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The role of individual blood flow parameters through ductus venosus in the first and second trimesters of pregnancy in predicting the condition of the fetus and newborn

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ABSTRACT

Objectives: To predict fetal and neonatal outcome during pregnancy based on detailed analysis of ductus venosus blood flow velocities in first and second-trimester fetuses.

Material and methods: A retrospective analysis was made in 680 patients with single pregnancies in years 2015 and 2016. The following ductus venosus blood flow velocities in first and second-trimester were analyzed: S-wave velocity, D-wave velocity, a-wave velocity, Tmax velocity, PIV. Results were divided into sub-groups with reduced value, normal value and increased value and compared with fetal and neonatal condition.

Results: The relationship between the increased PIV value in the first trimester of pregnancy and an increased risk of chromosomal aberrations was observed, whereas the increased DV PI value in the second trimester of pregnancy with reduced A -wave were associated with a higher incidence of FGR. No correlation between the remaining DV blood flow velocities in the first and second trimester of pregnancy and the more frequent occurrence of fetal and neonatal complications has been confirmed.

Conclusions: The increased DV PIV is a good prognostic tool for the detection of chromosomal aberrations in first trimester of pregnancy. In the second trimester, the increased DV PIV and the reduced A- wave velocity correlate with the fetal growth restriction. Ductus venosus seems to be an indirect indicator of intrauterine hypoxia with moderate prognostic value for adverse obstetric outcomes.

Key words: ductus venosus; Doppler examination; FGR; neonatal outcome

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INTRODUCTION

Ductus venosus is a vessel unique to the fetal circulation, whose task is to supply well-oxygenated blood from the umbilical vein to the coronary circulation and the central nervous system, thanks to the privileged blood stream directed through the foramen ovale to the left atrium. In the first half of pregnancy, ductus venosus carries 60% of the volume of oxygenated blood from the umbilical vein. In the second half of pregnancy, this flow is reduced to 20–30%, but in certain situations of hypoxia, changes in pressure in the umbilical vein or changes in blood viscosity, it may increase [1]. In ductus venosus, a characteristic three-phase

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flow diagram is observed with high velocities during contraction and relaxation of the ventricles and preserved flow towards the heart during atrial contraction [2]. An important role in prenatal diagnosis is played by Doppler examination of blood flow through ductus venosus. Its abnormal waveform and pulsation index for the veins are described in the case of chromosomal aberrations, cardiac defects and arrhythmias, intrauterine restriction of fetal growth, blood transfusion syndrome in unicellular twin pregnancy, edema fetus and intrauterine infections [3–5]. The aim of the study was to assess the usefulness of the analysis of individual parameters of blood flow velocity through ductus venosus in the prognosis of the condition of the fetus and newborn.

MATERIAL AND METHODS

Blood flow through ductus venosus velocity tests and ultrasound assessment of the fetal anatomy were performed in the first trimester between 11w0d and 13w6d and in the second trimester of pregnancy between 18 and 22 weeks of pregnancy in patients who were referred in the first trimester to the Prenatal Research Clinic. The total number of patients who underwent prenatal screening and subsequent pregnancy analysis was 680. Data on the clinical condition of the newborn and the analysis of the course of pregnancy in terms of specific complications were obtained based on hospitalization of the studied patients. Clinical evaluation of the condition of the newborn was performed in 643 cases. In the ultrasound examination carried out between 11w0d and 13w6d, all fetuses were measured with blood flow through ductus venosus velocity. In the study, between 18 and 22 weeks of gestation, DV PIV was measured in 161 fetuses as an extension of routine diagnostics. In 38 cases, the values of other blood flow velocities through ductus venosus were also recorded. In this study, the results of blood flow through ductus venosus, fetal anatomy and NT measurement obtained during the ultrasound examination were analyzed. The NT value above the 95th percentile for normal fetuses was considered an abnormal value. In the case of venous flow measurement, the rules of the Fetal Medicine Foundation (FMF) [4] test were used. For the purposes of this study, in addition to the qualitative assessment of the flow wave, the analysis of individual components of the flow through ductus venosus obtained during the Doppler examination was performed.

The following parameters were assessed: pulsation index for veins (PIV); maximum ventricular systolic velocity (Vs); maximum velocity in the early diastolic phase of the ventricles (Vd); maximum velocity during atrial contraction (Va); time-averaged maximum velocity (T max) — the average maximum velocity of blood flow.

The obtained results of blood flow through ductus venosus in the first trimester of pregnancy were compared with the reference values obtained in the group of uncomplicated pregnancies based on the following studies:„Ozhan M. Turana „Reference Ranges for Ductus Venosus Velocity Ratios in Pregnancies with Normal Outcome" [6] as well as R. Axt-Fliedner „Reference values of ductus venosus blood flow velocities and waveform indices from 10 to 20 weeks of gestation" [7].

