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The place of uterine artery and umbilical artery doppler in prediction of hypertensive disorders (pre-eclampsia) among pregnant women at a resource poor setting: A comparative study

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***Abstract*---Background**: Uterine and umbilical artery Doppler velocimetry have shown promise but the results of previous studies have not been conclusive/poor methodologies. **Aim:** To determine the predictive value of uterine and umbilical artery Doppler velocimetry for pre-eclampsia and pregnancy outcomes. **Methods**: A comparative study among 100 women who attended ante natal clinic in the hospital within the study period who has high risk for development of pre-eclampsia. The peak systolic velocity, end-diastolic velocity, Resistivity index, Pulsatility index and S/D ratio of the uterine and umbilical arteries were studied at 18-20 weeks and 36-37 weeks. sociodemographic data were recorded. Data were analysed using SPSS (version 26, Chicago11, USA). *P* value of ≤ 0.05 was significant. **Results:** Resistivity/Pulsatility indices at 18-20 weeks are better predictors of preeclampsia as against EDV at 36-37 weeks. Pregnant women at 18-20 weeks gestational showed that only mean RI (≈ 0.53 ± 0.02) of the umbilical artery was associated with adverse outcome (p = 0.009). However, at 36-37 weeks, the mean uterine artery EDV of 14.69± 2.04 was associated with adverse outcome (p = 0.001). **Conclusion** Adverse pregnancy outcome at n18-20 weeks was associated with resistivity index while EDV is more associated with adverse outcomes at 36-37 weeks.

***Keywords*---**Pre-eclampsia, uterine/umbilical arteries Doppler.

Introduction

Pre-eclampsia is clinically defined by hypertension and proteinuria[1]. It may 2-10% of pregnancies, account for about 76,000 maternal mortality and affect up to 10 million women annually[2,3]. In Nigeria, it accounts for up to 32.1% of the direct causes of maternal death[4]. In Abakaliki, our practice area, it accounted for 6.1% of maternal mortality in a 2013[5]. It is a multi-systemic disease condition apart from the foregoing, hence is imperative to provide accurate methods for prediction of pre-eclampsia in high risk patients to avert these fetomaternal/neonatal complications.

Method currently used to predict its occurrence include body mass index above 35kg/m^2, alpha-fetoprotein, umbilical/uterine arteries Doppler, kallikrenuria and SDS-PAGE proteinuria [6,7]. Only body mass index, alpha-fetoprotein and uterine artery Doppler (bilateral notching) showed specificities of 90% and above but low sensitivity[7]. Doppler velocimetry is a very important means for predicting pre-eclampsia. The clinical manifestation of pre-eclampsia follows evidence of placental malfunction on Doppler ultrasonography[8]. The uterine artery Doppler shows the maternal hemodynamic status. Raised Pulsatility index and Resistivity

index are associated with high risk of pre-eclampsia while early diastolic notch suggests bad pregnancy outcom[9,10]. The sensitivity and specificity of abnormal uterine artery in predicting pre-eclampsia for high risk women is 73.33% and 86.48% respectively and 57.14% and 95.83% for low risk patients.[11]

The umbilical artery Doppler velocimetry abnormalities reflect a reduction in uteroplacental blood flow and deterioration of umbilical artery Doppler velocimetry indices, suggests potential adverse foetal outcome[12]. Absence of end-diastolic flow and a reversal of flow in the umbilical artery waveforms is associated with an increased perinatal mortality rate ranging from 28% to 80%[13]. The presence of a high resistivity index of at least 0.58 of umbilical artery is associated with sensitivity and specificity of 66% and 50% in predicting preeclampsia[14]. Pre-eclampsia is one of the four major classes of hypertensive disorders of pregnancy associated with significant maternal, foetal/neonatal morbidity and mortality[15]. It is diagnosed by the presence of de novo hypertension after 20 weeks gestation accompanied by proteinuria and / or evidence of maternal acute kidney injury, liver dysfunction, neurological features, haemolysis or thrombocytopenia and/or foetal growth restriction[16]. The HELLP syndrome previously classified as a separate condition is no longer such, but rather a severe manifestation of pre-eclampsia[16].

