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Ductus Venosus Shunting in Pregnancies with Well-Controlled Gestational Diabetes Mellitus

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ABSTRACT

Objectives: Gestational diabetes mellitus (GDM) is a common metabolic disorder in pregnancy, and it can be identified in 20% to 25% of Southeast Asian pregnancies. For GDM, fetal hypermetabolic rate due to hyperinsulinemia may cause an increase in hepatic blood flow from the umbilical venous (UV), leading to a decrease in ductus venosus (DV) shunting. The objective of this study was to compare DV shunting between uncomplicated pregnancy and gestational diabetes mellitus.

Materials and Methods: A prospective cohort study was performed on 76 women with uncomplicated singleton pregnancies and 36 women with GDM. Ductus venosus flow (DVF) and umbilical venous flow (UVF) were measured to assess the degree of DV shunting at 28-32 weeks of gestation. Pregnancy and neonatal outcomes were also collected and analyzed, including antenatal complications, gestational age at delivery, birth weight, Apgar score, neonatal intensive care unit (NICU) admission, ventilator support, and neonatal morbidity.

Results: The baseline characteristics of both groups were not significantly different, except for mean maternal age. There was no difference in the degree of DV shunting between the GDM and the control groups after adjustment for maternal age and gestational age, 41.34 % vs 40.18 %, respectively ($p = 0.70$). After multiple linear regression analysis, DVF, UVF, and DV shunting with an adjustment for maternal age and gestational age (GA) did not show a statistically significant difference. No relationships were found between the hemodynamic variables and perinatal outcomes.

Conclusion: This study suggested that good control of maternal GDM may prevent an increase in fetal hepatic blood flow, as indicated by no significant change of DV shunting and UVF.

Keywords: Doppler sonography, fetal circulation, fetal ultrasonography.

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การศึกษาเปรียบเทียบการเปลี่ยนแปลงการไหลของหลอดเลือดดำสายสะดือเข้าสู่หลอดเลือด Ductus venosus ทารกในครรภ์ของมารดาที่เป็นเบาหวานขณะตั้งครรภ์

พันธบัตร วรินทักษะ, วิรดา ดุลยพัชร์, สมมาตร บำรุงพืช

บทคัดย่อ

วัตถุประสงค์*: เบาหวานขณะตั้งครรภ์เป็นโรคเมตาบอลิซึมที่พบได้บ่อยในสตรีตั้งครรภ์ โดยพบประมาณร้อยละ 20-25 ในภูมิภาคเอเชียตะวันออกเฉียงใต้ โดยการศึกษานี้จะทำการตรวจวัดสัดส่วนการเปลี่ยนแปลงของการไหลของเลือดในหลอดเลือด ductus venosus ของทารกในครรภ์ของสตรีตั้งครรภ์ที่มีภาวะดังกล่าว*

วัสดุและวิธีการ*: การศึกษาไปข้างหน้าของกลุ่มประชากร แบ่งเป็นกลุ่มสตรีตั้งครรภ์ความเสี่ยงต่ำ 76 คนและกลุ่มสตรีตั้งครรภ์ที่เป็นเบาหวานขณะตั้งครรภ์ 36 คน ศึกษาตั้งแต่ มีนาคม 2564 ถึง พฤศจิกายน 2564 โดยทำการตรวจหลอดเลือด Ductus venosus และหลอดเลือดดำสายสะดือของทารกในครรภ์ในช่วงอายุครรภ์ 28-32 สัปดาห์ ด้วย Doppler ultrasound จากนั้นนำข้อมูลที่ได้ไปคำนวณโดย สูตรเทียบสัดส่วนการไหลของหลอดเลือด Ductus venosus หลังจากนั้นติดตามเก็บข้อมูลของทารกในครรภ์หลังคลอดได้แก่ ภาวะแทรกซ้อนก่อนคลอด อายุครรภ์ที่คลอด น้ำหนักแรกคลอด คะแนน Apgar การนอนรักษาตัวในหอผู้ป่วยวิกฤตทารกแรกเกิด การใช้เครื่องช่วยหายใจ ภาวะแทรกซ้อนโดยภาพรวมแรกเกิดจากประชากรทั้งสองกลุ่ม และนำข้อมูลทั้งหมดที่ได้มาวิเคราะห์ข้อมูลทางสถิติ*

