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Evaluation of the relation between cerebroplacental ratio, umbilical-cerebral ratio, and cerebro-placental-uterine ratio with the occurrence of adverse perinatal outcomes in pregnancies complicated by fetal growth restriction

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Abstract

Introduction: Fetal growth restriction (FGR) is a major obstetric complication associated with an increased risk of adverse perinatal outcomes.

Objectives: This study aimed to evaluate the relationship between Doppler parameters, including the cerebroplacental ratio (CPR), umbilicocerebral ratio (UCR), and cerebro-placental-uterine ratio (CPUR), with adverse perinatal outcomes in singleton pregnancies complicated by FGR.

Patients and Methods: This was a prospective study of 100 women with a singleton pregnancy 28 and 36.8 weeks of gestation was complicated by FGR and mild abnormalities. Feto-maternal Doppler examinations were conducted by the CPR, UCR, and CPUR parameters. Adverse outcomes were defined as Apgar score <7 at 5 minutes, preterm birth <37-week, neonatal intensive care unit (NICU) admission, fetal distress, and emergency cesarean section. These outcome parameters were checked with the results of the last ultrasound which performed 1-2 weeks before delivery.

Results: Mean umbilical artery pulsatility index (UA-PI) (1.18 ± 0.31 versus 1.04 ± 0.21, P = 0.010) and mean uterine arteries (UtAs)-PI (1.18 ± 0.45 versus 0.96 ± 0.36, P = 0.20) were significantly higher in pregnancies that experienced adverse perinatal outcomes than those that did not experience them. Mean CPUR (1.82 ± 1.03 versus 2.25 ± 0.83, P = 0.039) was significantly lower in pregnancies that experienced adverse perinatal outcomes versus those that did not. In binary multivariate logistic regression analysis, CPR, UCR, and CPUR parameters were evaluated with adverse perinatal outcomes. Only CPUR had a significant relationship with adverse perinatal outcomes. CPUR had a substantial relationship with Apgar score <7 at 5 minutes (OR: 0.13; 95% CI: 0.02-0.63; P = 0.012).

Conclusion: CPUR is a new Doppler ratio associated with adverse perinatal outcomes in FGR pregnancies with minimal abnormalities.

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Introduction

Fetal growth restriction (FGR) is a serious obstetric complication in 5%–10% of pregnancies (1). It has a relationship with an increased risk of adverse perinatal outcomes, such as stillbirth, preterm birth, fetal acidosis, and low-Apgar score (1,2). FGR is the inability of a fetus to grow to its genetically determined size (3). FGR definitions varied between different guidelines and author groups. The international Delphi consensus defines FGR as the most recognized definition of FGR.

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) defines FGR according to Delphi consensus criteria. It includes estimated fetal weight (EFW) or abdominal circumference (AC)<3rd percentile or EFW or AC<10th percentile combined with abnormal Doppler information or a decline in growth centile (4).

Prediction of adverse perinatal outcomes is one of the main purposes of obstetrical practices in late pregnancy in pregnancies affected by FGR. Fetal Doppler ultrasound significantly improves surveillance and management, leading to improved results for perinatal mortality and morbidity (5,6).

The main challenges in pregnancies affected

Key point

The aim of this study was to evaluate the relationship between Doppler parameters including the CPR, UCR, and CPUR with adverse perinatal outcomes in singleton pregnancies complicated by FGR. The results showed CPUR is a novel Doppler ratio that is associated with adverse perinatal outcome in FGR pregnancies with minimal abnormalities.

by FGR are the evaluation of intrauterine fetal risks and the ideal timing of pregnancy termination. The survival of FGR pregnancies has improved with Doppler ultrasound (1).

An increase in blood flow resistance in the uterus, placenta, and fetal vessels is the cause of uteroplacental insufficiency. In pregnancies with uteroplacental insufficiency, the umbilical artery (UA) and maternal uterine arteries (UtAs) show increased resistance (7,8). The fetus can redistribute blood flow to vital organs such as the heart, brain, and adrenal glands. Vasodilatation of the fetal brain vasculature is identified as decreased pulsatility index (PI) of the middle cerebral artery (MCA) (8).

Doppler information obtained from the placental, uterine, and fetal vasculature improves uteroplacental insufficiency detection in the near term.

According to the false negative results of Doppler of the UA in fetus with FGR, the cerebral-placental ratio (CPR) has been conducted as a more sensitive test (9).

