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ORIGINAL RESEARCH

The Impact of Gestational Diabetes Mellitus on the Development of Preeclampsia in Twin Pregnancies: A Retrospective Cohort Study Conducted at a Tertiary Hospital

Hanglin Wu, Lin Zhang, Zhen Xie, Hongxia Cai, Jindi Zhang, Liming Yu

Department of Obstetrics and Gynecology, Hangzhou Women's Hospital, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Liming Yu, Department of Obstetrics and Gynecology, Hangzhou Women's Hospital, No. 369 Kun Peng Road, Hangzhou, Zhejiang, People's Republic of China, Email cxlm770522@sina.com

Purpose: This study aimed to examine the effects of gestational diabetes mellitus (GDM) on the risk of pregnancy complications in twin pregnancies and to investigate the relationship between glycemic levels and the risk of preeclampsia (PE) and abnormal fetal growth.

Patients and Methods: A retrospective cohort study of 736 twin pregnancies was conducted at a tertiary hospital. Propensity score matching and multivariable logistic models were utilized to compare maternal and neonatal outcomes between twin pregnancies with GDM and those without GDM. Multivariable logistic regressions were performed to address the intertwin correlation between glycemic levels and the primary outcomes.

Results: There was no significant difference in the risk of PE between non-GDM and GDM pregnancies (OR, 0.70; 95% CI: 0.38–1.27; P = 0.238). No statistically significant differences were observed in the prevalence of small for gestational age and large for gestational age between the study groups. A comparative analysis of twin pregnancies affected by PE and GDM versus those without GDM revealed that the former group exhibited similar maternal and neonatal outcome risks. Women with fasting blood glucose levels from 5.1 mmol/L (92mg/dL) to less than 5.3 mmol/L (95.6mg/dL) had a significantly higher risk of PE compared with women without GDM (OR, 2.90; 95% CI: 1.12–7.51; P = 0.028). In subgroups of glycosylated hemoglobin (HbA1c), HbA1c ≥ 5.5% had the highest risk of PE in the second and third trimesters compared with women without GDM (OR, 4.90; 95% CI: 1.00–24.12; P = 0.05).

Conclusion: The risk of PE was not increased in twin pregnancies complicated with GDM, but significantly increased in women with an HbA1c ≥5.5%. No significant associations were observed between the co-occurrence of GDM and PE and the incidence of pregnancy complications in twin pregnancies. Strict glycemic control may decrease the risk of PE in twin pregnancies with GDM.

Keywords: gestational diabetes mellitus, twin pregnancies, oral glucose tolerance test, glycosylated hemoglobin, preeclampsia

Introduction

Gestational diabetes mellitus (GDM) is a prevalent complication during pregnancy, affecting over 10% of women globally.[1] Previous systematic reviews have presented strong evidence demonstrating a significant increase in adverse pregnancy outcomes among women with GDM.[2–4] However, these reviews primarily focused on singleton pregnancies, resulting in a lack of understanding regarding the impact of GDM on twin pregnancies.

Several studies have observed an increased likelihood of developing hypertensive disorders and undergoing cesarean section in twin pregnancies with GDM,[5,6] while others have reported contradictory findings, with similar outcomes in twin pregnancies with and without GDM.[7–10] A meta-analysis by McGrath et al found no significant differences in adverse neonatal outcomes between twin pregnancies with GDM and controls.[11] Two recent reviews suggested that GDM may have a less severe impact on certain adverse perinatal outcomes and could be associated with a lower risk of neonatal death in twin pregnancies.[12,13] The conflicting results from cohort studies may be due to relatively small sample

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sizes and inadequate adjustment for confounding factors. For example, some studies did not account for aspirin use during pregnancy, which could have influenced their findings regarding hypertensive disorders.

Numerous investigations have examined the effects of GDM on maternal and neonatal outcomes in twin pregnancies, with a specific focus on chorionicity.[14–16] Liu et al discovered that the incidence of hypertensive disorders in pregnancies complicated by GDM was significantly elevated only in monochorionic (MC) twin gestations, while no such increase was noted in dichorionic (DC) twin pregnancies.[14] Similarly, a longitudinal cohort study corroborated these findings, indicating a correlation between GDM and gestational hypertension disorder, as well as an increased likelihood of a fetus being small for gestational age (SGA), specifically in MC twin pregnancies, but not in DC twin pregnancies.[15] In contrast to these studies, Ma et al reported an elevated risk of SGA in DC twins affected by GDM, whereas no such association was observed in MC twins in a large retrospective cohort analysis.[16]

In pregnancies with twins, GDM is currently screened using the diagnostic criteria designed for singleton pregnancies.[17] However, due to the increased nutritional requirements and different glucose tolerance in twin pregnancies, it is uncertain whether it is appropriate to diagnose and manage these women using the same criteria.[18,19] A recent study by Berezowsky Aet al showed that maintaining good control of blood sugar levels through dietary management in twin pregnancies with GDM did not reduce the risk of GDM-related complications, but instead increased the risk of having a baby with a small size for their gestational age.[20]

Due to the growing number of multiple pregnancies resulting from the widespread use of assisted reproductive technology,[21] it is imperative to address these controversies. The primary objective of this study was to examine whether a diagnosis of GDM is associated with an elevated likelihood of adverse maternal and perinatal complications in twin pregnancies, with a particular focus on preeclampsia (PE). Additionally, we sought to explore the relationship between glycemic levels, the presence of other metabolic disturbances, and the primary outcomes of interest.

