African Journal of FetoMaternal Medicine

Original Article

Mid-trimester Maternal Serum Placental Growth Factor (PLGF) And Soluble Fms-Like Tyrosine Kinase-1(sFlt-1) Combined with Fetal Doppler Studies in Prediction of Preeclampsia

Akintomiwa O. Bankole[1], Timothy A.O. Oluwasola[1,2], Oladapo Olayemi[1,2], Janet A. Akinmoladun[3], Bamidele K. Suleiman[1]

1. Department of Obstetrics and Gynaecology, University College Hospital, Ibadan. Nigeria.
2. Department of Obstetrics and Gynaecology, College of Medicine, University of Ibadan, Nigeria.
3. Department of Radiology, University College Hospital/University of Ibadan, Nigeria.

ABSTRACT

Background: There have been many studies on prediction of preeclampsia but there is no single test which has demonstrated sufficient predictive value. Combination of maternal biomarkers with fetal Doppler studies are the promising predictors. **Objective:** The purpose of this study was to evaluate midtrimester maternal serum PLGF, sFlt-1 and fetal Doppler studies in predicting preeclampsia. **Methodology:** This is a cohort study of 120 consenting pregnant women between the gestational ages of 18–24weeks had blood sample collected for PLGF and sFlt-1and Doppler obstetrics Ultrasound scan was performed at recruitment. The women were followed up longitudinally throughout pregnancy. Standard statistics methods were adopted as applicable. The level of statistical significance was set at 5% (*P*-value <0.05). **Results:** A total of 115 participants had complete data for analysis and 16 (13.9%) developed preeclampsia. There was a statistically significant difference in the serum level of sFlt-1 and the sFlt-1/PLGF in those that developed preeclampsia with *P*-values of 0.009 and 0.014 respectively. There was a significant statistical difference in those with abnormal uterine artery PI and RI, Umbilical artery PI and RI among those that developed preeclampsia. Combining sFlt-1 and sFlt-1/PLGF with uterine and umbilical arteries PI and RI on Receiver operating characteristics (ROC) curve yielded an Area under the curve (AUC) of 0.925 with a sensitivity of 93.8% at a specificity of 65.7%. **Conclusion:** The combination of the serum PLGF, sFlt-1 and fetal doppler in the midtrimester had highest sensitivity in predicting preeclampsia compared to when they are used singly, and this will form a valuable tool in predicting preeclampsia in those presenting late in second trimester.

KEY WORDS: preeclampsia, placental growth factor, sFlt-1, PlGF, sFlt-1/PlGF ratio, fetal doppler.

INTRODUCTION

Worldwide, hypertensive disorders of pregnancy, especially preeclampsia is one of the leading causes of maternal and perinatal mortality and morbidity, causing an amount of burden on the families of pregnant women and the health care system.[1] Preeclampsia is a leading cause of hypertension in

Correspondence
Dr. Akintomiwa O. Bankole
Department of Obstetrics and Gynaecology,
University College Hospital, Ibadan, Nigeria
Phone number: +2348034302923
Email address: drbankyw@gmail.com

pregnancy complicating about 2-8% of pregnancies.[2]Preeclampsia is the new onset of elevated blood pressure to ≥140mmHg systolic and ≥90mmHg diastolic measured on 2 occasions at least 4 hours apart and proteinuria (≥300mg in 24 hours urine specimen) after 20 weeks of gestation in a previously normotensive non-proteinuric woman.[2,3]

Preeclampsia/eclampsia is estimated to complicate 10 million pregnancies worldwide each year, resulting in 76,000 maternal death and 500,000 fetal/newborn death with 99% of these death occurring in low and middle-income countries.[1,2]In Nigeria, the incidence varies across the nations geo-political zones with incidence as low as 1.2% in Calabar to as high as 15.1% in Kaduna.[4,5]Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality in Nigeria accounting for 31.8% of maternal death in Nigeria'.

Preeclampsia is a multi-systemic syndrome, aetiology of which is still largely unknown but with advancing knowledge on the pathogenesis. The pathogenesis involves defective placentation, incomplete trophoblastic invasion of spiral arteries, placenta ischaemia, release of anti-angiogenic factors into maternal system, excessive maternal inflammatory response and wide-spread endothelial injury which later leads to clinical manifestation of the disease.[7,8]

Over the years, efforts to predict which women will develop preeclampsia have been largely unsuccessful as maternal history and risk factors alone usually do not predict the onset of the disease. Over the last three decades, extensive research in a bid to screen for aneuploidies has identified a series of biochemical and biophysical markers of impaired placentation used to predict pregnancy at risk. As such, improving the prediction of preeclampsia has been the focus of many research works both in asymptomatic populations at various gestations with varying prior risk.[9,10]

The concentration of angiogenic and anti-angiogenic factors in the maternal serum are noticed to be altered in preeclampsia. PLGF is found to be lower in preeclampsia than in normal pregnancies and this lower value is believed to be a result of placental hypoxia. On the other hand, sFlt-1, an anti-angiogenic factor that antagonizes PLGF and Vascular endothelial growth factor is found in higher values among patients with preeclampsia. Interestingly, this increase precedes the onset of the disease by weeks. [7,9]

There is no single test that has proved sufficient predictive value for Preeclampsia in clinical practice but there appears to be greater effectiveness in combination of multiple parameters instead.[10–12] The most effective strategies for the prediction of preeclampsia involve the use of a variety of individual parameters in combination. A combination of uterine artery pulsatility index (PI), biochemical markers at early gestation can be used to identify a proportion of pregnancies which are at high risk for early-onset preeclampsia. [13] There is paucity of studies in this regard in Nigeria which prompted the conduct of this study'

