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Second Trimester Uterine Artery Doppler Study as a Predictor of Preeclampsia and Intrauterine Growth Restriction

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Abstract **Background:** Impaired placentation with its associated increased impedance to blood flow in the uterine arteries is associated with complications in pregnancy such as pre-eclampsia and intra-uterine growth restriction (IUGR) among others. These complications are identified causes of maternal/perinatal morbidity and mortality. The uterine artery Doppler has potentials for screening for these pathological processes that are associated with impaired placentation. **Objective:** This study was designed to evaluate the predictive value of Doppler investigations of the uterine circulation in the second trimester (20-24 weeks of gestation) with regard to the development of some pregnancy complications such as pre-eclampsia and IUGR. **Methods:** This was a prospective longitudinal cross-sectional study of 354 low-risk women attending antenatal care at Alex Ekwueme Federal University Teaching Hospital Abakaliki. The study population was subjected to uterine artery Doppler study at 20-24 weeks gestation. The mean uterine artery Doppler indices such as pulsatitity index (PI), resistance index (RI) and presence of early diastolic notch (EDN) were obtained, and the outcomes of pre-eclampsia and intra-uterine growth restriction (IUGR) were studied. Data analysis was done using statistical package for social science (IBMSPSS) software (version 21, Chicago II, USA) at a statistical significance level of $p < 0.05$. **Results:** Out of the 354 women, 21(5.9%) developed pre-eclampsia and 27 (7.6% developed intra-uterine growth restriction. For pre-eclampsia, the resistance index showed a sensitivity of 66.7%, specificity of 91.9%, positive predictive value (PPV) of 34.2% and negative predictive value (NPV) of 97.8%; its pulsatility index showed a sensitivity of 71.4%, specificity of 95.5%, PPV of 50.0% and NPV of 98.2%; while for early diastolic notch had sensitivity of 66.7%, specificity of 94.3%, PPV of 42.4% and NPV of 97.8%. For intra-uterine growth restriction, resistance index showed a sensitivity of 59.3%, specificity of 92.4%, PPV of 39.0% and NPV of 96.5%; pulsatility index showed a sensitivity of 77.8%, specificity of 97.3%, PPV of 70.0% and NPV of 98.2%; while early diastolic notch had a sensitivity of 85.2%, specificity of 96.9%, PPV of 69.7% and NPV of 98.8%. **Conclusion:** The high negative predictive values indicated that women with normal Doppler velocimetry were unlikely to develop pre-eclampsia or intra-uterine growth restriction. Uterine artery Doppler, being non-invasive, can be included during routine sonography to identify patients at risk of developing pre-eclampsia or intra-uterine growth restriction. Early screening for pre-eclampsia and intra-uterine growth restriction will help in individualized antenatal surveillance and initiation of prophylactic therapy, and will help to reduce the adverse maternal and foetal complications of pre-eclampsia and intra-uterine growth restriction.

Keywords: *early diastolic notching, intra-uterine growth restriction, pre-eclampsia, pulsatility index, resistance index, uterine artery Doppler velocimetry*

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1. Introduction

The importance of obstetrics is reflected by the use of maternal and neonatal outcomes as an index of the quality of health and life among nations. Intuitively, index that reflects poor obstetrical and perinatal outcomes would lead to the assumption that medical care for the entire population is lacking. [1]

The complications of impaired placentation are significant contributors to maternal and perinatal morbidity and mortality in both developing and developed countries. [2] In the first trimester of a normal pregnancy, proliferating trophoblast invades the decidual segment of the maternal spiral arteries, replacing endothelium and destroying the medial elastic and muscular tissue of the arterial wall. [3] The arterial wall is then replaced by fibrinoid material. [3] During the second trimester, a second wave of endovascular trophoblastic invasion extends down the lumen of the spiral arteries deeper in the myometrim. [3] This results in dilated, thin-walled, funnel shaped, flaccid and low-resistance vessels that are passive conduits of the increased uteroplacental blood flow of pregnancy. [3,4,5,6,7] These remodeled high-capacitance, low-resistance uteroplacental vessels are without maternal vasomotor control. [8] This is a process that probably occurs between 8-18 weeks of pregnancy. [9]

The impairment or complete absence of this physiologic process leads to a situation in which the deeper segments of the spiral arteries are not remodeled but instead retain their musculo-elastic architecture and their ability to respond to endogenous vasoconstrictors, reducing maternal perfusion of the placenta and predisposing to relative placental hypoxia later in pregnancy. [3,10] This chronic placental ischemia causes adverse pregnancy outcome. [6]

Pregnancies affected by the complications of impaired placentation such as pregnancy induced hypertension, intrauterine fetal growth restriction and preterm birth have been shown to demonstrate increased impedance in the spiral artery. [2,11] Defective placentation may also play causative role in preterm labour, placenta abruption and second trimester miscarriages. [12] The pathophysiological pathways for this defective placentation process are diverse and none is completely explanatory in itself. [8] Immunological factor, endogenous vascular factors, and thrombogenic factors have been shown to have consistent relationships with the process and the clinical phenotype. [9] Most of these theories were derived from work restricted to cases of preeclampsia. Most of the pathophysiology on the placental level is shared between hypertensive disorders of pregnancy and intrauterine growth restriction. [8]

Pre-eclampsia is a specific pregnancy syndrome that is able to affect all organs of the body. [13] It is a multi-systemic disorder characterized by hypertension and new-onset proteinuria which develops after the 20th week of pregnancy, [14] and resolving within six weeks postpartum. The condition occurs in 5-8% of pregnancies and leads to about 50,000 deaths worldwide annually. [15,16] In developing countries, preeclampsia is a very common cause of maternal death, second only to post-partum hemorrhage. [10] Nigeria has one of the highest maternal mortality ratios in the world (814/100,000 live births); [17] and in a recent nationwide, cross-sectional study, 29% of all maternal deaths were attributed to the hypertensive disorders of pregnancy. [18] Pre-eclampsia can progress to several complicated conditions that could finally lead to maternal and foetal death. [19] Globally, pre-eclampsia has been estimated to cause between 10% and 25% of perinatal loss. [20] Indeed, delays in diagnosis and access to effective treatment are leading factors responsible for high maternal and perinatal mortality from pre-eclampsia. [21]

There are varied aetiologic factors for IUGR, however, true IUGR is classically caused by uteroplacental impairment, confirmed by typical abnormal functional parameters such as increased uterine artery Doppler pulsatility index with notching and reduced amniotic fluid. [8] IUGR occurs in about 3-5% of pregnant women. [22] In a population of women at high risk such as women with hypertension or previous IUGR, the prevalence rises to 25% or higher. [22] Growth restricted fetuses have a 4-8 fold increased risk of perinatal mortality compared to appropriately sized fetuses. [22] Suboptimal fetal growth is thought to be a significant contributor in 30-50% of intrauterine fetal deaths, of which placental dysfunction is likely the primary cause. [4] Of the fetuses that survive, 50% have significant short-term morbidity, [22] as well as long term problems.

