Diagnostic accuracy of spot albumin creatinine ratio and its association with fetomaternal outcome in preeclampsia and eclampsia

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ABSTRACT

Introduction: Hypertensive disorders in pregnancy are one of the leading causes of maternal and perinatal mortality. Proteinuria is one of the common and important features of preeclampsia. To evaluate the diagnostic accuracy of albumin-creatinine ratio (ACR) in woman with preeclampsia and eclampsia and examine the association between ACR and fetomaternal outcome. **Materials and Methods:** Prospective study carried out over a period of 1 year in the Department of Obstetrics and Gynaecology, after informed consent and ethical clearance total ninety pregnant women from gestational age 20 to 40 weeks were enrolled, including, thirty preeclampsia, thirty antepartum eclampsia, considered as cases and thirty normotensive pregnant women as controls. Preeclampsia was defined as per National High Blood Pressure Education Program 2000 working group. All patients were asked for a spot midstream urine sample, followed by 24 h urine collection. Urinary protein was estimated by the sulfosalicylic acid method and creatinine by the Jaffe's method. The urinary ACR was determined by automated analyzer. **Results:** Mean value of urinary ACR of controls was significantly lower (0.103 ± 0.037) as compared to both groups. On comparing between groups the difference was significant (<0.001), a strong correlation between urinary ACR levels and 24 h urinary proteins was observed. **Conclusion:** In our study, an association of raised ACR values with severity of disease as well as with adverse fetomaternal outcome was observed.

Key words: Albumin creatinine ratio, preeclampsia, urinary protein

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INTRODUCTION

Hypertensive disorders in pregnancy are one of the leading causes of maternal and perinatal morbidity and mortality across the world. It complicates approximately 10% of pregnancies.[1] Incidence has increased by 25% in the United States during the past two decades[2] and estimated maternal deaths are 50,000–60,000 per year worldwide.[3,4] Proteinuria is one of the common and important features of preeclampsia. Proteinuria ≥300 mg/24 h urine collection or Dipstick reading of 1+ is required for the diagnosis of preeclampsia. However, now there is modification in guidelines and recent recommendation state that it is not the essential component for the diagnosis of preeclampsia.[1]

Urine dipstick method is a semi-quantitative colorimetric test. It is inexpensive, easily available and simple to do. It is very commonly performed test for screening of proteinuria, but it should be used only if other quantitative methods are not available.[1] It has high false positive rate, so it is always followed by other quantitative test.[5] Quantification of proteinuria can be done by other methods like 24 h urine collection and protein estimation. This is the traditional

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method and considered as Gold standard, but it has many drawbacks. It is time-consuming, inconvenient, and inaccurate because of over or under collection of urine.[6]

Protein to creatinine (PC) ratio is an accurate, rapid, convenient method and over a dozen of studies[7-9] and three metaanalyses[10-12] had validated it. A spot urine PC ratio above 0.7 mg protein/mg creatinine is strongly suggestive of significant proteinuria.[1]

Albumin-creatinine ratio (ACR) like PC ratio, it is measured using a random spot urine specimen. It has increased sensitivity as compared to PC ratio. It also has the advantage that it can be performed using automated analyzer. Thus, this test is too rapid to be done on the same day and can be carried out in women attending antenatal clinic.[13-15]

Several international organizations such as International Society for the Study of Hypertension in pregnancy,[16] the Society of Obstetric Medicine of Australia and New Zealand,[17] and the Society of Obstetricians and Gynaecologist of Canada[18,19] had approved the spot urine ACR for detection of proteinuria but this is not accepted by all international bodies such as National High Blood Pressure Education Program (NHBPEP) 2000 Working Group.[20]

Very few studies[21-25] have been done to evaluate the association between severity of proteinuria and fetomaternal outcome.

The aim of the study is to evaluate the diagnostic accuracy of ACR in woman with preeclampsia and eclampsia and association between ACR and fetomaternal outcome.

MATERIALS AND METHODS

This is a prospective observational study carried out over a period of 1 year in Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow.

