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The predictive value of ultrasonographic parameters for adverse neonatal outcomes at 40-41 weeks of gestation

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Abstract

Objective: To investigate the role of the cerebroplacental ratio (CPR) and other ultrasonographic parameters associated with adverse neonatal outcomes in a cohort of singleton pregnancies at 40-41 weeks of gestation.

Methods: This prospective study included patients who attended the obstetric unit of a tertiary hospital at 40 0/7 and 40 6/7 weeks of gestation. A fetal Doppler ultrasound including the umbilical artery (UA) pulsatility index (PI) and middle cerebral artery (MCA) PI, placental calcification, fetal biometry and amniotic fluid index (AFI) of the study population were recorded. All patients were followed up until delivery. Umbilical pH <7.20, Apgar score <7 at the 5th minute, transfer of newborn to the nonatal intensive care unit, and cesarean section due to non-reassuring fetal status were considered as adverse neonatal outcomes.

Results: MCA PI and CPR were lower in the adverse neonatal outcome group compared with the control group (1.14±0.19 vs. 1.25±0.27; p=0.046 and 1.44±0.33 vs. 1.62±0.45; p=0.049, respectively). The mean birthweight and percentile for GA were lower in women with adverse neonatal outcomes (3371±396 vs. 3548±449, p=0.034; 45.21±26.93 vs. 59.4±27.06, p=0.011). Polyhydramnios during Doppler ultrasound examination (OR:6.32), oligohydramnios at hospitalization (OR:4.78), and fetal birthweight percentile (OR:0.98) for GA at birth were found as significant variables to predict adverse neonatal outcomes.

Conclusion: CPR may not be useful in prediction of adverse neonatal outcome at 40-41 weeks gestation. Fetal weight percentile for GA at birth and amniotic fluid abnormalities can help physicians predict adverse neonatal outcomes in women with pregnancies at 40-41 weeks gestation.

Keywords: Adverse neonatal outcome, cerebroplacental ratio, full-term pregnancy, oligohydramnios; polyhydramnios

Introduction

The expected delivery date in human pregnancies averages 40 weeks and term delivery varies from 37 to 42 weeks. The incidence of adverse neonatal outcomes in the full-term period is lower in uncomplicated pregnancies delivered between 39-40 weeks of gestation.[1] Early detection of high-risk pregnancies can prevent problems linked to maternal and perinatal morbidity and mortality after this period. By the time labor begins, placental blood flow can decrease up to 60%, and fetal distress can develop in patients with placental insufficiency.[2] Therefore, close follow-up is recommended for high-risk pregnancies.[3] Modified biophysical scoring including nonstress tests (NSTs) and amniotic fluid assessments are used in routine antenatal care of women with full-term low-risk pregnancies. However, it has been shown that adverse perinatal outcomes are also frequent in patients assessed as low-risk during prenatal follow-up or at the time of delivery.[4]

The global stillbirth rate has been reported recently as 13.9 per 1000 total births.[5] Complications or insufficiency of the placenta were observed as the most common preventable cause of stillbirth (75%).[6] To date, feto-maternal ultrasound, fetal cardiac function, and angiogenic markers have been studied associated with placental dysfunction.[7] In routine obstetric practice, ultrasound Doppler of the umbilical artery (UA) and the middle cerebral artery (MCA) are used for the diagnosis and follow-up of pregnancies with placental insufficiency. It has been shown that a low cerebroplacental ratio

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(CPR) obtained as MCA PI/UA PI is associated with adverse perinatal outcomes (fetal distress, hospitalization in neonatal intensive care unit (NICU), intrauterine death or perinatal mortality) in pregnant women beyond 36 weeks of gestation, even in the absence of fetal developmental delay.[8] However, in another study, only a weak association was shown between the CPR ratio and poor neonatal outcome at 35-37 weeks of gestation, with detection rates of about 13% to 26%.[9] Similar to this, CPR during hospitalization for delivery was found not to be associated with intrapartum compromise or poor neonatal outcomes.[10]

After 39 weeks of gestation, there is an increase in poor neonatal outcomes compared with the previous weeks of pregnancy.[1] The reason for this is assumed to be the relative insufficiency of the placenta in some pregnancies. Thus, there is a dilemma in extending pregnancy beyond 40 or 41 weeks because fetuses are more likely to show unexpected fetal compromise. During term pregnancy, gestational age (GA) from 40 0/7 and 40 6/7 weeks is a transitional period for perinatal decisions to determine a suitable delivery time. To date, few studies exist regarding the use of CPR to predict adverse neonatal outcomes in the second period of full-term pregnancies.