Identification of pregnancies at risk for preventable maternal and perinatal morbidity and mortality is a primary goal of obstetric care. [23] The epidemiologic study of adverse pregnancy outcomes shows a higher rate of these complications in developing countries than in developed ones. [24] Since uterine artery provides a good representation of the sum of resistances of the placental bed and of the placental perfusion, Doppler flow studies of the uterine artery, therefore, provides an accurate means of assessing uteroplacental resistance to blood flow and a good method of assessing impairment or absence of uteroplacental flow. [2] Uterine artery Doppler ultrasound is considered as a non-invasive modality which shows uteroplacental perfusion. [27]

The principle of Doppler ultrasound was described in 1842 by John Christian Doppler. [23] The development of Doppler ultrasound evaluation of uteroplacental and fetoplacental circulation is one of the most important achievements of modern obstetrics. [23] The first-application of Doppler velocimetry in obstetrics was reported by Fitzgerald, Drumm and McCallum et al. [25] It has been long assumed that insufficient uterine, placental and fetal circulations result in adverse pregnancy outcomes and that those abnormalities can be detected by the use of Doppler ultrasonography. [23,26]

Second trimester Doppler is usually performed between 20-24th weeks of pregnancy, when it is expected that the physiologic process of 1st and 2nd waves of trophoblastic invasion would have been completed; [2] and this reportedly could identify women who subsequently develop pre-eclampsia and IUGR. [28] Thus, uterine artery Doppler is imperative in developing countries because of the high prevalence of mortality and morbidity due to complications of impaired placentation; as predicting the risk of these outcomes helps obstetricians to consider appropriate antenatal surveillance and therapeutic interventions.

Pre-eclampsia is a major cause of maternal and perinatal morbidity and mortality, globally, and significantly in Nigeria. Perinatal mortality rates as high as 120 per 1000 for all cases of IUGR and 80 per 1000 after exclusion of anomalous infants have been reported; and as many as 53% of preterm stillbirths and 26% of term stillbirths are growth restricted. [29]

It would be remarkably ground breaking if pre-eclampsia and IUGR could easily be predicted earlier in pregnancy via a non-invasive and cost effective method. Uterine artery Doppler study in the second trimester could potentially serve as an important tool in this regard. Doppler analysis helps, not only in earlier detection of uteroplacental changes associated with the disease but helps to take decisions for early intervention.

This study was designed to adduce cut-off values of uterine artery Doppler indices for prediction of pre-eclampsia and IUGR later in the pregnancy in our environment. This would help obstetricians consider appropriate surveillance and therapeutic interventions.

The Research Question:

Can second trimester uterine artery Doppler study predict adverse pregnancy outcome later in the pregnancy?

Null Hypothesis:

Second trimester uterine artery Doppler study has no predictive value for adverse pregnancy outcome.

Alternative Hypothesis:

Second trimester uterine artery Doppler study is a predictor of adverse pregnancy outcome.

2. Study Design

This was a prospective longitudinal cross-sectional study of second trimester uterine artery Doppler study as a predictor of adverse pregnancy outcome at Alex Ekwueme Federal University Teaching Hospital, Abakaliki (AE-FUTHA). Participants for this study were from the population of low-risk women with singleton pregnancies between 20-24 weeks of gestation attending antenatal care at Alex Ekwueme Federal University Teaching Hospital, Abakaliki. The women recruited were those that met the inclusion criteria and gave consent to participate in the study.

The study lasted for a period of seven months. This was extrapolated from the finding that about 105 pregnant women attended antenatal care per antenatal clinic day. Each patient was adequately counseled about the study by the researcher or any of the research assistants; thereafter, an informed consent was obtained during the antenatal care visit, before they were recruited into the study.

Sample Size Determination

The overall antenatal care (ANC) coverage in Nigeria is 67% according to the Nigeria Demographic and Health Survey 2018, [30] and using the formula for qualitative data. The minimum sample size was calculated thus:

$$n = \frac{Z^2{}_{\alpha/2}\, p(1-p)}{d^2}$$

$$n = \textit{Sample size}$$

$$Z_{\alpha/2} = 1.96 \textit{ at confidence level of } 95\% \textit{ at } p < 0.05$$

$$p = \textit{Expected proportion in population based on previous studies} = 67\%$$

$$d = \textit{Absolute error or precision of } 5\% = 0.05$$

Therefore:

$$n = \frac{1.96^2\, x\ 0.67\ x\ 0.33}{0.05^2} = \frac{0.8494}{0.0025} = 339.76$$

$n \approx 340$

Twenty percent of the minimum sample size was added to correct for any attrition:

$$\frac{20\ x\ 340}{100} = 68$$

Thus, the final sample size was (340 + 68) = 408 participants.

Inclusion Criteria:

(1). Pregnant women in the age group 20-35years.
(2). Singleton pregnancy, gestational age 20-24 weeks based on reliable last menstrual period and/or a dating scan in the first trimester.
(3). Attending antenatal clinic and will be delivered at AE-FUTHA
(4). Willingness to enroll in the study

Exclusion Criteria:

(1). Known cases of medical illness in pregnancy such as pre-existing diabetes mellitus, cardiac disease, autoimmune conditions or thrombophilias, chronic kidney disease, chronic hypertension, morbid obesity.
(2). Multiple gestation.
(3). Molar pregnancy
(4). Detection of fetal anomalies during the targeted ultrasound examination or prior to that.
(5). Fetal demise at the time of targeted ultrasound examination.
(6). Rhesus isoimmunization
(7). History of intake of Aspirin, Heparin or smoking in the index pregnancy.
(8). Not willing to enroll in the study.

Outcome Measures

1. Maternal

Primary outcome: Pre-eclampsia/Eclampsia
Secondary outcome: Abruptio placentae

2. Fetal

Primary outcome: Intrauterine growth restriction/low birth weight

Secondary outcomes: Preterm birth, APGAR score at the 5th minute <7, Newborn intensive care unit (NICU) admission, and stillbirth.

