Comparative Study of the Umbilical Artery Doppler Indices of Healthy and Growth-Restricted Foetuses in Lagos

Abstract

Aim of the Study: This study compared the umbilical artery Doppler indices (UADI) in normal and foetal growth-restricted (FGR) foetuses to determine the relationship between the UADI and pregnancy outcomes. **Materials and Methods:** This was a case-control study that recruited one hundred and eighty pregnant women comprising 90 with FGR pregnancies and 90 with normal pregnancies. Foetal biometric parameters and UADI were measured in all the participants. The UADI and clinical outcomes (preterm delivery, birth weight, perinatal death, etc.) of the normal and FGR foetuses were compared. **Results:** The mean estimated foetal weights of the FGR pregnancies (subjects) and normal pregnancies (controls) were 2.76 ± 0.66 kg and 3.62 ± 0.37 kg, respectively ($P < 0.0001$). The mean APGAR score at 5 min was 6.93 ± 1.72 for subjects and 8.03 ± 0.94 for controls ($P < 0.0001$). Abnormal umbilical artery Doppler waveforms were detected: decreased end-diastolic flow in 25 (27.8%), absent end-diastolic in 7 (7.8%) and reversed end-diastolic flow in 4 (4.4%) of the FGR pregnancies. There were 74 (82.2%) preterm deliveries among the subjects, while only 7 (7.8%) of the controls had preterm deliveries. Six deaths (two perinatal and four neonatal deaths) were recorded among the subjects, while no death occurred among the controls. **Conclusion:** Foetuses with FGR showed significantly higher quantitative Doppler indices (increased RI, PI, SD ratio), and a higher prevalence of abnormal umbilical artery waveform pattern (qualitative) than the healthy foetuses (controls).

Keywords: *Doppler ultrasound, foetal growth restriction, perinatal outcome, pulsatility index, resistive index, systolic-diastolic ratio, umbilical artery*

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Introduction

Foetal growth restriction (FGR) is a pathologic slowdown in the foetal growth pace resulting in a foetus that cannot reach its growth potential, with estimated weight being below the 10th percentile for gestational age.[1,2] FGR occurs 3%–7% of all newborns.[3]

Low birth weight (LBW) foetuses include those that are small because of genetically determined factors (constitutionally small) and those that are growth-restricted because of uteroplacental insufficiency. Distinguishing the small for gestational age (SGA) pregnancies from growth-restricted foetuses (FGR) is important because most SGA pregnancies have a good prognosis, unlike FGR pregnancies.[4,5] SGA pregnancies often exhibit normal foetal Doppler parameters, whereas FGR often exhibits characteristic materno-foetal Doppler abnormalities.[6] After prematurity, FGR is the second leading cause of perinatal death. The perinatal mortality rate in growth-restricted foetuses is 6–10 times higher than that of appropriately grown foetuses.[7]

FGR is associated with stillbirth, perinatal morbidity, neonatal death and delayed complications like cerebral palsy.[7,8] Up to 53% of preterm stillbirths and 20% of term stillbirths are growth restricted. Causes of FGR could be maternal, foetal, or placental. Maternal diseases include chronic hypertension, pregnancy-induced hypertension (PIH), sickle cell disease (SCD), renal diseases, diabetes mellitus (DM), autoimmune diseases, etc.[9,10] Foetal causes are genetic abnormalities and intrauterine foetal infections. Morphological abnormalities and aberrant insertion of the umbilical cord are the placental causes.[9] The importance of FGR can be attributed

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to the fact that proper evaluation and management can produce a favourable outcome.[2]

FGR is classified as symmetric and asymmetric.[9] Symmetric FGR (20% to 30% of all FGR cases) implies a foetus whose entire body is proportionally small. Asymmetric FGR (70% to 80% of all FGR cases) affects an undernourished foetus which causes it to prioritise the growth of important organs like the brain and heart above the growth of the liver, muscle, and fat. This type of growth restriction is usually the result of placental insufficiency.[9]

