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Original Research

Does Amnioumbilicocerebral Ratio Better Predict Adverse Neonatal Outcomes in Comparison to Other Doppler Parameters in Late-Onset Fetal Growth Restriction?

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Abstract

Background: Pregnant women with late-onset fetal growth restriction (LFGR) are at high risk of perinatal morbidity and mortality. However, it is difficult to identify patients with a higher risk of adverse perinatal outcomes at the time of diagnosing FGR. The aim of this study is whether amniotic-umbilical-to-cerebral ratio (AUCR) is a better predictor than cerebroplacental ratio (CPR) and umblicocerebral ratio (UCR) in detecting short and long-term adverse perinatal outcomes (APO) in late-onset fetal growth restriction. **Methods**: Retrospective cohort study, Doppler examinations were performed between 35–37 weeks on pregnant women who were followed up in the obstetrics and gynecology outpatient clinic of Nisa Hospital between April 1st, 2012, and April 1st, 2022, and were considered to have delayed growth according to the Delphi consensus criteria. Sensitivity and specificity of measurements of UCR, CPR, and AUCR for predicting a negative intrapartum or postpartum outcome (fetal distress, Apgar score <7 at 5 minutes, umbilical arterial pH <7.1, admission of the newborn to the neonatal intensive care unit, intrauterine death) were evaluated. Receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) were compared for UCR, CPR, and AUCR. **Results**: In this study, 185 pregnant women were evaluated. It was determined that 56 women had negative intrapartum or postpartum outcomes. UCR values were statistically significantly higher in the group with APO ($p < 0.001$), and the CPR ($p < 0.001$) and AUCR ($p = 0.001$) values were significantly lower in this group. The AUC values for CPR, UCR, and AUCR were 0.70 [95% confidence interval (CI): 0.62–0.79], 0.70 (95% CI: 0.62–0.79), and 0.66 (95% CI: 0.58–0.75), respectively. In the multivariate Logistic regression analysis of UCR, CPR, and AUCR values, there was no statistically significant correlation between CPR, UCR, and AUCR Doppler parameters in fetuses with LFGR in terms of detecting APO ($p > 0.05$). **Conclusions**: A low AUCR and CPR, and a high UCR were significantly associated with APO in fetuses with LFGR. There was no difference in the diagnostic performance between AUCR, CPR, and UCR in predicting adverse outcomes.

Keywords: umblicocerebral ratio (UCR); cerebroplacental ratio (CPR); amniotic-umbilical-to-cerebral ratio (AUCR)

1. Introduction

Fetal growth restriction (FGR) is defined as the failure of the fetus to reach its growth potential. FGR is one of the leading causes of fetal morbidity and mortality [1]. FGR identified before 32 weeks is defined as early-onset, and FGR starting after 32 weeks is defined as late-onset fetal growth restriction (LFGR) [2]. Early-onset FGR (EFGR) is due to the reduced area of placental villous structures and is rarer than LFGR [3]. LFGR is due to impaired maturation of the villi rather than a reduction in placental surface area [3]. LFGR is associated with an increased risk of adverse perinatal outcomes (APO) such as hypoxemic events and mild neurodevelopmental delay in the short and long term compared with normally grown fetuses. Early recognition of LFGR in the second half of pregnancy is very important for predicting and preventing complications.

In the face of hypoxia and increased placental resistance, fetal cerebrovascular vasodilation occurs and this mechanism is called the brain-protective effect. Studies show that this physiologic regulation, which is intended to protect the baby at the time of birth, may unintentionally harm the fetus [4–6].

Studies in the literature have reported that the evaluation of Doppler parameters to evaluate uteroplacental adequacy and fetal vascular adaptation to hypoxia plays an important role in the surveillance of the fetus [4,5]. It is argued that umbilical artery (UA) and middle cerebral artery (MCA) Doppler measurements, the cerebroplacental ratio (CPR), which is defined as the ratio between MCA and UA pulsatility index (PI), and the umblicocerebral ratio (UCR), which is known as the inverse ratio, are more effective predictors is detecting fetal hypoxia and APO [6,7].

