ORIGINAL ARTICLE

Spot Urinary Albumin–Creatinine Ratio in Prediction of Pre-eclampsia: A Prospective Study

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Abstract

Background: Pre-eclampsia is a multisystem disorder with two-stage disease pathology where abnormal placentation precedes the endothelial dysfunction which ultimately leads to the systemic inflammatory response. Endothelial dysfunction is one of the hallmark pathologies of pre-eclampsia, microalbuminuria is the measure of the same and could be used as a marker for predicting pre-eclampsia in early gestation. This study has been carried out to predict pre-eclampsia among low-risk pregnant women with the use of spot urine albumin–creatinine ratio (ACR) and to derive at a definite cut-off value of spot urine ACR.

Materials and methods: This prospective study was done in ESIC Medical College & PGIMSR, Chennai, Tamil Nadu, India, for a period of 12 months. Low-risk singleton pregnant women between 16 and 20 weeks of gestational age who satisfied the inclusion criteria were considered. Participants who tested negative for urine albumin by urine dipstick method were subjected to a spot urine ACR test. Urine albumin was measured by the immunoturbidimetric method and urine creatinine by Jaffe's kinetic method. Urine albumin is expressed as mg/dL, urine creatinine as gm/dL, and ACR as mg/gm. All the participants were followed up to delivery. The primary outcome measure was pre-eclampsia, secondary outcome measures were gestational hypertension (GHTN), gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), and a cut-off value of urine spot ACR in the prediction of pre-eclampsia was calculated by receiver operative curve (ROC) analysis.

Results: Among 164 participants, the proportion of pregnant women affected with pre-eclampsia was 3.04%. The optimum value of ACR in predicting pre-eclampsia obtained was 25.89 mg/gm by applying the ROC curve. It also derived 80% sensitivity and 87% specificity with a positive predictive value (PPV) of 16% and a negative predictive value (NPV) of 99%.

Conclusion: The ACR test is widely available with easy interpretation and also convenient for pregnant women. Spot urine ACR value of more than 25.89 mg/gm in asymptomatic pregnant women when measured between 16 and 20 weeks of gestation can predict the development of pre-eclampsia with the sensitivity and specificity of 80 and 87%, respectively. The higher NPV value of 99% of spot urine ACR ratio may help in accurately diagnosing true negatives. However, additional prospective studies with higher sample size and cost–benefit analysis of the test are recommended to confirm these findings before routinely using urine spot ACR as a predictive marker.

Keywords: Pre-eclampsia, Prediction, Pregnant women, Prospective study, Spot urine albumin–creatinine ratio.

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Introduction

Hemorrhage, sepsis, and hypertension during pregnancy are important causes of maternal morbidity and mortality.[1] Globally, pre-eclampsia complicates 2–8% of pregnancies and accounts for more than 50,000 maternal deaths annually.[2,3]

The International Federation of Gynecology and Obstetrics (FIGO)'s initiative on pre-eclampsia has reported that there is a higher risk of developing pre-eclampsia among pregnant women in developing countries when compared to those in well-developed countries.[4] In India, the prevalence of pre-eclampsia is around 5.4% as per the National Heath Portal data of 2016.[5]

Pre-eclampsia is a multisystem disorder with two-stage disease pathology where abnormal placentation precedes the endothelial dysfunction that ultimately leads to a systemic inflammatory response.[6–8] It has been postulated that the mere presence of a placenta alone is sufficient for the development of pre-eclampsia and not necessarily the presence of a fetus.[9]

The disease is associated with a higher risk of maternal, and fetal complications and at present, there is no recommended strategy for the prevention of pre-eclampsia in all pregnant women except in high-risk women.[10] Oral aspirin when started during early gestation among women who are considered to be at an increased risk for pre-eclampsia would prevent the development of pre-eclampsia.[11,12] Hofmeyr et al. in collaboration with the World Health Organization (WHO) Calcium Trial reported that a higher dose of calcium supplementation (≥1 gm/day) may reduce the risk of pre-eclampsia, especially in women with low calcium intake.[13]

Pathophysiological changes associated with pre-eclampsia begin in the early weeks of pregnancy and antecede before the onset of clinical features. Many biochemical and radiological tests alone or in combination have been studied in the prediction

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of pre-eclampsia in early pregnancy, however, none of them are accurate in prediction.[2,10] Hence, in modern obstetrics, prediction of pre-eclampsia continues to be a clinical challenge and there is a need for an accurate and readily available biochemical or radiological test that can predict pre-eclampsia in early pregnancy.

