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Research Article

Comparison and Analysis of Cerebroplacental Ratio and Umbilicocerebral Ratio in the Prenatal Diagnosis and Severity Assessment of Fetal Growth Restriction: A Retrospective Study and Systematic Review

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What Does This Study Add to Clinical Work?

Compared with UCR and simple UA or MCA blood flow parameters, CPR-PI may be the most optimized ultrasound parameter for diagnosing and assessing FGR.

Abstract

Purpose: Doppler flow parameters of fetal umbilical artery (UA) and middle cerebral artery (MCA) have been widely used for fetal growth restriction (FGR), but their diagnostic efficacy remains contentious. The purpose of this study is to clarify the superiority of cerebroplacental ratio (CPR) and umbilicocerebral ratio (UCR) in terms of their correlation and predictive accuracy in diagnosing FGR.

Methods: Doppler flow parameters of the UA and MCA were tested for FGR patients and normal pregnant women during the third trimester. Collection of delivery gestational weeks and neonatal birth weight were conducted. Logistic regression and area under the curve (AUC) analysis were used to elucidate the association and diagnostic accuracy of CPR and UCR for diagnosing FGR.

Results: The CPR-EDV and CPR-MFV in FGR patients were higher, while the CPR-S/D, CPR-PI, and CPR-RI were lower ($P<0.05$). The UCR-EDV in the FGR group was lower than that in the NC group, while the UCR-S/D and UCR-PI were higher than those in the NC group ($P<0.05$). Only the CPR-PI (OR:0.166, 95% CI 0.049 ~ 0.563, P = 0.004) was independently associated with FGR. A positive correlation between CPR-PI and delivery gestational weeks was found, as well as neonatal birth weight. The AUC of CPR-PI for detecting FGR was 0.719 (95% CI 0.594 ~ 0.844; P=0.003), with a critical value of 1.57.

Conclusion: Compared with UCR and simple UA or MCA blood flow parameters, CPR-PI may be the most optimized ultrasound parameter for diagnosing and assessing FGR.

Keywords: Fetal growth restriction, Cerebroplacental ratio, Umbilicocerebral ratio, Middle cerebral artery doppler, Umbilical artery doppler, Blood flow parameters, Obstetric ultrasound, Pregnancy and complications

Introduction

Fetal growth restriction (FGR) is a condition associated with an increased risk of adverse pregnancy outcomes, including preterm birth and various complications during the perinatal period and it is also a significant contributor to illness and mortality among newborns [1,2]. Internationally, there is no unified "gold standard" for defining FGR. According to the 2021 guideline from the American College of Obstetricians and Gynecologists (ACOG), FGR is defined as a fetus with an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile for gestational age [3]. This definition does not take into account the individual growth potential of each fetus, which may result in underdiagnosis of some FGR cases with normal EFW or AC but below their growth potential. It may also lead to misdiagnosis of some small for gestational age (SGA) infants who have reached their growth potential but are smaller in size for their gestational age. Therefore, distinguishing between FGR and normal SGA, early and accurate diagnosis of FGR, and scientifically monitoring fetal development and intrauterine oxygen deficiency are important measures to improve the management of FGR and present a significant clinical challenge. Clinical practice has shown that Doppler ultrasound blood flow parameters in FGR fetuses often change, occurring earlier than fetal electronic monitoring or biophysical scoring, and can serve as one of the diagnostic criteria for FGR. Currently, the most examined blood flow parameters are from the fetal umbilical artery (UA) and the middle cerebral artery (MCA). There are many detection parameters of UA and MCA, while which parameters are more effective in the diagnosis and evaluation of FGR is still controversial. Therefore, this article aims to explore the application value of different Doppler parameters of fetal UA and MCA in the diagnosis and evaluation of FGR.

Methods

Clinical data and grouping

This retrospective study was performed in a single tertiary hospital (Beijing Chaoyang Hospital, Capital Medical University, Beijing, China). Thirty-three late-term singleton pregnant women diagnosed with FGR between May 1, 2019, and November 30, 2022, were selected as the FGR group. Thirty normal late-term singleton pregnant women during the same period were chosen as the normal control (NC) group. Exclusion criteria includes pregnant women with psychiatric disorders, coagulation function abnormalities, cognitive impairment, and familial genetic metabolic diseases, fetal brain developmental abnormalities, fetal arrhythmias, and congenital heart diseases. Delivery gestational weeks and newborn birth weights were collected for both groups. The FGR group had an average age of 31.39 ± 3.44 years (ranging from 26 to 39 years), while the control group had an average age of 32.53 ± 3.66 years (ranging from 27 to 40 years). There was no statistically significant difference in age between the two groups (P>0.05). This study obtained approval from our hospital's ethics committee and written informed consent was obtained from all patients.

