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The role of different Doppler parameters in predicting adverse neonatal outcomes in fetuses with late-onset fetal growth restriction

Geç başlangıçlı intrauterin büyüme kısıtlılığı saptanan fetuslarda farklı Doppler parametrelerinin olumsuz neonatal sonuçları öngörmedeki rolü

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Abstract

Objective: The aim of this study is to clarify the role of different Doppler parameters such as umbilicocerebral ratio (UCR), cerebroplacentouterine ratio (CPUR), aortic isthmus, renal artery, and umbilical vein flow Doppler in predicting adverse neonatal outcomes in fetuses with late -onset fetal growth restriction.

Materials and Methods: The study included all patients diagnosed with fetal growth restriction at 32-39 weeks' gestation between 01/02/2020 and 01/02/2022 and treated at the Department of Obstetrics and Gynecology, Inonu University School of Medicine.

Results: Patients included in the study had a median gestational week at delivery of 37 (minimum 33+0-maximum 39+0), median CPR of 1.42 (minimum-maximum 0.43-3.57), and median UCR of 0.7 (minimum-maximum 0.28-2.3). Receiver operating characteristic analysis was performed to determine the performance of the measured obstetric Doppler parameters in predicting the development of adverse neonatal outcomes. Umbilical venous blood flow showed the best performance in predicting adverse neonatal outcomes [area under the curve 0.952, 95% confidence interval (CI) 0.902-0.981, p<0.001]. Multivariate logistic regression analysis showed that fetuses with abnormal CPUR had a 4.5-fold (95% CI 0.084-0.583, p=0.02) increased risk of adverse neonatal outcome, whereas fetuses with abnormal umbilical venous flow had a 1.07-fold (95% CI 0.903-0.968, p<0.001) increased risk of adverse neonatal outcome.

Conclusion: The results of this study demonstrate that the use of UCR, CPUR, umbilical venous flow, and aortic isthmus PI Doppler parameters along with umbilical artery PI and CPR are effective in predicting adverse neonatal outcomes in fetuses with late -onset fetal growth restriction.

Keywords: Doppler ultrasound, fetal growth restriction, pregnancy, adverse outcomes, umbilical artery, and umbilical vein

Öz

Amaç: Bu çalışmanın amacı geç başlangıçlı fetal büyüme kısıtlılığı saptanan fetuslarda rutin obstetrik Doppler parametrelerine ek olarak umbilikoserebral oran (UCR), serebroplasentouterin oran, (CPUR), aortik istmus, renal arter Doppler ve umblikal ven kan akımı gibi farklı Doppler parametrelerinin fetustaki olumsuz neonatal sonuçları öngörmedeki rolünü açıklamaktır.

Gereç ve Yöntemler: İnönü Üniversitesi Tıp Fakültesi Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'ne 01.02.2020-01.02.2022 tarihleri arasında başvuran, gebeliğin 32-39. haftasında fetal büyüme kısıtlılığı saptanan, çalışma kriterlerine uygun tüm hastalar çalışmaya dahil edildi.

Bulgular: Çalışmaya dahil edilen hastaların doğumda median gestasyonel haftası 37 olup (en küçük 33+0-en büyük 39+0), median serebroplasental oran (CPR) 1,42 (minimum-maksimum 0,43-3,57) ve median UCR 0,7 (minimum-maksimum 0,28-2,3) saptandı. Ölçülen obstetrik Doppler parametrelerinin

PRECIS: We investigated the predictive value of different Doppler parameters for adverse neonatal outcomes in fetuses with late-onset fetal growth restriction.

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olumsuz neonatal sonuçların gelişimini öngörmesi açısından performansının saptanması için Receiver Operating Characteristic analizi yapıldı. Umblikal ven kan akımı olumsuz neonatal sonuçları predikte etmede en iyi performansı gösterdi [Area under curve 0,952, %95 güven aralığı (GA) 0,902-0,981, p<0,001]. Çok değişkenli lojistik regresyon analizi, anormal CPUR'ye sahip fetusların 4,5 kat (%95 GA 0,084-0,583, p=0,02) olumsuz neonatal sonuç riskine sahip olduğunu, anormal umbilikal ven kan akımı olan fetuslarda ise 1,07 (%95 GA 0,903-0,968, p<0,001) kat daha fazla olumsuz neonatal sonuç riski olduğunu gösterdi.

Sonuç: Bu çalışmanın sonuçları geç başlangıçlı fetal büyüme kısıtlılığı saptanan fetuslarda umblikal arter PI ve CPR ile birlikte UCR, CPUR, umblikal ven kan akımı ve aortik istmus PI Doppler parametrelerinin kullanımının neonatal olumsuz sonuçları predikte etmede etkin olduğunu göstermiştir.

Anahtar Kelimeler: Doppler ultrasonografi, fetal büyüme kısıtlılığı, gebelik, olumsuz sonuçlar, umblikal arter, umblikal ven

Introduction

The inability of a fetus to reach its intrauterine growth and developmental potential is known as fetal growth restriction (FGR). Fetuses affected by FGR may experience increased perinatal morbidity and mortality, as well as long-term risks associated with neurological, cardiovascular, endocrine and cognitive developmental disorders[1]. FGR occurs in 3-10% of pregnancies and in about 20% of stillbirths. FGR is often difficult to define because fetal growth cannot be determined by a single biometric measurement of fetal size and the idea of growth potential is speculative. FGR can be classified into two main types, each with different characteristics such as gestational age onset, ultrasound findings, and pathological features. In particular, early-onset FGR is associated with maternal vascular malperfusion of the placenta, characterized by abnormal transformation of the spiral arteries, pathological features of the placental villi, and multifocal infarcts. These factors contribute to placental insufficiency and are the major cause of placenta-associated FGR[2,3]. Late-onset FGR is typically identified after 32 weeks' gestation and has a different pathophysiology to early-onset FGR. Placental lesions in late-onset FGR tend to be less specific and milder, and there may be changes in the way oxygen and nutrients are diffused[4]. Although late-onset FGR is not as severe as early-onset FGR, it still results in unfavorable perinatal outcomes and long-term neurodevelopmental problems[5]. Although late-onset FGR is not yet fully understood, it may result in a lower diagnosis rate in fetuses with growth restriction near term[6]. Additionally, near-term fetuses have reduced tolerance to hypoxemia, possibly due to their higher metabolic rate compared to fetuses at earlier gestational ages. Therefore, frequent monitoring of pregnancies with late-onset FGR is essential, just as it is for pregnancies with early-onset FGR.

