Retrograde diastolic blood flow in the aortic isthmus is not a simple marker of abnormal fetal outcome in pregnancy complicated by IUGR – a pilot study

Obecność wstecznego przepływu rozkurczowego w cieśni aorty nie jest prostym markerem złego rokowania dla płodu w ciąży powikłanej IUGR – badania wstępne

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Abstract

Aim: *To evaluate the relation between retrograde diastolic blood flow in the aortic isthmus and adverse perinatal outcome in fetuses with IUGR.*

Materials and Methods: *The study included 33 fetuses with IUGR defined as the estimated fetal weight and abdominal circumference under the 10th percentile for a given gestational age. The Doppler examination of the blood flow in the aortic isthmus, umbilical artery, umbilical vein, middle cerebral artery, uterine arteries and ductus venosus was performed regularly. The study population was further divided into two subgroups, depending on the aortic isthmus blood flow direction, i.e. with and without retrograde isthmic diastolic flow. Furthermore, the relation between Doppler blood flow parameters and determinants of the perinatal outcome was analyzed. The perinatal outcome was reported as adverse if any of the following occurred: umbilical cord blood pH < 7,2; 5-minute Apgar score < 7; respiratory distress syndrome, intraventricular hemorrhage (III/IV grade); necrotizing enterocolitis; sepsis; intrauterine or neonatal death.*

Results: *There was no statistically significant difference in the incidence of adverse perinatal outcome between the antegrade and retrograde isthmic blood flow groups. Moreover, the study showed no statistically significant relationship between the retrograde blood flow in the aortic isthmus and the prevalence of abnormal flow in the analyzed vessels.*

Conclusion: *Retrograde diastolic blood flow in the aortic isthmus presents a low sensitivity and low predictive value in predicting the adverse perinatal outcome in pregnancies complicated with IUGR.*

Key words: **aortic isthmus** / **Doppler** / **intrauterine growth restriction** / / **perinatal outcome** /

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Streszczenie

Cel: *Celem pracy była ocena związku między występowaniem wstecznego przepływu rozkurczowego w cieśni aorty oraz nieprawidłowym rokowaniem dla płodu z cechami ograniczenia wzrastania (IUGR).*

Materiał i metody: *Badaniami objęto 33 płody z wykładnikami IUGR, który zdefiniowano na podstawie szacowanej masy ciała oraz obwodu brzucha płodu poniżej 10. percentyla dla danego wieku ciążowego. Przepływ krwi w naczyniach oceniano regularnie metodą dopplerowską. Badaniami objęto przepływ krwi w cieśni aorty, tętnicy pępowinowej, żyle pępowinowej, tętnicy środkowej mózgu, tętnicach macicznych oraz przewodzie żylnym. Grupa badana została podzielona na dwie podgrupy, w zależności od kierunku przepływu krwi w cieśni aorty tj. na podstawie obecności lub nieobecności wstecznego przepływu rozkurczowego. Ponadto, przeanalizowano związek pomiędzy parametrami dopplerowskimi przepływu krwi oraz wykładnikami nieprawidłowego stanu pourodzeniowego. Nieprawidłowy stan noworodka definiowano na podstawie następujących parametrów: pH z krwi pępowinowej <7,2; punktacja w skali wg Apgar <7 w 5 minucie; zespół zaburzeń oddychania, krwawienie dokomorowe (klasa III / IV); martwicze zapalenie jelit; posocznica; zgon wewnątrzmaciczny lub noworodka.*

Wyniki: *Nie stwierdzono statystycznie istotnych różnic w częstości występowania niekorzystnego rokowania dla noworodka między grupą bez i z wstecznym przepływem rozkurczowym w cieśni aorty. Ponadto, badania nie wykazały statystycznie istotnego związku pomiędzy obecnością wstecznego przepływu krwi w cieśni aorty oraz występowaniem nieprawidłowych wartości przepływu krwi w analizowanych naczyniach.*

Wnioski: *Obecność wstecznego przepływu rozkurczowego w cieśni aorty cechuje się małą czułością oraz niską wartością predykcyjną w przewidywaniu niekorzystnego rokowania dla płodu w ciążach powikłanych IUGR.*

