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Original Research

Assessing Fetal Circulatory Changes in Gestational Diabetes via Aortic Isthmus Doppler

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Abstract

Background: Gestational diabetes mellitus (GDM) is a common complication during pregnancy that can negatively impact fetal heart function and structure. This study aimed to investigate the hemodynamic characteristics of the fetal aortic isthmus in patients with GDM using Doppler ultrasound parameters. **Methods**: This was a cross-sectional observational study including 47 pregnant patients with GDM and 47 healthy pregnant patients as controls. Fetal biometric measurements and umbilical artery Doppler values were obtained. Aortic isthmus Doppler was used to measure systolic and diastolic flow velocity time integrals (S and D), peak systolic velocity (PSV), and systolic nadir (Ns) to calculate the isthmus flow index (IFI) = (S + D)/S and isthmus systolic index (ISI) = Ns/PSV. A generalized additive model was used to analyze the relationship between IFI, ISI and gestational age. **Results**: Compared to controls, the GDM group had significantly lower D (2.39 cm *vs.* 2.76 cm), Ns (11.48 cm/s *vs.* 14.06 cm/s), IFI (1.24 *vs.* 1.27) and ISI (0.14 *vs.* 0.16). Curve fitting showed IFI was lower in the GDM group for most gestational weeks and decreased with advancing weeks, while ISI remained constantly lower and decreased linearly. **Conclusions**: Fetal aortic isthmus Doppler parameters IFI and ISI were altered in GDM pregnancies, suggesting earlier changes in aortic arch hemodynamics compared to the umbilical artery. Combining IFI and ISI may provide more comprehensive assessment of fetal circulatory changes in GDM. These findings could enhance our understanding of the pathophysiologic impacts of maternal diabetes.

Keywords: gestational diabetes mellitus; fetal Doppler; aortic isthmus; isthmus flow index; isthmus systolic index

1. Introduction

Gestational Diabetes Mellitus (GDM) is a common complication during pregnancy, defined as diabetes that is first identified during pregnancy in women whose previous blood sugar levels were normal or who had undiagnosed prediabetes before pregnancy [1]. It accounts for over 80% of cases of diabetes in pregnant women. The reported global incidence of GDM ranges from 1% to 14% and is increasing annually [2]. Moreover, an Italian case-control study showed that the prevalence of GDM was significantly higher during the COVID-19 pandemic [3]. Poor blood sugar control in GDM can negatively affect the health of the mother and may lead to impaired fetal heart function and structure [4]. Studies have shown that a high blood sugar environment during pregnancy can cause changes in fetal heart function before any structural changes occur [5].

Maternal hyperglycemic environment of GDM patients can lead to placental dysfunction [6]. When its severe imbalance causes dysfunction of maternal-fetal blood flow exchange and hypoxia of fetal blood circulation, it can cause changes in fetal hemodynamics [7]. Ultrasound Doppler, a non-radiative and non-invasive technique, effectively monitors the hemodynamic changes in important blood vessels of the mother, fetus, and placenta, reflecting central and peripheral fetal circulation [8,9]. Currently, the umbilical artery (UA) Doppler ultrasound is commonly used to monitor fetal blood flow dynamics, indicating the vascular resistance in the terminal organs (placenta) of the fetal circulation [10,11]. Further research is needed to more accurately and effectively assess early indicators of abnormalities in the fetal circulatory system.

The aortic isthmus (AOI) is a crucial arterial segment located centrally in the fetal circulation, extending from the opening of the left subclavian artery on the aorta to the entrance of the arterial duct into the descending aorta. It connects the two circulatory systems, with the left ventricle supplying the brain circulation and the right ventricle supplying the body and placental circulation [12]. Changes in AOI blood flow spectrum can reflect the balance of output between the left and right ventricles and the differences in vascular resistance between the two circulatory systems, playing a regulatory role in the balance of blood perfusion above and below the diaphragm [13]. Given its unique anatomical location and physiological characteristics, AOI blood flow spectrum changes earlier when there are abnormalities in the fetal circulatory system [14]. Ruskamp *et al*. [15] believe that the isthmus flow index (IFI) is particularly sensitive to changes in the direction of diastolic blood flow in the AOI. Other researchers have demonstrated that changes in the isthmus systolic index (ISI) have been associated with increased placental resistance, increased afterload on the right ventricle, and increased right ventricular output [16].

