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Predicitivity of amnioumbilico-cerebral ratio on adverse neonatal outcomes compared to other doppler parameters

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Abstract

Objective: To evaluate the diagnostic accuracy of the amniotic-umbilical-to-cerebral ratio (AUCR), a new ratio used to predict short-term adverse perinatal outcomes (APO) in pregnant women.

Methods: This prospective cross-sectional study was conducted in an obstetrics outpatient clinic to show the sensitivity and specificity of umblico-cerebral ratio (UCR), cerebroplacental ratio (CPR), and AUCR measurements obtained in Doppler ultrasound examinations in pregnant women between 37 0/7 and 41 6/7 weeks of pregnancy in predicting negative intrapartum or postpartum outcomes (fetal distress, Apgar score <7 at 5 min, umbilical arterial pH <7.1, admission to neonatal intensive care unit, and intrauterine death).

Results: In this study, 260 pregnant women were evaluated, and 49 had negative intrapartum or postpartum outcomes. The UCR value was statistically significantly higher in the group with APO (p<0.001), but the CPR (p=0.001) and AUCR (p<0.001) values were lower. The AUC for CPR, UCR, and AUCR were 0.665 (95% CI: 0.566-0.763), 0.665 (95% CI: 0.566-0.763), and 0.686 (95% CI: 0.592-0.780), respectively. In the 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 regarding detecting APO (p>0.05). All patients included in the study gave birth within 24 hours after Doppler ultrasound.

Conclusion: This study found that CPR, UCR, and AUCR could predict APO in term pregnant women. There was no difference in their diagnostic performance.

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

Introduction

The use of fetal ultrasound has brought significant developments in obstetrics. Biometric measurements can estimate the weight of the fetus in the womb, and thus, risky conditions such as developmental delay or macrosomia can be predicted.[1] In addition to biometric measurements, it provides the opportunity for detailed anatomy scanning, allowing the detection and sometimes treatment of many anomalies in the intrauterine period.[2] In addition, Doppler ultrasound measurements, which evaluate blood flow in uteroplacental vessels, have begun to be frequently used in obstetric patient management. The most commonly examined vessels are the umbilical artery (UA), umbilical vein (UV), uterine artery (UtA), and middle cerebral artery (middle cerebral artery - MCA).[3] With the Doppler analysis, many diseases, such as intrauterine growth retardation, preeclampsia, fetal anemia, twin-to-twin transfusion syndrome, fetal cardiac anomalies, etc., can be diagnosed, followed up, and treated.[4]

Doppler ultrasonography (DUSG) is a fast, reliable, non-invasive examination method for evaluating uteroplacental and fetoplacental physiology and pathophysiology. In recent years, many reviews

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have been published on Doppler applications in obstetrics. In light of these, DUSG is widely used in the evaluation of fetal well-being, especially in high-risk pregnancies, and is used in the assessment of perinatal mortality and morbidity.[5] It has become an essential step in reducing the rate. DUSG provides findings earlier than other tests in the early diagnosis of fetal distress and provides a significant advantage with this feature.[6]

The incidence of perinatal adverse outcomes among low-risk pregnancies has been reported as 18% in the literature.[2] In addition to growth disorders, even in uncomplicated pregnancies, abnormal Doppler findings, and especially the cerebroplacental ratio (CPR), which is defined as the ratio between the middle cerebral artery (MCA) and the umbilical artery (UA) pulsatility index (PI), is effective in reducing adverse perinatal outcomes (APO).[3-7]

An important ultrasound marker in the evaluation of fetal health is the amniotic fluid volume (AFV). The amniotic fluid comprises a high percentage of fetal urine and lung fluid. The reabsorption of amniotic fluid occurs through fetal swallowing and absorption from the vessels in the amniotic layer of the placenta.[8] The single most profound vertical pocket technique (SDVP) and the amniotic fluid index (AFI) are widely used in routine obstetric care to measure AFV. SDVP is superior to AFI in reducing unnecessary labor induction and cesarean deliveries. Oligohydramnios (SDVP <2 cm) is known to be associated with APO.[9] However, decreased AFV is associated with APO.[10]

Few studies have investigated amniotic volume in umbilical-cerebral Doppler parameters in term pregnancies. For this reason, we used the amniotic-umbilical-to-cerebral ratio (AUCR), a new ratio obtained by the ratio of SDVP to umblicocerebral ratio (UCR), to evaluate its power in predicting APO in term pregnancies and its superiority over other known Doppler parameters such as CPR and UCR.