Several Doppler parameters have been associated with adverse perinatal outcomes in pregnancies complicated by late FGR (FGR ≥32 weeks). The low PI in the MCA, or CPR, relates to admission to the neonatal intensive care unit (NICU) and abnormal acid-base status. Also, the higher rate of Cesarean section due to fetal distress is related to increased resistance in the uterine arteries (UtAs) (10-12).

Alongside MCA and UA Doppler anomalies, the relations of these two components – CPR, described as the ratio between the MCA and UA-PI, and the inverse ratio, shown as the umbilicocerebral ratio (UCR), have been known to be more accurate predictors of perinatal complication than their components (13,14). In comparison between these two indices, CPR has been widely studied and is commonly used in clinical studies. In contrast, UCR has been less studied in FGR pregnancies. The TRUFFLE study explained that in the fetus with early FGR (FGR <32 weeks), the UCR showed better separation in the abnormal values than the CPR for survival at two years without neural development defects (15).

Some studies found no advantage in using the UCR over the CPR in pregnancies with FGR in predicting complications such as Apgar <7 at 5 minutes, umbilical cord pH <7.10, neonatal special care unit admission, grade III/IV intraventricular hemorrhage and neonatal death (16).

Therefore, it is worthwhile to see whether adding other Doppler parameters, such as the mean UtAs-PI, might increase its diagnostic accuracy. In this regard, the utility of CPR has been recently challenged by a novel Doppler parameter, the cerebro-placental-uterine ratio (CPUR), which has been shown in a few studies to improve its accuracy (8,17).

A Doppler index that integrates all information from the placental, uterine and fetal vasculature can improve the diagnosis of placental insufficiency in term pregnancies compared to CPR and UCR even more (18,19). FGR is a major and common obstetric complication that is challenging to determine fetal health and predict adverse perinatal outcomes (16).

Objectives

Our study explored the association between maternal, fetal, and placental Doppler parameters, including the CPR, UCR and CPUR and composite and individual adverse perinatal outcomes in singleton pregnancies affected by FGR.

Patients and Methods

This was a prospective study of 100 women with a singleton pregnancy 28 and 36.8 weeks of gestation was complicated by FGR and mild abnormalities.

Study design

Inclusion criteria were singleton pregnancies over 18 years old, gestational age between 28.0 weeks and 36.8 weeks. The gestational age was estimated from the last menstrual period and the first trimester crown-rump length. If the difference was more than 7-day, we calculated gestational age from the first trimester crown-rump length (9). Management, timing and method of delivery were managed in accordance to our national guidelines.

Women were chosen if they have singleton pregnancy and over 18 years old, without underlying disease and their first trimester fetal screening tests and mid-trimester anomaly scans were normal. The inclusion criteria were singleton pregnancies over 18 years old, 28 and 36.8 weeks of gestation complicated by FGR according to ISOUG-FGR definition following the Delphi consensus criteria (4) and FGR with mild abnormalities according to FIGO initiative on fetal growth (20, 21):

Estimated fetal weight (EFW) ratio <3rd percentile or AC <3rd percentile or at least 2 out of 3 of the following items:

- EFW or AC <10th percentile
- EFW or AC crossing percentiles >2 quartiles on growth percentiles
- UA-PI >95th percentile or MCA <5th percentile or CPR <5th percentile or UtAs-PI >95th

The exclusion criteria were considered fetal infection, antepartum hemorrhage, low-lying placenta, multiple gestations, ruptured membranes, pregnancies affected by chromosomal or structural anomalies, and maternal underling diseases such as respiratory diseases, hypertension, heart diseases, vascular and autoimmune diseases. Correspondingly, we excluded patients with absent or reverse UA Doppler and abnormal Doppler ductus venosus.

The fetal weight determined by Hadlock's formula (22). Doppler measurements of above arteries were obtained when the fetus was inactive and was not in breathing.

Pulsed Doppler information were obtained from 3 or more similar and continued waveforms by utilizing ultrasound machines Philips affinity 70 with a 2-9 MHz convex probe, during fetal inactivity, without fetal tachycardia, with an angle close to 0°. The UA was measured at a free loop of the umbilical cord. The MCA was measured at the point at which MCA transients of the sphenoid wing, near to the circle of Willis (13). The renal arteries Doppler were measures with an angle of less than 30°, in a coronal view, with emplacement of the Doppler gate 1-2 mm from the source of the renal artery of descending aorta. The renal artery closer to the probe was selected if both were easily seen. For UtAs examination, the probe was located in each of the iliac fossa and the waveforms were recorded within 1 cm from the point at where the uterine artery crosses the external iliac artery (8), then their average was calculated. Patients underwent serial ultrasounds (Doppler weekly, biophysical profile/ non-stress test, 1-2 times per week, growth velocity every 2 weeks) and the last Doppler measures that obtained 1-2 weeks before delivery were determined for the analysis.

