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Diagnostic Effectiveness of Third-Trimester Fetal Doppler Studies in Pregnancy to Predict Late-and-Term Stillbirth and Neonatal Mortality in the Samrakshan Program in India

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Abstract

Aim To determine the diagnostic effectiveness of third-trimester fetal Doppler studies in pregnancy for stillbirths and neonatal mortality in the Samrakshan program of the Indian Radiological and Imaging Association (IRIA).

Methods The mean uterine artery (UtA) pulsatility index (PI) > 95th percentile, umbilical artery PI > 95th percentile, middle cerebral artery (MCA) PI < 5th percentile, and/or cerebroplacental ratio (CPR) < 5th percentile in the third trimester fetal Doppler study was considered as abnormal. The results of the fetal Doppler study closest to childbirth were considered for analysis. Late stillbirth (SB) was defined as a fetal loss between 28 and 36 gestation weeks and the term SB was defined as a fetal loss at ≥ 37 gestation weeks. Neonatal death was defined as the demise of a live-born baby within the first 28 days of life. Parameters of diagnostic effectiveness such as sensitivity, specificity, positive and negative predictive values and likelihood ratios, diagnostic odds ratio, and the area under receiver operator characteristic (AUROC) curve were assessed.

Results Screening of 1,326 pregnant women in the third trimester of pregnancy between September 2019 and February 2022, identified 308 (23.23%) abnormal Doppler studies, 11 (0.83%) SB, and 11 (0.84%) neonatal deaths. An abnormal Doppler study was significantly associated with late stillbirths (OR 37.2, 95% CI: 2.05, 674) but not with term SB (OR: 3.38, 95% CI: 0.76, 15) or neonatal deaths (OR 1.39, 95% CI: 0.40, 4.87). Mean UtA PI, umbilical artery PI, MCA PI, and CPR were significantly associated

Keywords
- diagnostic effectiveness
- fetal Doppler
- neonatal mortality
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with late SB and not term SB. The AUROC of Doppler measures was excellent for late SB but did not show discriminatory ability for term SB or neonatal deaths.

Conclusion Integration of fetal Doppler with routine third-trimester antenatal scans can help identify pregnant women at high risk for late SB. The effectiveness of fetal Doppler to identify pregnant women at high risk for term SB and neonatal deaths needs further study on a larger sample size.

Introduction

India has a declining perinatal mortality rate that is still very high relative to the global rates.[1–3] The poor perinatal health in India is exacerbated by the high prevalence of pre-eclampsia (PE), fetal growth restriction (FGR), and preterm births in India.[3,4] An estimated 8 to 10% of pregnant women in India develop PE during pregnancy and an estimated 3.5 million children are born preterm every year.[5,6]

Fetal Doppler studies help to ascertain hemodynamic redistribution suggestive of fetal adaptation to undernutrition/hypoxia, placental disease, higher risk of PE, and distinguish FGR from small for gestational age (SGA) babies.[7] Conventionally, the umbilical artery (UA) has been used to identify FGR with an abnormal UA Doppler study predicting poorer outcomes among small fetuses.[7–9] However, UA Doppler indices have limitations as they may not pick up a mild placental disease.[10] Previous studies have reported that a significant proportion of fetuses with normal UA pulsatility indices (PI) have worse outcomes than fetuses with normal growth.[10–13] The cerebroplacental ratio (CPR) is more sensitive to hypoxia than UA or middle cerebral artery (MCA) PI and has a better correlation with adverse perinatal outcomes.[7,14,15] The uterine artery (UtA) PI can be abnormal even in the presence of a normal UA PI and predict poorer perinatal outcomes.[7] This recent information led to the integration of UtA PI, CPR (includes both UA and MCA PI) and estimated fetal weight (EFW) $<$ third percentile as core components of the diagnosis of FGR.[7] However, there is a lack of information on the effectiveness of these components to identify FGR in India.

Samrakshan is an ongoing national program of the Indian Radiological and Imaging Association (IRIA) started in July 2019 that integrates trimester-specific fetal Doppler studies with routine antenatal ultrasound studies to determine a customized risk assessment of preterm PE and FGR for each pregnant woman.[16] In this manuscript, we present the diagnostic effectiveness of individual abnormal fetal Doppler parameters with late- and-term stillbirths and neonatal deaths in a cohort of pregnant women screened in the third trimester of pregnancy using the Samrakshan protocols.

