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Original Article

Combination Of Spot Urine Protein-Creatinine Ratio and Uterine Artery Doppler in Predicting Preeclampsia in Ibadan: A Prospective Cohort Study.

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ABSTRACT

Background: Early prediction and prompt antenatal surveillance of preeclampsia has the potential to improve overall feto-maternal outcome. A combination of ≥2 biomarkers has the potential to increase the probability of deriving suitable predictive algorithms. **Objective:** To combine spot urine protein-creatinine ratio (UPCR) and uterine artery (UA) doppler velocimetry to predict the development of preeclampsia. **Methods**: This was a prospective cohort study of 110 healthy pregnant women between 16 to 20 weeks gestation recruited consecutively from February to May 2020, from the Antenatal clinic of the University College Hospital, Ibadan. Samples were collected for spot urine-protein creatinine ratio and UA Doppler velocimetry was conducted at 20 weeks. Abnormalities in UA Doppler parameters (A notch in the uterine artery, RI > 0.7 and PI > 1.4) were interpreted and an abnormal general Doppler result was reported. Participants were followed up until they developed preeclampsia or delivered. Chi-square test was used to compare categorical variables, and the student's t-test for means. The performance of the screening tests was evaluated. The ROC curves were generated to evaluate the efficiency of the combination of UPCR and UA. The performance of UPCR and UA doppler parameters combined had a test sensitivity (62.5%), specificity (100%), PPV (100%), NPV (97.06%) and an accuracy of 97.20% in predicting preeclampsia, calculating the area under the curve. **Results:** The prevalence of preeclampsia from the study was 7.48**%.** The combined biomarkers (UPCR + UA doppler parameters) had an improved sensitivity of 87.5% and a predictive accuracy of 99.07%. The area under the curve (AUC) for the combined parameters was 0.999 (95% CI, 0.997- 1.000). **Conclusion:** A combination of spot UPCR and UA Doppler parameters in the early second trimester is a useful screening tool for the prediction of preeclampsia

KEY WORDS: Preeclampsia, Prediction, UPCR, UA Doppler velocimetry,Biomarkers.

INTRODUCTION

Preeclampsia is a multi-systemic pregnancy-related disorder associated with significant maternal and perinatal morbidity and mortality.[1] It is a syndrome defined by gestational hypertension and proteinuria. [2]

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Proteinuria is spillage of 300 mg or more of protein in a 24-hour urine collection or a protein to creatinine ratio of 0.3 mg/dL using a spot urine protein and spot urine creatinine.[3]

Some presentations of pregnancy-related hypertension combined with clinical or laboratory abnormalities or intrauterine growth restriction should also be considered as potential preeclampsia.[2,4]

The global incidence of hypertensive disorders in pregnant women from 2002 to 2012 was ~4.6%, a figure that varied from 2.7% to 8.2% by region, and the worldwide incidence rate of preeclampsia was ~2.16%.[5] Preeclampsia and related hypertensive disorders of pregnancy impact 5-8% of all births in the United States.[6] In the developing world, severe forms of preeclampsia and eclampsia are more common, ranging from as low as 4% of all deliveries to as high as 18% in parts of Africa.[7] The incidence of preeclampsia in a State in Northern Nigeria according to Musa *et al* is 8.8% [8] while in a State in Southern Nigeria, it is 10%.[9] These variations in incidence rates vary according to differences in population characteristics, definitions, and criteria of diagnosis (including procedures, tests, and their methodologies).

The pathophysiology of preeclampsia is not yet known[5,11] Over the years, attempts have been made to predict preeclampsia using maternal risk factors, but these efforts have been largely unsuccessful as maternal history and risk factors alone usually do not predict the onset of the disease. A major challenge in modern obstetrics is the early identification of pregnancies at high risk of early-onset preeclampsia and undertaking the necessary measures to improve placentation and reduce the prevalence of the disease.[12] Several maternal Biophysical and Biochemical markers have been used to predict the occurrence of preeclampsia. These include Uterine artery doppler, pregnancy-associated plasma protein-A (PAPP-A), Placenta growth factor (PlGF), urinary protein-creatinine ratio, and a combination of markers such as PAAP-A and PlGF, or uterine artery doppler and PAPP-A.[12] Combination of two or more biomarkers has long been known to potentially increase the predictive ability of screening tests[11].

