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Second trimester umbilical artery Doppler in the prediction of adverse pregnancy outcomes in a low risk population: A prospective observational study

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Abstract
Introduction: Pregnancies with sustained high resistance uteroplacental circulation have been reported to be at significant risk of adverse outcomes. Assessment of fetoplacental circulation non-invasively using umbilical artery Doppler velocimetry has been suggested as a tool for prediction of perinatal outcomes.
Objectives: To determine the utility of second trimester umbilical artery Doppler velocimetry in the prediction of adverse perinatal outcomes (intrauterine growth restriction (IUGR), low birth weight (LBW) and stillbirth).
Methods: One hundred and twenty low-risk nulliparous women with viable singleton pregnancies who met the inclusion criteria had umbilical artery Doppler assessment between 22 and 26 weeks gestation. RI≤ 0.76, PI≤ 1.36 and SD ≤ 4.52 were considered as normal. Each participant was monitored till delivery to assess outcome. Diagnostic performance of the Doppler indices for the prediction of adverse pregnancy outcomes were determined.
Results: Thirteen (10.8%) women had at least one abnormal Doppler index, abnormal RI was recorded in 1(0.83%) woman, 12(10.0%) had abnormal PI while none had abnormal SD ratio. 50/120 (42%) women had at least one adverse outcome. The sensitivity and specificity of RI for IUGR, LBW and stillbirth were 0.0%, and 99.1%, 0.0% and 98.9% and 0.0% and 99.1% respectively. For IUGR the sensitivity and specificity of PI were 0.0% and 88.8% respectively, while PI had 12.0% sensitivity and specificity of 90.5% for LBW. For stillbirth, the sensitivity and specificity of PI were 66.7% and 91.5%.
Conclusion: Late second trimester umbilical artery Doppler velocimetry has a limited role in this low risk population for prediction of adverse pregnancy outcomes. The role of umbilical artery Doppler velocimetry in the prediction of adverse outcomes in high-risk pregnant women may be worthwhile.

Keywords: Adverse pregnancy outcomes, umbilical artery Doppler velocimetry, resistance index, pulsatility index

Introduction
Failure of pregnancies to establish low resistance circulations in the placenta has been reported to significantly increase the risk of adverse pregnancy outcomes such as preeclampsia, intrauterine growth restriction and low birth weight particularly in high-risk women [1, 2].
Doppler velocimetry of the umbilical artery is a non-invasive measure of fetoplacental hemodynamic state. Variations in umbilical artery Doppler indices such as pulsatility and resistance indices indirectly reflect the degree of impedance to flow in the fetoplacental circulation. Studies have reported a direct association between abnormal Doppler indices in the second trimester and fetal hypoxia, acidosis and adverse perinatal outcomes.[3] Hence these indices have been suggested reliable screening tests for the identification of patients likely to develop IUGR, low birth weight, and stillbirth.
The accuracy of prediction of adverse pregnancy outcomes using umbilical artery Doppler velocimetry has been reported to be a valuable tool in the prediction of adverse perinatal outcomes in high risk pregnancies, complicated by preeclampsia or IUGR [4], however, the value of abnormal second trimester umbilical artery Doppler indices in low risk patients in the prediction of adverse perinatal outcomes still requires further research. Previous studies have suggested that umbilical artery Doppler examination has no clear role in prediction of adverse pregnancy outcomes among low risk antenatal population [5-8].

There is also no consensus on the best indices or the ideal gestational age for screening.

The goal of antepartum fetal surveillance is to identify fetuses at risk of compromise and to improve fetal survival, hence, identification of predictors of adverse obstetric outcomes will be of significant benefit to the obstetrician and the patient. We therefore set out to determine the association between abnormal second trimester umbilical Doppler indices [pulsatility index (PI), resistance index (RI) and systolic/diastolic (SD) ratio] and adverse pregnancy outcomes in low risk nulliparous women.

