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Research paper

Effects of gestational diabetes mellitus on ductus venosus shunting during the third trimester

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is a frequent complication of pregnancy, which is associated with a higher risk of adverse perinatal outcomes. Fetal haemodynamic alterations induced by the hyperglycaemic environment could play an important role in the increased perinatal risk. Our aim is to evaluate the impact of GDM on umbilical venous and ductus venosus flow.

Material and methods: This was a prospective cross-sectional cohort study including 35 women complicated by GDM and 15 uncomplicated controls during the third trimester. All women underwent fetal biometric evaluation, Doppler and echocardiographic assessment, measurement of blood flow velocity, and measurement of mean diameters from umbilical vein (UV) and ductus venosus (DV). Blood flow volumes were computed and the DV shunt fraction was calculated (100 * QDV/QUV). Comparisons among groups were then performed.

Results: The DV diameter and absolute blood flow were significantly smaller in the GDM group ($p = 0.004$; $p = 0.013$) compared with the control group, also when normalized for fetal weight ($p = 0.016$). The degree of DV shunting of the GDM group was significantly smaller ($p = 0.002$) than in controls, while no relations were found between the haemodynamic variables considered and perinatal outcomes.

Conclusions: In pregnancies complicated by GDM, the blood flow directed to the DV is significantly decreased. This may reduce fetal compensatory capacities in late pregnancy and increase its perinatal risk.

Key words: gestational diabetes mellitus, Doppler, ductus venosus, umbilical vein.

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Introduction

Gestational diabetes mellitus (GDM) is the most frequent metabolic disorder in pregnancy, and its prevalence is increasing [1]. The prevalence varies between 4% and 25% of pregnancies, depending on the population and diagnostic criteria. Despite remarkable advances in the monitoring and management of diabetes in pregnancy, the gestations complicated by diabetes mellitus still have a high incidence of perinatal complications [2]. According to the Pedersen hypothesis, maternal hyperglycaemia leads to increased glucose transport across the placenta, with resultant fetal hyperglycaemia and hyperinsulinaemia [3]. High fetal glucose and insulin concentrations lead to an excess of fetal growth causing higher rates of macrosomia, which adversely affect neonatal outcomes [4]. This

increased risk may result from altered development of the fetal heart [5] and from adaptive cardiovascular changes. Moreover, the identification of fetuses at risk of complications among GMD pregnancies remains challenging due to the absence of reliable prognostic parameters of poor perinatal outcome. Although maternal glycaemic concentrations are strictly related to fetal growth, an optimal maternal metabolic control in diabetic pregnancies cannot completely protect the fetus from macrosomia [6], and this makes clinic surveillance particularly challenging.

The fetal liver has been shown to play a crucial role in the regulation of fetal growth [7-9], and it is involved in controlling the distribution and utilization of nutrients from the placenta.

The fetal liver has 2 sources of venous supply: well-oxygenated blood from the placenta through the umbilical vein (UV), and low-oxygenated blood from visceral organs through the portal vein. The distribution of fetal liver perfusion has been suggested to develop differently as an adaptive response to inadequate or excessive nutrient supply. Under circumstances of reduced oxygenation or nutrition, a higher proportion of blood from the UV bypasses the liver and perfuses the brain of the fetus, prioritizing oxygen and nutrient delivery as part of the so-called 'brain-sparing' effect [10-12].

Adaptive changes in liver blood flow also occur in fetuses with mothers affected by pregestational diabetes mellitus (PGDM) [13], in which the distribution of UV blood is significantly altered, with a smaller fraction of the UV blood directed through the DV and relatively more to the fetal liver, even if the umbilical venous flow normalized for fetal weight, is lower [14]. In studies of macrosomic fetuses in non-diabetic pregnancies [15], umbilical- and total venous liver flow was higher from the first trimester [16-18] and also when normalized for estimated fetal weight. This suggests that increased umbilical venous flow may be associated to excessive fetal growth in pregnant women uncomplicated by diabetes. However, to the best of our knowledge, no data are up to now available on fetal haemodynamics of the UV and DV in fetuses of GDM mothers.

We speculated that the UV blood distribution and the DV flow pattern may be altered in GDM pregnancies compared with low-risk gestations and that these potential changes may be related to the perinatal outcome. We therefore performed a prospective cross-sectional cohort study to investigate the development of UV flow distribution in fetuses from pregnancies complicated by GDM.