Generally, designation of a high-risk status is done based on Medical or Obstetric risk factors rather than laboratory or imaging tests because these tests have very low positive predictive values for pre-eclampsia[17,18,19]. Modalities that have been used for the prediction of pre-eclampsia include: Maternal BMI, maternal blood pressure, systolic and diastolic blood pressure and mean arterial blood pressure[20]. Out of the mentioned clinical parameters, mean arterial blood pressure, measured at booking had the best sensitivity of 76%[20]. Biochemical markers used in prediction of pre-eclampsia can be grouped as those associated with angiogenesis, such as placental growth factor and soluble fms-like thyroxine kinase1[21]. Placental growth factor assayed in the first trimester was three times likely to be associated with early onset pre-eclampsia than that done in late pregnancy[21]. Soluble fms-like thyroxine kinase 1 on the other hand, showed a stronger association with pre-eclampsia in the third trimester[21,22]. Sensitivities for placental growth factor and soluble fms-like thyroxine kinase1 were 32% and 26% respectively for a 5% false positive rate. This shows they are poor predictors of Pre-eclampsia. Soluble endoglin and vascular endothelial growth factors were found not to be consistently associated with Pre-eclampsia with sensitivity of about 18%[21,22]. Alpha fetoprotein on the other hand had a sensitivity of 96% but with a specificity of 9%[7]. Methylene hydrofolate showed weak association with pre-eclampsia while endothelial nitric oxide synthase showed a moderate association[23]. Ultrasound markers usually engaged in the prediction pre-eclampsia include uterine artery Doppler, umbilical artery Doppler and placental vascularization indices. First trimester uterine artery Doppler has a sensitivity of 47.8% and a specificity of 92.1% in predicting early onset pre-eclampsia. Umbilical artery Doppler on the other hand had 40% sensitivity and 91.58% specificity[24]. The placental vascularization indices used the most in predicting pre-eclampsia is the vascularization flow index (VFI). For early onset pre-eclampsia, it has a sensitivity of 89% and 77% for any other type of Pre-eclampsia[24]. Due to the placental capacitance, the umbilical artery is one of the

few arteries that normally has a forward diastolic flow and hence, often targeted during pregnancy[25]. Umbilical artery velocimetry measurements can indicate resistance to blood flow from the foetus to the placenta. Doppler velocimetry of the umbilical artery provides an indirect measure of placental function and foetal status[26]. Decreased diastolic flow with a resultant increase in the systolic-diastolic ratio suggests increased placental resistance and foetal compromise. Uterine artery Doppler appears to identify high risk women at risk of increased adverse pregnancy outcome and allow for interventions that might improve clinical outcome[27]. During pregnancy, there is a significant increase in uterine artery compliance between 8 and 16 weeks, which continues to a lesser extent until the 26th week of gestation[28]. The presence of a diastolic notch has been noted as better predictor of pre-eclampsia than an elevated resistivity index[29]. There is still incomplete data mas regards which indices of individual tool will best predict preeclampsia in the Nigerian women especially in Abakaliki, hence the need for this study.

Materials and Methods

This is a comparative cross-sectional study on the efficacy of uterine and umbilical arteries doppler in predicting pre-eclampsia among high risk women presenting at the teaching hospital Abakaliki, Southeast Nigeria. Patients who have their antenatal care with the facility are regarded as booked patients, while patients who have their antenatal care elsewhere or referred due to complications from pregnancy, labour or puerperium are regarded as unbooked. The consultants and the resident doctors, nurses and other ancillary health workers run the clinics. The study population included pregnant women with risk factor for preeclampsia at 18-20 weeks gestation, who consented to the study. these are women with a previous history of pre-eclampsia, chronic hypertension, chronic renal disease, heart disease, elderly primigravida/primigravida and haemoglobinopathies. The participants were consecutively recruited within the duration of ten months from August 2022 to May 2023.

The research team was made of of 2 Radiologists with specialization in Doppler velocimetry, and other research assistants in the department of OBGYN. All team members were trained on the research methodology, to understand the aims and objectives of the study, inclusion and exclusion criteria, data collection, study procedure and need for appropriate documentation. Recruited participants were followed up by the researcher and research assistants through antenatal care, labour and delivery. Inclusion criteria were women with singleton fetus at 18-20 weeks, chronic hypertension, diabetes Mellitus (White’s class A_1), renal disease, heart disease, elderly primigravida, previous Pre-eclampsia, haemoglobinopathies. The exclusion criteria were those who refused consent, foetal abnormality, wrong dates, patients on prophylaxis, raised blood pressure and proteinuria and multiple gestation.

