IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 5 Ser. 9 (May. 2024), PP 21-27
www.iosrjournals.org

Combination Of Uterine Artery And Umbilical Artery Doppler In Prediction Of Hypertensive Disorders (Pre-Eclampsia) Among High Risk Pregnant Women At A Teaching Hospital, Abakaliki: A Cohort Study.

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Abstract
Background*: a combination of uterine and umbilical artery doppler velocimetry has shown promise but the results of previous studies have not been conclusive.*
Objective*: determine the predictive value of combination of uterine and umbilical artery doppler velocimetry for pre-eclampsia prediction.*
Methods*: a cohort study among 100 antenatal attendees. The peak systolic velocity, end-diastolic velocity, resistivity index, pulsatility index and systolic/diastolic ratio of the uterine and umbilical arteries were studied at 18-20 weeks and 36-37 weeks. The data obtained were analysed using ibm spss software (version 26, chicago11, usa). Mean and standard deviation (mean ± 2sd), chi-square and student t-test was used for analysis. A receiver operating characteristic curve was used to determine the sensitivity, specificity and positive predictive values of the doppler parameters. A p value of ≤ 0.05 is significant.*
Results: *combination of uterine and umbilical artery dopplers resulted in better prediction of preeclampsia. Resistivity index and pulsatility index at 18-20 weeks are better predictors of preeclampsia as against edv at 36-37 weeks. Combination of the uterine and umbilical artery rishowed significant adverse pregnancy outcome.*
Conclusion; *the combination of uterine and umbilical arteries' doppler is a better predictor of preeclampsia/adverse outcome.*
Keywords*: pre-eclampsia, uterine artery, umbilical artery, doppler.*

Date of Submission: 14-05-2024 Date of Acceptance: 24-05-2024

I. Introduction

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 clinically defined by hypertension and proteinuria[1]. It is a major cause of maternal/perinatal morbidity and mortality. It complicates about 2-10% of pregnancies, accounting for about 76,000 maternal deaths and affecting about ten million women annually[2,3]. In Nigeria, pre-eclampsia/eclampsia accounts for up to 32.1% of the direct causes of maternal mortality[4]. In Abakaliki, pre-eclampsia/eclampsia accounted for 6.1% of maternal deaths in a 2013 review[5]. Although not very evident in global new born strategy, pre-eclampsia/ eclampsia accounts for about 1 in 4 perinatal deaths (25%)[6]. These are worrying figures for the pregnant woman and her unborn baby. The above figures enumerated above are in addition to other complications associated with pre-eclampsia, which affects every system of the body, as it is a multi-systemic disease condition. It is therefore imperative to provide accurate methods for prediction of pre-eclampsia to see if some strategies already documented to be effective can be instituted to avert foeto-maternal/neonatal complications associated with the condition.

Method currently employed to predict the occurrence of pre-eclampsia include body mass index above 35kg/m^2, alpha-fetoprotein, umbilical artery, uterine artery Doppler, kallikrenuria and SDS-PAGE proteinuria[7]. The only Doppler test that showed a sensitivity of above 60% were the resistivity indices of a combination of

uterine artery and umbilical artery Doppler velocimetry tests[7]. Doppler velocimetry is a veritable tool for prediction of pre-eclampsia. This is important as the clinical manifestation of pre-eclampsia is usually preceded by evidence of impaired placental function evident on Doppler ultrasonography[8]. The uterine artery Doppler represents the maternal hemodynamic status. Increased uterine artery Pulsatility index and Resistivity index are associated with increased risk of pre-eclampsia[9,10].

The umbilical artery Doppler velocimetry abnormalities reflect a reduction in uteroplacental blood flow. It has been demonstrated experimentally that the occlusion of the umbilical artery resulted in an immediate deterioration of umbilical artery Doppler velocimetry indices suggesting its potential in predicting an adverse foetal outcome[11].