Methods

This prospective cross-sectional research was conducted at Medipol University Bahçelievler Medipol Hospital with 260 pregnant women. Our institution's ethics committee approved the study (Date: June 1st, 2022, Reference number: E-10840098-772.02-3127), and informed consent was obtained from all participants.

Sociodemographic data, maternal age, body mass index (BMI), smoking, alcohol use, socioeconomic status, parity, maternal diseases, and the participants' previous and current pregnancy data were evaluated. All women underwent induction of labor at week 41 if the spontaneous onset of labor did not occur. 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 hours, oxytocin induction was initiated. In cases of a favorable cervix, artificial rupture of the membranes and oxytocin infusion were used. There were no cases of hyperstimulation. All patients were inducted with a low-dose oxytocin protocol. Less than 100 mU of oxytocin was started in the first 40 minutes of induction, and a total increase of less than 600 mU of oxytocin was achieved in the first two hours. There was no pathological finding in intrapartum fetal cardiotography before oxytocin induction in all patients.

Gestational age was calculated from the last menstrual period in all assessments and was confirmed using the crown-rump length (CRL) measurements in the first trimester. All participants were selected from among patients prescreened at 28-32 weeks to exclude early FGR. Doppler measurements were performed using Voluson scanners (GE, Turkey). Doppler parameters were set automatically and were 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 devices 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 the UA was studied in a free loop of the umbilical cord.[11]

CPR was defined as the ratio between MCA PI and UA PI, and UCR was defined as the ratio between UA PI and MCA PI. The single deepest vertical pocket (SDVP) technique was used to estimate AFV. AUCR was calculated as the ratio of SDVP to UCR: AUCR = SDVP/(UA PI/MCA PI).

Consecutive singleton pregnancies with maternal age between 18 and 35 years and between 37 0/7 and 41 6/7 weeks of gestation were included in this study. The exclusion criteria were multiple pregnancies, structural or chromosomal abnormalities, maternal medical complications, FGR, fetal infection, or maternal drug intake. All patients included in the study gave birth within 24 hours after Doppler ultrasound. Patients whose birth exceeded 24 hours after Doppler ultrasound were excluded from the study.

The primary outcome was to evaluate the importance of AUCR in the early detection of APO (fetal distress, Apgar score <7 at 5 min, umbilical arterial pH <7.1, admission to the neonatal intensive care unit, intrauterine death) in term pregnancies. The secondary outcome was to evaluate the diagnostic accuracy of such Doppler indices in detecting individual components of the primary outcome.

Statistical Analysis

The data analysis used number (n), percentage (%), mean, standard deviation, and minimum and maximum values. The normality of the data distribution was evaluated according to the skewness and kurtosis coefficient. Students' t-test was used to compare the mean of two independent groups. Pearson's 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, and in the model using the Enter method, UCR, CPR, and AUCR values explained 20.2% of APO according to Nagelkerke R Square (Nagelkerke R2). Receiver operating characteristic (ROC) curves were plotted for UCR, CPR, and AUCR values, and the areas under the ROC curves (AUC) were compared between UCR, CPR, and AUCR. Data were analyzed using the Statistical Package for the Social Sciences version 26.0 software package (SPSS 26.0). In the 95% confidence interval (CI), significance was considered $p<0.05$.

According to the literature, the incidence of APO among low-risk pregnancies has been reported as 18%.[2] Based on these data: (a) To detect APO, the sensitivity and specificity of AUCR should be 45% and 75%, respectively. (b) At least 240 participants were required to detect an alpha error of 0.05, a 10% increase in sensitivity and specificity values, and achieve 80% statistical power. Two hundred sixty participants were evaluated because patient losses were anticipated.

