-34 years age of pre-eclamptic was 60.87±20.48 while in normal pregnant women was 11.6±4.16 mg/g. Thus, mean level of urinary ACR was significant with p value <0.001 in two groups for each age interval.

All the result of this comparative study between two groups has shown that the level of urinary ACR was raised in pre-eclampsia in comparison to normal pregnant women. This was in agreement with other research worker like Quin Yan et al (2015) who studied 6758 pregnant women with pregnancy induced hypertension and proteinuria. Mean± SD of urinay ACR in pre-eclamptic and normal pregnant women was 87±0.23 and 13±0.06 respectively in their study.

Vneet Mishra (2016) [25] has reported that the mean ACR in normotensive group was 19.2±7.99 and in pre-eclamptic group was 51.95±18.75 mg/g. He concluded that spot urinary ACR values were higher in asymptomatic women in early pregnancy who developed pre-eclampsia later on. When measured early in the second trimester, an ACR ≥ 35.5 mg/g predicted pre-eclampsia well before the onset of clinical manifestation with high sensitivity and specificity.

Fad S. Moiety et al (2013) [26], cut off value for ACR for his group of patients were calculated to be 129.65 mg/g, above which severity of the disease was highly probable. The sensitivity and specificity were 100% and 58.o%. They concluded that ACR may be a reliable method for prediction and assessment of severity of pre-eclampsia.

Conclusions

The present study concluded that pre-eclampsia still remains a significant cause of maternal mortality and morbidity. Once the diagnosis of pre-eclampsia has been established treatment options are limited. For this reason, much attention has recently been focused on pre-eclampsia prevention. There is a need of a biochemical marker, which can assess the disease and its severity earlier, to reducing the undesired outcome in pregnancy. Hence, Urinary albumin-creatinine ratio can be used as an early diagnostic as well as prognostic marker in pre-eclampsia.

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