The feto-maternal-placental Doppler examinations including UA, PI, mean UtAs-PI, MCA-PI, and renal artery-PI in all cases were measured. The Doppler measurements were done by qualified investigators with adequate experience in our prenatal clinic. We conducted the recommendations of the ISUOG and national guidelines for prenatal diagnosis and management (18, 23). Mean UtAs-PI was calculated as the average PI of left and right UtAs, CPR was shown as MCA-PI/UA-PI. UCR was the inversion of CPR. CPUR was calculated as CPR/ mean UtAs-PI. Additionally, UA-PI and mean UtAs-PI were known as abnormal when they were >95th percentile (18). CPR and MCA-PI were known as abnormal when they were <5th percentile (18).

In order to adjust for the effect of the gestational age, EFW values and Doppler values were converted into centiles. These conversions were done according to references earlier published (17). Related outcome indices were method of delivery, Apgar score <7 at 5 minutes, gestational age at birth, admission to NICU and fetal distress. These outcome parameters checked with the results of the last ultrasound that performed 1-2 weeks before delivery and the relationship between adverse perinatal outcomes and Doppler parameters evaluated.

Adverse outcomes were defined as emergency cesarean section, preterm birth <37-week, Apgar score <7 at 5 minutes, fetal distress, and neonatal admission to the special care unit (10).

Emergency cesarean section defined as the cesarean section due to fetal distress, contraction in the previous cesarean, arrest of labor and other maternal and fetal causes of emergency termination of pregnancies.

Fetal distress is defined as the having a pathological or suspicious change in the cardiotocography tracings demonstrated by investigators according to the FIGO guidelines on cardiotocography (5).

Statistical analysis

We descripted qualitative variables with percentage and quantitative variables with mean and standard deviation and we used chi-square and *t* test for their comparison. Logistic regression models used for the prediction of adverse perinatal outcomes and CPR, UCR, and CPUR. Normal distribution of the collected data was assessed using the Kolmogorov–Smirnov test. All statistical analyses were performed using SPSS 25 software. All accomplished statistical tests were performed with a significance level of 0.05.

Results

This study included 100 singleton pregnancies 28 and 36.8 weeks of gestation affected by FGR that met the inclusion criteria. Descriptive information of women and Doppler parameters are shown in Table 1.

The mean of maternal age was 31.77 (±5.61) years and 43% of women were nulliparous. The mean of gestational age at delivery was 36.5 (±1.68) weeks and the mean of birthweight was 2246.5 (±453.8) gram. No stillbirth occurred in this cohort study but there were four cases

Table 1. General characteristics of the study population

Variable	All pregnancies (n = 100)
Antenatal variables	
Age, years (Mean ± SD)	31.77 ± 5.61
BMI kg/m^2 (Mean ± SD)	23.49 ± 4.3
Parity (Median ± IQR)	2 ± 2
Nulliparous, n (%)	43 (43%)
Prenatal Doppler variables	
UA-PI (Mean±SD)	1.13 ± 0.29
MCA-PI (Mean±SD)	2.00 ± 0.47
UtAs-PI (Mean ± SD)	1.11 ± 0.43
Renal PI (Mean ± SD)	2.17 ± 0.45
CPR (Mean ± SD)	1.87 ± 0.60
UCR (Mean± SD)	0.62 ± 0.35
CPUR (Mean ±SD)	1.97 ± 0.98
UA-PI >95th percentile, n (%)	30 (30%)
MCA-PI<5th percentile, n (%)	18 (18%)
UtAs-PI >95th percentile, n (%)	35 (35%)
Abnormal renal PI, n (%)	26 (26%)

IQR; Interquartile range, MCA; Middle cerebral artery, UA; Umbilical artery, CPR; Cerebroplacental ratio, UCR; Umbilicocerebral ratio, CPUR; Cerebro-placental-uterine ratio, SD; Standard deviation, PI; Pulsatility index, BMI; Body mass index; UtAs, Uterine arteries.

of neonatal death, two cases abruption and one case complicated with preeclampsia.

Concerning delivery 10% had an Apgar score <7 at 5 minutes, 33% had admission to NICU, 43% had fetal distress, and 30% had preterm birth <37 week. Emergency cesarean section occurred in 48%.