Sample Size Calculation

The sample size was calculated using the formula for sample size for comparative study by Gupta et al.[30]

$$n = \frac{2([a+b]^2 \mho^2)}{(\mu 1 - \mu 2)^2}$$

Where:
n = Sample size in each of the groups
μ1 = Population mean in treatment Group 1,
μ2 = Population mean in treatment Group 2
μ1−μ2 = The difference the investigator wishes to detect =10
Ʊ = Population variance (SD) = 20
a = Conventional multiplier for alpha = 0.05,
b = Conventional multiplier for power = 0.846
n = 32 participants per group making a total of 64 participants.
Anticipating a response rate of 90%, the number was increased to 70. But we recruited 100 participants in this study.

The recruitment of eligible participants had structured data collection sheet used to obtain the socio-demographic data of. An initial Obstetric ultrasound scan was done to determine the number of foetuses, exclude multiple gestation and rule out foetal malformation. The Doppler studies were done at 18-20 weeks and repeated at 36-37 weeks of gestation. A SONOSCAPE MEDICAL CORP. DIGITAL COLOR DOPPLER ULTRASOUND SYSTEM. MODEL S40 (2018-12) ultrasound scanning machine was used for the purpose of Obstetric scan and Doppler velocimetry. The peak systolic velocity, end-diastolic velocity, the Resistivity index, Pulsatility index and the Systolic/Diastolic ratio are the Doppler parameters that were studied for both the uterine and umbilical arteries. The uterine artery doppler was done using a trans abdominal pulsed, curved array 3.5-5MHz transducer. The patient was scanned in semi-recumbent position with lateral tilt. The probe was placed longitudinally in the lower lateral quadrant of the abdomen with little medial angulation. Colour Doppler was applied to identify the uterine artery as it crosses the external iliac artery. The wall filter was then set at 50-60Hz and the angle of ionization below 20°. A pulsed wave Doppler with a gate size of 2mm was then placed over it at about 1 cm below the cross over point of the uterine artery and the external iliac artery to generate the spectral wave pattern. Automatic tracing of the waveforms was done to generate Doppler parameters. The mean value of three consecutive waveforms was recorded. Abnormal uterine artery waveform was taken as resistivity index >0.58 and early diastolic notching. This umbilical artery doppler was done at free loop of umbilical cord and velocimetry was recorded. The measurement was done using a transabdominal pulsed, curved array 3.5-5MHz transducer. The participants were scanned in semi-recumbent position with a lateral tilt. The transducer was placed longitudinally in the lower lateral quadrant of the abdomen with a slight medial angulation. Automatic tracing of the waveforms was done to generate the Doppler parameters within 5 centimetres of the umbilical cord insertion no foetal abdomen. The angle of the foetal Doppler insonation was kept at 45^{0} for optimal recording. The mean value of three consecutive wave forms were recorded. The abnormal umbilical artery Doppler was taken as any of the following: raised PI above two standard deviations for the mean of the gestational age, reduction in end-diastolic volume, absence of diastolic flow or reversal of end-diastolic wave

pattern. The participants were followed up to delivery to assess pregnancy outcomes with the following measures; Abortion, gestational age at delivery, mode of delivery, neonatal outcomes that included status of neonate at birth (livebirth/stillbirth), APGAR scores at 1st and 5th minutes and NICU admission. Statistical analysis was processed using the IBM-SPSS software version 26.0 (IBM, Chicago 11, USA). The continuous variables were described as mean ± standard deviation (SD) using Student t-test while categorical variables were compared using Chi-square (x2). Receiver operating characteristics (ROC) and area under the curve (AUC) were used to represent the sensitivity, specificity, negative and positive predictive values of the parameters. P-value ≤ 0.05 was considered statistically significant.

