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Article

Gestational Diabetes Mellitus and the Longitudinal Fetal Growth Trajectories in Twin Pregnancies

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Abstract

Although it is well established that gestational diabetes mellitus (GDM) is associated with fetal overgrowth in singleton pregnancies, little is known about its role in twins. We aimed to explore the relationship between GDM and the longitudinal fetal growth in twin pregnancies. This was a retrospective matched cohort study of GDM and non-GDM twin pregnancies delivered ≥36 weeks without other complications. All the women performed ≥3 ultrasounds after 22 weeks. Linear mixed models (LMMs) were used to explore the relationships between longitudinal fetal growth trajectories and GDM. Group-based trajectory modeling (GBTM) and generalized estimating equation (GEE) were applied to identify the latent growth patterns and investigate their relationships with GDM. In total, 215 GDM and 645 non-GDM twins were included, the majority of the patients did not require medication therapy ($n = 202$, GDMA1). LMM revealed that, compared with non-GDM, GDM was associated with an average increase in fetal weight of 4.36 g (95% CI [1.25, 7.48]) per week. GBTM and GEE further revealed that GDM increased the odds of fetal weight trajectory to nearly 40% of the total fetal weight trajectory, classified into the high-speed group (a$OR = 1.39$, 95% CI [1.03, 1.88]), associating with a 49.44 g (95% CI [11.41, 87.48]) increase in birth weight. Subgroup analysis revealed that all these differences were only significant among the GDMA1 pregnancies ($p < .05$). GDM (GDMA1) is significantly associated with an increase in fetal weight during gestation in twin pregnancies. However, this acceleration is mild, and its significance requires further exploration.

Keywords: Gestational diabetes mellitus; Twin pregnancy; Fetal growth trajectory; Fetal weight

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Gestational diabetes mellitus (GDM) is one of the most common gestational complications during pregnancy (Sweeting et al., 2024). It is associated with fetal overgrowth, cesarean delivery (CD), neonatal hypoglycemia and other adverse perinatal outcomes in singleton pregnancies (Metzger et al., 2008). However, the evidence is limited and controversial with regard to twin pregnancies. While some scholars have argued that, by sharing the same pathological alterations theoretically under hyperglycemic conditions, a similar right shift in birth weight is also observed among mothers with GDM in twins (Hiersch et al., 2019; Tward et al., 2016), while others have reported no relationship between GDM and large or small for gestational age (LGA/SGA) infants (Lin et al., 2022). Conclusions regarding other perinatal outcomes, such as hypertensive disorders of pregnancy (HDP) and admission to the neonatal intensive care unit (NICU), have also varied (Dave et al., 2021; Lin et al., 2022; McGrath et al., 2017). Therefore, implementing universal glucose management for GDM twin pregnancies is challenging (Weitzner et al., 2023).

Many factors contribute to these inconsistencies. Despite the heterogeneity in GDM diagnosis and the difference in ethics among populations, the intrinsic greater baseline risk of twin pregnancy itself also accounts for this difference (Melamed et al., 2024; Sheehan et al., 2019). Some adverse outcomes, namely, SGA and CD, are more strongly related to HDP or fetal abnormalities, which are highly common in twin pregnancies (Dave et al., 2021) and often mask the true relationship with GDM. Moreover, only by observing the final birth weight and other perinatal outcomes can valuable information within the fetal growth process be missed. To the greatest extent, we aimed to explore the relationship between GDM and longitudinal fetal growth trajectories in twin pregnancies to provide insight for future clinical practice.

Materials and Methods

Study Population

This was a retrospective matched cohort study of women with GDM and non-GDM twin pregnancies who delivered between January 1, 2012 and June 30, 2023 at Peking University First Hospital. The inclusion criteria were: (1) parturition ≥36 weeks and (2) both fetuses were born alive. The exclusion criteria were: (1) pregnancies with maternal HDP, pregestational diabetes

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mellitus, or other systemic diseases; (2) complicated twins, such as twin-to-twin transfusion syndrome and selective intrauterine growth restriction; and (3) twins with chromosomal/genetic or structural anomalies. The control group was 3:1 matched according to maternal age, year of delivery, and complications (low risk). This study was approved by the Ethics Board of Peking University First Hospital (No. 2022-112), and informed consent was exempted because of the retrospective nature of the study.