Material and Methods

Study Population and Data Collection

This retrospective cohort study was conducted at Hangzhou Women's Hospital, a tertiary specialty hospital. Ethics approval was obtained from the medical ethics committee of Hangzhou Women's Hospital (No. 2023-A-130). The ethics committee waived the requirement of written informed consent for participation, given its nature as a retrospective cohort investigation. The researchers are committed to safeguarding the personal privacy of participants and ensuring the security of their information. The authors had promised to comply with the Declaration of Helsinki. The study population consisted of women with twin pregnancies who gave birth after 28 weeks of gestation between 2019 and 2023. Women who had terminated pregnancies or fetal reduction due to serious congenital anomalies were excluded, as were women with pre-existing diabetes mellitus or missing data on glycemic results.

In our medical institution, pregnant women were typically required to undergo an Oral Glucose Tolerance Test (OGTT) between the 24th and 25th weeks of gestation. Prior to the blood draw, patients were instructed to fast for a duration of 8 to 10 hours. Following the collection of fasting blood samples, the patients ingested a glucose solution composed of 165 mL of a 50% glucose injection (from China Otsuka Pharmaceutical Co., Ltd)., which was diluted with water to a total volume of 300 mL and thoroughly mixed. This glucose solution, containing 75 grams of glucose, was to be consumed within five minutes, commencing with the first sip. Blood samples were subsequently obtained from the forearm at one and two hours post-ingestion. In women newly diagnosed with GDM, an initial assessment of glycosylated hemoglobin (HbA1c) was conducted. If deemed necessary, this measurement was subsequently repeated after a three-month period of blood glucose management. All blood samples were transported to the laboratory department of our hospital within a 30-minute timeframe to ensure standardized testing and analysis. Blood glucose and triglyceride levels were quantified using an automated time-resolved fluorescence immunoassay analyzer (PerkinElmer, Shelton, CT, USA). The HbA1c levels were determined via ion exchange resin high-performance liquid chromatography employing a Variant II HbA1c analyzer (Bio-Rad, product model: 270–2001, USA).

GDM was diagnosed in accordance with the guidelines from the Chinese Society of Obstetrics and Gynecology.[22] For women who gave birth after January 1st, 2023, the updated guideline from 2022 was used for diagnosis.[23] According to the

updated guideline, GDM can also be diagnosed if a woman has a 2-hour plasma glucose level after an oral 75 g OGTT of ≥ 11.1 mmol/L (200mg/dL), if she did not have related symptoms. Dyslipidemia in twin pregnancies was defined when the level of triglycerides exceeds 4.89 mmol/L during the second trimester according to a large cohort study.[24]

The data was obtained by reviewing electronic medical records. Relevant information collected included demographic characteristics (maternal age, parity, pre-pregnancy body mass index (BMI), gestational weight gain, level of education, and history of autoimmune disease or chronic hypertension), obstetric characteristics (mode of conception, chorionicity, aspirin prescribed during pregnancy, corticosteroid treatment for fetal maturation, and use of insulin), and predefined outcomes. Maternal BMI was classified as underweight (<18.5 kg/m2), optimum (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2), and obese (≥30.0 kg/m2) based on the WHO standard.[25] Gestational weight gain was categorized as above, within, or below Institute of Medicine (IOM) recommendations for twin pregnancies.[26] Underweight women not recommended by IOM were categorized based on recommendations from a large population-based cohort study.[27] Metformin was not administered during any of the pregnancies, as it was not classified as a first-line treatment for use during the gestational period according to previous guidelines in China.[22] In the case of women with multiple measurements of HbA1c levels, we selected the most recent value, as it is likely to provide the most accurate representation of glycemic control.

The sample size was calculated to detect a 100% increase of the risk of PE from 10% to 20% in pregnancy twins complicated with GDM compared with those not. The calculation was based on recent studies.[14,15,28] To detect this difference with 80% power, a type 1 error of 5% and sample allocation ratio of 4:1, 115 women with GDM and 460 women without GDM were needed.

Outcome Definition

Our primary maternal outcome was the occurrence of PE, which was characterized by high blood pressure along with the presence of protein in the urine or damage to other maternal organs after the 20th week of pregnancy.[29] We also included cases of chronic hypertension with the onset of protein in the urine or other maternal organ damage during pregnancy in our primary outcome. Secondary maternal outcomes consisted of premature birth, cesarean delivery, postpartum hemorrhage or blood transfusion, admission to the intensive care unit (ICU), and chorioamnionitis or postpartum infection. Our primary neonatal outcomes were risk of SGA and large for gestational age (LGA).

Secondary neonatal outcomes included neonatal asphyxia, admission to the neonatal unit, need for ventilator support, neonatal jaundice, neonatal hypoglycemia, sepsis, blood transfusion, hemorrhage, malformation, fetal death, and neonatal death. SGA and LGA were determined using fetal growth standards for Chinese twin pregnancies.[30] SGA was defined as birth weight below the 10th percentile for gestational age, while LGA was defined as birth weight above the 90th percentile for gestational age. Additional details about the definitions of other outcomes can be found in Supplementary Appendix. 1.

