The Association of Abnormal Doppler and Abnormal Amniotic Fluid Volume in the Third Trimester of Pregnancy with Preterm Birth in Pregnant Women in Agra, India

Anjali Gupta[1] Rijo Mathew Choorakuttil[2] Praveen K. Nirmalan[3]

[1] Department of Clinical Radiology, Anjali Ultrasound and Colour Doppler Centre, Agra, Uttar Pradesh, India
[2] Department of Clinical Radiology, AMMA Center for Diagnosis and Preventive Medicine, Kochi, Kerala, India
[3] Department of Research, Chief Research Mentor, AMMA Healthcare Research Gurukul, AMMA Center for Diagnosis and Preventive Medicine, Kochi, Kerala, India

Address for correspondence Rijo M. Choorakuttil, MD, AMMA Center for Diagnosis and Preventive Medicine Pvt Ltd, Kochi 682306, Kerala, India (e-mail: rijomc@gmail.com).

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Abstract

Aim This article determines the association and diagnostic effectiveness of abnormal Doppler and abnormal amniotic fluid volume (AFV) in the third trimester of pregnancy with preterm births.

Methods The third trimester screening protocol of the Samrakshan program of the Indian Radiological and Imaging Association utilizes trimester-specific fetal Doppler studies and ultrasound assessments, estimation of the risk for preterm preeclampsia (PE), assessment of the fetal environment, growth, and structure, and staging of fetal growth restriction. A multivariate logistic regression model was used to explore associations of abnormal Doppler and AFV with preterm birth. The diagnostic effectiveness of Doppler and amniotic fluid measurements for preterm births was assessed.

Results One hundred and sixty-one (25.6%) of the 630 women had a preterm birth before 37 gestational weeks. Eighty (21.1%) of the 379 women with normal AFV and normal fetal Doppler studies in the third trimester had a preterm birth. The proportion of preterm birth declined from 35.14% in 2019 to 19.53% in 2022 (chi-square test $p = 0.009$). Preterm birth was associated with preterm PE (adjusted odds ratio: 3.66, 95% confidence interval: 1.42, 9.44) in a multivariate logistic regression model. Both abnormal fetal Doppler and AFV did not have a good discriminatory ability for preterm births.

Conclusion Integration of fetal Doppler studies helped reduce the preterm birth rate by providing an objective measure of fetal well-being, contrary to a common belief that the use of color Doppler in the third trimester may result in iatrogenic increased preterm birth. Preterm births are associated with preterm PE and early identification of high-risk women and early initiation of low-dose aspirin may have an added benefit on preterm birth rates.

Keywords
- amniotic fluid volume
- fetal Doppler
- preterm birth
- preeclampsia
- pregnancy

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Introduction

Doppler ultrasound studies are used to assess fetal well-being and growth and to decide the staging of fetal growth restriction (FGR) and optimal timing of childbirth.[1–3] Several studies have reported on the utility of Doppler studies for the identification of uteroplacental insufficiency, assessment of fetal cardiovascular adaptation to hypoxia, and categorizing fetuses based on growth for further management.[1,2,4–7] Amniotic fluid is considered a parameter of chronic changes in the fetal environment and is a part of the biophysical profile score used to assess fetal well-being in the third trimester.[1,2] Previous studies have reported that isolated oligohydramnios is not associated with adverse perinatal outcomes in fetuses that are not growth restricted.[8–10] Amniotic fluid may decrease progressively in early-onset FGR and 20 to 30% of cases may show oligohydramnios a week before acute deterioration.[11,12] The third-trimester screening protocol of the Samrakshan program of the Indian Radiological and Imaging Association utilizes trimester-specific fetal Doppler studies with routine ultrasound assessments, customized estimation of the risk for preterm preeclampsia (PE), assessment of the fetal environment, growth, and structure, and staging of FGR based on estimated fetal weight (EFW) and fetal Doppler studies for all pregnant women.