Instruments and measurement parameters

The SAMSUNG RS80A ultrasound machine with a convex probe and a probe frequency of 3.5~5MHz was used for the examinations. All examinations were independently conducted by the same experienced ultrasound physician. The ultrasound examination process involved placing the pregnant women in a supine position, exposing the abdomen adequately while ensuring patient privacy. Measurements included fetal head circumference, biparietal diameter, abdominal circumference, and femur length, along with an assessment of the placenta, umbilical cord, amniotic fluid, and fetal heart conditions.

Blood flow parameter measurements for UA and MCA

Whenever possible, measurements were taken when the fetus was in a state of quiet respiration, with the ultrasound beam forming an angle of <30% with the blood vessels. Measurements were taken after the appearance of 5~6 consistent and stable waveforms in the interface. The following measurements were recorded: peak systolic velocity (PSV), end diastolic velocity (EDV), Mean flow velocity (MFV), systolic-to-diastolic velocity ratio (S/D), pulsatility index (PI), and resistance index (RI).

Special Note: S/D = PSV/EDV, reflects vascular resistance, RI = (PSV - EDV)/PSV, reflects the ratio of the magnitude of velocity change to the maximum velocity, PI = 2(PSV-EDV)/(PSV+EDV), reflects the ratio of the decrease in velocity during diastole to the mean velocity. In a normal pregnancy, these values generally exhibit a gradual decrease. Cerebroplacental ratio (CPR): the ratio between MCA and UA. Umbilicocerebral Ratio (UCR): the ratio between UA and MCA.

Statistical methods

Statistical analysis was performed using SPSS 22.0 software. If the data is normally distributed, it is expressed as the mean value (standard deviation) and compared using t-tests. If the data is not normally distributed, it is expressed as the median (range of quartiles) and compared using Mann-Whitney U test, while categorical data were compared using chi-square tests. Logistic regression and receiver operating characteristic curve (ROC) analysis were employed to assess the diagnostic efficacy of various parameters for FGR. Pearson correlation analysis was used for relevant correlations, with statistical significance set at $P<0.05$.

Results

Comparison of gestational age at birth and birth weight between the FGR and NC groups

Compared to the normal control group, patients in the FGR group had significantly earlier delivery gestational weeks (37.53 vs. 39.57 weeks, *P*=0.000) and significantly lower birth weights for newborns (2262 vs. 3332g, *P*=0.000) (**Table 1**).

Comparison of UA blood flow parameters between the two groups

There were no significant differences in UA flow parameters, including PSV, EDV, MFV, S/D, PI, and RI, between the two groups, as shown in **Table 2**.

Table 1. Maternal characteristics and delivery outcomes.

	Total (n=63)	FGR (n=33)	NC (n=30)	*P*
Age (years)	31.90 ± 3.56	31.40 ± 3.44	32.53 ± 3.66	0.208
GA at ultrasoni time (weeks)	31.86 (30.86-35.57)	33.28 (31.21-35.57)	31.14 (30.14-34.86)	0.087
GA at birth (weeks)	38.50 ± 2.20	37.53 ± 2.55	39.57 ± 0.96	**0.000**
Birthweight (g)	2771.59 ± 714.15	2262.12 ± 540.69	3332.00 ± 384.09	**0.000**
Birthweight centile (%)	9.0 (1.0-43.0)	1.0 (1.0-5.0)	46.0 (22.0-64.0)	**0.000**

Data expressed as the mean value ± standard deviation if normally distributed and as the median (range of quartiles) if not normally distributed. GA: Gestational Age.

Table 2. Ultrasonographic and Doppler parameters of UA and MCA in FGR and NC groups.