Studies have explored the possibility of a combination of the Doppler indices of both tools to improve their ability to predict pre-eclampsia. Patnaik[12] in India studied the role of uterine and umbilical artery Doppler in the prediction of developing pre-eclampsia among 95 women in a longitudinal cohort study. Of the 95, 65 developed pre-eclampsia while 30 did not develop pre-eclampsia. He observed that a combination of the abnormal Doppler parameters of uterine and umbilical arteries were better at predicting pre-eclampsia than when used singly. The uterine artery Pulsatility index was the best predictor of pre-eclampsia. Values higher than 0.73 ± 0.26 were associated with pre-eclampsia and this was statistically significant $p<0.001$. A combination of the uterine and umbilical artery peak systolic velocity were better predictors of the severity of pre-eclampsia. However, the gestational age at which these measurements were taken were not stated. The authors neither used a receiver operating characteristic curve or Bayesian theorem to determine the sensitivity, specificity or positive predictive values of the parameters studied[13]. Despite the availability of these studies, there is still an incomplete data collection as regards which of the indices in the individual tools or collectively will better predict pre-eclampsia among South-eastern women of Nigeria and poor documentation of whether there are variations in the umbilical and uterine Doppler indices for African women of South Eastern Nigeria origin and the possible pregnancy outcome to be expected with such values.

Doppler velocimetry is an important tool in the prediction of pre-eclampsia. Uterine artery and umbilical artery velocimetry individually do not have a high sensitivity or specificity required. Therefore, a potential for an improvement in their ability to predict pre-eclampsia if used in combination while cut-off values of the Doppler indices for the uterine and umbilical arteries can be documented for women with or without pre-eclampsia in our environment. Any effort to predict its occurrence will likely provide opportunities for its prevention in the individuals involved. Predicting the occurrence of pre-eclampsia among high risk women have been done using maternal characteristics including blood group, BMI, genetic markers, biochemical markers and Doppler ultrasound studies. These modalities have been used either in combination or alone. They have shown very low clinical applicability due to their poor sensitivity, specificity and positive predictive value. A good predictor of a disease condition should have the above characteristics to be clinically applicable. Doppler studies of the uterine and umbilical arteries have shown promise in this regard.

There is currently a varying range of their effectiveness in the prediction of pre-eclampsia among high risk women with more promise for a combination of the Doppler parameters from the study of the two arteries. Available studies have either poor methodology or were done when early onset pre-eclampsia may have been missed and any possible benefit for prevention lost. This study seeks to correct some of the flaws noted in these studies while providing more reliable and robust data through which recommendations can be made in a longitudinal cohort design, while also providing some data on south eastern Nigerian women's cut off values for Doppler velocimetric studies of the uterine and umbilical arteries. Available studies either have a poor design or omit vital data that can help in making of recommendations for the use of Doppler studies in the prediction of pre-eclampsia. This study seeks to correct some of the flaws noted above to provide more robust and reliable data for making recommendations.

II. Materials And Methods

This was a longitudinal cohort study on the combination of uterine and umbilical artery Doppler in predicting pre-eclampsia at the departments of Obstetrics and Gynaecology and Radiology at the Teaching Hospital Abakaliki, Ebonyi State between 12th October 2021 to 31st July 2022. The inhabitants are mostly peasant farmers and traders. Pregnant women have intense preference for vaginal deliveries and tend to avoid Caesarean sections by all means.

The teaching hospital caters for both primary and referral cases from Ebonyi and environs including Enugu, Cross river, Abia, Benue and Imo states. The antenatal women are seen based on scheduled appointments and those who require admission are admitted into the antenatal ward.

The study included pregnant women with high risk factor for preeclampsia at 18-20 weeks gestation, who met the inclusion criteria and consented to the study. High risk women in this study were those women with a previous history of pre-eclampsia, chronic hypertension, chronic renal disease, heart disease, elderly primigravida and haemoglobinopathies.