Measurement of protein excretion in a 24-hour urine collection has been the longstanding "gold standard" for the quantitative evaluation of proteinuria in pregnancy[12]. However, 24-hour urine collection is time consuming, inconvenient, and not always reliable because of the difficulty in collecting the sample correctly. A more rapid test capable of accurately predicting the results of a 24-hour urine collection would be valuable. An alternative method for quantitative evaluation of proteinuria is the measurement of the Protein-Creatinine ratio (PCR) in a spot urine sample, which avoids the influence of variations in urinary solute concentration and provides a more convenient and rapid method to assess protein excretion. Therefore, it is an accurate test and provides efficient in-patient and out-patient monitoring. The usefulness of this method for assessing proteinuria in the non-pregnant population is well-substantiated in the literature.[13] Several international organizations including the Society of Obstetric Medicine of Australia and New Zealand,[14] and the Society of Obstetricians and Gynaecologists of Canada[15] have accepted the spot urine PCR as a reasonable method for the identification of significant proteinuria (0.3g/24 h) during pregnancy. Spot urine-protein creatinine ratio has been demonstrated to be useful in predicting preeclampsia in some studies.[2,16,17]

The prediction rate rises when it is combined with maternal history and other screening markers.[18] Prediction of preeclampsia by spot urinary Protein-Creatinine ratio and uterine artery doppler in early pregnancy might provide help in the early detection of cases of preeclampsia.

This hospital-based study aims to utilise a combination of biophysical and biochemical markers (UA Doppler parameters and UPCR) in predicting preeclampsia amongst normotensive pregnant women.

MATERIALS AND METHODS

This was a prospective cohort study that was conducted at the University College Hospital, (UCH) Ibadan, Nigeria. The study involved one hundred and ten pregnant women over 18 years of age, attending antenatal clinic at UCH, at gestational ages between 16 and 20 weeks with singleton fetus, and with no proteinuria on dipstick. Women having any risk factor for development of preeclampsia were excluded from the study.

Ethical approval was obtained from the University of Ibadan / University College Hospital Institutional Review Committee of the University College Hospital, Ibadan with the assigned number UI/EC/19/0626.

Informed consent was taken from the eligible pregnant women at first contact (16 to 20 weeks) and they were all clinically evaluated at the booking visit to rule out any risk factors for the development of preeclampsia. The blood pressure was taken as the average of two values in a sitting position using a standard calibrated sphygmomanometer (Accosons, A.C. Cossor and

Sons Surgical Ltd., London, England) with an appropriate sized cuff. The systolic blood pressure was taken as the first Korotkoff sound while the diastolic was taken as the fifth Korotkoff sound. Women with a blood pressure of less than 140/90mmHg were taken as normotensive and included in the study

They were given sterile urine containers without preservatives, and, after instruction, a midstream clean catch urine sample was collected. The urine sample was immediately tested for protein using a dipstick - Medi test Combi 9^R (Mache Rey- Nagel, Germany) and all patients negative for protein were included in the study. Within 30–60 minutes of collection, the urine samples were then transported to the chemical pathology laboratory and stored at –20^{o}C for analysis.