Słowa kluczowe: **cieśń aorty** / **Doppler** / **wewnątrzmaciczne ograniczenie wzrastania płodu** / **rokowanie** /

Introduction

Intrauterine fetal growth restriction (IUGR) is a complication of pregnancy with a complex etiology and fetuses with IUGR resulting from placental insufficiency are at increased risk of adverse short- and long-term outcomes. Fetal adaptive mechanisms to placental insufficiency include redistribution of the arterial circulation with preferential distribution of the cardiac output towards the left ventricle. This allows to maintain adequate oxygen supply to both, the brain and the heart [1]. In numerous reports on IUGR, considerable attention is paid to the sequence of consecutive hemodynamic changes that are reflected in the Doppler studies, illustrating changes in the feto-maternal circulation [2, 3, 4, 5, 6, 7, 8].

One of the early signs of abnormal placental blood flow is an increase in the placental vascular resistance indicated by an increased pulsatility index in the umbilical artery (UA PI). This phenomenon is also associated with ‘centralization of the fetal circulation’ following the fall in the vascular resistance in the cerebral circulation, evidenced by reduction of the pulsatility index in the middle cerebral artery (MCA PI). Hemodynamic decompensation with progressive cardiac dysfunction in the fetus is reflected in the values of the indices characterizing the abnormal blood flow in the veins. Absent or reversed end-diastolic flow in the ductus venosus (DV AEDV / REDV) is considered to be a late marker of advanced hemodynamic changes in fetuses with IUGR. Such venous changes are signs of advanced fetal compromise, often associated with metabolic acidosis, heart failure and increased risk of perinatal death [1, 2, 3, 4, 7, 8].

The potential role of blood flow in the aortic isthmus has been proposed as an indicator of the progression of fetal hemodynamic deterioration in IUGR, particularly as a short-term marker of adverse perinatal outcome, as well as a long-term predictor of neurodevelopmental outcome [9, 10, 11]. AoI is a blood connection between the right ventricle (mainly supplying the systemic and placental circulation) and the left ventricle (the source of blood to the cerebral circulation). Thus, the waveforms of blood flow through the aortic isthmus reflect the balance between ejection of blood from the ventricles and vascular resistance. In normal conditions, placental resistance is smaller than the vascular one in the upper parts of the fetal circulatory system. Normally, the movement of blood flow in the AoI is forward, i.e. to the descending aorta. The increase in placental resistance in fetuses with placental insufficiency reverses the direction of blood flow through the isthmus, pointing to a pathology. According to some authors, this symptom precedes hemodynamic decompensation [1,11].

The aim of the study was to evaluate the association between AoI Doppler changes and perinatal outcome in IUGR fetuses. The main objective was to test the retrograde diastolic flow in the aortic isthmus as a simple marker of fetal poor outcome.

Aim

The aim of the study was to evaluate the association between the retrograde blood flow in the AoI and adverse perinatal outcome in IUGR fetuses.

Materials and Methods

This prospective study on fetuses with IUGR was performed between 2009 and 2011. From the initial group of 50 fetuses, fetuses who met the following inclusion criteria were enrolled: gestational age confirmed by ultrasound in the first trimester, absence of structural malformations or chromosomal abnormalities, estimated birth weight <10th centile according to reference ranges, last Doppler examination performed within 48h before delivery, and a singleton pregnancy. Fetal well-being was monitored by CTG and ultrasound, which included assessment of the biophysical profile and blood flow in the selected vessels. All patients gave their written informed consent for the study.