Materials and Methods

Samrakshan utilizes an opportunistic screening approach focused on pregnant women seeking imaging services at departments of clinical radiology at hospitals, clinics, and diagnostic centers. A unique identification number was assigned to all participants in the screening program. Demographic details, clinical details including previous obstetric and imaging history, co-morbidity including prior history of PE, development of PE in the current pregnancy, gestational age at diagnosis of PE in the current pregnancy, and personal risk behaviors were collected from each participant. All women underwent routine third trimester-specific antenatal ultrasound exams for fetal biometric parameters. This analysis includes consecutive pregnant women in the third trimester screened in the Samrakshan program from September 2019 (after the first training continuous medical education program) to February 2022 and for whom Samrakshan radiologists could access details of childbirth. Women screened in the third trimester of pregnancy without childbirth outcome details or yet to deliver were not considered for this analysis.

Fetal Doppler studies were integrated with the antenatal scans for all women. Doppler studies included assessments of the mean UtA PI, UA PI, MCA PI, and CPR. All Doppler studies were performed by experienced FMF-certified fetal radiologists who had attended the Samrakshan continuous medical education (CME) workshops on trimester-specific ultrasound assessments as trainers and faculty for the Samrakshan program.

A transabdominal approach was used to assess the Doppler measures of interest. The UtA PI was assessed at the apparent crossover of the right and left uterine arteries at the external iliac arteries with the pulsed wave Doppler sampling gate set at nearly 2 mm.[17] A peak systolic velocity $>$ 60 cm/s confirmed that the uterine artery was being assessed.[17] The PI was estimated when three similar consecutive waveforms were obtained and a PI $>$ 95th percentile was considered abnormal (►**Fig. 1**).[17] The UA Doppler indices were measured at a free loop and a PI $>$ 95th percentile was considered abnormal (►**Fig. 2**).[18] The MCA was assessed by placing the pulsed wave Doppler gate at the proximal third of MCA close to its origin in the internal carotid artery and keeping the angle between the direction of blood flow and ultrasound beam as close to 0 as possible.[18] A minimum of 3 but fewer than 20 waveforms were recorded with the highest point of the waveform (the peak systolic volume) measured using auto trace or manual calipers.[18] An MCA PI $<$ fifth percentile was considered abnormal (►**Fig. 3**).[18] The CPR was estimated by dividing the MCA Doppler with the UA Doppler indices and a CPR $<$ fifth percentile was considered abnormal.[7,16] The