Endothelial dysfunction is one of the hallmark pathologies of pre-eclampsia as reported by Young et al.[14] and Khan et al.[15] Baweja et al.[16] in their exploratory study have stated that microalbuminuria is the measure of endothelial dysfunction and overt proteinuria is preceded by a microalbuminuria phase which could be used as an early marker of endothelial dysfunction in pre-eclampsia. Urinary microalbuminuria is also associated with the occurrence of medical conditions such as hypertension and diabetes in the general population as reported by Yuyun et al.[17] and Hillege et al.[18] Hence, this study has been carried out to evaluate spot urine ACR in the prediction of pre-eclampsia.

Among the methods of urinary protein quantification, the 24-hour urine protein measurement is considered as the gold standard for protein estimation, but its routine use is not recommended as it is time consuming, cumbersome, and less reliable without creatinine estimation.[19,20]

Urine protein–creatinine ratio (PCR) is an alternative method and has shown promising results for quantifying proteinuria.[21,22]

The studies with the use of spot urine ACR ratio in the prediction of pre-eclampsia had varied results without deriving a definite cut-off value.[21,23] The recent recommendation by the National Institute of Clinical Excellence (NICE) says that spot urine ACR or urine PCR is the quickest and most effective method to quantify proteinuria.[24]

This study has been carried out to predict pre-eclampsia among low-risk pregnant women with the use of spot urine ACR and to derive a definite cut-off value of spot urine ACR.

Materials and Methods

The present longitudinal prospective study was conducted in ESIC Medical College & PGIMSR, Chennai, Tamil Nadu, India, from April 2019 to March 2020 after obtaining the institute's ethical committee clearance. Singleton pregnant women between 16 and 20 weeks of gestational age attending the antenatal outpatient department were included. Pregnant women with hematuria, acute renal failure, chronic kidney disease, bad obstetric history, chronic hypertension, diabetes-complicating pregnancy, and multiple pregnancies were excluded from the study. Informed written consent was obtained from the willing participants. The demographic characteristics, medical details, and obstetric details were recorded. General and obstetric examinations were carried out and those who tested negative for urine albumin by urine dipstick method were subjected to a spot urine ACR test. Urine microalbumin analysis was done by immunoturbidometric method and urine creatinine estimation was done by Jaffe's kinetic method. At each antenatal visit, pregnant women were examined for the development of pre-eclampsia and other complications such as GHTN, GDM, and IUGR and were followed up till delivery. Women delivering in other hospitals were asked to attend a postnatal clinic along with a discharge summary to know the pregnancy outcome.

The objectives of the study were as follows:

- To find the proportion of women affected with pre-eclampsia.
- To predict the occurrence of pre-eclampsia in asymptomatic pregnant women with spot urine ACR measured between 16 and 20 weeks of gestation.
- To derive at a definite cut-off value of spot urine ACR by applying ROC.
- To find the association of pre-eclampsia, GHTN, GDM, and IUGR with their clinical characteristics.

A sample size of 168 was obtained by applying the sensitivity of spot urine ACR diagnostic test of about 87.5% obtained from previous research.[25] Precision value used in the calculation of sample size was 5% with a 95% confidence interval (CI) level. Continuous variables were expressed in terms of descriptive statistics. The categories were presented in terms of frequency and percentages. To find the association between various clinical attributes and disease occurrence, the Pearson Chi-squared test had been used. Diagnostic test analysis was done to test the spot urine ACR Variable to screen asymptomatic pregnant women. Sensitivity, specificity, PPV, NPV, and cut-off value of spot urine ACR in the prediction of pre-eclampsia were calculated by ROC analysis.

The data analysis was done using diagnostic test software Dx Test, version 1.0 and Statistical Package for Sciences software (SPSS) software, version 21.0. The statistical significance level was considered at $p < 0.05$.

Results

Among 168 participants, four participants were lost to follow-up, hence the final sample size studied was 164. The mean and median value of the study participants with respect to age, body mass index (BMI), birth weight, and spot urine ACR value is depicted in Table 1.

In this study, the proportion of pregnant women affected with pre-eclampsia was 3.04%. The corresponding number was 2.44% for GHTN.

The clinical characteristics such as age, BMI, abortion, parity, mode of delivery, and birth weight were studied to find their association with the disease occurrence. None of the factors were associated with pre-eclampsia and GHTN occurrence. Moreover, GDM and IUGR were found in only nulliparous women ($p = 0.045$). Pregnant women who had been diagnosed with IUGR were 7 (4.26%) and they had neonatal birth weights lesser than 2.5 kg ($p \leq 0.0001$). It is depicted in Tables 2 and 3.

The sensitivity and specificity of spot urine ACR in predicting pre-eclampsia were obtained from the ROC curve. The optimum value of spot urine ACR in predicting pre-eclampsia obtained was 25.89 mg/gm. It also derived 80% sensitivity and 87% specificity with a PPV of 16% and an NPV of 99%. The area under the curve was 0.916 with a standard error (SE) of 0.031 and 95% CI value between 0.856 and 0.976. This is shown in Figure 1 and Table 4.

