ORIGINAL ARTICLE

Fetal Cerebrovascular Flow Index from Three-Dimensional Power Doppler Ultrasonography in Gestational Diabetes Mellitus versus Low-Risk Pregnancy

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Objective: To compare fetal cerebrovascular flow indices using three-dimensional power Doppler (3DPD) ultrasound between gestational diabetes mellitus (GDM) and low risk pregnancy. Additionally, these comparisons were made among GDM patients based on treatment methods and relationship between fetal cerebrovascular flow indices, HbA1C levels, and perinatal outcomes.

Materials and Methods: The present study was a prospective cohort study comparing fetal cerebrovascular flow indices using 3DPD ultrasound between 80 low-risk pregnancies and 80 pregnancies complicated by GDM at Rajavithi Hospital. Participants underwent 3DPD ultrasound at 28 to 32 and 32 to 36 weeks of gestation to assess vascularization index (VI), flow index (FI), and vascularization flow index (VFI). The present study explored relationships between fetal cerebrovascular flow indices, maternal HbA1C levels, and neonatal outcomes.

Results: FI and VFI were significantly elevated in the GDM group compared to the low-risk group (p≤0.01 and 0.03). Among GDM patients, those managed with dietary control had higher VFI compared to those treated with medication at 1.51 versus 1.09 (p=0.024). However, no significant differences in fetal cerebrovascular flow indices were observed between well-controlled and poorly controlled GDM groups at 32 to 36 weeks, and no correlation was found between these indices, HbA1C levels or perinatal outcomes.

Conclusion: The 3DPD ultrasound provides a non-invasive method for assessing fetal cerebrovascular flow indices, particularly in GDM. The findings suggest that fetal brains in GDM cases adapt by increasing blood flow, as indicated by FI and VFI, while medication reduces pathological cerebral blood flow adaptation.

Keywords: Fetal cerebrovascular flow index; Three-dimensional power Doppler ultrasonography; Vascularization index; Flow index; Vascularization flow index; Gestational diabetes mellitus

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During pregnancy, the placenta produces hormones that affect the body, leading to a condition known as insulin resistance. In some pregnant women, this condition can result in elevated blood sugar levels, leading to gestational diabetes mellitus (GDM)[1].

According to the International Diabetes Federation in 2021, approximately 21.1 million pregnant women, or 16.7% of all pregnancies, experienced hyperglycemia during pregnancy. Among these, 80.3% were diagnosed with GDM, which is more common in low-income countries with limited access to healthcare services.

Pregnant women with a history of GDM are at an increased risk of developing type 2 diabetes within five to ten years postpartum. Additionally, infants born to mothers with high blood sugar levels may experience delayed brain development, excessive birth weight, obesity, and a higher likelihood of developing diabetes in the future[2].

The metabolic system during pregnancy significantly influences fetal brain development. Scientific evidence indicated that children born to mothers with diabetes may experience long-term learning and developmental issues[3,4]. This has led researchers to develop tools to study changes and functioning in the fetal brain to predict abnormalities. These tools include magnetic resonance imaging (MRI)[5] and fetal magnetoencephalographic devices[6], which are costly and complex to use.

Currently, ultrasound is considered a crucial

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and safe tool for assessing the fetus. Advances in technology have introduced 3D ultrasound systems that can provide realistic representations of the brain, blood vessels, and cerebral blood flow[7-9]. These systems are less complex and can be utilized by obstetricians and gynecologists. As a result, three-dimensional power Doppler (3DPD) ultrasound has emerged as a promising tool for evaluating cerebral blood flow and studying fetal brain changes in pregnant women with GDM.

Materials and Methods

A prospective cohort study was conducted involving 160 singleton pregnant women receiving antenatal care at Rajavithi Hospital between January and September 2024. The participants were divided into two groups (Figure 1) with 80 women in the low-risk pregnancies and 80 women with GDM. The study aimed to compare fetal cerebrovascular flow indices using 3DPD ultrasound between the two groups. Additionally, comparisons were made among GDM patients based on treatment methods such as diet control, medication, and blood sugar control. The study also examined the relationship between fetal cerebrovascular flow indices, HbA1C levels, and perinatal outcomes. The present study was approved by the Institutional Review Board of Rajavithi Hospital (No.66191).