Although both have been described at the same time, CPR has been extensively studied and is used more in clinical practice, and UCR has been studied less in FGR. However, a recent secondary analysis of the trial of umbilical and fetal flow in Europe (TRUFFLE) study [8,9] found that in EFGR, UCR was a better predictor of neurodevelopment-free survival at 2 years than CPR [9]. In addition, in recent studies, it was reported that the amniotic-umbilical-to-cerebral ratio (AUCR), a new ratio obtained by dividing the single deepest vertical pocket (SDVP) by the UCR, was also effective in predicting perinatal adverse events [10].

Therefore, there is no consensus on which ratio should be preferred in the evaluation of fetal risk in [11,12]. The aim of this study is whether AUCR is a better predictor than CPR and UCR in detecting short and long-term adverse perinatal outcomes (APO) in Late-onset Fetal Growth Restriction.

2. Materials and Methods

This retrospective cohort study was conducted by scanning the data obtained from the file registration system of patients who were admitted to the obstetrics and gynecology outpatient clinic of Nisa Hospital for pregnancy follow-up between April 1st, 2012, and April 1st, 2022. The study was designed according to the Declaration of Helsinki and was approved by our Institutional Review Board. Ethics committee approval and hospital institution approval were obtained before the study and written informed consent was obtained from the patients (Date: 18 April 2022, ethic approval number: E-10840098-772.02-2915). One hundred eighty-five pregnant women who met the inclusion and exclusion criteria were evaluated in the study. First, second, and third trimester Doppler ultrasound information in the pregnancy follow-up files of all pregnant women was examined. In our clinic, fetal follow-up is performed once in the first trimester, once in the second trimester, once in the early third trimester, and once between 35–37 weeks of gestation, a total of 4 times with Doppler ultrasound. Fetal follow-up is performed with weekly non-stress-test (NST) after 37 weeks in pregnant women with no risk. Fetal follow-up was performed with weekly NST and number of fetal movements (>10 fetal movements in 2 hours) in pregnant women with normal Doppler ratio at 35 weeks in late-onset FGR.

The inclusion criteria for the study were women aged 18–40 years who underwent Doppler examinations for LFGR at between 35 and 37 gestational weeks.

Fetuses were considered to have late growth restriction according to only the Delphi consensus criteria [13]:

- Gestational age ≥32 weeks of gestation

- Abdominal circumference (AC)/estimated fetal weight (EFW) ratio <3rd centile

Or at least two out of three of the following:

- UA-PI >95th centile or CPR <5th centile

- AC/EFW <10th centile

- AC/EFW crossing centiles >2 quartiles on growth centiles

The exclusion criteria were maternal drug intake, preeclampsia, multiple pregnancies, pregnancies with early-onset FGR, i.e., <32 weeks, fetal structural or chromosomal abnormalities, suspected or confirmed fetal infection.

Pregnant women whose gestational age was determined according to the crown-rump length (CRL) obtained in the first trimester were included in the study. All Doppler measurements were made using Voluson devices (GE Medical Systems, Zipf, Austria). Doppler parameters were set automatically. As our hospital routine, measurement was evaluated from three or more similar and sequential waveforms, in the absence of fetal tachycardia and with an insonation angle as close to 0° as possible, using ultrasound scanners equipped with a 3.5-MHz convex probe. MCA was studied at the point where it crossed the sphenoid wing through the circle of Willis, and UA was studied in a free loop of the umbilical cord [14]. CPR was calculated as the ratio between MCAPI and UAPI, and UCR was calculated as the ratio between UAPI and MCAPI [15]. The single deepest vertical pocket (SDVP) technique was used to estimate amniotic fluid volume (AFV). AUCR was calculated as the ratio of SDVP to UCR: AUCR = SDVP/(UAPI/MCAPI). Doppler indices measured between 35 and 37 weeks were used for analyses.

All socio-demographic data such as maternal age, body mass index (BMI), smoking, alcohol, socioeconomic status, parity and maternal diseases, and previous and current pregnancy data were evaluated.