Table 1: The mean and median value of the quantitative variables of the study

	Age (years)	*BMI*	*Birth weight (kg)*	*ACR value (mg/gm)*
Mean	26.74	23.58	2.79	32.18
SE of mean	0.281	0.35	0.04	7.73
Median	26.00	22.65	2.70	8.54
SD	3.601	4.42	0.45	99.02
Minimum	19	15.30	1.00	1.38
Maximum	42	36.10	3.90	826.83

Table 2: Association of baseline clinical characters with disease occurrence (pre-eclampsia and GHTN)

Variables Total sample size, n = 164	*Category*	*Pre-eclampsia*		*Chi-squared (continuity correction) test value (df)*	*p-value*	*GHTN*		*Chi-squared (continuity correction) test value (df)*	*p-value*
		Yes (5)	*No (159)*			*Yes (4)*	*No (160)*		
Age (years)	<35	4	155	0.843 (1)	0.359	3	156	1.239 (1)	0.266
	≥35	1	4			1	4		
BMI	<25	4	106	0.081 (1)	0.776	2	108	0.004 (1)	0.949
	≥25	1	53			2	52		
Abortion	Yes	0	23	0.069 (1)	0.792	0	23	0.008 (1)	0.929
	No	5	136			4	137		
Parity	Nullipara	3	89	0.000 (1)	1.000	2	90	0.000 (1)	1.000
	Multipara	2	70			2	70		
Mode of delivery	Vaginal	3	97	0.000 (1)	1.000	3	97	0.004 (1)	0.950
	Cesarean	2	62			1	63		
Birth weight (kg)	<2.5	2	25	0.759 (1)	0.384	1	26	0.000 (1)	1.000
	≥2.5	3	134			3	134		

Table 3: Association of baseline clinical characters with disease occurrence (GDM and IUGR)

Variables Total sample size, n = 164	*Category*	*GDM*		*Chi-squared (continuity correction) test value (df)*	*p-value*	*IUGR*		*Chi-squared (continuity correction) test value (df)*	*p-value*
		Yes (7)	*No (157)*			*Yes (7)*	*No (157)*		
Age (years)	<35	7	152	0.000 (1)	1.000	7	152	0.000 (1)	1.000
	≥35	0	5			0	5		
BMI	<25	3	107	1.353	0.245	5	105	0.000 (1)	1.000
	≥25	4	50			2	52		
Abortion	Yes	1	22	0.000 (1)	1.000	0	23	0.287 (1)	0.592
	No	6	135			7	134		
Parity	Nullipara	7	85	**4.012 (1)**	**0.045***	7	85	**4.012 (1)**	**0.045***
	Multipara	0	72			0	72		
Mode of delivery	Vaginal	7	93	3.0123 (1)	0.077	6	94	0.951 (1)	0.329
	Cesarean	0	64			1	63		
Birth weight (kg)	<2.5	0	27	0.423 (1)	0.575	7	20	**32.267 (1)**	**0.0001*****
	≥2.5	7	130			0	137		

Statistically significant, $p = <0.05$; *Just significant, $p = 0.045$; ***Highly significant, $p < 0.0001$

Discussion

Although hypertension and proteinuria were considered to be the classical criteria to diagnose pre-eclampsia, the recent endorsement is that in absence of proteinuria, other criteria such as thrombocytopenia, pulmonary edema, impaired liver and renal function, unexplained headache, and upper abdominal pain are also important for the diagnosis of pre-eclampsia, grading, and its management.[2,24]

The International Society for the Study of Hypertension in Pregnancy (ISSHP-2018)[10] and the American College of Obstetrics and Gynecology (ACOG-2020)[2] have proposed that the degree of proteinuria is not an important clinical factor for diagnosis and termination of pregnancy except in the nephrotic range (>5 gm/24 h) of proteinuria. Research by Chan et al.[26] and Mateus et al.[27] have reported that proteinuria of more than 5 gm/24 h is associated with adverse maternal and fetal outcomes. Hence, the practice of screening for proteinuria has become an essential investigation as a part of routine antenatal care.

Proteinuria during pregnancy is defined as 300 mg/dL or more of protein in a 24-hour urine collection[28,29] or a PCR of 0.30 or more.[23] Whenever the above-discussed methods are not available, urine dipstick of 2+ is considered an acceptable investigation for the quantification of proteinuria.[30]

Microalbuminuria is a marker of endothelial dysfunction which antecedes before the onset of clinical features and could be used as a predictive marker for pre-eclampsia in early pregnancy as reported by Baweja et al.[16]

In this study, the proportion of pregnant women affected with pre-eclampsia was 3.04%. The recent data released by the National Health Portal of India[5] and research carried out in northern India[31] have observed similar findings of about 5.4 and 2.5%, respectively. A prospective study by Agarwal et al.[32] and Mishra