Various parameters from conventional sonography and color Doppler sonography have been used to diagnose FGR and monitor its progression. Doppler ultrasound plays an important role in the diagnosis, monitoring, and management of FGR as it is an essential tool for detecting uteroplacental insufficiency and fetal cardiovascular adaptation to hypoxemia. In early-onset FGR, deterioration in fetal well-being usually follows a predictable pattern, with Doppler parameters showing increasing abnormalities before biophysical parameters become abnormal. However, in late-onset FGR, normal or slightly elevated umbilical Doppler indices and mildly abnormal cerebral Doppler findings may be present but not easily detectable[7]. Changes in umbilical artery (UA) Doppler and venous fields are rare, and are not an effective means of identifying the majority of late-onset FGR or predicting adverse outcomes in affected fetuses. Many studies have found an association between adverse perinatal outcomes (such as stillbirth, increased risk of caesarean section, and increased neurodevelopmental disorders at two years of age) and middle cerebral artery (MCA) vasodilation. This vasodilation is indicated by a decrease in the MCA pulsatility index (PI) or an altered ratio of MCA to UA PI[8]. In addition to all these parameters, there are recent studies showing that evaluation of various Doppler parameters such as umbilicocerebral ratio (UCR), cerebroplacentouterine ratio (CPUR), aortic isthmus, and renal artery Doppler can help diagnose FGR and predict adverse perinatal outcomes in this group of patients. Although each parameter can predict adverse neonatal outcomes in women with late-onset FGR, there has been no evaluation of these parameters in combination[9]. The aim of this study was to elucidate the specific contributions of different Doppler parameters in predicting adverse neonatal outcomes in fetuses diagnosed with late-onset FGR.

Materials and Methods

This study included all patients diagnosed with late-onset FGR at 32-39 weeks' gestation at the Department of Obstetrics and Gynecology, Faculty of Medicine, Inonu University between 01.02.2020-01.02.2022 and was conducted in accordance with the World Medical Association's Declaration of Helsinki (including the 2013 amendments) and with the approval of the Clinical Research Ethics Committee of Inonu University (Ethics Committee approval number: 2020/04). In addition, informed consent was obtained from all participants prior to enrolment.

Pregnant women were included if they met the following criteria: (i) 18-39 years of age; singleton live pregnancy; (ii) 32+0- 39+6 weeks of gestation (gestational age confirmed by first trimester ultrasound); and (iii) normal fetal anatomy.

Exclusion criteria were: (i) multiple pregnancy; (ii) major fetal anomalies (anomalies that are fatal or require prenatal or postnatal surgery), chromosomal anomalies, genetic syndromes and macroscopic placental anomalies; (iii) fetal death; and (iv) patients with eclampsia, placental abruption, disseminated intravascular coagulation.

Procedure

The diagnosis of late-onset FGR was made according to the Delphi procedure defined in 2016. All pregnant women underwent both gray-scale imaging and pulsed-wave Doppler ultrasonography with a spatial peak temporal average intensity of <100 mW/cm^2 using a 5-MHz probe (Voluson E6, GE Medical Systems). Routine fetal biometry was performed in all pregnant women with late FGR according to the International Society of Ultrasound in Obstetrics and Gynecology standard protocols, and the estimated fetal weight (EFW) was calculated using the Hadlock 4 formula[10,11]. All Doppler ultrasonography recordings were performed without fetal respiration or fetal movement. The average of three consecutive Doppler velocity waveforms from each vessel was used for analysis. To ensure that blood flow in the larger vessels was uniform and free of aliasing, the maximum speed of the color Doppler was set to high velocities. The high-pass filter was adjusted to 50 Hz, and the energy output was kept below 50 mW/cm^2. The sample volume size was adjusted to match the vessel diameter so that it was completely covered. In addition to fetal biometric measurements, UA PI, MCA PI, MCA-peak systolic velocity (PSV), cerebroplacental ratio (CPR), UCR, CPUR, uterine artery (Ut A) PI, ductus venosus PI, umbilical venous blood flow, aortic isthmus PI, and renal artery PI Doppler parameters were measured and recorded according to standards. The UA was sampled from the free loop, and PI was used to analyze the waveforms. The Doppler parameters of the MCA were measured so that the direction of blood flow and the angle between the ultrasound beams were close to 0°. An UA PI above the 95th percentile for gestational week, loss of end-diastolic flow, or end-diastolic reverse flow on UA Doppler was considered abnormal. MCA waveforms were assessed by PI and PSV. CPR was calculated by dividing MCA PI by UA PI, while UCR was calculated by dividing UA PI by MCA PI. A transabdominal approach was used to measure Ut A Doppler, with the probe angled medially in the parasagittal plane and positioned longitudinally in the lower lateral part of the abdomen. Color Doppler mapping was used to determine the point of intersection of the external iliac artery and the uterine artery, and the position of the probe was adjusted according to the orientation of the uterine artery to obtain the best insonation angle. The crossing point was used as a reference, and the sample volume was located one centimeter downstream. The contralateral uterine artery was subjected to the same procedure. The average of the two Ut A PIs was calculated as the mean Ut A PI. For Doppler measurement of the ductus venosus, color Doppler mapping was used to locate the vessel where the intra-abdominal portion of the umbilical vein joins the left inferior vena cava just below the diaphragm. Alternatively, the presence of aliasing in the midsagittal longitudinal plane of the fetal trunk or in the transverse oblique section of the upper abdomen, indicating high flow velocity in the ductus venosus, was used to identify the vessel. Triphasic ductus venosus waveforms were obtained from these standard sampling sites, and Doppler measurements were performed. To determine the umbilical blood flow, measurements were taken from the intra-abdominal portion of the umbilical vein before the first portal branches. The diameter of the umbilical vein was measured by vertically insonating and imaging the abdominal section of the vein. To calculate the internal diameter of the umbilical vein, three measurements were taken at an insonation angle that was perpendicular to the wall of the vessel and then averaged. Time-averaged maximum velocity (TAMXV) was calculated during fetal rest and apnea by measuring the maximum dimension of the waveform in steady flow for at least 10 s in another plane with an insonation angle <20°. Venous waveforms were obtained, and the maximum waveform size was measured on the basis of flow uniformity (absence of pulse). The blood flow in the umbilical vein (measured in milliliters per minute) was determined by the formula $\pi \times$ (umbilical vein diameter/2) $\times$ 0.5 $\times$ TAMXV. The measurements for aortic isthmus Doppler were obtained from either the longitudinal aortic arch or the sonographic plane of the three vessels and trachea. For renal artery Doppler measurements, a coronal section of the fetal abdomen was used to obtain a horizontal view of the aorta. The color Doppler mapping identified the renal arteries, and the scan plane was adjusted to minimize the angle of insonation. Both the right and left renal arteries were examined, and Doppler flow velocity waveforms were obtained from two different locations: near the proximal end of the aorta and before any visible major bifurcation at the distal end of the vessels. The average of the two renal artery PIs was calculated as the mean renal artery value PI. Ultrasound were examined by a single clinician who had received extensive training in fetal ultrasonography and held the Fetal Medicine Foundation Certificate of Competence in Doppler Ultrasound Examinations.