Research on the fetal circulatory status in GDM patients and its changes varies, and a single indicator cannot fully and objectively assess changes in fetal hemodynamics. Therefore, this study aimed to explore the characteristics and patterns of fetal blood flow changes in GDM patients by measuring IFI combined with ISI. It investigated the clinical value of IFI and ISI in assessing changes in fetal hemodynamics in GDM patients, providing clues and evidence for the early prenatal ultrasound detection of abnormal fetal circulatory load.

2. Materials and Methods

2.1 Study Population

The study included pregnant patients who underwent prenatal ultrasound at our hospital from September 1, 2022, to June 30, 2023. Fetuses of mothers with GDM were observed, while fetuses from normal pregnancies during the same period served as the control group, ensuring both groups had an equal number of samples.

The criteria for inclusion were as follows: the control group had no pregnancy complications; GDM diagnosis was based on a 75 g Oral Glucose Tolerance Test (OGTT) conducted between 24 to 28 weeks of pregnancy, with diagnostic thresholds for fasting, 1-hour post-glucose, and 2-hour post-glucose blood sugar levels set at 5.1, 10.0, and 8.5 mmol/L, respectively. Any value reaching or exceeding these thresholds indicated GDM, excluding other complications. Only single pregnancies were considered and the menstrual cycles of the pregnant patients were regular, with gestational age matching the last menstrual period.

Exclusion criteria included factors that could affect fetal and maternal hemodynamics due to umbilical cord and placental structure abnormalities; any cardiac morphological or functional abnormalities in the mother or fetus; intrauterine fetal growth restriction; failure to collect standard Doppler spectra due to maternal abdominal wall thickness or fetal position; significant maternal illness or other underlying diseases; and abnormal fetal chromosomal results.

2.2 Ultrasonography

GE Volusion E8 and GE Volusion S10 ultrasound machines were used with a 1–5 MHz two-dimensional probe and an obstetric ultrasound program. Fetal growth and development were assessed by measuring the head circumference (HC), biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC) to calculate gestational age.

UA parameters were obtained using pulse wave Doppler to measure peak systolic velocity (PSV), end-diastolic velocity (EDV), the ratio of peak systolic to end-diastolic velocity (S/D), and pulsatility index (PI).

AOI parameters were captured on the long-axis view of the aortic arch, as shown in Fig. 1. The study measured systolic and diastolic flow velocity time integrals (S and D) for both groups. Manual measurements of PSV and systolic nadir (Ns) in the AOI were conducted. The formulas IFI = (S + D)/S and ISI = Ns/PSV were used to obtain the data for both groups.

2.3 Statistical Analysis

Quantitative data was presented as mean ± standard deviation (SD), and categorical data as percentages. Differences between the GDM group and the control group were analyzed using Mann-Whitney U test. Effect sizes were determined using the Cohen's *d* method and Cohen's $d = 0.2$, 0.5 and 0.8 are defined cut-off values for small, medium and large effect sizes, respectively [17]. A combination of smooth curve fitting and generalized additive model was used to observe the relationship between IFI and ISI with gestational age. Data analysis was performed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA) and R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria), considering a p value < 0.05 as statistically significant.

3. Results

The study included 94 pregnant patients, with 47 in the GDM group and 47 in the control group. Table 1 presents demographic and obstetric ultrasound characteristics of the study population. The average age of the women was 28.84 ± 3.87 years, with a mean gestational age of 32.81 ± 3.31 weeks during the ultrasound examination. The two groups were well-matched in terms of maternal age and gestational age at assessment, with no significant statistical differences (all $p > 0.05$). For umbilical artery Doppler parameters, the GDM group showed slightly lower PSV, EDV, S/D, and PI compared to the control group, but these differences were not statistically significant (all $p > 0.05$), as shown in Table 1.

Table 2 presents the results of the fetal heart ultrasound Doppler examination of the aortic isthmus blood flow dynamics for both groups. In terms of ultrasound measurements, the GDM group had significantly lower diastolic flow velocity time integrals (D, 2.39 cm *vs*. 2.76 cm, Cohen's $d = 0.42$, $p = 0.015$) and nadir flow velocity during systole (Ns, 11.48 cm/s *vs*. 14.06 cm/s, Cohen's $d = 0.64$, $p < 0.001$) compared to the control group, indicating a moderate to large effect size. Although the GDM group had lower S and PSV than the control group, these differences were not statistically significant (all $p > 0.05$). The calculated IFI and ISI were lower in the GDM group compared to the control group (IFI, 1.24 *vs*. 1.27, $p = 0.042$; ISI, 0.14 *vs*. 0.16, $p = 0.014$, respectively), with Cohen's *d* values of 0.32 and 0.48, respectively, indicating moderate effect sizes.