Statistical Analysis

The study cohort's baseline characteristics were presented as mean ± standard deviation (SD) or frequency with its percentage based on the type of variable. Independent sample t tests or Mann–Whitney *U*-tests were utilized to analyze continuous variables with or without a Gaussian distribution, respectively. For categorical variables, Chi-square test or Fisher's exact test was used as appropriate. Maternal age, parity, pre-pregnancy BMI, gestational weight gain, level of education, history of autoimmune disease or chronic hypertension, mode of conception, chorionicity, aspirin prescribed during pregnancy, and corticosteroid treatment for fetal maturation were balanced through propensity score matching (PSM) between the GDM group and non-GDM group. The PSM method was performed as described by Rubin and Rosenbaum.[31] Patients in the non-GDM group were matched to individuals in the GDM group in a 1:2 matching ratio by using a greedy, nearest neighbor matching algorithm with a caliper of 0.1 (Detailed RStudio cord provided in Supplementary Appendix. 2). The standardized mean difference (SMD) of any variable in the PSM cohort was calculated to evaluate the balance between the study groups. An SMD less than 0.1 has been considered to indicate no significant difference in the mean or prevalence of a covariate between treatment groups.[32]

In the original study cohort, we conducted multivariable logistic regressions to assess the impact of GDM status on maternal outcomes. Further stratified analyses were performed to evaluate the effects according to chorionicity. For the PSM cohort, paired logistic regressions were utilized to validate the previous findings. When analyzing neonatal

outcomes, the logistic regressions were additionally adjusted for gestational age at birth, a significant factor for neonatal outcomes. Logistic regression models were employed to assess the impact of PE or GDM on the development of pregnancy outcomes, considering the presence or absence of other metabolic dysregulations.

Furthermore, fasting plasma glucose, OGTT 1-hour plasma glucose, OGTT 2-hour plasma glucose, and HbA1c were individually included in the multivariable logistic regressions to examine the relationship between glycemic levels and the risk of PE, SGA or LGA. The propensity score matching process was carried out using RStudio 2023.09.1, while other statistical analyses were conducted using SPSS version 25.0. The results were reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). A two-tailed P-value <0.05 was considered statistically significant.

Results

The research cohort consisted of 736 women with twin pregnancies, among whom 165 were diagnosed with GDM. The prevalence of GDM in our study was 22.4%. The baseline characteristics of the study cohort were outlined in Table 1.

Table 1 Baseline Characteristics of Study Cohort

Characteristics	Entire cohort				PSM cohort			
	Non-GDM (n = 571)	GDM (n = 165)	P-value	SMD	Non-GDM (n = 282)	GDM (n = 149)	P-value	SMD
Maternal age, year	30.5± 3.6	31.8± 4.1	<0.001	0.326	31.4± 3.7	31.5± 3.9	0.66	0.01
Parity								
Nulliparous	448 (78.5)	132 (80.0)	0.67	0.039	230 (81.6)	121 (81.2)	0.93	0
Multiparous	123 (21.5)	33 (20.0)			52 (18.4)	28 (18.8)		
Pre-pregnancy BMI, kg/m2								
Underweight (<18.5)	97 (17.0)	16 (9.7)	<0.001	0.38	37 (13.1)	16 (10.7)	0.71	0.064
Optimum (18.5–24.9)	432 (75.7)	115 (69.7)			216 (76.6)	113 (75.8)		
Overweight (25.0–29.9)	40 (7.0)	28 (17.0)			28 (9.9)	19 (12.8)		
Obese (≥30.0)	2 (0.4)	6 (3.6)			1 (0.4)	1 (0.7)		
Gestational weight gain								
Above recommendations	30 (5.3)	10 (6.1)	0.03	0.162	6 (2.1)	8 (5.4)	0.15	0.039
Comply with recommendations	242 (42.4)	51 (30.9)			102 (36.2)	47 (31.5)		
Below recommendations	299 (52.4)	104 (63.0)			174 (61.7)	94 (63.1)		
Highest level of education								
Primary or secondary school	93 (16.3)	37 (22.4)	0.18	0.146	46 (16.3)	28 (18.8)	0.32	0.04
University	436 (76.4)	118 (71.5)			225 (79.8)	111 (74.5)		
Higher professional education	42 (7.4)	10 (6.1)			11 (3.9)	10 (6.7)		
History of autoimmune disease or chronic hypertension								
Yes	12 (2.1)	3 (1.8)	0.82	0.021	6 (2.1)	3 (2.0)	1	0
No	559 (97.9)	162 (98.2)			276 (97.9)	146 (98.0)		
Mode of conception								
Spontaneous	282 (49.4)	69 (41.8)	0.09	0.153	115 (40.8)	63 (42.3)	0.76	0.048
ART	289 (50.6)	96 (58.2)			167 (59.2)	86 (57.7)		
Chorionicity								
Dichorionic	429 (75.1)	137 (83.0)	0.03	0.21	239 (84.8)	123 (82.6)	0.55	0.063
Monochorionic	142 (24.9)	28 (17.1)			43 (15.2)	26 (17.4)		
Aspirin prescribed during pregnancy								
Yes	51 (8.9)	21 (12.7)	0.15	0.114	30 (10.6)	16 (10.7)	0.98	0
No	520 (91.1)	144 (87.3)			252 (89.4)	133 (89.3)		
Corticosteroid treatment for fetal maturation								
Yes	221 (38.7)	95 (57.6)	<0.001	0.382	146 (51.8)	79 (53.0)	0.81	0.02
No	350 (61.3)	70 (42.4)			136 (48.2)	70 (47.0)		
Use of insulin								
Yes	0 (0)	2 (1.2)	-		0 (0)	1 (0.7)	-	
No	571 (100)	163 (98.8)			282 (100)	149 (99.3)		

Notes: Data are presented as mean ± standard deviation or number (%).