Study Procedure/Protocol:

This was a tertiary hospital based longitudinal cross-sectional study. All the study subjects were pregnant women attending antenatal clinic at AE-FUTHA with expected delivery at the AE-FUTHA. All study subjects were low-risk pregnancies. Following receipt of approval from the ethics committee of the hospital, all the 408 participants were enrolled using non-probability purposive sampling after obtaining informed consent and satisfying the inclusion and exclusion criteria.

Each participant's history and details pertaining age, parity, hospital number and phone numbers were obtained as noted in patient's antenatal folder. All the participants underwent general and routine antenatal examinations; subject's body mass index was also noted.

Urine protein was qualitatively measured using a dipstick on a clean catch urine sample passed into a universal bottle, as part of routine antenatal investigation. This was done by inserting the dipstick into the urine and the result read after 60 seconds, by comparing it with the standards placed on the container of the dipstick. The possible readings were as follows. Negative, Trace, + (30mg/dl), ++ (100mg/dl), +++(300mg/dl) and ++++ ($\geq$ 1000mg/dl). In this study, significant proteinuria would be defined as qualitative urine protein of ++ or more.

Blood pressure was measured with the patient seated on a chair. The non-dominant arm was supported at the level of the heart on a table ensuring that no tight clothing constricts the arm. The cuff of the mercury sphygmomanometer (Accoson brand) was placed on the arm with the centre of the bladder over the brachial artery, and blood pressures were measured by the nurses and midwives routinely.

As part of continuing care during antenatal visits, all subjects had a second trimester obstetric scan at the gestational age of 20-24 weeks. During the routine obstetric ultrasound scan, all participants also underwent a targeted uterine artery Doppler study.

All uterine artery Doppler studies for this study were performed at the Radiology Department of AE-FUTHA by 2 specialist and experienced radiologists specially assigned to this study, and the ultrasonography equipment used was SonoScap 4D Colour Ultrasound, Japan, 2016 with 3.5MHz trans-abdominal transducer.

The procedure was explained to each subject between the gestational age of 20 and 24 weeks. She was made to lie in supine position on an examination couch. After appropriate exposure, coupling gel was applied on the abdomen and routine obstetric scan was performed to establish the estimated fetal weight as well as to rule out any fetal congenital anomalies. Following that, the trans-abdominal transducer was placed in either the left or right iliac fossa, directed medially towards the lateral uterine walls and downward into the pelvis, to obtain the sagittal section of the uterus and cervical canal. This was followed by the introduction of the colour flow imaging to produce a colour map of flow over the region. The medial angulation was maintained until the uterine artery was visualized as it crosses the external iliac artery having originated from the internal iliac artery.

Measurements were taken approximately 1cm distal to the point of apparent crossover before any branching of the uterine arteries, and the angle of insonation was maintained at less than 300. Pulsed Doppler gate was placed in the middle of the vessel at this location to obtain flow waveforms, and when at least 3 consecutive consistent waveforms were produced, the image was frozen, and measurements for pulsatility index and resistance index were taken automatically. The mean PI and RI were calculated, and the presence or absence of early diastolic notching was noted. An abnormal Doppler study was when the PI >1.60, RI>0.58, or there was presence of notching (unilateral/bilateral). The thermal index during the Doppler imaging was less than 1.0, and exposure time was not more than 20 minutes for each woman. Results were immediately stored and transmitted to the Obstetrics and Gynaecology team managing the woman.

Follow-up

Following the uterine Doppler studies, antenatal clinic visits were routinely conducted, and patients followed up until delivery. At each visit, blood pressure was measured and urine protein estimation were done routinely. General examination along with examination of the uterus and its content, including symphysiofundal height measurement were routinely done. Development of the maternal/fetal outcomes of interest mentioned previously, were assessed for, and when required confirmed with ultrasound examination. Pre-eclampsia was diagnosed on the basis of blood pressure measurement of ≥ 140/90mmHg and significant proteinuria.

After delivery, the patients and their medical files (folders) were evaluated for the detection of the complications (adverse outcomes), as the primary and secondary outcomes of the study.

The parameters considered at delivery were gestational age at delivery, mode of delivery, birth weight, APGAR scores, neonatal viability, NICU admission and post-delivery blood pressure. Fetal growth restriction was determined by measuring birth weight and gestational age at the time of delivery. Fetal growth restriction (intra-uterine growth restriction) was retrospectively noted when the birth weight of a term newborn was < 2.5kg.

Statistical Analysis

The gathered data were entered in Microsoft Excel and then appropriate statistical analysis done using statistical package for social science (IBM SPSS) software (version 21, Chicago 11, USA).

Descriptive and inferential statistical analyses were carried out. Summary statistics were presented as percentages and proportions. Categorical variables were analyzed using Chi-Square ($\chi2$) or Fisher's exact test. The screening performance of the uterine artery Doppler indices was compared by constructing receiver operating characteristics (ROC) curve; and by evaluating the area under curve (AUC), suitable cut-off values of RI and PI for prediction of pre-eclampsia and intra-uterine growth restriction were adduced.

Ethical Considerations

Ethical clearance was obtained from the Health Research and Ethics committee of AE-FUTHA.

Dissemination of Results from the Study

The result from this study has been submitted to the Human Research and Ethics committee (HREC), AE-FUTHA. It has been presented at the departmental clinical conference and at the Society of Obstetrics and Gynecology of Nigeria (SOGON) conference.

3. Result

A total of 408 women attending antenatal care met the inclusion criteria of the study, and were recruited. Subsequently, 54 women were lost to follow-up in the prenatal period or did not deliver in AEFUTHA; therefore, data from 354 women were included in the final analysis.

Table 1 shows the demographic characteristics of the participants. Majority of the participants, 49.4% (175) were within the age bracket of 26-30 years, while the least age distribution were those within the age bracket 31-35 years (18.9%). Also, 20.6% (73) were nulliparous and 28.0% (99) of the study participants were primiparous women, and the rest 51.4% (182) were multiparas.