Material and methods

Study population

This was a prospective study on consecutive singleton pregnancies complicated by GDM and attending the antenatal clinic of the Department of Obstetrics and Gynaecology of Azienda Ospedaliera San Giovanni Addolorata for third trimester ultrasonographic evaluation between May 2020 and September 2021. Inclusion criteria were as follows: 1) absence of any maternal chronic disease (hypertension, renal or autoimmune diseases, thrombophilia), 2) absence of maternal smoking, or medication, 3) absence of fetal structural or chromosomal anomalies, and 4) delivery scheduled in our unit. As a control group, we selected from pregnancies undergoing ultrasonography during the same study period 15 uncomplicated singleton spontaneously conceived pregnancies accurately dated by first trimester crown rump length and with a normal 75 g oral glucose tolerance test (OGTT).

Screening for gestational diabetes was done by OGTT at 24 weeks of gestation. The diagnosis of gestational diabetes was made if one or more of the following criteria were met: fasting plasma glucose level ≥ 92 mg/dl, 1-hour level ≥ 180 mg/ dl, and 2-hour level ≥ 153 mg/dl. GDM was initially treated with diet and lifestyle recommendations. If this resulted in insufficient glycaemic control, insulin was prescribed. Insufficient control was considered when fasting blood glucose concentration was ≥ 95 mg/dl or 2-hour glucose was > 120 mg/dl on one-third or more occasions within a 1-week interval despite dietary therapy.

The local institutional Ethical Committee approved the study protocol (No. 0025937/2021), and each woman gave her written informed consent to take part in the study.

Ultrasound assessment

Recordings were performed using a GE (GE Healthcare, Zipf, Austria) Voluson S10 and a Samsung (Samsung Ltd., Seoul, Korea) Hera W10 ultrasound device equipped with 2-7 MHz volumetric probes. Fetal ultrasonographic evaluation was performed between 29 and 40 gestational weeks and included estimation of fetal biometric measurements, maternal and fetal Doppler, and fetal echocardiography. The blood velocity and the mean diameters of the UV and DV were measured for calculating blood flow volumes and DV shunt fraction.

The considered fetal biometric measurements included the biparietal diameter, head circumference, abdominal circumference, and femur length, obtained following ISUOG recommendations [19], and fetal weight computed with the Hadlock 4 formula [20]. Doppler assessment included pulsatility index (PI) measurements of the uterine artery, umbilical artery, and middle cerebral artery, and the calculation of the cerebroplacental ratio (middle cerebral artery PI/umbilical artery PI) according to ISUOG recommendations [21]. Fetal echocardiography included a comprehensive anatomic and functional evaluation obtained from 2-dimensional colour Doppler and pulsed-wave Doppler images.

The time-averaged maximum flow velocity (TAMXV) was measured in the intraabdominal part of the UV and in the DV for at least 10 seconds of uniform flow in periods of fetal quiescence, with the angle of insonation kept as close as possible to 0° and always below 20° (Figures 1A, 1B).

In order to measure their diameter, UV and DV were visualized by perpendicularly insonating the vessel wall after adequate magnification of the section of interest. The inner vessel diameter (D) was measured using the automated function of the ultrasound equipment designed for nuchal translucency assessment (Figures 1C, 1D). Blood flow volume (Q, $ml^{-1} * min^{-1}$) was calculated by the formula $Q = \pi * (D/2)^2 * h * TAMXV$. The

