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Original Research Article

A Hospital-Based Study Assessing the Association and Diagnostic Effectiveness of Abnormal Doppler and Abnormal Amniotic Fluid Volume (AFV) in the Third Trimester of Pregnancy with Preterm Births: An Observational Study

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Abstract

Aim: The aim of the present study was to determine 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 study population was recruited from at Department of Radiodiagnosis. All trimester-specific ultrasound and Doppler assessments were done. Total 500 women were included in the study. The data were collected prospectively and the study population included pregnant women with single-ton live fetuses.

Results: The clinical and demographic details of the 500 women screened in the third trimester. 60% had EFW 10th–50th percentile. And 80% had no FGR. 25% had Preterm births < 37 gestational weeks. 20% had Oligohydramnios and 2% had polyhydramnios. 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. 125 (25%) of the 500 women had a preterm birth before 37 gestational weeks. These included 80 (20%) of 400 women with no FGR, 25 (50%) of 50 women with stage 1 FGR, 66.66% of women with stage 2 (n = 3), stage 3 (n =3), or stage 4 (n =2) FGR, and 12 (28.58%) of the 42 women with an SGA baby. The AUROC curves and the positive likelihood ratios for abnormal AFV and abnormal fetal Doppler parameters indicated that abnormal fetal Doppler and AFV did not have a good discriminatory ability for preterm births. Neither abnormal AFV nor abnormal fetal Doppler studies 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.

Conclusion: 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.

Keywords: Doppler Assessment, Amniotic Fluid Volume, Preterm Birth.

Introduction

The evaluation of fetal growth is one of the key objectives of prenatal care. Fetal growth depends on several factors, including uteroplacental function, maternal disease, maternal cardiovascular function or cardiac disease, maternal nutrition, altitude, smoking and illicit drug use, and presence of pathological conditions, such as infection, aneuploidy and some genetic conditions. However, uteroplacental insufficiency or dysfunction represents one of the most frequent causes of abnormal growth in an otherwise normal fetus. Impaired fetal growth is associated with an increased risk of perinatal mortality and morbidity, and long-term adverse infant outcome. [1] Overall, growth-restricted fetuses have a higher rate of conditions associated with prematurity [2], experience worse neurodevelopmental outcome and are at increased risk of non-communicable diseases in adulthood, such as hypertension, metabolic syndrome, insulin resistance, Type-2 diabetes mellitus, coronary heart disease and stroke. [3] Prenatal recognition of fetal growth restriction (FGR) is a major factor identified in strategies aimed at preventing stillbirth, in which up to 30% of cases are associated with FGR or small-for-gestational age (SGA) in the late third trimester. [4,5]

The rationale behind the application of Doppler velocimetry in fetal growth assessment is that it can

identify uteroplacental function through evaluation of the uterine and umbilical arteries. Uteroplacental insufficiency is putatively mediated through spiral artery maladaptation and alterations in the villous vascular tree. On the fetal side, Doppler velocimetry allows evaluation of the middle cerebral artery (MCA) and ductus venosus as fetal cardiovascular adaptation progresses from hypoxia to acidemia. A lack of physiological transformation of the uterine arteries from high- to low-resistance vessels is thought to reflect inadequate trophoblastic invasion of the spiral arteries, leaving a high-resistance circulation. The persistence of high uterine artery mean pulsatility index (PI) (above the 95th percentile) is associated with placental insufficiency and maternal vascular malperfusion of the placenta. [6] Progressively increasing PI in the UA corresponds to a progressive reduction in the placental surface area available for gas and nutrient exchange and increased fetal afterload resistance, and is associated with placental vascular insufficiency reflected by absent and, in the end-stage phase, reversed end-diastolic flow (EDF) in the UA. [7] Placental biomarkers have a potential role in screening, diagnosis and therapy of placental disease linked to hypertensive disorders of pregnancy and/or FGR. [8] Several placental factors have been investigated, including placental proteins as well as microRNA and mRNA. Some placental proteins, such as pregnancy-associated plasma protein-A, are biomarkers of placental function in the first trimester, though its predictive ability is limited. [9,10]

The aim of the present study was to determine the association and diagnostic effectiveness of abnormal Doppler and abnormal amniotic fluid volume (AFV) in the third trimester of pregnancy with preterm births.