A foetus with asymmetric FGR has a small abdominal circumference (due to decreased liver size), scrawny limbs (because of decreased muscle mass) and thinned skin. If the damage producing asymmetric FGR continues for an extended period or is sufficiently severe, the foetus may lose its capacity to adjust and become growth-restricted symmetrically. Most FGR is a continuum from asymmetry (early stage) to symmetry (late stage).[2]

Umbilical artery Doppler sonography offers a non-invasive method of indirectly assessing abnormalities of the foetal and uteroplacental circulations, which are a major cause of FGR.[11] Doppler ultrasound provides information on vascular resistance and indirectly on the blood flow (haemodynamic data). The Doppler indices [systolic/diastolic ratio (S/D ratio), resistance index (RI) and pulsatility index (PI)] are related to vascular resistance.[11] UADI are sensitive to early detection of foetal compromise and predicting perinatal outcomes.[12] They could also help to determine the timing of delivery and anticipate perinatal complications.

The pulsatility index of the umbilical artery in a normal foetus decreases with advancing gestation.[11] This reflects a decrease in placental vascular resistance. In foetuses with FGR, there is an increase in the umbilical artery's pulsatility index secondary to the decrease, absence, or reversal of end-diastolic flow. The absent or reversed end-diastolic flow is strongly associated with an abnormal course of pregnancy and a higher incidence of perinatal complications.[12] PI and/or the SD ratio are usually adequate to manage most cases of suspected FGR. However, when the end-diastolic flow is absent, the S/D ratio and RI cannot be measured, so only the PI can be used in such scenarios.[13,14]

Neonatal complications reportedly associated with abnormal umbilical Doppler artery findings include intraventricular haemorrhage, periventricular leukomalacia, hypoxic-ischaemic encephalopathy, bronchopulmonary dysplasia, respiratory distress syndrome, hypoglycaemia, necrotising enterocolitis, sepsis, perinatal mortality, and possible neurodevelopmental sequelae.[15-18]

Long-term health consequences such as cognitive delay in childhood and non-communicable illnesses in adulthood, including obesity, type 2 diabetes mellitus, coronary heart disease, and increased risk of stroke, have been linked to FGR by epidemiological research.[19]

This study aimed to compare and contrast the foetal UADI and perinatal outcomes between FGR pregnancies and healthy pregnancies in our locality.

Materials and Methods

This was a prospective comparative study carried out at the Radiodiagnosis department of Lagos University Teaching Hospital from October 2017 to June 2018. The study protocol was approved by the Ethics and Research Committee of the hospital before commencement (ADM/DCST/HREC/APP/1482). Pregnant women, at 28–40 weeks gestation age (GA), with (subjects) and without (controls) clinical evidence of FGR, were recruited consecutively from the antenatal clinic of the Obstetrics and Gynaecology department of the hospital. We recruited 180 participants, comprising 90 subjects and 90 controls. Written informed consent was obtained from all the participants.

The inclusion criteria for the subjects were: pregnant women at 28–40 weeks GA with previous early dating ultrasound scan in the first trimester (< 10 weeks) and ultrasound estimated foetal weight <10th percentile for gestation age [calculated from the biparietal diameter (BPD), femur length (FL), head circumference (HC) and abdominal circumference (AC)].

Pregnant women who served as controls were those with singleton pregnancies at 28–40 weeks GA with previous early dating ultrasound scan in the first trimester (< 10 weeks), had ≤ 2 weeks discrepancy between USS and mean gestational age (MGA), ultrasound estimated foetal weight between the 10th percentile and 95th percentile for gestation age (using BPD, FL, HC, and AC), and without medical, surgical and obstetric complications that can affect foetal growth and development (e.g. chronic hypertension, SCD, DM, etc.).

The exclusion criteria for all the participants were: multiple gestations, GA < 28weeks, and foetuses with congenital anomalies.