Preterm births are an important contributor to perinatal mortality in India.[13] The World Health Organization has estimated that nearly 15 million annual global births are preterm.[13] The incidence of preterm births in India ranges from 13 to 19% of all live births and has a large variation within and between states.[13–17] This study aimed to determine the magnitude and direction of potential associations of abnormal Doppler and abnormal amniotic fluid volume (AFV) in the third trimester of pregnancy with preterm births and to assess the diagnostic effectiveness of abnormal Doppler and AFV for preterm births in a population of pregnant women in Agra of North India.

Methods

The study population was recruited from a single radiology center in the North Indian state of Uttar Pradesh. All trimester-specific ultrasound and Doppler assessments were done by a single Fetal Medicine Foundation-certified radiologist. The data were collected prospectively from 2019 to 2022 and the study population included pregnant women with singleton live fetuses. An informed consent was obtained from all participants prior to any ultrasound or fetal Doppler or other assessments at the study center. We excluded pregnant women for whom information on childbirth outcomes could not be retrieved or with incomplete data. The third trimester (28 gestational weeks onwards) protocol of Samrakshan includes the collection of clinical and demographic details of pregnant women, assessment of mean arterial blood pressure, Doppler ultrasound studies of the uterine artery (UtA), umbilical artery (UA), middle cerebral artery, estimation of the cerebroplacental ratio (CPR), determination of fetal biometry and growth, and assessment of the liquor and fetal heart rate, breathing, and movements. Details of maternal comorbidities including the onset of PE and FGR are noted in the medical records of the pregnant women. The four-quadrant amniotic fluid index (AFI) and the single deepest vertical pocket (SDP) were used to assess the adequacy of AFV.[18] Oligohydramnios was defined as AFI $\leq$ 5 cm or the absence of a pocket measuring at least 2 $\times$ 1 cm and SDP $>$ 8 cm was considered as polyhydramnios.

UtA Doppler indices were assessed in the third trimester using a transabdominal approach and a mean UtA pulsatility index (PI) $>$ 95th centile was considered abnormal. The pulsed wave Doppler sampling gate was set at approximately 2 mm and right-and-left uterine arteries were identified at the apparent crossover with the external iliac arteries. After the arteries were identified, pulsed wave Doppler was used to obtain the waveforms. The PI was measured after at least three identical waveforms were obtained.[19] UA Doppler indices were assessed at a free loop cord and UA PI $>$ 95th centiles were considered abnormal.[20] Fetal middle cerebral artery (MCA) Doppler waveforms were measured to obtain peak systolic volume using auto trace or manual calipers and an MCA PI $<$ 5th centile was considered abnormal. The pulsed wave Doppler gate was placed at the proximal third of MCA close to its origin in the internal carotid artery keeping the angle between the direction of blood flow and ultrasound beam as close to 0 as possible.[20] The CPR was estimated by dividing the MCA PI by the UA PI.[1] A CPR PI $<$ 5th was considered abnormal for the Samrakshan program.[21] Ductus venosus (DV) PI centile assessments and absent or reversed end-diastolic flow were assessed if mean UtA PI and/or CPR were abnormal.

EFW, fetal biometry, and growth velocity were assessed for all pregnant women. Fetal growth was staged using a composite model involving fetal weight and Doppler indices based on the model proposed by Figueras and Gratacós.[1] A fetus was considered as small for gestational age (SGA) if the EFW was 3rd to10th percentile with normal Doppler indices.[1]

The imaging and Doppler findings were communicated to the referring obstetrician who was the principal decision maker on childbirth. Information on the gestational age at delivery, if the child was alive or stillborn, birth weight of the child, onset of PE in the later parts of the trimester, and admission to a neonatal intensive care unit was collected from the treating obstetrician. Preterm birth was defined as childbirth before 37 gestational weeks.