The research team consisted of two Consultant Radiologists with specialization in Doppler velocimetry, the Researcher and 5 research assistants. All team members were trained on the research methodology. This training was commenced as soon as ethical approval was obtained. Patients who consented to the study were followed up through antenatal care, labour and delivery.

The inclusion criteria were women with singleton foetus at 18-20 weeks gestation with one or more of the following: Chronic hypertension, Diabetes Mellitus, Renal disease, Heart disease, Elderly primigravida, Previous Pre-eclampsia, Haemoglobinopathies. Exclusion criteria were- Foetal malformation, Unsure date, Patients on aspirin prophylaxis, calcium or low molecular weight heparin, Women with raised blood pressure and proteinuria, Multiple gestation.

Sample Size Calculation

The sample size was calculated using the formula for a prospective cohort study by Charan et al[14] as follows:

$$N = \frac{[Z_\alpha \sqrt{(1+1/m)\, p^*(1-p^*)} + Z_\beta \sqrt{p1\,(1-p1)/m + p2\,(1-p2)}]^2}{(p1-p2)^2}$$

Where

N= sample size per group
Z_α= standard normal variate for level of significance
m= Number of control subjects per experimental subjects
Z_β= standard normal variate for power
p1= Probability of events in control group
p2= Probability of events in experimental group
p*= p2+mp1
……..
m+1
Z_α= 1.96 (at 95% confidence interval)
Z_β= 1.282 (with power set at 90%)
M= 1:2 = 0.5
p1= 0.32 (according to study by Adekanmi et al[13])
p2= 0.61 (according to study by Adekanmi et al[13])
P*= 0.62
N= 36 Approx. 40. Therefore, total sample size for the two groups was 80.
We recruited 100 participants.
N= 100 (50 per arm).

Recruitment/ Study Procedure

High risk pregnant women who met the inclusion criteria were recruited from the antenatal clinic at 18-20 weeks gestation by systematic sampling after informed consent was obtained. Them a structured data collection sheet was then used to obtain the socio-demographic data of the participants. An initial Obstetric ultrasound scan was done to determine the number of foetuses, 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 S/D ratio are the Doppler parameters that were studied for both the uterine and umbilical arteries. The doppler studies were done with

Th a trans abdominal pulsed, curved array 3.5-5MHz transducer. The participants were scanned in a semi-recumbent position with a slight lateral tilt. The transducer was placed longitudinally in the lower lateral quadrant of the abdomen with a slight 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 then done to generate the Doppler parameters. The values of three consecutive waveforms were averaged and the mean recorded per visit. Abnormal uterine artery waveform was taken as high resistivity index >0.58 and early diastolic notching. This umbilical artery doppler was done at a free loop of umbilical cord and the velocimetry was recorded. The participants were scanned in a semi-recumbent position with a slight 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 then done to generate the Doppler parameters within 5 centimetres of the umbilical cord insertion into foetal abdomen. The angle of the foetal Doppler insonation was kept at 45^0 for optimal recording. The values of three consecutive waveforms were averaged and the mean

recorded per visit. 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 for assessment of pregnancy outcomes. The outcome measures were, abortion, gestational age at delivery (term/preterm), mode of delivery, neonatal outcomes which included status of neonate at birth (livebirth/stillbirth), APGAR score of less than 7 at the 1st and 5th minutes and NICU admission.

Data were collated and the coded data fed into the computer using the IBM-SPSS software version 26.0 (IBM, Chicago 11, USA). P-value ≤ 0.05 was considered significant.

Ethical Consideration

Ethical clearance was obtained from the health and research committee of the Teaching Hospital. All the participants signed informed consent before recruitment into the study. They were made to understand that opting out of the study had no consequences on the standard care and they can opt out any time if they do not wish to continue. All information including the history, examination and other findings including their identity were kept strictly confidential. All the patients were managed according to the departmental protocol. All the cost was borne by the researchers.