Ultrasonographic evaluation

All the participants were scanned on a Toshiba NemioXG diagnostic ultrasound system (Toshiba Corporation, Osaka, Japan) with a 3.5MHz curvilinear transducer and Doppler functionality.

The participants underwent B mode sonography, lying supine on the examination couch, to determine the foetal biometric parameters (BPD, HC, AC and FL) using previously described standard techniques.[20] The machine automatically calculated the estimated foetal weight using the Hadlock formula.[21] The amniotic fluid was assessed using the amniotic fluid index (AFI), the sum of the largest anteroposterior fluid pockets (with no foetal part or umbilical cord) in each of the four uterine quadrants. The AFI was normal if ≥ 5 but <25, and reduced (oligohydramnios) if <5.[22]

The umbilical artery Doppler examinations were conducted on a free-floating loop at the middle of the cord, away from its placenta and foetal abdominal insertion sites. The Doppler angle was <60°, for an optimal Doppler signal. The recording was done when foetal breathing movement or uterine contraction was absent [Figure 1]. The Doppler wall filter was set at 50 – 100Hz, spectral peak average intensities were below 100 m/wcm², and pulsed Doppler sample gate size was 2 mm. The following UADI were calculated automatically by the machine: Peak Systolic Velocity (PSV) in cm/s, End Diastolic Velocity (EDV) in cm/s, Pulsatility Index (PI), Resistive Index (RI), and Systolic/Diastolic Ratio (S/D Ratio).[11]

The umbilical artery waveform pattern was also analysed and classified into normal diastolic flow: the end-diastolic flow is in a forward direction and gives the characteristic saw-tooth pattern; reduced diastolic flow: The end-diastolic flow is in a forward direction, but the diastolic flow is reduced and the characteristic saw-tooth pattern is lost; absent diastolic flow: there is no flow in the umbilical artery at the end of diastole; reversed diastolic flow: occurs when the normal forward direction of the end-diastolic flow is reversed.[13,23]

The subjects and controls were followed-up till delivery, and the perinatal outcomes were noted. These outcomes were retrieved from the mothers' and babies' case files. These perinatal parameters (outcome measures) were assessed: normal APGAR (Appearance, Pulse, Activity, Grimace, and Respiration) score at 5 min, poor APGAR score (≤ 6) at 5 min, foetal distress, foetal bradycardia, meconium-stained liquor, foetal birth weight, preterm delivery, intrauterine death, intrapartum and early perinatal death, neonatal intensive care unit (NICU) admission at birth, and the duration of NICU admission. The mode of delivery was also noted: spontaneous vaginal delivery (SVD), induced labour, or Caesarian section for foetal distress.

All the ultrasound scans were performed by one radiology senior registrar (to eliminate inter-observer variability) under the supervision of a professor/consultant radiologist. Each ultrasound measurement was done three times and the average value was recorded (to reduce intra-observer variability). Blinding was done by ensuring that the sonologist was unaware of the status of each pregnant woman (whether belonging to the study group or control group) until after the sonographic examination had been performed.