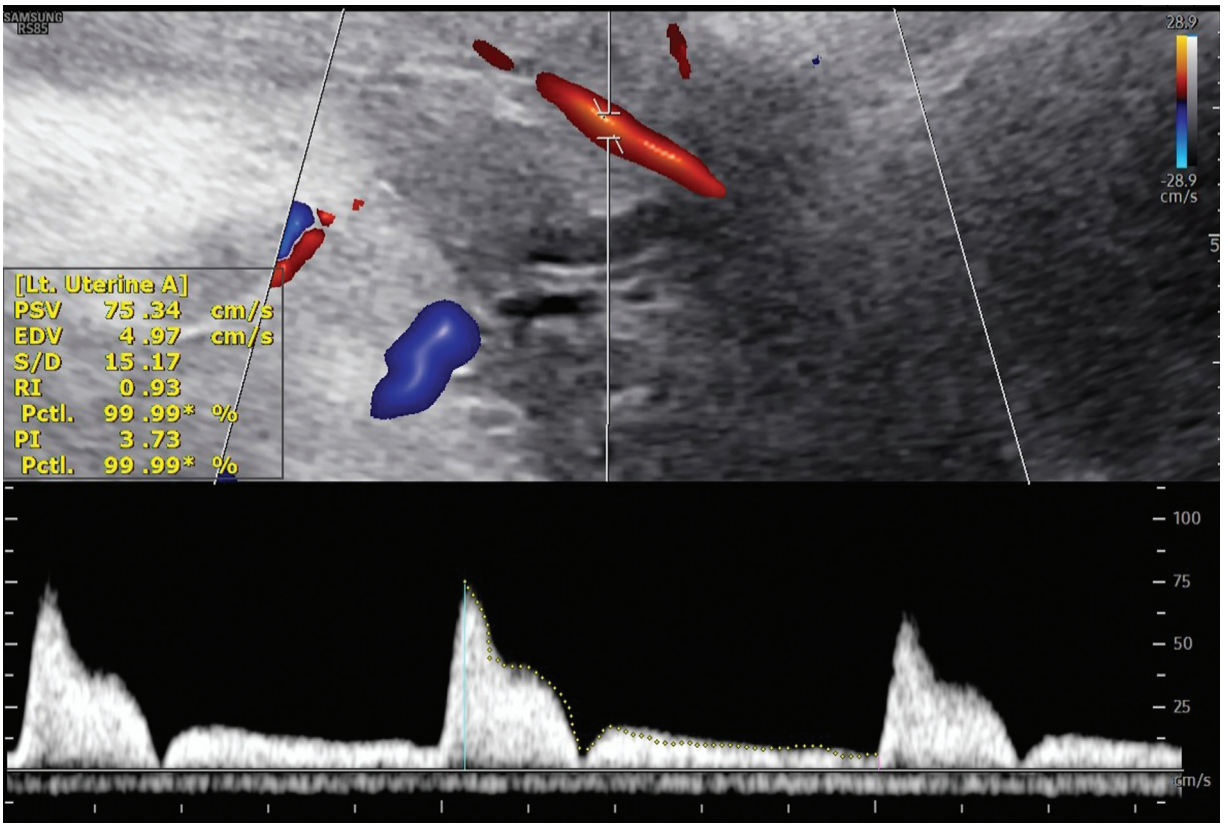

Fig. 1 Abnormal uterine artery waveform.

percentile values were determined using the Barcelona calculator available online and as an App.

Doppler measures were integrated with the fetal biometry and EFW assessments to clinically stage FGR for further management of the fetus.[7] The clinical staging was used to recommend the frequency and interval of repeat Doppler assessments and were communicated to the obstetrician to plan interactively for childbirth.