After informed consent and ethical clearance total ninety pregnant women from gestational age 20 to 40 weeks were enrolled, including, thirty preeclampsia, thirty antepartum eclampsia, considered as cases and thirty normotensive pregnant women taken as controls.

Preeclampsia was defined as per NHBPEP2000 working group, resting hypertension >140/90 mmHg after 20th weeks of pregnancy. Eclampsia is defined as preeclampsia with seizure.

Women with multiple pregnancy, chronic kidney disease, liver disease, cardiovascular disease, collagen vascular disease, chronic hypertension, diabetes, neoplasm, with major fetal anomaly, history of smoking, and using alcohol were excluded from the study.

Adverse maternal outcome was defined in terms of occurrence of preterm delivery, changes in fundus on eye examination and maternal mortality.

Adverse fetal outcome was defined as low birth weight babies, intrauterine fetal death, low Apgar score, neonatal resuscitation, neonatal death, and Neonatal Intensive Care Unit (NICU) admission.

Methodology
After taking informed consent and ethical clearance, all patients were asked for a spot mid-stream urine sample, followed by 24 h urine collection. Urinary protein was estimated by the sulfosalicylic acid method and creatinine by the Jaffe's method. The urinary ACR was determined by automated analyzer and data were expressed as mg/dl.

Statistical analysis
Pearson correlation test was used to detect a correlation between the ACR in the spot urine samples and 24 h urinary protein. Chi-square test, Student's *t*-test, and ANOVA were used for analysis of data.

RESULTS

A total of ninety pregnant women were included in the study. These were classified into three groups, Group I - Controls, normotensive pregnant women (30), Group II - Preeclampsia (30), Group IIa - Mild preeclampsia (15), Group IIb - Severe preeclampsia (15), and Group III - Eclampsia (30).

Demographic profile
Mean urinary ACR level was minimum in controls, and maximum in eclampsia and difference among groups was statistically significant.

Mean value of urinary ACR of controls was significantly lower (0.103 ± 0.037) as compared to both groups preeclampsia and eclampsia (1.901 ± 1.121 and 2.884 ± 1.499), respectively. On comparing between groups, the difference was significant (<0.001), mean urinary ACR of eclampsia was found to be significantly higher as compared to that of preeclampsia [Table 1].

When urinary ACR was compared between mild preeclampsia and severe preeclampsia, the difference

Table 1: Comparison of mean urinary albumin creatinine ratio in different study groups

Group	*n*	Mean	SD	Minimum	Maximum
Group I	30	0.103	0.037	0.007	0.089
Group II (Group IIa + IIb)	30	1.901	1.121	0.205	1.483
Group III	30	2.884	1.499	0.274	2.325
Total	90	1.629	1.576	0.166	1.299

F (ANOVA)=51.10; *P*<0.001. SD – Standard deviation

between groups was found statistically significant ($P < 0.001$) [Table 2].

When we analyzed a correlation between urinary ACR levels and 24 h urinary proteins, a strong correlation was observed, for which value of Pearson's correlation was found to be 0.986 ($P < 0.001$) [Figure 1]. As the disease severity (Group I to Group III) increased 24-hr urinary protein as well as albumin creatinine ratio was also increased and this increment after comparison between different groups was statistically significant [Table 3].

In the present study, association of urinary ACR with fetal outcome was evaluated, and it was found that mothers who had a significant increase in urinary ACR levels delivered low birth weight babies and also suffered with intrauterine fetal demise and this association was significant ($P < 0.001$). In cases whose babies had low Apgar scores and needed resuscitation, and NNU admission had significantly higher urinary ACR ($P < 0.05$). Neonatal deaths were also associated with raised maternal urinary ACR as compared to healthy neonates but this difference was statistically not significant [Table 4].

