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Research article

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Middle cerebral artery to uterine artery pulsatility index ratios in pregnancy with fetal growth restriction regarding negative perinatal outcomes

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Ethics Committee Approval
Ethical approval was obtained from Prof. Dr. Cemil Taşcıoğlu City Hospital's ethics committee (28.02.2022 / number E-2022/45).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Fetal growth restriction (FGR) causes a high risk of perinatal morbidity and mortality, and the timing of the correct delivery time decision remains controversial. Cerebroplacental ratio (CPR), umbilical artery, uterine artery (UA) and middle cerebral artery (MCA) Doppler studies are used to predict adverse perinatal outcomes in FGR. However, since there is insufficient reliability for each separately and together, the search for new methods continues. This retrospective study was conducted to determine the degree of neonatal morbidity in fetuses suspected of having FGR by evaluating the MCA to UA pulsatility index (PI) ratios together with frequently used Doppler examinations.

Methods: This was a retrospective cohort study conducted in a single-center hospital with the approval of the Medical Institutional Ethics Committee. A total of 424 pregnant women admitted to a tertiary hospital and diagnosed with FGR between July 2020 and December 2021 who were informed and approved were included in the study. Gestational age was confirmed by first trimester sonographic measurements of pregnancy. All pregnant women were examined by Doppler USG and umbilical artery, mean UA, fetal MCA, ductus venosus, CPR (MCA/umbilical artery pulsatility index ratio) and cerebrouterine ratio (MCA/UA) PI values were measured. Negative perinatal outcomes were recorded as blood gas level of the newborn at 7.2 and below, Apgar score of 7 and below at the fifth minute, and needing neonatal intensive care (NICU). Adverse perinatal and postnatal outcomes were recorded and compared with Doppler findings. If there were no signs of a negative perinatal outcome, it was considered a positive outcome. If at least one of the symptoms of adverse perinatal outcomes was present, it was considered a negative outcome

Results: Decreased CPR and decreased MCA to UA PI were significantly and positively associated with an increased likelihood of exhibiting negative perinatal outcomes in pregnancies with FGR ($P < 0.001$, $P < 0.001$, respectively). The receiver operating characteristic (ROC) curve analysis showed that the optimal cut-off value for MCA to uterine artery PI was 1.41 to predict FGR with 57.37% sensitivity and 62.50% specificity (AUC: 0.629; 95% CI: 0.581–0.675). When the CPR cut-off value was taken as 1.2069, the sensitivity was 42.86% and the specificity 83.93% in predicting negative perinatal outcomes in CPR values below this value ($P < 0.001$).

Conclusion: CPR is the most successful criterion in distinguishing between positive and negative perinatal outcomes. It has been demonstrated that the MCA to uterine artery PI ratio values after CPR can also be used for this distinction. MCA to UA PI ratio sensitivity was higher than CPR and umbilical artery. This situation shows that MCA to uterine artery PI ratio (alone or when evaluated together with PPV and NPV ratios) is a criterion that can be added to other Doppler examinations in predicting negative perinatal outcomes.

Keywords: Fetal growth restriction, Cerebroplacental ratio, Uterine artery pulsatility index, Middle cerebral artery pulsatility index, Doppler

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Introduction

Fetal growth restriction (FGR), defined as the failure of expected fetal growth, is an important cause of perinatal mortality and morbidity [1, 2]. It is known that more than half of stillbirths are associated with FGR due to the inability to detect FGR [3].

Early detection of fetuses at risk for adverse outcomes remains a challenge and is of great importance for clinicians and researchers to correct the abnormality and reduce perinatal mortality before permanent damage occurs. In current practice, the management of FGR aims to monitor fetal status and provide necessary prenatal support to optimally time labor induction.

Middle cerebral artery (MCA), uterine artery (UA), and umbilical artery Doppler measurements have been used for a long time to estimate negative perinatal consequences. In recent studies, Cerebroplacental ratio (CPR) has been suggested as a more reliable test with the advantage of its neuroprotective effect [4, 5]. Many CPR thresholds are recommended, but it is not yet accepted as an international reference gold standard, but is considered a useful method, and different accuracy rates have been reported in different studies [6-8]. Research is ongoing for a more precise method to estimate adverse perinatal outcomes.

This study aimed to reveal the ability of MCA, UA, umbilical artery, ductus venosus, and CPR to predict adverse perinatal outcomes in pregnant women diagnosed with FGR and to compare their reliability with MCA/UA pulsatility index (PI) ratios, which is an uncommon method.