MATERIALS AND METHOD

This study was a cohort study conducted at the University College Hospital (UCH), Ibadan, Nigeria between March 2020 and October 2020. UCH is the teaching hospital complex for the University of Ibadan. The research was approved by the University of Ibadan/University College Hospital Ethical Review committee with IRB research approval number: UI/EC/19/0345

The sample size was calculated using Epi info software for cohort study which yielded a total of 120 at an attrition rate of 20% A cohort of 120 pregnant women with uncomplicated pregnancy who satisfied the inclusion criteria between the gestational ages of 18-24weeks were recruited. The exclusion criteria included multiple gestation, chronic medical conditions, previous history of preeclampsia and presence of fetal anomaly. Informed consent was obtained and sample for serum PLGF and sFlt-1 were collected, and fetal Doppler studies was performed by the radiologist. The samples were stored until analyzed and result of Doppler findings documented in the proforma. The doppler examination included one uterine artery from the placental side, the umbilical artery, and one middle cerebral artery. To register the values, four out of five spectral continuous and identical waves were considered. Doppler indices measured were PI, RI and S/D ratio (Systolic peak velocity/ End diastolic velocity) and the ratio of PI and RI were calculated with respect to MCA/UA. RI and PI values above the 95th percentile standardized for the gestational age were

considered abnormal for the uterine and umbilical arteries, and below the 10th percentile for the middle cerebral artery.

The participants were followed up at the antenatal clinic by checking the blood pressure and urinalysis, on the ward in cases of admission and at the labour ward to find out the development of preeclampsia. The analysis of biomarkers was done using Human Placental Growth Factor (PLGF) and Human Soluble Vascular Endothelial Cell Growth Factor Receptor 1 (sFlt-1) ELISA KITS by Meslin Medical Co. The result of the serum PLGF and sFlt-1and fetal Doppler studies were compared among those that developed preeclampsia and those without the condition to evaluate the role of the biomarkers and doppler studies in prediction of preeclampsia.

Study Definition of Preeclampsia:

The presence of a systolic blood pressure greater than or equal to 140 mm Hg or a diastolic blood pressure greater than or equal to 90 mmHg, on two occasions at least 4 hours apart in a previously normotensive woman, and a urine dipstick protein of at least 2+

Data collected were checked for consistency and missing variables which were verified. It was analyzed using the Statistical Package for Social Sciences (SPSS) version 23. Data analysis was performed using descriptive and inferential statistics. T-test was used to analyze continuous variables while Chi- square was used for categorical variables. Receiver operating characteristic (ROC) curves were used to determine different cut-off for biomarkers and the doppler velocimetry PI and RI.

Sensitivity and specificity were also calculated. The level of statistical significance was set at *p*-value <0.05.

RESULTS

A total of 120 pregnant women at the Antenatal clinic of the University College Hospital, Ibadan were recruited for the study, however five participants were lost to follow-up, leaving a study cohort of 115 participants.

The demographic and obstetrics characteristics of the participants as shown in table 1 revealed significant differences in both systolic and diastolic blood pressure both at booking and recruitment of the participants. The mean age, mean gestational age at booking and at recruitment were similar in both groups of the participants. Among those that developed preeclampsia, nulliparous and primiparous had equal percentages of 43,7% while 42.4% of those without preeclampsia were nullipara.

The incidence of preeclampsia among the participants is as shown in figure 1. Sixteen of the participants developed preeclampsia giving an incidence of 13.9% for this study.

Table I: Demographic and Obstetrics Characteristics

	Development of preeclampsia		Test statistics	P-value
	Yes (n=16) n (%)	No (n=99) n (%)		
Age in years				
Less than 25	0(0)	8(8.2%)	Fisher's	0.234
25 - 29	6(37.6%)	34(34.3%)	Exact= 4.263	
30 - 34	5(31.2%)	43(43.4%)		
35 and above	5(31.2%)	14(14.1%)		
Mean Age ± SD	31.69±3.67	30.28±4.24	t= 1.249	0.214
Parity				
Nulliparous	7(43.7%)	42(42.4%)	χ^2=1.077	0.584
Primiparous	7(43.7%)	34(34.3%)		
Multiparous	2(12.6%)	23(23.3%)		
Tribe				
Yoruba	9(56.2%)	73(73.7%)	χ^2=4.715	0.174
Igbo	5(31.2%)	17(17.1%)		
Hausa	0(0)	5(5.2%)		
Others	2(12.6%)	4(4.0%)		
Gestational age at booking				
[illegible]	6(37.5%)	20(20.2%)	χ^2=2.355	0.193
>13 weeks	10(62.5%)	79(79.8%)		
Mean ± SD	15.70±5.26	16.62±3.54	t=0.857	0.377
Gestational age at recruitment				
18-20 weeks	7(43.7%)	32(32.3%)	χ^2=0.802	0.370
>20 weeks	9(56.3%)	67(67.7%)		
Mean ± SD	20.82±1.16	20.96±1.54	t=0.324	0.747
Booking Systolic BP Mean ± SD (mmHg)	118.13±9.19	109.88±9.08	t=3.362	**0.010***
Booking Diastolic BP Mean ± SD (mmHg)	74.50±6.95	69.96±6.94	t=2.428	**0.017***
Recruitment Systolic BP Mean ± SD (mmHg)	115.38±7.14	109.25±6.92	t= 3.269	**0.001***
Recruitment Diastolic BP Mean ± SD (mmHg)	73.38±7.40	70.26±5.52	t=1.989	**0.049***