Protocols and Definitions

All the women visited the hospital regularly during gestation, and their demographic and basic information, including their gestational age and chorionicity, was collected in the first trimester. From 22–26 weeks, an anomaly scan was performed for all the pregnancies to screen for structural abnormalities. At 24–28 weeks, a 75-g oral glucose tolerance test (OGTT) was routinely carried out, and GDM was diagnosed on the basis of the International Association of Diabetes and Pregnancy Study Group's Consensus Panel criteria (2010), with any of the glucose values meeting the following criteria: (1) fasting plasma glucose (FPG) ≥5.1 mmol/L (91.8 mg/dl); (2) 1-hour postprandial plasma glucose ≥10.0 mmol/L (180.0 mg/dl); and (3) 2-hour postprandial plasma glucose ≥8.5 mmol/L (153.0 mg/dl) (Metzger et al., 2010). Once confirmed, all patients were referred to the 'one-day care' clinic, where they received similar glucose surveillance as singleton pregnancies and initiated lifestyle interventions, including diet therapy, exercise recommendations, and weight management. However, if FPG failed to reach 5.3 mmol/L (95.4 mg/dl) or 2-hour postprandial plasma glucose level over 6.7 mmol/L (120.6 mg/dl) in 2 weeks, medical intervention was implemented, with a preference for insulin, and the dosage was adjusted during each antenatal visit until delivery (Juan & Yang, 2020). Between 28 and 33 weeks, another anomaly ultrasound scan was performed, followed by another ultrasound exam generally performed before delivery (approximately 36 weeks). During each scan, the fetal biparietal diameter, head circumference (HC), abdominal circumference (AC), and femur length (FL) were measured, and the fetal HC, AC, and FL were further used to estimate the fetal weight according to the Hadlock Formula 1985 (Hadlock et al., 1985).

The prepregnancy body mass index (BMI) was classified according to the standard of the Chinese Ministry of Health. Underweight was defined as a BMI under 18.5 kg/m^2, normal was defined as a BMI between 18.5 and 24 kg/m^2, and overweight/obese was defined as a BMI greater than 24 kg/m^2 (National Health and Family Planning Commission, 2013). Gestational weight gain (GWG) was defined as the difference between the maternal weight last measured before delivery and the self-reported prepregnancy weight. LGA and SGA were defined as fetal weights greater than the 90th or lower than the 10th percentile of the birth weight of Chinese twins of the same sex who were born at the same gestational age (Dai et al., 2017). Discordant twins were defined as any fetus born with fetal weight less than 3% of the gestational age or a birth weight discordance ≥25% with any fetus born SGA (Gynecology, 2021).

Outcomes

The primary outcome was the longitudinal trajectories of fetal weight. The secondary outcomes included the longitudinal fetal trajectories of other biometric indices, such as HC, AC, FL, and the HC/AC (index for disproportionate growth), as well as fetal growth related perinatal outcomes, namely, birth weight, LGA, SGA and the discordant twins.

Statistical Analysis

In the univariate analysis, distribution normality was first evaluated for continuous variables by histogram observation and the Kolmogorov–Smirnov test. If normality was confirmed, the data were presented as the means ± standard deviations, and the independent-samples t test was used for comparison. If normality was not achieved, the data were presented as the median values (25th and 75th percentiles), and the Mann–Whitney test was used instead. Categorical variables were expressed as the percentages (ratios), and Pearson's chi-square test was used to analyze differences between groups. In the multivariate analysis, the generalized estimating equation (GEE) was used to explore the relationships between GDM and birth weight, LGA, SGA, and discordant twins, with consideration of the relationships within the twin pair, and the models were further adjusted for maternal BMI, GWG, gestational age at delivery, fetal chorionicity and sex.

A linear mixed model (LMM) was fitted to examine associations between GDM and the longitudinal fetal growth trajectories of twins. The fixed effects were GDM, gestational week (continuous variable), and their interaction, as well as other covariates such as maternal age, BMI, mode of conception, OGTT results, fetal chorionicity and neonatal sex. The random effects included a random intercept and slope, and they were fitted at the level of each fetus to account for the relationship within the twin pair. The first-order antedependence covariance structure was selected for modeling the correlated repeated measurements. Kenward–Roger adjustment was further applied to address the upward bias of test statistics for fixed model effects in the scenario of longitudinal repeated measurement data. The GBTM approach was applied to identify latent fetal weight trajectories (z score transformed) for all twins, with gestational week used as the underlying time scale. The final model with the best performance was chosen according to the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC) and the graphics, with three trajectories presenting three different speeds of growth. GEE was also used to estimate associations between GDM and identified trajectories.