Data analysis was done using the IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). Test of normality was performed using Kolmogorov–Smirnov's test. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies. The categorical variables were analysed using chi-square, while continuous variables are analysed using students' t-test. The UADI were grouped into categories, including normal, reduced diastolic flow, absent diastolic flow and reversed diastolic flow, RI > 95th percentile (> 0.68), PI > 95th percentile (> 1.02), and S/D > 95th percentile (> 3.11). *P* value ≤ 0.05 was considered statistically significant. Measures of diagnostic accuracy of the Doppler indices were evaluated including sensitivity, specificity, positive predictive value, and negative predictive value.[24]
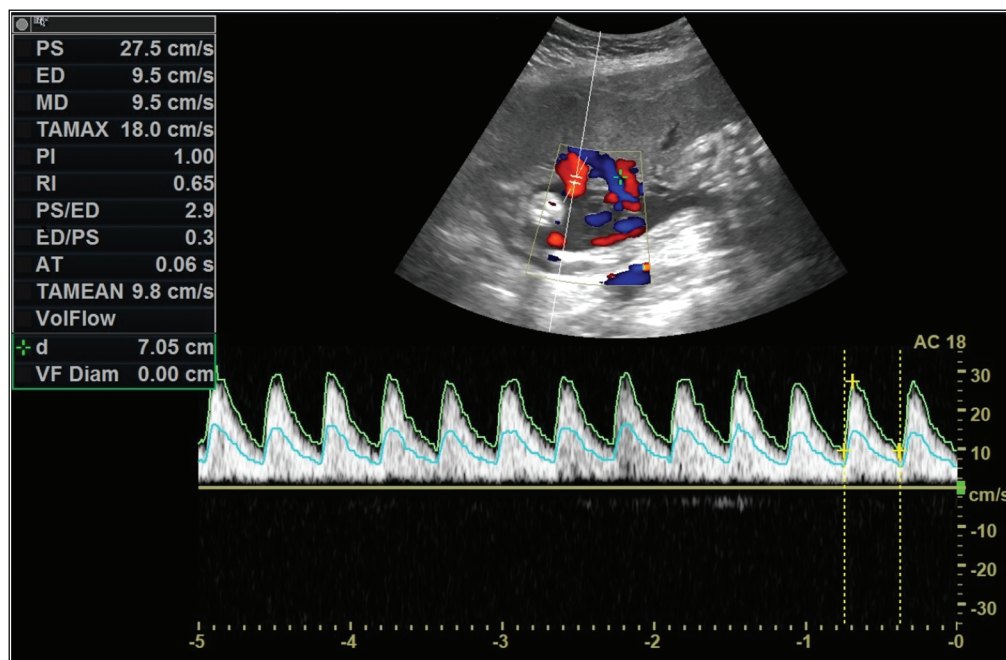

Figure 1: Triplex Doppler of the umbilical artery showing the characteristic saw-tooth appearance of a normal waveform pattern and normal indices (PI, RI, and S/D ratio)

Table 1: Clinical characteristics of the subjects and controls

	Subjects (*N* = 90)	Controls (*N*=90)	*P* value
Maternal age (years)	31.7±4.9	32.0±4.8	0.667
EGA	35w 1d ± 2w 5d	34w 6d ± 2w 6d	0.285
Birth weight (kg)	2.8±0.7	3.6±0.4	<0.0001
GA at delivery	37w 3d ±1w 3d	38w 2d ± 1w 4d	<0.0001
Caesarean section	3 (3.3%)	1 (1.1%)	0.001
Induction of labour	12 (13.3%)	0 (0%)	<0.0001
SVD	75 (83.4%)	89 (98.9%)	0.001

*EGA = estimated gestational age, GA = gestational age, w = weeks, d = days, SVD = spontaneous vertex delivery

Table 2: Doppler indices (RI, PI, and SD) of the study and control groups

Parameters	Subjects		Controls		*P* value
	Mean ±SD	Range	Mean ± SD	Range	
RI	0.74±0.17	0.5–1.26	0.68±0.11	0.4–0.8	<0.001
PI	1.27±0.64	0.7–4.7	1.02±0.29	0.5 -1.5	<0.001
SD ratio	3.49±1.08	2.66–4.88	3.11±0.71	2.30–3.4	<0.001
					<0.001
APGAR score*	6.93±1.72	3 – 9	8.03±0.94	6–10	<0.001
Birth weight (kg)	2.76±0.66	1.8–3.85	3.62±0.37	2.5–3.95	

*APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score at 5 min
RI = resistive index; PI = pulsatility index; SD ratio = systolic-diastolic ratio