Materials and methods

Study design and participants

A retrospective cohort study was conducted to evaluate the MCA/UA PI ratios in pregnancies with FGR between July 2020 and December 2021 in a tertiary hospital. Ethical Approval was obtained from Prof. Dr. Cemil Taşcıoğlu City Hospital's ethics committee (28.02.2022 / number E-2022/45). A total of 424 women aged 16–44 years, 27–40 weeks pregnant, diagnosed with FGR, who applied to the high-risk perinatology clinic were included in the study. As a result of data scans, routine laboratory, ultrasonographic measurements, and follow-up delivery data of the pregnant women who applied to the hospital were recorded. Gestational age was confirmed by first trimester sonographic measurements of pregnancy.

Gestational diabetes, cases with a fetal structural or chromosomal abnormality, history of hypertensive disease during pregnancy, history of chronic disease in the mother, smoking or drug use, fetal infections, and multiple pregnancies were determined as exclusion criteria from the study.

Criteria established by international consensus in the ISUOG Practice Guidelines were used to define FGR [9]. Negative perinatal outcomes were determined as fifth minute Apgar score <7, neonatal cord blood gas pH <7.2, and NICU requirement [10, 11]. If there were no signs of a negative perinatal outcome, it was considered a positive outcome. If at least one of the symptoms of adverse perinatal outcomes was present, it was considered a negative outcome.

All pregnant women were followed up, and negative perinatal and postnatal outcomes were determined and recorded. All patients underwent an ultrasonographic examination using a Mindray Resona 7 ultrasound (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China), diagnostic apparatus with a 1.2–6 MHz convex abdominal probe by a fetal medicine specialist (HAS).

UA, umbilical artery, fetal MCA, and CPR Doppler examinations were performed as described in the ISUOG guidelines; CPR value was determined by proportioning the MCA PI value with the umbilical artery PI values; and the MCA/UA ratio was determined by dividing the MCA PI value with the mean UA PI value [12]. The Hadlock formula was used for estimated fetal weight (EFW) calculations [13].

Statistical analysis

Statistica 13.3.1 (TIBCO Software Inc. CA, USA) and the MedCalc demo version (MedCalc Software Ltd, Ostend, Belgium) were used for all analyses. The assumption of normality for numerical variables was examined with the Shapiro-Wilk test. Since the assumption of normality was not provided, the variables were summarized in terms of median and 25th Quarter-75th Quarter (min.-max.). The difference between the two independent groups was investigated with the Mann-Whitney U test. Visually presented with Raincloud Plot. ROC (receiver operating characteristic curve) analysis was used to calculate the cut-off point and the area under the curve, and sensitivity (95% CI), specificity (95% CI), PPV (95% CI) and NPV (95% CI) values were also given. Spearman correlation coefficient was used to investigate the relationship between continuous variables. A network graph has been drawn for the visualization of the correlation coefficients. $P < 0.05$ was accepted as a statistical significance level.

Results

The demographic and obstetric characteristics are shown in Table 1. According to the perinatal results that were accepted as negative, the newborn's fifth minute Apgar score was 7 and below in 100 of the 424 pregnant women who participated in the study. Cord blood pH values of 23 newborns were measured as 7.2 and below. Two-hundred-fifty-seven newborns were admitted to the NICU (1–102 days). Three-hundred-tweleve patients (73.6%) had at least one of the signs of adverse perinatal outcome. If there were no signs of a negative perinatal outcome, it was considered a positive outcome. If at least one of the symptoms of adverse perinatal outcomes was present, it was considered a negative outcome (Table 2).

Table 1: Demographic and obstetric characteristics

	Mean	Standard deviation
Maternal Age (years)	28.33	5.98
Body Weight	83.68	8.47
Height	162.09	49.07
Gestational age at US (weeks)	35.72	2.75
Gestational age at delivery (weeks)	31.98	2.87

Table 2: Number of perinatal results

Newborn	Number	Percent
Positive Outcomes	112	26.4
Negative Outcomes	312	73.6
Total	424	100

Adverse perinatal outcomes: blood gas level of the newborn 7.2 and below, Apgar score of 7 and below at the fifth minute, needing neonatal intensive care (NICU); Negative outcome: had at least one of the signs of adverse perinatal outcomes. Positive outcome: no signs of adverse perinatal outcomes

Doppler evaluations, measured PI values, and all positive and negative perinatal outcomes were compared, and statistical significance was found between Doppler values and results (Table 3).