The data was initially entered in a program-specific online Google Form and stored in a password-protected Google Drive folder. All data were anonymized to patient identifiers before entry into the Google Form consistent with the tenets of the Declaration of Helsinki. The data was subsequently exported to the statistical software STATA v 12.0 (StataCorp, College Station, Texas, United States) for further analysis. The data of the last visit in the third trimester was considered for analysis. Continuous data were expressed as mean and standard deviation (SD), or median and interquartile range.

Categorical data were expressed as frequency distribution and proportions. The 95% confidence interval (CI) was estimated around point estimates. A bivariate analysis was used to explore the association of abnormal Doppler studies with AFV. A multivariate logistic regression model that included maternal age, EFW, type of conception, stages of FGR and SGA, AFV, abnormal Doppler, and preterm PE was used to explore associations with preterm birth. The diagnostic effectiveness of Doppler and amniotic fluid measurements for preterm births was assessed using sensitivity, specificity, predictive values, the area under receiver operator characteristic (AUROC) curves, and likelihood ratios. A p-value of < 0.05 was considered statistically significant.

Results

The initial data set included details of 1,304 third trimester screening assessments which reduced to 867 pregnant women when we included only the last visit closest to childbirth. An additional 237 pregnant women yet to have childbirth or without information on childbirth outcomes were excluded. The final analysis set included 630 pregnant women screened in the third trimester with a mean age ± SD of 28.8 ± 4.7 years. ►**Table 1** presents the clinical and demographic details of the 630 women screened in the third trimester. Sixty-nine (10.9%) of the screened pregnant women had been identified earlier as high risk for PE. Fifty-six (81.2%) of the 69 high-risk women and 549 (97.9%) of the 561 low-risk women did not develop PE. Overall, 25 (4.0%) of the 630 pregnant women developed PE and 20 (80.0%) of the 25 women had developed preterm PE before 37 gestational weeks.

►**Table 2** presents the distribution of abnormal fetal Doppler in the screened population. Mean UtA PI > 95th percentile ($p = 0.03$), UA PI > 95th percentile ($p = 0.03$), MCA < 5th percentile ($p < 0.001$), and CPR < 5th percentile ($p < 0.001$) were associated with the presence of abnormal AFV. ►**Table 3** presents the distribution of abnormal AFV with different stages of FGR and SGA.

One hundred and sixty-one (25.6%) of the 630 women had a preterm birth before 37 gestational weeks. These included 123 (24.21%) of 508 women with no FGR, 24 (36.92%) of 65 women with stage 1 FGR, 100% of women with stage 2 ($n = 2$), stage 3 ($n = 2$), or stage 4 ($n = 1$) FGR, and 9 (17.31%) of the 52 women with an SGA baby. Eighty (21.1%) of the 379 women with normal AFV and normal fetal Doppler studies in the third trimester had a preterm birth. ►**Table 4** presents the distribution of preterm births by fetal Doppler and abnormal AFV in the screened population. Twelve (60.0%) of the 20 women with preterm PE and 8 (42.11%) of the 19 women with in vitro fertilization had a preterm delivery. The proportion of preterm birth showed an annual declining trend from 35.14% in 2019 to 19.53% in 2022 (chi-square test $p = 0.009$). The proportion of preterm birth in the subgroup with normal fetal Doppler and AFV also showed an annual declining trend from 28.57% in 2019 to 18.82% in 2022; however, this trend was not statistically significant (Fisher's exact test $p = 0.29$).

Table 1 Clinical and demographic details of the 630 pregnant women screened in the third trimester