Our purpose in this study was to investigate whether there was a link between ultrasonographic markers including CPR and adverse perinatal outcomes in a cohort of women at 40-41 weeks gestation.

Methods

This was a prospective study including women at 40-41 weeks of gestation who visited a tertiary care unit between August 2021 and April 2022.

Patient characteristics

Women aged 18-45 years who gave birth before 42 weeks of gestation were enrolled in this study. Only one Doppler ultrasound examination was recorded per fetus and included in the analysis. GA was confirmed using the fetal crown-rump length at 11-13 weeks or fetal head circumference at 19-24 weeks gestation.[11] (Estimated fetal weight) EFW was estimated with the Hadlock IV formula using biparietal diameter, head circumference, abdominal circumference, and femur length.

Exclusion criteria were contractions at admission, multiple pregnancy, fetal abnormalities, moderate (30.1-35 cm) or severe polyhydramnios (>35.1cm), preeclampsia or gestational hypertension, GA not determined in first or second-trimester ultrasound, intrauterine growth restriction (IUGR), aneuploidy, and genetic syndromes, maternal obesity Class III [body mass index (BMI) >40 kg/m2), maternal pre-existing chronic medical diseases or bad obstetric history (previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortions, history of IUGR, stillbirth, preterm labor, low birth weight, and congenital anomaly), signs of intrauterine infection (fever, uterine tenderness, foul-smelling amniotic fluid, purulent cervical discharge, and maternal or fetal tachycardia), antepartum hemorrhage, and scarred uterus after previous cesarean section (CS) or myomectomy. IUGR is defined as either a very small fetus (abdominal circumference (AC) or EFW < 3rd percentile) or a small fetus (AC or EFW < 10th percentile) with additional abnormal Doppler findings or a decrease in AC or EFW by two quartiles or more (The Delphi consensus criteria).

A sonography was made and estimated fetal weight, Doppler measurements of umbilical and cerebral arteries, amniotic fluid volume, fetal movements, dense particles in the amniotic fluid, presence of placental calcification or placental lacunes were recorded. Oligohydramnios was defined as a single deepest pocket of <2 cm amniotic fluid or amniotic fluid index of <5 cm and polyhydramnios as a single deepest pocket of >8 cm of amniotic fluid or amniotic fluid index of >24 cm. CPR was determined as the ratio between MCA PI and UA PI. Doppler parameters were calculated using a high-quality automated recording of at least three consecutive waveforms and an insonation angle as low as possible (below 30 degrees). The first and second authors conducted all Doppler examinations while the fetus was in fetal quiescence. Hitachi Arietta 65 ultrasound devices and 1-5 MHz C253 convex probes were used for ultrasonographic examinations. Doppler ultrasound of fetal cerebral arteries can be performed at 40-41 weeks of gestation without any manipulation to elevate the fetal head from the pelvis.[12] However, we excluded patients with fetal head engagement to prevent non-accurate measurements of MCA Doppler PI.

Management

The obstetricians involved in the delivery were blinded to the results of the Doppler examinations. According to our hospital protocol, indications for hospitalization were active labor, rupture of membranes, polyhydramnios, oligohydramnios, and 41 and beyond weeks' gestation when there were no signs of labor. The study population, excluding those who required birth induction, was followed up until the birth. Cervical ripening was performed using prostaglandin E2 and labor induction with oxytocin when necessary.

Outcome measures

Small for gestational age (SGA) was described as birthweight under 10p, appropriate for gestational age (AGA)

as birthweight between 10p and 90p, and large for gestational age (LGA) as birthweight over 90p.[13,14] Neonatal cord pH <7.20, Apgar score <7 at the 5th minute, transfer of newborn to the NICU, and cesarean section due to non-reassuring fetal status were considered adverse neonatal outcomes. Indications for neonatal special care unit admission were tachypnea and hypoglycemia.