Materials and Methods

This was a prospective longitudinal study involving low risk nulliparous women with viable singleton pregnancies between 22 and 26 weeks gestational age attending antenatal clinic at State owned teaching hospital in southwestern Nigeria between 1st July, 2017 and 31st December, 2017.

All nulliparous women with viable singleton pregnancies at EGA 22-26 weeks and had low risk pregnancies attending antenatal clinic at the teaching hospital with intention to deliver in the same hospital were eligible to participate in the study. Exclusion criteria for the study include previous deliveries, history of hypertension, multiple gestations, and fetal structural anomalies in index pregnancy or those in whose gestational age was not reliable. Study was approved by our institutional review board. Consecutive nulliparous women who met the inclusion criteria were educated about the study and written informed consent was obtained from study participants. Anonymity of patients' information was ensured during this study.

Demographic and clinical information were obtained using a pretested study proforma: maternal age, religion, occupation, cigarette smoking, and alcohol intake, family history of preeclampsia and maternal height, weight and body mass index. Gestational age was calculated from the first day of the last menstrual period and confirmed by a first trimester ultrasound scan. The gestational age obtained from the first trimester scan was used in cases of discrepancy.

Umbilical artery Doppler Ultrasound

All sonographic examinations were performed trans-abdominally with the woman in semi-recumbent position by a board-certified radiologist using a Mindray DC-N2 color Doppler ultrasound imaging system. Each patient first had a routine obstetric ultrasound scan, then umbilical artery Doppler flow spectrum was recorded from a free floating central part of the umbilical cord away from the placenta and fetal cord insertion. The mean of three even velocity waveforms was analyzed for resistance Index (RI), pulsatility Index (PI) and systolic/diastolic SD ratio. RI≤ 0.76, PI≤ 1.36 and SD ≤ 4.52 were considered as normal based on 95th percentile cut off at average EGA of 24weeks in a similar population.[9] Results of the routine ultrasound scans were made available to the attending obstetrician, however the findings on Doppler velocimetry were stored in a secured database by the investigators and decisions on care were not subject to the interpretation of the Doppler ultrasound.

Obstetric outcomes

All study participants were followed up in the antenatal clinics till delivery. Blood pressure, weight gain, symphysio-fundal height and urinary protein analysis were assessed at each antenatal visit. Obstetric complications, the mode of delivery and perinatal outcomes (APGAR scores, fetal distress, fetal death or neonatal intensive unit admission) were recorded.

Adverse outcome was defined as development of intrauterine growth restriction at any gestational age, delivery of low birth weight babies or intrauterine fetal death. Intrauterine growth restriction was defined as estimated fetal weight below the 10th percentile for the gestational age [10]. Birth weight <2.5kg was defined as low birth weight.

Each patient had standard obstetric care and the diagnoses were made by the attending physicians.

Statistical Analysis

All data were coded and entered into Statistical Package for Social Science (SPSS), Windows version 20.0; (Chicago, IL, USA). Descriptive statistics were summarized as frequencies and percentages. Means and standard deviations were also reported for continuous variables. To determine the screening ability of second trimester umbilical Doppler velocimetry indices for predicting the development of intrauterine growth restriction, delivery of a low birth weight neonate or stillbirth, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Additionally, Receiver Operating Characteristics (ROC) analysis was constructed and Area under the curve (AUC) was plotted to determine the association between umbilical artery RI, PI and SD ratio with intrauterine growth restriction, low birth weight and stillbirth. P-value of <0.05 was considered statistically significant.

Results

Patients

A total of 136 women who met the inclusion criteria were enrolled in the study. Sixteen women were lost to follow up and were therefore excluded from the final analysis. A total of 120 women were included in the final analysis.

