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ORIGINAL PAPER

Efficacy of Pulsatility Index of Fetal Vessels in Predicting Adverse Perinatal Outcomes in Fetuses with Growth Restriction – Differences in Early- and Late-Onset Fetal Growth Restriction

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ABSTRACT

Background: *Doppler ultrasound of fetal vessels plays an important role in diagnosing fetal growth restriction (FGR). It also aids in early detection of fetal compromise and clinical decision making.*

Aim: *To determine the efficacy of the pulsatility index (PI) of the fetal umbilical artery (UA) and middle cerebral artery (MCA) in the third trimester of pregnancy for predicting adverse perinatal outcomes in the growth restricted fetuses. To study the differences in Doppler profiles in early- and late FGR (EFGR and LFGR, respectively) and their association with adverse outcomes.*

Materials and methods: *The study was approved by the Institute's Ethical Committee. Informed consent was taken from study participants. Eighty singleton pregnancies in the third trimester, which had been diagnosed with FGR, were studied. The UA and MCA Doppler PI and cerebroplacental ratio (CPR) (ratios of PI of MCA/UA) as well as perinatal outcomes were recorded. Adverse perinatal outcomes included perinatal death, hypoxia, seizures, respiratory distress, prolonged Neonatal Intensive Care Unit (NICU) stay, and low Apgar scores at one minute and five minutes. Statistical association of PI with adverse outcomes and differences in Doppler profiles of EFGR and LFGR were studied.*

Results: *Abnormal pulsatility in fetal vessels was associated with adverse perinatal outcomes. The UA PI was the most sensitive (66%) and CPR the most specific parameter (80%) for predicting adverse perinatal outcomes. Absent or reversal of diastolic flow in UA was associated with adverse perinatal outcomes in 75% and 40% of cases, respectively. The UA PI was the most sensitive parameter in both EFGR (70%) and LFGR (66%) and specific Doppler parameter in EFGR (75%). However, CPR and MCA PI were the most specific (89%) and diagnostically accurate in LFGR (79%).*

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Conclusion: *The UA PI is the most sensitive Doppler parameter for predicting adverse perinatal outcomes. Cerebroplacental ratio has a high specificity and accuracy and is an important parameter in LFGR cases.*

Keywords: fetal growth restriction, cerebroplacental ratio, perinatal outcomes, middle cerebral artery, umbilical artery, pregnancy-induced hypertension.

INTRODUCTION

Fetal growth restriction (FGR) is a commonly encountered complication in pregnancy, which has been associated with increased perinatal morbidity and mortality. It is a multifactorial condition, with one of the causes being placental insufficiency. The pathophysiology behind hypertensive disorders of pregnancy is a reduction in feto-placental circulation secondary to abnormal placental vascularity and placental ischemia (1). Hence, spectral Doppler evaluation of fetal and uterine vessels plays an important role in diagnosing and monitoring these conditions.

Doppler ultrasound aids in early detection of fetal compromise and is used for deciding the time and mode of delivery. Abnormalities in Doppler can help predict adverse perinatal outcomes (2).

The aim of our study was to determine the efficacy of the pulsatility index (PI) of the umbilical artery (UA) and middle cerebral artery (MCA) in the third trimester for predicting adverse perinatal outcomes in diagnosed cases of FGR. We have also studied differences in the Doppler profiles of early- and late FGR (EFGR and LFGR, respectively) and their association with adverse outcomes. ❑

MATERIALS AND METHODS

A prospective analytical cohort study was conducted in the Department of Radiodiagnosis of our Institution in collaboration with the Department of Obstetrics and Gynecology. The study was approved by the Institute's Ethical Committee. Informed consent was taken from all participants in the present study.

During the 18-month study period, 100 women were referred from the Department of Obstetrics and Gynecology; of which 80 (sample size) were available for follow-up.