III. Result

Out of 338 high risk pregnant women, 100 were eligible.
Out of the 100, 50 developed preeclampsia on followed up**.**

Table 1 Socio–Demographics Of Participants

Variable	Pre-eclampsia (n=50)	No Pre-eclampsia (n=50)	χ^2	*P*-value
Age (years)				
15-19	4 (8.0%)	5 (10.0%)	3.390	0.495
20-24	8 (16.0%)	5 (10.0%)		
25-29	23(46.0%)	17(34.0%)		
30-34	9 (18.0%)	14(28.0%)		
35-39	6 (12.0%)	9 (18.0%)		
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%)		
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 showed the socio-demographic characteristics of the participants. The distribution of the socio-demographic characteristics was not statistically significant between the two groups.

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
Combination of Uterine and umbilical artery 18-20 weeks				
Mean PSV (cm/s)	93.25±13.43	111.23±58.80	2.108	0.038
Mean EDV (cm/s)	26.05±8.65	42.23±24.50	4.405	<0.001
Mean RI	1.70±0.27	1.36±0.21	7.146	<0.001
Mean PI	2.07±0.11	2.35±1.15	1.656	0.101
Mean S/D	5.57±0.42	5.87±1.90	1.072	0.286

Combination of Uterine and umbilical artery 36-37 weeks				
Mean PSV (cm/s)	95.46±9.85	99.74±23.49	1.188	0.238
Mean EDV (cm/s)	37.48±6.38	44.71±12.95	3.543	0.001
Mean RI	1.34±0.11	1.19±0.14	6.121	<0.001
Mean PI	2.37±0.31	1.58±0.45	10.295	<0.001
Mean S/D	5.69±0.43	4.58±0.63	10.229	<0.001

Table 2 shows the values of the doppler parameters of high pregnant women with preeclampsia and no preeclampsia at 18-20 weeks and 36-37 weeks.

TABLE 3 Sensitivity, Specificity, Negative and Positive Predictive Values of Uterine and Umbilical Doppler Patterns in participants with pre-eclampsia

Data	Cut-off Point	AUC	Sensitivity	Specificity	PPV	NPV
Combination of Uterine and umbilical artery (18-20 weeks)						
PSV	98.36	0.658	64.00%	60.00%	65.22%	62.96%
EDV	29.50	0.718	64.00%	78.00%	79.19%	71.58%*
RI	1.20	0.145	70.00%	20.00%	46.54%	44.15%
PI	1.99	0.406	40.00%	16.00%	39.67%	44.82%
S/D ratio	5.65	0.402	40.00%	80.00%	50.79%	51.35%
Combination of Uterine and umbilical artery (36-37 weeks)						
PSV	97.14	0.634	64.00%	24.00%	47.63%	45.11%
EDV	39.94	0.656	64.00%	68.00%	65.43%	62.54%*
RI	1.33	0.250	30.00%	64.00%	48.48%	49.25%
PI	2.60	0.102	12.00%	76.00%	44.44%	48.78%
S/D ratio	5.88	0.110	12.00%	88.00%	66.67%	53.66%

A combination of the umbilical and uterine artery Doppler showed that the EDV had the best predictive values with cut-off values of 29.50 and 39.94 at 18-20 weeks and 36-37 weeks respectively