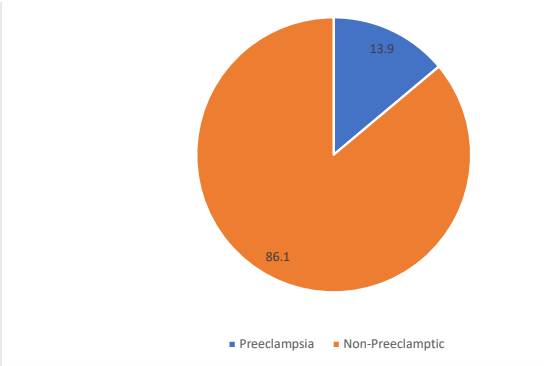

Figure I: Incidence of Preeclampsia

From table 2, in about two- third of those that developed preeclampsia, the diagnosis was made at a gestational age of 37weeks and above with 62.5%

of those that developed preeclampsia having 2+ of protein on dipstick urinalysis. In the majority of those that developed preeclampsia, 87.5%, the systolic BP at diagnosis was ≥160mmHg.

Table 2 Obstetrics characteristics of participants with Preeclampsia

Variables	N (16)	%
Gestational Age at Diagnosis(weeks)		
<34	1	6.2
34-36	5	31.3
>37	10	62.5
Mean±SD 37.18±2.58		
Urinalysis at diagnosis		
2	10	62.5
3	6	37.5
Systolic BP at Diagnosis		
140-159mmHg	2	12.5
≥160mmHg	14	87.5
Mean±SD 168.38±12.55		
Diastolic BP at Diagnosis		
90-109mmHg	9	56.3
≥110mmHg	7	43.7
Mean±SD 105.50±9.73		
Gestational Age at Delivery (weeks)		
<34	1	6.3
34-36	5	31.2
37 and above	0	62.5
Mean±SD 37.18±2.59		
Mode of delivery		
SVD	3	13.7
EMLSCS	13	81.3
Presence of complication		
Yes	2	12.5
No	14	87.5
Types of complication		
Pulmonary edema	2	100
Others	0	0

Table 3: Bivariate analysis of serum biomarkers and the Development of Preeclampsia

Variables	Preeclampsia (16)	No preeclampsia (99)	Test statistics	*p*-value
PLGF (pg/ml) Median (Interquartile range)	7.60(4.40)	9.00(3.20)	2.891	0.089
sFlt-1(pg/ml) Median (IR)	790(1161)	600(290)	6.836	**0.009***
sFlt-1/PLGF Median (IR)	104.73(101.25)	67.73(29.66)	6.064	**0.014***

Sixty-two-point five percent delivered at a gestational age of 37 weeks and above and in 81.3%, the delivery was via EMLSCS. Only 2 of those that developed preeclampsia developed complication and no maternal mortality was recorded in the study.

From table 3, the median value of PLGF was observed to be lower in those that developed preeclampsia, however this was not statistically significant. The median values of sFlt-1 and sFlt-1/PLGF were found to be significantly higher among the participants that developed preeclampsia with *p*-values of 0.009 and 0.014 respectively.

From the Table 4, the mean uterine artery PI and RI, umbilical artery PI and RI were seen to be higher among those that developed preeclampsia. For MCA PI and RI, the mean values were lower for those with preeclampsia. There was a significant statistical difference in those with abnormal uterine artery PI and RI, Umbilical artery PI and RI among those that developed preeclampsia.

Table 4: Bivariate analysis of Doppler findings and the Development of Preeclampsia

Variables	Preeclampsia (16)	No preeclampsia (99)	Test statistics	*p*-value
Uterine Artery PI				
Normal	3(18.7%)	80(80.8%)	χ^2=26.413	**0.000***
Abnormal	13(81.3%)	19(19.2%)		
Mean±SD	1.08±0.25	0.94±0.56	t= 2.30	0.340
Uterine Artery RI				
Normal	7(43.7%)	87(87.9%)	χ^2=17.970	**0.000***
Abnormal	9(56.3%)	12(12.1%)		
Mean±SD	0.69±0.15	0.57±0.13	t=0.04	**0.001***
UA PI				
Normal	9(56.3%)	80(80.8%)	χ^2=4.748	**0.049***
Abnormal	7(43.7%)	19(19.2%)		
Mean±SD	1.12±0.21	1.02±0.23	t=0.00	0.094
UA RI				
Normal	8(50%)	78(78.8%)	χ^2=6.053	**0.026***
Abnormal	8(50%)	21(21.2%)		
Mean±SD	0.71±0.07	0.66±0.09	t=0.25	**0.040***
MCA PI				
Normal	15(93.7%)	91(91.9%)	χ^2=0.064	0.800
Abnormal	1(6.3%)	8(8.1%)		
Mean±SD	1.77±0.29	1.78±0.36	t=0.61	0.437
MCA RI				
Normal	14(87.5%)	90(90.9%)	χ^2=0.185	0.650
Abnormal	2(12.5%)	9(9.1%)		
Mean±SD	0.80±0.08	0.79±0.08	t=0.08	0.776
Presence of uterine artery diastolic notch			χ^2=0.002	0.967
Yes	3(18.75%)	19(19.2%)		
No	13(81.3)	80(80.8%)		
UA S/D	3.31±0.94	2.96±0.80	t= 1.156	0.121
MCA S/D	3.75±0.85	3.76±1.28	t=0.04	0.968
PI: MCA/UA	1.62±0.39	1.80±0.44	t=1.517	0.132
RI: MCA/UA	1.13±0.17	1.21±0.15	t=1.762	0.081

Maternal and fetal outcome from the study were depicted in table V. The commonest mode of delivery for those with preeclampsia was EMLSCS as 81.3% were delivered through this route compared to 31.3% caesarean rate among those without preeclampsia. There was a significant statistical difference in APGAR score at 5mins as 12.5% of those with preeclampsia had their babies APGAR score <7 compared to 2.0% in those without preeclampsia.