Ethics

The Institutional Review Board of a tertiary institution approved the study (no: 2021.06.111). Written informed consent was given by women who agreed to participate in this study. The study was performed in accordance with World Medical Association's Helsinki Declaration (2013, Brazil, Fortaleza).

Statistical Analysis

The SPSS version 22 software package was used for statistical analysis (IBM Corp, Armonk, NY). Mean (standard deviation), median (interquartile ranges), and n (%) are used to summarize statistics. Normal distribution was evaluated using the Kolmogorov-Smirnov test. Qualitative factors were compared using the Chi-square test or Fisher's exact test. Parametric variables were compared between two groups using the Mann-Whitney U-test or Student's t-test. The multivariable logistic regression test was used to identify factors associated with adverse neonatal outcomes. Polyhydramnios during ultrasoound examination, oligohydramnios at hospitalization, CPR, and birthweight percentile at birth were evaluated to define analysis of the association of antenatal and intrapartum parameters with adverse neonatal outcomes in the study population. ROC curve analysis was conducted for birthweight percentile in order to establish a cutt-off value for predicting adverse neonatal outcome. The minimum sample size was calculated as 180 patients with a power of 80% and a type 1 error of 0.05 (7). P<0.05 was accepted as the significance level.

Results

Participants and baseline characteristics

A total of 203 pregnancies met the selection criteria, but 18 were dismissed because they were lost to follow-up or delivered at another hospital. One hundred eighty-five singleton pregnancies, with 92 male and 93 female fetuses were included. The population characteristics are shown in Table 1. The mean maternal age was 26.38±5.01 years, nulliparous women made up 53.8% of the population, the mean BMI during ultrasound evaluation was 29.48±3.87 kg/m2, and gestational ages at Doppler ultrasound examination and delivery were 40.61±0.44 and 40.86±0.43 weeks, respectively. The mean estimated fetal weight at Doppler ultrasound examination was higher than the mean birthweight (3623±321 vs. 3521±408 g, respectively, p=0.034). 63.8% of patients underwent induction of labor. The total number of cesarean section was 48 (25.9%). The most common indications in study population for cesarean section were non-assured fetal status (n=16, 8.6%), macrosomia at the ultrasound (n=8, 4.3%), and cephalopelvic disproportion (CPD) (n=7, 3.8%). No instrumental deliveries were performed in women who had vaginal births.

Table 1. Characteristics of the study population

n=185, parameter	
Maternal age (years)	26.38±5.01
Smoking (n, %)	10 (5.4%)
Parity nullipara (n, %)	100 (53.8%)
Term pregnancy BMI (kg/m²)	29.48±3.87
Gestational age at ultrasound in weeks	40.61±0.44
Gestational age at delivery in weeks	40.86±0.43
Ultrasound-delivery interval in days	0 (0-11)
Estimated fetal weight in grams	3623±321
Estimated fetal weight centile	65.02±22.4
Umbilical artery (UA) pulsatility index (PI)	0.80±0.15
Middle cerebral artery (MCA) PI	1.23±0.25
Cerebroplacental ratio (CPR)	1.59±0.44
Birthweight (grams)	3521±408
Birthweight percentile	57.27±27.45
Fetal sex-Female	93 (50.3%)
Onset of labor Induction-Spontaneous	66 (36.1%)
Mode of delivery Cesarean	48 (25.9%)
Apgar score <7	2 (1.1%)
Neonatal special care unit	21 (11.4%)
Neonatal intensive care unit	6 (3.2%)
Abnormal fetal heart rate requiring CS	14 (7.57%)
Intrauterine ex	1 (0.5%)