Characteristic	Distribution
Age in years, mean ± SD	28.8 ± 4.7
Women aged > 35 years, *n* (%)	58 (9.21)
Gestational age at assessment, mean ± SD	34.5 ± 2.4
Spontaneous Conception, *n* (%)	610 (96.8)
Nulliparous, *n* (%)	371 (58.9)
Chronic hypertension, *n* (%)	9 (1.4)
Diabetes Mellitus, *n* (%)	7 (1.1)
Systemic lupus erythematosus, *n* (%)	1 (0.2)
EFW < 3rd percentile, *n* (%)	34 (5.4)
EFW 3rd–10th percentile, *n* (%)	88 (14.0)
EFW 10th–50th percentile, *n* (%)	388 (61.6)
EFW > 50th percentile, *n* (%)	120 (9.0)
No FGR, *n* (%)	508 (80.6)
Stage 1 FGR, *n* (%)	65 (10.3)
Stage 2 FGR, *n* (%)	2 (0.3)
Stage 3 FGR, *n* (%)	2 (0.3)
Stage 4 FGR, *n* (%)	1 (0.2)
SGA, *n* (%)	52 (8.3)
Oligohydramnios, *n* (%)	126 (20.0)
Polyhydramnios, *n* (%)	16 (2.5)
Both liquor and fetal Doppler normal, *n* (%)	379 (60.2)
Both liquor and fetal Doppler abnormal, *n* (%)	55 (8.7)
Only fetal Doppler abnormal, *n* (%)	109 (17.3)
Only liquor abnormal, *n* (%)	87 (13.8)
Preterm preeclampsia, *n* (%)	20 (3.2)
Preterm births < 37 gestational weeks, *n* (%)	161 (25.6)
Birth weight in grams, mean ± SD	2741.1 ± 510.8
Birth weight < 2,500 g, *n* (%)	123 (19.5)
Stillbirths, *n* (%)	2 (0.3)
Neonatal mortality, *n* (%)	5 (0.8)

Abbreviations: EFW, estimated fetal weight; FGR, fetal growth restriction; SD, standard deviation; SGA, small for gestational age.

Preterm births were associated with preterm PE (adjusted odds ratio [OR]: 3.66, 95% CI: 1.42, 9.44) in a multivariate logistic regression model that adjusted for maternal age, EFW, type of conception, and stages of FGR and SGA, abnormal AFV, and abnormal Doppler. The type of conception (adjusted OR: 1.48, 95% CI: 0.55, 3.98) was not associated with preterm births after adjusting for maternal age, EFW, stages of FGR and SGA, abnormal AFV, and abnormal Doppler in the multivariate logistic regression model.

Table 2 Distribution of abnormal fetal Doppler parameters in the screened population

Fetal Doppler parameter	*N*, % (95% CI)
Mean uterine artery PI > 95th percentile	44, 7.0 (5.2%, 9.2%)
Umbilical artery PI > 95th percentile	78, 12.5 (10.0%, 15.2%)
Middle cerebral artery PI < 5th percentile	71, 11.3 (9.0%, 14.0%)
Cerebroplacental ratio < 5th percentile	77, 12.2 (9.9%, 15.0%)
Any abnormal fetal Doppler	164, 26.0 (22.8%, 29.6%)

Abbreviations: CI, confidence interval; PI, pulsatility index.

Table 3 Distribution of abnormal liquor with stages of fetal growth restriction and small for gestational age babies in the screened population

Stages	*N*, %, 95% CI
No FGR ($n = 508$)	93, 18.3, 15.2–21.9
Stage 1 FGR ($n = 65$)	32, 49.2, 37.5–61.1
Stage 2 FGR ($n = 2$)	1, 50.0, 9.5–90.6
Stage 3 FGR ($n = 2$)	2, 100.0, 34.2–100
Stage 4 FGR ($n = 1$)	0, 0.0
SGA ($n = 52$)	14, 26.92, 16.8–40.3

Abbreviations: CI, confidence interval; FGR, fetal growth restriction; SGA, small for gestational age.