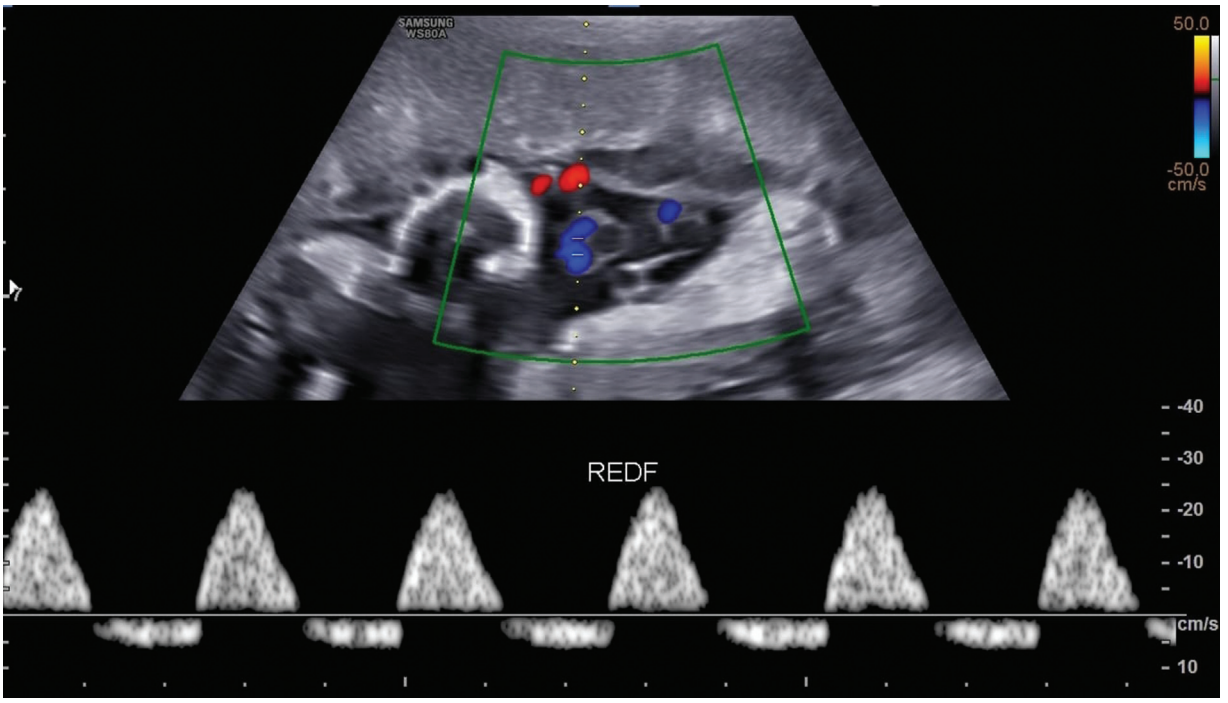

Fig. 2 Reversal of diastole in umbilical artery in early FGR stage III. FGR, fetal growth restriction.

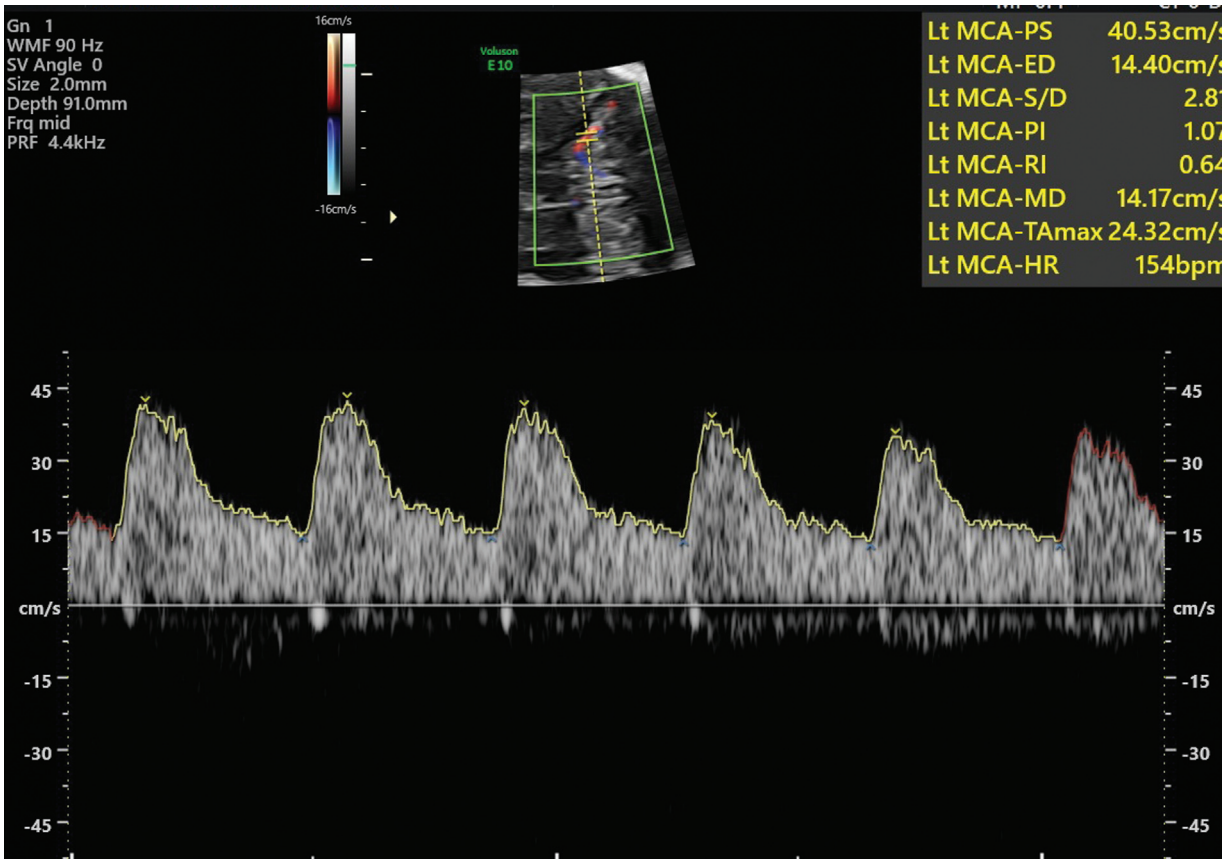

Fig. 3 Middle cerebral artery waveform in early FGR. FGR, fetal growth restriction.

