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ORIGINAL PAPER

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The predictive value of fetal middle cerebral artery/descending aorta ratio doppler parameter in the evaluation of perinatal results of intrauterine growth restriction

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ABSTRACT

Introduction. Although there are various reasons for intrauterine growth restriction (IUGR), the main cause is inadequate utero-placental and feto-placental circulation.

Aim. To determine the predictive values of fetal middle cerebral artery/descending aorta (MCA/DA) Doppler parameter in the evaluation of perinatal outcomes in pregnancies with IUGR.

Material and methods. 15 with IUGR and 35 normal newborn, who were born at the 34th gestational week or over included into the study. Doppler ultrasonography (US) measurements were performed. The ratio of pulsatility index/resistive index (PI/RI) from MCA, umbilical artery (Umb), DA was determined. Neonatal characteristics such as Apgar scores, neonatal intensive care unit (NICU) requirement, weight and sex were also recorded.

Results. In the IUGR group, mean MCA/DA RI-PI, MCA/UmB RI-PI were 0.88±0.19, 0.86±0.28, 1.22±0.18 and 1.55±0.39, respectively. In the control group, mean MCA/DA RI-PI, MCA/UmB RI-PI were 1.15±0.13, 1.09±0.41, 1.37±0.35 and 1.82±0.44, respectively. There were statistically significant relationship between MCA/DA PI with cord blood pH value and NICU requirement, age with gravida, parity, MCA/UmB RI, MCA/UmB PI; gravida with age and parity; parity with age, gravida, weight, MCA/DA RI, PI ratios.

Conclusion. Intrauterine MCA and DA Doppler US parameters of IUGR can be used safely in predicting perinatal outcomes in pregnancies with IUGR over 34 weeks.

Keywords. fetal MCA/DA Doppler parameters, IUGR, perinatal outcomes

Introduction

Although there are various reasons for intrauterine growth restriction (IUGR), the main cause is inadequate utero-placental and feto-placental circulation. IUGR is a fetal development disorder in which the expected fetus weight for gestational age is below the 10th percentile.[1] The fetus progressively deviates from the normal growth curve. Among the maternal, utero-placental and fetal causes that adversely affect the growth potential of the fetus, most cases of IUGR are caused by primary

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or secondary utero-placental circulatory failure. Inadequate nutrient and oxygen transfer from the placenta to the fetus, chromosomal abnormalities and intrauterine infections may cause the fetus to be small.[2-4] The risk of perinatal morbidity and mortality was increased in all IUGR patients, regardless of etiologic causes. Mortality rates are 4-8 times higher than in non-IUGR fetuses. Half of the infants with growth restriction have serious short-term and long-term morbidities such as meconium aspiration, pneumonia and metabolic disorders.[5,6] IUGR is present in 3-10% of all pregnancies and approximately 20% of stillbirths. In the presence of maternal hypertension or previous history of IUGR in pregnant women, the risk of IUGR is reported to be 25% or more. Low birth weight associated with IUGR is associated with at least 60% of neonatal deaths worldwide.[2,7] Doppler ultrasonography (US) is used to detect placental deficiencies. Placental deficiencies may cause perinatal death, intrauterine growth restriction (IUGR) and preeclampsia. Doppler US applications are important in the management of these cases.[8,9] To demonstrate systemic arterial features of the uterine arteries to the placenta, middle cerebral artery (MCA) and descending aorta (IA), venous examination is required for detailed cardiovascular status and respiratory system evaluation.[10] Middle cerebral artery (MCA) Doppler flow indicates cerebral resistance. Ductus venosus (DV) shunt with umbilical venous blood passes through the liver and leads to the heart and brain. Cardiac afterload changes due to parallel regulation of fetal circulation determine how this increased blood volume is distributed to the circulation. Increase in right ventricular afterload or decrease in left ventricular afterload leads to direct cardiac output to the left ventricle and thus to the coronary circulation and brain.[11] Diastolic velocity increases in MCA, which is a brain-protective effect. Decrease in MCA pulsatility index (PI) is a direct evidence of brain sparing effect. The brain protective effect of placental respiratory function impairment is due to hypoxia-induced cerebrovascular dilatation. These compensatory changes usually occur in the presence of sufficient cardiac output. When placental insufficiency enters the terminal period, insufficient cardiac function results in a decrease in MCA flow, which is called normalization.[12] In the last stage of placental insufficiency, cardiac output is reduced as a result of hypoxic or ischemic myocardial dysfunction and coronary vasodilation occurs. Cardiac dysfunction becomes serious if this does not adequately support myocardial nutrition.[13] Increases cardiac dysfunction and high afterlood central venous pressure. Increased central venous pressure leads to pulsations of the venous system and umbilical vein.[14] Used to determine appropriate cordocentesis and transfusion time in anemic fetuses.[15] Normal blood in the fetal descending aorta (FDA) shows a severe pulsatility with minimal diastolic component. The descending part of the aorta provides fetal abdominal organs, umbilical-placental circulation and perfusion of the lower extremities. As pregnancy progresses, fetal aortic diameter increases, peripheral resistance decreases and as a result, diastolic flow increases in the aorta. However, there is no significant decrease in the systolic/diastolic (S/D) ratio of FDA. Elevated S/D ratio, resistive index (RI) and PI ratios in FDA are considered to herald that poor perinatal outcomes such as IUGR and perinatal mortality may occur.[16]