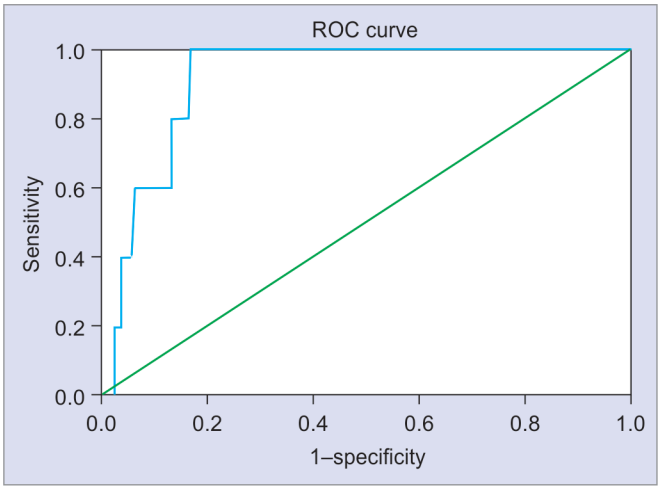

Fig. 1: The ROC curve to predict pre-eclampsia. The best cut-off value of 25.89 has 80% sensitivity and 87% specificity. At this duration, the sensitivity 0.80 and specificity is 0.87 (1 – specificity = 0.13)

Table 4: Area under the curve for ACR

			95% CI	
Area	*SE*	*p-value*	*Lower bound*	*Upper bound*
0.916	0.031	0.002	0.856	0.976

The spot urine ACR cut-off value obtained in this study was 25.89 mg/gm by applying ROC calculations. Urine microalbumin analysis was done by immunoturbidometric method and urine creatinine estimation was done by Jaffe's kinetic method. The sensitivity and specificity value of spot urine ACR in predicting pre-eclampsia obtained was very much similar to the results obtained from other research (Table 5).

The NPV obtained was high (99%) and was similar to the value obtained by the previous research which explains that spot urine ACR with cut-off value of 25.89 mg/gm has a high negative predictive ability to detect true negatives.[33]

The positive predictive value obtained was about 16% which was similar to the value reported by Fatema et al.,[34] however, the value was lesser compared to the results obtained from the other research. This discrepancy could have been due to the inclusion of pregnant women with advanced gestational age in their studies who would have already developed mild pre-eclampsia.

The limitation observed in this study is that the number of pregnant women affected with pre-eclampsia is small; therefore, the findings should be interpreted with caution. Hence, we would suggest a prospectively designed study with a higher sample size to predict pre-eclampsia by spot urine ACR test.

Conclusion

Spot urine ACR test is widely available with easy interpretation and is convenient for pregnant women. Spot urine ACR value of more than 25.89 mg/gm in asymptomatic pregnant women when measured between 16 and 20 weeks of gestation can predict the development of pre-eclampsia with the sensitivity and specificity of 80 and 87%, respectively. The higher NPV of spot urine ACR may help in accurately diagnosing true negatives. However additional prospective studies with higher sample size and cost–benefit analysis of the test are recommended to confirm these findings before routinely using spot urine ACR as a predictive marker.

Table 5: Sensitivity, specificity, PPV, and NPV values obtained in different pieces of research from the spot urine ACR cut-off value

Study	*ACR cut-off value*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Baweja et al.[16]	35.5 mg/mmol	83.3	61.2	63.0	78.6
Gupta et al.[31]	9.85 mg/gm	67	76	–	–
Agarwal et al.[32]	0.2	62	84	56	92
Mishra et al.[25]	≥35.5 mg/mmol	87.5	96.30	77.78	98.11
Upadhyay and Dayal[33]	>0.2	75	89.6	40	97.5
Fatema et al.[34]	32 mg/gm	80	49.54	12.69	96.42
This study	25.89 mg/gm	80	87	16	99

et al.[25] have reported a pre-eclampsia incidence of about 15.8 and 12.8%, respectively, in their research. The above-discussed varied proportion of the disease occurrence would be due to differences in the geographic location of the studied population.

It is well known that advanced maternal age, nulliparity, and high BMI are associated with pre-eclampsia and GHTN.[9] In this study, none of the above-mentioned factors were significantly associated with the disease occurrence which can be attributed to the insufficient sample studied.

A prospective exploratory study by Baweja et al. in Australia[16] has shown that women who developed pre-eclampsia had a higher spot urine ACR (median 50 mg/mmol) when compared to women who were unaffected (median 28 mg/mmol). The spot urine ACR value of 35.5 mg/mmol in a midstream sample of urine between 17 and 20 weeks predicted pre-eclampsia with sensitivity and specificity of 83.3 and 61.2%, respectively. However, the method used for urinary albumin estimation was high-performance liquid chromatography (HPLC) which may not be available in clinical settings of developing countries.

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