Data from the ultrasound assessments were anonymized and transcribed to an online Google form integrated with a Google spreadsheet located in a dedicated password-protected Google Drive folder for live updating of entries. The data were subsequently exported to STATA v14.0 (College Station, Texas, USA) for statistical analysis. The fetal Doppler measures closest to childbirth were considered for analysis for women who had multiple Doppler studies. An abnormal Doppler study was defined as the presence of any one or more of an abnormal mean UtA PI, UA PI, MCA PI, and CPR PI. The proportion of abnormal Doppler studies was expressed as a proportion and the 95% confidence intervals around the point estimates. The loss of a fetus from 28 weeks of pregnancy until childbirth was defined as SB in the third trimester. SB was further categorized as late SB (from 28 weeks to 36 weeks) and term SB from 37 weeks till delivery. Neonatal deaths were defined as the loss of a liveborn baby within 28 days of childbirth. The data were initially explored for missing data, errors in data entry, outliers, the distribution of data (normality of distribution, the width of the interquartile range [IQR] and the IQR/median ratio), and floor and ceiling effects of the data, and pooling around certain ranges or values. We considered a $<5\%$ cut-off for errors as reasonable for data inclusion. Additionally, potential data errors that were identified were verified with the medical records of the participating investigators. A bivariate logistic regression model was used to determine the magnitude and direction of the association of abnormal Doppler studies with late stillbirth, term stillbirth, and neonatal deaths. The diagnostic effectiveness of abnormal Doppler studies and late stillbirths, term stillbirths and neonatal deaths was expressed as the sensitivity, specificity, positive and negative predictive values (PPV and NPV) and likelihood ratios (LR+ and LR −), and area under receiver operator characteristic (AUROC) curves. The point estimates and 95% confidence intervals (CI) of the point estimates were estimated.

Results

Third-trimester Samrakshan protocol-specific assessment and childbirth outcomes details from September 2019 to February 2022 were available for 1,326 women and these were included in the analysis. There were 308 (23.23%, 95% CI: 20.95, 25.50) abnormal Doppler studies, 11 (0.83%, 95% CI: 0.47, 1.48) SB including 5 late SB and 6 term SB, and 11 (0.84%, 95% CI: 0.47, 1.49) neonatal deaths in this cohort (►**Table 1**). ►**Tables 2** to **4** present the diagnostic effectiveness of Doppler studies for late-and-term stillbirths and neonatal deaths in this population. An abnormal Doppler study was significantly associated with late stillbirths (OR 37.2, 95% CI: 2.05, 674) but not with term SB (OR: 3.38, 95% CI: 0.76, 15) or neonatal deaths (OR 1.39, 95% CI: 0.40, 4.87). Mean UtA PI, Umbilical artery PI, MCA PI and CPR were significantly associated with late SB but not with term SB. The AUROC of Doppler measures was excellent for late SB (all AUROC >0.85) but did not show discriminatory ability for term SB or neonatal deaths (►**Tables 2** to **4**). Of the 308

Table 1 Prevalence of abnormal Doppler studies, stillbirths, and neonatal deaths in the 1,326 pregnant women screened in Samrakshan in the third trimester of pregnancy

	n, %, (95% CI)
Abnormal Doppler Study	308, 23.23% (20.95, 25.50)
Mean Uterine Artery PI >95th percentile	156, 11.56% (10.03,13.50)
Umbilical Artery PI >95th percentile	89, 6.71% (5.36, 8.06)
Middle Cerebral Artery PI <5th percentile	123, 9.28% (7.71, 10.84)
Cerebroplacental Ratio <5th percentile	154, 11.61% (9.89, 13.34)
Late stillbirth (28 to 36 weeks)	5, 0.38% (0.16,0.88)
Term stillbirth (37 weeks until childbirth)	6, 0.45% (0.21, 0.99)
Neonatal death (<28 days of childbirth)	11, 0.84% (0.47, 1.49)

subjects with an abnormal Doppler test, 295 (95.78%) had normal liquor, 13 (4.22%) had oligohydramnios, and none had polyhydramnios. The liquor was normal in all the cases with stillbirths or neonatal mortality in this cohort.