Estimation of protein was done by the pyrogallol red method and creatinine by modified Jaffe's method using LANDWIND LWC 100 plus fully automated biochemistry analyser (Shenzhen Landwind industry co Ltd) with commercially available reagents. Data was expressed as urine protein (mg/dl) / urine creatinine (g/dl) = UPCR (mg/g) or mg/mmol by multiplying by a factor of 0.113.[34] The cut-off value for protein-creatinine ratio (mg of protein /mmol of creatinine) was taken as 35.5 as in a previous study conducted by Baweja et al and Mishra et al.[2,17] Protein-creatinine ratio was calculated and those with a ratio equal to or more than 35.5 mg/mmol were considered test positive while those with a ratio less than 35.5mg/mmol were considered test negative

At gestational age of 20 weeks, the women had doppler ultrasound performed by the radiologist using trans-abdominal 3.5MHz convex transducer with a GE Voluson P6 model. At least 3 spectral continuous and identical waves were considered and the doppler insonation angle was maintained at 30 to less than 60 degrees.

Doppler indices measured for both arteries include Pulsatility index (PI), Resistivity index (RI) An early diastolic notch was defined as a V-shaped deflection towards the baseline in early diastole. The abnormality in the doppler flow velocimetry is considered as the presence of a diastolic Notch in the uterine artery and RI and PI values greater than 0.7 and 1.4 respectively based on a previous study done by Modak et al[34] and any value above these cut-offs was taken as abnormal. Alterations in any of the uterine artery parameters were interpreted as an abnormal result of this artery and consequently, an abnormal general Doppler result was reported.

Participants were then followed up at the antenatal clinic until delivery. At each clinic visit, their blood pressure was measured, and they were evaluated for the development of any signs and symptoms of preeclampsia such as epigastric pain, reduced urinary output and visual disturbances and their urine was tested for protein. Based on this, the women were categorized as those who developed preeclampsia and those who remained normotensive. In those patients who developed preeclampsia, the gestational age was noted.

Data was analysed using the Statistical Product and Service Solution (SPSS) version 25. Continuous variables were expressed as mean and standard deviation (mean ± SD), while categorical variables were expressed as frequency and percentages. Pearson's Chi-square test (X^2) was used to express relationships between categorical variables. An independent t-test was used for continuous variables (expressed as means and standard deviation). Bivariate logistic regression analysis was done accordingly. The performance of the screening tests was evaluated by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and ROC curve. The ROC curves were generated to evaluate the efficiency of the combination of UPCR and uterine artery doppler parameters in predicting preeclampsia, calculating the area under the curve. The level of statistical significance was set at a *p*-value <0.05.

RESULTS

One hundred and ten participants were recruited for this study; however, 3 patients were lost to follow up and the data of 107 participants were eventually included in the final analysis. Eight women developed preeclampsia and the incidence of preeclampsia in this study was found to be 7.48%**.** The women who developed preeclampsia have a mean age of 35.38±4.4 years while the mean age of women who did not develop preeclampsia was 32.57±3.6 years and a comparison of the mean ages shows no statistical significance (p = 0.731). About 50% of women who developed preeclampsia were multiparous.

Out of the total UPCR positive patients (> 35.5mg/mmol), 5 women developed preeclampsia,

Table 1: Sociodemographic data and the development of Preeclampsia

	Development of preeclampsia		Test statistics	*p*-value
	Yes (n=8) n (%)	No (n=99) n (%)		
Age in years				
20-24	0 (0.0)	2 (2.0)	χ^2= 1.370	0.731
25-29	1 (12.5)	14 (14.1)		
30-34	3 (37.5)	52 (52.5)		
≥35	4 (50.0)	31 (31.3)		
Mean Age ± SD	35.38±4.4	32.57±3.6	t = 2.067	0.068
Tribe				
Yoruba	4 (50.0)	84 (84.8)	χ^2= 6.939	0.063
Igbo	0 (0.0)	3 (3.0)		
Hausa	4 (50.0)	11 (11.1)		
Ijaw	0 (0.0)	1 (1.0)		
Occupation				
None	0 (0.0)	10 (10.1)	χ^2=1.808	0.810
Unskilled	2 (25.0)	22 (22.2)		
Skilled	2 (25.0)	17 (17.2)		
Professional	4 (50.0)	50 (50.5)		
Parity				
Nulliparous	1 (12.5)	32(32.7)	χ^2=1.822	0.480
Primiparous	3 (37.5)	34(34.7)		
Multiparous	4 (50.3)	32 (32.7)		