Figures II to V show ROC curves constructed for PLGF, sFlt-1, sFlt-1/PLGF, uterine and umbilical arteries PI and RI.

Table 5: Maternal and Fetal Outcome in Preeclampsia

Variables	Preeclampsia (16)	Non-preeclamptic (99)	Test statistics	*p*-value
Mode of Delivery				
SVD	3(18.7%)	68(68.7%)	Fisher's Exact=26.57	**0.000***
ELLSCS	0(0%)	12(12.1%)		
EMLSCS	13(81.3%)	19(19.2%)		
Birth weight				
<2.5kg	3(18.7%)	4(4.1%)	χ^2=5.214	0.055
≥2.5kg	13(81.3%)	95(95.9%)		
Apgar Score at 1 min			χ^2=0.882	0.348
<7	2(12.5%)	6(6.1%)		
≥7	14(87.5%)	93(93,9%)		
Apgar Score at 5 min			χ^2=4.506	0.034*
<7	2(12.5%)	2(2.0%)		
≥7	14(87.5%)	97(98%)		
NICU Admission			Fisher's Exact=0.882	0.348
Yes	2(12.5%)	6(6.1%)		
No	14(87.5%)	93(93.9%)		
Neonatal Outcome			Fisher's Exact=1.097	0.295
Alive	15(93.7%)	99(100%)		
Dead	1(6.3%)	0(0%)		

Table 6: Performance of Variables in Predicting Preeclampsia based on ROC curve

Variables	AUC	Sensitivity (%)	Specificity (%)	95% CI	*p*-value
PLGF <8.15pg/ml	0.693	68.8	67.7	0.532 - 0.855	**0.013**
sFlt-1 >622.5pg/ml	0.734	81.3	57.6	0.607 – 0.861	**0.003**
sFlt-1/PLGF >75.4	0.771	81.3	66.7	0.635 – 0.908	**0.001**
UtA PI >1.06	0.786	81.3	82.8	0.664 – 0.908	**0.000**
UtA RI 0.66	0.784	75	76.8	0.658 – 0.911	**0.000**
UA PI >0.98	0.692	75	60.6	0.562 – 0.821	**0.014**
UA RI >0.70	0.701	62.5	69.7	0.563 – 0.839	**0.010**
Combined Variables	0.925	93.8	65.7	0.862 – 0.988	**0.000**

Table 7: Logistic regression analysis of independent variables

Independent variables	Outcome = Development of preeclampsia		
	Odds ratio	95% CI	*p*-value
sFlt-1 (>622.5pg/ml)	1.000	1.000 – 1.001	0.070
sFlt-1/PLGF (>75.4)	1.030	1.005 – 1.057	**0.021***
Uterine artery PI (>1.06)	8.221	1.024 – 65.987	**0.047***
Uterine artery RI (>0.66)	0.315	0.050 – 1.999	0.221
Umbilical Artery PI (>0.98)	1.953	0.232 – 16.453	0.538
Umbilical Artery RI (0.70)	3.357	0.408 – 27.634	0.260

From table 6, the ROC curve for PLGF yielded an AUC of 0.693 with a sensitivity and specificity of 68.8% and 67.7% respectively at a cut-off value of 8.15pg/ml. The ROC curve for sFlt-1 and sFlt-1/PLGF yielded an AUC of 0.734 with p-value of 0.003 for sFlt-1 and AUC of 0.771 with p-value of 0.001 for sFlt-1/PLGF. At a cut-off value of 622.5pg/ml, sFlt-1 has a sensitivity and specificity of 81.3% and 57.6% respectively for predicting preeclampsia and at cut-off value of 75.4, sFlt-1/PLGF has a sensitivity and specificity of 81.3% and 66.7%.

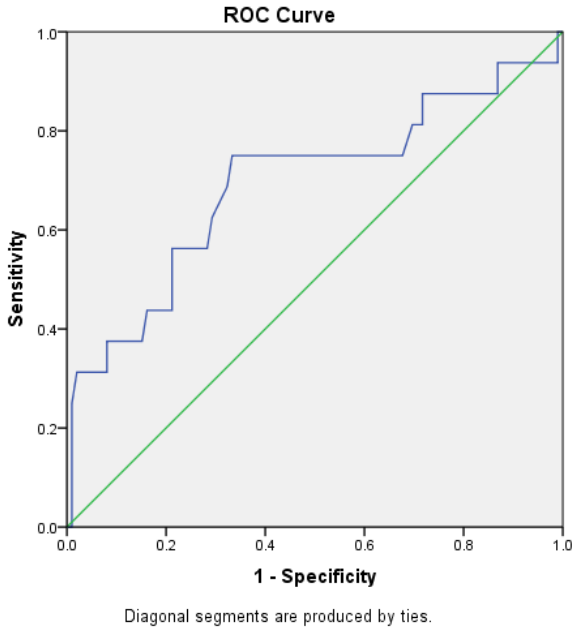

Figure II: ROC curve of PLGF; AUC= 0.693, 95% CI (0.532 – 0.855), *p*=0.013

For uterine artery PI, the AUC is 0.786 and at cut-off value >1.06, it has sensitivity and specificity of 81.3% and 82.8% respectively. The AUC for uterine artery RI is 0.784 and at cut-off value >0.66, it has a sensitivity of 75% and specificity of 76.8%. The ROC curve for umbilical artery PI and RI yielded AUC of 0.692 and 0.701 respectively.