Discussion

The results from Samrakshan show a significantly strong association of the individual Doppler tests with late stillbirths. Abnormalities of the individual Doppler tests showed AUROC curves suggestive of an excellent discriminatory ability to differentiate between late stillbirths and normal childbirth. Clinically, we can use the sensitivity of a test to rule out the condition of interest. A normal result in a test with a very high sensitivity suggests a low probability for the condition of interest in that person. Individual Doppler tests in this cohort had a very high sensitivity suggesting that the presence of a normal Doppler test can be used to clinically rule out a high risk for late stillbirth in this population. The upper limits of the 95% confidence interval of the LR+ for the individual Doppler tests were >10 suggesting that fetal Doppler tests have a clinical utility in the identification of pregnant women at high risk for late stillbirths. A low positive predictive value of fetal Doppler was anticipated as the PPV is dependent on the prevalence of the condition and the prevalence of late-and-term stillbirths and neonatal deaths is low in this cohort.

Fetal Doppler tests did not have good diagnostic effectiveness to identify pregnant women at risk for term stillbirths or neonatal mortality. The tests had a poor AUROC curve suggesting poor discrimination between pregnant women at high risk for term stillbirths and neonatal mortality and those with normal childbirth and were not significantly associated with term stillbirths or neonatal mortality. An LR+ of 10 or more suggests the test has diagnostic utility in clinical practice and indicates an increased probability of the conditions of interest. None of the fetal Doppler tests had an LR+ >5 for term stillbirth and neonatal deaths. Clinically, we can use the specificity of a test to rule in the condition of interest. An abnormal result in a test with a very high specificity suggests a high probability of the abnormality of interest in that person. The fetal Doppler tests had a very

Table 2 Diagnostic effectiveness of abnormal Doppler studies for late stillbirths in the population screened using Samrakshan protocol in the third trimester

	Mean UtA PI > 95th percentile (95% CI)	UA PI >95th percentile (95% CI)	MCA PI <5th percentile (95% CI)	CPR <5th percentile (95% CI)	Abnormal Doppler study (95% CI)
Sensitivity	100% (47.8,100)	100% (47.8,100)	80% (28.4,99.5)	100% (47.8,100)	100% (47.8,100)
Specificity	88.6% (86.8, 90.3)	93.6% (92.2, 94.9)	91% (89.4, 92.5)	88.8% (87.0, 90.5)	77.2% (74.8, 79.4)
PPV	3.23% (1.06,7.37)	5.62% (1.85,12.6)	3.28% (0.9, 8.18)	3.29% (1.08, 7.51)	1.64% (0.53, 3.78)
NPV	100% (99.7, 100)	100% (99.7, 100)	99.9% (99.5, 100)	100% (99.7, 100)	100% (99.6, 100)
LR+	8.02 (6.03, 10.70)	14.3 (10.4,19.6)	8.33 (5.09, 13.6)	8.18 (6.15,10.9)	4.01 (3.09, 5.21)
LR-	0.09 (0.01, 1.34)	0.09 (0.01,1.27)	0.28 (0.07,1.1)	0.09 (0.01, 1.33)	0.11 (0.01, 1.53)
Odds Ratio	85.2 (4.69, 1548)	160 (8.79, 2924)	30.3 (4.73, 194)	87.1 (4.79, 1584)	37.2 (2.05, 674)
AUROC	0.94 (0.93, 0.95)	0.97 (0.96, 0.98)	0.86 (0.66, 1)	0.94 (0.93, 0.95)	0.89 (0.87,0.90)

Abbreviations: AUROC, area under receiver operator characteristic curve; CI, confidence interval; CPR, cerebroplacental ratio; LR, negative likelihood ratio; LR +, positive likelihood ratio; MCA, middle cerebral artery; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value; UA, umbilical artery; UtA, uterine artery.