ผลการศึกษา*: ในกลุ่มประชากรที่ทำการศึกษาทั้งสองกลุ่มไม่มีความแตกต่างกันในข้อมูลพื้นฐานของประชากร ยกเว้นอายุของมารดาที่ทำการศึกษา จากการเก็บข้อมูลพบว่า ค่าความต่างเฉลี่ยของปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือดดำสายสะดือของกลุ่มที่มารดาเป็นเบาหวานขณะตั้งครรภ์ มีค่าต่ำกว่ากลุ่มควบคุมโดยมีค่า 110.84 ± 36.93 มล./นาที/กก. และ 125.86 ± 36.37 มล./นาที/กก. ตามลำดับ โดยไม่พบการเปลี่ยนแปลงในค่าเปรียบเทียบสัดส่วนของการไหลของหลอดเลือด Ductus venosus ที่ร้อยละ 41.34 ± 13.35 ในกลุ่มที่มารดาเป็นเบาหวานขณะตั้งครรภ์ และร้อยละ 40.18 ± 17.31 ในกลุ่มควบคุม ซึ่งไม่แตกต่างกันในเชิงสถิติ (p = 0.70) โดยหลังจากใช้สมการถดถอยหลายตัวแปรแล้วไม่พบความแตกต่างของค่าปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือดดำสายสะดือ ปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือด Ductus venosus และค่าเปรียบเทียบสัดส่วนของการไหลของหลอดเลือด Ductus venosus ในประชากรทั้งสองกลุ่ม นอกจากนั้นยังไม่พบความสัมพันธ์ของการสัดส่วนการเปลี่ยนแปลงการไหลของหลอดเลือด Ductus venosus ต่อผลลัพธ์ของสุขภาพทารกแรกเกิด*

สรุป*: จากการศึกษานี้พบว่า ในกลุ่มมารดาเป็นเบาหวานขณะตั้งครรภ์ที่ควบคุมระดับน้ำตาลได้ดี อาจส่งผลป้องกันการเพิ่มขึ้นของการไหลเวียนของเลือดไปที่ตับของทารกในครรภ์ ซึ่งบ่งชี้จากการที่ไม่พบการเปลี่ยนแปลงที่มีนัยสำคัญของค่าเปรียบเทียบสัดส่วนของการไหลของหลอดเลือด Ductus venosus และค่าปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือดดำสายสะดือ*

คำสำคัญ: *เบาหวานขณะตั้งครรภ์, ปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือด Ductus venosus, ปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือดดำสายสะดือ, ผลลัพธ์ของทารกแรกเกิด, สัดส่วนการเปลี่ยนแปลงการไหลของหลอดเลือด Ductus venosus*

Introduction

Gestational diabetes mellitus (GDM) is a common metabolic disorder in pregnancy as it can be identified around 20% to 25% of Southeast Asian pregnant women[1]. Metabolic derangement in GDM patients are characterized by insufficient insulin secretion from pancreatic β-cells[2]. The coexistence of insulin secretory defects and insulin resistance can increase maternal blood glucose levels[3]. According to the Pedersen hypothesis, maternal hyperglycemia leads to an increased glucose transport across the placenta and fetal hyperglycemia[4] The consequence is an accelerated fetal oxidative metabolism, affecting neonatal outcomes[5]. This includes an altered cardiovascular adaptive development[6]. Such fetuses develop an increased umbilical venous flow (UVF), an increased umbilical perfusion of the fetal liver, an enlarged fetal liver, and a low ductus venosus (DV) flow[7-9].

Generally, blood flow from the placenta to the fetus through umbilical vein (UV) is the main source of oxygen and nutrition during fetal life. The fetal hepatic blood flow pattern may be affected by maternal pathological conditions such as maternal diabetes, chronic hypertension, renal disease, and autoimmune disease[10]. The ductus venosus (DV) is a narrow, trumpet-shaped vessel within the fetal liver parenchyma. It is connected to the UV, serving as a physiological vascular shunt that allows oxygenated blood from the placenta to the fetal brain and myocardium. In a normal fetus, the UVF is distributed to the left and the right hepatic lobes at 55% and 20%, respectively. Additionally, 25% of UV blood bypasses the hepatic circulation and directly shunts through the DV[11]. Hence, an assessment of fetal DV shunting may be useful for detecting the impact of maternal diabetes on fetal circulation.

Few studies have evaluated the blood flow pattern through UV and DV during pregnancy. Different distributions of blood flow through UV and DV among fetal growth restriction (FGR), macrosomia in non-diabetic mothers, and normal growth fetuses have been reported[12, 13]. In addition, the association of UV, ductus venosus flow, and DV shunting in diabetic pregnancies has also been studied. Such, an increased DV pulsatility index (PI) in diabetic mothers when compared to low-risk pregnancies, an increased UVF, a reduced DVF, and a decreased DV to UV ratio have been revealed[9, 14].