Mean UA-PI (1.18 ± 0.31 versus 1.04 ± 0.21, P = 0.010) and mean UtAs-PI (1.18 ± 0.45 versus 0.96 ± 0.36, P = 0.20) were significantly higher in pregnancies that experienced adverse perinatal outcomes versus those that did not experience them. Mean CPUR (1.82 ± 1.03 versus 2.25 ± 0.83, P = 0.039) was significantly lower in pregnancies that experienced them than those that did not (Table 2).

In our study at least one adverse perinatal outcome occurred in 66 of 100 cases (66%). Furthermore UA PI >95th percentile (P = 0.017), UtAs PI >95th percentile (P<0.001), and abnormal renal PI (P = 0.020) were significantly higher in pregnancies that experienced compared to those did not experience composite adverse outcome (Table 2).

In univariate logistic regression analysis individual Doppler parameters (UA-PI >95th percentile, MCA-PI<5th percentile, uterine arteries PI >95th percentile and abnormal renal PI were evaluated with premature birth, fetal distress, Apgar at <7 at 5 minutes, NICU admission and emergency cesarean section (Table 3).

In binary multivariate logistic regression analysis CPR, UCR, and CPUR parameters evaluated with premature birth, Apgar at <7 at 5 minutes, NICU admission, fetal distress and emergency cesarean section and only CPUR had a significant relationship with adverse perinatal outcomes (Table 4).

In this study the relationship between combined Doppler parameters CPR, UCR and CPUR and adverse perinatal outcomes investigated. CPUR had a significant relationship with Apgar score <7 at 5 minutes (OR: 0.13; 95% CI: 0.02-0.63; P = 0.012). High CPUR reduces the chance of Apgar score <7 at 5 minutes by 87%.

Discussion

Fetal growth restriction is the inability of a fetus to grow to its genetically determined size (3). It is associated with a marked increase in perinatal complications (3). Sheppard and Bonnar explained that in FGR pregnancies, regardless of whether there is preeclampsia or not, atheromatous-like lesions partially or completely occluded the spiral arteries. These changes were not seen in pregnancies with preeclampsia in the absence of FGR (24). Pathological studies have shown that increased resistance in the umbilical arteries becomes obvious if there is at least 60% destruction of the placental vessels (8). In fetal hypoxemia, there is an increase in redistribution blood flow to the heart, brain, spleen and adrenal glands. In pregnancies with FGR, resistance to blood flow in the uterine arteries is elevated. The fetus with FGR is at risk during pregnancy, labor, and after birth. Fetal Doppler information are conducted as indirect values of fetal well-being, which is based on the Doppler parameters of blood flow redistribution in the fetus (25). Considering the false positive results of UA Doppler in fetus with FGR, the use of CPR as a more sensitive test was recommended (9).

While uterine arteries PI and CPR are associated independently with pregnancy impairments in pregnancies with late FGR, but their diagnostic accuracy for composite adverse perinatal outcome is low (10). Although CPR in some studies predicts adverse perinatal outcome independently, the advantages of uteroplacental cerebral ratio in predicting FGR have not been completely evaluated. Perinatal diagnosis and management of late FGR is challenging; therefore, the new Doppler ultrasound indices such as utero-placental-cerebral ratio could demonstrated to be vital in the prompt detection and

Table 2. Comparison between the different Doppler indices in fetuses with and without adverse perinatal outcomes

	Composite adverse outcome (n= 66)	No adverse outcome (n=34)	*P* value
UA-PI (Mean ± SD)	1.18 ± 0.31	1.04 (0.21)	0.010
MCA-PI (Mean ± SD)	2.00 ± 0.48	1.98 (0.46)	0.848
UtAs-PI (Mean ± SD)	1.18 ± 0.45	0.96 (0.36)	0.020
Renal PI (Mean ± SD)	2.11 ± 0.42	2.29 (0.49)	0.060
CPR (Mean ± SD)	1.82 ± 0.63	1.98 (0.52)	0.204
UCR (Mean ± SD)	0.64 ± 0.34	0.57 (0.36)	0.350
CPUR (Mean ± SD)	1.82 ± 1.03	2.25 (0.83)	0.039
UA-PI > 95th percentile, n (%)	25 (37.9%)	5 (14.7%)	0.017
MCA-PI <5th percentile, n (%)	15 (22.7%)	3 (8.8%)	0.105
CPR<5th percentile, n (%)	9 (13.6%)	2 (5.9%)	0.324
UtAs-PI >95th percentile, n (%)	32 (48.5%)	3 (8.8%)	<0.001
Abnormal renal PI	22 (33.3%)	4 (11.8%)	0.020

Composite adverse perinatal outcome defined as the presence of any one of the following: Apgar <7 at 5 min, NICU admission, preterm birth, fetal distress and emergency cesarean section, MCA, middle cerebral artery; UA, umbilical artery; CPR, cerebroplacental ratio; CPUR; Cerebro-placental-uterine ratio, PI; Pulsatility index, UCR; Umbilicocerebral ratio, SD; Standard deviation; UtAs, Uterine arteries.