In the second trimester of pregnancy, ultrasound examinations were performed in accordance with the recommendations of PTU PTGiP [8].

The following pregnancy complications were analyzed based on the course of hospitalization: gestational diabetes, gestational arterial hypertension, fetal growth restriction, ODFD, assessment of the birth weight of the newborn, assessment of the newborn's acid-base balance immediately after birth, the need to stay in the Neonatal Intensive Care Unit (NICU) , the occurrence of genetic and structural defects and neonatal deaths.

The following statistical tests were used in the study: Kruskal Wallis ANOVA, Mann-Whitney U-Test, frequency analysis using Fisher's exact test, supplemented with the analysis of standardized residuals and calculation of the odds ratio with confidence interval, statistical regression analysis for the parameter DV PIV I trimester and DV PIV II trimester. When verifying the hypotheses, the significance level was adopted for $p = 0.05$. The calculated p-values are presented. Statistical analyses were performed using the TIBCO Statistica 13.3 and R 3.5.3 software.

RESULTS

A statistically significant difference was found for the following parameters: DV PIV in the first trimester of pregnancy, Va in the first trimester of pregnancy, DV PIV in the second trimester of pregnancy, and Va in the second trimester of pregnancy. In the case of DV PIV in the first trimester of pregnancy, a statistically significant difference was found for the birth weight of the newborn between the increased and normal value ($p = 0.03$) and the increased and decreased value ($p = 0.04$). It has been shown that an increase in the DV PIV parameter by one unit increases the chance of the occurrence of a chromosomal aberration almost twice (OR 1.98) (Tab. 1). For Va in the first trimester of pregnancy, the exact Fisher test turned out to be statistically significant for the ODFD variable ($p = 0.005$) (Tab. 2). The analysis of standardized residuals showed that in the group with the increased value, a thirteen times higher chance of ODFD was observed. There was a statistically significant difference between the reduced and normal velocity in relation to the birth weight of the newborn ($p = 0.032$). For the DV PIV II trimester, a statistically significant difference was shown in the following complications: suspicion of heart disease ($p = 0.037$), fetal growth restriction ($p = 0.002$) and the need to stay in the

Table 1. The relationship between the individual values of the pulsation index for the veins of ductus venosus DV PIV (N, O, P) in the first trimester of pregnancy and the occurrence of complications in the further course of pregnancy and perinatal complications

DV PIV (n = 680)										
Complication	**Normal value (n = 440)**			**Decreased value (n = 48)**			**Increased value (n = 192)**			**p (exact Fisher test)**
	Yes	**No**	**No data**	**Yes**	**No**	**No data**	**Yes**	**No**	**No data**	
Suspicion of a heart disease	7	421	12	0	46	2	4	177	11	0.323
Death of the newborn	4	407	29	0	47	1	4	178	10	0.505
Gestational hypertension	14	399	27	2	45	1	4	179	9	0.672
FGR	29	384	27	2	45	1	10	173	9	0.761
Genetic aberration of the fetus	5	433	2	0	48	0	6	186	0	0.353
ODFD	35	378	27	4	43	1	9	173	10	0.47
GDM	92	321	27	12	35	1	37	146	9	0.73
NICU	3	44	1	43	368	29	18	164	10	0.737

FGR — fetal growth restriction; ODFD — operative delivery for fetal distress; GDM — gestational diabetes mellitus; NICU — Neonatal Intensive Care Unit

Table 2. The relationship between individual a-wave velocity values in ductus venosus DV Va (N, O, P) in the first trimester of pregnancy and the occurrence of complications in the further course of pregnancy and perinatal complications

DV PIV (n = 680)										
Complication	**Normal value (n = 635)**			**Decreased value (n = 36)**			**Increased value (n = 9)**			**p (exact Fisher test)**
	Yes	**No**	**No data**	**Yes**	**No**	**No data**	**Yes**	**No**	**No data**	
Suspicion of a heart disease	11	603	21	0	34	2	0	7	2	0.102
Death of the newborn	8	590	37	0	34	2	0	8	1	0.757
Gestational hypertension	17	584	34	3	31	2	0	8	1	0.207
FGR	40	561	34	0	34	2	1	7	1	0.256
Genetic aberration of the fetus	11	623	1	0	35	1	0	9	0	0.197
ODFD	43	557	35	1	33	2	4	4	1	0.005
GDM	135	466	34	5	29	2	1	7	1	0.623
NICU	61	537	37	2	32	2	1	7	1	0.697

FGR — fetal growth restriction; ODFD — operative delivery for fetal distress; GDM — gestational diabetes mellitus; NICU — Neonatal Intensive Care Unit

Neonatal Intensive Care Unit (p = 0.008) (Tab. 3). It was calculated that an increase in the pulsation index for the veins of ductus venosus in the second trimester of pregnancy by one unit causes a 38-time greater risk of fetal growth restriction. For the DV Va II trimester, the Fisher exact test showed a statistically significant difference in relation to the FGR (p = 0.025) (Tab. 4). It was found that the reduced value of a-wave velocity causes an 11-time greater risk of fetal growth restriction than for the normal values. Other parameters of blood flow through the venous duct showed no statistical significance for any of the complications.