Doppler blood flow velocimetry was performed by means of GE Voluson E8 (General Electric Healthcare, Europe) with a variable-frequency 3.5 and 5.0 MHz transducer, operating in real time with the option of pulse wave and color Doppler. During the examination, the patients maintained a reclining position, slightly on the left side to avoid hemodynamic changes caused by the compression of the inferior vena cava. All Doppler studies were performed in the absence of fetal body movements and respiratory activity. Doppler blood flow studies were performed in the umbilical artery (UA) and umbilical vein (UV), middle cerebral artery (MCA), ductus venosus (DV), uterine arteries (UT), and the aortic isthmus (AoI). The study was done by calculating the pulsatility index (PI) in the UA and MCA and the ratio of MCA PI and UA PI called the cerebroplacental ratio (CPR). PI values in the UA above 95th percentile were considered abnormal, whereas in case of the MCA PI abnormal values were those below 5th percentile [4]. CPR ratio was defined as abnormal if the values were <1.08 [4]. The absence of the end-diastolic flow and the presence of the reverse flow in the UA were defined as AEDV and REDV. DV blood flow was characterized on the basis of venous pulsation index (PVIV), and the presence of reverse flow during atrial contraction was noted (REDV DV). Values above the 95th percentile were considered to be abnormal [4]. The evaluation of the blood flow in the umbilical vein was based on the presence or absence of a pulsatile flow. The presence of pulsations was considered as abnormal. The analysis of blood flow in the uterine arteries was performed for PI values and the presence of the "notch". PI values > 1.2 and/or the presence of the "notch" were considered as abnormal [4]. The analysis of the Doppler studies was based on the standards presented in the cited papers [4, 6, 12, 13, 14].

In order to analyze the blood flow through the aortic isthmus, the parameters of blood flow velocities were set so as to avoid the phenomenon of turbulent flow through the AoI during color coding. The study was performed after obtaining the sagittal section of the aortic arch or on the three vessels view and trachea in the mediastinum. After obtaining a satisfactory image, the Doppler sample was put in the place of the aortic isthmus, i.e. below the last branch of the outgoing arc. After obtaining a good quality waveform, the flow was analyzed on the basis of the direction of the blood flow during diastole, i.e., forward to the descending aorta or back to the aortic arch. Based on a waveform analysis and direction of the blood flow, the study group was further divided into two subgroups, i.e. with the diastolic flow into the descending aorta and the group with the retrograde flow [1].) If antegrade and retrograde flows were seen simultaneously, the type of flow was defined as follows: in cases of some reversal of diastolic flow but with predominant antegrade flow, the flow was defined as antegrade, and in cases of predominant retrograde flow, it was qualified as retrograde.

Perinatal outcome during the neonatal care unit stay was recorded. The evaluation included maternal age, obstetric history, birth weight, umbilical cord arterial pH and Apgar score at 1 and 5 min, as well as the presence of oligohydramion. Newborn outcome was considered abnormal in the presence of at least one of the following criteria: umbilical artery pH <7.2; 5-minute Apgar score ≤7 points; respiratory distress syndrome; intracranial hemorrhage (grade III or IV); necrotizing enterocolitis; sepsis; intrauterine demise or newborn death.

Next, selected parameters characterizing the course of pregnancy and newborn outcome with abnormal Doppler results were compared. The relationship between the direction of the flow in the AoI and prevalence of abnormal Doppler parameters in other selected vessels was also analyzed. The prognostic value of abnormal Doppler parameters in relation to the abnormal pregnancy course and abnormal newborn outcome was also determined. Sensitivity, specificity, positive and negative predictive value of Doppler parameters were calculated. Two-sided Fisher's exact test was used to compare the parameters in nominal scale in the two groups. Parameters expressed on an interval scale as the arithmetic mean and standard deviation were described. The compatibility of these parameters with normal distribution was checked with the Shapiro-Wilk test. In cases when compliance with normal distribution was confirmed, the parameters were compared using the Student's t test; otherwise the nonparametric Mann-Whitney test was used. Mann-Whitney test was also used for the evaluation of the parameters in the ordinal scale nonparametric. The collected data were analyzed by Statistica version 8.0 (StatSoft, Inc., 2007) and a package GraphPad Instat software company. The level of statistical significance was set at $p<0.05$.

Results

Optimal Doppler blood flow assessment in the AoI could be collected in all cases. Epidemiological data, Doppler characteristics and perinatal outcome in the total study group are described. The comparison of pregnancy course and selected parameters characterizing fetal and newborn outcomes are presented in Table I. Gestational age at delivery and birth weight in abnormal newborn outcome group were significantly lower when compared to the group with normal newborn outcome. Moreover, in the group with abnormal newborn outcome, lower Apgar scores, pH values and longer postpartum hospitalization were observed more frequently.