The gestational age of low-risk pregnant women will align with that of pregnant women diagnosed with GDM at the time they participate in the study. GDM is diagnosed using the two-step screening method based on standard guidelines. First, a 50-gram glucose challenge test was administered, during which the participant consumed 50 grams of glucose. If the blood glucose level was at, or above 140 mg/dL, it was considered abnormal, prompting further diagnostic testing with the 100-gram 3-hour oral glucose tolerance test (OGTT). For the OGTT, participants must fast for at least eight hours before blood was drawn at four points, before glucose consumption and at one, two, and three hours afterward. The Carpenter and Coustan criteria were used to diagnose GDM if at least two values met or exceeded the threshold. Pregnant women would be excluded from the study if they were diagnosed with diabetes before pregnancy, having hypertension, significant fetal abnormalities, fetal weight below the tenth percentile for gestational age, anemia, or if the fetus had died or was delivered before an ultrasound between 28 and 32 weeks of gestation. Women diagnosed with GDM would receive standard

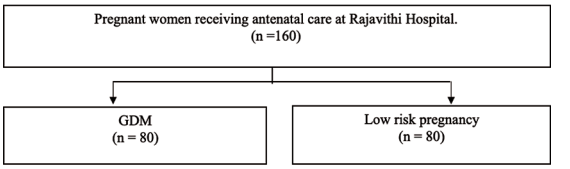

Figure 1. Flow chart illustrating the number of participants enrolled in the study.

care, including blood glucose control through dietary management as a nutritionist recommended, insulin injection, or oral metformin. The goal was to maintain blood glucose levels within the following target ranges, fasting glucose at 70 to 95 mg/dL, one-hour postprandial glucose at 110 to 140 mg/dL, and two-hour postprandial glucose at 100 to 120 mg/dL in more than 70% of measurements. If additional diabetes medication were required between 28 and 36 weeks, HbA1C levels of 6% or greater, or if blood glucose control remained below 70%, they would be classified as poorly controlled GDM[10].

All participants underwent a 3DPD ultrasound of the fetal brain and fetal weight assessments between 28 and 32 weeks of gestation. For participants with GDM, HbA1C levels would also be collected. A second data collection would be taken four weeks later, at 32 to 36 weeks of gestation, repeating the 3DPD ultrasound and fetal weight assessment. The ultrasound machine used was the Voluson S8 or S10 model (GE Healthcare). Ultrasounds were performed transabdominally using a 5 MHz transducer targeting the fetal skull base. Power Doppler assessed the circle of Willis using a pulse repetition frequency of 0.9 Hz. The software's virtual organ computer-aided analysis (VOCAL) created spherical regions around fetal cerebral vessels and calculated the vascularization index (VI), flow index (FI), and vascularization flow index (VFI) (Figure 2). Each cerebral blood FI would be recorded three times, with an average taken, ensuring each session lasted no more than ten minutes and the thermal index remains at 1.0 or less to prevent any potential adverse effects on the mother and fetus. Ultrasounds would be conducted by maternal-fetal medicine fellows and faculty, with interobserver repeatability assessed in the first ten cases.

All pregnant women participating in the study had their baseline data collected, including details about GDM, diabetes treatment, blood glucose control, HbA1C levels for women with GDM, VI, FI, VFI, fetal weight, fetal abdominal circumference, delivery details such as neonatal weight, gestational age at delivery, and indications for delivery, and

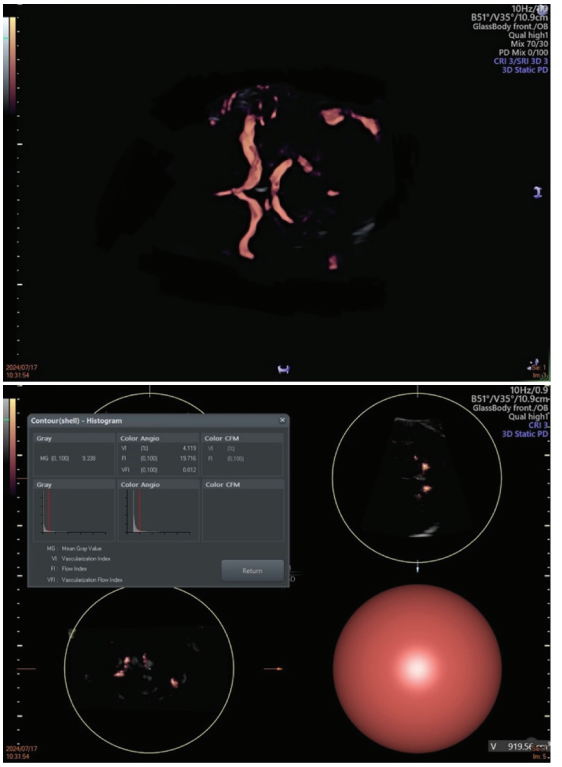

Figure 2. The software's virtual organ computer-aided analysis (VOCAL) creates spherical regions around fetal cerebral vessels and calculates the vascularization index (VI), flow index (FI), and vascularization flow index (VFI).