The demographic characteristics and obstetric outcomes are summarized in table 1. The mean age of the participants was 30.12 ± 4.48 years and the mean gestational age at recruitment was 23.67 ± 1.49 weeks. Average systolic blood pressure at screening was 112.4±10.8 mmHg and the average diastolic blood pressure was 68.9±8.7mmHg. About two-thirds of the women had spontaneous vaginal delivery, while the remaining one-third had caesarean delivery. Average birth weight of the babies was 3.01 ± 0.54 kg, 2/120 babies (1.7%) weighed >4kg at birth while 22/120 babies (18.3%) had low birth weight. Majority of the babies (87.5%) had normal APGAR scores at delivery, while 10% had mild birth asphyxia. Neonatal intensive care admission was required in 15/120 (12.5%) of the babies.

Umbilical artery Doppler indices/Obstetric outcomes

Thirteen (10.8%) participants had at least one abnormal Doppler parameter. Abnormal PI was recorded in 12/13(92.3%) patients with abnormal umbilical arterial indices while only one of thirteen patients (7.69%) had abnormal RI and no patient had abnormal SD ratio. At least one adverse pregnancy outcome occurred in 50/120 (42%) women. Of the 50 women, 10 (20%) had preeclampsia, 9(18%) had pregnancy induced hypertension without proteinuria, 13 (26%) had intrauterine growth restriction, 25 (50%) had low birth weight fetuses, and there were 3(6%) still-births. (Table 2)

Diagnostic performance of umbilical artery Doppler indices for adverse pregnancy outcomes

The performance of abnormal umbilical artery Doppler parameters in the prediction of intrauterine growth restriction, delivery of low birth weight babies and stillbirths were evaluated

and presented in table 3.

For any adverse pregnancy outcomes, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of abnormal umbilical Doppler parameters were 16.3%, 93.0%, 61.5% and 61.7% respectively.

For IUGR, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of abnormal Doppler indices were 0.0%, 87.9%, 0.0% and 87.8% respectively while for LBW, the sensitivity, specificity, PPV and NPV of abnormal Doppler indices were 12.0%, 89.5%, 23.1% and 79.4% respectively. For stillbirth, the sensitivity, specificity, PPV and NPV of abnormal Doppler indices were 66.7%, 90.6%, 15.4% and 99.1% respectively.

The association between the Umbilical RI, PI, and intrauterine growth restriction, delivery of low birth weight fetuses and stillbirth are presented in Table 4.

Umbilical artery Resistance Index

The sensitivity, specificity, PPV and NPV of RI for IUGR were 0.0%, 99.1%, 0.0% and 89.1% respectively with an area under ROC 0.51. For LBW, the sensitivity, specificity, PPV and NPV were 0.0%, 98.9%, 0.0% and 78.9% respectively with an area under ROC of 0.51 while Sensitivity, specificity, PPV and NPV for stillbirth were 0.0%, 99.1, 0.0% and 97.5% respectively with an area under ROC 0.50.

Umbilical artery Pulsatility index

The sensitivity, specificity, PPV and NPV of PI for IUGR were 0.0%, 88.8%, 0.0% and 87.9% with an area under ROC 0.56 while for LBW the sensitivity, specificity, PPV and NPV were 12.0%, 90.5%, 25.0% and 79.6% respectively with an area under ROC 0.49. Sensitivity, specificity, PPV and NPV for stillbirth were 66.7%, 91.5%, 16.7%, and 99.1% respectively with an area under ROC 0.21.

Umbilical artery systolic/diastolic ratio

None of the women in this study group had abnormal SD ratio, hence its diagnostic performance was not further explored.

The receiver operating characteristic (ROC) curve with area under the curve (AUC), 95% confidence intervals and p- value were evaluated and represented in figure 1. Umbilical artery PI for IUGR had the highest AUC of 0.556 while umbilical artery PI for stillbirth had the lowest with 0.209.