Fetuses with antegrade flow in the AoI comprised group 1 (n = 16), while those with the retrograde flow constituted group 2 (n = 17). The characteristics of the study groups and the relationship between the type of diastolic blood flow in the AoI and parameters characterizing the newborn outcome are presented in Table II. There were no statistically significant differences between the two analyzed groups with regard to the parameters characterizing the abnormal newborn outcome.

Then, the distribution of Doppler results in groups with antegrade and retrograde flow in the aortic isthmus was compared. The relationship between the direction of the flow in the AoI and prevalence of abnormal Doppler parameters in the selected vessels were analyzed. There were no statistically significant differences between the analyzed Doppler parameters in both groups (Table III).

The value (sensitivity, specificity, positive and negative predictive value) of Doppler parameters in prediction of abnormal neonatal outcome was also assessed. The highest sensitivity was observed in relation to the UA, CPR and UT.

Table I. Demographic and obstetric data depending on the newborn outcome.

		Normal neonatal outcome (n=17)	Adverse neonatal outcome (n=16)	*p*
Maternal age (years)		29,35 ± 5,99	28,13 ± 6,06	0,563
Parity (%)	Primipara	60,00	73,33	0,699
	Multipara	40,00	26,67	
Gender (%)	Female	70,59	66,67	1,000
	Male	29,41	33,33	
Gestational age at delivery (weeks)		37,12 ± 2,37	32,13 ± 3,36	**0,000025**
Birth weight (g)		1932 ± 530	1155 ± 445	**0,000184**
Birth weight <2500 g (%)		82,35	100,00	0,229
Cesarean section (%)		88,24	100,00	0,274
Apgar 1' (points)		9 (3-10)	8 (1-10)	**0,025283**
Apgar 5' (points)		10 (9-10)	9 (5-10)	**0,000843**
Hospital stay after delivery (days)		13 ± 9	36 ± 20	**0,001955**
Oligohydramion (%)		41,18	40,00	1,000

Apgar – Apgar score

Table II. Demographic and obstetric data in groups with antegrade and retrograde flow in the aortic isthmus.

		Antegrade flow (n=16)	Retrograde flow (n=17)	*p*
Maternal age (years)		28,31 ± 6,81	29,18 ± 5,22	0,684
Parity (%)	Primipara	78,57	56,25	0,260
Gender (%)	Female	75,00	62,50	0,704
	Male	25,00	37,50	
Gestational age at delivery (weeks)		34,38 ± 3,72	35 ± 3,98	0,645
Gestational age at delivery < 34 weeks (%)		50,00	29,41	0,296
Birth weight (g)		1449 ± 558	1688 ± 680	0,286
Cesarean section (%)		93,75	93,75	1,000
pH ≤7,2 (%)		25,00	0,00	0,101
Apgar 1' (pkt)		8 (1-10)	9 (1-10)	1,000
Apgar 5' (pkt)		9 (6-10)	10 (5-10)	0,424
Apgar 5' ≤7 (%)		12,50	13,33	1,000
Hospital stay after delivery (weeks)		24 ± 18	21 ± 19	0,504
RDS (%)		6,25	18,75	0,599
ICH (%)		18,75	12,50	1,000
ICH grade III/IV (%)		6,25	0,00	1,000
NEC (%)		12,50	6,25	1,000
Oligohydramion (%)		37,50	43,75	1,000
Intrauterine demise (%)		0,00	5,88	1,000
Neonatal death (%)		6,25	5,88	1,000
Adverse neonatal outcome (%)		56,25	41,18	0,494

Apgar – Apgar score; RDS – respiratory distress syndrome; ICH – intracranial hemorrhage; NEC – necrotizing enterocolitis

Table III. Distribution of Doppler results in groups with antegrade and retrograde flow in the aortic isthmus.