Results

The participants' mean age was 28.68±4.47 (range, 18-40) years, and their mean gravidity, parity, and BMI were 1.62±0.93, 0.61±0.90, and 29.14±3.31 kg/m^2, respectively (Table 1). The mean week of birth, UAPI, MCAPI, SDP, and fetal weight of the study group were 37.60±0.81, 0.87±0.24, 1.42±0.31, 5.45±1.51 and 3137.48±272.79 g, respectively. The group's mean week of birth and birth weight were 39.28±2.06 and 3382.71±304.82 g, respectively. Approximately half of the newborns (51.5%) were born with NSD, and 58.8% were females. Fifteen percent of the newborns had fetal distress, 7.3% required intensive care, 8.1% had blood gas pH below 7.1, and 8.1% had an Apgar score of less than seven at the 5th minute. Of the mothers, 18.8% had APO. The participants' mean UCR, CPR, and AUCR were 0.64±0.21, 1.75±0.68, and 9.57±4.30, respectively.

Gravidity ($p<0.001$) and parity ($p<0.001$) averages in the study group were statistically significantly lower in the APO group. The UAPI value ($p<0.001$) and the mean week of delivery ($p=0.043$) were statistically significantly higher in the APO group, but the mean TEC value ($p=0.026$) was found to be lower. The APO group's cesarean section rate was significantly higher ($p<0.001$). The UCR value was statistically significantly higher in the APO group ($p<0.001$), and the CPR ($p=0.001$) and AUCR ($p<0.001$) values were lower (Table 2).

Table 1. Distribution of descriptive characteristics of the participants

Variables	All pregnancies (n = 260)	
Age (Mean±SD)	28.68±4.47	Range: 18-40
Gravidity (Mean±SD)	1.62±0.93	Range: 1-6
Parity (Mean±SD)	0.61±0.90	Range: 0-5
BMI (Mean±SD)	29.14±3.31	Range: 22.03-43.25
The week when USG was performed (Mean±SD)	37.60±0.81	Range: 36.5-41.0
UAPI (Mean±SD)	0.87±0.24	Range: 0.24-1.86
MCAPI (Mean±SD)	1.42±0.31	Range: 0.78-2.30
SDVP (Mean±SD)	5.45±1.51	Range: 1.30-11.00
Estimated Fetal weight (Mean±SD)	3137.48±272.79	Range: 2490-4790
Mean gestational age at birth in weeks (Mean±SD)	39.28±2.06	Range: 37.0-70.0
Mean birth weight in grams (Mean±SD)	3382.71±304.82	Range: 2630-4750
Sex (n/%)		
Male	107	41.2
Female	153	58.8
Type of delivery (n/%)		
NSD	134	51.5
CS	126	48.5
Fetal distress (n/%)		
No	221	85.0
Yes	39	15.0
Neonatal intensive care requirement (n/%)		
No	241	92.7
Yes	19	7.3
Arterial blood gas pH (n/%)		
≥7.1	239	91.9
<7.1	21	8.1
Apgar at 5 minute (n/%)		
≥7	239	91.9
<7	21	8.1
APO (n/%)		
No	211	81.2
Yes	49	18.8
UCR (Mean±SD)	0.64±0.21	Range: 0.12-1.41
CPR (Mean±SD)	1.75±0.68	Range: 0.71-8.25
AUCR (Mean±SD)	9.57±4.30	Range: 1.00-37.29

UCR, umbilicocerebral ratio; CPR, cerebroplacental ratio; AUCR, amnioumblicocerebral ratio, BMI; body mass index, MCA PI;middle cerebral artery pulsatility index ,UAPI; umbilical artery pulsatility index, SDVP;single deepest vertical pocket