Aim

To determine the predictive values of fetal MCA/DA Doppler parameter in the evaluation of perinatal outcomes in pregnancies with IUGR.

Material and methods

The study was performed as a retrospective cohort. A total of 50 newborns, including 15 patients with IUGR and 35 normal newborn, who were born at the 34th gestational week or over between January 2017-December 2018 at the Obstetrics and Gynecology Clinic, University of Health Sciences Adana City Training and Research Hospital were included in this study. Doppler US was performed by a specialist physician using the Samsung Medison H60 ultrasound device with 3.5 MHz convex transducer considering fetal movements and Doppler waveforms were obtained. Measurements were performed in the absence of fetal movement and during the apnea period, the angle of insonation is as close to 0 as possible (<20) and cover the sample volume vessel. PI, RI ratios of MCA, UmB, DA (just below renal bifurcation) were calculated in two measurements. At the time of sonographic examination, pregnant women were at the 26-28th weeks of pregnancy. There was mean 11 weeks between Doppler examination and delivery. Deliveries were carried out when pregnants' labour started. In addition, newborn characteristics such as 1st and 5th minute Apgar scores, NICU needs, weight and sex were also recorded. SNAPPE-2 scoring was used to evaluate patients who needed NICU.

Statistical analysis

SPSS 23.0 program was used for statistical analysis. In the evaluation, numerical data were expressed as mean ± standard deviation (ss), median, distribution range (min-max), and categorical data were expressed as percentage (%).The normality of distribution for the variables was evaluated using the Shapiro-Wilk test. Independent test and Mann-Whitney test were used to evaluate the differences between the groups. To analyze intraobserver reproducibility, the evaluation was repeated twice at 5 minute intervals. The 95% confidence interval for the area under the curve (AUC) and the de-

Table 1. Maternal Demographic Datas

	IUGR Group (n:15)		Control Group (n:35)		p value
	Min-Max	Mean±Sd	Min-Max	Mean±Sd	
Age (years)	19-39	26.32±4.27	21-44	27.32±4.85	0.674
Height (cm)	150-171	158.05±7.01	151-176	163.44±7.19	0.018*
Weight (kg)	52-102	71.18±10.54	56-146	75.63±14.58	0.012*
BMI (kg/m^2)	23.39-38.15	26.12±4.57	21.30-48.50	31.25±5.36	0.369
Time of birth (week)	35-39	37.33±1.36	36-40	38.41±1.22	0.035*

Table 2. Gravida and Parity Numbers of Groups

		IUGR Group (n:15)		Control Group (n:35)		p value
		n	%	n	%	
Gravida	1	6	12.0	6	12.0	0.004*
	2	6	12.0	7	14.0	
	3	2	4.0	13	26.0	
	4	1	2.0	4	8.0	
	5	0	0.0	2	4.0	
	6	0	0.0	2	4.0	
	7	0	0.0	1	2.0	
Parity	0	8	16.0	9	18.0	0.035*
	1	5	10.0	15	30.0	
	2	1	2.0	6	12.0	
	3	1	2.0	3	6.0	
	4	0	0.0	2	4.0	