	Antegrade flow (n=16)	Retrograde flow (n=17)	*p*
Abnormal MCA PI (%)	73,33	58,82	0,472
Abnormal UA PI (%)	83,33	66,67	0,640
UA AEDV/REDV (%)	21,43	46,15	0,237
UV pulsations (%)	28,57	42,86	0,695
UT PI (mean ± SD)	1,51 ± 0,96	1,46 ± 0,72	0,885
Abnormal UT PI (%)	54,55	57,14	1,000
UT notch (%)	83,33	42,86	0,051
DV reversed flow (%)	0,00	14,29	1,000
Abnormal DV PVIV (%)	35,71	27,27	1,000
Abnormal CPR (%)	66,67	66,67	1,000

AoI – aortic isthmus, MCA- middle cerebral artery; PI- pulsatility index; UA, umbilical artery; AEDV – absent end-diastolic flow; REDV – reversed end-diastolic flow; UV – umbilical vein; UT – uterine artery; DV – ductus venosus; PVIV – pulsatility index for veins; CPR- cerebroplacental ratio;

Table IV. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of Doppler parameters in relation to the abnormal newborn outcome.

	sensitivity (95% CI)	specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR
AoI retrograde flow	0.44 (0.20-0.70)	0.41 (0.18-0.67)	0.41 (0.18-0.67)	0.44 (0.20-0.70)	0.7
Abnormal MCA PI	0.69 (0.41-0.89)	0.38 (0.15-0.65)	0.52 (0.30-0.74)	0.55 (0.23-0.83)	1.1
Abnormal UA PI	0.90 (0.59-0.99)	0.38 (0.14-0.68)	0.56 (0.31-0.78)	0.83 (0.36- 0.99)	1.5
UV pulsations	0.50 (0.23- 0.77)	0.79 (0.49- 0.95)	0.70 (0.35-0.93)	0.61 (0.36-0.83)	2.3
Abnormal UT PI	0.83 (0.52-0.98)	0.69 (0.39-0.91)	0.71 (0.42-0.92)	0.82 (0.48-0.98)	2.7
Abnormal DV PVIV	0.30 (0.07-0.65)	0.67 (0.38-0.88)	0.38 (0.09-0.76)	0.59 (0.33-0.82)	0.9
Abnormal CPR	0.82 (0.48- 0.98)	0.46 (0.19-0.75)	0.56 (0.30-0.80)	0.75 (0.35- 0.97)	1.5

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; CI, confidence interval; AoI – aortic isthmus, MCA- middle cerebral artery; PI- pulsatility index; UA, umbilical artery; UV – umbilical vein; UT – uterine artery; DV – ductus venosus; PVIV – pulsatility index for veins; CPR- cerebroplacental ratio;

The presence of diastolic retrograde flow in the AoI was characterized by a low sensitivity of approximately 44% in prediction of abnormal neonatal outcome in the analyzed group of patients (Table IV).

Discussion

Currently, one of the major problems associated with the surveillance of pregnancies complicated by IUGR is the correct assessment of fetal well-being and the timing of delivery, in order to balance the benefits of leaving the baby in utero, so that a more mature newborn can be born, and the consequences of an earlier delivery. The risk of prolonged gestation associated with hemodynamic compromise and fetal organ failure, as well as the risk related to the early delivery with all the complications of prematurity must always be considered.

Recently, much attention has been paid to Doppler assessment of the hemodynamic changes in placental and fetal circulation in the diagnosis and monitoring of IUGR fetuses.

Due to great diversity and lack of a uniform model which would reflect hemodynamic changes in pregnancy complicated by IUGR, as well as the absence of clear standards for the diagnostic and therapeutic management, the pursuit for new Doppler indices that could be used clinically in fetal surveillance continues. Recently, the literature has reported the appearance of a new hemodynamic marker, i.e. assessment of the blood flow through the fetal aortic isthmus. It is the only arterio-arterial connection in the fetal circulation that links the right and left ventricle, offering parallel supply to the lower and the upper body of the fetus, respectively [15].

The blood flow in the AoI reflects fetal hemodynamic disturbances, including vascular resistance in the placenta, right and the left ventricle insufficiency, and indirectly points to a possible fetal brain hypoxia [15, 16]. Therefore, it was proposed to use the AoI flow as an indicator of fetal hemodynamic compromise, predictor of perinatal complications and late neurological disorders [1, 10, 11].