Pregnant women with late-onset FGR were scheduled for delivery at 37-39 weeks' gestation, unless there was a pregnancy complication requiring delivery. Labor management of pregnant women enrolled in the study was performed according to the routine follow-up and delivery protocols used in our hospital. The frequency of follow-up was individualized according to the week of gestation and the presence of associated circumstances (oligohydramnios, abnormal Doppler findings, maternal risk factors, comorbidity).

The following parameters were recorded; Age, gravidity, parity, abortion, body mass index (BMI), presence of FGR in obstetric history, smoking, presence of hypertensive disease/preeclampsia, abdominal circumference (AC), EFW, amniotic fluid index (AFI), UA systol/diastole (S/D) ratio, UA Doppler PI, UA Doppler RI, MCA Doppler PI, MCA PSV, CPR, UCR, Ut A Doppler PI, CPUR, ductus venosus Doppler PI, umbilical venous blood flow (mL/min), aortic isthmus and renal artery Doppler PI, day between delivery and last ultrasound scan, meconium-stained amniotic fluid, induction of labour, mode of delivery, birthweight, gender, need for active resuscitation at birth (respiratory support with endotracheal tube), APGAR score 1st minute, APGAR score 5th minutes, umbilical cord blood pH, umbilical cord blood base excess, umbilical cord blood partial oxygen pressure (pO_2), umbilical cord blood partial carbon dioxide pressure (pCO_2), need for neonatal intensive care unit, length of stay in neonatal intensive care unit, use of respiratory support (mechanical ventilation or continuous positive airway pressure or both), neonatal death. An adverse neonatal outcome was defined if one of the following criteria was met: Apgar score less than 7 at 5 min, umbilical artery pH less than 7.10, need for neonatal intensive care, or neonatal death.

Power analysis: The area under the curve (AUC) of the umbilical venous flow estimation score (0.85) was used as the alternative hypothesis, and an AUC value of 0.5 was used as the null hypothesis. The expected incidence of the primary outcome was 32.5%[12]. The sample size was calculated as 90, which was calculated by taking the amount of type I error (alpha) 0.05 and the power of the test 0.85. MedCalc version 20 was used for sample size calculations.

Statistical Analysis

Statistical analysis of the study was performed using SPSS 20.0 software and included the Kolmogorov-Smirnov test to ensure normality of distribution. The relevant statistical analyses conducted included Mann–Whitney U, Pearson chi-squared test, the chi-squared test with Yates correction, and Fisher's exact chi-squared test. ROC analysis was used to determine the diagnostic performance and to identify the optimal cut-off points for relevant variables. Logistic regression analysis was used to estimate the odds ratios. Statistical significance was set at a p-value <0.05 for all tests performed.

Results

In this study, 149 patients with late-onset FGR in the fetus between 32-39 weeks of gestation were identified at the Department of Obstetrics and Gynecology, Inonu University Medical Faculty Hospital between 01/02/2020 and 01/02/2022. As the measurement of all Doppler parameters could not be completed in 8 patients due to the fetal position, 141 patients were included in the study. The median gestational week at delivery was 37 [minimum (min) 33+0- maximum (max) 39+0], the median EFW was 2224 g (min-max 1086-2764), the median UA PI was 1.02 (min-max 0.66-2.85), median CPR 1.42 (min-max 0.43-3.57), median UCR 0.7 (min-max 0.28-2.3), median ductus venosus PI 0.77 (min-max 0.32-1.58), and median birthweight 2345 g (min-max 1070-2840). The rate of cesarean section for fetal distress was 31.5%, and the rate of cesarean delivery was 93.7% in the study cohort. When neonatal outcomes were analyzed, the need for neonatal intensive care was 54.6% and the neonatal mortality rate was 0.7%. The clinical, sonographic, and Doppler sonographic data and neonatal outcomes of the study cohort are summarized in Table 1.