CS: Cesarean section

Labor results and perinatal outcomes

Adverse perinatal outcomes occurred in 28 (15.1%) patients including one stillbirth. The cesarean rate in the adverse neonatal group was more prevalent than in the normal group (39.6% vs. 18.4%, p<0.001). Women with adverse neonatal outcomes had lower mean birthweights and birthweight percentiles than women with normal outcomes (3371±449 vs. 3548±396, p=0.034; 45.21±26.93 vs. 59.43±27.06, p=0.011, respectively) (Table 2). LGA rate in the normal group was higher than in the adverse neonatal outcome group although it was not significant sta-

tistically (p=0.086). The umbilical cord pH of the adverse neonatal group was significantly lower compared with the non-adverse outcome group (7.25±0.07 vs. 7.28±0.04, p=0.034). Fetuses in the adverse neonatal group required the neonatal special care unit more than the normal group (42.9% vs. 5.7%, p<0.001). The fetuses of six (21.04%) patients in the adverse outcome group were transferred to the NICU. Neonatal sepsis (n=1), hypernatremia (n=1), tachypnea (n=3), and neonatal convulsions (n=1) were observed in babies transferred to the NICU. Six fetuses (21.04%) had a umbilical venous bloud pH <7.20. One of the patients that were examined at 40+2 weeks of gestation was diagnosed as having a stillbirth 2 days after. She had a vaginal birth and the birthweight was 3030 g (22.5p). Shoulder dystocia occurred in one multiparous patient with a birthweight of 3920 g.

Table 2. Comparison of the maternal and pregnancy parameters according to the adverse neonatal outcome

	No adverse neonatal outcomes (n=157)	Adverse neonatal outcomes (n=28)	p
Maternal age in years	26.15±4.94	27.43±5.38	0.22
Term pregnancy BMI	29.59±4.03	28.86±2.73	0.24
Gestational age at ultrasound in weeks	40.61±0.45	40.59±0.37	0.77
Gestational age at delivery in weeks	40.88±0.44	40.75±0.37	0.16
Ultrasound-delivery interval in days	0 (0-11)	0 (0-7)	NS
Estimated fetal weight in grams	3628±320	3530±317	0.14
Estimated fetal weight centile	65.89±22.71	60.08±20.59	0.21
Dense particles in amnion	69 (43.9%)	9 (32.1%)	0.24
Placental lacunes	35 (22.3%)	5 (17.9%)	0.80
Placental calcification	75 (47.8%)	15 (53.6%)	0.57
Reduced fetal movement	42 (26.9%)	4 (14.3%)	0.23
Polyhydramnios at hospitalization	18 (11.5%)	8 (28.6%)	0.016
Oligohydramnios at hospitalization	11 (7%)	7 (25%)	0.003
UA PI	0.80±0.16	0.81±0.12	0.64
MCA PI	1.25±0.27	1.14±0.19	0.046
CPR	1.62±0.45	1.44±0.33	0.049
Birth induction	99 (63.9%)	18 (64.3%)	NS
Mode of delivery-CS	29 (18.4%)	19 (39.6%)	<0.001
Mode of delivery			<0.001
according to indication	6 (20.7%)	-	
Failed birth induction	10 (34.5%)	1 (5.3%)	
CPD	7 (24.1%)	1 (5.3%)	
Macrosomia	5 (17.2%)	0	
Elective CS	1 (3.4%)	-	
Labor progress failure	-	16 (84.2%)	
Fetal distress	-	1 (5.3%)	
Placental abruption			
Meconium-stained amniotic fluid	8 (5.1%)	4 (14.3%)	0.088

CPD: Cephalopelvic disproportion, CS:Cesarean section

Comparison of groups

MCA PI and CPR were lower in the adverse neonatal group compared with the normal group (1.14±0.19 vs. 1.25±0.27; p=0.046 and 1.44±0.33 vs. 1.62±0.45; p=0.049, respectively) (Table 3). UA PI values did not differ significantly between the groups (p=0.64). Mild polyhydramnios diagnosis during Doppler ultrasound examination was present more frequently in the adverse neonatal group (28.6% vs. 11.5%, p=0.016). Oligohydramnios at hospitalization was more frequent in the adverse neonatal group (25% vs. 7%, p=0.049). There was no difference between the groups in terms of maternal age, GA at ultrasound examination, GA at delivery, ultrasound-delivery interval, estimated fetal weight, dense particles in amnion fluid, presence of placental lacunes or calcification, and reduced fetal movement.