Table 3: Statistical relationship between Doppler measurements-PI values and positive and negative perinatal outcomes

	Groups										
	Positive perinatal outcomes					Negative perinatal outcomes					*P*-value
	Median	Min	Max	Percentiles 25	75	Median	Min	Max	Percentiles 25	75	
Umb.A-PI	1.06	0.60	1.50	0.90	1.20	1.14	0.20	5.23	0.92	1.30	0.003
Ut.A-PI	1.01	0.48	2.11	0.83	1.26	1.09	0.50	2.89	0.90	1.34	0.025
MCA-PI	1.51	0.95	3.44	1.40	1.80	1.40	0.90	4.40	1.30	1.60	<0.001
Duc.V-PI	0.50	0.20	2.00	0.40	0.60	0.60	0.20	1.30	0.40	0.70	0.002
CPR	1.51	0.77	3.16	1.27	1.89	1.29	0.27	7.00	1.08	1.60	<0.001
MCA/Ut. A	1.56	0.67	4.60	1.23	2.08	1.33	0.44	5.27	1.03	1.73	<0.001

Min: Minimum, Max: Maximum, PI: Pulsatility Index, Umb.A: Umbilical Artery, MCA: Middle Cerebral Artery, Duc.V: Ductus Venosus, CPR: Cerebroplacental ratio

Separate ROC analysis results in terms of the relationship between umbilical artery PI, CPR and MCA/UA PI ratio Doppler measurements, and perinatal outcomes are given in Table 4.

The predictive and cut-off values of CPR PI (Figure 1a), MCA /UA PI (Fig. 1b), and umbilical artery PI (Fig. 1c) for negative perinatal outcomes were evaluated by applying ROC analysis. Decreased CPR and decreased MCA to uterine artery PI were significantly and positively associated with an increased probability of indicating a negative perinatal outcome (P < 0.001, P < 0.001, respectively). The optimal cut-off for MCA to UA PI was 1.4118 to predict FGR with 57.37% sensitivity and 62.50% specificity, demonstrated by ROC analyzes (AUC 1~4 0.629; 95% CI, 0.581–0.675).

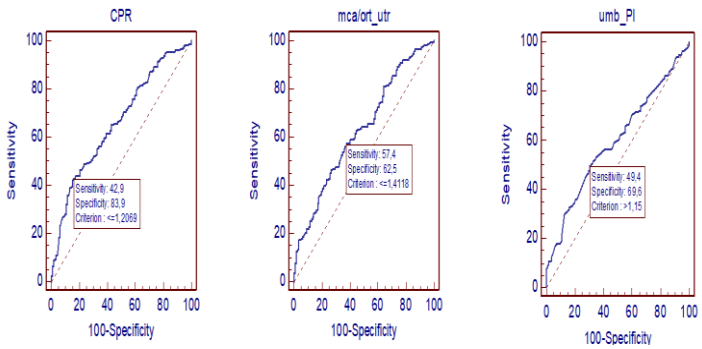
When the CPR cut-off value was taken as 1.2069, the sensitivity was 42.86% and the specificity 83.93% in predicting negative perinatal outcomes in CPR values below this value (P < 0.001). When the cut-off value for the umbilical artery was taken as 1.15, the sensitivity of umbilical artery PI values above this value was 49.35%, and the specificity was 69.64% to predict adverse perinatal outcomes (P = 0.003). When the cut-off value for the MCA/UA PI ratio was taken as 1.4118, values below this value had a sensitivity of 57.37% and a specificity of 62.50% (P < 0.001) in predicting negative perinatal outcomes (Table 4 and Figure 1).

Table 4: ROC results for CPR, MCA to uterine artery and umbilical artery

	CPR (MCA PI/UMB A. PI)	MCA PI/ Ut. A. PI	Umbilical Artery PI
AUC	0.661 (0.614-0.707)	0.629 (0.581-0.675)	0.596 (0.547-0.643)
	P < 0.001	P < 0.001	P = 0.001
Criterion	≤1.2069	≤1.4118	>1.15
Sensitivity	42.86	57.37	49.35
95% CI	37.3 - 48.6	51.7 - 62.9	43.6 - 55.1
Specificity	83.93	62.50	69.64
95% CI	75.8 - 90.2	52.9 - 71.5	60.2 - 78.0
PPV	88.0	81.0	81.7
95% CI	81.7 - 92.7	75.2 - 85.9	75.4 - 87.0
NPV	34.8	34.5	33.3
95% CI	29.1 - 40.8	28.0 - 41.5	27.3 - 39.8

CPR was calculated by dividing the MCA PI by the UA PI, and MCA/ uterine artery PI ratio by dividing the MCA PI by the uterine artery PI. AUC: area under the curve, CI: confidence interval, CPR: cerebroplacental ratio, MCA: middle cerebral artery, PI: pulsatility index, UA: umbilical artery, PPV: positive predictive value, NPV: negative predictive value.

Figure 1: ROC results for CPR, MCA to uterine artery and umbilical artery



Predictive and cut-off values of (a) CPR PI, (b) MCA/uterine artery PI, (c) UA PI for adverse perinatal outcomes in pregnancies with FGR by receiver operating characteristic curve. MCA PI, CPR and MCA/uterine artery PI were three predictors of adverse perinatal outcomes, with AUCs of 0.661, 0.629 and 0.596, respectively (P < 0.001, P < 0.001, P = 0.001). CPR was calculated by dividing the MCA PI by the UA PI, and MCA/ uterine artery PI ratio by dividing the MCA PI by the uterine artery PI. AUC: area under the curve, CI: confidence interval, CPR: cerebroplacental ratio, MCA: middle cerebral artery, PI: pulsatility index, UA: umbilical artery.