Table 1. Clinical characteristics and Doppler velocimetry data of the study cohort

Variable		Patients with late-onset FGR (n=141)
Age (years)*		29 (18-43)
Gravidity*		2 (1-6)
Parity*		0 (0-5)
Abortus*		0 (0-4)
Body mass index (kg/m²)**		27.97±3.72
Estimated fetal weight (gr)**		2153.38±381.91
Amniotic fluid index (cm)*		11.4 (0-22)
Maxiumum vertical pocket (cm)*		4 (0-8)
Umbilical artery S/D*		2.82 (1.23-7.92)
Umbilical artery PI*		1.02 (0.66-2.85)
Umbilical artery RI*		0.67 (0.48-1.22)
MCA PI*		1.44 (0.78-2.57)
MCA-PSV*		51.2 (30.8-72.0)
CPR*		1.42 (0.43-3.57)
UCR*		0.7 (0.28-2.3)
Uterine artery PI*		0.93 (0.42-2.05)
CPUR*		1.64 (0.21-5.64)
Ductus venosus PI*		0.77 (0.32-1.58)
Umbilical vein flow*		120.8 (19.94-180.13)
Aortic isthmus PI*		2.45 (1.8-3.57)
Renal artery PI*		2.14 (1.47-3.16)
Day between birth and last ultrasound scan*		1 (0-6)
Gestational age at birth (week)*		37 (33-39)
Birthweight (gr)**		2273.09±456.03
APGAR 1*		8 (5-8)
APGAR 5*		10 (6-10)
Cord blood pH*		7.33 (7.12-7.49)
Cord blood base excess*		-4.2 (-16.3-15.1)
Cord blood pO_2**		22.02±9.02
Cord blood pCO_2**		41.34±8.74
Duration of hospital stay in NICU (day)*		0 (0-54)
FGR in obstetric history***		32 (22.7)
Smoking***		11 (7.8)
Hypertension***		36 (25.5)
BPD percentile***	**<3p**	81 (57.4)
	3p-10p	18 (12.8)
	>10p	42 (29.8)
HC percentile***	**<3p**	94 (66.7)
	3p-10p	21 (14.9)
	>10p	26 (18.4)

AC percentile***	<3p	131 (92.9)
	3p-10p	10 (7.1)
	>10p	0 (0.0)
FL percentile***	<3p	102 (72.3)
	3p-10p	23 (16.3)
	>10p	16 (11.4)
EFW percentile***	<3p	96 (68.1)
	3p-10p	45 (31.9)
	>10p	0 (0.0)
Meconium stained amniotic fluid***		27 (19.1)
Cesarean section for fetal distress***		45 (31.9)
Labor induction***		32 (22.7)
Mode of delivery***	Vaginal Delivery	9 (6.4)
	Cesarean section	132 (93.6)
Gender***	Female	73 (51.7)
	Male	68 (48.3)
Need for active resuscitation at birth***		5 (3.5)
NICU requirement***		64 (45.4)
Neonatal respiratory support***		40 (28.4)
Neonatal mortality***		1 (0.7)

* Median (Min-Max) **Mean ± SD ***n (%)
FGR: Fetal growth restriction, BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, EFW: Estimated fetal weight, FGR: Fetal growth restriction, S/D: Systole/diastole, PI: Pulsatility index, RI: Resistive index, MCA-PSV: Middle cerebral artery-Peak Systolic Velocity, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio, CPUR: Cerebroplacentouterine ratio, pO_2: Partial oxygen pressure, pCO_2: Partial pressure of carbon dioxide, NICU: Neonatal Intensive Care Unit. Statistically significant p values are indicated in bold

The results of multivariate logistic regression analysis with forward selection of characteristics to determine independent predictors for the adverse neonatal outcome group with clinical data (age, parity, BMI, smoking, hypertensive disease/ preeclampsia, gestational age at birth) are shown in Table 2. After the forward feature selection, the variables gestational week and age were included in the model. According to the regression equation created, it was observed that the gestational week had a decreasing effect on the need for neonatal intensive care [odds ratio (OR): 0.205, 95% confidence interval (CI) 0.116-0.362; p<0.001] and the age variable had an increasing effect on the need for neonatal intensive care (OR: 1.113, 95% CI 1.011-1.225; p=0.030). In addition, the results of multivariate logistic regression analysis with forward selection of characteristics to determine independent predictors for the adverse neonatal outcome group with sonographic data (UA PI, MCA PI, CPR, UCR, Ut-A PI, CPUR, umbilical vein flow, aortic isthmus PI, renal artery PI, AFI, AC, EFW) are shown in Table 3. After the forward feature selection, the variables CPUR, umbilical vein flow, and EFW were included in the model (OR: 0.222, 95% CI 0.084-0.583; p=0.002, OR: 0.935, 95% CI 0.903-0.968; p<0.001 and OR: 0.996, 95% CI 0.993-0.998; p=0.001, respectively). According to the regression equation, it was observed that all three parameters had a decreasing effect on the need for neonatal intensive care. While fetuses with abnormal CPUR had a 4.5-fold increased risk of adverse neonatal outcome, fetuses with abnormal umbilical venous flow had a 1.07-fold increased risk of adverse neonatal outcome.

Table 2. Multivariate logistic regression analysis of clinical data for adverse neonatal outcomes

	Odds ratio	95% Confidence interval	p-value
Age	1.113	(1.011-1.225)	0.030
Parity	0.879	(0.555-1.391)	0.581
BMI	0.979	(0.857-1.120)	0.761
Smoking	0.720	(0.101-5.153)	0.744
Hypertensive disease/ preeclampsia	0.587	(0.206-1.669)	0.318
Gestational age at birth	0.205	(0.116-0.362)	**<0.001**
FGR in obstetric history	0.844	(0.243-2.937)	0.790

FGR: Fetal growth restriction, BMI: Body mass index. Statistically significant p values are indicated in bold

Table 3. Multivariate logistic regression analysis of the sonographic parameters for adverse neonatal outcomes

	Odds ratio	95% Confidence interval	p-value
CPUR	0.222	(0.084-0.583)	0.002
Umbilical vein flow	0.935	(0.903-0.968)	<0.001
EFW	0.996	(0.993-0.998)	0.001

CPUR: Cerebro-placental-uterine ratio, EFW: Estimated fetal weight. Statistically significant p values are indicated in bold

The presence of at least one of the following parameters in the neonates of pregnant women in the study cohort was considered an adverse neonatal outcome: APGAR 5 minute score <7, umbilical artery pH <7.10, need for neonatal intensive care or neonatal death. An adverse neonatal outcome was observed in 77 (54.6%) of the pregnant women enrolled in the study. It was found that MCA PI, CPR, CPUR, umbilical venous blood flow, and birthweight were significantly lower (compared to normal) in infants with adverse neonatal outcomes (p<0.001, p<0.001, p<0.001, p<0.001, and p<0.001, respectively). However, compared with neonates without adverse neonatal outcomes, UA PI and aortic isthmus PI were significantly higher in neonates with adverse neonatal outcomes (p<0.001 and p<0.001, respectively), whereas no significant difference was found between the two groups for ductus venosus PI, MCA PSV, and renal artery PI (p=0.392, p=0.401, and p=0.304, respectively). The clinical, sonographic, and Doppler sonographic data and neonatal outcomes of patients with and without adverse neonatal outcomes are compared in Table 4.