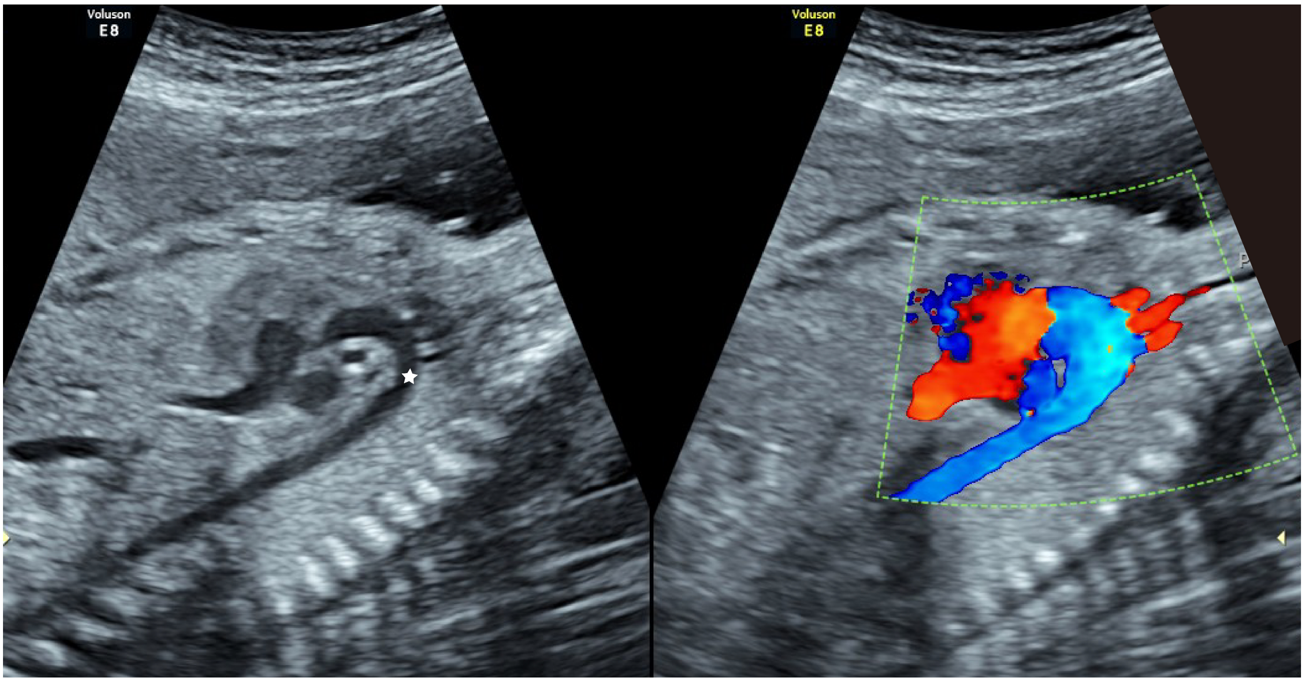

Fig. 1. Longitudinal arch view showing aortic isthmus (AOI) (white star).

Table 1. Characteristics of the two study groups: pregnant women with and without gestational diabetes mellitus.

	Total (N = 94)	Controls (N = 47)	GDM (N = 47)	*p* value
Age (years)	28.84 ± 3.87	28.55 ± 3.57	29.13 ± 4.17	0.504
GA (weeks)	32.81 ± 3.31	33.30 ± 3.00	32.32 ± 3.56	0.239
UA parameters				
PSV (cm/s)	43.10 ± 7.72	44.01 ± 8.49	42.19 ± 6.82	0.311
EDV (cm/s)	18.18 ± 4.54	18.88 ± 4.98	17.48 ± 3.98	0.243
S/D	2.44 ± 0.40	2.40 ± 0.43	2.47 ± 0.37	0.229
PI	0.87 ± 0.16	0.86 ± 0.17	0.88 ± 0.14	0.369

GDM, gestational diabetes mellitus; GA, gestational age; UA, Umbilical Artery; PSV, peak systolic; EDV, velocityend-diastolic velocity; S/D, the ratio of peak systolic to end-diastolic velocity; PI, Pulsatility Index.