DISCUSSION

Blood Doppler flow in ductus venosus is an important parameter used in prenatal diagnostics [8, 9]. When performing Doppler examination of venous flow, its flow waveform is assessed using quantitative indicators such as DV PIV, DV Vs, DV Vd, DV Va and DV Tmax, and qualitative indicators - presence, absence or inversion of the "a wave". In the first trimester of pregnancy, the relationship between abnormal parameters of blood flow through the venous duct and an increased risk of heart defects and chromosomal aberrations has been known for a long time [10]. The relationship between abnormal values of blood flow through ductus venosus and an increased risk of chromosomal aberration may be explained by the more frequent coexistence of heart defects in genetic syndromes or developing circulatory failure in the fetus [11]. It is noteworthy that in the case of a fetus without an accompanying heart defect, the parameters of blood flow through ductus venosus may be completely normal. In the study of Czuba B. et al. [12] it was found that the inclusion of DV in the study increases the

Table 3. Relationship between individual DV PIV (N, O, P) pulsation index values in the second trimester of pregnancy and the occurrence of complications in the further course of pregnancy and perinatal complications

	DV PIV (n = 161)									
Complication	**Normal value (n = 152)**			**Decreased value (n = 4)**			**Increased value (n = 5)**			**p (exact Fisher test)**
	No	**Yes**	**No data**	**No**	**Yes**	**No data**	**No**	**Yes**	**No data**	
Suspicion of a heart disease	141	3	8	3	0	1	3	0	2	0.037
Death of the newborn	132	0	20	4	0	0	5	0	0	0.999
Gestational hypertension	128	4	20	4	0	0	5	0	0	0.999
FGR	127	5	20	3	1	0	2	3	0	0.002
Genetic aberration of the fetus	149	3	0	4	0	0	4	1	0	0.207
ODFD	124	8	20	3	1	0	5	0	0	0.474
GDM	95	37	20	4	0	0	3	2	0	0.714
NICU	117	15	20	1	3	0	3	2	0	0.008

FGR — fetal growth restriction; ODFD — operative delivery for fetal distress; GDM — gestational diabetes mellitus; NICU — Neonatal Intensive Care Unit

Table 4. Relationship between individual a-wave velocity values in ductus venosus DV Va in the second trimester of pregnancy and the occurrence of complications in the further course of pregnancy and perinatal complications

	DV PIV (n = 38)									
Complication	**Normal value (n = 22)**			**Decreased value (n = 16)**			**Increased value (n = 0)**			**p (exact Fisher test)**
	No	**Yes**	**No data**	**No**	**Yes**	**No data**	**No**	**Yes**	**No data**	
Suspicion of a heart disease	21	0	1	14	0	2	0	0	0	0.562
Death of the newborn	21	0	1	14	0	2	0	0	0	0.562
Gestational hypertension	21	0	1	14	0	2	0	0	0	0.562
FGR	20	1	1	9	5	2	0	0	0	0.025
Genetic aberration of the fetus	22	0	0	15	1	0	0	0	0	0.421
ODFD	19	2	1	14	0	2	0	0	0	0.485
GDM	15	6	1	13	1	2	0	0	0	0.18
NICU	14	7	1	7	7	2	0	0	0	0.53

FGR — fetal growth restriction; ODFD — operative delivery for fetal distress; GDM — gestational diabetes mellitus; NICU — Neonatal Intensive Care Unit

detection rate and lowers the false-positive rate for trisomy 21. Wagner et al. [13] performed a retrospective analysis comparing the predictive value of a-wave alone, DV PIV alone, and both parameters together for the detection of trisomy 21. Reversed wave occurred in 2.3% of fetuses with normal karyotype and 66.1% of fetuses with trisomy 21. DV PIV above the 95th percentile occurred in 8.3% of fetuses with normal karyotype and 77.2% of fetuses with trisomy 21 [13]. Abnormalities in blood Doppler flow through the DV also occur in fetuses with normal karyotype who have been diagnosed with a heart defect. Timmermann [14] in his study pointed to the relationship between thickened NT, heart defect and increased DV PIV parameter in fetuses with normal karyotype. Martinez et al. [15] showed that information on venous flow increased the detection rate of heart defects by 11% in relation to the NT measurement alone. Also, Oh C. et al. [16] proved the correlation between the incidence of DV RAV and an increased risk of the presence of a heart defect, chromosomal aberrations and perinatal death. The analyzed material confirmed the usefulness of the assessment of blood flow through ductus venosus, especially the values of the pulsation index for the veins for ductus venosus, in detecting chromosomal aberrations.