Table 4. Comparison of clinical characteristics, Doppler velocimetry, and neonatal outcome data of patients with and without adverse neonatal outcome

		Adverse neonatal outcome (–) (n=77)	Adverse neonatal outcome (+) (n=64)	p-value
Age (years)*		27 (18-43)	29 (17-42)	**0.029**
Gravidity*		2 (1-5)	2 (1-6)	0.947
Parity*		1 (0-3)	0 (0-5)	0.072
Abortus*		0 (0-1)	0 (0-4)	**0.007**
Body mass index (kg/m^2)**		27.70±3.91	28.39±3.49	0.247
Estimated fetal weight (gr)**		2380.90±197.50	1878.28±374.41	**<0.001**
Amniotic fluid index (cm)*		12 (4.5-22)	11 (0-22)	0.747
Maximum vertical pocket (cm)*		4 (1.6-8)	3.84 (0-7.4)	0.126
Umbilical artery S/D*		2.42 (1.23-4.67)	4.03 (2.05-7.92)	**<0.001**
Umbilical artery PI*		0.92 (0.66-1.55)	1.38 (0.71-2.85)	**<0.001**
Umbilical artery RI*		0.6 (0.5-0.96)	0.77 (0.51-1.22)	**<0.001**
MCA PI*		1.53 (1.03-2.57)	1.28 (0.78-2.06)	**<0.001**
MCA-PSV*		48.6 (30.8-72.0)	54.8 (30.8-72.0)	0.401
CPR*		1.68 (0.89-3.57)	0.92 (0.43-2.29)	**<0.001**
UCR*		0.6 (0.28-1.12)	1.09 (0.44-2.3)	**<0.001**
Uterine artery PI*		0.75 (0.42-1.42)	1.32 (0.55-2.05)	**<0.001**
Ductus venosus PI*		0.82 (0.32-1.58)	0.72 (0.32-1.58)	0.392
CPUR*		2.48 (0.66-5.64)	0.75 (0.21-2.54)	**<0.001**
Umbilical venous flow*		136.8 (33.13-180.13)	101.63 (19.94-122.75)	**<0.001**
Aortic isthmus PI*		2.31 (1.8-2.99)	2.67 (2.15-3.57)	**<0.001**
Renal artery PI*		2.12 (1.47-3.16)	2.16 (1.47-3.16)	0.304
Day between birth and last ultrasound scan*		0 (0-6)	1 (0-6)	**0.011**
Gestational age at birth (week)*		38 (36-39)	36 (33-39)	**<0.001**
Birthweight (gr)**		2542.08±265.09	1949.45±427.22	**<0.001**
APGAR 1st minute score*		8 (6-8)	6 (5-8)	**<0.001**
APGAR 5th minute score*		10 (8-10)	8 (6-10)	**<0.001**
Cord blood pH*		7.33 (7.14-7.41)	7.33 (7.12-7.49)	0.561
Cord blood base excess*		-4.2 (-13.5-8.7)	-3.3 (-16.3-15.1)	0.729
Cord blood pO_2**		21.14±7.39	23.08±10.63	0.740
Cord blood pCO_2**		40.35±7.17	42.53±10.26	0.189
Duration of hospital stay in NICU (day)*		0 (0-0)	9.5 (0-54)	**<0.001**
FGR in obstetric history***		16 (20.78)	16 (25.00)	0.694
Smoking***		5 (6.49)	5 (7.81)	1.000
Hypertension***		16 (20.78)	20 (31.25)	0.220
BPD percentile ***	<3p	42 (54.55)	37 (57.81)	0.544
	3p-10p	12 (15.58)	6 (9.38)	
	>10p	23 (29.87)	21 (32.81)	

HC percentile* **	**<3p**	52 (67.53)	41 (64.06)	0.644
	3p-10p	9 (11.69)	11 (17.19)	
	>10p	16 (20.78)	12 (18.75)	
AC percentile* **	**<3p**	68 (88.31)	62 (96.88)	0.111
	3p-10p	9 (11.69)	2 (3.13)	
	>10p	0 (0.00)	0 (0.00)	
FL percentile* **	**<3p**	62 (80.52)	39 (60.94)	**0.021**
	3p-10p	7 (9.09)	16 (25.00)	
	>10p	8 (10.39)	9 (14.06)	
EFW percentile* **	**<3p**	36 (46.75)	58 (90.63)	**<0.001**
	3p-10p	41 (53.25)	6 (9.38)	
	>10p	0 (0.00)	0 (0.00)	
Meconium stained amniotic fluid* **		6 (7.79)	21 (32.81)	**<0.001**
Cesarean section for fetal distress* **		14 (18.18)	31 (48.44)	**<0.001**
Labor induction* **		27 (35.06)	5 (7.94)	**<0.001**
Mode of delivery* **	**Vaginal Delivery**	9 (11.69)	0 (0.00)	**0.004**
	Cesarean section	68 (88.31)	64 (100.00)	
Gender* **	**Female**	44 (57.14)	29 (45.31)	0.162
	Male	33 (42.86)	35 (54.69)	
Need for active resuscitation at birth* **		0 (0.00)	5 (7.81)	**0.018**
Neonatal respiratory support* **		2 (2.60)	38 (59.38)	**<0.001**
Neonatal mortality* **		0 (0.00)	1 (1.64)	0.445

* Median (Min-Max) **Mean ± SD ***n (%)
BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, EFW: Estimated fetal weight, FGR: Fetal growth restriction, S/D: Systole/diastole, PI: Pulsatility index, RI: Resistive index, MCA-PSV: Middle cerebral artery-Peak Systolic Velocity, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio, CPUR: Cerebroplacentouterine ratio, pO_2: Partial oxygen pressure, pCO_2: Partial pressure of carbon dioxide, NICU: Neonatal Intensive Care Unit. Statistically significant p values are indicated in bold