Table 1. Demographic characteristics of the participants

Demographic Variables	No of Participants (n=354)	Percentage
Age (years)		
20-25	112	31.6%
26-30	175	49.4%
31-35	67	18.9%
Parity		
Nullipara	73	20.6%
Primipara	99	28.0%
Multipara	182	51.4%

Abnormal uterine artery Doppler resistance index (RI) was found in 41 (11.6%) of participants, while 313 (88.4%) had normal uterine artery Doppler RI. Thirty (8.5%) of the participants had abnormal uterine artery Doppler pulsatility index (PI), while 324 (91.5%) had normal uterine artery Doppler PI. Early diastolic notching (EDN) of the uterine artery, either unilaterally or bilaterally, was present in 33 (9.3%) of the participants, while it was absent in 321 (90.7%) as noted in Table 2.

Table 2. Uterine artery Doppler characteristics of the participants

Uterine Artery	No of Participants (n=354)	Percentage
RI		
Normal	313	88.4%
Abnormal	41	11.6%
PI		
Normal	324	91.5%
Abnormal	30	8.5%
Diastolic notch		
Normal	321	90.7%
Abnormal	33	9.3%

Table 3 shows the pregnancy outcome among the participants. Pre-eclampsia, intra-uterine growth restriction (IUGR), placenta abruption, preterm delivery, stillbirth, low APGAR score of < 7 in the 5th minute after delivery and NICU admission are complications associated with abnormal uterine artery Doppler.

The association between uterine artery Doppler RI and pre-eclampsia, IUGR or placenta abruption is summarized in Table 4. For predicting pre-eclampsia, abnormal RI had a sensitivity of 66.7%, specificity of 91.9%, positive predictive value (PPV) of 34.2%, and negative predictive value (NPV) of 97.8%. The sensitivity of RI for predicting IUGR was 59.3%; while its specificity, PPV, and NPV were 92.46%, 39.0%, and 96.5% respectively. For predicting placenta abruption, RI had the sensitivity of 80% while its specificity, PPV, NPV were 89.4%; 9.8%, and 99.7% respectively.

Table 5 shows that abnormal uterine artery Doppler PI had a sensitivity of 100% in predicting placenta abruption, while having 71.4% and 77.8% for the prediction of pre-eclampsia and IUGR respectively. However, the specificity of PI for IUGR, pre-eclampsia and placenta abruption was 97.3%, 95.5% and 92.8% respectively. The odd ratios were 53.0 and 123.7 for pre-eclampsia and IUGR respectively, while the odd ratio for placenta abruption was undefined.

Table 3. Pregnancy outcomes

Pregnancy Outcome Variables	No of Participants (n=354)	Percentage
Normal pregnancy		
Yes	313	88.4%
No	41	11.6%
Pre-eclampsia		
No	333	94.1%
Yes	21	5.9%
Intrauterine growth restriction		
No	327	92.4%
Yes	27	7.6%
Placenta abruption		
No	349	98.6%
Yes	5	1.4%
Preterm delivery		
No	347	98.0%
Yes	7	2.0%
Birth weight (kg)		
Normal	321	90.7%
Abnormal	33	9.3%
Immediate outcome condition		
Alive	349	98.6%
Stillbirth	5	1.4%
APGAR Score at 5mins		
Normal	311	87.9%
Abnormal	43	12.1%
Admission into newborn intensive care unit		
No	311	87.9%
Yes	43	12.1%

Table 4. Association of Uterine Artery Doppler (UAD) RI with pregnancy outcomes

UAD RI	Pre-eclampsia		IUGR		Placenta Abruption	
	Present (n=21)	Absent (n=333)	Present (n=27)	Absent (n=327)	Present (n=5)	Absent (n=349)
Abnormal (n=41)	14(34.1%)	27(65.9%)	16(39.0%)	25(61.0%)	4(27.4%)	37(72.6%)
Normal (n=313)	7 (2.2%)	306(97.8%)	11 (3.5%)	302(96.5%)	1 (0.3%)	312(99.7%)
χ2 (P-value)	66.148 (<0.001)		64.882 (<0.001)		81.705* (<0.001)	
OR (95% C.I. of OR)	22.7 (8.4–60.9)		17.6 (7.2–42.4)		33.7 (3.7–309.8)	
Sensitivity (%)	66.7		59.3		80.0	
Specificity (%)	91.9		92.4		89.4	
PPV (%)	34.2		39.0		9.8	
NPV (%)	97.8		96.5		99.7	
Accuracy (%)	90.4		89.8		89.3	

* Fisher's exact test used

Table 5. Association of Uterine Artery Doppler (UAD) PI with pregnancy outcomes

UAD PI	Pre-eclampsia		IUGR		Placenta Abruption	
	Present (n=21)	Absent (n=333)	Present (n=27)	Absent (n=327)	Present (n=5)	Absent (n=349)
Abnormal (n=30)	15(50.0%)	15 (50.0%)	21(70.0%)	9 (30.0%)	5(16.7%)	25 (83.3%)
Normal (n=324)	6 (1.8%)	318(98.2%)	6 (1.8%)	318(98.2%)	0 (0.0%)	324(100%)
χ2 (P-value)	114.068 (<0.001)		180.995 (<0.001)		54.774* (<0.001)	
OR (95% C.I. of OR)	53.0 (18.0-155.9)		123.7 (40.2-380.3)		Undefined	
Sensitivity (%)	71.4		77.8		100	
Specificity (%)	95.5		97.3		92.8	
PPV (%)	50.0		70.0		16.7	
NPV (%)	98.2		98.2		100	
Accuracy (%)	94.1		95.8		92.9	

* Fisher's exact test used

For the prediction of IUGR, pre-eclampsia and placenta abruption using uterine artery doppler early diastolic notching is shown on Table 6; EDN had a sensitivity of 85.2%, 66.7% and 60% respectively; and a specificity of 96.9%, 94.3% and 91.4% respectively; The PPV was 69.7%, 42.4%, and 9.1% respectively for IUGR, pre-eclampsia, and placenta abruption; while NPV was 98.8%, 97.8% and 99.4% respectively.

The association between uterine artery Doppler RI and other adverse neonatal outcomes as shown in Table 7. This shows that for the prediction of preterm birth, APGAR scores of < 7 in the 5th minute, newborn NICU admission and stillbirth, RI had a sensitivity of 42.9%, 37.2%, 37.2% and 80.0% respectively; while its specificity was 89.1%, 92.06, 92.0% and 89.4%.

Table 8 showed that abnormal PI had a sensitivity of 80.0% in the prediction of stillbirth; and 46.5%, 46.5% and 42.9% for newborn NICU admission, APGAR score of < 7 in the 5th minute, and preterm birth respectively. Its specificity for stillbirth, newborn NICU admission, APGAR score < 7 in the 5th minute, and preterm birth was 92.6%, 96.8%, 96.8%, and 92.2% respectively.