Deliveries were managed according to the institution's routine protocol, and vaginal delivery was decided after 38 weeks in the absence of other contraindications. Labor was induced in cases of an unfavorable cervix, by administration of a slow-release vaginal prostaglandin E2 (10 mg). If the onset of labor did not occur within 12 h, oxytocin induction was initiated. In cases of a favorable cervix, artificial rupture of the membranes and oxytocin infusion were used. Epidural anesthesia was not used in any patients during normal deliveries. All patients received the same dose of oxytocin induction. There were no pathologic findings in intrapartum fetal cardiotocography before oxytocin induction in any patients. Indication for cesarean primary delivery for non-reassuring fetal status was based on abnormal fetal heart-rate monitoring with the presence of more than one non-reassuring criterion or any abnormal feature, including a baseline of <100 or >180 bpm, variability <5 bpm for more than 90 min, sinusoidal patterns (for more than 10 min), recurrent atypical variable decelerations and late decelerations for more than 30 min, and a single prolonged deceleration for more than 3 min.

The primary outcome of the study was to calculate the sensitivity and specificity of UCR, CPR, and AUCR measurements in LFGR to predict negative intrapartum outcomes (fetal distress, defined as the occurrence of emergency cesarean section (CS) for fetal distress or non-reassuring fetal status, defined as the presence of a pathologic cardiotocography tracings interpreted by physicians according to the International Federation of Gynecology and Obstetrics (FIGO) consensus guidelines on cardiotocography) or postpartum outcomes (Apgar score at 5 minutes <7, umbilical arterial pH <7.1, admission of the newborn to the neonatal intensive care unit, grade III/IV intraventricular hemorrhage (IVH), neonatal seizure, intrauterine death). Relationships between Doppler parameters and these results were estimated using regression analyses. Receiver operating characteristic (ROC) curves were plotted and the area under the ROC curve (AUC) was compared between CPR, UCR, and AUCR.

In the analysis of the data, number (n), percentage (%), mean, standard deviation, and minimum and maximum values were used. The normality of the data was evaluated according to the skewness and kurtosis coefficient. Students' *t*-test was used to compare the mean of two independent groups. Pearson Chi-square test and Fisher's exact test were used to compare the ratios in two or more groups. Multivariate logistic regression analysis was performed for UCR, CPR, and AUCR values. In the model using the Enter method, UCR, CPR, and AUCR values explained 20.2% of APO according to Nagelkerke R Square (Nagelkerke R^2). ROC curves were plotted for UCR, CPR, and AUCR values, and the AUCs were compared between UCR, CPR, and AUCR. Data were analyzed using the Statistical Package for the Social Sciences version 26.0 (SPSS 26.0, IBM Corp., Chicago, IL, USA) statistics package. In the 95% confidence interval (CI), *p*-values less than 0.05 were considered significant.

3. Results

Table 1 presents the distribution of the descriptive characteristics of the participants. The mean maternal age of the participants was 27.11 ± 5.31 (range, 17–43) years, and the mean gravidity, parity, and BMI were 1.97 ± 1.32, 0.73 ± 0.90 and 28.56 ± 4.59 kg/m^2, respectively. Of the study group, 13.6% had a systemic disease and 8.7% were smokers. The mean MCAPI and UAPI values of the group were 1.52 ± 0.34 (range, 0.50–2.90) and 0.93 ± 0.19 (range, 0.54–1.55), respectively.

Some 15.8% of the participants had oligohydramnios, 7.6% had unilateral or bilateral notches, and 5.4% had poor fetal movement. Of the participants whose mean gestational week of delivery was 37.19 ± 0.36, 65.2% gave birth via CS. The mean Apgar score at the 5th minute, which determined the presence of APO, was 8.54 ± 0.94, the mean pH was 7.29 ± 0.09, 18.5% had fetal distress, and 17.4% required intensive care. Just over half of the mothers (51.1%) gave birth to baby boys and the mean birth weight was 2388.18 ± 172.73 g. The participants' mean UCR, CPR, and AUCR scores were 0.70 ± 0.28, 1.61 ± 0.53, and 67.90 ± 33.83, respectively.