Table 3. Univariate logistic regression analysis for prediction of adverse outcome by combining different parameters

	Parameters[a]	OR (CI 95%)	*P* value[b]
Premature birth <37 week	MCA-PI<5th percentile	5.21 (1.77-15.30)	0.001
	UtAs-PI >95th percentile	5.83 (2.30-14.75)	<0.001
	UA-PI >95th percentile	2.95 (1.19-7.32)	0.017
Fetal distress	UA-PI >95th percentile	2.70 (1.21- 6.50)	0.025
	Abnormal renal PI	2.78(1.10-6.99)	0.026
	UtAs-PI >95th percentile	2.43 (1.05-5.64)	0.036
NICU admission	UA-PI>95th percentile	5.50 (2.17-13.89)	<0.001
	MCA-PI<5th percentile	4.28 (1.47-12.44)	0.005
	UtAs-PI >95th percentile	4.32 (1.77-10.53)	0.001
	Abnormal renal PI	5.36 (2.05-13.98)	<0.001
Emergent cesarean	Abnormal renal PI	3.30 (1.27- 8.56)	0.012

[a] Parameters that showed highest predictive values for adverse outcome in our analysis.
[b] Significant as $P<0.05$.
NICU, neonatal intensive care unit; UA, umbilical artery; MCA, middle cerebral artery; PI; Pulsatility index, UtAs, Uterine arteries.

- MCA PI< 5th percentile increased the chance of preterm birth by 5.2 times ($P= 0.001$)and NICU admission by 4.2 times ($P= 0.005$).
- Umbilical PI > 95th percentile increased the chance of preterm birth by 2.9 times ($P= 0.017$), fetal distress by 2.7 times ($P= 0.025$) and NICU admission by 5.5 times ($P< 0.001$).
- Uterine arteries PI>95th percentile increased the chance of preterm birth by 5.8 times ($P<0.001$), fetal distress by 2.4 times ($P= 0.036$) and NICU admission by 4.3 times ($P= 0.001$)
- Abnormal renal PI increased the chance fetal distress by 2.7 times (P=0.026), NICU admission by 5.3 times ($P< 0.001$) and emergence cesarean by 3.3 times ($P= 0.012$).

Table 4. Results of binary multivariate logistic regression analysis for FGR pregnancies

Adverse perinatal outcome	CPR		UCR		CPUR	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Premature birth <37 wk	0.81 (0.15-4.45)	0.817	1.44 (0.14-14.31)	0.755	0.64 (0.29-1.40)	0.267
Apgar <7 at 5 min	0.29 (0.00-29.27)	0.600	0.00 (0.00-95.24)	0.251	0.13 (0.02-0.63)	0.012
Emergent cesarean	1.14 (0.28-4.63)	0.855	1.07 (0.13-8.35)	0.948	0.91 (0.49-1.66)	0.760
Fetal distress	0.85 (0.19-3.68)	0.834	1.87 (0.20-17.22)	0.579	0.97 (0.52-1.81)	0.940
Admission to NICU	0.17 (0.02-1.25)	0.083	0.50 (0.04-6.34)	0.600	0.79 (0.36-1.74)	0.565

UCR, umbilical-cerebral ratio; CPR, cerebroplacental ratio; CPUR, cerebroplacental uterine ratio; CI, confidence interval; NICU, neonatal intensive care unit.
Significant as $P<0.05$

management of pregnancies complicated by late FGR (26).

The results of our study showed a significant association of CPUR with adverse perinatal outcomes.

Previously Yang et al in a prospective cohort study of singleton pregnancies with late FGR (n=114) showed a novel index, the uteroplacental cerebral ratio that defined as (UA-PI + mean UTAs-PI)/MCA-PI had a higher sensitivity (80.5%) and a specificity (72.9%) for prediction of adverse outcomes in pregnancies with FGR than mean uterine arteries and CPR, accordingly explained that uteroplacental cerebral ratio may be used as a better prediction parameter for prognostic detection of late FGR (26).