Table 3 Diagnostic effectiveness of abnormal Doppler studies for term stillbirths in the population screened using Samrakshan protocol in the third trimester

	Mean UtA PI > 95th percentile	UA PI >95th percentile	MCA PI <5th percentile	CPR <5th percentile	Abnormal Doppler study
Sensitivity	16.7% (0.42, 64.1)	0% (0, 45.9)	16.7% (0.42, 64.1)	33.3% (4,33, 77.7)	50% (11.8, 88.2)
Specificity	88.6% (86.8, 90.3)	93.6% (92.2, 94.9)	91% (89.4, 92.5)	88.8% (87, 90.5)	77.2% (74.8, 79.4)
PPV	0.67% (0.02, 3.63)	0% (0, 4.3)	0.84% (0.02, 4.59)	1.34% (0.16, 4.76)	0.99% (0.21, 2.87)
NPV	99.6% (99, 99.9)	99.5% (98.9, 99.8)	99.6% (99, 99.9)	99.7% (99.1,99.9)	99.7% (99.1, 99.9)
LR+	1.87 (0.45, 7.8)	1.11 (0.08, 16.2)	2.38 (0.57, 9.93)	3.19 (1.17, 8.71)	2.19 (1.04, 4.62)
LR-	0.89 (0.61, 1.31)	0.99 (0.81, 1.22)	0.86 (0.59, 1.27)	0.72 (0.42, 1.26)	0.65 (0.31,1.36)
Odds ratio	2.11 (0.35, 12.9)	1.12 (0.07, 20.1)	2.76 (0.45, 16.9)	4.4 (0.93, 20.9)	3.38 (0.76, 15)
AUROC	0.52 (0.36, 0.69)	0.47 (0.46, 0.48)	0.54 (0.38, 0.71)	0.61 (0.40, 0.82)	0.64 (0.42, 0.86)

Abbreviations: AUROC, area under receiver operator characteristic curve; CI, confidence interval; CPR, cerebroplacental ratio; LR, negative likelihood ratio; LR +, positive likelihood ratio; MCA, middle cerebral artery; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value; UA, umbilical artery; UtA, uterine artery.

Table 4 Diagnostic effectiveness of abnormal Doppler studies for neonatal deaths in the population screened using Samrakshan protocol in the third trimester

	Mean UtA PI > 95th percentile	UA PI >95th percentile	MCA PI <5th percentile	CPR <5th percentile	Abnormal Doppler study
Sensitivity	0% (0, 28.5)	27.3% (6.02, 61)	18.2% (2.28, 51.8)	18.2% (2.28, 51.8)	27.3% (6.02, 61)
Specificity	88.5% (86.6, 90.2)	93.8% (92.3, 95)	91.1% (89.4, 92.6)	88.9% (87, 90.5)	77.2% (74.8, 79.5)
PPV	0% (0, 2.43)	3.57% (0.74, 10.1)	1.69% (0.21, 5.99)	1.36% (0.17, 4.83)	1% (0.21, 2.89)
NPV	99.1% (98.3, 99.5)	99.4% (98.7, 99.7)	99.2% (98.6, 99.7)	99.2% (98.5, 99.6)	99.2% (98.5, 99.7)
LR+	0.36 (0.02, 5.47)	4.67 (1.89, 11.6)	2.33 (0.77, 7.13)	1.87 (0.62, 5.69)	1.28 (0.53, 3.11)
LR-	1.08 (0.96, 1.22)	0.76 (0.5, 1.09)	0.87 (0.65, 1.16)	0.89 (0.67, 1.19)	0.92 (0.64, 1.32)
Odds ratio	0.34 (0.02, 5.69)	6.18 (1.74, 21.9)	2.68 (0.66, 11)	2.1 (0.52, 8.54)	1.39 (0.40, 4.87)
AUROC	0.44 (0.43, 0.45)	0.61 (0.47, 0.75)	0.55 (0.43, 0.67)	0.54 (0.42, 0.66)	0.52 (0.38, 0.67)

Abbreviations: AUROC, area under receiver operator characteristic curve; CI, confidence interval; CPR, cerebroplacental ratio; LR, negative likelihood ratio; LR +, positive likelihood ratio; MCA, middle cerebral artery; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value; UA, umbilical artery; UtA, uterine artery.

high specificity (>85%) for term stillbirths and neonatal mortality in this cohort suggesting that an abnormal Doppler test could be used clinically to stratify pregnant women that must be monitored more intensely than pregnant women with normal fetuses.