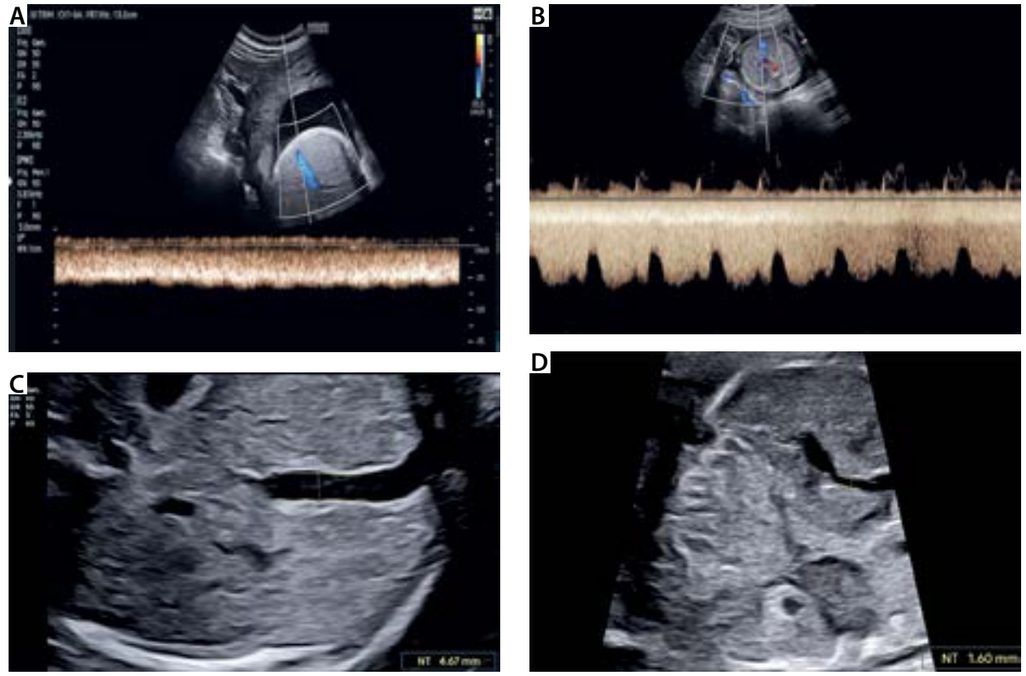

Figure 1. Example of visualization of UV (**A**) and DV (**B**) flow velocity waveforms and diameter measurement of UV (**C**) and DV (**D**)

UV – umbilical vein, DV – ductus venosus

velocity profile parameter *h* was 0.7 for DV and 0.5 for UV. The DV shunt fraction (%) was calculated as $100 * Q_{DV}/Q_{UV}$. The flow volume was normalized based on the estimated fetal weight (EFW) as Q/EFW ($ml * min^{-1} * kg^{-1}$).

All the recordings were performed by 2 of the authors (JLAL and AC). Intra- and inter-observer variability was assessed in previous studies [22, 23].

Statistical analysis

Power analysis demonstrated that the sample size was adequate (0.05 type 1 error (α); 0.1 type 2 error (β); standard deviation 20%). Descriptive data are shown as median and interquartile range (IQR) for continuous variables, and number (*n*) and percentage (%) for categorical variables. Maternal and fetal characteristics were compared using the Fisher exact test or c^2 test for categorical variables, whereas continuous variables were compared using the Mann-Whitney *U*-test. Correlations between ultrasonographic parameters and outcome variables were examined using Pearson's coefficient. A 2-sided *p* value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS software version 27 (SPSS, System for MacOS, Chicago, IL., USA).

Results

Of 69 women evaluated for eligibility, 10 were not considered according to the exclusion criteria while a further 9 cases were excluded due to being lost at follow-up, inadequate ultrasonographic imaging, or incomplete acquisition of all clinical data. Of the remaining 50 women, 35 were complicated by GDM and were assigned to the study group while 15 showed no complications and were assigned to the control group (Figure 2). The general characteristics of the study population are reported in Table 1. There were no relevant differences for the maternal characteristics between the 2 groups about the maternal age, ethnicity, parity, and mode of delivery, although pregnancies complicated by GDM showed a trend of higher body mass index that did not reach statistical significance. Similarly, the gestational age at delivery, estimated fetal weight, and maternal and fetal Doppler PI values were similar between groups Table 2.

Subgroup analysis did not demonstrate differences between insulin-treated gestational diabetic patients and diet-only-treated women.

The UV flow velocities and UV volume flow in the study group did not differ significantly from those in the control group, even when normalized for EFW. The DV diameter was lower in the GDM group when compared to control pregnancies ($p < 0.005$), while no changes were evident in DV TAMXV. Consequently, the control group showed higher DV volume flow and normalized DV flow volume than the study group ($p < 0.005$) (Figures 3A-D). Finally, fetuses from GDM mothers showed lower percentage of shunting values (Table 3). No relevant relation was found between the perinatal outcome variables and the ultrasonographically assessed parameters.