	FGR (n=33)	NC (n=30)	*P*
UA-PSV	45.15 ± 8.24	44.13 ± 8.78	0.637
UA-EDV	17.20 ± 6.55	17.85 ± 5.07	0.665
UA-MFV	29.85 ± 6.73	30.37 ± 6.63	0.760
UA-S/D	2.50 (2.2-2.9)	2.60 (2.20-2.82)	0.971
UA-PI	0.90 (0.80-1.04)	0.92 (0.76-0.96)	0.504
UA-RI	0.60 (0.54-0.68)	0.61 (0.55-0.65)	0.634
MCA-PSV	52.36 ± 11.02	47.20 ± 11.08	0.069
MCA-EDV	13.00 ± 5.43	9.60 ± 4.92	**0.012**
MCA-MFV	26.85 ± 6.96	22.33 ± 6.78	**0.012**
MCA-S/D	4.62 ± 2.23	5.92 ± 2.98	0.054
MCA-PI	1.47 ± 0.33	1.75 ± 0.39	**0.004**
MCA-RI	0.75 ± 0.09	0.80 ± 0.08	**0.019**
CPR-PSV	1.21 ± 0.38	1.14 ± 0.46	0.486
CPR-EDV	0.67 (0.40-1.03)	0.47 (0.36-0.76)	**0.024**
CPR-MFV	0.99 ± 0.46	0.78 ± 0.32	**0.044**
CPR-S/D	1.74 ± 0.90	2.36 ± 1.20	**0.023**
CPR-PI	1.61 ± 0.51	2.02 ± 0.46	**0.001**
CPR-RI	1.24 ± 0.26	1.36 ± 0.18	**0.042**
UCR-PSV	0.92 ± 0.33	0.99 ± 0.31	0.354

UCR-EDV	1.63 ± 0.98	2.30 ± 1.40	**0.031**
UCR-MFV	1.22 ± 0.53	1.46 ± 0.49	0.060
UCR-S/D	0.64 (0.43-0.88)	0.49 (0.37-0.62)	**0.019**
UCR-PI	0.69 ± 0.26	0.52 ± 0.12	**0.001**
UCR-RI	0.78 (0.72-0.96)	0.74 (0.70-0.79)	0.056
Data expressed as the mean value ± standard deviation if normally distributed and as the median (range of quartiles) if not normally distributed. GA: Gestational Age; CRP: Cerebroplacental Ratio; UCR: Umbilicocerebral Ratio.			

Comparison of MCA blood flow parameters between the two groups

In the FGR group, fetal MCA-EDV values and MCA-MFV values were significantly higher than those in the normal control group (MCA-EDV: 13.00 ± 5.42 vs. 9.60 ± 4.92, *P*=0.02; MCA-MFV: 26.85 ± 6.96 vs. 22.33 ± 6.78, *P*=0.012). Additionally, MCA-PI values and MCA-RI values in the FGR group were significantly lower than those in the normal control group (MCA-PI: 1.47 ± 0.33 vs. 1.75 ± 0.39, *P*=0.004; MCA-RI: 0.75 ± 0.09 vs. 0.80 ± 0.079, *P*=0.019). Furthermore, MCA-PSV values in the FGR group were higher than those in the normal control group, but the difference did not reach statistical significance (52.36 ± 11.02 vs. 47.20 ± 11.08, *P*=0.069). Similarly, MCA-S/D values in the FGR group were lower than those in the normal control group, but the difference was not statistically significant (4.62 ± 2.23 vs. 5.92 ± 2.97, *P*=0.054) (**Table 2**).

Comparison of CPR and UCR parameters between the two groups

When exploring the differences between the CPR and UCR parameters explored, CPR-EDV (0.67 (0.40-1.03) vs. 0.47 (0.36-0.76), *P*=0.024) and CPR-MFV (0.99 ± 0.46 vs. 0.78 ± 0.32, *P*=0.044) were higher, while CPR-S/D (1.74 ± 0.90 vs. 2.36 ± 1.20, *P*=0.023), CPR-PI (1.61 ± 0.51 vs. 2.02 ± 0.46, *P*=0.001) and CPR-RI (1.24 ± 0.26 vs. 1.24 ± 0.26, *P*=0.042) were lower in patients with FGR. Instead, for UCR, UCR-EDV (1.63 ± 0.98 vs. 2.30 ± 1.40, *P*=0.031) was lower in FGR group while UCR-S/D (0.64 (0.43-0.88) vs. 0.49 (0.37-0.62), *P*=0.019) and UCR-PI (0.69 ± 0.26 vs.0.52 ± 0.12, *P*=0.001) were both higher when compared with the NC group.