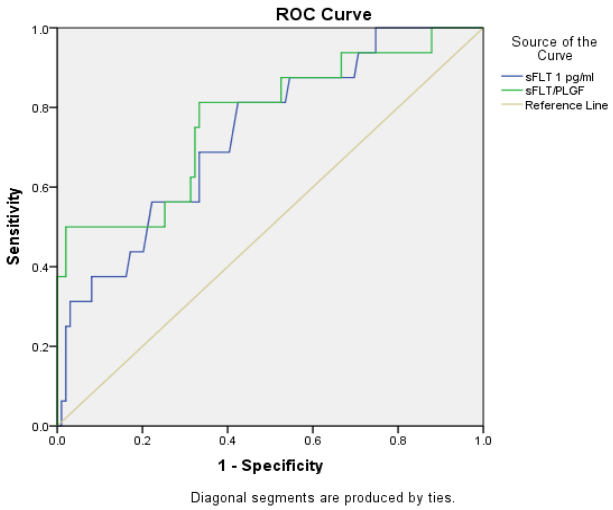

Figure III: ROC Curve for sFlt-1 and sFlt- 1/PLGF; For sFlt-1, AUC=0.734, 95% CI(0.607 – 0.861), *p*=0.003. for sFlt- 1/PLGF; AUC=0.771, 95% CI(0.635 – 0.908), *p*=0.001

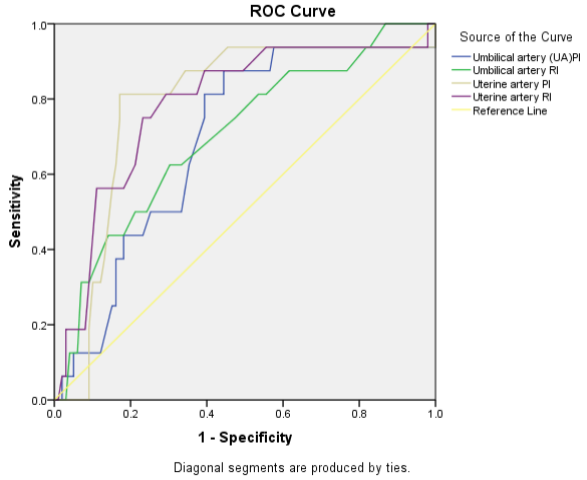

Figure IV: ROC curve for uterine and umbilical arteries PI and RI

At a cut-off value of 0.98, umbilical artery PI has a sensitivity of 75% and specificity of 60.6% and at a value greater than 0.70, umbilical artery RI has a sensitivity of 62.5% and a specificity of 69.7%. Combining the variables, it yielded an AUC of 0.925 with a sensitivity of 93.8% at a specificity of 65.7%.

From the table 7, a logistic regression analysis was performed to ascertain the likelihood of development of preeclampsia. It was noted that with uterine artery PI above 1.06, the odd of developing preeclampsia was 8.221. Also, the odd ratio of developing preeclampsia with abnormal umbilical artery PI and RI were 1.953 and 3.357 respectively.

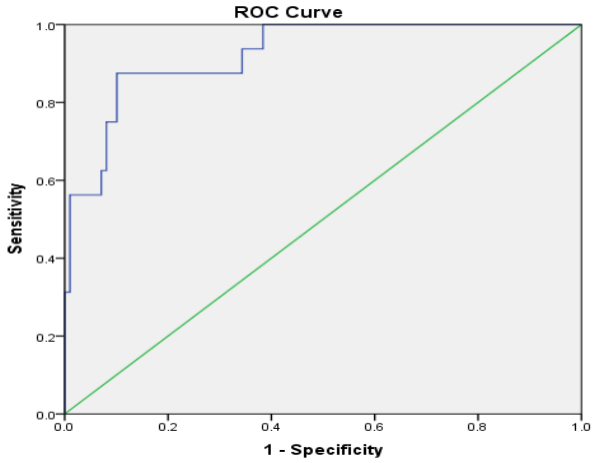

Figure V: ROC curve of combined variables (sFlt-1, sFlt-1/PLGF, Uterine artery PI, Uterine artery RI, Umbilical artery PI and Umbilical artery RI); combined AUC= 0.925, 95% CI (0.862- 0.988) with *p*-value of <0.001

DISCUSSION

The mean age of participants that developed preeclampsia and those with normal pregnancies were similar and this is in tandem with what was reported by previous authors.[37,47] The majority of the participants in both groups of participants were of Yoruba ethnicity. This could be due to the fact that the study was conducted in the Southwest of Nigeria which is which is majorly occupied by the Yoruba ethnic group.

The incidence of preeclampsia from this study is 13.9%, higher than 1.2% rate reported by Kooffreh ME et al and 2-8% rate reported by Steegers EAP et al but comparable to 13.6% rate reported by Azubuike S et al.[4,5,7] This variation may be due to the fact that preeclampsia has a racial predilection. There was a statistically significant increase in both systolic and diastolic blood pressure at the recruitment into the study by the participants that developed preeclampsia with p-values of 0.001 and 0.049. This finding is similar to what was reported by Udenze IC et al with increase of both systolic and diastolic blood pressure with p-values of 0.005 and 0.001 respectively.[47]

Among the participants that developed preeclampsia, the diagnosis was made in 62.5% at a gestational age of 37 weeks and above. This is comparable to 58.9% that was reported by

Benovska et al.[38] Caesarean delivery was noted to be the major route of delivery among the participants that developed preeclampsia. This may be necessary as urgent delivery is needed to halt the progression of the disease and to prevent maternal and perinatal morbidity and mortality. This finding is in support of what was reported by Linhares JJ et al in which a preeclamptic patient was showed to be 2.5 times more likely to have caesarean delivery.[48]