ROC analysis was performed to determine the performance of the measured obstetric Doppler parameters in predicting the development of adverse neonatal outcomes. While umbilical venous blood flow showed the best performance in predicting adverse neonatal outcomes (AUC 0.952, 95% CI 0.902-0.981, p<0.001), ductus venosus PI and renal artery PI had no predictive value for adverse neonatal outcomes (AUC 0.542, 95% CI 0.456-0.627, p=0.398 and AUC 0.551, 95% CI 0.464-0.635, p=0.303 respectively) (Figures 1 and 2). Additionally, UCR, CPUR, and aortic isthmus PI values, which were evaluated for predicting the development of adverse neonatal outcomes, were also found to have predictive values (AUC 0.853, 95% CI 0.783-0.907, p<0.001; AUC 0.912, 95% CI 0.853-0.953, p<0.001, and AUC 0.829, 95% CI 0.756-0.887, p<0.001, respectively). ROC analysis of Doppler parameters in predicting adverse neonatal outcomes is summarized in Table 5. The ROC curves of Doppler parameters evaluated for prediction of adverse neonatal outcomes are shown in Figures 1 and 2.

Discussion

This study demonstrated that UA PI, MCA PI, mean Ut A PI and the CPR, UCR and CPUR ratios derived from the ratio of these parameters to each other were effective in predicting composite adverse neonatal outcomes, such as Apgar score less than 7 at 5 min, cord blood pH less than 7.10, or the need for neonatal intensive care in fetuses with late-onset FGR. Additionally, when all obstetric Doppler parameters were compared, umbilical venous blood flow showed the best performance in predicting adverse neonatal outcomes, whereas aortic isthmus PI, which is not commonly used in routine clinical practice, proved effective in predicting adverse neonatal outcomes in fetuses with late-onset FGR. The study found that Doppler assessment of the ductus venosus, a critical aspect of the management of fetuses with early-onset FGR, did not predict adverse neonatal outcomes in fetuses with late-onset FGR. Additionally, renal artery PI was ineffective in predicting composite adverse neonatal outcomes. Late-onset FGR occurs when the fetus fails to attain its growth potential and is typically identified after the 32nd week of gestation[4]. Although there are fewer perinatal complications

Table 5. ROC analysis of Doppler parameters in the prediction of adverse neonatal outcomes

Variables	Cut-off	Sensitivitity	Specificity	LR+	LR-	PPV	NPV	AUC (95%CI)	p-value
UmbAS/D	3.45	78.12 (66.0-87.5)	92.21 (83.8-97.1)	10.03	0.24	89.3	83.5	0.843 (0.772-0.944)	**<0.001**
UmbA PI	1.23	75.00 (62.6-85.0)	97.4 (90.9-99.7)	28.87	0.26	96.0	82.4	0.853 (0.783-0.907)	**<0.001**
UmbA RI	0.72	70.31 (57.6-81.1)	94.81 (87.2-98.6)	13.54	0.31	91.8	79.3	0.815 (0.741-0.875)	**<0.001**
MCA PI	1.33	59.38 (46.4-71.5)	85.71 (75.9-92.6)	4.16	0.47	77.6	71.7	0.715 (0.633-0.788)	**<0.001**
CPR	1.13	68.75 (55.9-79.8)	94.81 (87.2-98.6)	13.23	0.33	91.7	78.5	0.852 (0.783-0.906)	**<0.001**
UCR	0.82	71.87 (59.2-82.4)	93.51 (85.5-97.9)	11.07	0.30	90.2	80.0	0.853 (0.783-0.907)	**<0.001**
Ut A PI	1.09	67.19 (54.3-78.4)	93.51 (85.5-97.9)	10.35	0.35	89.6	77.4	0.860 (0.792-0.913)	**<0.001**
DV PI	0.74	53.97 (40.9-66.6)	59.74 (47.9-70.8)	1.34	0.77	52.3	61.3	0.542 (0.456-0.627)	0.398
CPUR	1.02	76.56 (64.3-86.2)	97.4 (90.9-99.7)	29.48	0.24	96.1	83.3	0.912 (0.853-0.953)	**<0.001**
UmbV flow	118.9	92.19 (82.7-97.4)	92.21 (83.8-97.1)	11.83	0.08	90.8	93.4	0.952 (0.902-0.981)	**<0.001**
AoI PI	2.5	71.87 (59.2-82.4)	83.12 (72.9-90.7)	4.26	0.34	78.0	78.0	0.829 (0.756-0.887)	**<0.001**
RenAPI	1.99	69.84 (57.0-80.8)	44.16 (32.8-55.9)	1.25	0.68	50.6	64.2	0.551 (0.464-0.635)	0.303
MCA-PSV	52.0	53.97 (40.9-66.6)	58.44 (46.6-69.6)	1.30	0.79	51.5	60.8	0.541 (0.455-0.626)	0.401

LR: Likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under curve, UmbA: Umbilical artery, S/D: Systole/diastole, PI: Pulsatility index, RI: Resistive index, MCA: Middle cerebral artery, PSV: Peak systolic velocity, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio, CPUR: Cerebroplacentouterine ratio, DV: Ductus venosus, Umb V: Umbilical vein, AoI: Aortic isthmus, RenA: Renal Artery. Statistically significant p values are indicated in bold