All the statistical analyses were conducted via SPSS 25.0, SAS 9.4 (SAS Institute, Cary, NC), and R language 4.3.1 (WR Foundation, Vienna, Austria), with a two-tailed alpha of 0.05 considered statistically significant.

Results

Characteristics and Perinatal Outcomes

In total, 215 GDM twin pregnancies and 645 non-GDM twin pregnancies were included in the study, with only 13 (6.0%) patients requiring medication therapy. As shown in Table 1, no differences were found in maternal gravidity, parity, mode of conception or chorionicity between the two groups (all $p > .05$); however, those with GDM had a greater proportion of overweight/obese individuals (35.3% vs. 23.9%, $p = .004$) than did the control group, and they also had a lower total GWG (14.60 kg vs. 16.35 kg, $p < .001$). Moreover, both groups presented similar levels of gestational age, mode of delivery, LGA, SGA and discordant twins at birth (all $p > .05$).

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Table 1. Characteristics and outcomes of the study population

	GDM	Control group	*p* value
Maternal characteristics and outcomes	*N* = 215	*N* = 645	
Age ($\bar{x} \pm s$)	32.75 ± 0.26	32.50 ± 0.15	.395
Gravidity, *M* (P25, P75)	2 (1,2)	1 (1, 2)	.429
Parity, *M* (P25, P75)	0 (0,0)	0 (0, 0)	.789
Conception mode IVF-ET, *n* (%)	138 (64.2%)	383 (59.4%)	.212
Chorionicity DCDA, *n* (%)	178 (82.8%)	535 (82.9%)	.958
BMI kg/m^2 [n, (%)]			
<18.5	14 (6.5%)	44 (6.8%)	.004
18.5≤BMI<24	125 (58.1%)	447 (69.3%)	
≥24	76 (35.3%)	154 (23.9%)	
Maternal GWG (kg), *M* (P25, P75)	14.60 (11.20,18.80)	16.35 (13.30, 19.80)	<.001
OGTT (mmol/L)			
Fasting	5.12 (4.63, 5.31)	4.59 (4.38, 4.79)	<.001
1 hour	9.65 (8.74, 10.22)	7.81 (6.92, 8.63)	<.001
2 hours	8.44 (7.19, 9.15)	6.53 (5.85, 7.24)	<.001
Gestational age at birth M (P25,P75)	37.1 (37.4, 38.0)	37.5 (37.1, 38.0)	.141
Cesarean delivery, *n* (%)	191 (88.8%)	546 (84.7%)	.129
Neonatal outcomes	*N* = 430	*N* = 1290	
Birth weight[a] (g, $\bar{x} \pm s$)	2719.27 ± 15.86	2693.49 ± 9.26	.163
Neonatal sex[a] Male, *n*, (%)	231 (53.7%)	678 (52.6%)	.676
Large for gestational age[a], *n*, (%)	60 (14.0%)	149 (11.6%)	.187
Small for gestational age[a], *n*, (%)	17 (4.0%)	49 (3.8%)	.885
Discordant twins, *n*, (%)	4 (1.9%)	21(3.3%)	.292

Note: GDM, gestational diabetes mellitus; IVF-ET, in-vitro fertilization and embryo transfer; DCDA, dichorionic diamnionicity; BMI, body mass index; GWG, gestational weight gain; OGTT, oral glucose tolerance test.
[a]Each infant was analyzed separately.

Relationships Between GDM and Perinatal Outcomes

After adjusting for confounders, GEE revealed that GDM was significantly associated with a right shift in birth weight among GDM twins, with an average increase of 49.44 g (95% CI [11.41, 87.48]) per fetus. However, it was not associated with a higher odds of LGA, SGA or discordant twins (all $p > .05$). The results are shown in Table 2 and Figure 1.