Table 3. Mean values of MCA, DA and Umb RI and PI ratios

	IUGR Group (n:15)			Control Group (n:35)			p value
	Min-Max	Ort ±Std	Patient number with RI<1	Min-Max	Ort ±Std	Patient number with RI<1	
MCA RI/DA RI	0.65-1.22	0.88±0.19	6	0.85-1.32	1.15±0.13	9	0.771
MCA PI/DA PI	0.34-1.41	0.86±0.28		0.72-1.93	1.09±0.41		0.283
MCA RI/Umb RI	0.98-1.77	1.22±0.18	3	1.06-2.21	1.37±0.35	0	0.865
MCA PI/UmB PI	0.71-2.55	1.55±0.39		1.29-2.91	1.82±0.44		0.547

fined variables was estimated. p<0.05 was considered significant.

Results

The maternal demographic data of the groups included in the study are shown in Table 1.

62% of the newborns in the IUGR group were female and 38% were male. 54% of the newborns in the control group were female and 46% were male. Mean maternal age of the infants was 26.32±4.27 years and 27.32±4.85 years in the patient and control groups, respectively. Mean delivery time of IUGR and patient group was 37.33±1.36 and 38.41±1.22 week, respectively.

Table 2 shows the gravida and parity values of both groups. Accordingly, a statistically significant relationship was found between the two groups in terms of gravida and parity (p<0.05).

In the IUGR group, mean MCA RI/DA RI was 0.88±0.19, mean MCA PI/DA PI was 0.86±0.28, mean MCA RI/UmB RI was 1.22±0.18 and mean MCA PI/UmB PI 1.55±0.39. The number of patients whose MCA/DA RI ratio was less than 1 was 6 and the number of patients whose MCA/Umb RI ratio was less than 1 was 3. In the control group, mean MCA RI/DA RI was 1.15±0.13, mean MCA PI/DA PI was 1.09±0.41, mean MCA RI/Umb RI was 1.37±0.35 and MCA PI/UmB PI was 1.82±0.44. No statistically significant relationship was found between all groups (p>0.05).

Table 4. Evaluation of MCA, DA and Umb RI and PI ratios below 1 for the diagnosis of IUGR

	RI	PI
Sensitivity	88 %	70 %
Specificity	96.7 %	91.3 %
Positive Predictive Value	81 %	76 %
Negative Predictive Value	79 %	71 %
Precision	96.7 %	91.3 %

MCA, DA and UmB RI and PI values below 1 is important for the diagnosis of IUGR. Table 4 shows that

Table 5. Mean Weight and Cord Blood pH Values

		IUGR Group (n:15)		Control Group (n:35)		p value
		Min-Max	Mean±Sd	Min-Max	Mean±Sd	
Weight	Girl	1663-2752	2189.9 ±244.3	2350-4150	3421.3 ±423.1	0.115
	Boy	1748-2580	2210.1 ±307.8	2650-4320	3314.6 ±447.6	
	Total	1696-2632	2242.5± 296.7	2370-4255	3364.5± 421.5	
Cord Blood pH Values	Girl	7.24-7.41	7.32±0.044	7.22-7.39	7.32±0.037	0.742
	Boy	7.22-7.40	7.30±0.041	7.33-7.40	7.31±0.044	
	Total	7.22-7.41	7.32±0.05	7.22-7.40	7.32±0.038	

Table 6. Datas of 1st and 5th Minute Apgar Scores and Neonatal Intensive Care Requirement of Newborns

		IUGR Group (n:15)		Control Group (n:35)		p value
		n	%	n	%	
Apgar Scores 1st Minute	4	1	2.0	-	-	0.654
	5	-	-	-	-	
	6	1	2.0	4	8.0	
	7	6	12.0	6	12.0	
	8	5	10.0	14	28.0	
	9	2	4.0	8	16.0	
	10	-	-	3	6.0	
Apgar Scores 5st Minute	6	1	2.0	-	-	0.857
	7	-	-	-	-	
	8	4	8.0	8	16.0	
	9	7	14.0	16	32.0	
	10	3	6.0	11	22.0	
NICU requirement	Evet	6	40.0	3	8.57	0.789
	Hayır	9	60.0	32	91.43	

Table 7. The Relationship Between MCA PI / DA PI Value with Cord pH and NICU Requirement

		MCA PI/DA PI	Cord Blood pH Value	NICU requirement
MCA PI/DA PI	r	1	-0.013	-0.509*
	p		0.956	0.022
Cord Blood pH Value	r		1	-0.137
	p			0.004
NICU requirement	r			1
	p			