Our study did not confirm preliminary observations that there is a strong association between retrograde flow in the AoI and adverse perinatal outcome. Some authors postulated that [17-19] the best correlation between AoI and perinatal outcome is obtained when the Doppler waveform pattern is classified as antegrade or retrograde. Del Rio et al., defined AoI patterns according to the proposed classification of the isthmic flow index (IFI) into five types of flow [1]. However, they found that classification of the IFI waveform patterns into further types did not improve the predictive value for adverse outcome. They found that AoI-PI was significantly associated with the risk of adverse perinatal outcome, and hypothesized that this continuous variable might be of greater predictive value than the bimodal classification into antegrade and retrograde. Thus, AoI Doppler used as a continuous variable could allow the establishment of cut-off points for significant risk of perinatal death or adverse perinatal outcome, which might be of help for indication of delivery [1].

Prospective studies of Del Rio et al., focused their attention on short-term perinatal complications. The study included 51 fetuses (41 fetuses without retrograde and 10 fetuses with retrograde flows in the AoI) [1]. Del Rio et al., demonstrated that retrograde flow in the AoI and AEDV or REDV in the DV independently, significantly correlated with the occurrence of complications and perinatal mortality.

However, in our study no significant role of the presence of retrograde diastolic flow in the AoI in the prediction of abnormal neonatal outcome was found and the sensitivity of this marker was surprisingly low (44.0%). However, it should be noted that these studies used different criteria for abnormal neonatal outcome, making it difficult to compare. In the above-mentioned study by Del Rio, apart from the qualitative description of blood flow through the AoI, the blood flow velocities were also evaluated (EDV-end-diastolic velocity, PSV-peak systolic velocity; TAMXV-time-averaged maximum velocity). Lower velocities significantly correlated with adverse perinatal outcome, what may reflect a reduced blood flow through the fetal AoI in cases of placental insufficiency [1]. In addition, the study of Hidar et al., performed in 32 fetuses with IUGR, revealed a statistically significant correlation between the retrograde blood flow in the AoI and perinatal mortality [20].

Our results are not consistent with these reports. Retrograde flow in the AoI did not correlate with abnormal neonatal outcome or with any of the parameters characterizing abnormal neonatal outcome. These differences may be due to several factors. It is known that gestational age at delivery and birth weight have a significant influence on the neonatal outcome and the incidence of late complications in pregnancies with IUGR. In our study, both these parameters, together with maternal age, parity or fetal gender, in both groups of patients with normal and abnormal neonatal outcome presented comparable values, what excluded the impact of these factors on the results of statistical analysis.

Undoubtedly, the obtained results are influenced by different criteria of abnormal neonatal outcome used in these studies. In addition, the final result may also depend on the time elapsed between any change in the Doppler studies was noticed and the delivery. Furthermore, an additional limitation of our study is a relatively small sample group and a retrospective nature of the analysis.

In our study the statistical relationship between the direction of diastolic flow in the AoI and the Doppler parameters characterizing the blood flow in the other selected vessels was also examined. The statistical analysis did not show any significant relationship between the direction of diastolic flow in the AoI and the studied parameters. Both, experimental and clinical studies performed in chronic hypoxic models suggested that retrograde flow in the AoI might occur before deterioration of the UA wave forms in cases with placental insufficiency [21,22]. However, some recent studies [6, 7] have reported that retrograde blood flow in the AoI is consistently associated with the presence of AREDV in the UA [10,11].

Our results are not in agreement with these findings. The rate of redistribution of fetal arterial circulation, evaluated by vasodilatation in the MCA did not differ between the antegrade and retrograde groups (73.33% vs. 58.82%, respectively). These findings are consistent with previous reports and might be explained by a poor correlation between MCA and perinatal outcome [17]. A higher incidence of AEDV/REDV in the UA and the presence of pulsation in the UV in the group with retrograde flow, although without any statistical significance, has been noticed. There was no correlation between the presence of absent or reversed flow in the DV during atrial contraction and retrograde flow in the AoI. Previous studies suggest that the blood flow through the foramen ovale is decreased in fetuses with AoI retrograde flow, which in turn is associated with an increased right heart preload and the pulsatility of venous indices [18, 23]. On the other hand, deterioration of venous indices is related to increased afterload and decreasing cardiac function [24].