The Relationship Between GDM and Longitudinal Fetal Growth

After accounting for confounders, LMM analysis indicated no statistical significant difference in average fetal weight between pregnancies with GDM and those without GDM ($\beta = -4.13$ g, 95% CI [−22.39, 14.14], $p = .658$). Furthermore, across all fetuses, there was a significant average weekly increase in weight of 156.50 g (95% CI [148.20, 164.79], $p < .001$). Specifically, male fetuses, dichorionic diamniotic twins, and fetuses conceived via in-vitro fertilization exhibited greater weight gains compared to their respective counterparts, with average increases of 24.85 g (95% CI [13.81, 35.89]), 30.75 g (95% CI [15.14, 46.36]), and 26.61 g (95% CI [13.95, 39.27) respectively (all $p < .001$). No relationship was observed between maternal age, BMI and gestational fetal weight on average (both $p > .05$). Compared with the control group, GDM was associated with an increased fetal weight of 4.36 g (95% CI [1.25, 7.48], $p = .008$, Figure 2) per fetus on average from week 22 until delivery. GBTM further identified three latent fetal growth patterns, including the low increased ($n = 229$), moderate increased ($n = 883$), and high increased ($n = 608$) group, characterized by distinctive longitudinal fetal growth speed. GEE analysis

Table 2. Relationships between GDM and the fetal growth related perinatal outcomes

Outcomes	Estimates/Adjusted odds ratio	95% confidence interval		*p* value
		Lower	Upper	
Birth weight[a]	49.44	11.41	87.48	.011
Large for gestational age[b]	1.41	1.00	2.00	.053
Small for gestational age[b]	0.89	0.48	1.65	.705
Discordant twins[b]	0.47	0.15	1.49	.201

Note: GDM, gestational diabetes mellitus.
[a]Presented as estimates.
[b]presented as the adjusted odds ratio. The models were adjusted for maternal body mass index, gestational weight gain, gestational age at delivery, fetal chorionicity and sex.

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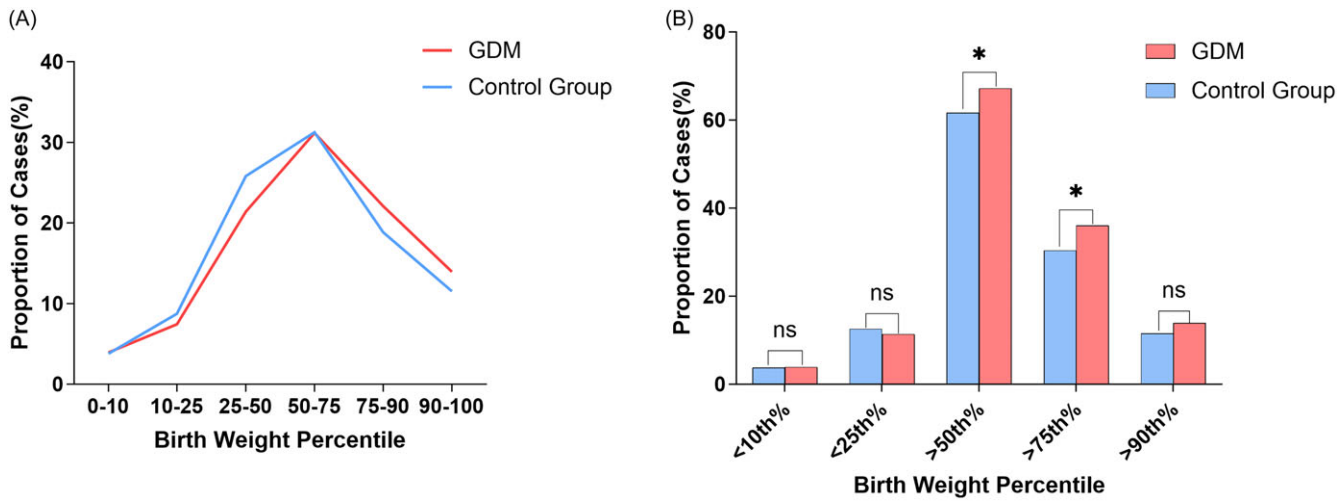

Figure 1. Birth weight distributions of GDM and non-GDM twin pregnancies.
A. Birth weight as a continuous variable. B. Birth weight as a categorical variable.
Note: GDM, gestational diabetes mellitus, *ns,* not significant. *Indicates $p < .05$.