Ethical Issues

Ethical clearance was obtained from the research and ethics committee of the Teaching Hospital, Abakaliki with approval number 15/01/21-19/03/21. Approval date was 19 March 2021. Every participant signed-written informed consent before recruitment into the study. The study objectives, procedures and implication of the study was explained in detailed to each participant before obtaining their consent. They were made to understand that opting out of the study had no consequences on their care and they are free to opt out at any time they don't wish to continue. All information, examination and other findings were kept strictly confidential and used only for the purpose of the research. Those that developed the condition were managed according to departmental protocol at no extra cost.

Results

During the study period, a total of 746 pregnant women attended antenatal at hospital. Of these, 338 were high risk pregnant women and 100 were eligible for the study. Out of the 100 high risk women, 50 developed preeclampsia on follow up.

Table 1. Socio–Demographic Characteristics of Participants

Variable	Pre-eclampsia group (n=50)	No Pre-eclampsia group (n=50)	x^2	P-value
Age (years)				
≤19	4 (8.0%)	5 (10.0%)	3.390	0.495
20-29	31(62.0%)	22(44.0%)		
30-39	15 (30.0%)	23(46.0%)		
Marital status				
Married	43(86.0%)	41(82.0%)	0.298	0.585
Unmarried	7 (14.0%)	9 (18.0%)		
Occupation				
Civil servant	16(32.0%)	18(36.0%)	4.358	0.360
Artisan	15(30.0%)	15(30.0%)		
Trading	7 (14.0%)	10(20.0%)		
Student	8 (16.0%)	2 (4.0%)		
Housewife	4 (8.0%)	5 (10.0%)		
Religion				
Christianity	43(86.0%)	45(90.0%)	0.379	0.568
Muslim	7 (14.0%)	5 (10.0%)		

Variable	Pre-eclampsia group (n=50)	No Pre-eclampsia group (n=50)	x^2	P-value
Residence				
Urban	46(92.0%)	44(88.0%)	0.444	0.505
Rural	4 (8.0%)	6 (12.0%)		
Parity				
0	20(40.0%)	16(32.0%)	1.444	0.486
1-4	21(42.0%)	27(54.0%)		
5 or more	9 (18.0%)	7 (14.0%)		

Table 1 shows similar socio-demographic characteristics of the participants in the two groups. The distribution of the socio-demographic characteristics was not statistically significant between the two groups showing non-bias in recruitment.

Table 2: Doppler findings of high-risk pregnant women with and without pre-eclampsia at 18-20 weeks and 36-37 weeks

Doppler Parameters	Pre-eclampsia group (n=50) Mean ± SD	No Pre-eclampsia group (n=50) Mean ± SD	t-test	P-value
Uterine artery 18-20weeks				
Mean PSV (cm/s)	34.63±6.07	40.78±11.36	3.376	0.001
Mean EDV (cm/s)	10.31±2.59	14.28±4.58	5.336	<0.001
Mean RI	1.13±0.23	0.75±0.20	8.875	<0.001
Mean PI	0.83±0.22	1.22±0.96	2.777	0.007
Mean S/D	2.98±0.31	2.96±0.70	0.196	0.845
Uterine artery 36-37 weeks				
Mean PSV (cm/s)	37.36±2.66	41.47±8.47	3.272	0.001
Mean EDV (cm/s)	13.66±2.12	16.46±5.60	3.306	0.001
Mean RI	0.72±0.11	0.68±0.15	1.743	0.084
Mean PI	1.00±0.30	0.83±0.34	2.586	0.011
Mean S/D	2.86±0.31	2.62±0.61	2.472	0.015
Umbilical artery 18-20weeks				
Mean PSV (cm/s)	58.62±9.72	70.45±52.0	1.582	0.117
Mean EDV (cm/s)	15.74±6.99	27.95±22.31	3.694	<0.001
Mean RI	0.57±0.09	0.60±0.11	1.728	0.087
Mean PI	1.24±0.11	1.13±0.55	1.463	0.147
Mean S/D	2.59±0.22	2.90±1.62	1.374	0.173
Umbilical artery 36-37 weeks				
Mean PSV (cm/s)	58.10±7.34	58.27±17.80	0.063	0.950
Mean EDV (cm/s)	23.82±4.51	28.25±8.79	3.172	0.002
Mean RI	0.62±0.03	0.51±0.03	16.733	<0.001
Mean PI	1.37±0.07	0.74±0.16	25.149	<0.001
Mean S/D	2.83±0.23	1.96±0.30	16.407	<0.001