Inclusion criteria

- Gestational age >28 weeks (third trimester)
- Ultrasonography (USG) diagnosed cases of FGR

Exclusion criteria

- Preexisting maternal comorbidities such as diabetes and renal failure
- All cases of maternal essential hypertension or chronic hypertension
- Fetal congenital anomalies diagnosed on USG which could result in growth restriction
- Twin pregnancies

Criteria for fetal growth restriction

All scans were done on a Philips IU22 ultrasound machine. The gestational age of the fetus was assigned according to the baseline scan which was done in the first trimester. Routine antenatal ultrasound biometric measurements were performed to estimate fetal weight and for growth monitoring. An estimated fetal birth weight (EFW)/abdominal circumference (AC) < third percentile or AC/EFW < 10^{th} percentile with deranged Doppler parameters (UA PI> 95^{th} percentile) for the gestation were the criteria set for FGR. Fetuses whose gestational age based on the above criteria was less than or equal to 32 weeks were classified as early-onset FGR (3, 4).

The diagnosis of PIH was done by obstetricians according to standard clinical criteria (5).

Doppler data acquisition

Doppler UA assessment was performed in a free loop of the cord in a longitudinal section. Fetal MCA (vessel in the near field) was evaluated using a two-mm pulsed-wave sample gate placed at the proximal third of the MCA at the level of the circle of Willis on an axial section of the fetal head. Using the tracer method, PI was calculated from the graphs obtained in the UA and MCA. The CPR ratio (PI MCA/PI UA) was also calculated. The spectral pattern of UA was studied for its diastolic flow pattern. Absence or reversal of end-diastolic flow (EDF) was recorded.

Parameter assignment

Assignment of parameters as normal/abnormal was based on the following criteria: UA PI values were based on nomogram charts given by Merz E

et al (6); MCA PI values were based on the chart given by Bahlmann *et al* (7); and CPR (MCA PI/ UA PI) ≤ 1.08 was considered abnormal (8).

The sample population was followed up and data regarding normal/abnormal perinatal outcomes were collected. Adverse outcomes, including stillbirth, perinatal deaths, perinatal seizures, hypoxia, abnormal Apgar scores at one minute and five minutes (a score of > 7 was taken as normal), sepsis, respiratory distress, necrotizing enterocolitis, and prolonged admission to NICU, were all recorded.

Fetuses with birth weight < 2500 grams were taken as low birth weight irrespective of the gestational age (9).

Statistical analysis

Data was analyzed using a SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. The Chi-square test or Fischer's exact test (for 2x2 tables only) was used as a test of significance for qualitative data. Continuous data were represented as mean and standard deviation. Independent t-test or Mann Whitney U test was used as a test of significance to identify the mean difference between two quantitative variables and qualitative variables, respectively.

Analysis of variance (ANOVA) or Kruskal Wallis test was the test of significance to identify the mean difference between more than two groups for quantitative and qualitative data, respectively.

The probability that the result is true (p-value) of < 0.05 was considered as statistically significant. ❑

RESULTS

In our study, the 80 participants had a mean age of 25 years. Of all subjects, 50 were primigravida and 30 multigravida. There were 36 cases of EFGR and 44 LFGR. Forty-two of all subjects had associated pregnancy-induced hypertension (PIH). Twenty LFGR and 22 EFGR cases had associated PIH. The mean amniotic fluid index (AFI) among subjects was 8.5 ± 3.4 cm.

In our study, 47 fetuses (58.2%) had a low birth weight (LBW). Adverse outcomes were seen in 39 (48.8%) newborns, of which eight had hypoxia, six seizures, 20 neonatal sepsis and 18 other conditions such as respiratory distress, necrotizing enterocolitis, etc. Amongst these fetuses, few had more than one adverse outcome. Thirty-eight neonates had a one-minute Apgar score of < 7 (Table 1).

There were seven cases of neonatal death. Forty-six of participants had to undergo an emergency caesarian section, with an abnormal CPR being seen in 14 of these cases. Thirty-three fetuses were born prematurely, of which 16 had an abnormal CPR.