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

	Normal (n=211)	APO(n=49)	p-value
Maternal age (Mean±SD)	28.82±4.51	28.04±4.29	0.270
Gravidity (Mean±SD)	1.72±0.96	1.20±0.65	<0.001***
Parity (Mean±SD)	0.71±0.94	0.18±0.57	<0.001***
BMI (Mean±SD)	29.15±3.20	29.07±3.82	0.885
UAPI (Mean±SD)	0.83±0.18	1.06±0.37	<0.001***
MCAPI (Mean±SD)	1.43±0.30	1.39±0.34	0.472
SDVP (Mean±SD)	5.57±1.38	4.92±1.88	0.026*
Estimated fetal weight (Mean±SD)	3143.49±266.82	3111.61±298.69	0.462
Mean gestational age at birth in weeks (Mean±SD)	39.03±0.73	40.34±4.38	0.043*
Mean birth weight in grams (Mean±SD)	3381.61±290.13	3387.45±364.75	0.917
Interval scan to delivery: days, median (range)	1(0-2)	1(0-1)	0.793
Sex (n/ %)			
Male	89 (83.2%)	18 (16.8%)	0.485
Female	122 (79.7%)	31 (20.3%)	
Type of delivery (n/%)			
Spontane vaginal delivery	126 (94.0%)	8 (6.0%)	<0.001
Cesarean section	85 (67.5%)	41 (32.5%)	
Emergency Cesarean section non-reassuring fetal status.	0	39(30.9%) Spontane vaginal delivery	
Fetal distress (n/%)			
No	211 (95.5%)	10 (4.5%)	NA
Yes	0 (0.0%)	39 (100.0%)	
Neonatal intensive care requirement (n/%)			
No	211 (87.6%)	30 (12.4%)	NA
Yes	0 (0.0%)	19 (100.0%)	
Arterial blood gas pH (n/%)			
≥7.1	211 (88.3%)	28 (11.7%)	NA
<7.1	0 (0.0%)	21 (100.0%)	
Apgar at 5 minute (n/%)			
≥7	211 (88.3%)	28 (11.7%)	NA
<7	0 (0.0%)	21 (100.0%)	
UCR (Mean±SD)	0.60±0.16	0.80±0.31	<0.001
CPR (Mean±SD)	1.82±0.69	1.47±0.58	0.001
AUCR (Mean±SD)	10.04±4.10	7.54±4.62	<0.001

Independent Samples Test. Pearson Chi-square. NA: Not applied. *p<0.05, **p<0.01, ***p<0.001. UCR, umbilicocerebral ratio; CPR, cerebroplacental ratio; AUCR, amnioumblicocerebral ratio, BMI; body mass index, MCA PI; middle cerebral artery pulsatility index, UAPI; umbilical artery pulsatility index, SDVP;single deepest vertical pocket

The AUC for CPR, UCR, and AUCR were 0.665 (95% CI: 0.566-0.763), 0.665 (95% CI: 0.566-0.763), and 0.686 (95% CI: 0.592-0.780), respectively (Figure 1A, B and C, Table 3).

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

	AUC (95% CI)	Cut off	p-value	Sensitivity (%)	Specificity (%)
CPR	0.665 (0.566-0.763)	1.5699	<0.001	63.3	60.2
UCR	0.665 (0.566-0.763)	0.6498	<0.001	61.2	64.0
AUCR	0.686 (0.592-0.780)	8.2345	<0.001	65.3	64.0

AUC, area under the curve; UCR, umbilicocerebral ratio; CPR, cerebroplacental ratio.

Multivariate logistic regression analyses of CPR, UCR, and AUCR according to APO status are denoted in Table 4. An increase in UCR was found to increase the risk of having APO by 2.646 times (OR, 95% CI:.[1.452-6.655]; p=0.032). A decrease in CPR increased the risk of having APO by 2.263 times (OR, 95% CI:.[1.073-6.110]; p=0.039). A reduction in AUCR increased the risk of having APO by 3,935 times (OR, 95% CI:.[1.984-6.214]; p=0.011). There was no statistically significant correlation between CPR, UCR, and AUCR Doppler parameters regarding detecting APO (p > 0.05).