Although the levels of ACR were higher with preterm vaginal birth, this association was not significant. Total four women expired during the study and mean ACR level of these women were almost doubled than alive women, but
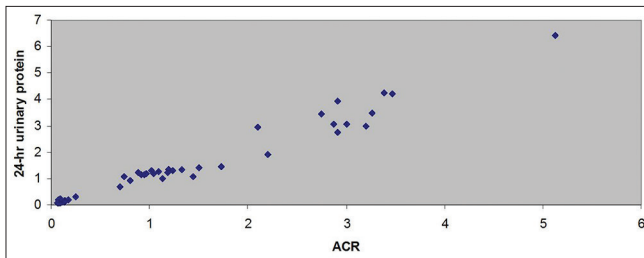

Figure 1: Pearson's correlation value = 0.986 ($P < 0.001$); (very strong correlation)

Table 2: Comparison of mean urinary albumin creatinine ratio exploring association with severity of disease

Group	n	Mean	SD	Minimum	Maximum
Group IIa	15	1.184	0.613	0.700	3.260
Group IIb	15	2.619	1.061	1.020	5.130
Group III	30	2.884	1.499	0.450	7.260
Total	60	2.393	1.403	0.450	7.260

F (ANOVA)=9.897; *P*<0.001. SD – Standard deviation

this association was statistically nonsignificant ($P > 0.05$). Similarly, cases with high grade of fundus changes and need for magnesium sulfate administration had significantly higher urinary ACR [Table 5].

DISCUSSION

Hypertensive disorders in pregnancy stand out to be one of the leading causes of maternal and neonatal morbidity and mortality. Timely and effective intervention has utmost importance in the prevention of these complications. Proteinuria has been an important constituent of preeclampsia.

Since long time Gold standard test for detection of proteinuria was the estimation of protein after 24 h of urine collection. However, this test is time consuming, cumbersome, and causes delay in decision-making. Spot urinary ACR can substitute this test because this test is rapid, easy to do and accurate.

In this study, strong correlation ($r = 0.986$) was observed between the spot ACR and the 24 h urinary protein estimation. Similar result was achieved by many studies.[26]

Although the diagnosis of severe preeclampsia is no longer dependent on the presence of proteinuria, women with hypertensive disorders of pregnancy with increasing ACR might be considered serious and we should not delay the management of preeclampsia in these patients.

Massive proteinuria (>5 g) has been eliminated from the consideration of grade of severity of preeclampsia.[1] This result was concluded on the basis of two important facts, first one is that few studies[21-23] reported that severity of proteinuria is only weakly associated with adverse maternal and neonatal outcome and should not be used to decide the management guideline but our study, in contrast, reported significant association of ACR with adverse fetomaternal outcome.

Second, proteinuria may be absent in up to 10% of women with preeclampsia and 20% of women with eclampsia at the time of initial presentation.[24,25]

With regard to preeclampsia, one study had reported that microalbuminuria might be a good predictor of this condition with a high sensitivity but a low positive predictive value.[27] In contrast, another study reported that microalbuminuria is not a good predictor of preeclampsia.[28]

Table 3: Albumin creatinine ratio and 24 h urinary protein between group comparison (Student's t-test)

Parameter	Group I (n=30)		Group IIa (n=15)		Group IIb (n=15)		Group III (n=30)		Statistical significance	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*P*
24-h urinary protein (g/24 h)	0.13	0.05	1.29	0.63	2.96	1.41	0	0	68.837	<0.001
ACR (mg/mg)	0.10	0.04	1.18	0.61	2.62	1.06	2.88	1.50	44.833	<0.001

SD – Standards deviation; ACR – Albumin creatinine ratio

Table 4: Association between albumin creatinine ratio levels and fetal outcome

Variable	Total, n (%)	ACR levels		Statistical significance	
		Mean	SD	F	P
Birth weight (kg)					
<2.0	12 (13.3)	2.60	0.94	16.499	<0.001
2.0-2.5	25 (27.8)	2.62	1.42		
>2.5	53 (58.9)	0.94	1.40		
IUD					
No	87 (96.7)	1.52	1.45	13.939	<0.001
Yes	3 (3.3)	4.75	2.20		
Apgar (n=87)					
Low	47 (54.0)	2.28	1.30	41.14	<0.001
Normal	40 (46.0)	0.63	1.06		
Resuscitation need (n=87)					
No	66 (75.9)	1.14	1.38	23.263	<0.001
Yes	21 (24.1)	2.71	0.95		
NNU admission (n=87)					
No	58 (66.7)	0.94	1.30	40.749	<0.001
Yes	29 (33.3)	2.68	0.98		
Neonatal death (n=87)					
No	79 (90.8)	1.44	1.47	2.978	0.088 (NS)
Yes	8 (9.2)	2.36	0.88		