Increased uterine artery resistance may explain impaired maternal uterine perfusion to the placental bed, raised UA-PI indicates raised placental resistance to fetal blood flow and thus decreased nutrient and oxygen transfer. The fetal adaptation for maximizing oxygenation of the brain is decreased cerebral vascular resistance. Higher UtAs-PI and lower CPR measurements have been related with adverse outcomes in SGA infants such as neonatal acidosis, NICU admission, fetal distress, and perinatal mortality (8).

In our study CPUR had a significant relationship with Apgar <7 score at 5 minutes and high CPUR reduced the chance of low Apgar by 87%.

Macdonald et al in a prospective cohort study in a population of 347 pregnancies affected by FGR showed that a new combination of Doppler parameters, CPUR had the strongest relationship with other main parameters of placental dysfunction, such as fetal growth velocity in third-trimester and neonatal fat information. The CPUR may cause to better detection of fetus at increased risk of adverse outcomes that can advantage from necessary intervention (8).

A retrospective cohort study in a population of 114 patients, Graupner et al showed that CPUR is a predictive index in >40 weeks for composite adverse perinatal outcome and cesarean delivery due to intrapartum fetal distress in low-risk pregnancies (18).

The findings from our study showed that the UCR and CPR are not significantly associated with adverse perinatal outcomes in pregnancies by FGR.

Recently, several studies have shown that CPR could play a role in predicting adverse perinatal outcomes in pregnancies with placental insufficiency without FGR. CPR could be used as a screening test for adverse perinatal outcome for general population (6). The low CPR is related to perinatal impairment at term, but the poor diagnostic accuracy prevents the possibility of accepting CPR as a screening test (27).

Earlier, Di Mascio et al in a multicenter retrospective cohort study with 312 pregnancies affected by FGR showed CPR and UCR were significantly related with adverse perinatal outcomes in pregnancies affected by late FGR; however, they have a poor prognostic accuracy when converting these figures into predictive models on their own (13).

A few studies have paid attention to UCR that determined whether it could be recommended as a proper predictor of pregnancy outcomes (5).

A secondary analysis of the TRUFFLE study with the purpose of evaluation the relationship between CPR, MCA, and UCR with the neonatal and 2-year infant outcome showed that the UCR had better separation in the abnormal range for survival without neural development defects (OR: 0.88; CI: 0.78–0.99) (14). There are opposite results about both parameters, since some authors have supported that their use for screening is limited. The value of either UCR or CPR for predicting adverse pregnancy and neonatal outcomes is limited (28).

This is consistent with a recent meta-analysis that described the limited value of these indices for prediction of adverse perinatal outcomes (28).

This limitation could be related to the new FGR definition that most fetuses will actually have a CPR<5^{th} percentile, therefore, its use for differentiating fetuses at risk becomes trivial (13-29).

In another study by Leavitt et al that was a second analysis of multicenter prospective cohort study on 197 pregnancies of 26 and 36.8 weeks, which complicated by FGR did not find any benefit in using the UCR over CPR (16).

Similarly, a large prospective observational study for late-onset FGR by Akolekar et al showed that the utilizing of CPR in the prediction of adverse pregnancy outcome was poor, especially for birth weight <3^{th} percentile, cesarean section due to fetal distress and fetal acidosis (30).

The finding that UCR had a low-utility in predicting adverse perinatal outcomes was too similar to the finding reported in a study by Kalafat and colleagues (15).

The strengths of our study related to its prospective design and the utilizing of simple, reproducible and confirmed ultrasound methods. Another strength is the uniform high-quality data, because all ultrasound measurements performed by qualified researchers with adequate experience.

The limitations of this study are relatively small sample size, and lack of histological evaluation of the placenta, that can be useful in better understanding the role of Doppler parameters.

Conclusion

Fetal growth restriction is associated with long-term and short-term complications specifically neural developmental disturbances in fetuses with cerebral redistribution, early detection is essential to prevent adverse outcomes in pregnancies affected by FGR. The prenatal detection of FGR in third trimester is challenging, thus, the novel ultrasound parameters such as CPUR could be important in the rapid diagnosis and management. CPUR is a new Doppler ratio associated with adverse perinatal outcomes in FGR pregnancies with minimal abnormalities. For using the CPUR into clinical work, published CPUR reference measures and more prospective documents are required.

Limitations of the study

One of the limitations of this study is a relatively small sample size. Additionally, data on histological evaluation of the placenta are lacking, which would have been useful to understand better the role played by each Doppler parameter.