Table 3. Comparison of the neonatal outcomes between the groups

	No adverse neonatal outcome group (n=157)	Adverse neonatal outcome group (n=28)	p
Birthweight in grams	3548±396	3371±449	0.034
Birthweight percentile	59.43±27.06	45.21±26.93	0.011
SGA	10 (6.4%)	4 (14.3%)	0.234
AGA	119 (75.8%)	23 (82.1%)	0.464
LGA	28 (17.8%)	1 (3.6%)	0.086
Fetal sex female	78 (49.7%)	15 (53.6%)	0.70
Apgar score <7	0	2	-
Umbilical cord pH	7.28±0.04	7.25±0.07	0.034
Umbilical pH<7.2	0	6 (21.4%)	-
Neonatal special care unit	9 (5.7%)	12 (42.9%)	<0.001
Neonatal intensive care unit	-	6 (21.4%)	-

AGA:Appropriate for gestational age, LGA:large for gestational age, SGA:small for gestational age

After adjusting for potential confounding factors, polyhydramnios during the first examination (OR:6.32, p=0.001), oligohydramnios at hospitalization (OR:4.78, p=0.008), and fetal birthweight percentile (OR: -0.98, p=0.010) for GA were found as independent variables to predict adverse neonatal outcomes (Table 4). The sensitivity of the model was very low (17.9%) but the specificity was high (98.1%). When birthweight percentile cut-off is taken as 60.75, APO can be predicted with a sensitivity of 68% and a specificity of 50% (AUC:0.647).

Table 4. Multivariable logistic regression analysis of the association of antenatal and intrapartum parameters with adverse neonatal outcomes in the study population

Variable	B	SE	Wald x^2	Exp (b) (95% CI)	P
Polyhydramnios during ultrasound examination	1.844	0.569	10.51	6.32 (2.07-19.28)	0.001
Oligohydramnios at hospitalization	1.564	0.590	7.035	4.78 (1.50-15.17)	0.008
CPR	-0.735	0.568	1.677	0.48 (0.16-1.46)	0.195
Birthweight percentile	-0.022	0.009	6.588	0.98 (0.96-0.99)	0.010

CPR: cerebroplacental ratio

Discussion

Follow-up and optimal timing for labor induction are key points of clinical management to prevent adverse obstetric and perinatal outcomes in full-term and post-term pregnancies. We investigated in this study CPR and ultrasonographic factors associated with adverse neonatal outcomes beyond 40 weeks of gestation. MCA PI and CPR were found significantly lower in the adverse neonatal group compared with the normal group (p=0.046 and p=0.049; respectively). However, we did not find CPR as significant to predict the adverse neonatal outcome when all variables were evaluated together. Similar to our study, some studies have shown that UA PI, MCA PI, and CPR were not predictive or had very low predictivity for the adverse neonatal outcome at birth in non-SGA fetuses.[15-18] In contrast, some others showed that MCA PI or CPR in term pregnancies were related to intrapartum fetal compromise or adverse neonatal outcomes.[10, 19, 20] At 40 weeks of gestation, higher SGA rates and lower CPR values were found related to emergency cesarean section.[21] CPR evaluation within 14 days before delivery has also been demonstrated to be useful in identifying AGA pregnancies that are at risk for fetal hypoxia and placental insufficiency.[22] Due to dynamic changes in the placenta, the timing of Doppler evaluations can be important to evaluate its effect on perinatal outcomes. The heterogeneity between studies in the interval doppler sonography and delivery time can playing a role in the contraversy regarding the effect of CPR on neonatal outcome.

In our study population, polyhydramnios (OR: 6.32), oligohydramnios at delivery (OR: 4.78), and a lower birthweight percentile (OR: 0.98) were found to be independent variables to predict adverse neonatal outcomes at 40-41 weeks of gestation. Assessment of amniotic fluid is an essential component of fetal surveillance procedures; the prevalence of oligohydramnios increases with GA and it is related to perinatal mortality and morbidity.[23] And, with our findings we can support the affirmations that amniotic fluid abnormalities can be a risk factor for adverse neonatal outcomes in full term pregnancies. Recently, ACOG has recommended the timing of delivery in women with mild, idiopathic polyhyramnios at 39 0/7-40 6/7 weeks of gestation.[24] The presence of idiopathic polyhydramnios at term pregnancy was reported with a high risk of stillbirth, neonatal death, NICU admission, macrosomia, and cesarean section.[25] So, delivery timing in patients with mild polyhydramniosis at term can be individualized according to patient characteristics to prevent adverse neonatal outcomes.