In Table 2, a comparison of the descriptive characteristics of the participants according to the presence of APO is given. The MCAPI value was statistically significantly lower in the group with APO (p = 0.001), and the UAPI value was significantly higher (p = 0.001). The UCR value was statistically significantly higher in the group with APO ($p < 0.001$); CPR ($p < 0.001$) and AUCR (p = 0.001) values were significantly lower in the same group.

The AUCs for CPR, UCR, and AUCR were 0.70 (95% CI: 0.62–0.79), 0.70 (95% CI: 0.62–0.79), and 0.66 (95% CI: 0.58–0.75), respectively (Figs. 1,2,3) (Table 3).

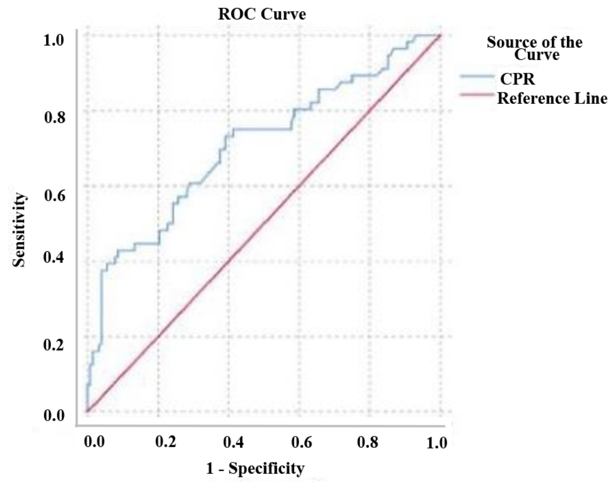

Fig. 1. Receiver operating characteristic (ROC) curve for prediction of perinatal outcome based on the cerebroplacental ratio (CPR) values.

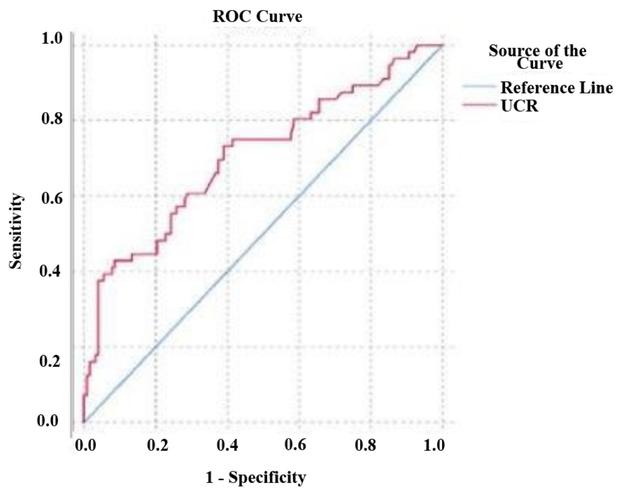

Fig. 2. ROC curve for prediction of perinatal outcome based on the umblicocerebral ratio (UCR) values.

Table 4 Multivariate logistic regression analysis of UCR, CPR, and AUCR in the group with APO. There was no statistically significant correlation between CPR, UCR, and AUCR Doppler parameters in fetuses with LFGR in terms of detecting APO ($p > 0.05$).

Table 1. Distribution of descriptive characteristics of the participants.