For the prediction of other adverse neonatal outcomes using uterine artery Doppler early diastolic notch (EDN), a sensitivity of 100%, 34.9%, 34.9%, 28.6% was noted respectively for stillbirth, newborn NICU admission, APGAR scores of < 7 in the 5th minute and preterm birth. Its specificity was 91.1%, 94.2, 94.2, and 92.0 respectively for preterm birth, APGAR scores of < 7 in the 5th minute, newborn NICU admission, and stillbirth, as shown on Table 9.

The area under curve (AUC) was assessed using receiver operator characteristics curve. The AUC for predicting pre-eclampsia and IUGR using PI was 0.952 (95% CI: 0.911-0.992) and 0.956 (95% CI: 0.929-0.984) respectively; with cut-off points of >1.51 and >1.50 respectively. The AUC for predicting pre-eclampsia and IUGR using RI was 0.829 (95%CI: 0.716-0.942) and 0.839 (95%CI: 0.752-0.927) respectively; with a cut-off points of >0.54 for both pre-eclampsia and IUGR, as shown on Figure 1 and Figure 2, and Table 10 and Table 11.

The logistic regression of RI for pre-eclampsia found an odd ratio of 6.923 with a p-value of 0.003. PI noted an odd ratio of 15.463 with a p-value of 0.001; while EDN had an odd ratio of 2.227 with a p-value of 0.354. All were within 95% confidence interval of odd ratio as shown on Table 12.

As shown on Table 13, the logistic regression of IUGR on RI noted an odd ratio of 2.569 with a p-value of 0.248; PI showed an odd ratio of 17.479 with a p-value of <0.001; while EDN noted an odd ratio of 36.322 with a p-value of <0.001. All were with 95% confidence interval of odd ratio.

Table 6. Association of Uterine Artery Doppler EDN with pregnancy outcomes

EDN	Pre-eclampsia		IUGR		Placenta Abruption	
	Present (n=21)	Absent (n=333)	Present (n=27)	Absent (n=327)	Present (n=5)	Absent (n=349)
Abnormal (n=33)	14(42.4%)	19 (57.6%)	23(69.7%)	10 (30.2%)	3(9.1%)	30 (90.9%)
Normal (n=321)	7 (2.2%)	314(97.8%)	4 (1.3%)	317(98.8%)	2(0.6%)	319(99.4%)
χ2 (P-value)	86.846 (<0.001)		199.007 (<0.001)		15.409* (0.007)	
OR (95% C.I. of OR)	33.1 (11.9–91.5)		182.3 (53.0–626.3)		16.0 (2.6–99.2)	
Sensitivity (%)	66.7		85.2		60.0	
Specificity (%)	94.3		96.9		91.4	
PPV (%)	42.4		69.7		9.1	
NPV (%)	97.8		98.8		99.4	
Accuracy (%)	92.7		96.1		91.0	

* Fisher's exact test used

Table 7. Association of Uterine Artery Doppler (UAD) RI with adverse neonatal outcome

UAD RI	Preterm		APGAR Score @ 5min		NICU Admission		Imm Outcome	
	Present (n=7)	Absent (n=347)	Abnormal (n=43)	Normal (n=311)	Yes (n=43)	No (n=311)	Stillborn (n=5)	Alive (n=349)
Abnormal (n=41)	3(7.3%)	38 (92.7%)	16(39.0%)	25 (61.0%)	16(39.0%)	25 (61.0%)	4(9.8%)	37 (90.2%)
Normal (n=313)	4(1.3%)	309(98.7%)	27 (8.6%)	286(91.4%)	27 (8.6%)	286(91.4%)	1(0.3%)	312(99.7%)

UAD RI	Preterm		APGAR Score @ 5min		NICU Admission		Imm Outcome	
	Present (n=7)	Absent (n=347)	Abnormal (n=43)	Normal (n=311)	Yes (n=43)	No (n=311)	Stillborn (n=5)	Alive (n=349)
χ2 (P-value)	6.821* (0.036)		31.391 (<0.001)		31.391 (<0.001)		23.183* (<0.001)	
OR (95% C.I. OR)	6.1 (1.38–28.3)		6.8 (3.2–14.2)		6.8 (3.2–14.2)		33.7 (3.7–309.8)	
Sensitivity (%)	42.9		37.2		37.2		80.0	
Specificity (%)	89.1		92.0		92.0		89.4	
PPV (%)	7.3		39.0		39.0		9.8	
NPV (%)	98.7		91.4		91.4		99.7	
Accuracy (%)	88.1		85.3		85.3		89.3	

* Fisher's exact test used

Table 8. Association of Uterine Artery Doppler (UAD) PI with adverse neonatal outcome

UAD PI	Preterm		APGAR Score @ 5min		NICU Admission		Imm Outcome	
	Present (n=7)	Absent (n=347)	Abnormal (n=43)	Normal (n=311)	Yes (n=43)	No (n=311)	Stillborn (n=5)	Alive (n=349)
Abnormal (n=30)	3(10.0%)	27 (90.0%)	20(66.7%)	10 (33.3%)	20(66.7%)	10 (33.3%)	4(13.3%)	26(86.7%)
Normal (n=324)	4 (1.2%)	320(98.8%)	23 (7.1%)	301(92.9%)	23 (7.1%)	301(92.9%)	1 (0.3%)	323(99.7%)
χ2 (P-value)	10.884* (0.016)		91.299 (<0.001)		91.299 (<0.001)		33.451* (<0.001)	
OR (95% C.I. OR)	8.9 (1.9–41.8)		26.2 (11.0–62.4)		26.2 (11.0–62.4)		49.7 (5.4–461.0)	
Sensitivity (%)	42.9		46.5		46.5		80.0	
Specificity (%)	92.2		96.8		96.8		92.6	
PPV (%)	10.0		66.7		66.7		13.3	
NPV (%)	98.8		92.9		92.9		99.7	
Accuracy (%)	91.2		90.7		90.7		92.4	

* Fisher's exact test used

Table 9. Association of Uterine Artery Doppler (UAD) EDN with adverse neonatal outcome