Table 2, shows that peak systolic velocity (PSV), end diastolic velocity EDV), pulsaltility index (PI) and resistivity index (RI) of uterine artery all showed predicted pre-eclampsia to a significant extent at 18 – 20 weeks of gestation. At 36 – 37 weeks, PSV and EDV still showed high significance but RI is not significant while the is weak significant correlation with PI and Systolic/Diastolic (S/D) ratio. The umbilical artery only showed a significant correlation at 18 – 20 weeks by EDV while at 36 – 37 weeks of gestation all the parameters checked except th PSV, were all statistically significant.

This table showed that at 18-20 weeks gestational age, the uterine artery PI showed the best predictive values with cut-off point of 0.85. At 36-37 weeks, the uterine artery EDV showed the best predictive values with a cut-off point of 13.66. The umbilical artery Doppler study showed that at 18-20- and 36-37-weeks gestational age, the umbilical artery EDV showed the best predictive values with cut-off point at 18.46 and 25.34 respectively.

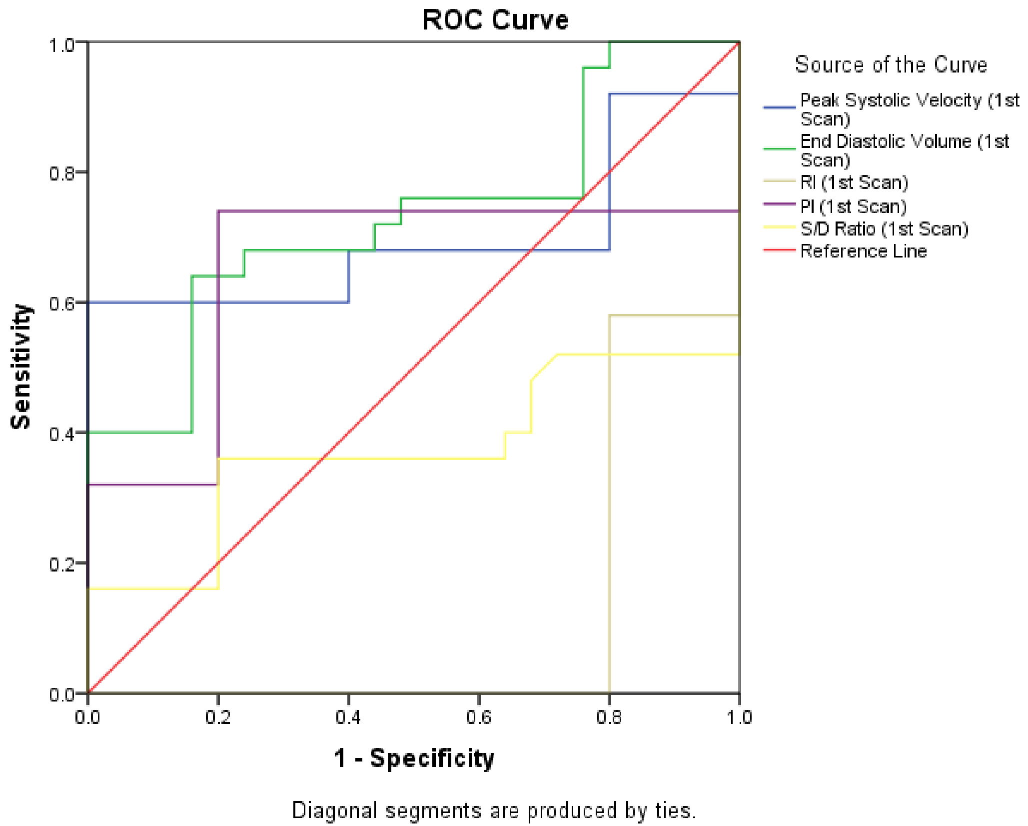

Fig. 1: Receiver Operating Characteristics (ROC) curve showing the trade-off between sensitivity and 1 – specificity of Uterine Doppler indices at 18-20 weeks