Abbreviations: GDM, gestational diabetes mellitus, PSM, propensity score matching, SMD, standardized mean difference, BMI, body mass index, ART, assisted reproductive technology.

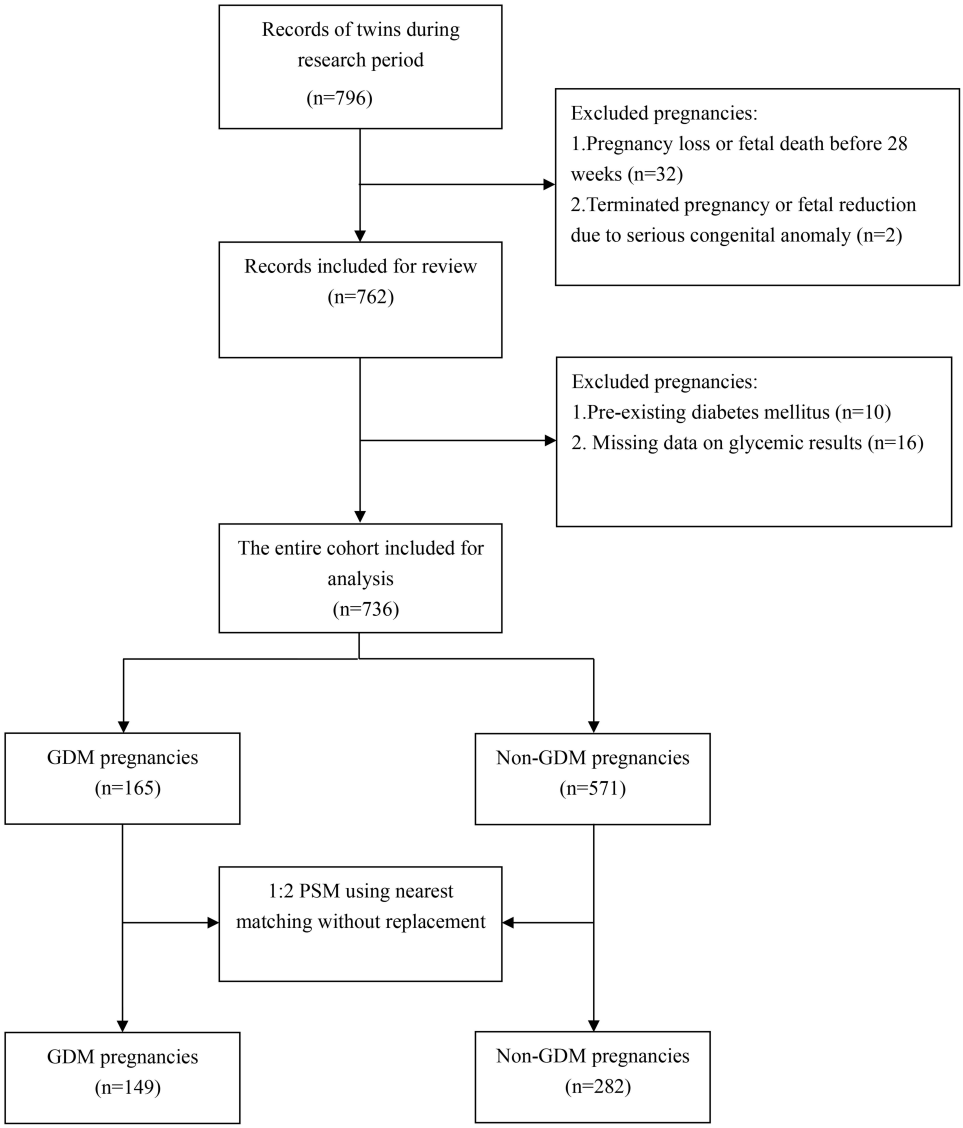

Figure 1 Selection of eligible participants.
Abbreviations: GDM, gestational diabetes mellitus; PSM, propensity score matching.

Women with GDM were observed to be of older age compared to those without GDM (31.8 ± 4.1 vs 30.5 ± 3.6, P < 0.001). Those with GDM were also more likely to be overweight or obese (overweight: 7.0 vs 17.0%; obesity: 0.4 vs 3.6%) and had lower gestational weight gain (P=0.03). Additionally, women diagnosed with GDM were more likely to have a DC pregnancy and receive corticosteroid treatment for fetal maturation. No significant differences were found in other variables. Only two women used insulin therapy for blood glucose control after being diagnosed with GDM. Following PSM, 149 women with GDM and 282 women without GDM remained for further analysis (Figure 1). The baseline characteristics of all covariates were well-balanced between the two study groups (SMD < 0.1).