Variables	All pregnancies (n = 184)	
Demographic characteristics		
Maternal age (Mean ± SD)	27.11 ± 5.31	Range: 17–43
Gravidity (Mean ± SD)	1.97 ± 1.32	Range: 1–10
Parity (Mean ± SD)	0.73 ± 0.90	Range: 0–3
BMI (Mean ± SD)	28.56 ± 4.59	Range: 19.53–44.15
Smoking (%)		
No	168	91.3
Yes	16	8.7
Disease (%)		
No	159	86.4
Yes	25	13.6
Systemic disease (%)		
No	159	86.4
Hypertension (HT)	4	2.2
Hypothyroidism	11	6.0
Epilepsy	2	1.1
Gestational HT	2	1.1
Asthma	1	0.5
Anemia	1	0.5
Gestational diabetes	1	0.5
Rheumatic disease	3	1.6
Fetal movement		
Good (>10 fetal movements in 2 hours)	174	94.6
Poor (<10 fetal movements in 2 hours)	10	5.4
Prenatal Ultrasound and Doppler variables		
MCAPI (Mean ± SD)	1.52 ± 0.34	Range: 0.50–2.90
lUAPI (Mean ± SD)	0.93 ± 0.19	Range: 0.54–1.55
Oligohydramnios (Single deepest pocket <2 cm) (%)		
No	155	84.2
Yes	29	15.8
Uterine Artery Notch (%)		
No	170	92.4
Unilateral or bilateral	14	7.6
Outcome parameters		
Mean gestational age at birth in weeks (Mean ± SD)	37.19 ± 0.36	Range: 35.6–38.0
Type of delivery (%)		
Spontaneous vaginal delivery	64	34.8
Cesarean section (CS)	120	65.2
CS primary	58	
CS secondary	62	
5th min Apgar (Mean ± SD)	8.54 ± 0.94	Range: 6–10
Fetal distress		
No	150	81.5
Yes	34	18.5
pH (Mean ± SD)	7.29 ± 0.09	Range: 7.04–7.41
APO		
No	128	69.6
Yes	56	30.4
Intensive care requirement (%)		
No	152	82.6
Yes	32	17.4
Gender (%)		
Female	94	51.1
Male	90	48.9
Mean birth weight in grams (Mean ± SD)	2388.18 ± 172.73	Range: 1840–2800
UCR (Mean ± SD)	0.70 ± 0.28	Range: 0.34–1.80
CPR (Mean ± SD)	1.61 ± 0.53	Range: 0.56–2.98
AUCR (Mean ± SD)	67.90 ± 33.83	Range: 7.50–176.59

UCR, umbilicocerebral ratio; CPR, cerebroplacental ratio; AUCR, amnioumblicocerebral ratio; BMI, body mass index; MCAPI, middle cerebral artery pulsatility index; UAPI, umbilical artery pulsatility index; APO, adverse perinatal outcomes; SD, standard deviation.

Table 2. Comparison of the descriptive characteristics of the participants according to their APO (adverse perinatal outcome) status.

	Normal (n = 128)	APO (n = 56)	*p* value
Maternal age	27.27 ± 5.27	26.77 ± 5.42	0.560
Gravidity	2.05 ± 1.41	1.79 ± 1.07	0.204
Parity	0.80 ± 0.93	0.57 ± 0.81	0.118
BMI	28.52 ± 4.48	28.66 ± 4.87	0.850
Disease			
No	110 (85.9%)	49 (87.5%)	0.776
Yes	18 (14.1%)	7 (12.5%)	
Smoking			
No	118 (92.2%)	50 (89.3%)	0.573*
Yes	10 (7.8%)	6 (10.7%)	
Fetal movement			
Good (>10 fetal movements in 2 hours)	121 (94.5%)	53 (94.6%)	0.999*
Poor (<10 fetal movements in 2 hours)	7 (5.5%)	3 (5.4%)	
MCAPI	1.51 ± 0.29	1.34 ± 0.33	0.001
UAPI	0.91 ± 0.20	1.07 ± 0.31	0.001
Oligohydramnios (Single deepest pocket <2 cm) (%)			
No	107 (83.6%)	48 (85.7%)	0.716
Yes	21 (16.4%)	8 (14.3%)	
Uterine Artery Notch			
No	115 (89.8%)	55 (98.2%)	0.067*
Unilateral	13 (10.2%)	1 (1.8%)	
Gestational Age at delivery (weeks) median	37.20 ± 0.34	37.17 ± 0.41	0.702
Interval scan to delivery: days, median (range)	1 (0–2)	1 (0–1)	0.762
Type of delivery			
Spontane vaginal delivery	52 (40.6%)	12 (21.4%)	0.012
Cesarean section	76 (59.4%)	44 (78.6%)	
Emergency Cesarean section	0	34 (60.27%)	
5th min apgar	8.88 ± 0.45	7.77 ± 1.27	<0.001
Fetal distress			
No	128 (100.0%)	22 (39.3%)	NA
Yes	0 (0.0%)	34 (60.7%)	
pH	7.31 ± 0.06	7.24 ± 0.12	<0.001
Intensive care requirement			
No	127 (99.2%)	25 (44.6%)	<0.001
Yes	1 (0.8%)	31 (55.4%)	
Sex			
Female	70 (54.7%)	24 (42.9%)	0.140
Male	58 (45.3%)	32 (57.1%)	
Mean birth weight in grams	2387.03 ± 171.21	2390.80 ± 177.69	0.892
UCR	0.63 ± 0.20	0.86 ± 0.36	0 < 0.001
CPR	1.74 ± 0.50	1.34 ± 0.51	0 < 0.001
AUCR	73.24 ± 32.83	55.70 ± 33.20	0.001