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Authors' contribution

Conceptualization: SK, BM.
Methodology: SK, BM.
Validation: SK, BM, FF, EZ.
Formal analysis: MJT, SK, BM.
Investigation: SK, BM.
Resources: SK, BM.
Data curation: MJT, SK, BM.
Writing–original draft: BM.
Writing–review and editing: SK, BM.
Visualization: SK, BM.
Supervision: SK, BM.
Project administration: SK, BM.
Funding acquisition: SK, BM.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This study was a prospective study performed in Beheshti hospital, a tertiary perinatology hospital in Isfahan, Iran (between December 2021 and November 2022), which was approved by the Ethics

Committee of Isfahan University of Medical Sciences (Ethical code #IR.MUI.MED.REC.1401.235). Informed written consent was obtained from all participants before their enrolment. Besides, the authors have entirely observed ethical issues, including plagiarism, data fabrication, and double publication.

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References

1. Coenen H, Braun J, Köster H, Möllers M, Schmitz R, Steinhard J, et al. Role of umbilicocerebral and cerebroplacental ratios in prediction of perinatal outcome in FGR pregnancies. Arch Gynecol Obstet. 2022;305:1383-92. doi: 10.1007/s00404-021-06268-4.
2. Khalil A, Morales-Rosello J, Khan N, Nath M, Agarwal P, Bhide A, et al. Is cerebroplacental ratio a marker of impaired fetal growth velocity and adverse pregnancy outcome? Am J Obstet Gynecol. 2017;216:606.e1-606.e10. doi: 10.1016/j.ajog.2017.02.005.
3. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018;218:S745-S61. doi: 10.1016/j.ajog.2017.11.577.
4. Roeckner JT, Pressman K, Odibo L, Duncan JR, Odibo AO. Outcome-based comparison of SMFM and ISUOG definitions of fetal growth restriction. Ultrasound Obstet Gynecol. 2021;57:925-30. doi: 10.1002/uog.23638.
5. Di Mascio D, Rizzo G, Buca D, D'Amico A, Leombroni M, Tinari S, et al. Comparison between cerebroplacental ratio and umbilicocerebral ratio in predicting adverse perinatal outcome at term. Eur J Obstet Gynecol Reprod Biol. 2020;252:439-43. doi: 10.1016/j.ejogrb.2020.07.032.
6. Buca D, Liberati M, Rizzo G, Gazzolo D, Chiarelli F, Giannini C, et al. Pre- and postnatal brain hemodynamics in pregnancies at term: correlation with Doppler ultrasound, birthweight, and adverse perinatal outcome. J Matern Fetal Neonatal Med. 2022;35:713-9. doi: 10.1080/14767058.2020.1731456.
7. Miranda J, Rodriguez-Lopez M, Triunfo S, Sairanen M, Kouru H, Parra-Saavedra M, et al. Prediction of fetal growth restriction using estimated fetal weight vs a combined screening model in the third trimester. Ultrasound Obstet Gynecol. 2017;50:603-11. doi: 10.1002/uog.17393.
8. MacDonald TM, Hui L, Robinson AJ, Dane KM, Middleton AL, Tong S, et al. Cerebral-placental-uterine ratio as novel predictor of late fetal growth restriction: prospective cohort study. Ultrasound Obstet Gynecol. 2019;54:367-75. doi: 10.1002/uog.20150.
9. Contag S, Visentin S, Goetzinger K, Cosmi E. Use of the renal artery Doppler to identify small for gestational age fetuses at risk for adverse neonatal outcomes. J Clin Med. 2021;10:1835. doi: 10.3390/jcm10091835.
10. Rizzo G, Mappa I, Bitsadze V, Słodki M, Khizroeva J, Makatsariya A, et al. Role of Doppler ultrasound at time of diagnosis of late-onset fetal growth restriction in predicting adverse perinatal outcome: prospective cohort study. Ultrasound Obstet Gynecol. 2020;55:793-8. doi: 10.1002/uog.20406.
11. Vollgraff Heidweiller-Schreurs CA, De Boer MA, Heymans MW, Schoonmade LJ, Bossuyt PMM, Mol BWJ, et al. Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;51:313-22. doi: 10.1002/uog.18809.
12. Dunn L, Sherrell H, Kumar S. Review: Systematic review of the utility of the fetal cerebroplacental ratio measured at term for the prediction of adverse perinatal outcome. Placenta. 2017;54:68-75. doi: 10.1016/j.placenta.2017.02.006.