IUD – Intrauterine fetal demise; NNU – Neonatal unit; ACR – Albumin creatinine ratio; SD – Standard deviation; NS – Not significant

Table 5: Association between albumin creatinine ratio levels and maternal outcome

Variable	Total, n (%)	ACR levels		Statistical significance	
		Mean	SD	F	P
Mode of delivery					
FTVD	26 (28.9)	1.30	1.55	1.055	0.353 (NS)
LSCS	59 (65.6)	1.72	1.62		
PTVD	5 (5.6)	2.25	0.85		
Fundus changes					
I	14 (15.55)	3.29	1.01	25.557	<0.001
II	10 (11.1)	2.84	1.20		
III	6 (6.7)	3.61	2.02		
IV	1 (1.1)	1.51			
WNL	59 (65.5)	0.79	0.96		
MgSO$_4$ need					
No	47 (52.22)	0.45	0.52	126.95	<0.001
Yes	43 (47.78)	2.86	1.35		
Maternal mortality					
No	86 (95.6)	1.56	1.56	3.785	0.055 (NS)
Yes	4 (4.4)	3.11	1.14		

FTVD – Full term vaginal delivery; PTVD – Preterm vaginal delivery; WNL – Within normal limit; LSCS – Lower segment caesarean section; ACR – Albumin creatinine ratio; SD – Standard deviation; NS – Not significant

Other author had reported that microalbuminuria early in the third trimester of pregnancy is a good predictor of hypertensive complications in pregnancy and birth weight of the babies, but it cannot predict intrauterine growth - restriction (IUGR) and neonatal outcome.[29]

Other proposed that the appearance of clinical proteinuria in preeclampsia is preceded by a microalbuminuria. However, these authors observed this microalbuminuria (determined during 11–13 weeks of pregnancy) in 55% of normal pregnancies and only 75% of pregnancies that complicated by preeclampsia.[30]

As per one study incidence of induced labor (P = 0.045) and cesarean section (P < 0.001) was more associated with microalbuminuria group, which could be due to the significant association of maternal complication (P < 0.001) in the same group.[31] In our study, it was also found that adverse neonatal outcome like fetal complication, IUGR was significantly more in babies of microalbuminuria group (P = 0.010*). It was also found that prematurity, low birth weight, low Apgar score, and more incidence of NICU admission in babies of pregnant women with microalbuminuria.

Another one more study which was in consensus with the results of our study.[31]

Gangaram *et al*.[15] compared the diagnostic value of the ACR with that of the 24-h urine protein test among pregnant women with hypertension. They reported that the value of the two tests in this context was the same and concluded that measurement of the micro ACR may be a good substitute for a random urine protein test.

However, the relationship of maternal complications such as preeclampsia and preterm labor with microalbuminuria is still controversial. Further research with a large sample size is needed to establish the relationship between microalbuminuria and maternal complication. In one study, women with ACR >312 mg albumin/g creatinine at 17–20 weeks of gestation were found to be at 8-fold higher risk of developing preeclampsia.[32]

CONCLUSION

A spot ACR in mid-stream urine might be considered for replacement of 24 h urine protein excretion in the evaluation of preeclampsia and eclampsia. This test also has the potential to replace urinary dipstick method in routine antenatal clinic, but more data are required. In our study, association of raised ACR values with severity of disease as well as with adverse fetomaternal outcome was observed. However, limitation of our study is small sample size, so more studies with good sample size are required to validate these results. It appears that ACR could be very useful test in near future not only for predicting the development of preeclampsia, but it also predict its severity and fetomaternal outcome.

Conflicts of interest
There are no conflicts of interest.

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