Discussion

FGR is a fetal developmental disorder in which the fetus fails to develop and grow adequately, which is a major cause of adverse perinatal outcomes, including stillbirths [14, 15]. The aim of FGR management is to make a timely decision for delivery, thereby minimizing fetal morbidity and mortality.

It is thought that uteroplacental circulatory failure plays a role most frequently in the etiology, and therefore, the fetus, which cannot receive nutrients and oxygen from the placenta, cannot develop and grow sufficiently [15]. While studies continue to provide information about the fetus's nutritional level and growth rate, many authors stated that Doppler assessments are a reliable, noninvasive predictor of adverse perinatal outcomes in high-risk pregnancies [16-18]. Hypoxemia, which develops as a result of uteroplacental circulatory failure, causes protective changes in vascular flow to protect vital organs, such as the brain, which is defined as the centralization of blood flow, which causes changes in Doppler blood flow resistances. Studies have shown that MCA and umbilical artery Doppler measurements are good indicators of negative pregnancy outcomes [19]. Our MCA and umbilical Doppler indexes are similar to the literature [19, 20].

CPR is a useful index of fetal stress and hypoxemia, combining increased umbilical artery and decreased MCA impedance [20, 21]. This index is significantly more sensitive than UA and MCA separately [22]. CPR is also more successful than other velocimetry measures alone in predicting adverse perinatal outcomes [20-23]. In our study, CPR was remarkably low in FGR with negative obstetric outcomes. In addition, similar to previous studies, CPR was the most accurate predictor of negative obstetric outcomes among the previously mentioned parameters [24, 25].

Despite many studies suggesting that they accurately predict negative perinatal outcomes, Doppler indices of the uterine artery are rarely used in clinical evaluation. Uterine artery Doppler changes are detected before the findings of the uteroplacental insufficiency clinic in the fetus [26]. Uterine artery Doppler findings are also accepted as predictors of true FGR and poor perinatal outcomes in small fetuses [27, 28]. Some similar studies have shown that uterine artery PI values in small for gestational age (SGA) fetuses can be accurate in predicting adverse perinatal outcomes [29]. A separate evaluation of Doppler indices with MCA PI or UA PI may not show some small alterations, but the calculation of the ratio may propose more possibilities to show small alterations in blood flow in a timely and accurate. The success of MCA/UA ratios in predicting adverse perinatal outcomes is not fully known. Except for a few studies that predicted perinatal outcomes in patients with preeclampsia, there is insufficient information in the literature about MCA/UA PI ratios. The MCA/UA PI ratio was proposed in another study as a good predictor of neonatal outcomes in third-trimester pregnancies with preeclampsia [30]. Another similar study showed that a low MCA/UA PI ratio was associated with negative obstetric outcomes in pregnancies with preeclampsia [31]. Similar results were obtained in the study of Zhou et al. in which they investigated MCA/UA ratios in term pregnant women, and it was suggested that MCA to UA ratios could help predict negative perinatal outcomes [32].

In our study, CPR is the most successful criterion in distinguishing between positive and negative perinatal outcomes. It has been demonstrated that the MCA to UA PI ratio values after CPR can also be used for this distinction. MCA to UA PI ratio sensitivity was higher than CPR and umbilical artery. This situation shows that the MCA to UA PI ratio (perhaps alone or when evaluated together with PPV and NPV ratios) is a criterion that can be added to other Doppler examinations in predicting negative perinatal outcomes.

Limitations and strengths of the study

The strengths of this study are that the Doppler studies were performed by a fetal medicine specialist and the use of simple, reproducible and validated ultrasound modalities. It is the first study to assess the MCA/UA PI ratio in FGR with negative perinatal outcomes.

A relatively small retrospective cohort, lack of a control group, and inability to perform consecutive Doppler follow-ups, especially in pregnancies with pathological Doppler values, are some of the limitations of our study. We believe more specific results can be achieved in larger series, especially in pregnancy with close Doppler and perinatal outcome follow-ups.

Conclusion

In this study, it was revealed that MCA/uterine artery ratios are a valuable criterion in predicting adverse perinatal outcomes in pregnant women with FGR, as well as frequently used CPR values. In conclusion, our study shows that MCA/UA PI ratio and CPR are two good indicators of negative obstetric outcomes. These two indicators may be useful in predicting negative obstetric results and supporting the timing of delivery to reduce morbidity and mortality caused by FGR.

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