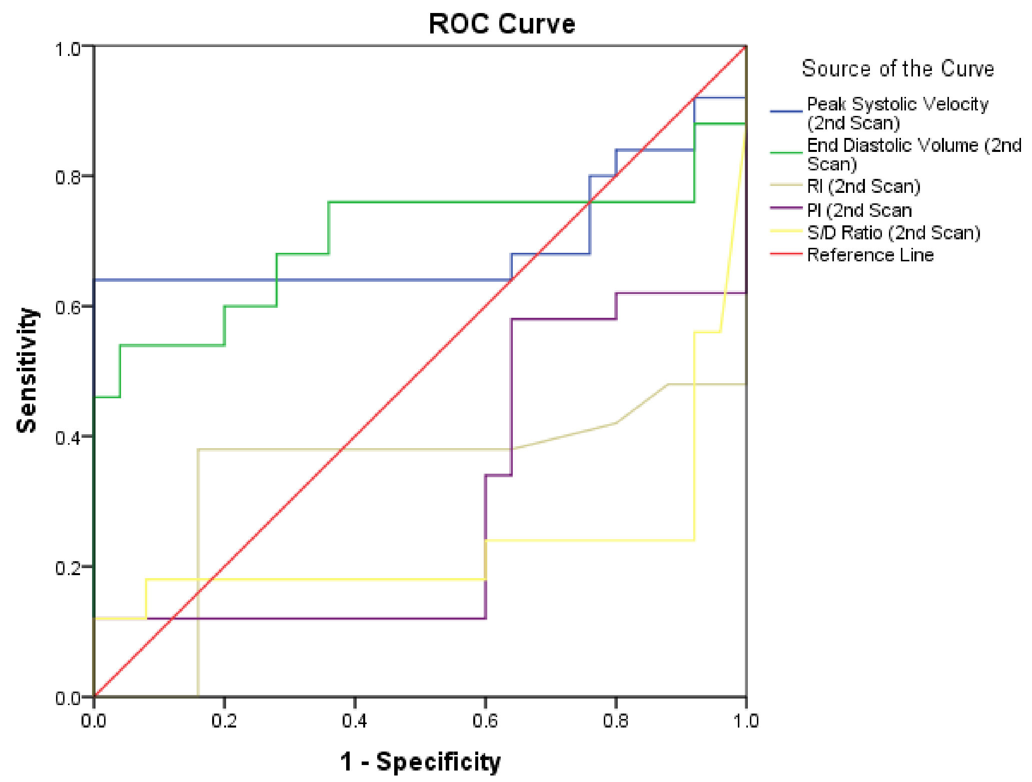

Fig. 2: Receiver Operating Characteristics (ROC) curve showing the trade-off between sensitivity and 1 – specificity of Uterine Doppler indices at 2nd Scan