TABLE 1. Distribution of adverse perinatal outcomes in fetuses*

S. No.	Adverse outcome	Number of fetuses
1.	Perinatal death	7
2.	Hypoxia	8
3.	Seizures	6
4.	Sepsis	20
5.	Low Apgar score	38
6.	Miscellaneous: NEC, prolonged NICU stay	18

*The number of cases to outcomes is not exclusive – few fetuses had more than one adverse outcome

TABLE 2. Statistical analysis of pulsatility index values of fetal vessels

Vessel	PI values	Adverse outcome	Normal outcome	p value	Sensitivity	Specificity	PPV	NPV	DA
UA	Abnormal	26	9	0.007	66%	78%	74%	71%	72%
	Normal	13	32						
MCA	Abnormal	21	10	<0.001	53.85%	75.61%	67.74%	63.27%	65%
	Normal	18	31						
MCA/UA (CPR)	Abnormal	25	8	<0.001	64%	80%	75%	70%	72%
	Normal	14	33						

PI=pulsatility index, MCA=middle central artery, UA=umbilical artery, PPV=positive predictive value, NPV=negative predictive value, DA=diagnostic accuracy

TABLE 3. Analysis of Doppler parameters with birth weight

Vessel	PI values	LBW	NBW	p value	Sensitivity	Specificity	PPV	NPV	DA
UA	Abnormal	30	5	0.001	63.83%	84.85%	85.71%	62.22%	72.5%
	Normal	17	28						
MCA	Abnormal	21	10	0.194	44.68%	69.7%	67.74%	46.94%	55%
	Normal	26	23						
MCA/UA PI (CPR)	Abnormal	27	6	<0.001	57.45%	81.82%	81.82%	57.45%	67.5%
	Normal	20	27						

PI=pulsatility index, MCA=middle central artery, UA=umbilical artery, CPR=cerebroplacental ratio, LBW=low birth weight, NBW-normal birth weight, PPV=positive predictive value, NPV=negative predictive value, DA=diagnostic accuracy

Vessel	PI values	Adverse outcome	Normal outcome	Sensitivity	Specificity	PPV	NPV	DA
UA	Abnormal	17	3	70	75	85	56	72
	Normal	7	9					
MCA	Abnormal	15	4	62	66	78	47	63
	Normal	9	8					
MCA/UA PI (CPR)	Abnormal	17	4	70	66	80	53	69
	Normal	7	8					

PI=pulsatility index, MCA=middle central artery, UA=umbilical artery, CPR=cerebroplacental ratio, PPV=positive predictive value, NPV=negative predictive value, DA=diagnostic accuracy

TABLE 4. Statistical analysis of Doppler parameters in early-onset fetal growth restriction

Vessel	PI values	Adverse outcome	Normal outcome	Sensitivity	Specificity	PPV	NPV	DA
UA	Abnormal	10	5	66	82	66	82	77
	Normal	5	24					
MCA	Abnormal	9	3	60	89	75	81	79
	Normal	6	26					
MCA/UA PI (CPR)	Abnormal	9	3	60	89	75	81	79
	Normal	6	26					

PI=pulsatility index, MCA=middle central artery, UA=umbilical artery, CPR=cerebroplacental ratio, PPV=positive predictive value, NPV=negative predictive value, DA=diagnostic accuracy

TABLE 5. Statistical analysis of Doppler parameters in late-onset fetal growth restriction

Correlating adverse perinatal outcomes with PI and CPR

An abnormal PI of the MCA (p=0.007), UA (p=0.001), and MCA/UA PI ratio (p=0.001) was associated with adverse perinatal outcomes (Table 2). The UA PI was the most sensitive and CPR the most specific parameter for predicting adverse outcomes. The UA PI and CPR showed an equal diagnostic accuracy of 72 %.

Correlating low birth weight with PI and CPR

Abnormal values of UA PI (p=0.001), and CPR (p=< 0.001) were associated with LBW fetuses (Table 3). The PI of MCA did not show any cor-

relation with birth weight. The diagnostic accuracy of the arteries in predicting LBW was as follows: UA (72%) > CPR (67%) > MCA (55%).

Early- *vs* late-onset fetal growth restriction – Doppler correlates

In our study there were 36 cases with early-onset FGR and 44 cases of late-onset FGR. The proportion of cases with adverse outcomes was higher in EFGR than LFGR: 66% (24 out of 36) and 44% (15 out of 44), respectively.