Figure 2 displayed the absolute risks and fully adjusted odds ratios of maternal and neonatal outcomes in pregnancies with and without GDM. The multivariable logistic regression analysis of the entire cohort indicated no statistically significant difference in the risk of PE between pregnancies without GDM and those with GDM (OR, 0.70; 95% CI: 0.38–1.27; P = 0.238), despite the fact that the absolute risk of PE was higher in GDM pregnancies (8.8% in the non-GDM group vs 15.8% in the GDM group). Women without GDM had a lower likelihood of requiring admission to the intensive care unit compared to women with GDM (OR, 0.19; 95% CI: 0.06–0.57; P = 0.003). There was a significantly

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Outcomes	Non-GDM		GDM		Fully adjusted odds ratio (95% CI)	P-value
	No of events/total	Risk/100	No of events/total	Risk/100		
Maternal outcomes[a]						
Preeclampsia	50/571	8.8	26/165	15.8	0.70 (0.38, 1.27)	0.238
PTB <37 weeks	347/571	60.8	119/165	72.1	0.68 (0.42, 1.10)	0.118
PTB <34 weeks	49/571	8.6	24/165	14.5	0.78 (0.42, 1.44)	0.422
PTB <32 weeks	15/571	2.6	11/165	6.7	0.44 (0.18, 1.10)	0.080
Cesarean delivery	564/571	98.8	161/165	97.6	2.32 (0.62, 8.76)	0.214
Postpartum hemorrhage or blood transfusion	26/571	4.6	14/165	8.5	0.59 (0.28, 1.27)	0.178
Admission to intensive care unit	8/571	1.4	10/165	6.1	0.19 (0.06, 0.57)	0.003
Chorioamnionitis or postpartum infection	66/571	11.6	18/165	10.9	1.07 (0.60, 1.92)	0.821
Neonatal outcomes[b]						
Small for gestational age	236/1140	20.7	65/330	19.7	1.05 (0.75, 1.47)	0.762
Large for gestational age	120/1140	10.5	32/330	9.7	1.55 (0.97, 2.47)	0.065
Neonatal asphyxia	28/1140	2.5	15/330	4.5	0.97 (0.45, 2.12)	0.944
Neonatal unit admission	645/1140	56.6	203/329	61.7	1.23 (0.89, 1.69)	0.214
Ventilator support	87/1140	7.6	40/329	12.2	0.97 (0.54, 1.74)	0.926
Neonatal jaundice	604/1140	53.0	183/329	55.6	1.27 (0.94, 1.71)	0.117
Neonatal hypoglycemia	137/1140	12.0	35/329	10.6	1.25 (0.82, 1.91)	0.300
Sepsis	52/1140	4.6	36/329	10.9	0.52 (0.31, 0.88)	0.014
Blood transfusion	41/1140	3.6	18/329	5.5	1.62 (0.68, 3.88)	0.275
Hemorrhage	11/1140	1.0	4/329	1.2	1.37 (0.36, 5.20)	0.644
Malformation	43/1140	3.8	15/329	4.6	0.88 (0.46, 1.68)	0.686
Fetal death	2/1142	0.2	0/330	0	.	.
Neonatal death	1/1140	0.1	2/330	0.6	.	.

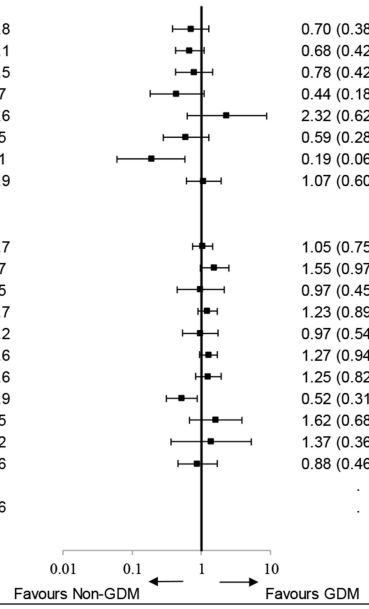

Figure 2 Adjusted odds ratios of maternal and neonatal outcomes in pregnancies with and without gestational diabetes mellitus.
Notes: [a]Adjusted for maternal age, parity, BMI, weight gain, education level, mode of conception, chorionicity, history of autoimmune disease or chronic hypertension, aspirin prescribed and corticosteroid treatment. [b]Adjusted for maternal age, parity, BMI, weight gain, education level, mode of conception, chorionicity, history of autoimmune disease or chronic hypertension, aspirin prescribed, corticosteroid treatment and gestational age at delivery.
Abbreviations: GDM, gestational diabetes mellitus; CI, confidence interval; PTB, preterm birth.

lower risk of sepsis in twin newborns born to mothers without GDM (OR, 0.52; 95% CI: 0.31–0.88; P = 0.014). No significant differences were found in other maternal and neonatal outcomes between the study groups.

The ORs for maternal and neonatal outcomes between pregnancies with GDM and those without GDM in the PSM cohort were presented in Figure 3. The incidence of PE did not differ significantly between non-GDM and GDM pregnancies (OR, 0.72; 95% CI: 0.40–1.32; P = 0.292). Women without GDM had a lower likelihood of requiring admission to the ICU compared to women with GDM (OR, 0.25; 95% CI: 0.09–0.73; P = 0.011). There was a reduced risk of sepsis in twin newborns without maternal GDM, although the result did not reach statistical significance (OR, 0.54; 95% CI: 0.29–1.01; P = 0.055). Based on the PSM cohort, there were no differences in the other maternal and neonatal outcomes.