EDN	Preterm		APGAR score @ 5min		NICU Admission		Imm Outcome	
	Present (n=7)	Absent (n=347)	Abnormal (n=43)	Normal (n=311)	Yes (n=43)	No (n=311)	Stillborn (n=5)	Alive (n=349)
Abnormal (n=33)	2(6.1%)	31 (93.9%)	15(45.5%)	18 (54.5%)	15(45.5%)	18 (54.5%)	5(15.1%)	28(84.9%
Normal (n=321)	5(1.6%)	316(98.4%)	28 (8.7%)	293(91.3%)	28 (8.7%)	293(91.3%)	0 (0.0%)	321(100%)
χ2 (P-value)	3.130 (0.077)		37.834 (<0.001)		37.834 (<0.001)		49.333* (<0.001)	
OR (95% C.I. OR)	4.1 (0.8–21.9)		8.7 (4.0 – 19.2)		8.7 (4.0–19.2)		Undefined	
Sensitivity (%)	28.6		34.9		34.9		100	
Specificity (%)	91.1		94.2		94.2		92.0	
PPV (%)	6.1		45.5		45.5		15.2	
NPV (%)	98.4		91.3		91.3		100	
Accuracy (%)	89.3		87.0		87.0		92.1	

* Fisher's exact test used

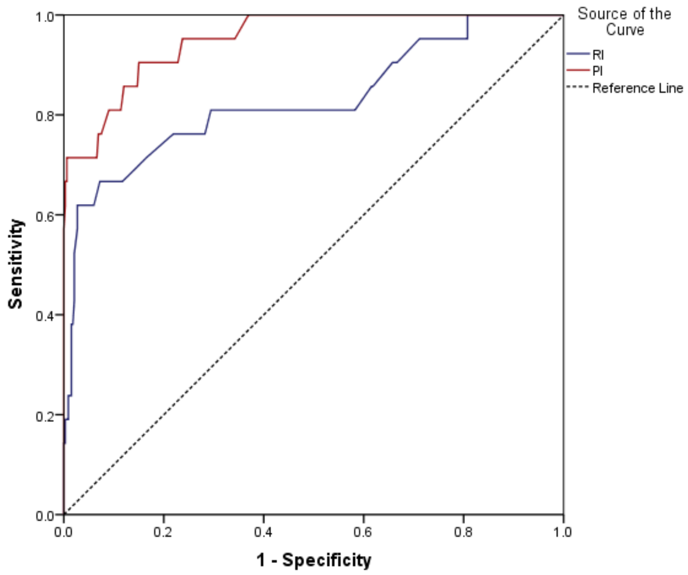

Figure 1. Pre-eclampsia dependent ROC curves for PI and RI

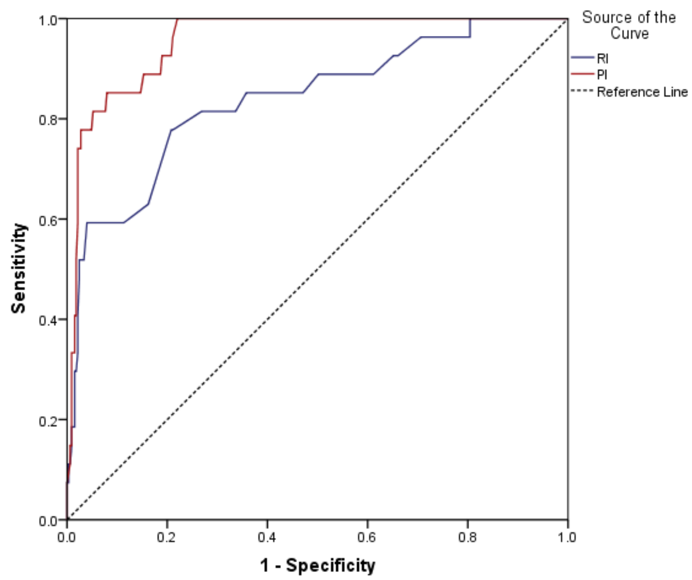

Figure 2. IUGR dependent ROC curves for PI and RI

Table 10. Area under the Curve for Pre-eclampsia

Test Result Variables	Area	P-value	95% C.I. of Area	Cut-off Point
RI	0.829	<0.001	0.716-0.942	>0.54
PI	0.952	<0.001	0.911-0.992	>1.51

Table 11. Area under the Curve for IUGR

Test Result Variables	Area	P-value	95% C.I. of Area	Cut-off Point
RI	0.839	<0.001	0.752-0.927	>0.54
PI	0.956	<0.001	0.929-0.984	>1.50

Table 12. Logistic regression of pre-eclampsia on RI, PI and EDN

Test Result Variables	OR	P-value	95% C.I. of OR
RI			
Normal (*ref.*)			
Abnormal	6.923	0.003	1.956-24.507
PI			
Normal (*ref.*)			
Abnormal	15.463	0.001	3.118-76.685
EDN			
Normal (*ref.*)			
Abnormal	2.227	0.354	0.409-12.115

Table 13. Logistic regression of FGR on RI, PI and EDN

Test Result Variables	OR	P-value	95% C.I. of OR
RI			
Normal (*ref.*)			
Abnormal	2.569	0.248	0.519-12.714
PI			
Normal (*ref.*)			
Abnormal	17.479	<0.001	3.900-78.329
EDN			
Normal (*ref.*)			
Abnormal	36.322	<0.001	8.274-159.452

4. Discussion

The ability to correctly predict the risk of pre-eclampsia and intra-uterine growth restriction is an essential part of modern obstetric care. The performance of Doppler study has been considered a tool for predicting adverse pregnancy outcomes in recent years. This longitudinal prospective cross-sectional study was carried out to assess the role of second trimester uterine artery Doppler analysis in predicting pre-eclampsia and intra-uterine growth restriction (IUGR), and to adduce cut-off values for predicting pre-eclampsia and IUGR among low-risk women.

In this study, the age range of women was between 20-35 years. The ages below 20 years or higher than 35 years were avoided as such extremes of reproductive age are at high risk of pre-eclampsia and/or intra-uterine growth restriction. The largest proportion of the women in this study, 49.4%, was within the age range of 26-30 years. This was similar to 40.7% reported by Onoh et al [31] in the study in Abakaliki, and 41.3% reported in Uyo by Olatunbosun et al [32]. This was higher than 19% reported in Bangladesh by Mariana et al [33]. The age difference in the different studies may be due to racial, ethnic or cultural differences which manifest in the prevalent age at marriage.