An abnormal UA PI was seen in 20 of all EFGR cases, of which 17 had adverse perinatal outcomes, with a positive predictive value of 85% (Table 4). In EFGR patients, both UA PI and CPR had an equal sensitivity of 70% in predicting adverse outcomes. However, UA PI had a higher specificity and diagnostic accuracy than the other parameters.

The number of fetuses with abnormal UA PI in LFGR was 15, of which 10 showed adverse outcomes. In this group, UA PI was the most sensitive parameter (66%). However, the specificity and diagnostic accuracy of MCA PI and CPR were higher than UA PI. Both MCA PI and CPR showed similar efficacy in predicting adverse outcomes (Table 5).

It was observed that MCA PI and CPR were more predictive for adverse outcomes in LFGR than EFGR (Tables 4 and 5).

Pulsatility index and birth weight correlation – EFGR and LFGR groups

Of the 80 studied cases, 47 fetuses (32 from the EFGR group and 15 from the LFGR one) had a low birth weight. All fetuses with abnormal UA PI in the EFGR group had a LBW. Seventeen of the 19 cases with abnormal MCA PI and 19 of the 21 cases with abnormal CPR had a LBW. The sensitivity of UA PI in predicting LBW was 62%, with 100% specificity in EFGR cases (Table 6).

In LFGR cases, UA PI had a sensitivity of 46%, and MCA PI and CPR had a specificity of 79% in predicting LBW (Table 7).

Correlation of spectral pattern in UA with perinatal mortality and morbidity

A total of seven fetal deaths were observed in our study, among which two (28%) showed absent end-diastolic flow and two (28%) reversal of diastolic flow.

In the total study population, reversal of end-diastolic flow was seen in five cases and absent end-diastolic flow (AEDF) in eight cases. A mor-

Vessel	PI values	SGA	AGA	Sensitivity	Specificity	PPV	NPV	DA
UA	Abnormal	20	-	62%	100%	100%	25%	91%
	Normal	12	4					
MCA	Abnormal	17	2	53%	50%	89%	11%	52%
	Normal	15	2					
MCA/UA CPR	Abnormal	19	3	59%	50%	86%	81%	61%
	Normal	11	3					

PI=pulsatility index, MCA=middle central artery, UA=umbilical artery, CPR=cerebroplacental ratio, PPV=positive predictive value, NPV=negative predictive value, DA=diagnostic accuracy

TABLE 6. Analysis of Doppler parameters with birth weight in early-onset fetal growth restriction

Vessel	PI values	SGA	AGA	Sensitivity	Specificity	PPV	NPV	DA
UA	Abnormal	7	8	46%	72%	46%	72%	63%
	Normal	8	21					
MCA	Abnormal	6	6	40%	79%	50%	71%	65%
	Normal	9	23					
MCA/UA CPR	Abnormal	6	6	40%	79%	50%	71%	65%
	Normal	9	23					

PI=pulsatility index, MCA=middle central artery, UA=umbilical artery, CPR=cerebroplacental ratio, PPV=positive predictive value, NPV=negative predictive value, DA=diagnostic accuracy

TABLE 7. Analysis of pulsatility index with birth weight in late-onset fetal growth restriction

S. No	Diastolic wave pattern in the umbilical artery	Total number of cases	Perinatal deaths	*Adverse outcomes	Low Apgar scores
1.	Absent diastolic flow	8	2	6	8
2.	Reversal of diastolic flow	5	2	3	

*Adverse outcomes excluding perinatal mortality

TABLE 8. Perinatal outcomes in fetuses showing absence or reversal of end-diastolic flow in the umbilical artery

tality rate of 40% (2/5) was associated with a diastolic reversal and 25% (2/8) with AEDF (Table 8).

Six out of the eight cases with AEDF had adverse perinatal outcomes, including two cases with respiratory distress and hypoxia, two sepsis, one necrotizing enterocolitis and one prolonged NICU stay. Three out of the five cases with reversal of diastolic flow showed adverse outcomes such as seizures and sepsis.