Low birth weight (< 2.5Kg) and low APGAR score (< 6) at 5 min were the main outcome measures against which the abnormal UADI were compared to calculate their efficacy using the following formulae: Sensitivity = True positive / (True positive + False Negative) x 100%; Specificity = True Negative / (True Negative + False Positive) x 100%; Positive Predictive Value (PPV) = True Positive / (True positive + False Positive) x 100%; and Negative Predictive Value (NPV) = True Negative / (True Negative + False Negative) x 100%.[24] True positive: the patient has the disease, and the test is positive; False positive: the patient does not have the disease, but the test is positive; True negative: the patient does not have the disease, and the test is negative; False negative: the patient has the disease, but the test is negative.[24]

Results

One hundred and eighty pregnant women were enrolled, comprising 90 pregnant women with FGR (Subjects) and 90 pregnant women without FGR (Controls). The mean age of the subjects and controls were was 31.7±4.9 years and 32.0±4.8 years, respectively [Table 1]. The mean gestational age (GA) at delivery was 37weeks 3days (± 1 week 3days) in subjects and 38 weeks 2 days (± 1 week 4days) in the controls group [Table 1].

Fifty (55%) women with FGR foetuses were primiparous, 24 (26.7%) had PIH, 11 (12.2%) had SCD, one (1.1%) had renal disease, while six (6.7%) had DM. A previous history of FGR was present in 17 subjects (18.9%).

Of all the women with FGR foetuses, 84 (93.3%) had live births, two (2.2%) had stillbirths, and four (4.5%) had

Table 3: Term and preterm deliveries in the subjects and controls

Parameter	Subjects, *n* (%)	Controls, *n* (%)	*P* value
Term	16 (17.8%)	83 (92.2%)	<0.0001
Preterm	74 (82.2%)	7 (7.8%)	<0.0001
Total	90 (100%)	90 (100%)	–

neonatal deaths. SVD was the highest mode of delivery (75 women, 83.4%) [Table 1] and was associated with one perinatal death and one neonatal death. Caesarean section (three women, 3.3%) accounted for one perinatal death and one neonatal death, while labour induction (12 women, 13.3%) accounted for two neonatal deaths. There was no death in the control group.

Thirty-six (40%) of the foetuses with FGR had abnormal UADI. The umbilical artery Doppler indices of the subjects and controls are shown in [Table 2].

Seven foetuses (7.8%) had absent end-diastolic flow (AEDF), four (4.4%) had reversed end-diastolic flow (REDF), while 25 (27.8%) had decreased end-diastolic flow in the FGR group. No abnormal umbilical artery waveform was detected in the control group.

FGR pregnancies with abnormal umbilical artery Doppler were associated with higher rates of oligohydramnios, preterm delivery [Table 3], and low birth weight. They also had increased NICU admission and neonatal mortality. All the stillbirths that occurred in the study group had abnormal UADI. Of those admitted in the NICU, neonatal mortality was highest among those with AEDF or REDF. Eight foetuses (8.9%) from the study group were admitted

to the NICU because of birth asphyxia, out of which three (3.3%) died, while the remaining were discharged alive. In comparison, only one baby (1.1%) in the control group was admitted to NICU for physiological jaundice and was discharged alive.

The relationships of resistive index (RI) and APGAR score at 5 min were: 34 (75.6%) of the foetuses with high RI (> 0.68) had low APGAR score (≤6) at 5 min, while 11 (24.4%) had normal APGAR score (>6) in the study group.

PI and S/D ratio showed an inverse relationship to low APGAR score and LBW. PI >1.02 was seen in 36 (76.6%) and 37(78.7%) of babies with low APGAR score (≤6) and low birth weight (<2.5kg), respectively, in the study group. PI >1.02 was seen in zero (0%) and one (2.8%) of babies with low APGAR score and LBW, respectively, in the control group.

S/D ratio >3.11 was seen in 35(74.5%) and 36 (76.6%) babies with low APGAR score and low birth weight, respectively, in the study group, while S/D >3.11 was seen in zero (0%) and one (1.1%) of babies low APGAR score and LBW, respectively, in the control group.

The abnormal waveform patterns detected include decreased end-diastolic flow in 48 (53.3%), AEDF in 14 (15.6%) and REDF in eight (8.9%) FGR foetuses. Normal waveform pattern was recorded in 20 (22%) of the study group (in those with RI ≤0.68). By contrast, there was a normal waveform pattern in all the control foetuses.