Independent Samples *t*-test. Pearson's Chi-square, *Fisher's Exact Test, NA, Not available; UCR, umbilicocerebral ratio; CPR, cerebroplacental ratio; AUCR, amnioumblicocerebral ratio; BMI, body mass index; MCAPI, middle cerebral artery pulsatility index; UAPI, umbilical artery pulsatility index.

Table 3. Area Under Curve analysis of different doppler parameters in predicting APO.

	AUC (95% CI)	Cut off	Sensitivity (%)	Specificity (%)	*p* value
UCR	0.707 (0.621–0.792)	0.6562	69.6	62.5	0.000
CPR	0.707 (0.621–0.792)	1.5239	69.6	62.5	0.000
AUCR	0.668 (0.58–0.756)	61.2500	64.3	64.8	0.000

CI, confidence interval; AUC, area under the curve; UCR, umbilicocerebral ratio; CPR, cerebroplacental ratio; AUCR, amnioumblicocerebral ratio.

4. Discussion

Doppler ultrasound measurements play an important role in the early detection of APO in FGR. Increased placental insufficiency in FGR leads to a pathophysiologic distribution of blood flow, such as loss of fetal cerebral blood flow advantage and decreased renal perfusion [16].

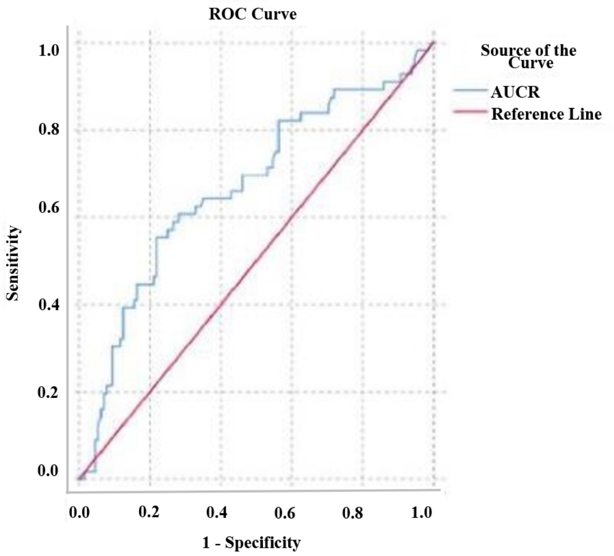

Fig. 3. ROC curve for prediction of perinatal outcome based on the amniotic-umbilical-to-cerebral ratio (AUCR) values.

Table 4. Multivariate Logistic regression analysis of UCR, CPR, and AUCR by APO status in LFGR.

	OR	95% CI		*p* value
UCR	1.640	0.473	3.510	0.630
CPR	1.557	0.235	3.301	0.646
AUCR	0.999	0.984	1.014	0.907

UCR, umbilicocerebral ratio; CPR, cerebroplacental ratio; AUCR, amnioumblicocerebral ratio; OR, odds ratio; CI, confidence interval.

The relationship with placental insufficiency in fetuses with LFGR is weaker than in fetuses with EFGR [16]. For this reason, umbilical artery Doppler findings are insufficient in detecting APO in LFGR [17]. In the study of Lees *et al*. [6], it was found that 20% of fetuses with LFGR with normal UAPI values had a decrease in MCAPI due to the brain-protective effect. It has also been reported that LFGRs with low MCAPI values are associated with fetal distress, stillbirth, and long-term negative neurologic development [18].