neonatal Apgar scores. Statistical analysis was performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). Categorical data were presented as frequencies and percentages. In contrast, continuous data were reported as means and standard deviations (SD) for normally distributed data or as medians, minimum, and maximum values for non-normally distributed data. Categorical data comparisons were conducted using the chi-square or Fisher's exact test. For continuous data comparisons between two independent groups, Student's t-test was used for normally distributed data, and the Mann-Whitney U test was applied for non-normally distributed data. When comparing continuous data across more than two groups, a one-way analysis of variance (ANOVA) was used for normally distributed data, and the Kruskal-Wallis test was used for non-normally distributed data. Relationships between the fetal cerebrovascular index and HbA1C, as well as birth weight, were analyzed using simple linear regression. In contrast, the relationship between the fetal cerebrovascular index and perinatal outcomes was analyzed using binary logistic regression. Statistical significance was set at a p-value less than 0.05. The sample size was calculated using the formula for comparing two independent means[11], based on a previous study by Pérez-Martín et al. (2022)[12], which utilized 3DPD ultrasound to compare pregnant women with and without GDM. The study reported that the mean FI in the non-GDM group was 34.3 (SD 2.8), while that in the GDM group was 35.5 (SD 2.6). The calculation was performed using a power of 80% and a significance level of 0.05.

Results

Data were collected from 160 pregnant women, as shown in Table 1, comparing the baseline characteristics between low-risk pregnant women and those with GDM. It was found that maternal age, body mass index (BMI), and cesarean section rates were significantly higher in the group with GDM, while the gestational age at delivery was significantly lower in the GDM group. There were no significant differences between the groups in terms of nationality, nulliparity, gestational age at ultrasound, newborn weight, fetal non-reassuring status, or preterm labor (Table 1). Among the analyzed variables, maternal age, BMI, and newborn weight demonstrated normal distribution patterns.

When comparing fetal cerebrovascular flow indices recorded using 3DPD ultrasound between the low-risk group and the GDM group, the FI and VFI showed significant differences. The mean FI was higher in the GDM group than the low-risk group, with values of 24.19 and 21.82, respectively ($p<0.001$). Similarly, the median VFI was also higher in the GDM group, with values of 1.36 and 1.12, respectively ($p=0.03$) (Table 2). In the multivariate analysis adjusting for maternal age, BMI, gestational age at delivery, and mode of delivery, GDM was significantly associated with both FI ($p<0.001$) and VFI ($p=0.010$).

When comparing the group treated with medication versus the group managed through dietary control, the median VFI in the dietary-controlled group was significantly higher than that in the medication-treated group, with values of 1.51 and 1.09, respectively ($p=0.024$) (Table 3). Furthermore, when comparing all three groups, including low-risk pregnant women, GDM managed with dietary control, and GDM managed with medication, the dietary-controlled group had the highest fetal cerebrovascular flow indices. The mean FI values for these groups were 21.82, 24.64, and 23.06, respectively ($p<0.001$), and the median VFI values

Table 1. Characteristics of pregnant women compared between GDM and low-risk pregnancy

Characteristics	Low-risk pregnancy (n=80)	GDM (n=80)	p-value
Maternal age (years old); mean [SD]	28.83 [5.67]	32.06 [5.46]	<0.001
Nationality; n (%)			0.632
Thai	41 (51.2)	37 (46.3)	
Myanmar	24 (30.0)	31 (38.8)	
Laos	10 (12.5)	7 (8.8)	
Cambodia	5 (6.3)	4 (5.0)	
Other	0 (0.0)	1 (1.3)	
BMI (kg/m^2); mean [SD]	22.32 [3.23]	23.67 [3.31]	0.010
Nulliparity; n (%)	45 (56.3)	52 (65.0)	0.257
Multiparity; n (%)	35 (43.8)	28 (35.0)	
Gestational age at ultrasound scan (weeks); median (min-max)	30 (28 to 32)	30 (28 to 32)	0.661
Gestational age at birth (weeks); median (min-max)	39 (35 to 41)	38 (36 to 40)	0.012
Newborn weight (g); mean [SD]	3,086.55 [428.87]	3,038.94 [474.90]	0.507
Fetal reassuring status; n (%)	67 (83.8)	60 (75.0)	0.171
Fetal non-reassuring status; n (%)	13 (16.3)	20 (25.0)	
Term; n (%)	77 (96.3)	75 (93.8)	0.468
Preterm; n (%)	3 (3.8)	5 (6.3)	
Vaginal delivery; n (%)	51 (63.7)	35 (43.8)	0.011
Cesarean delivery; n (%)	29 (36.3)	45 (56.3)	