13. Di Mascio D, Herraiz I, Villalain C, Buca D, Morales-Rosello J, Loscalzo G, et al. Comparison between cerebroplacental ratio and umbilicocerebral ratio in predicting adverse perinatal outcome in pregnancies complicated by late fetal growth restriction: a multicenter, retrospective study. Fetal Diagn Ther. 2021;48:448-56. doi: 10.1159/000516443.
14. Stampalija T, Arabin B, Wolf H, Bilardo CM, Lees C. Is middle cerebral artery Doppler related to neonatal and 2-year infant outcome in early fetal growth restriction? Am J Obstet Gynecol. 2017;216:521.e1-521.e13. doi: 10.1016/j.ajog.2017.01.001.
15. Kalafat E, Khalil A. Umbilicocerebral ratio: potential implications of inversing the cerebroplacental ratio. Ultrasound Obstet Gynecol. 2020;56:159-62. doi: 10.1002/uog.21985.
16. Leavitt K, Odibo L, Nwosu O, Odibo AO. Comparing the cerebro-placental to umbilico-cerebral Doppler ratios for the prediction of adverse neonatal outcomes in pregnancies complicated by fetal growth restriction. J Matern Fetal Neonatal Med. 2022;35:5904-8. doi: 10.1080/14767058.2021.1901880.
17. Morales-Roselló J, Buongiorno S, Loscalzo G, Abad García C, Cañada Martínez AJ, Perales Marín A. Does uterine Doppler add information to the cerebroplacental ratio for the prediction of adverse perinatal outcome at the end of pregnancy? Fetal Diagn Ther. 2020;47:34-44. doi: 10.1159/000499483.
18. Graupner O, Meister M, Lecker L, Karim-Payab S, Franz C, Carow J, et al. Role of the cerebro-placental-uterine ratio in predicting adverse perinatal outcome in low-risk pregnancies at term. Arch Gynecol Obstet. 2022. doi: 10.1007/s00404-022-06733-8.
19. Graupner O, Kuschel B, Axt-Fliedner R, Enzensberger C. New markers for placental dysfunction at term - potential for more. Geburtshilfe Frauenheilkd. 2022;82:719-26. doi: 10.1055/a-1761-1337.
20. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet. 2021;152:3-57. doi: 10.1002/ijgo.13522.
21. Figueras F, Gratacos E. Stage-based approach to the management of fetal growth restriction. Prenat Diagn. 2014;34:655-9. doi: 10.1002/pd.4412.
22. Chien PF, Owen P, Khan KS. Validity of ultrasound estimation of fetal weight. Obstet Gynecol. 2000;95:856-60. doi: 10.1016/s0029-7844(00)00828-0.
23. Bhide A, Acharya G, Baschat A, Bilardo CM, Brezinka C, Cafici D, et al. ISUOG Practice Guidelines (updated): use of Doppler velocimetry in obstetrics. Ultrasound Obstet Gynecol. 2021;58:331-9. doi: 10.1002/uog.23698.
24. Sheppard BL, Bonnar J. An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. Br J Obstet Gynaecol. 1981;88:695-705. doi: 10.1111/j.1471-0528.1981.tb01268.x.
25. Morales-Roselló J, Khalil A. Fetal cerebral redistribution: a marker of compromise regardless of fetal size. Ultrasound Obstet Gynecol. 2015;46:385-8. doi: 10.1002/uog.15664.
26. Yang Z, Lv W, Zhao B, Yao J, Yang Y, Yin Z. Uteroplacental-cerebral ratio: a Doppler parameter for prognostic prediction of late-onset fetal growth restriction: single center prospective cohort study. J Clin Med. 2022;12:275. doi: 10.3390/

jcm12010275.
27. Buca D, Rizzo G, Gustapane S, Mappa I, Leombroni M, Bascietto F, et al. Diagnostic accuracy of Doppler ultrasound in predicting perinatal outcome in appropriate for gestational age fetuses: a prospective study. Ultraschall Med. 2021;42:404-10. doi: 10.1055/a-1072-5161.
28. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52:430-41. doi: 10.1002/uog.19117.
29. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48:333-9. doi: 10.1002/uog.15884.
30. Akolekar R, Ciobanu A, Zingler E, Syngelaki A, Nicolaides KH. Routine assessment of cerebroplacental ratio at 35-37 weeks' gestation in the prediction of adverse perinatal outcome. Am J Obstet Gynecol. 2019;221:65.e1-65.e18. doi: 10.1016/j.ajog.2019.03.002.