The CPR and UCR, the ratios between MCAPI and UAPI, were first described in 1987. It has been reported that these two ratios are more valuable than UAPI and MCAPI alone in predicting high perinatal morbidity and mortality [19,20]. CPR has been used more often than UCR because it is more easily interpreted in clinical practice [6,19]. In fetuses with growth restriction, CPR was described as being moderately to highly significant in the determination of perinatal morbidity and mortality, and the strength of this relationship was found to be even higher in the case of EFGR [7]. In this study, CPR was found to be statistically lower in the group with APO compared with the other group. Intrauterine Growth Restriction, PORTO study, it was found that the APO risk was 11 times higher in FGR with CPR <1 [21]. In addition, some recent studies showed that CPR might be useful in detecting increased placental vascular resistance in fetuses, even in healthy fetuses without FGR [22,23]. It can therefore be speculated that CPR can be used as a screening test for perinatal deterioration in the general population. Although Buca *et al*. [23] found that low CPR was associated with APO at term, CPR could not be adopted as a screening tool due to insufficient diagnostic accuracy in the study.

In the literature, there are few studies evaluating UCR in the early detection of APO. Whereas, in cases of placental insufficiency, because there is lower cerebral and higher umbilical artery impedance, the UCR tends to asymptote towards infinity, emphasizing the differences between abnormal values. CPR shows an asymptote tendency towards zero. Therefore, it can be hypothesized that the UCR is a more valuable ratio. In the secondary analysis of the TRUFFLE study, the relationship between MCA, CPR, and UCR in FGR was investigated, and it was found that UCR was a more valuable ratio than other Doppler parameters in determining the probability of being healthy without neurodevelopmental disorders (odds ratio (OR) = 0.88, 95% CI: 0.78–0.99) [8]. However, when the literature is examined, different results have been reported for both ratios. Some authors emphasize that the use of Doppler for APO in FGR is limited and there is no difference between CPR and UCR rates [7,18,24].

AUCR may be considered to have a positive effect on the prediction of APO because reduced renal blood flow in FGR leads to impaired fetal urine production and decreased AFV. Stumpfe *et al*. [10] found that the addition of SDVP to the UCR improved the predictive accuracy of negative outcomes in fetuses and that the estimation made using UCR was superior to CPR in their study with 165 term pregnant women with Small for Gestational Age (SGA). Although a statistically significant relationship was found between CPR, UCR, and AUCR and negative perinatal outcomes in fetuses with LFGR in this study, there was no statistically significant correlation between CPR, UCR, and AUCR in Doppler parameters in terms of detecting APO.

This study had some limitations. These included being a retrospective study, having a relatively small number of patients with APO, having Doppler findings measured by different physicians, obstetricians not being blinded to prenatal examination results, the cross-sectional single measure design that could not account for serial changes in Doppler indices, the evaluation of adverse intrapartum outcomes, and the use of cardiotocography alone to perform instrumental deliveries, which might overestimate the number of fetuses with actual fetal distress.

The use of close ultrasound modalities in the definition and follow-up of FGR, and being one of the few studies evaluating cases by combining Doppler parameters and amniotic fluid volume were among the strengths of the present study.

5. Conclusions

A low AUCR and CPR, a high UCR were significantly associated with APO in fetuses with late-onset fetal growth restriction in this study. There was no difference in the diagnostic performance between AUCR, CPR, and UCR in predicting adverse outcomes. Further large prospective studies are needed to confirm these findings and ascertain whether combining different obstetric and fetal characteristics might improve the diagnostic APO in singleton pregnancies with LFGR.

Availability of Data and Materials

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

Author Contributions

DKG and NC designed the research study. DKG and NC performed the research. DKG analyzed the data. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was designed according to the Declaration of Helsinki and was approved by Medipol University Review Board. Ethics committee approval and hospital institution approval were obtained before the study and written informed consent was obtained from the patients (Date: 18 April 2022, ethic approval number: E-10840098-772.02-2915).

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Conflict of Interest

The authors declare no conflict of interest.

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