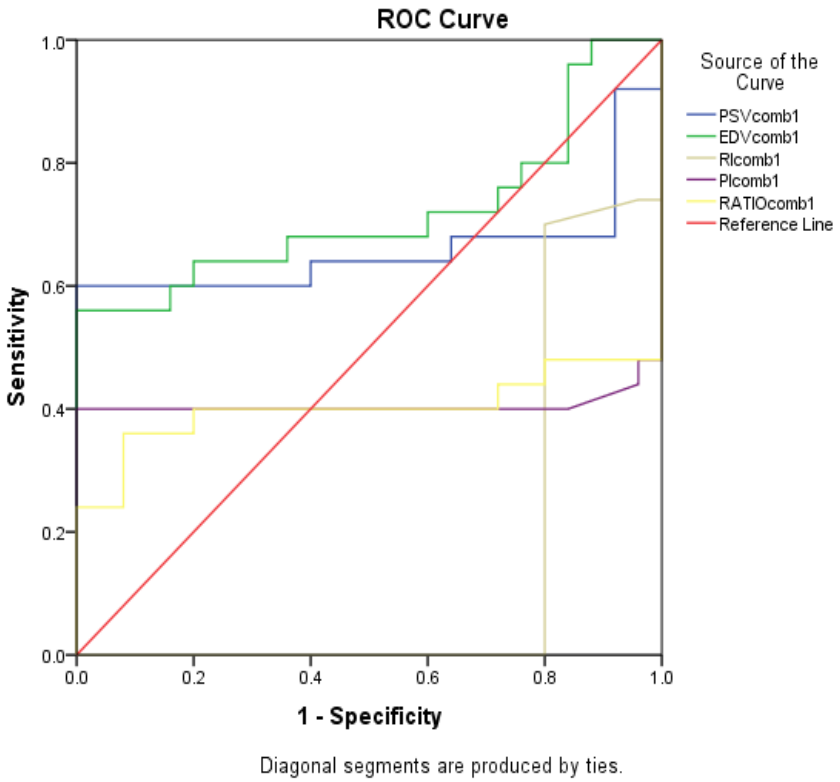

Fig. 1: Receiver Operating Characteristics (ROC) curve showing the trade-off between sensitivity and 1 – specificity of Combination of Uterine and umbilical artery indices at 1st scan

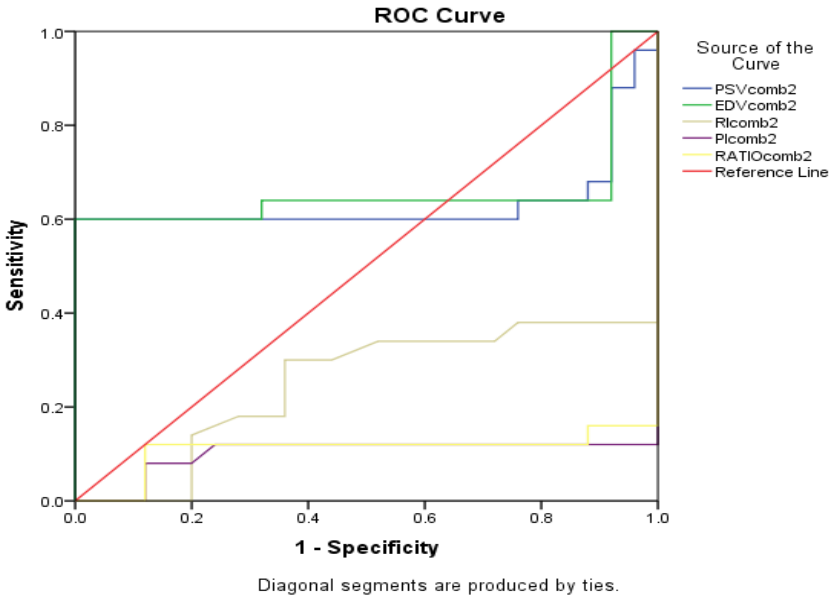

Fig. 2: Receiver Operating Characteristics (ROC) curve showing the trade-off between sensitivity and 1 – specificity of Combination of Uterine and umbilical artery indices at 2nd Scan

Table 4: Comparison of adverse pregnancy outcomes and Doppler indices at 18-20 weeks and 36-37 weeks respectively