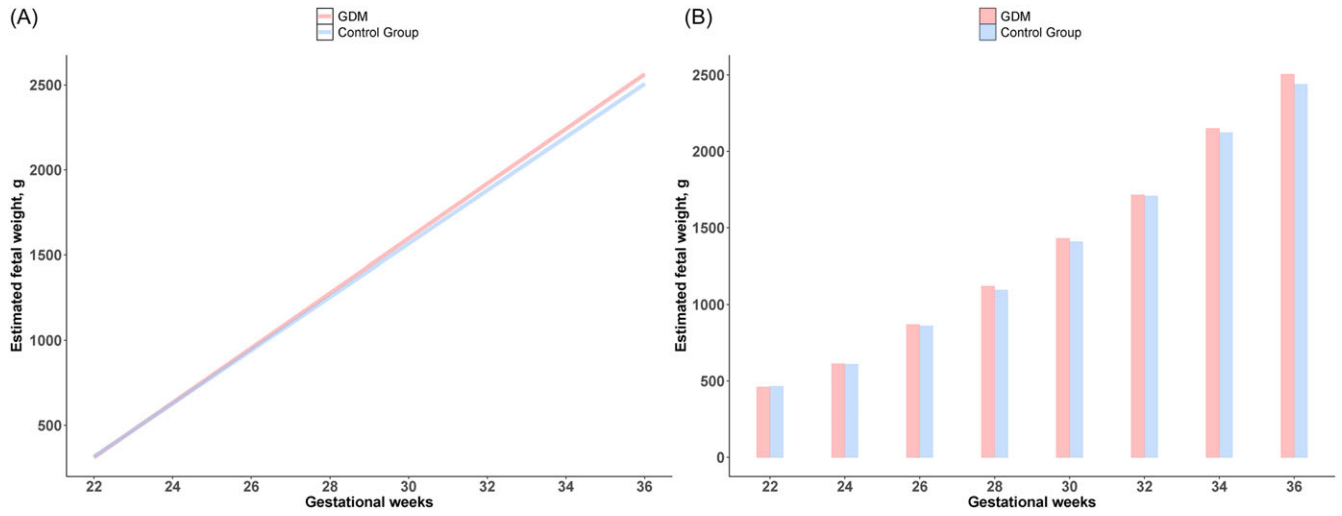

Figure 2. Growth trajectories of the estimated fetal weights of GDM and non-GDM twin pregnancies.
A. Line chart, B. Bar chart. Both were analyzed by the linear mixed model.
Note: GDM, gestational diabetes mellitus.

further proved that GDM increased the odds of the trajectory being classified into the high-speed group by nearly 40% (a*OR* = 1.39, 95% CI [1.03, 1.88], $p = .034$; Figure 3). However, no associations were detected between GDM and other fetal biometric trajectories, such as AC, HC, FL and HC/AC (all $p > .05$). The data are shown in Table 3 and Supplementary Table 1.

Subgroup analysis revealed that this increase in fetal weight was observed only among GDM pregnancies that did not require medication therapy (GDMA1), with an average amount of 4.45 g (95% CI [1.32, 7.59], $p = .008$) per fetus per week, and it increased the odds of the fetal weight trajectory being classified into the high-speed group by 39% (a*OR* = 1.39, 95% CI [1.03, 1.89], $p = .033$). However, no relationship was detected between GDM patients who needed medical therapy (GDMA2) and accelerated fetal growth ($p > .05$). Moreover, no associations were detected between any of the GDM subtypes and the growth trajectories of the other biometric indices (all $p > .05$). The results are shown in Table 4 and Supplementary Tables 2 and 3.

Discussion

In this study, we found that GDM (GDMA1) is associated with a mild increase in fetal weight in twin pregnancies and that it is not correlated with other adverse perinatal outcomes.