Materials and Methods

The study population was recruited from at Department of Radiodiagnosis, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India for six months. All trimester-specific ultrasound and Doppler assessments were done. Total 500 women were included in the study. The data were collected prospectively and the study population included pregnant women with single-ton live fetuses. [11]

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 ≤ 5 cm or the absence of a pocket measuring at least 2 × 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. [12] 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. [12] The CPR was estimated by dividing the MCA PI by the UA PI. [14] A CPR PI < 5th was considered abnormal for the Samrakshan program. [13] 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. [14] A fetus was considered as small for gestational age (SGA) if the EFW was 3rd to10th percentile with normal Doppler indices. [14] 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 esti- mated 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

Table 1: Clinical and demographic details

Characteristic	Distribution
Age in years, mean ± SD	29.5 ± 4.6
Women aged > 35 years, n (%)	50 (10)
Gestational age at assessment, mean SD	33.7 ±2.6
Spontaneous Conception, n (%)	480 (96)
Nulliparous, n (%)	300 (60)
Chronic hypertension, n (%)	8 (1.6)
Diabetes Mellitus, n (%)	6 (1.2)
Systemic lupus erythematosus, n (%)	3 (0.6)
EFW < 3rd percentile, n (%)	30 (6)
EFW 3rd–10th percentile, n (%)	75 (15)
EFW 10th–50th percentile, n (%)	300 (60)
EFW > 50th percentile, n (%)	120 (19)
No FGR, n (%)	400 (80)
Stage 1 FGR, n (%)	50 (10)
Stage 2 FGR, n (%)	3 (0.6)
Stage 3 FGR, n (%)	3 (0.6)
Stage 4 FGR, n (%)	2 (0.4)
SGA, n (%)	42 (8.4)
Oligohydramnios, n (%)	100 (20)
Polyhydramnios, n (%)	10 (2)
Both liquor and fetal Doppler normal, n (%)	300 (60)
Both liquor and fetal Doppler abnormal, n(%)	50 (10)
Only fetal Doppler abnormal, n (%)	85 (17)
Only liquor abnormal, n (%)	65 (13)
Preterm preeclampsia, n (%)	15 (3)
Preterm births < 37 gestational weeks, n (%)	125 (25)
Birth weight in grams, mean SD	2720.1 ± 510.2
Birth weight < 2,500 g, n (%)	100 (20)
Stillbirths, n (%)	2 (0.4)
Neonatal mortality, n (%)	3 (0.6)

The clinical and demographic details of the 500 women screened in the third trimester. 60% had EFW 10th–50th percentile. And 80% had no FGR. 25% had Preterm births < 37 gestational weeks. 20% had Oligohydramnios and 2% had polyhydramnios.

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

Fetal Doppler parameter	*N*, % (95%CI)
Mean uterine artery PI > 95th percentile	40, 8 (5.2-9.2)
Umbilical artery PI > 95th percentile	60, 12 (10.0-15.2)
Middle cerebral artery PI < 5th percentile	55, 11 (9.0-14.0)
Cerebroplacental ratio < 5th percentile	60, 12 (9.9-15.0)
Any abnormal fetal Doppler	130, 26 (22.8-29.6)

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) was associated with the presence of abnormal AFV.

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=400)	80, 20% (15.2–21.9)
Stage 1 FGR (n =50)	25, 50% (37.5–61.1)
Stage 2 FGR (n =3)	2, 66.66% (9.5–90.6)
Stage 3 FGR (n =3)	3, 100% (34.2–100)
Stage 4 FGR (n =2)	0, 0.0
SGA (n =42)	12, 28.58% (16.8–40.3)

125 (25%) of the 500 women had a preterm birth before 37 gestational weeks. These included 80 (20%) of 400 women with no FGR, 25 (50%) of 50 women with stage 1 FGR, 66.66% of women with stage 2 (n = 3), stage 3 (n =3), or stage 4 (n =2) FGR, and 12 (28.58%) of the 42 women with an SGA baby.