The increasing fetal UVF and DV shunting ratios in maternal diabetes has been proposed; therefore, these parameters were studied to detect fetal circulation disturbances in well-controlled GDM mothers. This leads to the main objective of this study where the fetal UVF and DV shunting at 28-32 weeks of gestation among well-controlled GDM mothers and uncomplicated pregnant women were determined. Additionally, postnatal outcomes were also gathered, including gestational age (GA) at delivery, birth weight, Apgar score, neonatal intensive care unit admission, ventilator support, and composite adverse outcomes.

Materials and Methods

Study design and participants

This prospective cohort study was conducted in pregnant women who attended the antenatal care clinic before 18 weeks of gestation at Ramathibodi Hospital, Mahidol University, from March 2021 to November 2021. The study was approved by the Institutional Review Board of Ramathibodi Hospital

(COA. MURA2021/90) and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

The sample size was calculated based on the data of the study, which found 18% of the mean DV shunting in maternal diabetes[9]. With a two-sample independent formula using a standard deviation (SD) of 12.58 and 90% power of the study, at least 33 participants in the GDM group and 67 participants in the control group were needed. The two-to-one allocation ratios of the GDM and the control groups were calculated.

All pregnancy dating was performed using standard fetal biometry ultrasonography according to the American College of Obstetricians and Gynecologists (ACOG) 2017 guidelines[15]. All women between 18 and 22 weeks of gestation were screened for any fetal anomaly according to the American Institute of Ultrasound in Medicine (AIUM) 2013 protocol[16].

GDM at our institution is diagnosed using universal screening with fasting blood sugar (FBS) and glycosylated hemoglobin (HbA1c) administered to all pregnant women regardless of the risk factors at the first antenatal care (ANC) visit. The value of FBS ≥ 92 mg/dL and < 126 mg/dL were considered positive for GDM. Among the pregnant women who had normal GDM screening at the first ANC, a 75 g oral glucose tolerance test (OGTT) was performed at 24-28 weeks of gestation. GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Group (IADPSG)[17], and the criteria for GDM diagnosis were established when any single threshold value was met or exceeded as follows:

- Fasting value, ≥ 92 mg/dl
- 1-hour value, ≥ 180 mg/dL
- 2-hour value, ≥ 153 mg/dL

All pregnant women diagnosed with GDM were recommended for nutritional planning and management with self-monitoring blood glucose (SMBG) level surveillance[18, 19]. Two weeks after the GDM diagnosis, poor glycemic controlled GDM was defined as 50% or more of SMBG level records, which exceeded the optimal goal[20].

The inclusion criteria were established for all singleton pregnancies of women aged 20 years or older, at 18-22 weeks of gestation, who had been confirmed by early ultrasound examination before 18 weeks of gestation and were willing to participate. The informed consent was obtained from all participants. The pregnant women with pre-gestational diabetes or with fetal, placental, and umbilical cord structural anomalies or FGR, according to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) criteria 2020[21], were excluded at the time of diagnosis before being recruited to any group. Those who could not obtain Doppler studies of UV and/or DV and had incomplete clinical data acquisition and unwillingness to participate were also excluded. Participants were categorized into the control group and the GDM group. The control group consisted of women with uncomplicated pregnancies who were willing to participate and had no underlying diseases diagnosed before pregnancy.

Outcome measures

All participants at 28-32 weeks' gestation underwent the ultrasonographic examination for the DVF and UVF using GE Voluson® E10 (GE Healthcare, Chicago, IL, US) with a curvilinear transducer. After fetal size and deepest vertical pocket (DVP) were measured, the diameters of the UV, the DV, and their flow velocimetry according to the ISUOG 2013 guideline[22] of standard Doppler study. The UVF and DVF were obtained as follows:

1. UV diameter, under the magnification of the image > 30%, was measured perpendicularly from inner wall to inner wall of UV lumen at the straight portion of the intra-abdominal UV before the first branching of the portal vein from a transverse view of the upper abdomen[11] (Fig. 1A). The UV diameter was calculated as the average of three measurements[23].