Table 4 Preterm births by fetal Doppler studies and liquor status in the screened population

Characteristic	Preterm births *n*, (%), 95% CI
Both fetal Doppler and liquor normal ($n = 379$)	80 (21.1), 17.3–25.5
Both fetal Doppler and liquor abnormal ($n = 55$)	14 (25.4), 15.8–38.3
Only fetal Doppler abnormal ($n = 109$)	40 (36.7), 28.3–46.1
Only abnormal liquor ($n = 87$)	27 (31.0), 22.3–41.4
Mean uterine artery PI > 95th percentile ($n = 44$)	19 (43.2), 29.7–57.8
Umbilical artery PI > 95th percentile ($n = 78$)	25 (35.9), 22.7–43.0
Middle cerebral artery PI < 5th percentile ($n = 71$)	19 (26.8), 17.8–38.1
Cerebroplacental ratio < 5th percentile ($n = 77$)	25 (32.5), 23.1–43.5
Oligohydramnios ($n = 126$)	33 (26.2%)
Polyhydramnios ($n = 16$)	8 (50.0%)

Abbreviations: CI, confidence intervals; PI, pulsatility index.

The AUROC curves and the positive likelihood ratios for abnormal AFV and abnormal fetal Doppler parameters indicate that abnormal fetal Doppler and AFV did not have a good discriminatory ability for preterm births (►**Table 5**). Neither abnormal AFV (adjusted OR: 1.04, 95% CI: 0.66, 1.64) nor abnormal fetal Doppler studies (adjusted OR: 1.35, 95% CI: 0.85, 2.13) were significantly associated with preterm births in a multivariate logistic regression model that adjusted for preterm PE, EFW, type of conception, stages of FGR and SGA, and maternal age. Preterm births were not associated with mean UtA PI (adjusted OR: 1.01, 95% CI: 0.97, 1.04), UA PI (adjusted OR: 1.18, 95% CI: 0.84, 1.67), MCA PI (adjusted OR: 1.33, 95% CI 0.97, 1.82), or CPR (adjusted OR: 1.01, 95% CI: 0.98, 1.02) in a multivariate logistic regression model that adjusted for maternal age, EFW, type of conception, and stages of FGR and SGA, and abnormal AFV.

There was no maternal mortality, 2 stillbirths, and 5 early neonatal deaths in this population for a perinatal mortality rate of 11.1/1,000 childbirths and a neonatal mortality rate of 8.0/1,000 live births. One of the stillbirths was a term stillbirth at 41 gestational weeks in a woman with no maternal comorbidity, adequate liquor, normal fetal Doppler studies, EFW 10th to 50th centiles, and no FGR. The other stillbirth was at 29 weeks in a preterm PE with stage 4 FGR, adequate liquor but abnormal UtA, UA, MCA, and CPR PI, reversal of end-diastolic flow, and DV > 95th percentile with decelerating fetal health advised immediate childbirth.

Discussion

PE did not develop in 81.2% of pregnant women on low-dose aspirin and 97.9% of low-risk women in this study. Preterm PE was more common than term PE in the study population. We found that a little over 1 in 4 pregnant women that were screened had an abnormal Doppler study. The distribution of UA, MCA, and CPR abnormalities were nearly similar in the screened population. We found that abnormal Doppler parameters were associated with abnormal AFV in the screened population. Two-thirds (60.2%) of the screened population had normal fetal Doppler and AFV and the remaining women had an isolated abnormal fetal Doppler (17.3%), or isolated abnormal AFV (13.8%) or abnormality of both AFV and fetal Doppler (8.7%).

Previous studies reported a low risk of adverse outcomes in pregnant women with isolated oligohydramnios in the absence of PE or FGR suggesting that these women can be carried to term in the absence of any other complications.[8–10] We found that 25.6% of the screened population had a preterm birth. Preterm birth was associated with preterm PE but was not associated with abnormal Doppler parameters, abnormal AFV, or type of conception in this population. Both abnormal Doppler parameters and abnormal AFV did not show good discriminatory ability for preterm births in this population.