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

Characteristics	Preterm births *n*, (%), 95% CI
Both fetal Doppler and liquor normal (n=300)	60 (20%) 17.3–25.5
Both fetal Doppler and liquor abnormal (n =50)	13 (26), 15.8–38.3
Only fetal Doppler abnormal (n=85)	32 (37.64), 28.3–46.1
Only abnormal liquor (n=65)	21 (32.30), 22.3–41.4
Mean uterine artery PI > 95th percentile (n =40)	16 (40), 29.7–57.8
Umbilical artery PI > 95th percentile (n =60)	21 (35), 22.7–43.0
Middle cerebral artery PI < 5th percentile (n =55)	14 (25.45), 17.8–38.1
Cerebroplacental ratio < 5th percentile (n=60)	20 (33.34), 23.1–43.5
Oligohydramnios (n=100)	27 (27%)
Polyhydramnios (n =10)	5 (50%)

Table 4 presents the distribution of preterm births by fetal Doppler and abnormal AFV in the screened population.

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	LRþ 95% CI
Abnormal liquor	26.4, 18.9–32.9	79.4, 74.5–82.1	29.4, 21.6–37.1	76.4, 71.3–79.2	0.54, 0.48–0.56	1.16, 0.86–1.62
Mean UtA PI > 95th percentile	12.8, 7.26–17.8	94.6, 92.2–96.5	44.7, 28.3–59.0	76.6, 72.1–79.2	0.55, 0.51–0.56	2.24, 1.25–3.91
Umbilical artery PI > 95th percentile	18.2, 11.9–24.1	88.4, 86.1–91.9	36.6, 25.3–47.6	75.5, 71.9–79.3	0.53, 0.50–0.57	1.64, 1.1–2.48
MCA PI < 5th percentile	13.7, 7.3—17.9	88.7, 85.7–91.6	27.3, 16.9–38.6	76.4, 70.9–78.2	0.52, 0.47–0.53	1.1, 0.65–1.75
CPR < 5th percentile	16.4, 10.3–22.1	88.7, 85.7–91.6	33.7, 22.2–44.1	75.4, 71.6–78.9	0.52, 0.49–0.55	1.4, 0.9–2.18

The AUROC curves and the positive likelihood ratios for abnormal AFV and abnormal fetal Doppler parameters indicated that abnormal fetal Doppler and AFV did not have a good discriminatory ability for preterm births. Neither abnormal AFV nor abnormal fetal Doppler studies 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, UA, MCA or CPR in a multivariate logistic regression model that adjusted for maternal age, EFW, type of conception and stages of FGR and SGA, and abnormal AFV.

Discussion

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.14,15 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. [14,15-18] 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. [14,15] Previous studies have reported that isolated oligohydramnios is not associated with adverse perinatal outcomes in fetuses that are not growth restricted. [19-21] Amniotic fluid may decrease progressively in early-onset FGR and 20 to 30% of cases may show oligohydramnios a week before acute deterioration. [22,23] 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.

The clinical and demographic details of the 500 women screened in the third trimester. 60% had EFW 10th–50th percentile. And 80% had no FGR. 25% had Preterm births < 37 gestationalweeks. 20% had Oligohydramnios and 2% had polyhydramnios. 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. 125 (25%) of the 500 women had a preterm birth before 37 gestational weeks. These included 80 (20%) of 400 women with no FGR, 25 (50%) of 50 women with stage 1 FGR, 66.66% of women with stage 2 (n = 3), stage 3 (n =3), or stage 4 (n =2) FGR, and 12 (28.58%) of the 42 women with an SGA baby. The AUROC curves and the positive likelihood ratios for abnormal AFV and abnormal fetal Doppler parameters indicated that abnormal fetal Doppler and AFV did not have a good discriminatory ability for preterm births. Neither abnormal AFV nor abnormal fetal Doppler studies 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. 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. [19-21] We found that 25% 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.

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 post neonatal period in India. [24] 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. We also found that 20% 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 ante- partum 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 inter- actions 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.

Conclusion

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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