2. UVF velocity was obtained by pulsed-wave Doppler during fetal quiescence for 2-4 s, requiring an insonation angle close to zero or less than 15° with

angle correction, with the sample volume covering the width of UV (Fig. 1B). The reported velocity of the UVF was derived from the average of two measurements. UVF, along with absolute UVF (mL/min) and corrected UVF by estimated fetal weight (EFW) (UVF/kg), was calculated using the following formula:[24]

UVF = 0.5 × maximum venous time-averaged velocity (TA max) (cm/s) × 3.14 × (UV diameter/2)^2 (cm^2) × 60(s)

1. DV diameter was measured from the inner wall of the DV to the inner wall of the DV lumen at the isthmus (Fig. 1C) in accordance with a previous standardized technique[25, 26]. The inner diameter of the DV to reduce random error, the procedure was usually repeated three times, and the calculated mean diameter was used for statistical analysis[23].

2. The DVF velocity was recorded in a separate axial direction using sagittal insonation, rarely in an oblique transection of the fetal abdomen with an expanded sample volume covering the isthmus of the DV. The angle of insonation was kept as low as possible and not much greater than 15° (Fig. 1D). The velocity was recorded for 2-4 s during fetal quiescence. The reported velocity of the DVF was derived from the average of two measurements.

DVF, including absolute DVF (mL/min) and corrected DVF for EFW (DVF/kg), was calculated using the formula below[27].

DVF = 0.7 x the venous time-averaged maximum velocity (TA max) (cm/s) × 3.14 × (DV diameter/2)^2 (cm^2) × 60(s)

The DV shunting was calculated from the formula below[9].

DV shunting (%) = DVF/UVF x 100

The Doppler study above was performed by Maternal and Fetal Medicine specialists and Maternal and Fetal Medicine fellow. DV/UV diameter and flow ratios were assessed in 17 participants (3 times per each participant) for inter-observer agreements among 3 investigators.

All participants were scheduled for a follow-up according to the standard care for maternal diabetes at Ramathibodi Hospital. The participants diagnosed with fetal complications such as FGR, oligohydramnios, and abnormal fetal testing on fetal surveillance were scheduled for a follow-up according to the management guidelines for specific diseases

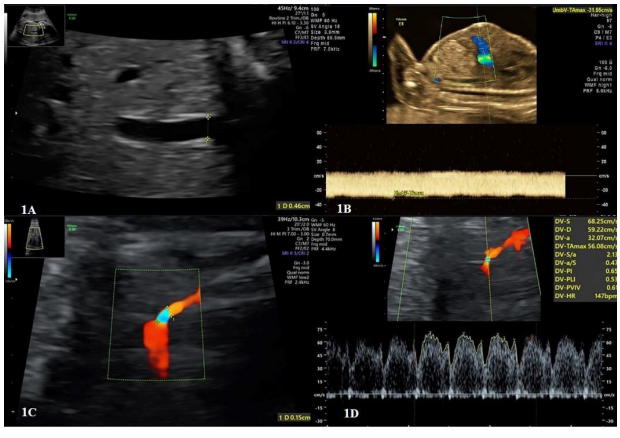

Fig. 1. UVF and DVF measurement. (1A) UV diameter is measured perpendicularly from the inner wall to the inner wall of the UV lumen, at the straight portion of the intra-abdominal UV before the first branching of the portal vein from a transverse view of the upper abdomen, under the magnification of the image > 30%. (1B) UVF velocity is obtained by pulsed-wave Doppler during fetal quiescence for 2 to 4 seconds, requiring the insonation angle close to zero or less than 15 degrees with angle correction. (1C) DV diameter is measured from the inner wall to the inner wall of the DV lumen at the isthmus. (1D) DVF velocity is obtained in sagittal insonation during fetal quiescence with an expanded sample volume covering the isthmus of the DV, with an insonation angle less than 15 degrees.
UVF: umbilical venous flow, DVF: ductus venous flow, UV: umbilical vein, DV: ductus venosus.

The main outcome was the comparison of DV shunting (%) between the GDM group and the control group. Subsequently, maternal age, GA, blood pressure, pregnancy, and neonatal outcomes were collected and analyzed, including antenatal complications, GA at delivery, birth weight, Apgar score, NICU admission, ventilator support, and neonatal morbidity for evaluating the correlation between DV shunting and postnatal outcomes.