The association between glycemic levels in pregnancies with GDM and the risk of PE was illustrated in Figure 4. Women with fasting blood glucose levels ranging from 5.1 mmol/L (92mg/dL) to less than 5.3 mmol/L (95.6mg/dL) exhibited a significantly elevated risk of PE compared to women without GDM (OR, 2.90; 95% CI: 1.12–7.51; P = 0.028). Conversely, the risk of PE in women with fasting blood glucose levels ≥ 5.3 mmol/L was similar to that of women without GDM. As the levels of 1-hour or 2-hour blood glucose in OGTT increased, the risk of PE gradually rose, although no significantly higher risk of PE was observed in any subgroup. Among subgroups categorized by HbA1c levels, those with HbA1c ≥ 5.5% had the highest risk of PE in the second and third trimesters compared to women without GDM (OR, 4.90; 95% CI: 1.00–24.12; P = 0.05). In terms of the risk of SGA or LGA, no significant differences were observed in any subgroup of twin pregnancies with GDM when compared to non-GDM women (Supplementary Figure 1 and Supplementary Figure 2).

GDM did not demonstrate a significant association with the incidence of PE or SGA infants in both MC and DC twin pregnancies. In DC twin pregnancies, GDM was linked to a decreased probability of delivering a LGA fetus, but this association was only evident after adjusting for relevant confounding factors (Supplementary Table 1). A comparative analysis of twin pregnancies affected by PE and GDM versus those without GDM revealed that the former group exhibited similar maternal and neonatal outcome risks (Supplementary Figure 3). Additionally, when contrasting GDM

Outcomes	Non-GDM		GDM		Odds ratio (95% CI)	P-value
	No of events/total	Risk/100	No of events/total	Risk/100		
Maternal outcomes						
Preeclampsia	25/282	8.9	19/149	12.8	0.72 (0.40, 1.32)	0.292
PTB <37 weeks	182/282	64.5	104/149	69.8	0.94 (0.74, 1.20)	0.618
PTB <34 weeks	24/282	8.5	20/149	13.4	0.66 (0.36, 1.20)	0.172
PTB <32 weeks	10/282	3.5	10/149	6.7	0.54 (0.22, 1.29)	0.164
Cesarean delivery	279/282	98.9	146/149	98	1.01 (0.83, 1.23)	0.932
Postpartum hemorrhage or blood transfusion	13/282	4.6	13/149	8.7	0.53 (0.24, 1.14)	0.103
Admission to intensive care unit	5/282	1.8	10/149	6.7	0.25 (0.09, 0.73)	0.011
Chorioamnionitis or postpartum infection	31/282	11	15/149	10.1	1.09 (0.59, 2.02)	0.795
Neonatal outcomes[a]						
Small for gestational age	125/563	22.2	59/298	19.8	1.14 (0.83, 1.57)	0.422
Large for gestational age	66/563	11.7	27/298	9.1	1.40 (0.88, 2.22)	0.154
Neonatal asphyxia	10/563	1.8	10/298	3.4	0.79 (0.24, 2.59)	0.701
Neonatal unit admission	334/563	59.3	178/297	59.9	1.08 (0.90, 1.31)	0.412
Ventilator support	43/563	7.6	35/297	11.8	0.82 (0.43, 1.54)	0.532
Neonatal jaundice	311/563	55.2	158/297	53.2	1.14 (0.94, 1.40)	0.185
Neonatal hypoglycemia	78/563	13.9	32/297	10.8	1.35 (0.88, 2.07)	0.166
Sepsis	21/563	3.7	30/297	10.1	0.54 (0.29, 1.01)	0.055
Blood transfusion	18/563	3.2	16/297	5.4	0.63 (0.19, 2.08)	0.449
Hemorrhage	5/563	0.9	2/297	0.7	1.32 (0.18, 9.99)	0.786
Malformation	19/563	3.4	14/298	4.7	0.76 (0.36, 1.59)	0.468
Fetal death	1/564	0.2	0/298	0	.	.
Neonatal death	0/563	0.1	2/298	0.7	.	.

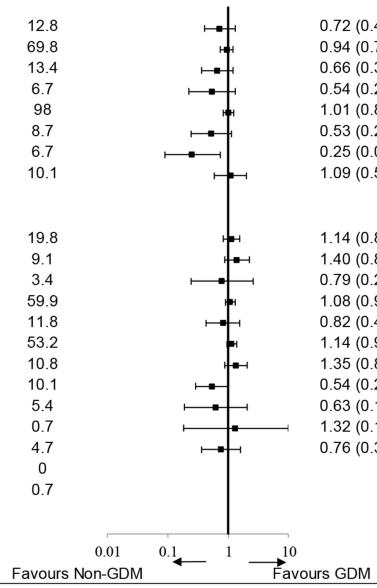

Figure 3 Odds ratios of maternal and neonatal outcomes in the propensity score matching cohort.
Notes: [a]Adjusted for gestational age at delivery.
Abbreviations: GDM, gestational diabetes mellitus; CI, confidence interval; PTB, preterm birth.