Minimizing the risk for preterm births is important from practice and public health perspectives. Preterm birth has an immediate impact on perinatal mortality rates, use of health care infrastructure and resources, and long-term impact on

Table 5 Diagnostic effectiveness of abnormal liquor and abnormal Doppler parameters for preterm births in the screened population

Characteristic	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	AUROC 95% CI	LR+ 95% CI
Abnormal liquor	25.5, 18.9–32.9	78.5, 74.5–82.1	28.9, 21.6–37.1	75.4, 71.3–79.2	0.52, 0.48–0.56	1.18, 0.86–1.62
Mean UtA PI > 95th percentile	11.8, 7.26–17.8	94.7, 92.2–96.5	43.2, 28.3–59.0	75.8, 72.1–79.2	0.53, 0.51–0.56	2.21, 1.25–3.91
Umbilical artery PI > 95th percentile	17.4, 11.9–24.1	89.2, 86.1–91.9	35.9, 25.3–47.6	75.7, 71.9–79.3	0.53, 0.50–0.57	1.62, 1.1–2.48
MCA PI < 5th percentile	11.9, 7.3–17.9	88.9, 85.7–91.6	26.8, 16.9–38.6	74.7, 70.9–78.2	0.50, 0.47–0.53	1.1, 0.65–1.75
CPR < 5th percentile	15.5, 10.3–22.1	88.9, 85.7–91.6	32.5, 22.2–44.1	75.4, 71.6–78.9	0.52, 0.49–0.55	1.4, 0.9–2.18

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

the health of the population.[1,2,13,22,23] Preterm babies are four times more likely to die in the early-or-late neonatal period and 1.7 times more likely to die in the postneonatal period in India.[13] The association of preterm PE with preterm births is anticipated as PE can deteriorate rapidly, and immediate or early childbirth may be needed to prevent maternal and/or fetal mortality. Early identification of pregnant women with a high risk for preterm PE and early initiation of low-dose aspirin 150 mg once daily at bedtime may help to reduce the subgroup of pregnant women that are at risk for preterm births. PE did not develop in 80% of the high-risk pregnant women that were recommended low-dose aspirin and only 2.1% of the low-risk group developed PE providing an evidence-based pathway to reduce the risk for preterm birth in this population.

We also found that 21.1% of the pregnant women with normal Doppler and normal liquor volume in the study had preterm birth. A proportion of these preterm births may be attributable to fetal distress, rupture of membranes or antepartum hemorrhage, or other risk factors that occurred after the diagnostic window. We found a declining trend of preterm births throughout the study in this subgroup; however, this trend was not statistically significant. The regular proactive interaction of the fetal radiologist in this setting with the managing obstetrician after the third-trimester screening till childbirth may have contributed to this decline. Our results suggest that regular systematic interactions between the fetal radiologist and the obstetrician in the third trimester till childbirth can help to further reduce the incidence of preterm birth in this subgroup. We had not collected data on cervical competence or other maternal risk factors for preterm birth as part of the screening protocol and hence cannot comment on their possible contribution to the preterm birth rate.

A potential consequence of surveillance with fetal Doppler is an increased incidence of preterm births attributable to an abnormal Doppler study especially if associated with abnormal AFV or PE. Any such increase in the preterm birth rate after the integration of fetal Doppler studies can add further strain to the health care infrastructure especially as preterm birth rates are increasing annually. However, we found an annual decrease rather than an increase in the preterm birth rates of the study population and that abnormal Doppler parameter or AFV was not associated with preterm birth. Our results on the preterm birth rate suggest that integration of fetal Doppler studies can help to reduce the preterm birth rate as they provide an objective measure of fetal well-being.

The single-center nature and data measurement by a certified fetal radiologist are strengths of the study but limit the generalization of these results to the larger population of pregnant women in India. The lack of information on specific maternal risk factors for preterm births is a limitation of the study. In conclusion, we found that abnormal Doppler studies or abnormal AFV were not associated with preterm birth in the screened population. First-trimester identification of high-risk pregnant women and early initiation of low-dose aspirin can help reduce the pool of women at risk for preterm birth. There is a large subgroup of preterm births with normal fetal Doppler and AFV that can be addressed through regular systematic interactions between the fetal radiologist and the managing obstetrician.

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Conflict of Interest
None declared.

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