Table 2. Fetal echocardiographic doppler results of the aortic arch isthmus.

	Total (N = 94)	Controls (N = 47)	GDM (N = 47)	Cohen's *d* (95% CI)	*p* value
S (cm)	10.54 ± 3.34	10.59 ± 2.67	10.49 ± 3.92	0.03 (–0.37, 0.43)	0.273
D (cm)	2.58 ± 0.87	2.76 ± 0.81	2.39 ± 0.90	0.42 (0.01, 0.83)	0.015
PSV (cm/s)	87.23 ± 22.43	89.34 ± 16.39	85.13 ± 27.19	0.19 (–0.22, 0.59)	0.090
Ns (cm/s)	12.77 ± 4.21	14.06 ± 3.86	11.48 ± 4.18	0.64 (0.23, 1.06)	<0.001
IFI	1.26 ± 0.09	1.27 ± 0.08	1.24 ± 0.09	0.32 (–0.09, 0.73)	0.042
ISI	0.15 ± 0.04	0.16 ± 0.04	0.14 ± 0.04	0.48 (0.07, 0.89)	0.014

GDM, gestational diabetes mellitus; 95% CI, 95% confidence interval; S, systolic flow velocity time integrals; D, diastolic flow velocity time integrals; PSV, peak systolic velocity; Ns, systolic nadir; IFI, isthmus flow index; ISI, isthmus systolic index.

Curve fitting graphs indicated that for most of the gestational weeks studied, the IFI of the GDM group was lower than that of the control group, and the IFI of the two groups was close only at about 30 weeks gestation. As the gestational weeks increased, the IFI of the GDM group exhibited a fluctuating downward trend (Fig. 2a). Throughout the entire study period, the ISI of the GDM group was consistently lower than that of the control group and showed a linear downward trend as the gestational weeks increased (Fig. 2b).

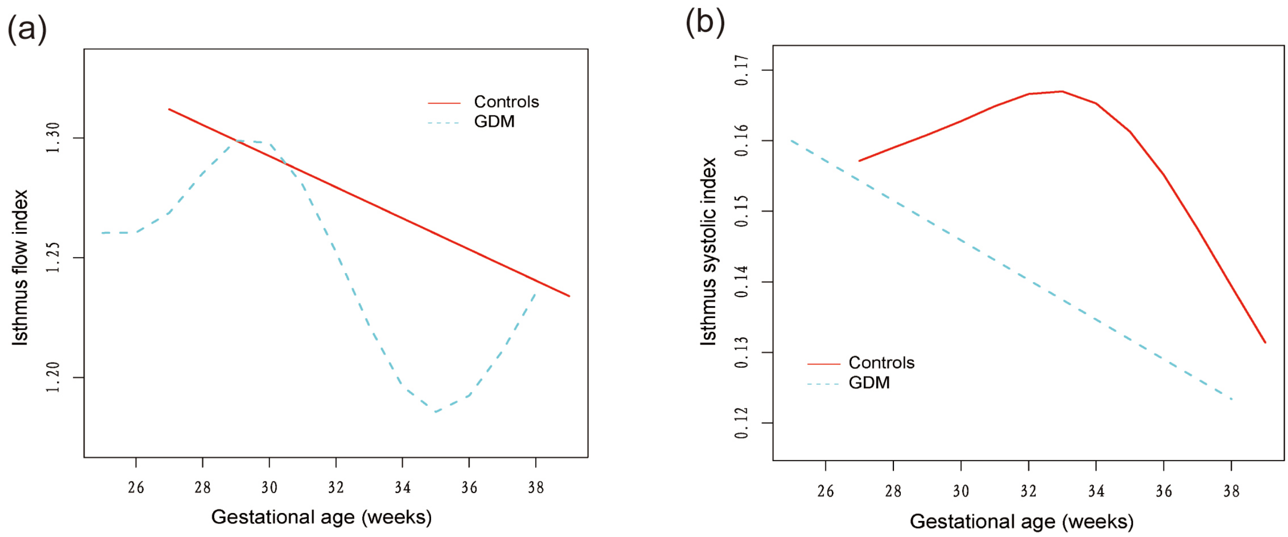

Fig. 2. The association between isthmus flow index (a) and isthmus systolic index (b) with gestational age in GDM and control group.