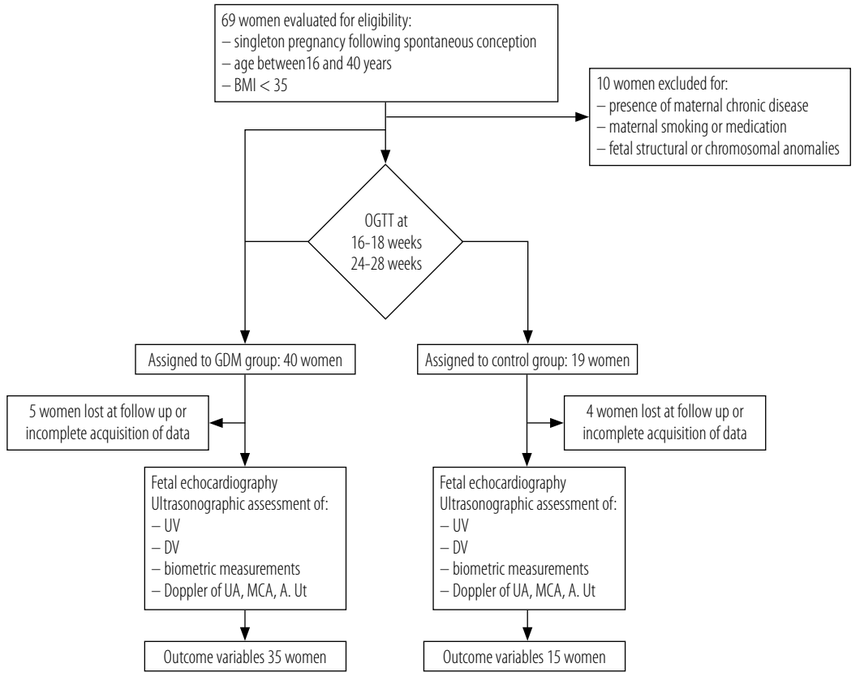

Figure 2. Flow diagram of the study design

BMI – body mass index, OGTT – oral glucose tolerance test, GDM – gestational diabetes mellitus, UV – umbilical vein, DV – ductus venosus, UA – umbilical artery, MCA – middle cerebral artery

Table 1. General characteristics of the study population

Maternal characteristics and outcomes			
	GDM ($n = 35$)	Controls ($n = 15$)	p
	Median (IQR)	Median (IQR)	
Maternal age	31 (27-36.5)	31 (28-37)	0.44
Pre-pregnancy BMI	24.1 (23.05-26.55)	21.8 (21-23.8)	0.57
	n (%)	*n*	*p*
Treatment			
Insulin	11 (31.4)	–	
Diet	24 (68.6)	–	
Ethnicity			
Caucasian	18 (51.4)	11 (73.3)	0.32
Asiatic	14 (40.0)	3 (20.0)	0.3
Hispanic	3 (8.6)	1 (6.7)	0.93
Parity			
0	14 (40.0)	5 (33.3)	0.18
≥ 1	21 (60.0)	10 (66.6)	0.52
Spontaneous vaginal delivery	17 (48.6)	8 (53.3)	0.42
Induction of labour	9 (25.7)	2 (13.3)	0.68
Operative vaginal delivery	2 (5.7)	0	0.57
Caesarean section	9 (25.7)	5 (33.3)	0.47
Elective	3 (8.6)	3 (20.0)	0.93
Emergency	6 (17.1)	2 (13.3)	0.35

GDM – gestational diabetes mellitus, IQR – interquartile range

Table 2. Neonatal characteristics and outcomes of the study population

Neonatal characteristics and outcomes			
	GDM ($n = 35$)	Controls ($n = 15$)	p
	Median (IQR)	Median (IQR)	
Gestational age at delivery (weeks^{+days})	38.3 (37.4-39.8)	39 (38.1-40.4)	0.42
Birthweight (g)	3260 (2930-3535)	3190 (2675-3378)	
Umbilical artery acid-base data			
pH	7.26 (7.23-7.31)	7.25 (7.22-7.28)	0.32
pCO_2 (kPa)	46.6 (43.75-58)	49.8 (42.1-60.1)	0.65
pO_2 (kPa)	24.3 (16.75-39.2)	22.2 (18.1-33.2)	0.71
Base deficit (mmol * l^{-1})	–4.8 (–6.1 to –3.45)	–6 (–6.1 to –2.8)	0.75
Lactate (mmol * l^{-1})	3.15 (2.52-4.46)	3.1 (2.95-3.4)	0.73
Umbilical vein acid-base data			
pH	7.3 (7.24-7.32)	7.33 (7.31-7.35)	0.07
pCO_2 (kPa)	46 (42.32-48.95)	39.8 (38.5-44.7)	0.06
pO_2 (kPa)	35 (25.15-41.45)	29.6 (26.55-33.8)	0.84
Base deficit (mmol * l^{-1})	–4.2 (–5.85 to –3.5)	–4.5 (–5.6 to –3.0)	0.74
Lactate (mmol * l^{-1})	2.69 (2.25-3.82)	2.7 (2.33-3.10)	0.47
	n (%)	*n* (%)	*p*
Male sex	19 (54.3)	7 (46.7)	0.63
5-min Apgar score < 7	1 (2.9)	0	0.57
Transfer to neonatal intensive care unit	1 (2.9)	0	0.57