Both combined 13 cases showed AEDF or reversal of diastolic flow, of which eight fetuses had low APGAR scores at one minute and five minutes. ❑

DISCUSSION

Intrauterine growth restriction can result from multiple causes. Based on the underlying pathophysiology, FGR can result from disorders involving the placental circulation such as hypertensive disorders of pregnancy (HDP), maternal renal failure, or from non-vascular causes such as intrauterine infections, fetal chromosomal anomalies, etc. (10).

Depending on the time of onset, FGR can be classified as early-onset presenting before 32 weeks of gestation and late-onset presenting > 32 weeks (3, 4). Compared to LFGR, EFGR cases show more severe placental changes, increased association with PIH (70% compared to 10% in LFGR), and more severe Doppler changes (11). In our study, 61% of EFGR cases had associated PIH. Pregnancy-induced hypertension is correlated with defective placental trophoblastic invasion, which results in increased resistance in placental vessels seen as spectral changes in the umbilical arteries (12).

In FGR, the earliest changes to be observed are a decrease in diastolic flow in UA due to an increase in resistance that occurs in the small arteries and arterioles of the placental tertiary villi. With increasing uteroplacental insufficiency, redistribution of blood flow towards the fetal brain occurs, which is known as the 'brain-sparing effect' (13).

Spectral Doppler evaluation of fetal vessels is used for recognition of compromised fetal circulation and management of FGR. Umbilical artery Doppler serves as a valuable tool in predicting perinatal outcomes (14, 15).

In our study, UA PI was the most sensitive parameter for predicting adverse outcomes (85%). In previous studies by Nina *et al* (16) and BN Lakkar *et al* (17), the sensitivity of UA PI was 66% and 58%, respectively. However, the most sensitive overall parameter varied in different studies: MCA PI in the study by Nina *et al* (16), MCA/UA PI and MCA PI in BN Lakkar *et al* (17), and MCA/UA S/D ratios in S Shaheen *et al* (18).

Being a ratio, CPR can recognize even small changes occurring in the placental vessels and cerebral vessels secondary to decreased placental flow seen in FGR fetuses. Cerebroplacental ratio was found to be more sensitive than UA PI in mild cases of FGR and therefore, it serves as an important parameter in detecting mild FGR (19). An abnormal CPR denotes a brain-sparing effect and is a compensatory mechanism due to fetal hypoxia (15).

In our study, CPR was the most specific parameter, with a high positive predictive value. The sensitivity and diagnostic accuracy of CPR were close to that of UA PI (Table 2). A study conducted by Gaekwad *et al* (12), including 106 singleton pregnancies with PIH, showed the highest specificity (98.55%), PPV (94.44%), and diagnostic accuracy (80.19%) of CPR compared to PI of MCA or UA alone. In their study, 80% of fetuses with abnormal CPR were admitted to NICU and 70.6% had a low Apgar score (less than 7) at five minutes (12). Dunn *et al* (20) reviewed 21 studies regarding the utility of CPR at

term in predicting fetal outcomes and noted that an abnormal CPR was associated with low APGAR scores, NICU admissions, low birth weight, and emergency caesarian sections. In our study, an abnormal CPR was associated with adverse outcomes in 25 out of 33 cases (75%) (Table 2), and low birth weight fetuses in 27 out of 33 (81%) cases (Table 3).

Previous studies had shown an association between cerebral vasodilatation and long-term neurological complications in fetuses (21). However, TRUFFLE (22) and other studies found no such correlation (23, 24). The recommended criteria for termination of pregnancy in early-onset IUGR are based on cardiotocogram (CTG) and abnormalities in ductus venosus flow patterns, and not on cerebral vasodilatation (10).