Table 2: Association of spot UPCR, and uterine artery RI, PI band Diastolic Notch with the onset of Preeclampsia

Uterine Artery Doppler Components	Development of preeclampsia		Test statistics	*p*-value
	Yes (n=8) n (%)	No (n=99) n (%)		
Urine Protein (mg/dl) Mean ± SD	22.48 ± 8.30	19.67 ± 6.03	t= 6.524	**<0.001***
Urine Creatinine (g/dl) Mean ± SD	0.05 ± 0.02	0.11 ± 0.03	t= 0.434	0.665
Uterine Artery Doppler (PI) **<1.4**	1 (12.5) 7 (87.5)	2 (2.02) 97 (97.98)	χ^2= 2.983	**<0.004***
Mean ± SD	1.48 ± 0.25	1.17 ± 0.19	t= 4.405	**<0.001***
Uterine Artery Doppler (RI) **<0.7**	5 (62.5) 3(37.5)	3(3.03) 96(96.97)	χ^2= 37.872	**0.01***
Mean ± SD	1.08 ± 0.34	0.75 ± 0.12	t= 6.025	**0.030***
Uterine Artery Doppler (Diastolic Notch) Present Absent	3 (37.5) 5 (62.5)	2 (2.0) 97 (98.0)	χ^2= 10.244	**0.001***

Of the UPCR negative (<35.5mg/mmol), only 3 women developed the disease. Uterine Artery doppler velocimetry showed increased PI (cut-off value > 1.4 based on a previous study by Modak et al[34]) in 3 women (14.52%) out of which only 1 woman eventually developed preeclampsia. In the RI subjects, 8 women values above cut-off (≥ 0.7), and 5 of them developed preeclampsia. Out of the 8 women who developed preeclampsia, only 3 (37.5%) had diastolic notching (all unilateral), and the remaining 5 (62.5%) showed no notching.

Table 3: Performance of UPCR and UA doppler in the prediction of preeclampsia

Findings	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value
UPCR (mg/mmol)	62.5	100	100	97.06	97.20	0.004
PI	12.5	97.78	33.33	93.27	91.59	0.004
RI	62.5	96.97	62.5	96.96	94.39	0.001
Diastolic Notch	37.5	97.98	60	95.1	93.46	0.001
PI+RI+DN	50	97.97	66.6	96.04	94.39	0.004
UPCR+Uterine Artery indices	87.5	100	100	99	99.07	<0.001

Positive Predictive Value (PPV); Negative Predictive Value (NPV)

Table 4: AUC of UPCR and Uterine Artery Doppler Indices

Test Result Variable(s)	AUC	*p*-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Urine Protein to Creatinine Ratio (mg/mmol)	0.979	<0.001	0.949	1.000
Uterine Artery Doppler (PI)	0.949	<0.001	0.907	0.992
Uterine Artery Doppler (RI)	0.960	<0.001	0.921	1.000
Combined UPCR and Doppler Indices	0.999	<0.001	0.997	1.000

Spot UPCR had a sensitivity of 62.5%, specificity of 100%, PPV of 100% and NPV of 97.06%. Out of 16 women with abnormal uterine artery doppler (RI 0.7, /PI > 1.4 /diastolic notch present), 7 women had only false-positive results i.e., tests are positive (above cut-off) but who do not have the disease. For preeclampsia screening, findings of a combination of UPCR and uterine artery doppler indices had a sensitivity of 87.5%, specificity of 100%, PPV of 100%, and NPV of 99%. The accuracy of the combined spot UPCR and uterine artery doppler (including all the parameters of PI, RI, and diastolic notch) for the prediction of preeclampsia was 99.07%.