The diagnostic efficacy of CPR-PI for FGR as assessed by logistic regression and ROC analysis

On multivariable logistic regression analysis of various Doppler parameters, only the value of CPR-PI (OR:0.166 ,95% CI 0.049-0.563, *P*=0.004) was independently associated with FGR. In addition, the CPR-PI value was positively correlated with delivery gestational age and neonatal birth weight by correlation analysis (**Table 3**). Finally, to evaluate the sensitivity and specificity of CPR-PI for diagnosing FGR, ROC curve analysis was used in this study. The results showed that the area under the curve (AUC) of CPR-PI for detecting late FGR was 0.719 (95% CI 0.594-0.844; *P*=0.003) and the cut-off was 1.57 (**Table 4; Figure 1**).

Discussion

FGR is a common and important complication in obstetrics, and it increases the risk of adverse pregnancy outcomes, including preterm birth and various perinatal complications [4]. The results of this study showed that compared to the normal control group, pregnant women in the FGR group had significantly earlier delivery gestational weeks and significantly lower birth weights for newborns, which inevitably leads to a higher rate of preterm births and perinatal complications. Moreover, researches have shown that infants affected by FGR are more likely to experience cognitive delays in childhood and diseases in adulthood, including neurological development disorders, coronary heart disease, hypertension, type 2 diabetes, and more [5].

The etiology of FGR can be broadly categorized into maternal,

Table 3. Pearson correlation analysis between CPR-PI with GA at birth and Birth weight.

	GA at birth	**Birthweight**	**Brithweight centile**
Pearson Correlation	0.484	0.590	0.415
P	0.000	0.000	0.001

Table 4. Logistic regression analysis and predictive performance of CPR-PI for antenatal diagnosis of FGR.

	Adjusted OR (95%CI)	***P***	**AUC (95%CI)**	***P***
CPR-PI	0.166 (0.049-0.563)	0.004	0.719 (0.594-0.844)	0.003

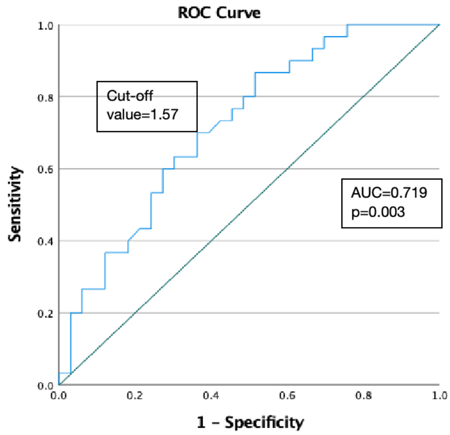

Figure 1. Receiver operating characteristics curves of CPR-PI for prediction of FGR.

fetal, and placental factors. Although etiology is complex and multifactorial, it often results in inadequate uteroplacental perfusion and fetal growth restriction. Currently, it remains challenging to distinguish FGR caused by inadequate growth potential from normal SGA with normal growth potential but slower overall development. Given the potential for severe adverse outcomes associated with FGR, clinicians often manage cases where EFW or abdominal circumference falls below the 10th percentile as FGR. In addition to closely monitoring dynamic changes in fetal weight and abdominal circumference, clinicians pay special attention to changes in fetal Doppler blood flow signals. This is because an increasing body of research has demonstrated a close relationship between FGR and abnormal fetal blood flow [6-8]. By examining fetal vascular blood flow signals, it is possible to assist in distinguishing FGR from normal SGA and effectively monitor the intrauterine status of FGR fetuses, thereby reducing adverse outcomes associated with FGR.

UA is a branch of the internal iliac artery and serves as the channel for the fetus to receive maternal nutrients and undergo metabolism. As gestational weeks progress, UA blood flow resistance gradually decreases to meet the needs of pregnancy and delivery. However, in the case of FGR, due to placental dysfunction or fetal growth restriction, UA blood flow undergoes abnormal changes, primarily characterized by reduced diastolic blood flow, disappearance, or even reversal [9]. However, current studies have found that UA, as a clinical standard for the identification and management of early FGR [10], is often normal in fetuses with late-onset FGR [11]. The results of this study also showed that there was no significant difference in UA parameters between the late-onset FGR group and the normal group, suggesting that more accurate indicators are needed for the diagnosis and evaluation of late-onset FGR.