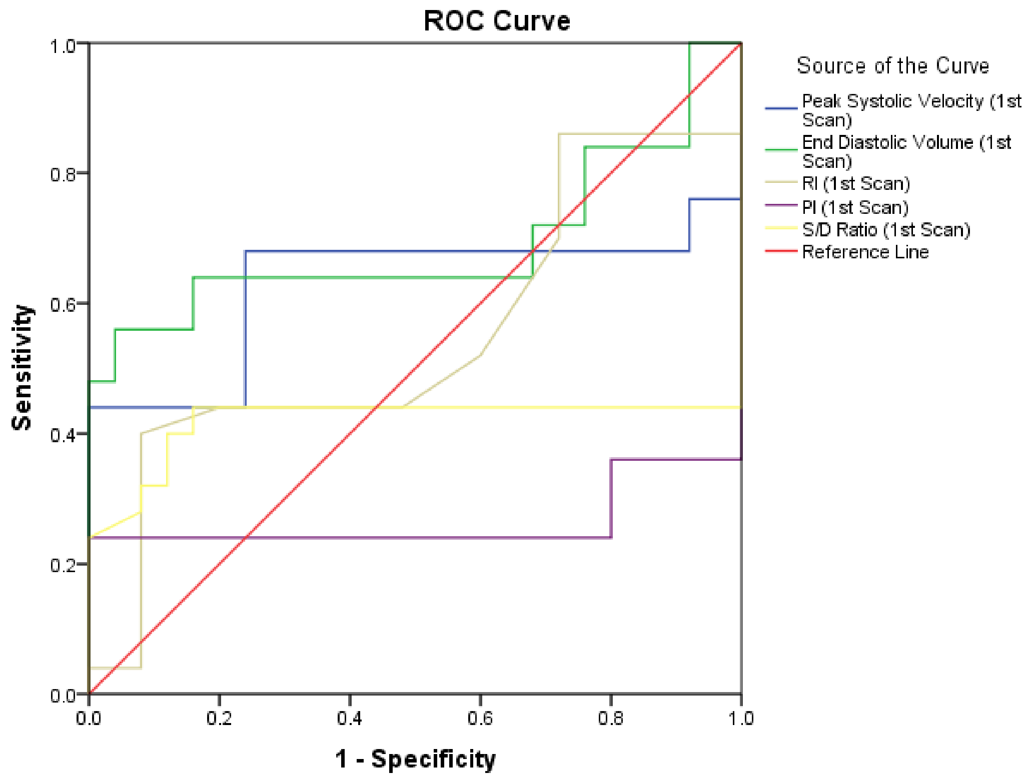

Fig. 3: Receiver Operating Characteristics (ROC) curve showing the trade-off between sensitivity and 1 – specificity of Umbilical Doppler indices at 1st scan

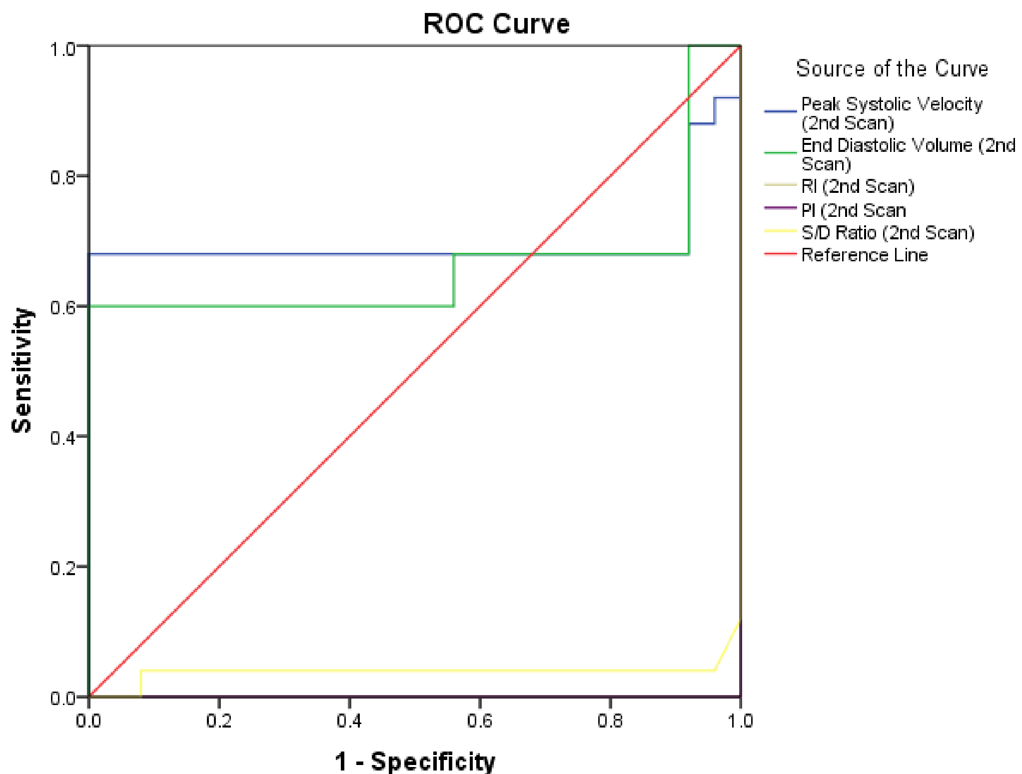

Fig. 4: Receiver Operating Characteristics (ROC) curve showing the trade-off between sensitivity and 1 – specificity of Umbilical Doppler indices at 2nd Scan

Further analysis at 18-20 weeks gestational age, showed only the mean RI of 0.53 ± 0.02 of umbilical artery was associated with adverse pregnancy outcome. This was significant with *p*-value = 0.009. At 36-37 weeks however, the mean uterine artery EDV of 14.69± 2.04 was associated with adverse pregnancy outcome. This was also significant with *p*-value of 0.001.