GDM – gestational diabetes mellitus, IQR – interquartile range

Discussion

Main findings

In this prospective cross-sectional study, we demonstrated that in fetuses of pregnancies complicated by GDM the distribution of UV blood flow is significantly altered and characterized by a smaller amount of the UV blood directed through the DV as expressed by the reduced DV shunt fraction and DV flow volume, even when normalized for EFW.

The reduced DV shunting in GDM fetuses is mainly caused by the reduction of DV diameter, because the DV flow velocity did not differ from control fetuses.

A possible explanation for the smaller amount of blood directed to the DV shunt is related to the DV intrinsic mechanism of regulation of its diameter: it has been documented that DV is provided with a reversible dilation mechanism that allows an increase in the degree of shunting from UV during hypoxia and hypovolaemia, and that ductal diameters are significantly greater in growth-restricted fetuses than in control fetuses [24, 25]. In diabetic fetuses, the hyperglycaemic environment may influence the fetal distribution of the UV and DV flow distribution in favour of a larger amount of blood flow towards the intrahepatic perfusion.

Although the UV volume flow is not increased in comparison to low-risk pregnancies, the fetuses of mothers with GDM direct a higher fraction of umbilical venous return to the liver, and this preferential UV distribution to the liver can be related to the augmented fat deposition and higher rate of incidence of macrosomia, as described in previous studies [26].

Comparison with other studies

To the best of our knowledge, no prospective studies exist that investigate the fetal distribution of the UV and DV flow pattern in gestational diabetic pregnancies. However, the findings of this study are in line with those of Lund et al. [13], who showed in pre-gestational diabetic pregnancies a reduced DV volume flow, a smaller DV shunt fraction, and greater blood flow directed to the fetal liver perfusion. These results validate the hypothesis that in both PGDM and GDM fetuses the amount of blood flow directed to DV is reduced in relation to the blood supply from the placenta through the UV and in relation to the fetal weight. However, Lund et al. also showed an increase of the absolute amount of UV volume flow, which was not shown in our study, and the UV flow volume normalized for EFW was strikingly low during late gestation, possibly signifying a relative discrepancy between fetal demand and substrate availability. A possible explanation for this discrepancy of results can be attributable to a lesser entity of the haemodynamic intrahepatic alterations in GDM fetuses in comparison to PGDM fetuses, which could also explicate the higher incidence of macrosomia and adverse neonatal outcomes in the latter group.

Boito et al. [14] found a fetal liver volume increase in fetuses of insulin-dependent diabetic mothers, which was related