There was no significant statistical difference in PLGF level between the two groups of the participants. The ROC curve analysis of PLGF at a cut-off value of 8.15pg/ml gave a sensitivity of 68.8% and specificity of 67.7%. The sensitivity of 68.8% reported for PLGF is higher than what was reported by Benovska et al who reported detection rate of 43.6% but similar to 67% reported by Wu et al in 2015 in a systematic review of previous studies on the use of biomarkers to predict preeclampsia.[35,38]

Serum sFlt-1 was observed to be higher in those that developed preeclampsia compared to those with normal pregnancy. The AUC of 0.734 for the sFlt-1 was similar to what was reported by Gallos et al in 2016 with AUC of 0.733, however their study recruited both the high and low risk participants. This study revealed a sensitivity of 81.3% for sFlt-1 in predicting preeclampsia. This finding is similar to sensitivity of 82% reported by Benovska et al in 2018 with sensitivity of 82.1% when sFlt-1 was considered alone, however this was a retrospective study and participants with risk factors were not excluded.[36,38] Comparing with other biomarkers that have been used previously, it is higher than the sensitivity of 37.5% with the use PP13 reported by Villa PM et al and sensitivity of 20% with the use of PAPP-A reported in the study conducted by Anderson UD et al but lower than the sensitivity of 88.9% reported by Salako BL et al on detection of preeclampsia using microalbuminuria in pregnancy.[13,29,30]

From this study, the ratio of sFlt-1 to PLGF was found to be higher among those that developed preeclampsia which corroborated earlier works which reported similar findings.[34,38] The ratio has a sensitivity of 81.3% which is higher than 74.4% reported by Benovska et al. The cut-off value for the ratio in this study was 75.4 compared to 22.9 used by Benovska and this may explain the higher sensitivity in this study. The sensitivity in this study was lower than 95.8% reported by Taraseviciene et al.[38,49] The study was a case control study, and the recruitment of participants was between gestational age of 26-40 weeks. This difference could be explained by different cut-off employed by the various studies and the gestational age at the recruitment of the participants.

There was a significant statistical difference in the uterine artery PI and RI in those with preeclampsia as the uterine artery PI predicted 81.3% of preeclampsia which is similar to a high sensitivity reported in a study by Adekanmi et al in which sensitivity of 86% was reported but in contrast to Lopez-Mendez who observed no significant difference in the uterine artery PI and RI. This difference could be as a result of the reference value used for the indices and the population differences in the two studies.[42,50]

The participants with abnormal umbilical artery doppler PI and RI were more likely to develop preeclampsia. This finding is similar to what was observed by Lopez-Mendez and Adekanmi et al who reported significant difference in the umbilical artery doppler of those that developed preeclampsia, however their studies enrolled participants with risk factors for preeclampsia. There was no significant difference in the mean values of fetal middle cerebral artery PI and RI. This is in contrast to Lopez Mendez who reported a significant statistical difference in the fetal MCA PI among those with preeclampsia compared to those that did not have preeclampsia with *p*-value of 0.009. This could be as a result of the difference in gestational age at recruitment of the participants in their study (24-37 weeks) and participants enrolled were those with risk factors for developing preeclampsia.

The combination of the biomarkers and the uterine and umbilical arteries PI and RI were noted to have highest sensitivity compared to when they are used singly. The ROC curve yielded an AUC 0.925 with a sensitivity of 93.8%. This high AUC was similar to what was reported by Li et al with findings of AUC of 0.915 with sensitivity of 92% combining activin A, Inhibin A, PLGF and uterine artery PI.[51] This above finding is in support of earlier studies on the utility of biomarkers and uterine artery Doppler findings to predict preeclampsia in the second trimester of pregnancy.[11]

CONCLUSION

Combination of midtrimester serum PLGF and sFlt-1 and uterine and umbilical arteries PI and RI showed the highest sensitivity in predicting preeclampsia compared to when they are used singly. This will be of value in identifying women that will develop preeclampsia as they form the basis of an effective screening test to identify the at-risk women.

IMPLICATION FOR CLINICAL PRACTICE

Significant number of pregnant women book late in the second trimester and may not benefit from the FIGO recommendation of first trimester screening for preeclampsia. As there is no identified pharmacological intervention to prevent preeclampsia beyond 16 weeks, utilization of serum sFlt-1 and sFlt-1/PLGF, uterine and umbilical arteries PI and RI will help in disease surveillance and proper resources allocation for their management.

REFERENCES:

1. Osungbade KO, Ige OK. Public Health Perspectives of Preeclampsia in Developing Countries: Implication for Health System Strengthening. Journal of Pregnancy January 2011(2090-2727):481095 doi:10.1155/2011/481095
2. Brown MA, Lindheimer MD, Swiet M De, Assche A Van, Moutquin J. The Classification and Diagnosis of the Hypertensive Disorders of Pregnancy : Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP) Hypertension in Pregnancy. 2001;20(1): 9-14
3. Guideline American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013 Nov. 122 (5):1122-31.
4. Kooffreh ME, Ekott M, Ekpoudom DO. The prevalence of pre - eclampsia among pregnant women in the University of Calabar Teaching Hospital , Calabar. saudi J Heal Sci. 2014;3(3):133–6.
5. Azubuike S, Danjuma I. Hypertension in Pregnancy among Rural Women in Katsina State . J Basic Clin Reproductive Sci. 2017;6(1):140–6.
6. Jamilu Tukur, Tina Lavin, Abiodun Adanikin, Muhammed Abdussalam, Kuti Bankole, Mabel Ikpim Ekott, et al. Quality and outcomes of maternal and perinatal care for 76,563 pregnancies reported in a nationwide network of Nigerian referral-level hospitals. E-Clinical Medicine. 2022 Apr 28;47:101411. doi: 10.1016/j.eclinm.2022.101411.
7. Steegers EAP, Dadelszen P Von, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376(10):631–44.
8. Valenzuela FJ, Pérez-Sepúlveda A, Torres MJ, Correa P, Repetto GM, Illanes SE. Pathogenesis of preeclampsia: The genetic component. J Pregnancy. 2012;2012(10) Article ID 632732, 8 pages doi:10.1155/2012/632732.
9. Kane SC, Da Silva Costa F, Brennecke SP. New directions in the prediction of pre-eclampsia. Aust New Zeal J Obstet Gynaecol. 2014;54(2):101–7.
10. Park HJ, Shim SS, Cha DH. Combined screening for early detection of pre-eclampsia. Int J Mol Sci. 2015;16(8):17952–74.
11. Nicolaides KH, Casanova C, Pugliese G, Gallo D. Biophysical and biochemical prediction of preeclampsia at 20-24 weeks ' gestation Submitted by Dahiana Marcela Gallo Gordillo For the degree of International Doctor in Medicine University of Granada : Ultrasound Obs Gynecol. 2016;47(5):554–9.
12. Austdal M. Biomarkers for prediction and characterization of preeclampsia using magnetic resonance metabolomics.PLos ONE 2015;9(3):e91923
13. Villa PM. Prediction and Prevention of Pre-Eclampsia. BMC Pregnancy and Childbirth. 2013;13:110.
14. Edmond K, editor. Dewhurst ' s Textbook of Obstetrics & Gynaecology. In: Dewhurst ' s Textbook of Obstetrics & Gynaecology. 9th ed. Blackwell Publishing Ltd; 2018. p. 73–84.
15. James JL, Whitley GS, Cartwright JE. Pre-eclampsia : fitting together the placental , immune and cardiovascular pieces. J Pathol. 2010;221(4):363–78.
16. Shelly K. Review of Risk Factors , Diagnosis condition and Management Procedure of Preeclamsia in industrial and non-industrial areaof Bangladesh. research work done by KamrunNaher Shelly, ID NO: 2013-1-79-004 in partial fulfillment of the requirement for the Degree of Masters of Pharmacy.Department of Pharmacy, East West University Dhaka, Bangladesh. 2013;Pg1-54.
17. Saldanha CL, Ara S, Parvez T. The role of cystatin c in the prediction of outcome in hypertensive disorders of pregnancy. Int J Reprod Contraception, Obstet Gynecol. 2017;6(5):1825-32.
18. Costa FDS, Murthi P, Keogh R, Woodrow N. Early