To date, although many studies have shown a positive relationship between GDM and gestational fetal growth acceleration in singleton pregnancies (Li et al., 2020; Sovio et al., 2016; Zou et al., 2022) evidence is lacking with respect to twins. The only study from Canada revealed that only GDMA2 twin pregnancies were related to accelerated fetal growth during gestation, not GDMA1 pregnancies, and the author further stressed that all the other biometric indices were comparable between GDM and non-

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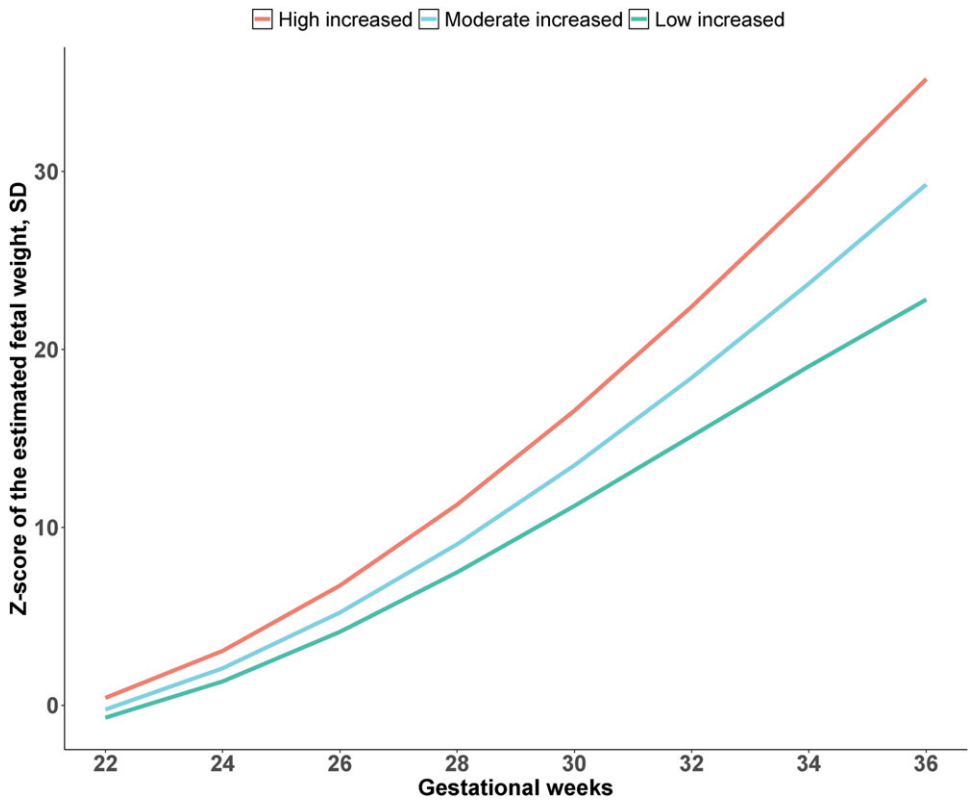

Figure 3. Three different patterns of fetal weight trajectories analyzed via the group-based trajectory model approach.

Table 3. Associations between GDM and the weekly change of fetal biometric indices

		GDM			
			95% confidence interval		
Biometric indices	Non-GDM	Estimates	Lower	Upper	*p* value
Estimated fetal weight (g)	[Reference]	4.36	1.25	7.48	.008
Head circumference (mm)	[Reference]	0.02	−0.13	0.17	.803
Abdominal circumference (mm)	[Reference]	0.10	−0.32	0.52	.652
Femur length (mm)	[Reference]	0.02	−0.01	0.05	.120
Head to abdominal circumference	[Reference]	−0.01	−0.01	0.01	.889

Note: GDM, gestational diabetes mellitus. The models were adjusted for maternal age, body mass index, fetal chorionicity, mode of conception, oral glucose tolerance test results and the neonatal sex.

GDM twin pregnancies (Ashwal et al., 2021). Despite these differences, we both showed that this GDM-related right shift in fetal weight was mild in twins, and our study further quantified this difference to be 4.36 g per week during gestation and 49.44 g at delivery, which explains why some scholars found that GDM did not increase or decrease the odds of LGA or SGA in twin pregnancies (Alkaabi et al., 2020; Lin et al., 2022). Greco et al. (2023) also proved this theory by using meta-regression to compare the relationships between adverse perinatal outcomes and GDM in both singleton and twin pregnancies and showed that, compared with singleton pregnancies, the odds ratio of CD, NICU admission, stillbirth, and neonatal death was indeed lower in twin pregnancies (relative risk, all $p < .05$). The evidence from placental studies also revealed that certain placental variations, such as vascular malperfusion lesions, villous immaturity and villitis of unknown etiology, were more common in singleton pregnancies with GDM than in twin pregnancies (all $p < .05$) (Weiner et al., 2018).