GDM=gestational diabetes mellitus; BMI=body mass index; SD=standard deviation

Table 2. Comparison of fetal cerebrovascular index between GDM and low-risk pregnancy

Cerebrovascular index	Low-risk pregnancy (n=80)	GDM (n=80)	p-value
VI; median (min-max)	5.06 (2.82 to 15.06)	5.57 (2.40 to 14.91)	0.174
FI; mean (SD)	21.82 (2.60)	24.19 (4.45)	<0.001
VFI; median (min-max)	1.12 (0.55 to 3.31)	1.36 (0.48 to 3.96)	0.030

GDM=gestational diabetes mellitus; VI=vascularization index; FI=flow index; VFI=vascularization flow index; SD=standard deviation

Table 3. Comparison of fetal cerebrovascular index between treatment methods of GDM

Cerebrovascular index	Diet control (n=57)	Medication (n=23)	p-value
VI; median (min-max)	5.88 (2.67 to 14.91)	5.09 (2.40 to 8.35)	0.047
FI; mean (SD)	24.64 (4.20762)	23.06 (4.92553)	0.076
VFI; median (min-max)	1.51 (0.53 to 3.96)	1.09 (0.48 to 2.42)	0.024

GDM=gestational diabetes mellitus; VI=vascularization index; FI=flow index; VFI=vascularization flow index; SD=standard deviation

were 1.12, 1.51, and 1.09, respectively (p=0.006) (Table 4). Among these parameters, only the FI demonstrated a normal distribution. Post hoc analysis revealed that the diet-controlled GDM group had significantly higher FI and VFI compared to the low-risk group, while no significant differences were observed between the medication-treated group and the other groups.

However, when comparing fetal cerebrovascular flow indices, VI, FI, and VFI, after treatment in the groups with well-controlled and poorly controlled blood sugar levels between 32 and 36 weeks of gestation, no significant differences were observed (p=0.445, 0.955, and 0.544). Additionally, statistical analysis revealed no correlation between fetal cerebrovascular flow indices of VI, FI, and VFI, and HbA1C levels (p=0.361, 0.061, and 0.071), and birth weight (p=0.374, 0.941, and 0.456). Furthermore, there were no associations between cerebrovascular indices and perinatal outcomes, including preterm birth, fetal non-reassuring status, and cesarean delivery (Table 5). From the present study, no cases of neonatal asphyxia were observed. The intra-observer intraclass correlation coefficients (ICC) of

Table 4. Comparison of fetal cerebrovascular index between treatment methods of GDM and low-risk pregnancy

Cerebrovascular index	Low-risk pregnancy (n=80)	Diet control (n=57)	Medication (n=23)	p-value
VI; median (min-max)	5.06 (2.82 to 15.06)	5.88 (2.67 to 14.91)	5.09 (2.40 to 8.35)	0.066
FI; mean (SD)	21.82 (2.60)*	24.64 (4.21)*	23.06 (4.93)	<0.001
VFI; median (min-max)	1.12 (0.55 to 3.31)*	1.51 (0.53 to 3.96)*	1.09 (0.48 to 2.42)	0.006

GDM=gestational diabetes mellitus; VI=vascularization index; FI=flow index; VFI=vascularization flow index; SD=standard deviation
* Post hoc analysis revealed statistically significant differences between groups

Table 5. Relationship between fetal cerebrovascular flow index and perinatal outcomes

Perinatal outcomes	Cerebrovascular index	OR	95% CI	p-value
Preterm birth	VI	0.95	0.37 to 2.45	0.344
	FI	0.86	0.66 to 1.12	0.535
	VFI	2.52	0.07 to 96.02	0.447
Fetal non-reassuring status	VI	1.20	0.63 to 2.28	0.885
	FI	1.12	0.95 to 1.33	0.185
	VFI	0.42	0.03 to 5.64	0.725
Cesarean delivery	VI	0.92	0.55 to 1.51	0.246
	FI	1.02	0.90 to 1.16	0.995
	VFI	0.98	0.14 to 7.07	0.328

OR=odds ratio; CI=confidence interval; VI=vascularization index; FI=flow index; VFI=vascularization flow index

cerebrovascular flow indices, VI, FI, and VFI, were 0.91, 0.93, and 0.93, respectively. The inter-observer ICC values were 0.92, 0.90, and 0.86, respectively.