Table 8. Comparison of age, birth week, gravida, weight, BMI and parity values with MCA, DA and Umb RI and PI values in IUGR group

		Age	Time of birth (week)	Gravi-da	Parity	Weight	BMI	MCA RI/ DA RI	MCA PI/ DA PI	MCA RI/ Umb RI	MCA PI/ UmB PI
Age	r	1	-.038	.651**	.523*	-.164	-.273	-.381	-.355	-.437	-.453*
	p		.872	.002	.018	.490	.245	.098	.125	.044	.045
Time of birth (week)	r		1	-.021	-.031	-.248	-.325	-.234	-.176	.050	-.005
	p			.928	.898	.291	.162	.320	.459	.834	.983
Gravida	r			1	.781**	-.306	-.135	-.324	-.333	-.304	-.318
	p				.000	.189	.569	.163	.152	.193	.171
Parity	r				1	-.607**	-.391	-.439	-.419	-.378	-.378
	p					.005	.089	.043	.036	.101	.101
Weight	r					1	.720**	.042	-.047	.146	.031
	p					.	.000	.828	.812	.538	.897
BMI	r							1	-.215	-.154	-.189
	p								.363	.517	.425

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

the MCA, DA and UmB RI and PI ratio below 1 is determinative for the diagnosis of IUGR.

There was no statistically significant relationship between the two groups in terms of weight and cord blood pH values of the newborns (p>0.05) (Table 5).

There was no statistically significant relationship between the groups in terms of 1st and 5th minute apgar scores and NICU needs of newborns (p>0.05) (Table 6).

A statistically significant relationship was found between MCA PI/DA PI value with cord blood pH value and NICU requirement (p<0.05) (Table 7).

Regression analysis was used to compare the age, time of birth, gravida, weight, BMI and parity values of the IUGR group with MCA, IA and Umb RI and PI values. Accordingly, statistically significant results were found between age with gravida, parity, MCA RI/Umb RI and MCA PI/UmB PI, gravida with age and parity, parity with age, gravida, weight, MCA RI/DA RI and MCA PI/DA PI, weight with BMI (Table 8).

Discussion

IUGR is a fetal development disorder in which the expected fetus weight for gestational age is below the 10th percentile.[17] Most cases of IUGR are caused by primary or secondary utero-placental circulation failure. Inadequate nutrient and oxygen transfer from the placenta to the fetus, chromosomal abnormalities and intrauterine infections cause small fetal size.[18]

Doppler US is currently used routinely in the diagnosis and follow-up of fetal and maternal vessels. Growth and development in the fetus is ensured by normal fetomaternal circulation which provides sufficient oxygen and nutrient intake as a result of maternal circulation. Doppler US provides rapid and reliable noninvasive evaluation of physiopathological changes in fetomaternal circulation.[19,20]

There are some maternal demographic factors affecting IUGR formation. Physiological variables including maternal height, weight, parity, ethnicity, fetal gender and gestational age are known to affect fetal growth. One of the most important of these is maternal age. Maternal age is too young or too old to be a high risk factor for IUGR.[21,22] Similarly, advanced maternal age was associated with low birth weight.[21] In our study, mean maternal age of the patients in the IUGR group was 28.15±5.19 years and the mean maternal age of the patients in the control group was 28.91±5.31 years. In addition, a significant relationship was found between maternal age and gravida, parity, MCA RI/Umb RI and MCA PI/UmB PI.

Maternal weight at birth, low weight before pregnancy and poor weight gain during pregnancy are associated with IUGR.[23] In our study, the mean maternal weight of IUGR group was 70.11±9.75 kg and the mean maternal weight of control group was 79.57±16.14 kg. A statistically significant relationship was found between the groups in terms of maternal weight (p<0.05).