In this study, 88.4% had normal pregnancy, 5.9% developed pre-eclampsia while 7.6% developed IUGR. The prevalence of pre-eclampsia in the index study was similar to 6.0% in Sokoto by Singh et al [34] and 5.6% in south Nigeria by Adokiye et al. [35] It also aligned with a large multi-centre cohort study of healthy nulliparous women with singleton pregnancies which found an incidence of pre-eclampsia of 5.3% [36]. It, however, was lower than 11.3% in a similar study by Mariana et al in Bangladesh; [33] 24.7% reported in Iran by Razavi et al [7] and 8.8% in Jos, Nigeria by Musa et al [21]; but it was higher than a prevalence of 3.6% earlier reported by Onoh et al in Abakaliki [37]. These differences might be due to variations in study design, study population; or differences in socio-economic condition.

It was also noted in the index study that 7.6% of the pregnancies resulted in intrauterine growth restriction. This was similar to 7.9% reported in Ethiopia by Roro et al [38] and 7.9% in another report by Razavi et al; [7] but lower than 8.9% reported in France by Gaudineau. [39]

In this study, abnormal uterine artery Doppler resistance index (RI) was regarded as RI>0.58; and abnormal pulsatility index (PI) was regarded as PI>1.6; as was reported by previous studies. [40,41,42] There was a significant association between RI and development pre-eclampsia (p<0.001), with a sensitivity of 71.4%, specificity of 95.5%, and positive predictive value (PPV) and negative predictive value (NPV) of 50.0% and 98.2% respectively. This was in consonance with the sensitivity of 70.0% and specificity of 94.9% reported by Gupta et al. [43] These findings were also similar to those reported by Pranita et al [44] and Razieh et al, [45] however, the index study had lower sensitivity (71.4% v 96.3%), and higher specificity (95.5% v 76.9%) compared to the findings by Razieh et al. [45] The findings were comparable with what was reported by Cnossen et al. [46]

The mean RI was significantly associated with the development of intrauterine growth restriction in this study. This study discovered that RI had a modest sensitivity and PPV of 59.3% and 39.0% respectively; with high specificity and NPV of 92.4% and 96.5% respectively, for the prediction of IUGR. The odd ratio was 17.6 with a confidence interval of 7.2-42.4. These were similar to the findings by Razieh et al [45] and are comparable to the findings by Adefisan et al [41], with similar sensitivity but with higher specificity. However, in a large prospective cohort study evaluating the role of second trimester uterine artery Doppler studies in predicting small-for-gestational age newborns among low-risk women, Parry et al [47] reported a low sensitivity of RI using similar a cut off. They concluded that uterine artery Doppler studies were not clinically useful for predicting small-for-gestational age. The discrepancies might be related to differences in the study population and methodology used, as well as different definitions of an abnormal RI (cut-off) used in these studies.

Resistance index in this study also was significantly associated with the subsequent development of placenta abruption with a p-value < 0.001; and a sensitivity of 80%, specificity of 89.4%, a NPV of 99.7% and an insignificant PPV of 9.8%. The negligible PPV may be due to the fact that only a small proportion of the study population had abruption placentae.

The mean PI was strongly associated with the development of pre-eclampsia in the index study. The PI had a high sensitivity, specificity and NPV of 71.4%, 95.5% and 98.2% respectively with a modest PPV of 50%. This was similar to the findings of Noor et al [48] and Barati et al, [49] while Jamal et al [50] found a lower sensitivity. Again, the discrepancies might be due to the differences in study design, study population, differences in cut-off points for PI, and the prevalence of pre-eclampsia.

Similar to the significant association between RI and placenta abruption in this study, PI had 100% sensitivity and NPV for the prediction of placenta abruption; its specificity was 92.8%; however, its PPV was very low. This was higher than the sensitivity of 44.4% but with comparable specificity of 95.2% as reported by Veluathar et al, [51] however the uterine artery Doppler analysis was done in the first trimester by Veluathar et al. This implied that the predictive value of uterine artery indices increases in the second trimester compared to the first trimester.

Early diastolic notch between 20-24 weeks of gestation as demonstrated in this study had a sensitivity of 66.7%; a high specificity and NPV of 94.3% and 97.8% respectively; and a modest PPV of 42.4% in the prediction of pre-eclampsia. This is comparable to the findings reported by Mariana et al, [52] and the findings were similarly replicated by Rupnawar et al. [44] However, these contrasted with the findings by Okwudire et al [53] in Port-Harcourt who reported no significant association between bilateral notching and pre-eclampsia. The differences in study population, study design and prevalence of pre-eclampsia in the different studies might have accounted for the discrepancies.

In this study, there was a strong predictive value of early diastolic notching for intra-uterine growth restriction (P<0.001), as the sensitivity, specificity, PPV and NPV were all as high as 85.2%, 96.9% 69.7% and 98.8% respectively. These were highly in consonance with the findings by Abidoye et al [54] which had higher sensitivity of 100% and PPV of 80.0%. This also correlated with the finding by Methari; [22] and similarly, the incidence of intrauterine growth restriction was significantly higher in infants of women with bilateral notch as compared to the infants of women with no report of notch in their ultrasonography. [53] The predictive values of RI, PI and EDN for pre-eclampsia as found in this study were in consonance with the findings reported by Pereira et al. [55]

This study found a modest sensitivity of 60% for predicting placenta abruption by EDN. It also noted a highly strong specificity and NPV of 91.4% and 99.4% respectively; and a low PPV of 9.1%. This was contrasting to the 100% sensitivity and 43.2% specificity reported by Velauthar et al. [51] Again, the discrepancies might be due to the differences in study design, differences in study population and race.

The association of uterine artery Doppler parameters with other adverse neonatal outcomes such as preterm birth, APGAR score <7 in the 5th minute, newborn NICU admission, and stillbirth were generally significant. The sensitivity of RI and PI were average for all these neonatal outcomes but RI and PI have high sensitivity for prediction of stillbirth. The sensitivity of early diastolic notching was modest for APGAR score of <7 in the 5th minute and newborn NICU admission, it is also statistically insignificant for prediction of preterm birth. The specificity and NPV of PI, RI and EDN for adverse neonatal outcomes were strongly significant. Velauthar et al [51] reported an EDN sensitivity of 100% for stillbirth, as found in this study; however, he reported a significant but lower specificity than what was found in this study. In contrast to the index study, Veluathar reported a low predictive accuracy of PI and RI with a sensitivity of 14.5% for stillbirth. The discrepancy might be due to the difference in methodology, study population and cut-off point for the uterine artery indices. Importantly, the study by Velauthar was done in the first trimester, which could explain the sharp contrasts in the two studies. Also in contrast to this study, Verma et al [56] reported that there was no association between deranged second trimester uterine artery Doppler parameters and spontaneous preterm delivery.