RI of >0.68 had a sensitivity, specificity, PPV, and NPV of 72.9%, 76.2%, 77.8% and 71.1%, respectively, for predicting LBW (< 2.5kg); and 93.5%, 72.9% and 95.6%, respectively, for predicting low APGAR score.

PI >1.02 had sensitivity, specificity, PPV and NPV of 77.1%, 76.2%, 78.7% and 74.4%, respectively, for predicting LBW (< 2.5kg); and 100%, 72.9%, 66% and 100%, respectively, for predicting low APGAR score.

S/D ratio >3.11 had a sensitivity, specificity, PPV and NPV of 75%, 73.8%, 76.6%, and 72.1%, respectively, for predicting LBW (<2.5kg) and 96.8%, 71.2%, 63.8% and 97.7%, respectively, for predicting low APGAR score.

Discussion

Foetal growth restriction (FGR) is often a sequela of chronic foetal hypoxaemia secondary to impairment of the uteroplacental circulation and is associated with significant perinatal morbidity and mortality.[9,25] Available evidence shows the benefits of umbilical artery Doppler in the management of FGR: for distinguishing FGR from constitutionally small foetuses and for detecting FGR foetuses at risk of adverse perinatal outcomes. Umbilical artery Doppler abnormalities may become evident up to a week earlier than cardiotogographic changes.[12,26] This study was conducted to assess the efficacy of umbilical artery Doppler in predicting adverse outcomes of FGR pregnancy in our locality.

Fifty (55%) of the 90 women in the FGR group were primigravida. This is roughly similar to the observations of previous investigators (54 – 60%).[27,28] Manandhar et al. also identified primigravidity as a risk factor for FGR.[17] The contribution of primigravidity to the evolution of FGR could be due to it also predisposing to PIH, which is a major risk factor for FGR. Indeed, 24 (26.7%) of the FGR group in this study had preeclampsia. The other identifiable risk factors in the subjects were a history of previous FGR pregnancies in 17 women (18.9%), SCD (12.2%), DM (6.7%), and renal disease (1.1%).

The mean birth weight of the FGR group was 2.8 ± 0.7 Kg. This is much higher than that reported by some previous studies.[25,27,29-32] We may reasonably surmise that differences in severity of FGR, gestational age at delivery, and possibly differences in neonatal weighing scales used account for the observed disparity. Nevertheless, the overall pattern in all the studies cited is still in keeping with the grossly diminished foetal birth weight of FGR.

FGR foetuses have an increased risk of NICU admission due to various perinatal morbidities.[16] Eight (8.9%) of the FGR foetuses in this study were admitted to NICU due to birth asphyxia. NICU admissions in some of the previous studies were much higher: Gyawali[27] et al. (30/140 = 21.4%), Afroze and Begum (22/50 = 44%),[25] Netam et al. (18/100 = 18%),[29] Bhowmik et al. (8/50 = 16%),[30] and Ali et al. (53/100 = 53.7%).[31] The reason(s) for the much higher NICU admission elsewhere may be due to more severe FGR complications at delivery and possible underutilisation of NICU services in Nigeria due to prohibitive cost.

Abnormal UADI were detected in 36 (40%) FGR foetuses in this study. This prevalence is lower than that described by Gyawali et al. (72/140 = 51.4%),[27] Afroze and Begum (33/50 = 66%),[25] and Ali et al. (50/100 = 50%),[31] Borowski et al. (14/18 = 77.8%),[33] and Anshul et al. (46/100 = 46%)[34]; but higher than Ghosh[35] et al. (102/353 = 28.4%) and Arora[36] et al. (44/134 = 32.8%). Despite the differences in prevalence, all the aforementioned studies were unanimous in identifying AEDF or REDF as the most ominous findings of umbilical Doppler sonography. In this study, seven foetuses and four foetuses in the FGR group had AEDF and REDF, respectively. Three of the eight NICU admissions had AEDF/REDF and all the three died. Other studies also reported higher mortality in foetuses with AEDF or REDF.[15,31]