In the literature, the stillbirth rate at 41 weeks of gestation was reported higher in fetuses with a birthweight of 3-10p (0.24%) than those of 10-90p (0.14%) and 90-97p (0.15%).[26] In addition, it was also noted that the rate of composite poor neonatal outcome was considerably higher in identified SGA than in undiagnosed SGA in pregnancies between 41.0 and 41.6 weeks (10.0% vs. 2.5%, respectively; p=0.035).[27] In our study population, birthweight percentile according to gestational age was lower in the adverse neonatal group (p=0.011), although SGA, AGA, and LGA rates were not statistically different between the two groups. In addition, we found that a birthweight percentile of 60.75 can predict adverse neonatal outcome with a sensitivity of 68% and a specificity of 50%.

Placental function gradually deteriorates over prolonged pregnancies . In a prolonged-gestation model in mice, it was observed that adding 24 hours to the gestation, which would be comparable to adding around 2 weeks to gestation in humans, resulted in fetal hypoxia and growth restriction.[28] After 39 weeks of pregnancy, cesarean section rates gradually increase; some studies have reported emergency cesarean rates as 7.0% at 41 weeks gestation and 10.9% at 42 weeks gestation.[1,29] Recently, it was demonstrated that elective labor induction at 39 weeks gestation was associated with a reduction in cesarean births and lower NICU admissions in low-risk nulliparous wo-

men.[30,31] We observed a higher rate of cesarean deliveries in the adverse perinatal outcome group compared to the normal group. This was mainly because a high percentage (84.2%) of cesarean deliveries in the normal group were performed due to non-assured fetal status. However, it should be noted that the rate of cesarean deliveries in the normal group was not low. This could be attributed to the higher occurrence of macrosomia in this group, as well as the preference of clinicians for elective cesarean sections.

Ultrasonographic markers related to suspicion or risk of relative placental insufficiency can lead to a clinical decision of labor induction in full-term pregnancies. In a study investigating the importance of intravillous and intrafibrinous particulate microcalcification in the placenta, a higher incidence of calcification was observed in intrauterine fetal demise cases.[32] Placental lacunes and grade 3 calcification were also reported to be associated with SGA and preeclampsia, respectively, in the late second trimester and third trimester.[33] Moreover, we found no differences between the groups regarding ultrasonographic and clinical features such as placental lacunes, placental calcification, dense particles in amniotic fluid, or reduced fetal movement. Variability in the evaluation of ultrasonographic parameters among physicians can lead to difficulties in comparison of studies.

This study has important strengths because we focused our prospective research on a low-risk study population at 40-41 weeks of gestation when perinatal mortality and morbidity are relatively high compared with earlier weeks of gestation. Doppler ultrasonography of patients was performed the week before delivery to allow accurate predictions and to reduce variability related to GA. The ultrasonography and clinical parameters were examined together for the prediction of adverse neonatal outcome. In addition, our findings support the hypothesis that some non-small fetuses at 40 weeks of gestation or later also have the risk of poor neonatal outcomes due to possible placental dysfunction.

The study has some limitations. Our sample size is relatively small to evaluate all factors in prediction of the adverse neonatal outcome at full-term pregnancy. Doppler ultrasonography in full-term pregnancies may not be possible in all patients so we excluded patients on whom we could not perform ultrasound examinations due to fetal head engagement. Lastly, we do not know the growth rates of fetuses included in this study.

Conclusion

CPR may be useful to identify and closely follow up fetuses at risk for fetal comprimise; however, there is no evidence to support its use to determine the delivery time in full-term or late-term pregnancies. Fetal weight percentile and amniotic fluid evaluation can be used to optimize neonatal outcomes of full-term pregnancies. Our findings support the hypothesis that some non-small fetuses at 40 weeks of gestation or later also have the risk of poor neonatal outcomes due to placental dysfunction.

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