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

	OR	95% CI		p-value
CPR	2.263	1.073	6.110	0.039
UCR	2.646	1.452	6.655	0.032
AUCR	2.935	1.984	6.214	0.011

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

Discussion

Fetal hypoxia detected in term infants is the physiologic, corrective response to adverse postnatal perinatal hypoxia. In the case of hypoxia, most fetal cardiac output is directed from the periphery to the critically vital organs, especially to the brain.[12] Decreased cerebral impedance resulting from hypoxia causes an increase in diastolic flow in the MCA and a decrease in the UA's diastolic flow due to increased placental resistance.[13] For this reason, Doppler ultrasound can be considered a valuable diagnostic tool in the early prediction of the presence of APO in cases of fetal hypoxia. The use of Doppler ultrasound in the evaluation of fetal hemodynamics has significantly reduced perinatal morbidity and mortality rates in pregnancies with FGR.[1-3]

Gass et al. reported that the incidence of APO among low-risk pregnancies was 18% in their study.[2] In addition to growth disorders, it is known that abnormal Doppler findings, especially CPR, effectively reduce APO in healthy pregnancies.[3-7] In the present study, per the literature, CPR in healthy pregnant women without IUGR was found to be statistically significant in detecting APO.

There are few studies in the literature evaluating the early detection of APO using UCR, also known as the inverse ratio. In cases of placental insufficiency, because of 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, the hypothesis that the UCR is a more valuable ratio can be defended. The secondary analysis of the TRUFFLE study investigated the relationship between MCA, CPR, and UCR in FGRs and found that the UCR was a more valuable ratio than other Doppler parameters in determining the probability of being healthy without neurodevelopmental impairment.[14] Hecker et al. found that the UCR obtained from a Doppler ultrasound performed 14 days before birth detected infants with SGA with APO with a sensitivity of 93%8. In another study evaluating CPR, UCR, and their relationship with adverse perinatal outcomes in 130 patients with gestational diabetes, MCA PI was found to have the best predictive value. No significant correlation was found between UA PI and CPR. In addition, a significant correlation was found between low birth umbilical pH and UCR.[15] However, different results were reported regarding CPR and UCR when the literature was reviewed. Some authors emphasize that using Doppler for adverse perinatal outcomes in FGR is limited, and there is no difference between CPR and UCR.[16-18]

In hypoxia, cerebral blood flow increases due to the fetal brain protective effect, and renal perfusion decreases. This leads to impaired fetal urine production and a decrease in AFV. The literature emphasizes that a reduction in AFV is associated with an increased risk of APO.[10-19] Decreased AFV (AFI <5 cm) leads to a higher rate of 5-minute Apgar scores <7.[20] In addition, low AFI is an independent predictor of delivery timing for fetuses with SGA at birth.[21] Destegül et al. found that CPR in term fetuses with isolated oligohydramnios was lower than in fetuses without oligohydramnios in their study perfor-

med with 98 patients. In patients with CPR <1.08, they found an increase in cesarean section rates due to fetal distress, low 1st and 5th minute APGAR scores, and higher neonate intensive care unit acceptance rates.[22] In light of the literature, it can be thought that AUCR, a new ratio calculated using SDVP, is effective in detecting APO status. In their study with term pregnant women with SGA, Stumpfe et al. found that adding SDVP to the UCR ratio improved the prediction of APO in fetuses and that the estimation made using UCR was superior to CPR.[2] In this study, it was found that CPR, UCR, and AUCR were statistically significant in terms of predicting APO in term and post-term pregnant women. There was no statistically significant correlation between CPR, UCR, and AUCR Doppler parameters regarding detecting APO.

This mail limitation of this study could be attributed to its relatively small sample size. In the cross-sectional single-measurement design in which serial changes in Doppler measurements were not evaluated, obstetricians were not blinded to prenatal examination results. They overestimated the number of fetuses with actual fetal distress because cardiotocography alone was used to assess APO. Also, the role of Doppler in detecting more serious but rare outcomes, such as fetal death, could not be evaluated because there were no cases of intrauterine death. The strengths of this study were its prospective design, Doppler measurements made by a single specialist, use of near-term ultrasound modalities in the definition and follow-up of FGR, and being one of the few studies to evaluate fetuses by combining Doppler parameters and AFV.

Conclusion

In the present study, low CPR and AUCR and high UCR were significantly associated with adverse perinatal outcomes in term pregnant women.

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