The severity and temporal association of Doppler changes vary in early-onset and late-onset FGR. In a study conducted on 126 pregnant women with EFBW < 10% of gestational age, Novac *et al* (25) reported that umbilical and MCA Doppler abnormalities were more common in EFGR than LFGR. While UA abnormalities are more severe and are increasingly encountered in EFGR, they may be subtle in LFGR (18, 23, and 24). High impedance umbilical arterial flow and an overall decrease in fetal growth are seen in EFGR (19). In our study, 20 out of the 36 EFGR cases showed an abnormal UA PI, of which 17 had adverse fetal outcomes. The UA PI was the most sensitive, specific, and accurate parameter for predicting adverse outcomes and LBW in EFGR (Table 4).

An abnormal CPR was found to be superior to the biophysical profile in predicting adverse outcomes in EFGR cases (23). It was associated with low APGAR scores at fivemins, LBW weight, perinatal mortality, and NICU stay. In our study of EFGR cases, 19 of 22 fetuses with abnormal CPR had a LBW (Table 6) and 16 a low five-minute APGAR score of < 7. The seven neonatal deaths in our study were all in the EFGR group, and five of them had an abnormal CPR.

Decreased resistance in MCA with minimal UA changes is more common in LFGR (19). Late-onset FGR may even present with MCA abnormalities alone with normal UA Doppler parameters (27). The early onset of decreased resistance in MCA in LFGR has been attributed to an increased oxygen requirement of the brain at this gestational age (26). In our study, the number of LFGR cases with abnormal UA PI exceeded those with abnormal CPR/MCA PI (Table 5).

In the LFGR group, UA PI was the most sensitive parameter to predict adverse outcomes and LBW, and the positive predictive value, specificity and diagnostic accuracy of CPR and MCA were higher than UA PI. Five cases of LFGR showed an abnormal CPR and a normal UA PI, and three of them had low APGAR scores at birth.

Figueras *et al* observed that the late-onset FGR fetuses were less tolerant to hypoxia and acute fetal compromise, which could result in increased perinatal morbidity despite normal Doppler parameters (19). In in our study, two of the LFGR group of fetuses with adverse perinatal outcomes had normal Doppler parameters but prolonged NICU stay, both owing to hypoxia.

Absent or reversal of end-diastolic flow in UA are signs of significant placental compromise and are associated with increased fetal morbidity and mortality (10), with possible long-term neurological deficits compared to fetuses with preserved diastolic flow (28). Studies have shown that absence or reversal of end-diastolic flow predicted adverse outcomes better than CPR in EFGR (29).

In our study population, we found that absent/reversal of EDF was associated with low five-minute APGAR scores in eight (61%) out of 13 cases and NICU admissions in 12 (92%) cases. In our study, mortality in cases with AEDF and REDF was 25% and 40%, respectively, which was in agreement with the study by Gerber *et al* (29), wherein mortality was 22%.

The estimated fetal birth weight and Doppler parameters are helpful in monitoring fetal well-being, timing the delivery and planning the mode of delivery. In cases where the EFBW is < 10^{th} percentile and < third percentile with normal doppler parameters, the risk of still birth is low and Doppler studies are repeated every fortnightly. In cases where in the UA PI > 95^{th} percentile and CPR < 5th percentile, Doppler studies are repeated 1-2 times/week, and steroids administered for lung maturation. The risk of still birth is high in cases with absent (6.8%) or reversal of end diastolic flow (19%), which require inpatient monitoring with Doppler repeated every second day (30).

Based on the above recommendations, pregnant women need to be counselled regarding

the risk to the fetus and the need for close monitoring. ❑

CONCLUSIONS

An abnormal PI of the fetal vessels is associated with adverse perinatal outcomes. The UA PI is the most sensitive parameter and CPR the most specific parameter for predicting adverse perinatal outcomes. Doppler profiles in early-onset and late-onset FGR cases are different. For predicting adverse outcomes in EFGR, both UA PI and CPR are equally sensitive, and UA PI remains the most specific and accurate parameter. However, in LFGR, though UA PI is the most sensitive parameter, CPR is the most specific and accurate one. Absent or reversal of end-diastolic flow in the UA indicates a severe prognosis with increased perinatal mortality. ❑

Informed consent: obtained from all participants, including a statement that images/data may be used for publication purposes with anonymity.

Data availability: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest: none declared.

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