Statistical analysis

The data analysis was performed using Stata version 17 (StataCorp LLC., College Station, TX, US). Intra-class correlations were performed using a two-way mixed-effects model to evaluate the consistency of agreements. Inter-observer agreements of DV/UV diameter and flow ratios were assessed using the Bland-Altman plot (Fig. 2) among 17 participants. The mean DVF and UVF of fetuses with maternal diabetes were compared with those of low-risk fetuses using an independent sample t-test. The associations between each ultrasound measurement as a dependent variable and maternal diabetes as an independent variable, with an adjustment for maternal age and GA, were determined using multiple linear regression. The neonatal outcomes of the maternal diabetes group, including GA at delivery, birth weight, Apgar score, NICU admission, ventilator support, and composite adverse outcomes, were compared with those of low-risk fetuses using independent sample t-test, chi-square test, or Fisher's exact test.

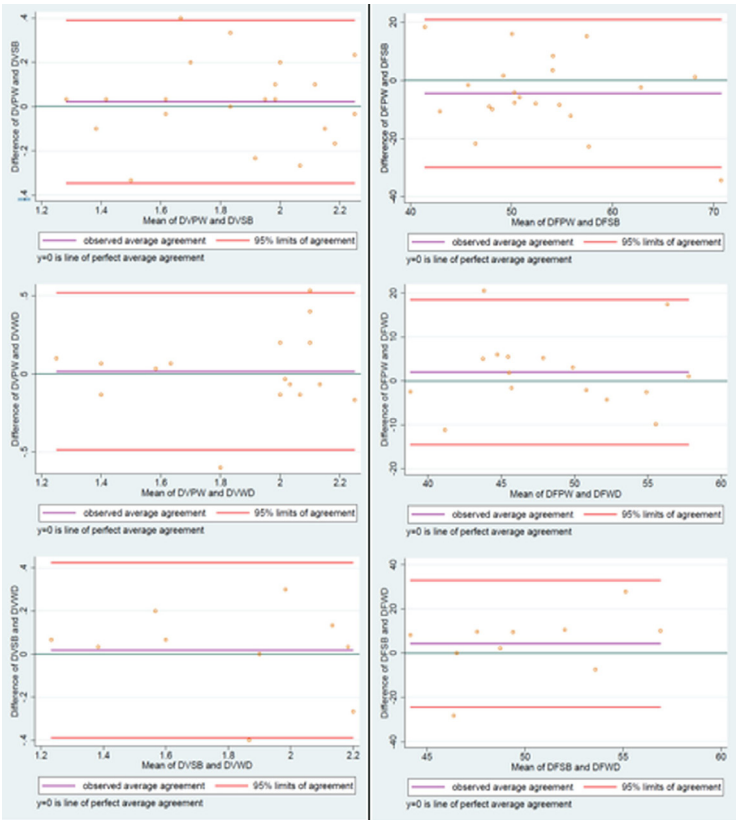

Fig. 2. Bland–Altman plot showed a difference in values within the 95% limit of agreement of inter-observer agreement of DV diameter (1A), DVF TA max (1B), UV diameter (1C) and UV TA max (1D).

DVF: ductus venosus flow, UV: umbilical vein, TA: time-averaged

Results

Two hundred and fifty-eight pregnant women were enrolled, but 139 women were excluded (Fig. 3). Therefore, DVF, UVF, and pregnancy outcomes were examined in 119 pregnant women, consist of 76 uncomplicated singleton pregnancies in the control group and 43 GDM pregnant women. Seven women in the GDM group were excluded because Doppler studies could not be performed. Ultimately, 76 participants in the control group and 36 in the GDM group who were diagnosed at the first antenatal care (ANC) visit 25 women and a 75 g oral glucose tolerance test at 24-28 weeks of gestation 11 women followed postnatal outcomes. Intra-observer reliability was assessed using a two-way mixed-effects model revealing that DV diameter, DVF time-averaged maximum velocity, UV diameter and UV (TA) max had the intra-class correlations coefficient (ICC) at 0.68, 0.59, 0.92 and 0.8, respectively. In addition, the inter-observer agreement of DV diameter, DVF TA max, UV diameter, and UV TA max exhibited by the Bland-Altman plot showed a difference in values within the 95% limit of agreement (Fig. 2).