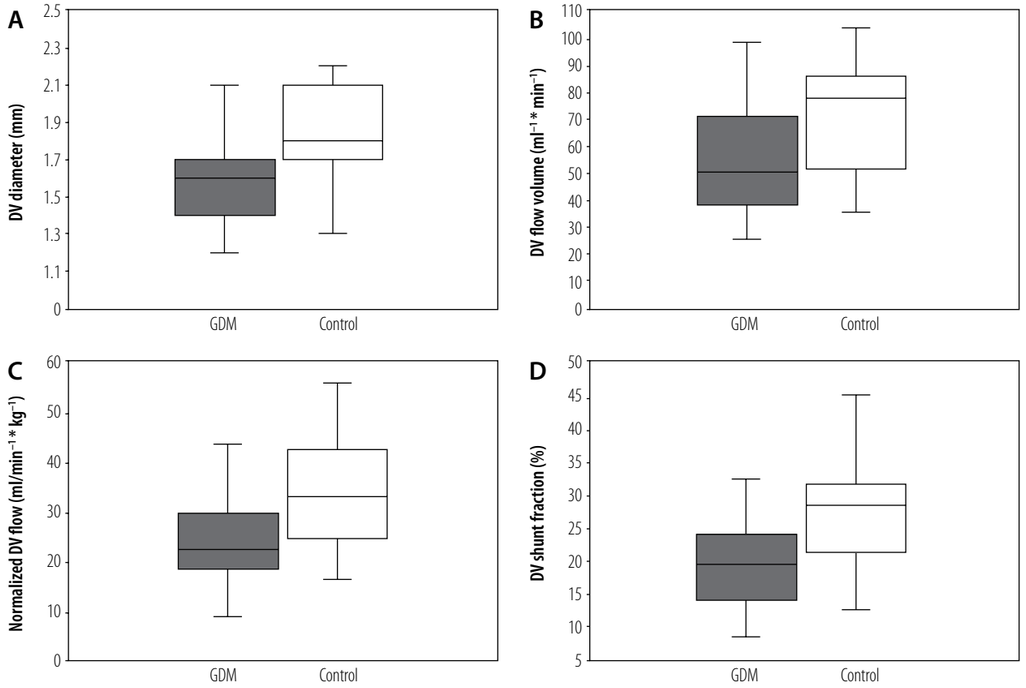

Figure 3. Box-whisker plots showing DV diameter (**A**), DV flow volume (**B**), normalized DV flow volume (**C**) and DV shunt fraction (**D**) in the GDM and control groups

DV – ductus venosus, GDM – gestational diabetes mellitus

Table 3. Analysis of continuous variables of UV and DV parameters. Comparisons between the diabetic and the control group using the Mann-Whitney *U*-test

Parameter	GDM group median (IQR)	control group median (IQR)	*p*
Umbilical vein (UV)			
Diameter (mm)	5.88 (5.27-6.45)	5.5 (5.25-5.95)	0.104
TAMXV (cm/sec)	22 (20-24)	21.4 (20.75-23)	0.824
Flow volume (ml * min^{-1})	301.91 (226.78-379.36)	260.63 (239.75-284.0)	0.126
Normalized UV flow for EFW (ml/min^{-1} * kg^{-1})	130.46 (103.84-152.43)	118.58 (86.93-42.38)	0.320
Ductus venosus (DV)			
Diameter (mm)	1.56 (1.39-1.69)	1.80 (1.70-2.10)	0.004
TAMXV (cm/sec)	39 (37-43.5)	41 (33-45)	0.610
Flow volume (ml^{-1} * min^{-1})	50.65 (39.21-69.19)	78.33 (55.02-85.61)	0.013
Normalized DV flow for EFW (ml/min^{-1} * kg^{-1})	22.78 (18.77-29.21)	32.97 (25.33-38.33)	0.016
Shunt fraction (%)	19.58 (14.19-23.68)	28.33 (22.30-31.64)	0.002

GDM – gestational diabetes mellitus, IQR – interquartile range

to maternal HbA1c levels reflecting the degree of maternal glycaemic control, but, in line with our results, it did not correlate with a parallel increase of umbilical venous volume flow.

Strengths and limitations

The prospective design, inclusion of consecutive pregnancies, and monocentric design with identical methods applied to the study and control group represent the major strengths of the present study. Another major strength of the study is the control of potential confounder variables such maternal and fetal Doppler characteristics.

The major limitation of this study is the small sample size of participants with a consequent scarcity of adverse neonatal outcomes, which limited the possibility of correlation analysis with UV and DV flow parameters, and the lack of information about the maternal glycaemic control did not allow us to correlate the circulatory changes with the degree of maternal metabolic control.

Other limitations include the cross-sectional nature of the study, which was not suitable for evaluation of the natural history of prenatal circulatory alterations and timing and progression of the events.

However, our results are consistent with previous studies that evaluated the intrahepatic blood flow in diabetic pregnancies, suggesting the potential role of these indices in identifying high-risk fetuses among GDM pregnancies.

Future perspectives

Further follow-up studies are required to confirm the results of the present study. Knowing how important the distribution of umbilical blood is to the fetus, further research in this section of the circulation will be valuable for detection of those GDM fetuses at particular risk.

Furthermore, in fetuses identified by an altered UV blood distribution it may be useful to extend the haemodynamic evaluation during the perinatal period in order to correlate pre- and postnatal data and to clarify the impact of the intrahepatic haemodynamic changes on the future cardiovascular health of offspring of mothers with diabetes [27].

Conclusions

Our findings suggest that alterations in the intrahepatic haemodynamics, expressed by a decrease of DV volume flow and a reduced DV shunt fraction, occur in GDM fetuses. These changes could reduce the compensatory capabilities of these fetuses and expose them to an increased vulnerability of hypoxia near term. These findings may be considered in the identification of such fetuses and may prompt prenatal monitoring and intervention aimed at reducing their risk of stillbirths and adverse perinatal outcomes.

Conflict of interest

The authors declare no conflict of interest.

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