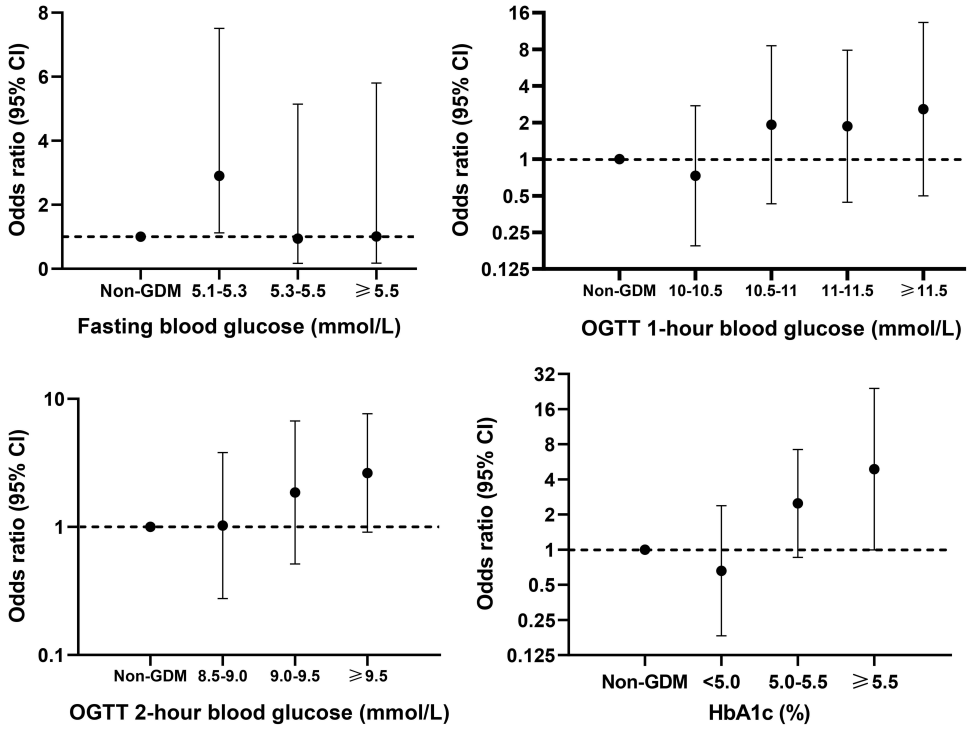

Figure 4 The association between glycemic outcomes in pregnancies affected by gestational diabetes mellitus and the risk of preeclampsia. The reference category is Non-GDM group with the point on the null line.
Abbreviations: GDM, gestational diabetes mellitus; CI, confidence interval; OGTT, Oral Glucose Tolerance Test; HbA1c, glycosylated hemoglobin.

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twin pregnancies complicated by dyslipidemia with those unaffected by dyslipidemia, findings indicated that the former group had a reduced risk of neonatal jaundice, while other outcomes remained comparable (Supplementary Figure 4).

Discussion

In the present study, the frequency of GDM in twin pregnancies was 22.4%. The incidence of PE did not show a significant increase in twin pregnancies complicated by GDM, regardless of the chorionicity. However, twin pregnancies with a fasting blood glucose level ranging from 5.1 mmol/L (92mg/dL) to less than 5.3 mmol/L (95.6mg/dL) exhibited a significantly elevated risk of PE compared to those without GDM. In twin pregnancies affected by GDM, there was a notable correlation between HbA1c and PE when HbA1c levels were≥5.5%. Twin pregnancies with GDM had a heightened likelihood of requiring admission to the ICU compared to those without GDM. Neonatal outcomes were similar between twin pregnancies affected by GDM and those not affected by GDM.

The reported prevalence of GDM in twin pregnancies in previous studies ranged from 20.4% to 31.2%, which is generally consistent with the results of our study.[8,14,33–35] Liu et al found a significantly lower incidence of GDM in women with MC twin pregnancies, which is in line with our findings.[14] Our study found that twin pregnancies with GDM had lower gestational weight gain compared to women without GDM, possibly due to the implementation of GDM awareness and education programs in our hospital. As a result, only two twin pregnancies with GDM required insulin therapy for blood glucose control during our study period, which is less than the number reported in a previous study.[8]

In a study conducted by Liu, et al, it was found that the incidence of hypertension disorders during pregnancy in twin pregnancies with and without GDM was 13.3% and 7.5%, respectively, which was comparable with the incidence of PE in our study.[14] However, they discovered that the risk of hypertension disorders during pregnancy in twin pregnancies with GDM was 1.57 times higher than that in women without GDM after adjusting for other factors, which contradicted our findings. In our study, aside from factors such as maternal age, pre-pregnancy BMI, nulliparity, and mode of conception, we also considered gestational weight gain, education level, and the use of aspirin during pregnancy when evaluating the impact of GDM on the risk of PE. It has been reported that the use of aspirin in women with twin pregnancies can lower the risk of PE.[36] As a result, more women with twin pregnancies and GDM were able to avoid developing PE, which may have weakened the association between GDM and the risk of PE.

In our study, we observed a significantly increased risk of PE in women with fasting blood glucose levels ranging from 5.1 mmol/L to less than 5.3 mmol/L, compared to women without GDM. This finding aligns with previous research.[37–39] Contrary to these studies, we did not find an increased risk of PE in twin pregnancies with fasting blood glucose levels ≥ 5.3 mmol/L. This discrepancy may be attributed to the relatively small sample size of women in this subgroup. It is also possible that women with slightly higher fasting blood glucose levels may have been less diligent in adhering to exercise and dietary interventions for glucose control, thereby increasing their risk of PE. Our study did not find a strong association between elevated post-load glucose levels and an increased risk of PE, which is consistent with previous findings.[32] Previous studies have reported an association between maternal HbA1c levels and the risk of PE in women with GDM, with HbA1c thresholds ranging from ≥5% to ≥5.8%.[40–43] Our study found that an HbA1c threshold of ≥5.5% was independently associated with a nearly five-fold increased risk of PE, supporting the findings of previous research.