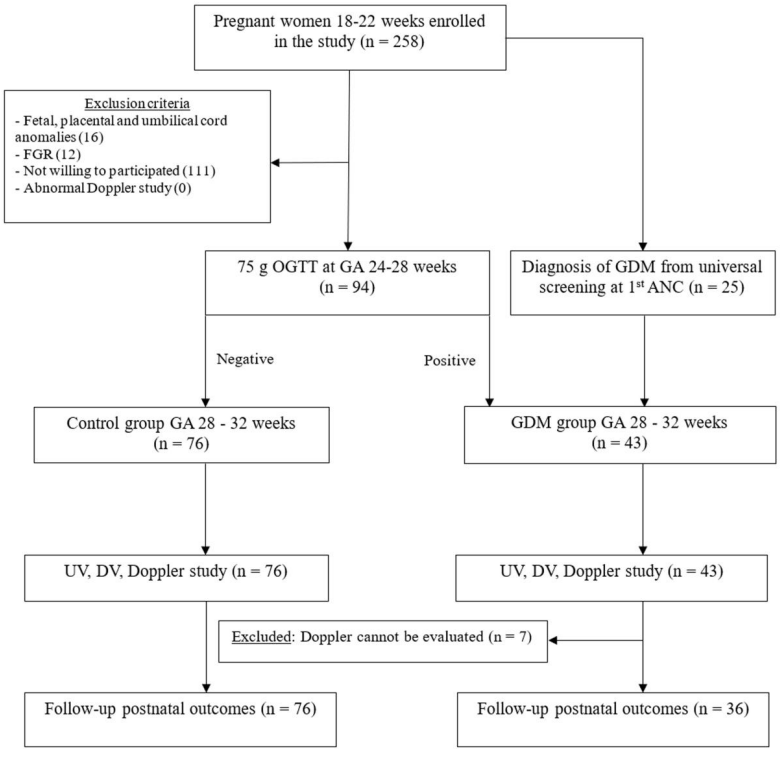

Fig. 3. Study flow diagram.

FGR: fetal growth restriction, OGTT: oral glucose tolerance test, GA: gestational age, GDM: gestational diabetes mellitus, ANC: antenatal care, UV: umbilical vein, DV: ductus venosus.

Table 1 presents the baseline characteristics of the participants. The baseline characteristics of both groups were not significantly different except for the mean maternal age. The mean age of the diabetic group was remarkably higher than that of the control group (33.48 ± 4.66 years vs 30.76 ± 5.84 years, p = 0.016).

Table 1. Baseline characteristics.

Characteristics	GDM group (n = 36)	Control group (n = 76)	p value[a]
Age (years)	33.48 ± 4.66	30.76 ± 5.84	0.016
Gravida			
Nulliparous	15 (41.7)	30 (39.5)	0.168
Multiparous	21 (58.3)	46 (60.5)	
Number of term delivery			
0	19 (52.8)	43 (56.6)	0.099
1	11 (30.6)	28 (36.8)	
2	3 (8.3)	5 (6.6)	
3	3 (8.3)	0 (0.0)	
History of preterm delivery			
1	0 (0.0)	2 (2.6)	1.000
GA (days)	203.19 ± 5.53	204.67 ± 6.62	0.245
Pre-pregnant BMI (kg/m^2)	23.13 ± 4.30	21.87 ± 3.5	0.107
Current BMI (kg/m^2)	25.42 ± 4.47	25.38 ± 3.85	0.957

GDM: gestational diabetes mellitus, GA: gestational age, BMI: body mass index.
Data are presented as number (%), mean ± standard deviation, or median (interquartile range).
[a] p values correspond to the independent samples t-test, Mann–Whitney U test, chi-square test, or Fisher's exact test.

The DV diameter, DV TA max, absolute DVF, and adjusted DVF were slightly lower in the GDM group than in the control group. However, the differences were not statistically significant. When we assessed the DV/UV diameter and flow ratios, no significant differences were observed between the diabetic and the control groups. The UV diameter, DV diameter, UVF, DVF, DV/UV diameter, and DVF/UVF ratios are listed in Table 2.

Table 3 shows the results of the multivariate analyses with the adjusted maternal age and GA. The mean difference in UVF in the GDM group was slightly lower than that in the control group at 110.84 ± 36.93 mL/min/kg and 125.86 ± 36.37 mL/min/kg, respectively. However, the difference was not statistically significant. Likewise, no significant difference was observed between DVF and DV shunting.

Table 2. Comparison of primary outcomes between the GDM and control group.