The AUC of uterine artery doppler indices RI and PI were 0.960 (95% CI 0.921- 1.000; p <

0.001) and 0.949 (95% CI 0.907 – 0.992; p < 0.001 and cut-off of 0.71 and 1.33 respectively as derived from the ROC curves. The AUC for the combined UPCR and doppler parameters was 0.999 as shown in the table. This is also depicted in the Receiver Operating Characteristics (ROC) curves below.

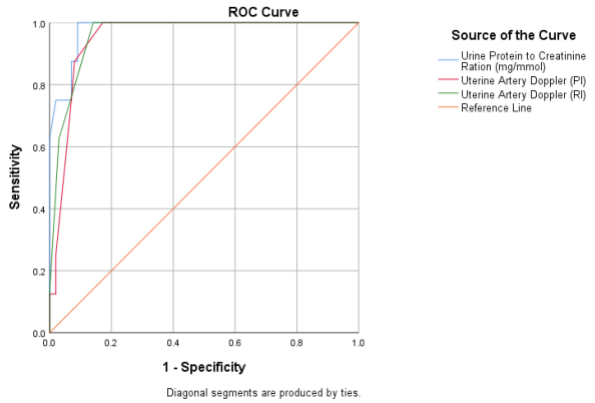

Figure 1a: ROC Curve for Spot UPCR and UA (PI and RI) for prediction of Preeclampsia

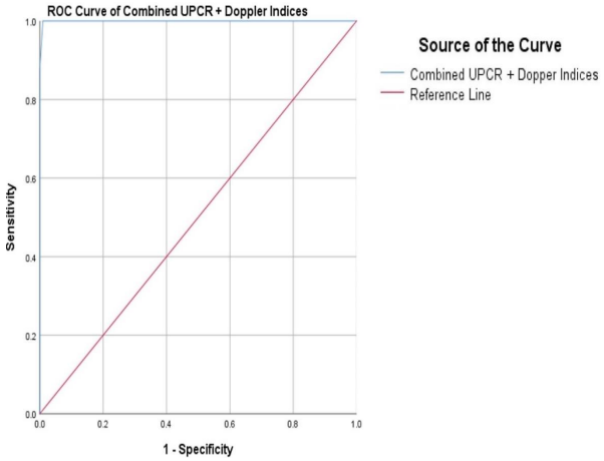

Figure 1b: ROC Curve for combined UPCR and Uterine Artery Doppler indices for prediction of Preeclampsia

DISCUSSION

Prediction of preeclampsia is necessary to identify women at risk of developing the disease later during pregnancy and initiate measures tailored towards heightened antenatal surveillance and prevention or early recognition of complications thereby reducing the morbidity and mortality associated with the disease.

One hundred and ten (110) pregnant women were recruited for this study out of which 3 were lost to follow up, hence 107 women completed the study and were included for analysis, giving a response rate of about 97%**.** Most of the participants in both groups were of Yoruba ethnicity. This could be attributed to the fact that the study was conducted in the Southwestern part of Nigeria predominantly occupied by the Yoruba ethnic group. The mean age of women who developed preeclampsia is 35.4 years and this is comparable to that of unaffected women (32.6years) (p=0.068). This was found to be higher than that of a similar study in Jos by Musa et al where the mean age of the women who developed preeclampsia was 29.7 years.[8]

About 50% of the women who developed preeclampsia were ≥ 35 years old and multiparous. Advanced maternal age (≥ 35 years) is associated with a 1.2 to 3 fold increased risk of development of preeclampsia as corroborated by this study.[35] Other studies also show that older age patients may be more at risk of developing severe preeclampsia.[36] Preeclampsia is often thought of as being a disease of first pregnancies. The incidence of preeclampsia in subsequent pregnancies, after a previous normal pregnancy, is lower. However, in this study, up to 50% of women who developed preeclampsia were found to be multiparous. The incidence of preeclampsia from this study was found to be 7.48% which is much higher than the worldwide incidence of 2.16%[5] as well as a figure of 5.6% reported by Adokiye et al,[37] but closely related to a figure of 7.6% obtained by Okwudire et al[38] in Port-Harcourt, Nigeria and also similar to some studies in Northern and Southern Nigeria of 8.8% and 10% reported by Musa and Salako et al respectively.[8,9] The differences in incidence rates obtained in the different studies quoted reflect the difference based on study designs (retrospective study by Adokiye et al) as well as the variations in different regions of the world.