Discussion

Pre-eclampsia is a disorder of widespread vascular endothelial dysfunction which occurs after 20 weeks gestation and up to 6 weeks after delivery[1]. It is associated with maternal/perinatal morbidity and mortality. Doppler velocimetry is a veritable tool for prediction of pre-eclampsia. In our environment there have been a few documentations of Doppler study values for women with or without pre-eclampsia and its predictive value for diagnosing pre-eclampsia have not been comprehensively documented. In this study, the distribution of the sociodemographic characteristics of the participants were not statistically significant between the groups, laying credence to the recruitment process.

The sensitivity, specificity, negative and positive predictive values of the Doppler studies conducted on the uterine and umbilical arteries showed that at 18-20

weeks gestation, the Pulsatility index of the uterine artery was the best predictor of pre-eclampsia with a cut-off level of 0.85. This finding may be explained by the fact that pulsatility index (PI) shows the difference between peak systolic and end diastolic shift when divided by mean velocity[31]. It therefore provides more information than the resistivity index and S/D ratio as it includes data from the whole blood flow cycle through the uterine artery. At 36-37 weeks of gestation, uterine artery end diastolic velocity showed the best predictive values at a cut-off level of 13.66. Flow velocity depends on the vessel properties and pathological changes in the vessel. During pregnancy, the uterine arteries are converted to low pressure, high capacitance vessels to ensure adequate supply of nutrients to the baby. In women destined to have pre-eclampsia, this change does not occur. Low capacitance tends to show an increase in the value of EDV as occurs in pre-eclampsia. This may explain the finding noted in this study. For the umbilical artery Doppler study, the umbilical artery EDV showed the best predictive values at 18-20 weeks and 36-37 weeks with cut-off values of 18.46 and 25.36 respectively. This finding may be accounted for by the fact that as pregnancy advances, the resistivity index and pulsatility index of the umbilical artery reduces due to progressive maturation of the placenta and increase in the number of tertiary stems. Therefore, the measurement of velocity changes which EDV represents are more sensitive than resistivity and pulsatility indices. This study is similar to that done by Adekanmi et al[32] which also suggested that the uterine artery pulsatility index was the best predictor of pre-eclampsia at earlier gestational ages. The pulsatility index was also noted in their study to be the best predictor of pre-eclampsia at 32-34 weeks. The single study of the umbilical and uterine Doppler velocimetry had good predictive values as well as a combination of both at 18-20 weeks and 36-37 weeks respectively.

Adverse pregnancy outcomes were associated with umbilical artery resistivity index of 0.51 and above and this finding was statistically significant. At 36-37 weeks however, only the uterine artery was associated with adverse pregnancy outcomes. These findings were statistically significant.

From the foregoing it can be deduced that at earlier gestation, resistivity index which represents impedance to flow is associated with adverse pregnancy outcomes while at the later stages of pregnancy, the EDV becomes associated with adverse pregnancy. This is because as explained earlier, placental maturation is at its peak at 36-37 weeks gestation, therefore velocity changes depict abnormalities better than impedance related parameters. Adverse pregnancy outcomes studied were abortion, preterm delivery, neonatal intensive care admission, APGAR scores at delivery and status of neonate at birth (live/still birth).

Doppler studies are important tools that can help predict pre-eclampsia in women. At earlier gestational age, pulsatility and resistivity indices are better predictors of pre-eclampsia and adverse pregnancy outcomes while at later gestational ages, the EDV are better predictors. The single measurements of the umbilical and uterine artery Doppler velocimetry performed well is good in the prediction of pre-eclampsia and adverse pregnancy outcome in high risk pregnant women.

Conclusion

From this study, it could be deduced that individual Doppler assessment of arteries showed encouraging results in the prediction of preeclampsia among high risk pregnant women. RI and PI at 18-20 weeks are better predictors while EDV at 36-37 weeks are better.

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Conflict Of Interest
None delared

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