Table 1: Socio-demographic variables of respondents

Variable	Frequency	Percent
Age Group (years)		
< 35	94	78.3
≥ 35	26	21.7
Mean ± SD	30.12 ± 4.48	
Range	22 – 40	
Ethnicity		
Igbo	7	5.8
Yoruba	113	94.2
Marital status		
Single	8	6.7
Married	112	93.3
Religion		
Islam	3	2.5
Christianity	117	97.5
Educational status		
Secondary	11	9.2
Tertiary	109	90.8
Occupation		
Housewife	21	17.5
Business	24	20.0
Professional	63	52.5
Artisan	8	6.7
Schooling	4	3.3
BMI(Kg/m^2)		
< 30.0	103	85.8
≥ 30.0	17	14.2
Mean ± SD	26.39±3.67	
Range	18.75-37.20	
EGA @ recruitment(weeks)		
Mean ± SD	23.67 ± 1.49	
Range	22-26	
Birth weight (kg)		
< 2.5	22	18.3
2.5-4.0	96	80.0
> 4.0	2	1.7
Mean ± SD	3.01 ± 0.54	
Range	1.00 – 4.60	
Blood pressure @ recruitment	SBP	DBP
Mean ± SD	112.4±10.8	68.9±8.7
Range	90-140	50-90

Table 2: Pregnancy outcomes

Variable	Frequency	Percentage
Pregnancy outcomes		
Normal	70	58
Adverse pregnancy outcomes	50	42
Preeclampsia	10	20 (10/50)
Pregnancy induced hypertension	9	18 (9/50)
IUGR	13	26 (13/50)
LBW	25	50 (25/50
Stillbirths	3	6 (3/50)

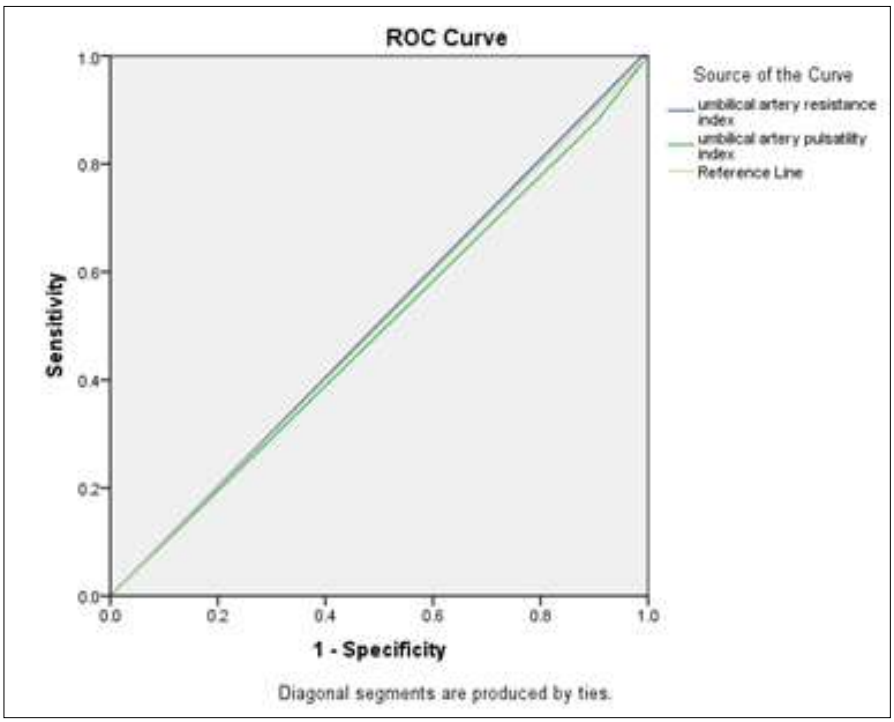
Table 3: Evaluation of diagnostic performance of abnormal umbilical artery Doppler indices in detecting adverse pregnancy outcomes.