The lack of statistical significance for fetal Doppler tests in the third trimester to identify pregnant women at risk for term stillbirths or neonatal mortality may be a true lack of significance or may be driven by the low prevalence of term stillbirths and neonatal mortality in this cohort. The lack of significance must also be considered within the context of the absence of a natural slow progression for late FGR.[7,10] Late FGR usually has a mild placental disease and may not show abnormal UA PI measures.[10] These fetuses may have an

abnormal MCA PI suggestive of chronic hypoxia and cerebral vasodilation and an abnormal CPR.[10,19] Late FGR fetuses may show rapid acute fetal deterioration without identifiable signs before labor and may have intrapartum fetal distress and neonatal acidosis leading to mortality.[7,19,20] The lack of a significant association of third-trimester Doppler studies with term stillbirths and neonatal mortality in this cohort may reflect an acute deterioration in late-stage FGR and diminished placental reserve.[7,19,20] Kady et al had reported that a stillborn fetus had a high chance of FGR before demise, with an OR of 5.3 if EFW was <10th customized centile, and OR of 11.2 for EFW <2.5 centiles.[19] Figueras et al had previously reported that perinatal outcome in small-for-gestational-age fetuses with normal umbilical artery Doppler is suboptimal and questioned the role of umbilical artery Doppler to discriminate between normal-SGA and growth-restricted fetuses.[20] Exploring the associations in a larger cohort of pregnant women will help to determine the magnitude and direction of associations with term stillbirths and neonatal deaths more accurately.

An EFW < third percentile is a core component of the diagnosis of FGR[7] but has its limitations in clinical practice in India. We must consider that the determination of EFW percentiles in USG machines in India is not based on normative data from an Indian population and therefore introduces limitations in interpretation. These limitations extend to fetal biometry assessments as well as they are based on normative data from other populations. Serial longitudinal assessments using the same formula to estimate biometry and fetal weights help to minimize this limitation. However, antenatal care service uptake is suboptimal in India and with limited longitudinal follow-ups with the same practitioner. Additionally, migration of pregnant women to their parental house for childbirth is a common cultural occurrence and might result in antenatal assessments by multiple practitioners at different locations limiting the possibility of serial assessments. We must also consider that changes in fetal biometry and fetal weights is a slow process and rarely shows significant acute changes. It is not pragmatic to expect a significant discernible shift in fetal weights or biometry within a short period closer to term, which limits the utility of biometry and EFW to stratify risk in pregnant women with late FGR.

Doppler studies provide objective measures that can help early identification of fetal deterioration. Previous studies have reported that absent or reversed end-diastolic velocities, is found nearly 1 week before the acute deterioration of the fetus and in nearly 40% of fetuses with acidosis.[21] A large systematic review has previously reported that ductus venosus (DV) Doppler has predictive capacity for perinatal mortality.[22] Previous studies have reported that an abnormal DV is observed before the loss of short-term variability (STV) in computerized cardiotocography (cCTG) in 50% of cases and is abnormal 48 to 72 hours before the biophysical profile (BPP) in ~90% of cases.[23,24] Data on the DV Doppler assessment is not presented in this manuscript as the test was performed only in cases with an abnormal UA Doppler PI or abnormal CPR or suspicion of advanced FGR based on the discretion of the radiologist and was not routinely done for all pregnant women in the Samrakshan protocol.

Conclusion

The integration of fetal Doppler studies provides an objective assessment of fetal hemodynamic circulation and can be used clinically to identify pregnant women at risk for stillbirths and neonatal mortality in India. Early identification of fetuses at risk for fetal deterioration will help the clinical management of childbirth and reduce perinatal mortality in India.

Conflict of Interest
None declared.

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