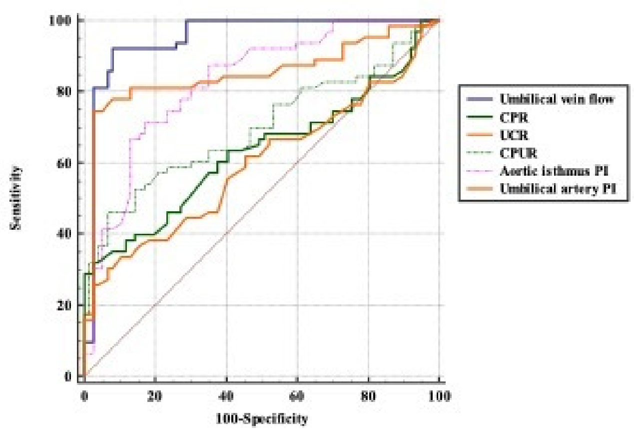

Figure 1. ROC curves showing predictive value of umbilical vein flow, CPR, UCR, CPUR, aortic isthmus PI, and UA PI for adverse neonatal outcomes

in late-onset FGR compared with early-onset FGR, there is still a greater risk of adverse short- and long-term outcomes, such as hypoxemic episodes and minor neurodevelopmental delays, compared with fetuses that are growing normally[7]. Identification of fetuses at a higher risk of adverse perinatal outcomes is critical to improving the outcome of pregnancies with late-onset FGR. Several Doppler indices have been associated with adverse outcomes in pregnancies affected by late-onset FGR. A recent study showed that assessing umbilical venous blood flow may be a more effective way of identifying fetuses with late FGR who

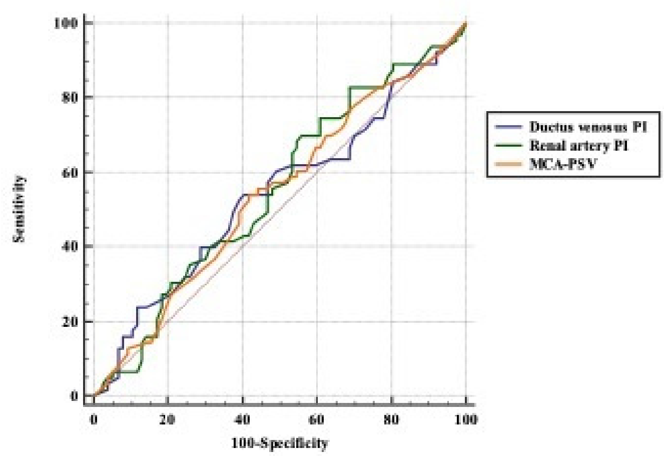

Figure 2. ROC curves showing the predictive value of ductus venosus PI, renal artery PI, and middle cerebral artery PSV for adverse neonatal outcomes

are at a greater risk of adverse perinatal outcomes. However, the precise role of Doppler ultrasound in predicting outcomes in pregnancies affected by late FGR remains to be determined. The results of this study suggest that umbilical venous blood flow is the most effective obstetric Doppler parameter for predicting adverse neonatal outcomes in pregnancies that are complicated by late-onset FGR. Rizzo et al.[12] recently conducted a study that evaluated 243 consecutive singleton fetuses that were affected by the late FGR. The study found that the composite rate of adverse perinatal outcomes was 32.5%. To adjust for fetal size, the ratio of umbilical venous blood flow to the abdominal circumference (UVBF/AC) was used to measure umbilical venous blood flow. Using a multivariable logistic regression analysis, the study found that Ut A PI, CPR, and UVBF/AC were all independently associated with adverse perinatal outcomes. They found that UVBF/AC was more accurate than the mean Ut A PI and CPR in predicting composite adverse outcomes(13). Triunfo and colleagues conducted a study on how effective various fetal Doppler parameters are in predicting perinatal outcomes in late-onset FGR and reported that umbilical venous blood flow had poor diagnostic performance for adverse perinatal outcomes. According to their report, combining all the Doppler parameters under study increased the accuracy of diagnosing adverse perinatal outcomes, but it remained considerably lower(14). This discrepancy may be explained by variations in the study sample, which consisted of only 40 cases of FGR, inconsistencies in the definition of late FGR, and differences in reported outcomes. The measurement of blood flow in the umbilical vein using obstetric Doppler ultrasound is a challenging task, and the consistency of the reproducibility of assessment of this vessel in terms of intra- and interobserver variability is not well-documented in the existing literature. Even minor errors in the factors involved in the calculation of umbilical venous blood flow can lead to significant errors in the estimation of the absolute flow. This is particularly evident in the case of the umbilical vein diameter, as its values are divided by two and squared in the calculation of vessel area, as mentioned in the reference(15). Despite these limitations, the clinical role of umbilical venous blood flow deserves further investigation.

Insufficient blood flow between the uterus and placenta is associated with changes in blood flow resistance throughout the fetal vasculature, uterus, and placenta. As a result, the uterine and umbilical arteries demonstrate higher resistance to placental flow, caused by uteroplacental insufficiency. In response to fetal hypoxia, the fetus adapted by redirecting blood flow to essential organs. A decrease in MCA PI indicates vasodilation of the fetal cerebral vessels(16). The ratio of MCA PI to UA PI is known as CPR. In the third trimester, having a significantly low CPR is significantly correlated with unfavorable perinatal outcomes in small for gestational age and appropriate for gestational age fetuses(17). Recently, our study group conducted a study that found that CPR values below the 5th percentile were better predictors of adverse neonatal outcomes than UA PI and CPR <1 in late-onset FGR pregnancies(18). At present, CPR appears to be the most promising method for identifying high-risk fetuses in the late stages of pregnancy, but its clinical application is not uniform. Low CPR values have been associated with stillbirth, even after adjustment for fetal size, and cerebral vasodilation has been shown to be a more sensitive indicator of placental insufficiency than elevated UA-PI(19). This study revealed that in cases of late-onset FGR pregnancies, the CPR, UCR, and CPUR ratios, calculated from the UA PI, MCA PI, and mean Ut A PI values, were all able to predict composite adverse neonatal outcomes, such as low Apgar scores at 5 min, umbilical cord blood pH less than 7.10, and the need for neonatal intensive care. Additionally, fetuses with an abnormal CPUR were found to have a 4.5 times higher risk of adverse neonatal outcomes. Recent research aligns with our study's findings, indicating that reversing CPR to obtain UCR is a more sensitive indicator of adverse perinatal outcomes(20). Although using inverse ratios derived from the same Doppler values, the TRUFFLE study showed a stronger association between UCR and neonatal neurodevelopmental disability(21). Although a high UCR PI at 36 weeks' gestation is linked with perinatal mortality near term, it is not routinely measured in clinical practice. Recently, a new Doppler parameter known as CPUR has been proposed by MacDonald et al.(22), which is calculated by dividing CPR by the mean Ut A PI. This combination of Doppler measurements was found to have the strongest correlation with placental insufficiency. The researchers showed that CPUR was a more effective predictor of FGR than either mean Ut A PI or CPR alone in a prospective study that analyzed fetal growth in 347 women who had not previously given birth and were at 36 weeks' gestation. They showed that a low CPUR ratio with ~90% specificity had a sensitivity of 50% for birth weight <10th percentile, 68% for <5th percentile and 89% for <3rd percentile(22). Although the use of these ratios is not always an optimal approach, their use in clinical practice does not preclude the clinical evaluation of a single Doppler parameter. Several of the ratios examined in this study, including UCR and CPUR, represent innovative Doppler ratios that demonstrate a significant correlation with placental insufficiency and greater sensitivity for identifying FGR than traditional Doppler parameters. If these findings can be replicated in future studies in separate subject groups, these parameters could be used to more accurately identify fetuses that are at an increased risk of stillbirth during the antenatal period, potentially leading to more effective obstetric interventions.