In twin pregnancies with GDM, we observed a heightened likelihood of admission to the ICU. This discovery aligns with the findings of an 8-year retrospective study, which also noted a significant independent correlation between GDM and ICU admission. In our study, women with GDM who were admitted to the ICU were primarily affected by severe postpartum hemorrhage (4 cases), followed by PE (3 cases), pulmonary hypertension (1 case), heart failure (1 case), and acute fatty liver of pregnancy (1 case). Conversely, the control group primarily experienced ICU admission due to severe postpartum hemorrhage (7 cases), followed by PE (1 case). Although the occurrence of PE did not show an increase, we posited that the severity of PE within the study groups was more pronounced, a hypothesis that is substantiated by prior research.[44–46] One potential mechanism for this phenomenon may be that GDM could enhance placental inflammation, thereby exacerbating the severity of PE.[47]

In the present study, we did not find strong evidence of a relationship between blood glucose levels and fetal growth, which aligns with the findings of Ashwal et al. They observed similar fetal growth in twin fetuses with and without

GDM.[48] This may be due to the tendency for earlier delivery and inherent lower fetal growth in twin pregnancies compared to singleton pregnancies. The role of dietary therapy in fetal growth in twin pregnancies cannot be ruled out, there is currently insufficient evidence to justify altering the diagnostic criteria for GDM in twin pregnancies.

This study examines the perinatal outcomes of GDM in twins categorized by their chorionicity, which is similar across both DC and MC twins, contrasting findings from other studies,[14–16] It is noteworthy that the prevalence of PE among women with GDM in our study cohort was nearly twice that of women without GDM. However, this difference did not reach statistical significance after controlling for confounding variables. Furthermore, these women may also be at an increased risk of delivering SGA infants, which can be attributed to impaired placental blood flow and a consequent reduction in oxygen and nutrient supply to the fetus.[49] We propose that infants born from twin pregnancies complicated by GDM may have a degree of protection against being SGA in a hyperglycemic environment, which aligns with findings from prior research.[50] However, the observed lower risk of LGA in DC twins should be interpreted with caution, as the notable difference was only evident after statistical adjustment, potentially attributable to random variation.

The existing literature provides limited evidence concerning the perinatal outcomes of twins born to mothers with GDM and PE. Our research indicates that women with PE who also have GDM may experience a non-significant increase in the risks of preterm birth and infections. Conversely, the presence of GDM appears to mitigate the adverse effects of PE on fetal growth, thereby decreasing the likelihood of SGA outcomes. Further investigations are warranted to elucidate the underlying pathophysiological mechanisms. The relationship between lipid profiles in GDM and their potential as indicators of preexisting insulin resistance remains a subject of ongoing debate.[51] A robust study conducted in China established a significant association between lipolysis and GDM.[52] Maternal hyperlipidemia may elevate oxidative stress in the fetus, potentially leading to vascular damage and disruption of normal placentation processes.[53] Our research represents the first attempt to compare twin pregnancies affected by dyslipidemia in the context of GDM with those that are not affected. However, we did not identify any correlation between PE or fetal growth and dyslipidemia. Given the limited sample size within the subgroups, there is a pressing need for extensive multicenter cohort studies to clarify the relationship between these variables.

The current study exhibited several strengths. Firstly, we included a greater number of relevant confounding factors in multivariable logistic regressions compared to previous similar studies, enhancing the reliability of our findings. Secondly, we employed two statistical methods to assess the potential increase in the risk of adverse maternal and perinatal complications in twin pregnancies among those diagnosed with GDM, and the results remained largely unchanged, thereby bolstering the robustness of our findings. Lastly, we collected data on OGTT results and the degree of glycemic control during gestation, allowing us to investigate the correlation between glycemic levels and the primary outcomes. However, there are some limitations to be noted in our study. Firstly, the study was conducted at a single tertiary specialty hospital in China, which may restrict the generalizability of our results to other populations. Secondly, only two women in our study required insulin therapy, so our results may not be applicable to those receiving insulin therapy. Thirdly, in our cohort, nearly 50% of twin pregnancies were conceived through assisted reproductive technology, which aligns with international guidelines that recommend preventive treatment with aspirin for PE in such cases.[54,55] However, it is noteworthy that the majority of these women were not prescribed aspirin, a factor that may have influenced our results. Finally, due to the limited number of women in our study, we were unable to assess those with HbA1c levels ranging from 5.5% to less than 6.0%. The potential risk of hypoglycemia during gestation associated with strict glycemic control could not be evaluated in the present study due to a lack of related information, although we did not find strong evidence of a correlation between blood glucose levels and fetal growth.

Conclusion

The incidence of PE did not show a significant increase in twin pregnancies complicated by GDM, regardless of the chorionicity. However, it was notably elevated in subgroups with a fasting blood glucose level ranging from 5.1 mmol/L (92mg/dL) to less than 5.3 (95.6mg/dL) mmol/L or an HbA1c level of ≥5.5%. No significant associations were observed between the co-occurrence of GDM and PE and the incidence of pregnancy complications in twin pregnancies. Neonatal outcomes were found to be similar between twin pregnancies with GDM and those without.

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Disclosure

The authors report no conflicts of interest in this work.

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