MCA is preferred in the evaluation of fetal cerebral circulation because it carries more than 80% of cerebral blood flow and is the most easily visualized sonographic vascular structure. Doppler flow sampling should be done from the proximal segment close to the Willis polygon. Middle cerebral artery PI reference values vary according to gestational week.[24] Under normal conditions, high resistance current wave pattern is observed in fetal cerebral circulation. In the presence of fetal hypoxia, peripheral blood circulation decreases and brain blood flow increases. In this case known as brain-protective effect, the diastolic flow rate increases and the PI value decreases. Presence of brain protective effect is determined by cerebroplacental ratio expressed as MCA PI/UmB PI ratio. If this ratio is below the 5th percentile according to gestational age, it shows that there is brain protective effect in fetus.[25] In our study, no statistically significant relationship was found between the groups in terms of MCA RI/AO, MCA PI/AO PI, MCA RI/Umb RI and MCA PI/UmB PI (p>0.05).

Blood perfusion of fetoplacental unit is evaluated by UmB Doppler sampling. End-diastolic flow is usually absent in the first trimester. As the gestational week progresses, placental vascular resistance decreases, the diastolic component increases, and from the 14th week, low-resistance current wave begins to be seen in UmB. The UmB current is best analyzed at the level of the free-floating umbilical cord. Quantitative Doppler US parameters such as S / D ratio, PI and RI are sufficient in the evaluation and follow-up of most cases with IUGR. The use of Umb Doppler US examination in the second trimester in the follow-up of high-risk cases significantly reduces the risk of perinatal death.[26] Diastolic flow loss in UmB reflects increased placental resistance from obliteration of placental villi, and reverse flow in Doppler US can be seen after 70% of placental villi occlusion.[27] Progressive hypoxemia may cause redistribution of blood flow to the brain, heart, and adrenals, and leads to increased diastolic flow in MCA.[28,29] DV Doppler US waveform may reflect diastolic pressure due to increased cardiac output in the right ventricle.[5] In our study, the mean MCA RI/Umb RI was 1.25± 0.19 and the MCA PI/UmB PI was 1.61±0.49 in the IUGR group, and the mean MCA RI/Umb RI was 1.32±0.22 and the mean MCA PI/UmB was 1.84±0.54 in the control group. There was no significant relationship between the groups (p>0.05). In the study of Seyam et al., 100 pregnant women in 28-41 week with IUGR fetus were followed up, serial Doppler US was performed and were examined in 3 groups. Patients with normal Umb Doppler US findings were classified as group 1 (16%), group 2 (77%) with diastolic flow loss, and group 3 (7%) with reverse flow. From group 1 to 3, gestational age and birth

weight at birth were significantly lower, and oligohydramnios and NICU hospitalization were higher. There was no perinatal death in Group 1. From group 1 to 3, the rate of cesarean section due to fetal stress increased and the need for mechanical ventilation increased.[30]

In our study, cord blood pH was 7.32±0.06 and 7.33±0.041 in IUGR and control groups, respectively. Yoon et al. used UmB Doppler US and biophysical profile (BPP) to determine fetal acid-base status in 24 fetuses with IUGR.[31]They found that Doppler US and BPP correlated with the degree of fetal acidemia, and Doppler US was more effective than BPP in detecting fetal acidemia.

Fetal PI is calculated sonographically using EFW and FL measurement. This index is more useful for diagnosing IUGR in the newborn. However, the correlations between fetal PI and neonatal PI are weak. Therefore, PI provides limited benefit during pregnancy.[32,33]Another parameter is the transcerebellar diameter (TCD) which is not affected by IUGR and can therefore be used independently.[34] It has been shown that the TCD/AC ratio predicts IUGR if the mean is above 2 SD, but this ratio is not routinely used until further studies have proven it.

Sensitivity of the relationship between abnormal PI and IUGR in UmB Doppler is around 12% in the first trimester.[34] Cnossen et al. examined datas in 79547 pregnant with PE and 41131 fetuses with IUGR.[35] They reported that, UmB Doppler US performed in the second trimester shows a higher estimate than it performed in first trimester, and increased PI findings are more accurate. In addition, PI increase is the best predictor of general and severe IUGR for low-risk patients. In our study, no statistically significant relationship was found between the groups in terms of MCA PI/AO PI and MCA PI/UmB PI ($p>0.05$).

Conclusion

MCA/AO Doppler US parameter has a positive predictive value in predicting neonatal outcomes in patients with IUGR born at 34 weeks of gestation or over. In addition, significant correlations were found between MCA PI/DO PI with cord blood pH and NICU requirement. Therefore, both Doppler US findings and the patient's general condition and additional clinical findings should be taken into consideration when making a delivery decision. Doppler US plays an important role in accurate timing of delivery and predicting neonatal outcomes.

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