Doppler Indices	Adverse Outcome		
	Yes (n=23)	No (n=27)	P-value
18-20 weeks			
Mean uterine PSV	33.81±6.38	35.33±5.82	0.385
Mean uterine EDV	10.72±3.27	9.96±1.84	0.309
Mean uterine RI	1.08±0.27	1.18±0.18	0.100
Mean uterine PI	0.88±0.26	0.79±0.17	0.175
Mean uterine S/D Ratio	3.04±0.33	2.94±0.29	0.238
Mean umbilical PSV	58.55±7.39	58.68±11.48	0.962
Mean umbilical EDV	16.84±8.97	14.80±4.68	0.309
Mean umbilical RI	0.53±0.02	0.60±0.11	0.009*
Mean umbilical PI	1.21±0.12	1.27±0.09	0.062
Mean umbilical S/D Ratio	2.54±0.16	2.63±0.26	0.124
Mean combined PSV	92.37±11.18	94.01±15.27	0.671
Mean combined EDV	27.56±10.67	24.76±6.39	0.259
Mean combined RI	1.61±0.28	1.78±0.23	0.024*
Mean combined PI	2.09±0.13	2.06±0.09	0.410
Mean combined S/D Ratio	5.58±0.40	5.57±0.45	0.947
36-37 weeks			
Mean uterine PSV	37.51±2.10	37.23±3.09	0.717
Mean uterine EDV	14.69±2.04	12.78±1.79	0.001*
Mean uterine RI	0.75±0.13	0.70±0.08	0.170
Mean uterine PI	1.00±0.31	1.00±0.30	0.935
Mean uterine S/D Ratio	2.78±0.29	2.93±0.32	0.079
Mean umbilical PSV	59.17±5.03	57.18±8.85	0.346
Mean umbilical EDV	24.85±3.34	22.95±5.21	0.139
Mean umbilical RI	0.61±0.03	0.62±0.03	0.140
Mean umbilical PI	1.39±0.02	1.35±0.09	0.073
Mean umbilical S/D Ratio	2.81±0.06	2.85±0.30	0.501
Mean combined PSV	96.68±6.94	94.42±11.82	0.424
Mean combined EDV	39.54±5.10	35.73±6.91	0.034*
Mean combined RI	1.36±0.14	1.33±0.08	0.364
Mean combined PI	2.38±0.31	2.35±0.31	0.756
Mean combined S/D Ratio	5.58±0.33	5.78±0.50	0.108

This table shows that at 18-20 weeks gestational age, only the mean RI of the 0.53 ± 0.02 of the umbilical artery was associated with adverse pregnancy outcome. This was significant with p-value of 0.009. At 36-37 weeks gestational age, the mean uterine artery EDV of 14.69± 2.04 was associated with adverse pregnancy

outcome. This was significant with p-value of 0.001. A combination of the uterine and umbilical artery RI with mean of 1.61 $\pm$ 0.28 was also found to be associated with adverse pregnancy outcome. This was statistically significant with p-value of 0.024.

IV. Discussion

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. 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. 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, though the combination of both uterine and umbilical artery parameters were more effective as shown in this study.

A combination of uterine and umbilical artery resistivity indices at 18-20 weeks was associated with adverse pregnancy outcomes at values of 1.33 and above. This finding was statistically significant. At 36-37, a combination of uterine and umbilical artery EDV were associated with adverse pregnancy outcomes. These findings were statistically significant.

It can be deduced that at earlier gestation, resistivity index is associated with adverse pregnancy outcomes while at the later stages of pregnancy, the EDV becomes associated with adverse pregnancy outcome. 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.

V. Conclusion

This study shows that combination of both uterine/umbilical arteries' Doppler values was slightly superior in pre-eclampsia prediction than single artery measurements. RI/PI at 18-20 weeks and EDV at 36-37.

Acknoeledgement

We are deeply grateful to the research and ethics committee of the Alex Ekwueme University Teaching Hospital, Abakaliki for approving this study protocol. We also express our profound gratitude to our research assistants who helped us in data collection.

Conflict Of Interest
None declared.
Funding
None received

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