This investigation aimed to assess whether the Doppler indices of aortic isthmus PI and renal artery PI, in conjunction with other Doppler parameters commonly used in clinical practice, could be used to predict adverse neonatal outcomes in late-onset FGR pregnancies. The results of this analysis suggest that the PI of the aortic isthmus is a reliable predictor of adverse neonatal outcomes in pregnancies affected by late-onset FGR, whereas the PI of the renal artery provides no predictive information. The section of blood vessels between the origin of the left subclavian artery and the point where the ductus arteriosus meets the aorta is known as the aortic isthmus. Some experts have suggested that the aortic isthmus is the only arterial link between the right and left fetal circulatory systems. In summary, the circulatory pattern of the blood reflects the balance between the output of the ventricles and the impedance of the placental or cerebral vasculature. Recent experimental and clinical studies have shown that the Doppler flow pattern observed in the aortic isthmus can indicate disturbances in fetoplacental hemodynamics and provide valuable insights into the overall circulatory dynamics of the fetal heart[23]. A prospective observational cohort study consisting of 70 singleton pregnancies with early-onset FGR by Choudhary et al.[24] found that all aortic isthmus Doppler indices, including aortic isthmus PI, were associated with adverse perinatal outcomes in early FGR. Del Río et al.[25] reported a higher incidence (41%) of aortic isthmus PI >95th percentile in severe FGR. However, the PORTO study, a large-scale investigation that included a substantial number of late-onset FGR cases, did not demonstrate any clinical benefit of aortic isthmus PI[26]. The usage of color Doppler flow imaging has simplified the examination of the renal arteries and other small fetal vessels. Typically, the fetal kidneys receive approximately 2-3% of the total cardiac output under normal circumstances. The renal arteries, along the rest of the peripheral circulation, respond to neurohumoral stimuli triggered by factors such as arterial wall constriction, acidosis, and hypoxia. The increased reactivity of renal arteries in response to changes in fetal oxygenation compared with umbilical arteries argues for their use in detecting fetuses at a risk of adverse consequences of hypoxia. Fetal renal artery Doppler blood flow velocities have been assessed in several clinical scenarios, such as FGR. Stigter et al.[27] carried out an observational study using a prospective design to investigate changes in the renal circulation in preterm infants with severe FGR using Doppler ultrasound during a period of gradual deterioration in prenatal fetal well-being. The study's findings revealed that there was no association between renal artery PI and birthweight, cord blood pH, or AFI corrected for gestational age. Contag et al.[28] conducted a retrospective analysis of 9.700 ultrasound data from 2.852 pregnant women aged 20-40 weeks, but they found that renal artery Doppler indices did not improve the detection of fetuses that would develop any component of adverse neonatal outcomes. These findings suggest that, while studies have indicated that altered renal blood flow is associated with hemodynamic changes in fetuses with complicated FGR, renal artery Doppler PI is unlikely to improve the prediction of fetuses at a high risk of adverse neonatal outcomes in late-onset FGR pregnancies.

Study Limitations

While our investigation provides valuable insights, it is important to acknowledge some limitations, such as the restricted sample size and the focus on a single center population. Nevertheless, the number of participants was sufficient to evaluate the efficacy of these Doppler parameters in predicting adverse neonatal outcomes. Additionally, we could not analyse placental biomarkers, so we could not build multiparametric predictive models combining these new Doppler parameters with biomarkers; however, our study was not designed to do this. A major strength is that multiple Doppler parameters in the same cohort were evaluated together by a single experienced clinician, which minimizes the bias in the results. Another strength is the prospective cohort design.

Conclusion

Although late-onset FGR is associated with lower rates of perinatal morbidity and mortality compared with early-onset FGR, the incidence of adverse outcomes such as hypoxemic events and long-term neurodevelopmental abnormalities is still higher in fetuses with late-onset FGR than in normal fetuses. To effectively manage pregnancies affected by late-onset FGR, it is crucial to identify fetuses at an increased risk of adverse perinatal outcomes. Our study evaluated the effectiveness of various Doppler blood flow parameters in predicting adverse neonatal outcomes in fetuses with late-onset FGR. In addition to MCA PI and CPR Doppler parameters, this study found that umbilical venous blood flow and aortic isthmus PI Doppler parameters, which are not commonly used in clinical settings, as well as the recently introduced UCR and CPUR ratios, were effective in predicting adverse neonatal outcomes in this group of patients. The clinical application of these Doppler parameters in fetuses with late-onset FGR appears to be of critical value in the management of these patients. Therefore, further investigation is required to develop multiparametric predictive models that integrate these novel Doppler parameters with maternal characteristics to accurately identify pregnancies affected by late-onset FGR that have an increased likelihood of short- and long-term morbidity.

Ethics

Ethics Committee Approval: The study protocol was approval of the Clinical Research Ethics Committee of Malatya University (Ethics Committee approval number: 2020/04).

Informed Consent: Informed consent was obtained from all participants before enrollment.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Design: R.M., Data Collection or Processing: R.M., C.Y., Analysis or Interpretation: R.M., H.Ö., Ş.Y., Literature Search: C.Y., H.Ö., Writing: R.M., C.Y., H.Ö., Ş.Y.

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