Parameter	GDM group (n = 36)	Control group (n = 76)	p value[a]
EFW (g)	1,280.14 ± 184.98	1,329.16 ± 220.08	0.25
DV diameter (mm)	1.91 ± 0.27	1.99 ± 0.28	0.15
DV Tmax (cm/s)	46.48 ± 9.28	47.9 ± 11.41	0.51
DV flow (ml/min)	56.38 ± 18.01	64.31 ± 26.76	0.11
DV flow/kg (ml/min/kg)	44.4 ± 15.22	49.36 ± 22.54	0.23
UV Diameter (mm)	5.01 ± 0.65	5.23 ± 0.69	0.11
UV TA max (cm/s)	23.86 ± 4.8	25.53 ± 5.48	0.12
UV flow (mL/min)	140.91 ± 36.93	165.88 ± 52.67	0.012
UV flow/kg (mL/min/kg)	110.84 ± 29.18	125.86 ± 36.37	0.032
DV/UV diameter ratio (%)	38.35 ± 5.37	38.54 ± 7.19	0.88
DV shunting (%)	41.34 ± 13.35	40.18 ± 17.31	0.72

g: gram, mm: millimeter, cm/s: centimeter/second, mL: milliliter, min: minute, kg: kilogram, EFW: estimated fetal weight, DV: ductus venosus, UV: umbilical vein.
Data are presented as mean ± standard deviation or median (interquartile range).
[a] Independent samples t-test.

Table 3. Multivariable analysis using multiple linear regression analysis adjusted for age and GA.

Parameter	Adjusted mean difference between GDM and control group	95% confidence interval	p value
DV diameter (mm)	- 0.036	(- 0.149 to 0.077)	0.527
DV Tmax (cm/s)	- 1.277	(- 5.828 to 3.274)	0.579
DV flow (mL/min)	- 5.251	(- 15.401 to 4.898)	0.307
DV flow/kg (mL/min/kg)	- 4.966	(- 13.462 to 3.531)	0.249
UV Diameter (mm)	- 0.172	(- 0.450 to 0.106)	0.223
UV TA max (cm/s)	- 0.999	(- 3.181 to 1.184)	0.366
UV flow (mL/min)	- 17.604	(- 37.132 to 1.924)	0.077
UV flow/kg (mL/min/kg)	- 14.296	(- 28.645 to 0.053)	0.051
DV/UV diameter ratio (%)	0.369	(- 2.421 to 3.160)	0.794
DV shunting (%)	- 1.112	(- 9.807 to 7.583)	0.800

GA: gestational age, g: gram, mm: millimeter, cm/s: centimeter/second, mL: milliliter, min: minute, kg: kilogram, EFW: estimated fetal weight, DV: ductus venosus, UV: umbilical vein.

The pregnancy outcomes revealed five neonates in the GDM group with unfavorable outcomes, including the need for ventilator support (n = 2), asymptomatic hypoglycemia (n = 2), and persistent pulmonary hypertension (n = 1). No such event was observed in neonates in the control group. Nevertheless, the differences in these features were not statistically significant, nor were the other perinatal outcomes (Table 4).

Table 4. Comparison of secondary outcomes between the GDM and control group.

Outcome	GDM group (n = 36)	Control group (n = 76)	p value[a]
Delivery			
Preterm	2 (5.6)	2 (2.6)	0.593
Term	34 (94.4)	74 (97.4)	
Birth weight (g)	3,074.33 ± 427.98	3,182.55 ± 373.49	0.175
Mode of delivery			
Vaginal delivery	24 (66.7)	45 (59.2)	0.449
Cesarean section	12 (33.3)	31 (40.8)	
Apgar score in the 5th minute			
≥ 7	36 (100.0)	76 (100.0)	
Ventilator support	2 (5.6)	0 (0.0)	0.101
Composite outcomes	5 (13.9)	7 (9.2)	0.455
TTNB	1 (2.8)	4 (5.3)	1.000
SGA	1 (2.8)	3 (4.0)	1.000
LGA	1 (2.8)	0 (0.0)	0.321
Asymptomatic hypoglycemia	2 (5.6)	0 (0.0)	0.101
Persistent pulmonary hypertension	1 (2.8)	0 (0.0)	0.321

g: gram, TTNB: transient tachypnea of the newborn, SGA: small for gestational age, LGA: large for gestational age.
Data are presented as number (%) or mean ± standard deviation.
[a] p value corresponds to independent samples t-test, chi-square test, or Fisher's exact test.

Discussion

This study evaluated fetal UVF, DVF, and DV shunting between well-controlled GDM and uncomplicated pregnancies during 28-32 weeks of gestation. Only a significantly lower UVF was observed in the GDM group than in the control group. The insight gained from this study was that, in well-controlled GDM, the distribution of umbilical venous flow to the fetal liver or DV was not altered.