The MCA is a branch of the internal carotid artery and serves as a crucial source of blood supply to the fetal brain. MCA exhibits higher resistance in early pregnancy, gradually decreasing after around 28 weeks of gestation [12]. Studies have found that when a fetus experiences intrauterine hypoxia, anemia, or other pathological conditions for various reasons and enters a state of decompensation, a "brain protection effect" can occur. This effect is characterized by increased resistance in the UA and decreased blood flow resistance, as well as increased velocity in MCA [13]. The results of this study showed that in the late-onset FGR group, the EDV and MFV of fetal MCA were significantly increased, while the PI and RI values were both significantly decreased. These changes are considered to be related to the reactive regulatory mechanisms that occur in response to fetal hypoxia in FGR. This suggests that the EDV, MFV, PI and RI of fetal MCA may be sensitive indicators for diagnosing and assessing late-onset FGR.

Arbeille *et al.* first proposed the concept of CPR in 1987 [14]; in the same year, Arduini *et al.* introduced the concept of UCR, which is calculated by reversing the numerator and denominator of CPR [15]. It is worth noting that some recent studies have focused on the efficacy of Doppler ultrasound calculation of the CPR for the effective diagnosis of FGR, but the research results are controversial [6,13,16]. A Study by Ozge *et al.* [17], calculated the ratio of the PI values of UA and MCA to obtain CPR, suggesting that CPR may help identify adverse perinatal outcomes in fetuses with FGR. Additionally, according to a recent research, offspring born to patients of FGR with a CPR<1 have a significantly increased risk of delayed neurodevelopment at the age of 3 years [18].

The effectiveness of umbilicocerebral ratio (UCR) compared to cerebroplacental ratio (CPR) for predicting adverse pregnancy and neonatal outcomes is still a matter of debate and may vary depending on the specific context and population being studied. Some studies suggest that UCR may have advantages over CPR in certain situations [19], while others indicate similar predictive abilities between the two ratios [20]. In this study, we calculated the ratios of six parameters of UA and MCA separately to obtain CPR-PSV, CPR-EDV, CPR-MFV, CPR-S/D, CPR-PI, and CPR-RI, and swapped the numerator and denominator to obtain UCR-PSV, UCR-EDV, UCR-MFV, UCR-S/D, UCR-PI, and UCR-RI. Comparing these 12 parameters separately, the results indicate that in the late-onset FGR group, CPR-EDV, CPR-MFV, UCR-S/D, and UCR-PI values are significantly elevated, while CPR-S/D, CPR-PI, CPR-RI, and UCR-EDV values are significantly decreased compared to the normal group.

On multivariable regression analysis, only the CPR-PI was independently associated with late-onset FGR and showed a fair accuracy in predicting the late-onset disease when exploring the diagnostic performance. Furthermore, the results of correlation analysis indicated a significant negative relationship between the CPR-PI value with the GA at birth and the birthweight, suggesting that the CPR-PI value could serve as an important monitoring indicator for fetal well-being. We also calculated the cut-off value for CPR-PI as 1.57 using the AUC curve. When CPR-PI is less than 1.57, caution should be exercised regarding the occurrence of late-onset FGR, as well as the possibility of preterm birth and low birth weight infants.

In summary, our research findings suggest that compared to UCR and other parameters, CPR-PI has a greater advantage in diagnosing and assessing late-onset FGR, providing more reliable auxiliary evidence for clinical decision-making. However, some studies have found that the effectiveness of CPR-PI in predicting adverse outcomes of FGR is low, while combining MCA-PI, uterine artery PI, and umbilical vein blood flow normalized for fetal abdominal circumference (UVBF/AC) shows higher predictive efficiency for adverse outcomes of FGR [11]. Therefore, further research with larger, multi-center clinical studies is needed to confirm the reliability and clinical utility of using the CPR-PI value in the diagnosis and monitoring of FGR.

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None.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

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Author Contributions Statement

Jing-jie Zheng: Data analysis and Manuscript writing/editing; Hui-rong Zhao: Data analysis and Manuscript writing/editing; Min-hong Mao: Data collection or management; Li-yuan Guo: Data collection or management; Han-xue Zou: Data analysis; Zhi-hui Liu: Data collection or management

Jing Liu: Protocol/project development; Chen Chen: Protocol/project development.

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