Abnormal umbilical artery Doppler	Composite Adverse Pregnancy Outcomes	IUGR	LBW	SB
Sensitivity	16.3	0.0	12.0	66.7
Specificity	93.0	87.9	89.5	90.6
PPV	61.5	0.0	23.1	15.4
NPV	61.7	87.8	79.4	99.1
PPV: positive predictive value NPV: Negative predictive value IUGR: Intrauterine growth restriction LBW: Low birth weight SB: stillbirth				

Table 4: The association between the Umbilical PI, RI, SD and intrauterine growth restriction, delivery of low birth weight fetuses and stillbirth

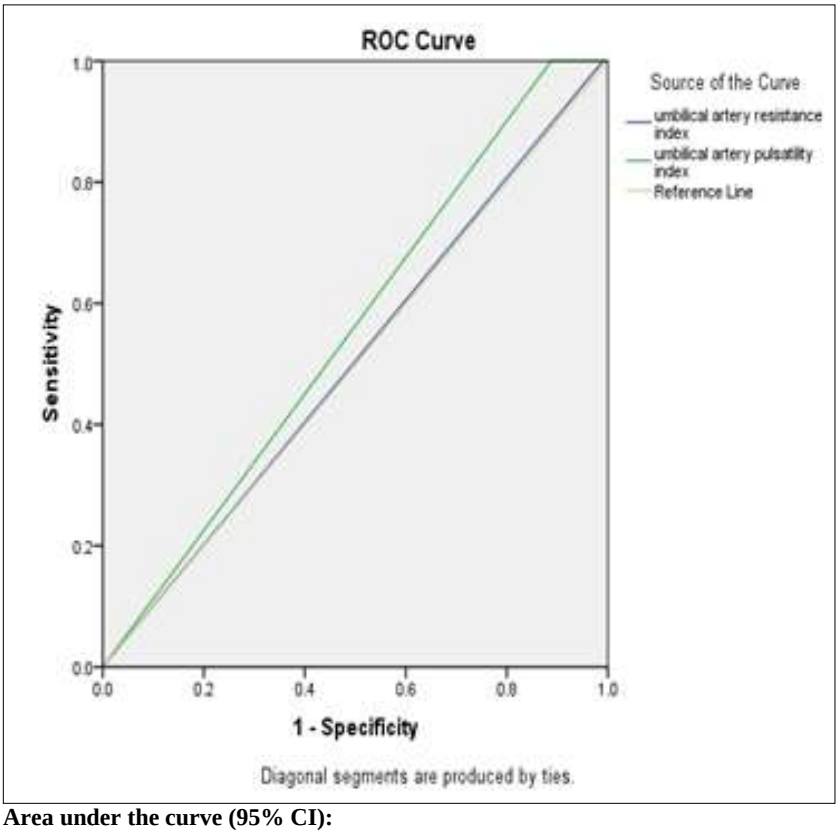
Diagnostic Indices	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
RI 0.76					
IUGR	0.0	99.1	0.0	89.1	0.51
LBW	0.0	98.9	0.0	78.9	0.51
Stillbirth	0.0	99.1	0.0	97.5	0.50
PI 1.36					
IUGR	0.0	88.8	0.0	87.9	0.56
LBW	12.0	90.5	25.0	79.6	0.49
Stillbirth	66.7	91.5	16.7	99.1	0.21

PI: Pulsatility index, RI: Resistance index, SD: Systolic/diastolic ratio, IUGR: Intrauterine growth restriction, LBW: Low birth weight, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under curve