Figueras et al., analyzing the sequence of hemodynamic changes determined that the abnormal flow in the AoI occurs about 1-2 weeks after it is observed in the UA and MCA, and about 1 week before the changes in the DV [2] . However, there is no consensus on the presented results in the literature. Makikallio et al., did not show any differences of Doppler indices characterizing the blood flow in the UA between the fetuses with or without retrograde flow in the AoI [17], while other authors significantly correlated the appearance of retrograde flow in the AoI with the development and progression of placental failure [1, 11]. Also, some animal studies noted the appearance of the retrograde flow in the AoI before advanced changes in the UA and DV occurred [21, 25]. It was shown that an increase in placental vascular resistance was associated with the appearance of reverse flow in the AoI, even in the absence of AEDV or REDV in the UA [21]. Gratacos et al., noticed that cardiovascular Doppler parameters, and the IFI among them, are significantly associated with perinatal mortality in early-onset IUGR [26]. However, the results of this study suggest that before 26 weeks and after 28 weeks, gestational age alone is the strongest and almost unique predictor of perinatal mortality in early-onset IUGR and, among Doppler parameters, the DV may provide the most useful information and allow stratification between high and low risks of perinatal mortality.

However, in the absence of clear research results in the literature, it is difficult to assess precisely the significance of blood flow changes in the AoI. Most of these reports are observational studies, and their value is relatively low. It is therefore necessary to carry out further research to clarify the current uncertainties.

Conclusion

In summary, the assessment of blood flow in the fetal AoI had a low predictive value in relation to abnormal neonatal outcome in our group of pregnancies complicated by IUGR. Retrograde flow in the AoI in fetuses with IUGR did not correlate with abnormal parameters characterizing blood flow in the other studied vessels. The presence of retrograde flow in the AoI should not be regarded as a simple indicator for early delivery in pregnancy complicated by IUGR. The role of Doppler studies of the AoI as an additional clinical parameter in the routine assessment of hemodynamically compromised growth-restricted fetuses deserves further evaluation in large longitudinal studies.

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References:

1. Del Rio M, Martinez JM, Figueras F, [et al.]. Doppler assessment of the aortic isthmus and perinatal outcome in preterm fetuses with severe intrauterine growth restriction. *Ultrasound Obstet Gynecol.* 2008, 31 (1), 41-47.
2. Figueras F, Benavides A, Del Rio M, [et al.]. Monitoring of fetuses with intrauterine growth restriction: longitudinal changes in ductus venosus and aortic isthmus flow. *Ultrasound Obstet Gynecol.* 2009, 33 (1), 39-43.
3. Korbelak T, Ropacka-Lesiak M, Bręborowicz G. Ocena przepływu krwi w tętnicy pępowinowej w ciąży prawidłowej jako predykcja zaburzeń czynności serca płodu w czasie porodu. *Ginekol Pol.* 2012, 83 (1), 38-45.
4. Ropacka-Lesiak M, Korbelak T, Bręborowicz GH. Ocena przepływu krwi w tętnicy środkowej mózgu w ciąży niepowikłanej. *Ginekol Pol.* 2011, 82 (3), 185-190.
5. Kennelly MM, Farah N, Turner MJ, Stuart B. Aortic isthmus Doppler velocimetry: role in assessment of preterm fetal growth restriction. *Prenat Diagn.* 2010, 30 (5), 395-401.
6. Benavides-Serralde A, Scheier M, Cruz-Martinez R, [et al.]. Changes in central and peripheral circulation in intrauterine growth-restricted fetuses at different stages of umbilical artery flow deterioration: new fetal cardiac and brain parameters. *Gynecol Obstet Invest.* 2011, 71 (4), 274-280.
7. Rizzo G, Capponi A, Arduini D, Romanini C. The value of fetal arterial, cardiac and venous flows in predicting pH and blood gases measured in umbilical blood at cordocentesis in growth retarded fetuses. *BJOG.* 1995, 102, 963-969.
8. Hecher K, Snijders R, Campbell S, [et al.]. Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation: relationship with fetal blood gases. *Am J Obstet Gynecol.* 1995, 173 (1), 10-15.
9. Eronen M, Kari A, Pesonen E, [et al.]. Value of absent or retrograde end-diastolic flow in fetal aorta and umbilical artery as a predictor of perinatal outcome in pregnancy induces hypertension. *Acta Pediatr.* 1993, 82, 919–924.
10. Fouron JC, Gosselin J, Amiel-Tison C, [et al.]. Correlation between prenatal velocity waveforms in the aortic isthmus and neurodevelopmental outcome between the ages of 2 and 4 years. *Am J Obstet Gynecol.* 2001, 184, 630–636.
11. Fouron JC, Gosselin J, Raboisson MJ, [et al.]. The relationship between an aortic isthmus blood flow velocity index and the postnatal neurodevelopmental status of fetuses with placental circulatory insufficiency. *Am J Obstet Gynecol.* 2005, 192, 497–503.
12. Gomez O, Figueras F, Martinez JM, [et al.]. Sequential changes in uterine artery blood flow pattern between the first and second trimesters of gestation in relation to pregnancy outcome. *Ultrasound Obstet Gynecol.* 2006, 28, 802–808.
13. Baschat AA. Relationship between placental blood flow resistance and precordial venous Doppler indices *Ultrasound Obstet Gynecol.* 2003, 22, 561–566.
14. Del Rio M, Martinez JM, Figueras F, [et al.]. Doppler assessment of fetal aortic isthmus blood flow in two different sonographic planes during the second half of gestation. *Ultrasound Obstet Gynecol.* 2005, 26, 170–174.
15. Fouron JC. The unrecognized physiological and clinical significance of the fetal aortic isthmus. *Ultrasound Obstet Gynecol.* 2003, 22, 441–447.
16. Makikallio K. Opinion. Is it time to add aortic isthmus evaluation to the repertoire of Doppler investigations for placental insufficiency? *Ultrasound Obstet Gynecol.* 2008, 31, 6–9.
17. Makikallio K, Jouppila P, Rasanen J. Retrograde net blood flow in the aortic isthmus in relation to human fetal arterial and venous circulation. *Ultrasound Obstet Gynecol.* 2002, 19, 147–152.
18. Makikallio K, Jouppila P, Rasanen J. Retrograde aortic isthmus net blood flow and human fetal cardiac function in placental insufficiency. *Ultrasound Obstet Gynecol.* 2003, 22, 351–357.
19. Kaukola T, Rasanen MD, Herva R, [et al.]. Suboptimal neurodevelopment in very preterm infants is related to fetal cardiovascular compromise in placental insufficiency. *Am J Obstet Gynecol.* 2005, 193, 414–420.
20. Hidar S, Zaafouri R, Bouguizane S, [et al.]. Prognostic value of fetal aortic isthmus Doppler waveform in intrauterine growth retardation: prospective longitudinal study. *J Gynecol Obstet Biol Reprod.* 2004, 33 (8), 745-752.
21. Bonnin P, Fouron JC, Teyssier G, [et al.]. Quantitative assessment of circulatory changes in the fetal aortic isthmus during progressive increase of resistance to umbilical blood flow. *Circulation.* 1993, 88, 216–222.
22. Sonesson SE, Fouron JC. Doppler velocimetry of the aortic isthmus in human fetuses with abnormal velocity waveforms in the umbilical artery. *Ultrasound Obstet Gynecol.* 1997, 10, 107–111.
23. Kiserud T, Chedid G, Rasmussen S. Foramen ovales changes in growth-restricted fetuses. *Ultrasound Obstet Gynecol.* 2004, 24, 141–146.
24. Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, intracardiac and arterial blood flow measurements in intrauterine growth retardation: relationship with fetal blood gases. *Am J Obstet Gynecol.* 1995, 173, 10–15.
25. Sonesson SE, Fouron JC. Doppler velocimetry of the aortic isthmus in human fetuses with abnormal velocity waveforms in the umbilical artery. *Ultrasound Obstet Gynecol.* 1997, 10, 107–111.
26. Cruz-Lemini M, Crispi F, Van Mieghem T, [et al.]. Risk of perinatal death in early-onset intrauterine growth restriction according to gestational age and cardiovascular Doppler indices: a multicenter study. *Fetal Diagn Ther.* 2012, 32, 116–122.