screening for preeclampsia. Rev Bras Ginecol Obs. 2011;33(11):367–75.
19. Gudmundsson S. Fetal middle cerebral to uterine artery pulsatility index ratios in normal and pre-eclamptic pregnancies. Obs Gynecol. 2006;28(6):794–801.
20. Deurloo KL. Early Prediction of Preeclampsia and IUGR. Prenatal Diagnosis. 2007;27:1011-1016
21. Magee L, Newstead J, Ng J, Ct A, Von Dadelszen P. Pre-eclampsia as a marker of cardiovascular disease. Fetal Matern Med Rev. 2008;19(4): 271-292
22. Bartsch E, Medcalf KE, Park AL, Ray JG, Al-Rubaie ZTA, Askie LM, et al. Clinical risk factors for pre-eclampsia determined in early pregnancy: Systematic review and meta-analysis of large cohort studies. BMJ. 2016;353: i1753.
23. Olayemi O, Strobino D, Aimakhu C, Adedapo K, Kehinde A, Odukogbe AT, Salako B. Influence of duration of sexual cohabitation on the risk of hypertension in nulliparous parturients in Ibadan; A cohort study. Aust N Z J Obstet Gynaecol. 2010 Feb; 50(1): 40-4.
24. Wangi I, Dilmohamed A, Pierre Y. Difference InThe Trend of Preeclampsia Between Black Women and White Women Living In The Uk . J anine. 2016;6(Oct):62–73.
25. Poon LC, Nicolaides KH. Early Prediction of Preeclampsia. Hindawi Publishing Corporation Obstetrics and Gynecology International Volume 2014, Article ID 297397, 11 pages http://dx.doi.org/10.1155/2014/297397.
26. Roberts JM, Hubel CA. The Two Stage Model of Preeclampsia : Variations on the Theme. Placenta. 2010;30(suppl A:1–12.
27. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of Preeclampsia. Annu Mech Dis. 2010;5:173–92.
28. Cerdeira AS, Agrawal S, Staff AC, Redmann CW. Angiogenic factors: potential to change clinical practice in pre-eclampsia? BJOG. 2018;125(11):1389–95.
29. Anderson UD, Olsson MG, Kristensen KH, Åkerström B, Hansson SR. Review: Biochemical markers to predict preeclampsia. Placenta. 2012;33(SUPPL.):S42–7.
30. Salako BL, Odukogbe ATA, Olayemi O, Adedapo KS, Aimakhu CO, et al. Microalbuminuria in pregnancy as a predictor of preeclampsia and eclampsia. West Afr J Med. 2003 Dec;22(4):295-300.
31. Verlohren S, Stepan H, Dechend R. Angiogenic growth factors in the diagnosis and prediction of pre-eclampsia. Clin Sci. 2012;52:43–52.
32. Dragan I, Georgiou T, Prodan N, Akolekar R, Nicolaides KH. Screening for pre-eclampsia using sFlt-1 / PlGF ratio cut-off of 38 at 30 – 37 weeks ' gestation. Ultrasound Obs Gynecol. 2017;49(December 2016):73–7.
33. Herraiz I, Simón E, Gómez-Arriaga PI, Martínez
34. Moratalla JM, García-Burguillo A, López Jiménez EA, et al. Angiogenesis-related biomarkers (sFlt-1/PLGF) in the prediction and diagnosis of placental dysfunction: An approach for clinical integration. Vol. 16, International Journal of Molecular Sciences. 2015. p. 19009–26.
35. Sovio U, Gaccioli F, Cook E, Hund M, Charnock-jones DS, Smith GCS, et al. Preeclampsia Prediction of Preeclampsia Using the Soluble fms-Like Tyrosine Kinase 1 to Placental Growth Factor Ratio A Prospective Cohort Study of Unselected Nulliparous Women. Hypertension. 2017;69:731–8.
36. Wu P, Berg C Van Den, Alfirevic Z, Brien SO. Early Pregnancy Biomarkers in Pre-Eclampsia : A Systematic Review and Meta-Analysis. Int J Mol Sci. 2015;16:23035–56.
37. Gallos DM, Wright D, Campenero M, Nicolaide KH, Cassanova C. Competing risk model in screening for preeclampsia by maternal factors and biomarkers at 19-24weeks gestation. Am J Obstet Gynecol 2016; 214:619.e1-17
38. Park HJ, Kim SH, Jung YW, Shim SS, Kim JY, Cho YK, et al. Screening models using multiple markers for early detection of late-onset preeclampsia in low-risk pregnancy. BMC Pregnancy Childbirth. 2014;14(35):1–11.
39. Benovská M, Opluštilová A, Pinkavová J, Hodická Z, Cermáková Z. The New Possibilities in Early Diagnosis of Preeclampsia by Soluble fms-Like Tyrosine Kinase-1 and Placental Growth Factor in 16-20 Weeks Gestation. Lab Med. 2018;49(2):112–7.
40. Kienast C, Moya W, Rodriguez O, Jijón A. Predictive value of angiogenic factors , clinical risk factors and uterine artery Doppler for pre-eclampsia and fetal growth restriction in second and third trimester pregnancies in an Ecuadorian population Predictive value of angiogenic factors , clinic. J Matern Fetal Neonatal Med. 2016;29(4):537–43.
41. Padmini CP, Das P, Chaitra R, Adithya MS. Role of Doppler indices of umbilical and middle cerebral artery in prediction of perinatal outcome in preeclampsia. Int J Reprod Contraception, Obstet Gynecol. 2016;5(3):845–9.
42. Cnossen JS, Morris RK, ter Riet G, Mol BW, Van der Post JA, Coomarasamy A, Zwinderman AH, Robson SC, Bindels PJ, Kleijen J, Khan KS : Use of uterine artery Doppler ultrasonography to predict preeclampsia and intrauterine growth restriction; a systematic review and bivariable

metaanalysis . CMAJ 2008;178(6):701-11.
43. Lopez-Mendez MA, Martinez-Gaytan V, Cortes-Flores R, Ramos-Gonzalez RM, Ochoa-Torres MA, Garza-Veloz I, Martinez-Acuna MI, Badillo-Almaraz JI, Martinez-Fierro ML. Doppler ultrasound evaluation in preeclampsia. BMC Res Notes. 2013;6(1):477–82.
44. Singh M, Sharma A, Singh P. Role of Doppler Indices in the Prediction of Adverse Perinatal Outcome in Preeclampsia. Natl J Med Res. 2013;3(4):315–31s8.
45. Dover N, Gulerman HC, Celen S, Kahyaoglu S, Yenicesu O. Placental growth factor: As an early second trimester predictive marker for preeclampsia in normal and high-risk pregnancies in a turkish population. J Obstet Gynecol India. 2013;63(3):158–63.
46. Adekanmi AJ, Roberts A, Adeyinka AO, Umeh EO, Anor F, et al. Normal second and third trimester uterine and umbilical doppler indices among healthy single gestation in Nigeria women. West Afr J Radiol 2017;24:1-7
47. Kurmanavicius J, Florio I, Wisser J, Hebisch G, Zimmermann R, Muller R , et al. Reference resistance indices of the umbilical, fetal middle cerebral and uterine arteries at 24-42 weeks of gestation. Ultrasound Obstet Gynecol 1997;10:112-20
48. Udenze IC, Arikawe AP, Makwe CC, Olowoselu OF. A prospective cohort study on the clinical utility of second trimester mean arterial blood
49. pressure in the prediction of late onset preeclampsia among Nigeria women. Niger Clin Pract 2017;20:741-5
50. 48. Linhares JJ, Macedo NM, Arruda GM, Vasconcelos JL, Saraiva TV, Ribero AF. Factors associated with mode of delivery in women with preeclampsia. Rev Bras Ginecol Obstet. 2014 Jun;36(6):259-63
51. 49. Tarasevičienė V, Grybauskienė R, Mačiulevičienė R. sFlt-1, PlGF, sFlt-1/PlGF ratio and uterine artery Doppler for preeclampsia diagnostics. Medicina 2016;52:349-353
52. 50. Adekanmi AJ, Roberts A, Akinmoladun JA,Adeyinka AO. Uterine and umbilical artery doppler in women with pre-eclampsia and their pregnancy outcomes. Niger Postgrad Med J 2019;26:106-12.
53. 51. Li J, Zheng Y, Zhu Y, Li J. Serum biomarkers combined with uterine artery Doppler in prediction of preeclampsia. Experimental and therapeautic medicine 2016;12:2515-20