This study also showed that foetuses with abnormal UADI had more preterm deliveries at <37 weeks of gestation (17.8% vs. 7.8%), increased neonatal admission (8.9% vs. 1.1%) low APGAR score (40% vs. 0%) than the controls. Also noted was that AEDF and REDF resulted in perinatal death, while decreased diastolic flow recorded no perinatal death but had low APGAR score (≤6) and low birth weight. This could imply that the perinatal outcome of the FGR pregnancies depends on the severity of uteroplacental insufficiency. More

severe adverse outcomes are associated with AEDF/REDF than with decreased diastolic flow. Afroze and Begum[25] reported eight cases of AEDF and two cases of REDF. Both REDF babies died (one stillborn and the other died on the seventh day of life), while three of the eight AEDF had intrauterine foetal death (IUFD), two had neonatal death (on the first and second days of life), and three survived. Netam[29] *et al.* reported a 100% mortality of foetuses with AEDF or REDF, Bhowmik[30] *et al.* had four cases of REDF (all <32 weeks GA) with associated IUFD within one week of diagnosis, Madazli[37] *et al.* study of severely growth-restricted foetuses with AEDF found perinatal mortality of 40%, while Brodszki[38] *et al.* recorded 59% perinatal mortality in their analysis of the outcomes of 44 foetuses with REDF.

In high-risk pregnancies, utilising umbilical artery Doppler reduces perinatal mortality by 29% (CI = 2 – 48%).[39] AEDF/REDF (the severest finding in the spectrum of umbilical artery Doppler waveform abnormalities) is said to be present one week (on average) before the onset of acute deterioration, with up to 40% of foetuses with acidosis showing abnormal umbilical flow patterns.[40] After three weeks, the risk of stillbirth of a foetus with isolated REDF supersedes the risk of prematurity.[15]

The Doppler indices (S/D, PI and RI) show variable levels of efficacy in predicting the perinatal outcome of FGR pregnancies. This study showed the sensitivity, specificity, PPV, NPV of S/D ratio ≥ 3.11 to be 75%, 73.8%, 76.6% and 74.4%, respectively, which is comparable to the study done by Chanprapaph[41] *et al.* (66.7%, 78.85%, 74.42% and 68.02%) and Gyawali[27] *et al.* (76%, 76.9%,79.2% and 73.5%, respectively), respectively. Fleischer[42] *et al.* also reported that S/D ratio >3 had sensitivity of 78% in predicting FGR– comparable to this study (sensitivity = 75% for S/D >3.11). Similarly, Wang[43] *et al.* documented sensitivity, specificity and PPV of umbilical arterial S/D ratio to predict IUGR of 80.0%, 83.7% and 50.0%, respectively.

In this study, UADI were sampled from the free-floating loop of the cord, away from its placental and foetal abdominal insertions. Many of the previous studies did not state where their sampling was done. While it is theoretically acceptable to sample the umbilical artery anywhere along the cord, waveforms obtained near the placental insertion have higher end-diastolic velocity (EDV) than waveforms obtained adjacent its foetal abdominal insertion. The higher EDV results in lower SD ratio and RI values.[19] For simplicity and consistency, the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) recommends obtaining waveform samples at the free loop of the umbilical cord,[19] which was adopted in this study.

The limitations of this study include the relatively small sample size, convenient sampling method, and participant recruitment from a tertiary hospital setting. Also, the ultrasound scan to delivery time interval data and the specific indications for delivery in foetuses with FGR could not be recorded.

In conclusion, foetuses with FGR showed significantly higher quantitative Doppler indices (increased RI, PI, SD ratio), higher prevalence of abnormal umbilical artery waveform pattern (qualitative), and higher adverse perinatal incidents than healthy foetuses (controls).

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