Contrary to the first trimester of pregnancy, Doppler ultrasonography of the venous flow in the second trimester of pregnancy is not a mandatory component of the examination. The most common application of the Doppler examination of ductus venosus is the assessment of the cardiovascular capacity of the fetus in the case of identified abnormalities, *e.g.*, intrauterine growth restriction. Węgrzyn P. et al. [17] compared the values of individual DV indices: PVIV, PIV, PLI and the S/A ratio in 89 fetuses diagnosed with fetal growth restriction and 119 healthy ones between 22–42 weeks of gestation. Their study showed

that in healthy fetuses these parameters gradually decrease with the duration of pregnancy, however, compared to the groups of fetuses with fetal growth restriction, they remain higher [17]. Analysis of the duration of blood flow abnormalities through ductus venosus in the form of the absence or inverted a-wave was performed by Turan et al. [18]. Based on the conducted research, he concluded that the persistence of the absence or the reverse a-wave for more than seven days is associated with an almost certain risk of intrauterine fetal death [18]. Alfirevic in his analysis of blood Doppler flows in high-risk pregnancies showed that the assessment of early and late changes in ductus venosus in pregnancies complicated with early FGR did not significantly correlate with the difference in perinatal death. The benefit of evaluating DV as a parameter influencing the decision to induce labor in the case of late births has been observed in the form of better long-term neurological outcomes in children [19]. In the study by Dahlbäck et al. [20] on changes in the velocity of ductus venosus in 358 high-risk pregnancies between 20–42 weeks of gestation, the DV PI and the following coefficients of its velocity were analyzed: S/Es, S/a and Es/a [systolic (S), final systolic (Es), atrial contraction (a)] and compared these results with the flows in umbilical vessels. These results were compared with specific complications: preterm labor (< 37 Hbd and < 34 Hbd), low birth weight (< 10 percentile and < 3 percentile), Apgar score < 7 points, arterial < 7.1 and venous < 7.2 blood pH, treatment within the Neonatal Intensive Care Unit and perinatal mortality. It was observed that S/Es > 2 SD, DV-PIV > 2 SD and all types of pulsations are associated with poorer blood pH results: umbilical artery < 7.1 and umbilical vein pH < 7.2, S/Es > 2 SD is also related to more frequent occurrence of SGA. It has been shown that the systolic coefficients were less abnormal than the diastolic coefficients, while changes in the end-diastolic velocity of ductus venosus may give false positive results towards the deteriorating condition of the fetus. It was found that umbilical vein pulsation better predicts unfavorable obstetric outcomes than specific indicators of ductus venosus [20]. On the other hand, the Fetal Medicine Foundation recommends the evaluation of the DV PIV in the case of fetal growth restriction, as a significant increase in the pulsation index in ductus venosus along with other abnormalities may be associated with an increased risk of intrauterine death before 34 Hbd. It is also one of the abnormalities suggesting induction of labor after 34 weeks of pregnancy [21]. The analyzed own material showed a relationship between increased values of DV PIV and a decreased value of wave velocity and an increased risk of fetal growth restriction. This is consistent with the pathophysiology of fetal growth restriction, in which a reduced blood exchange area in the placental villi leads first to an increase in vascular resistance in the umbilical artery and its reduction in the middle cerebral artery, and then to an increase in vascular resistance in DV, absence of reverse wave or the presence of reverse wave during atrial contraction due to an increase in venous pressure in the right atrium and right ventricle [22, 23]. No statistically significant results were obtained for the remaining parameters and complications.

CONCLUSIONS

Ductus venosus is an indirect indicator of intrauterine hypoxia, it does not show a high prognostic value for unfavorable obstetric outcomes. Doppler examination of blood flow through the venous duct plays a significant role in the prenatal diagnosis of the first trimester. Especially DV PIV has a prognostic value for the detection of chromosomal aberrations. In the second trimester of pregnancy, the assessment of Doppler blood flow parameters through ductus venosus, especially DV PIV, and the a-wave assessment is helpful in the detection of fetuses with an increased risk of intrauterine growth restriction.

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Conflict of interest

All authors declare no conflict of interest.

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