The WHO estimated the incidence of preeclampsia to be higher in developing countries than in developed countries[39] as corroborated by this study, so the increase in the incidence of preeclampsia noted in this study could also be accounted for, by racial differences. In this study, the spot UPCR at 16 to 20 weeks is significantly higher in women who subsequently developed preeclampsia with a mean value of 47.11 ± 18.02mg/mmol compared to women who remained unaffected with a mean value of 17.82 ± 6.77mg/mmol. This is in tandem with studies

conducted by Mishra et al, Baweja et al and Modak et al. [2,17,34] The sensitivity of spot UPCR at the cut-off of ≥ 35.5 mg/mmol as a screening test to predict preeclampsia in this study was found to be 62.5% which is lower than the values obtained from studies done by Mishra et al and Modak et al[2,34] (87.5% and 80%) respectively and this may be due to the difference in gestational ages at recruitment of the patients.

The mean uterine artery RI and PI in this study was 1.08 and 1.48 respectively in the category of women who eventually developed preeclampsia both of which showed statistically significant association with the development of preeclampsia. This is similar to a report from Adekanmi et al[40] and Modak et al.[34] However, the mean RI from a study by Okwudire et al[38] in Port-Harcourt, Nigeria showed no significant association with the development of preeclampsia. In this study, the sensitivity of PI in predicting preeclampsia was noted to be low (12.5%) and comparable to that of a study by Modak et al who reported a sensitivity of 20%. Using a binary logistic regression performed to show the effect of UA doppler parameters on the likelihood of development of preeclampsia, the low sensitivity of PI in predicting preeclampsia in this study is in contrast to that obtained from a study by Adekanmi et al[40] in Ibadan, Nigeria with high PI sensitivity; This could be because Adekanmi et al recruited high-risk pregnant women for their study as opposed to this study where normotensive pregnant women were recruited.

The secondary outcome measures in this study include the development of Pregnancy-induced hypertension (PIH) and IUGR. Three women developed PIH while two women had IUGR. The spot UPCR and UA doppler parameters of the women who developed PIH and IUGR were also found to be significantly higher than those of unaffected women and are comparable to a study by Gupta et al.[41]

On binary logistic regression analysis using UPCR and the UA doppler findings, the combined parameters were statistically significant giving the sensitivity, specificity, PPV, NPV and predictive accuracy of 87.5%, 100%, 100%, 99% and 99.07% respectively. However, a similar study by Modak et al[34] did not compute a combined screening performance, which is a major limitation of their study and which this study improved upon. Combining UPCR with UA doppler parameter better predicted preeclampsia in the study cohort as compared to individual biomarkers

CONCLUSION

This study showed that a combination of spot UPCR and UA doppler parameters (RI, PI, Uterine artery notching) done in the early second trimester in normotensive pregnant women is a reliable screening algorithm in predicting preeclampsia occurring later during pregnancy.

The study cohort or sample size is not large enough to generalize the study and as such a large cohort is required to validate a more reliable study outcome. Also, the study was majorly limited to one ethnic group and ethnic homogenization of participants may not afford generalization of the findings and this further underscore the need for multi-centre participation.

RECOMMENDATION

A combination of UPCR and UA doppler findings of PI and RI can be incorporated into our routine obstetrics practice especially at the lower level of care so that any woman with a higher risk of developing preeclampsia will be referred to a higher centre early enough before complications arise. Also, heightened feto-maternal surveillance should be instituted at the higher level of care for women at increased risk of developing the disease based on the test results.

CONFLICT OF INTEREST: None

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