Using the receiver operator characteristics curve (ROC) of RI and PI, the corresponding area under the curve (AUC) for the prediction of pre-eclampsia noted a predictive performance of 0.829 (95% CI:0.716-0.942) and 0.952 (95% CI:0.911-0.992) respectively with a p-value of less than 0.001 for both RI and PI; and a cut-off point of 0.54 and 1.51 respectively. This was comparable to the pulsatility index AUC of 0.659 (95%.CI = 0.562-0.756, P = 001) as reported by Verma et al [56]. The RI and PI cut-off points of 0.54 and 1.51 respectively for the prediction of pre-eclampsia were comparable to the cut-offs used in the methodology of the study.

The receiver operator characteristics curve was also plotted for IUGR, and the corresponding AUC of RI and PI for the prediction of IUGR noted a predictive performance of 0.839 (95% CI:0.752-0.927) and 0.956 (95% CI: 0.929-0.984) respectively; and cut-off points of 0.54 and 1.50 respectively. Similarly, the cut-off points found in this study were comparable to 0.58 and 1.60 for RI and PI respectively, used in the methodology of this study.

The test results of multivariable logistic regression analysis showed that the chance of pre-eclampsia was 6.92 times higher in low-risk women with a mean uterine artery Doppler RI at 20-24 week gestation of more than 0.58, which was statistically significant (P=0.003). The chance of developing pre-eclampsia was 15.46 times higher when PI>1.6, which was significant (p = 0.001), whereas presence of early diastolic notching was not statistically significant (P = 0.354).

The multivariable logistic regression analysis for IUGR noted that the chance of IUGR was not significantly predicted by RI>0.58 (p= 0.248); while PI>1.6 predicted a 17.48 times higher chance of developing IUGR (p< 0.001); and the presence of EDN had a very high prediction with a 36.32 times higher chance of developing IUGR (p < 0.001).

5. Conclusion

Second trimester uterine artery pulsatility index, resistance index and the presence of diastolic notch can be used as a predictor for pre-eclampsia and intra-uterine growth restriction. The uterine artery doppler data of this study suggest that pre-eclampsia and intra-uterine growth restriction are strongly associated with defective invasion of the spiral arteries. Pulsatility index of the uterine artery between 20-24 weeks of gestation is better than the resistance index and presence of early diastolic notch in ruling out subsequent development of pre-eclampsia in the index pregnancy. However, the presence of early diastolic notch is better than the individual doppler indices of pulsatility index and resistance index in ruling out subsequent development of intra-uterine growth restriction.

By obtaining high negative predictive values, this study concluded that women with normal uterine artery doppler analysis are unlikely to develop pre-eclampsia or intra-uterine growth restriction. Although, the uterine artery Doppler parameters have high negative predictive values for the prediction of pre-eclampsia and intra-uterine growth restriction, the strength or the association between abnormal results is not so considerable to justify their introduction as a screening test. However, uterine artery Doppler, being non-invasive can be included during routine sonography to identify patients at risk of developing pre-eclampsia and intra-uterine growth restriction.

Early screening for pre-eclampsia and intra-uterine growth restriction will help in vigilant and individualized antenatal surveillance and initiation of prophylactic therapy, early, to reduce the adverse maternal and fetal complications of pre-eclampsia and intra-uterine growth restriction.

Limitations

The limitation of this study was that it was an hospital based study, and as such, demographic data may not be a complete representation of the sample of the population of the region. The short period of the study and the relatively small number of cases studied are further shortcomings of this study.

Recommendations

We recommend further multiple centres studies with wider coverage of the general population. Further studies, combining uterine artery Doppler analysis along with biochemical tests, will prove more effective in screening patients for pre-eclampsia and intra-uterine growth restriction.

Appendix I

Data Extraction Form

Title of Research: Second Trimester Uterine Artery Doppler study as a Predictor of Pre-eclampsia and Intra-uterine Growth Restriction

Respondent's Initial
Hospital Number:
Respondent's Serial Number:

(A). Socio-Demographic Data

1. Age (years): 20 – 25 ☐ 26-30 ☐ 31-35☐
2. Marital Status: Single ☐ Married ☐ Remarried ☐

3. Party: Nullipara ☐ Primipara ☐ Multipara ☐
4. Occupation: Unemployed ☐ Unskilled ☐ Skilled ☐ Professional ☐
5. Religion: Christian ☐ Muslim ☐ Traditionalist ☐
6. Educational status: Primary ☐ Secondary ☐ Tertiary ☐
7. Husband's Occupation: Unemployed ☐ Unskilled ☐ Skilled ☐ Professional ☐
8. Last menstrual Period:
9. Estimated Date of Delivery:
10. Gestational Age at Doppler Study: 20 ☐ 21 ☐ 22 ☐ 23 ☐ 24 ☐

(B). Clinical Data

1. Body mass index at time of Doppler study (kg/m^2):
   19-24.9 ☐ 25-29.9 ☐ ≥30 ☐
2. Urinalysis on the day of Doppler Study: Nil + ☐ ++ ☐ ≥+++ ☐
3. Blood Pressure (mmHg) on the day of Doppler Study: <140/90 ☐ 140/90 ☐ 159/109≥1 ☐ 60/110 ☐
4. Pregnancy Outcome: Normal pregnancy ☐ Pre-eclampsia ☐ intrauterine growth restriction ☐ placenta abruption ☐ preterm labour/delivery ☐ stillbirth ☐
5. Delivery: Spontaneous virginal delivery ☐ Induction of labour ☐ caesarean section ☐
6. If induction of labour, indication:
7. If caesarean Section, indication:

(C). Doppler Study:

Uterine artery	R1	P1	Diastolic notch
Rt			
Lt			
Mean			

(D). Neonatal Outcome

1. Sex: Male ☐ Female ☐
2. Birth weight (kg): 1.0-<1.5 ☐ 1.5-2.4 ☐ 2.5-3.9 ☐
3. Immediate Outcome Condition: Alive ☐ Stillborn ☐
4. APGAR Score: 1st ☐ 5th ☐ 10th
5. Admission Newborn intensive care unit: Yes ☐ No ☐
6. Reason for admission:

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