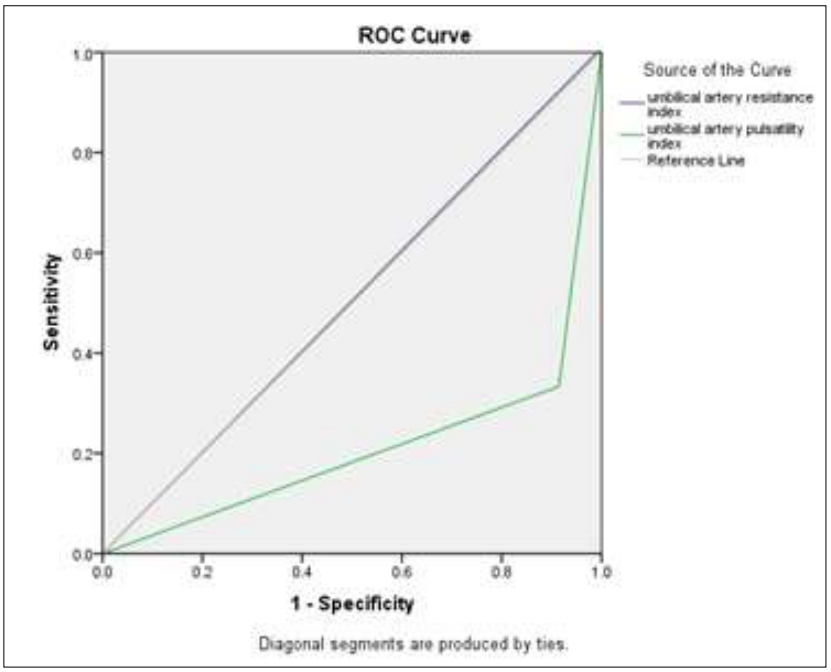
Area under the curve (95% CI):
UA RI: 0.505 (0.339 – 0.670); *p* value: 0.956
UA PI: 0.556 (0.404-0.708); p value: 0.510

IUGR



Area under the curve (95% CI):
UA RI: 0.505 (0.378-0.632); p value: 0.936
UA PI: 0.487 (0.358-0.616); p value: 0.846

LBW



Area under the curve (95% CI)
UA RI: 0.504 (0.175-0.834); P value: 0.980
UA PI: 0.209 (0.000-0.530); P value: 0.086

Stillbirth

Fig 1: Receiver operating characteristic curve for umbilical artery Doppler

Discussion

Pregnancy is associated with a number of vascular adaptations in the mother, placenta and growing fetus and maintenance of good utero-placental circulation is necessary for a normal course of pregnancy [2]. Abnormal vascular resistance patterns result in adverse pregnancy outcomes such as IUGR, LBW and stillbirths. Umbilical artery Doppler has been employed in obstetric care for monitoring pregnancies at risk of adverse

perinatal outcomes by serially evaluating the fetoplacental blood flow. The utility of umbilical artery Doppler indices as a screening tool in the prediction of subsequent development of adverse pregnancy outcomes in low-risk population has however not been widely researched. In this prospective longitudinal study, we set out to determine the utility of second trimester umbilical Doppler indices in the prediction of subsequent development of intrauterine growth restriction, delivery of neonates with low birth weight and stillbirth among low risk nulliparous women.

In this study, at least one abnormal Doppler index was recorded in 10.8% of the participants. Of all patients with abnormal umbilical arterial indices, 7.69% had abnormal RI while 92.3% had abnormal PI. The sensitivity of abnormal umbilical artery Doppler RI were 0.0% for IUGR, low birth weight and stillbirth respectively. The sensitivity of abnormal umbilical artery PI were 0.0%, 12.0% and 66.7% for IUGR, LBW and stillbirth respectively. The specificity of abnormal umbilical artery Doppler RI and PI were 99.1%, 98.9% and 99.1% and 88.8%, 90.5% and 91.5% for IUGR, low birth weight and stillbirth respectively.

Fetal growth is a significant indicator of fetal wellbeing. IUGR predisposes fetuses to severe complications [11-13]. While the uterine arteries are the more frequently evaluated vessels, the ability of umbilical artery Doppler to predict IUGR later in pregnancy remains debatable.

Previous study evaluating the ability of umbilical artery Doppler indices in the prediction of IUGR reported sensitivities ranging from 61.5% to 73.8% and 42.9% to 61.0% for PI and RI respectively [14-16]. We found a sensitivities of 0.0% for IUGR using both PI and RI in this study, these shows no value for these indices in the screening of low risk pregnant women for IUGR compared to the referenced studies carried out in selected population of high risk pregnancies.