Several studies have examined fetal UVF and DVF in high-risk pregnancies[12-14]. Nevertheless, the alteration of the DVF was observed exclusively in

severely compromised fetuses[13]. Limited evidence of DV shunting assessed in fetuses with maternal diabetes has been previously provided; and some studies have been conducted on various types of maternal diabetes, including pre-gestational DM, well-controlled GDM, and GDM treated with insulin[9, 28]. One study assessed the diameters of the UV, DV, and DV PI in pre-gestational DM and GDM compared with normal reference values of pregnant women without any risks between 28 and 36 weeks of gestation[14]. The only abnormal finding in this study was an increased DV PI in both pre-existing, insulin-dependent and gestational diabetes groups compared to low-risk pregnancies. Another study compared UVF, DVF, and DV shunting in fetuses with pre-gestational DM and low-risk pregnancies[9]. It demonstrated a significantly increased UVF and reduced DVF, resulting in decreased DV shunting. Likewise, a recently published study regarding DV shunting in the GDM group managed by diet control, with or without insulin therapy[28], demonstrated a significantly reduced DV diameter, absolute DVF, and DV shunting in fetuses of GDM mothers compared to low-risk pregnant ones.

The present study found no statistically significant differences between DVF and DV shunting, but significantly lower UVF was found in well-controlled GDM pregnancies than in low-risk pregnancies. Our findings differed from previously published studies that showed reduced DVF and DV shunting in the maternal diabetes groups[1, 12-14, 29]. Those studies included pregnancies with pre-gestational DM or GDM with insulin therapy. Pregnancies diagnosed with pre-gestational DM or GDM receiving insulin therapy might be readily affected by abnormal glucose metabolism, especially in maternal diabetes with suboptimal blood glucose control[30]. Detrimental effects on the fetus may occur during early pregnancy; and consequently, a decrease in DV shunting might be detected because of the fetal compensatory process to acquire sufficient oxygen supply[31].

Nevertheless, previous studies found that increased distribution of UVF to the fetal liver contributed to higher birth weight in pre-gestational diabetic pregnant women due to increased insulin-like growth factor 1 and 2 production and induced somatic growth of the fetus[12-14, 29]. Additionally, there is an evidence that UVF studied in early and late gestations is associated with fetal macrosomia[29, 32, 33]. This might be explained by an increase in UVF due to the increased placental size in the first trimester[29, 32, 33]. The most recent study demonstrated a reduction in DV diameter, DVF, and DV shunting among women with GDM[28]. They recruited a large number of maternal GDM women (31.4%) who required insulin treatment. No data was derived from a subgroup analysis of fetal DV shunting between the diet control GDM and the GDM with insulin therapy. Theoretically, in the fetus of GDM pregnancies, there may be liver enlargement, with more umbilical blood distributed to the fetal liver at the expense of the DV flow. This decreased DV shunting is expected to be more pronounced in cases with the fetuses' poor glycemic control, which is associated with liver enlargement, and their outcomes such as large for gestational age infants or macrosomia. However, this study did not find such effects, possibly because it included only the cases with well-controlled blood glucose levels. Consequently, no changes in blood distribution to the liver were observed.

Moreover, the composite neonatal outcomes did not differ significantly between these two groups, indicating good glycemic control of the participants in the GDM group.

The strengths of our study included the examination of DV shunting at 28-32 weeks of gestation and the observation that the trend of DV shunting remained relatively constant across gestational ages during this period[26]. However, there are several limitations to note: 1. We only evaluated UV-DV circulation once at 28-32 weeks, so any changes occurring other pregnancy period were not assessed. This means that our study did not include the data on well-controlled cases beyond 32 weeks of gestation, the time when a marked reduction of DV flow has been shown to occur in pre-gestational

diabetes mellitus[9]. 2. The intra-observer variability contributes to the total variation of measurements and in this study, this variability was moderate. Hence, further evaluation of reproducibility is needed in future studies. We acknowledge that a stricter measurement protocol including higher numbers of repeat measurements, particularly for the diameter of the DV, would have reduced random error and increased the likelihood of exposing differences[23]. 3. The small size of the DV makes it particularly susceptible to measurement errors. The high DV flow rates observed may be due to the measurement technique. Using color Doppler can affect the spatial representation of the vessel wall, potentially leading to overestimation of diameters. Nevertheless, assuming the technique was consistent throughout the study, the comparison between the two groups can still be considered valid.

Conclusion

This study suggested that good control of maternal GDM may prevent an increase in fetal hepatic blood flow, as indicated by no significant changes of DV shunting and UVF.

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Potential conflicts of interest

The author declares no conflicts of interest.

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