Unfortunately, in our study, due to the relatively small sample size of GDMA2 patients, a significant relationship was not detected in relation to fetal overgrowth. Hiersch et al. (2018) also reported that the higher prevalence of GDM in twin pregnancies is due mainly to GDMA1 instead of GDMA2 and that GDMA1 is less likely to contribute to adverse perinatal outcomes (Ashwal et al., 2021). Therefore, we highly agree with the recommendation to differentiate GDMA1 and GDMA2 in research and in clinical practice, to identify those GDM twins that are truly at risk, and to provide customized management accordingly (Melamed et al., 2024).

Another underlying question that must be addressed is the glucose demand for twin pregnancies, since it is the major fuel for fetal growth and metabolism in all pregnancies (Beardsall & Ogilvy-Stuart, 2020). Considering that both glucose need and insulin resistance are evaluated in twins, understanding the maternal-to-pancreatic reaction physiologically is extremely essential for GDM diagnosis and management. Moreover, the literature also revealed that the optimal threshold of the glucose tolerance test for screening for GDM might differ between twin pregnancies and singleton pregnancies (Rebarber et al., 2014; Zhao et al., 2022). Furthermore, Hiersch et al. (2021) showed that if the 75-g oral glucose tolerance test result for diagnosing GDM in twins

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Table 4. Associations between GDM subtypes and the weekly change of fetal biometric indices

	GDM subtypes								
		Without medication				Medication required			
			95% CI				95% CI		
Biometric indices	Non-GDM	Estimates	Lower	Upper	*P* value	Estimates	Lower	Upper	*P* value
EFW (g)	[Reference]	4.45	1.32	7.59	0.008	1.40	−9.04	11.83	0.786
HC (mm)	[Reference]	0.01	−0.14	0.16	0.885	0.22	−0.26	0.70	0.365
AC (mm)	[Reference]	0.08	−0.34	0.50	0.708	0.49	−0.85	1.84	0.473
FL (mm)	[Reference]	0.02	−0.01	0.05	0.149	0.05	−0.04	0.15	0.279
HC/AC	[Reference]	−0.01	−0.01	0.01	0.945	−0.01	−0.01	0.01	0.554

Note: GDM, gestational diabetes mellitus; CI, confidence interval; EFW, estimated fetal weight; HC, head circumference; AC, abdominal circumference; FL, femur length.
The models were adjusted for maternal age, body mass index, fetal chorionicity, mode of conception, oral glucose tolerance test results and the neonatal sex.

aligns with the same level of maternal beta-cell dysfunction observed in singletons (at risk of future type 2 diabetes), the values should be set at 5.8 mmol/L (104 mg/dL) for fasting, 11.8 mmol/L (213 mg/dL) for 1 hour postprandial, and 10.4 mmol/L (187 mg/dL) for 2 hours postprandial. These findings indicate the necessity of exploring natural physiological glucose metabolism for twin pregnancies; moreover, more prospective scientifically designed studies are needed to provide longitudinal data on glucose and insulin during the gestational process.

In this study, we testified that GDM (GDMA1) was associated with a mild acceleration of fetal growth in twin pregnancies with specific values. The exclusion of other circumstances that affect fetal growth, the adjustment for crucial confounders such as BMI, the reference of the fetal growth chart of twins and the similar conclusions drawn by two rigorous statistical approaches (LMM and GBTM) added to the scientific nature of the study. However, owing to the retrospective design, the study acknowledges its limitations in generalizing the findings. Moreover, the heterogeneity of the ultrasound exams performed by different sonographers also caused measurement bias in the study. Most importantly, without the regular follow-up of these mothers and infants, the long-term relationship between GDM and twins remains unexplored.

In conclusion, GDM (GDMA1) is related to an increase in fetal weight in twin pregnancies from gestation until birth, but it does not increase the odds of LGA at delivery. However, whether this is beneficial for twins in the long term requires further exploration.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2025.6.

Data availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions. X.S., M.Y. and H.Y. contributed to the conception and design of the study. X.S., N.C., and Y.Z. collected, entered and validated the medical data. X.S., X.K., and C.L. performed the statistical analysis. X.S. wrote the first draft of the manuscript. M.Y., J.J. and H.Y. revised the manuscript. H.Y. funded and supervised the study. All the authors met the ICMJE criteria for authorship and approved the final manuscript for submission.

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Competing interests. None.

Ethical statement. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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