4. Discussion

The study design was a cross-sectional observational study to investigate the characteristics of hemodynamic changes in the aortic arch of fetuses from mothers with GDM. We used color Doppler ultrasound to assess and compare the hemodynamics of the umbilical artery and aortic arch between two groups of fetuses. The findings revealed no significant changes in the umbilical blood flow ultrasound parameters between the GDM group and the healthy control group. However, the aortic arch parameters, including the IFI and ISI, were significantly lower in the GDM group, indicating that hemodynamic changes in the fetal aorta occur earlier than in the umbilical flow in GDM pregnancies.

These changes could be attributed to the maternal high blood sugar environment, which may decrease the left ventricular diastolic function and compliance of the fetus [18]. This leads to altered blood flow dynamics in the left atrium, increased blood flow resistance through the pulmonary veins and foramen ovale, reduced valve mobility, and consequently, changes in left ventricular blood flow. This increases the compensatory output of the right ventricle during diastole, affecting aortic isthmus blood flow during this phase [19–21].

A previous cross-sectional observational study [22], including those patients with pre-gestational and gestational diabetes, validated the hypothesis that the IFI of fetuses from diabetic mothers is lower than that of non-diabetic mothers, consistent with our findings. However, our study more precisely analyzed patients with GDM, complementing previous research. Unfortunately, a further study [23] on Type 1 diabetic patients during pregnancy did not measure IFI and ISI, despite identifying differences in aortic arch hemodynamics compared to a control group. A study in China on hypertensive pregnant patients found that changes in ISI were significant for predicting fetal intrauterine hypoxia in hypertensive disorders complicating pregnancy (HDCP) [24]. Yet, there has been no research performed using ISI to predict fetal conditions in GDM patients. Our study may be the first to suggest that ISI is a clinically valuable indicator for GDM patients.

While previous studies focused on IFI, our research found that the IFI of fetuses from GDM patients fluctuated with gestational age, with IFI values of both groups converging at certain weeks. This suggests that a single blood flow parameter may not adequately assess fetal conditions [16]. Therefore, combining IFI with ISI offers a more comprehensive and objective reflection of fetal hemodynamic changes in GDM patients. Incorporating these into routine fetal echocardiography could provide additional monitoring information for fetuses of diabetic mothers, helping early identification of risks for fetal circulatory dysfunction and enabling timely interventions. Previous studies [25–27] have shown that detecting and monitoring fetal aortic isthmus Doppler examination can also identify fetal growth restriction (FGR) at an early stage and provide a reference for the treatment of FGR.

Nevertheless, our study has limitations. First, as a cross-sectional observational study, we had no monitoring during the entire pregnancy with Doppler parameters fluctuation curve. Second, postnatal outcomes for the fetuses studied are not yet available. An ongoing project aims to further assess fetal blood flow parameters, establishing a monitoring system for prenatal and postnatal risks. Additionally, since color Doppler ultrasound relies on operator skill, to minimize repeatability issues, all ultrasound assessments were performed by a doctor with over five years of experience. Finally, as our study participants were from a single center in China and the sample size was small, the findings may not be widely representative. We hope that these results can be further validated in larger-scale and multicenter studies.

5. Conclusions

The aim of this study was to investigate the hemodynamic characteristics of the fetal aortic isthmus in patients with GDM. The results indicated that, compared to the control group, the GDM group showed a decreased systolic peak velocity and reduced diastolic flow time integral in the fetal aortic isthmus, with significant decreases in the IFI and ISI. This suggests that in GDM pregnancies, fetal aortic isthmus blood flow changes may occur earlier than in the umbilical artery. The findings of this study suggest that IFI and ISI may have important clinical value in monitoring GDM pregnancies, potentially aiding in the early identification of fetal circulatory dysfunction risk. These findings could enhance our understanding of the pathophysiologic impacts of maternal diabetes.

Availability of Data and Materials

All data points generated or analyzed during this study are included in this article and there are no further underlying data necessary to reproduce the results.

Author Contributions

LZ and XC participated in the conception and design of the experiments; XC and LS performed most of the experiments; JL and LS analyzed and interpreted the data; XC and LZ drafted the paper and, together with JL and LS, critically revised it for intellectual content. All authors read and approved the final manuscript. And that all authors agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and institutional review board approval was obtained (the Medical Ethics Committee of the First People's Hospital of Xiaoshan District, Hangzhou, Ethical Approval NO. 202278). Informed consent was given by all participants engaged in the study.

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Conflict of Interest

The authors declare no conflict of interest.

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