Previous studies have suggested an association between abnormal umbilical artery Doppler indices and lower birth weight [17-22]. Our study however shows that second trimester umbilical artery RI, PI and SD in our low risk nulliparous population have low sensitivities of 0.0%, 12.0% and 0.0% respectively for the prediction of delivery of low birth weight babies. Although Torres *et al*. [23] reported 62.5% sensitivity for RI in hypertensive pregnant women who delivered low birth weight babies, no similar results were found in this study. The sensitivity for PI (12%) is comparable to 13.3% reported by Hernandez-Andrade *et al*. [24] but lower than 27.7% reported by Ayubba *et al*. [3]

De Paco *et al*. [8] in a study of 4565 fetuses at 19-22 weeks gestation evaluating the performance of the umbilical artery during the second trimester ultrasound scan, reported that an umbilical artery PI > 90th percentile was significantly associated with the delivery of an SGA neonate (birthweight < 5th and <10th percentiles) with a likelihood ratio of 1.7 (95% CI 1.2-2.4) for birthweight < 10th percentile. This report was similar to findings of Hernandez-Andrade *et al* in their study of unselected 2986 singleton pregnancies, however Hernandez-Andrade *et al* further emphasized the emerging role of Doppler assessment of cerebroplacental ratio. Exploration of evaluation of this cerebroplacental ratio will be considered in future studies.

This study reported sensitivity 66.7% for PI for the prediction of stillbirth. Piexoto *et al*. in their study among unselected women in their third trimester concluded that abnormal umbilical artery PI is associated with adverse perinatal outcomes including perinatal death [25]. Abnormal PI was reported by Romero Arauz *et al*. [22] to be significantly associated with likelihood of perinatal death, this study was however done in patients with preeclampsia in the early third trimester. Similar findings were reported by Monaghan *et al*. [26] Our study similarly shows that about two-thirds of women with abnormal UA PI are likely to have a perinatal death. A meta-analysis of sixteen randomized controlled trials showed that Doppler velocimetry of the umbilical and fetal arteries can reduce stillbirths by 35% and perinatal mortality by 29% [27] with the appropriate interventions.

The ability of late second trimester umbilical Doppler indices to predict adverse outcomes may be low in this low risk study population. It is important however to note that the negative predictive values of Doppler indices for prediction of adverse obstetric outcomes in this study was high and ranged between 78.9-99.1%. This may suggest that even though an abnormal umbilical artery Doppler does not have enough sensitivity to warrant intervention in these low risk population, it is suggested that adverse obstetric outcomes are unlikely in the presence of normal late second trimester umbilical Doppler indices. This is in agreement with previous researches.

The strength of this study is its prospective nature with adequate follow up. Variations in sociodemographic and obstetric characteristics was also limited because a homogenous group was studied. All fetuses were assessed by the same radiologist using the same protocol for Doppler and biometric measurements, thus limiting inter-observer error.

The relatively small size of the study population and the small number of patients with obstetric complications are limitations of this study. Though every Doppler ultrasound was done and interpreted by the same board-certified radiologist with several years of experience, subjectivity of interpretation of Doppler scans cannot be overlooked.

Based on our results, there is a limited role for routine umbilical Doppler in low risk women between 22-26 weeks gestation for prediction of intrauterine growth restriction, delivery of low birth weight babies or stillbirth. Although a fetus may present with abnormal UA flow early in gestation, the progression of this abnormality over time is a much more accurate indicator of fetal outcome. The optimal gestational age for follow up UA Doppler may need to be explored in further studies evaluating the clinical utility of these indices in predicting pregnancy outcomes in these cohort of patients.

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Authors' contribution: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ASA, AAA and JOA. The first draft of the manuscript was written by AAS, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Authors' declaration: The manuscript has been read and approved by all authors. The requirements for authorship as stated earlier have been met, and each author believes the manuscript represents an honest work.

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