Discussion

The present study found that when comparing cerebrovascular flow indices in fetal brains, the FI and VFI were higher in the GDM group, suggesting an adaptive mechanism to increase cerebral blood flow in fetuses of mothers with GDM. However, among GDM cases treated with medication versus dietary control, VFI was significantly reduced in the medication group. This indicates that medication might help reduce fetal cerebral blood flow adaptation. Comparing the indices among GDM cases treated with medication, dietary control, and low-risk pregnancies, FI and VFI were lowest in the medication-treated GDM group and the low-risk group, respectively. This suggests that medication might mitigate pathological effects on the fetal brain.

Previous research[12] also found higher FI in the GDM group compared to controls at 35.5±2.6 versus 34.3±2.8 (p=0.02), consistent with the present study. However, no significant differences were observed for VI and VFI. Additionally, a negative correlation between FI, VI, and VFI with maternal blood sugar levels was identified, supporting the hypothesis that fetal brains in GDM cases undergo adaptive changes to increase cerebral blood flow.

Studies have explored the use of 3DPD ultrasound to evaluate fetal cerebrovascular flow indices. For instance, a 2003 study demonstrated the effectiveness of measuring VI, FI, and VFI to assess blood flow and vascularization in fetal brains, making it a reliable tool for monitoring central nervous system development[13]. In 2010, studies confirmed its high reliability, with an ICC exceeding 0.90[14]. A study in 2012 found that cerebrovascular flow indices were not correlated with gestational age, allowing their use in analyzing fetal vascular adaptation in complicated pregnancies[15].

Research on fetal growth restriction (FGR) in 2009 and 2017 revealed higher cerebral vascular indices in FGR fetuses, reflecting a brain-sparing response to hypoxia[16,17]. Similar findings have been reported in fetuses with congenital heart defects (CHD), with significantly higher VI, FI, and VFI indices compared to normal fetuses[18].

Regarding GDM-related fetal brain abnormalities, a 2015 study using fetal magnetoencephalography (fMEG) observed delayed auditory evoked responses (AER) in fetuses of GDM mothers, particularly after maternal glucose intake. This delay was attributed to insulin resistance in the fetal brain[6]. In 2018, another study highlighted an increased risk of behavioral issues in children born to GDM mothers, potentially linked to elevated inflammatory markers (TNF-α, IL-6) and decreased insulin receptor activity in brain

regions critical for memory and learning[3].

Strengths of the present study include being the first prospective cohort to investigate fetal cerebrovascular flow indices in GDM. It examined treatment differences, maternal glycemic control, and correlations with HbA1C and perinatal outcomes. The inclusion of diverse Southeast Asian populations enhances generalizability, and comparing data at similar gestational ages reduces bias.

However, the small sample size for perinatal outcomes may limit the detection of associations. Excluding women with certain preexisting conditions and the single-center design could introduce selection bias. Unmeasured confounders, such as socioeconomic status or lifestyle factors, may also influence outcomes. As an observational study without random sampling, causal inferences between GDM, treatment methods, and cerebrovascular indices are limited. Clinical application requires strict adherence to ultrasound protocols to ensure accuracy.

Given that the present study is a short-term observational design, it cannot determine the relationship between fetal cerebrovascular flow and long-term perinatal outcomes, such as neurodevelopment. This highlights an important opportunity for future research to explore the association between fetal cerebrovascular flow indices and subsequent neurodevelopmental outcomes.

The 3DPD ultrasound provides a non-invasive and accurate method for assessing fetal cerebral blood flow and vascularization, particularly in complicated pregnancies, such as GDM. The findings suggest that fetal brains in GDM cases adapt by increasing blood flow, as indicated by FI and VFI, while medication reduces pathological cerebral blood flow adaptation. This technique could aid in diagnosing and monitoring fetal complications in the future.

What is already known about this topic?

The infants born to mothers with diabetes may have long-term learning and developmental issues. This has led researchers to develop tools to study changes and functioning in the fetal brain to predict abnormalities.

What does this study add?

The brain of a fetus whose mother has GDM adapts by increasing cerebral blood flow. At the same time, treatment with medication reduces this adaptation in the fetal cerebral blood flow, as assessed by 3DPD ultrasound.

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Conflicts of interest

The authors declare no conflict of interest.

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