Perinatal outcomes among twin pregnancies with gestational diabetes mellitus: A nine-year retrospective cohort study

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Objective: To compare the outcomes between gestational diabetes mellitus (GDM) vs. non-GDM twin gestations.

Methods: A retrospective cohort study of 2,151 twin pregnancies was performed in a tertiary hospital in Foshan, China, 2012–2020. Pregnancy and neonatal outcomes were compared between women with vs. without GDM using 1:1 propensity score matching (PSM) and multivariable logistic models. For neonatal outcomes, generalized estimating equation (GEE) approach was used to address the intertwin correlation.

Results: Of the 2,151 participants, 472 women (21.9%) were diagnosed with GDM. Women with GDM were older and more likely to be overweight or obese, and more likely have chronic hypertension, assisted pregnancies and dichorionic twins. In the PSM cohort of 942 pregnancies, there was no statistical difference when comparing GDM twin pregnancies and non-GDM in any of the perinatal outcomes, especially in terms of preterm birth (PTB) <37 weeks (P = 0.715), large for gestational age (LGA) (P = 0.521) and neonatal respiratory distress (NRDS) (P = 0.206). In the entire cohort, no significant adjusted ORs for these outcomes were obtained from logistic regression models adjusted for confounders (aOR for PTB < 37 weeks: 1.25, 95% CI: 0.98–1.58; aOR for LGA: 1.26, 95% CI: 0.88–1.82; and aOR for NRDS, 1.05, 95% CI: 0.68–1.64).

Conclusion: Twin pregnancies with GDM and adequate prenatal care have comparable perinatal outcomes to those without.

KEYWORDS

twin pregnancy, gestational diabetes mellitus, pregnancy outcome, neonatal outcome, perinatal outcome
Introduction

Gestational diabetes mellitus (GDM) is one of the most common obstetric complications with an increasing prevalence worldwide, mainly due to the increasing prevalence of obesity in reproductive age, advanced maternal age, stricter diagnostic criteria and universal screening for GDM (1–3). This pregnancy complication is known to lead to short- and long-term adverse outcomes for both mothers and children, including hypertensive disorders of pregnancy (HDP), macrosomia, shoulder dystocia, cesarean section, neonatal respiratory morbidities, neonatal hypoglycemia, metabolic syndrome and cardiovascular disease (4–8).

Along with the increasing prevalence of GDM, the incidence of twin pregnancy has been increased in the last two decades because of the substantial improvement and expanded use of assisted reproductive technology (ART) (9, 10). Women with twin pregnancies have an increased risk of GDM compared to singletons (11, 12). It is recommended by the American College of Obstetrician and Gynecologist (ACOG) that the management of GDM twin gestations follows the same strategy for singleton gestations (13). However, it is uncertain whether the diagnostic criteria and glucose target for singleton is also appropriate for twin gestation, given that twin pregnancies are higher nutrition and energy demanded and have different clinical characteristics from singletons, such as more occurrence of prematurity and fetal growth retardation. Unfortunately, the current evidence on the outcomes among GDM twin pregnancies is limiting and conflicting. Some authors have reported that GDM twin pregnancies have similar outcomes with non-GDM ones (14, 15) whereas others have found GDM twin pregnancies with GDM have increased risks of adverse outcomes, including cesarean section (16–18), hypertensive complications (19–22), accelerated fetal growth (22–24) and neonatal respiratory morbidity (18). The conflicting findings may be due to several limitations including relatively small population, inadequate adjustment for confounders, and lack of addressing the intertwin correlation when analyzing neonatal outcomes (16, 18, 19).

In light of this, we aimed to compare the pregnancy and neonatal outcomes between GDM and non-GDM twin pregnancies.

Methods

Study design and population

This retrospective study was performed at a tertiary hospital in Foshan, China. The study population comprised women with twin pregnancies who gave birth beyond 26 weeks of gestation in the hospital from January 1st, 2012 to December 31st, 2020. In this study, pregnancies with congenital anomalies, twin-to-twin transfusion (TTTS), monoamniotic twins, unknown chorionicity, fetal loss or intruterine death were excluded. To ensure the data completeness of maternal BMI, we excluded women who had their first prenatal visit after 14 weeks of gestation. Furthermore, based on the objective of the current study, those with pre-existing diabetes were excluded.

Diagnosis of GDM

In the present study, GDM was diagnosed by an oral 75 g glucose tolerance test (OGTT) between 24 and 28 weeks of gestation if: fasting plasma glucose ≥ 5.1 mmol/L or 1-h plasma glucose ≥ 10.0 mmol/L or 2-h plasma glucose ≥ 8.5 mmol/L, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (25).

Baseline covariates

All electric medical records of eligible population were reviewed to collect relevant information on baseline characteristics, including demographic characteristics (maternal age, marital status, ethnicity and body mass index [BMI] at first trimester), obstetric characteristics (parity, mode of conception, chorionicity and fetal gender) and obstetric complications (chronic hypertension, pregnancy-induced hypertension [PIH], pre-eclampsia [PE], intrahepatic cholestasis of pregnancy [ICP] and hepatitis B). Maternal BMI was calculated by dividing weight (in kilograms) by height (in meters squared) and was categorized as underweight (BMI<18.5 kg/m²), normal weight (18.5–23.99 kg/m²), overweight (24–27.99 kg/m²) and obese (≥28 kg/m²) based on the standard of the Working Group on Obesity in China (26). Mode of conception included spontaneous and assisted reproductive technology (ART) conception. Chorionicity was assessed at the first sonographic examination before 14 weeks of gestations and confirmed by physical examination of the intertwin membranes after birth, if available. PIH was defined as a new development of a blood pressure of ≥140/90 mmHg after 20 weeks of gestation in the absence of proteinuria and PE was defined when a blood pressure of ≥140/90 mmHg and proteinuria of ≥300 mg/24 h were simultaneously found (27). ICP was diagnosed based on the presence of pruritus with elevated serum total bile acid (TBA) level (≥10 μmol/L).

Outcomes of interest

Maternal outcomes of interest included preterm birth (PTB <37 weeks, <34 weeks and <32 weeks), cesarean section and premature rupture of membrane (PPROM). Neonatal
outcomes of interest included low birth weight (<2,500 g), macrosomia (>4,000 g), small for gestational age (SGA), large for gestational age (LGA), neonatal respiratory distress syndrome (NRDS), neonatal asphyxia, ventilator support, neonatal jaundice, neonatal hypoglycemia, neonatal unit admission, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), hypoxic ischemic encephalopathy (HIE), intracranial hemorrhage (ICH), sepsis and neonatal death. SGA and LGA was defined when the birth weight was below or above the 10th percentile for gestational age and sex based on twin birthweight curves in Chinese twins, respectively (28, 29). Due to the low incidence of BPD, NEC, ICH, HIE, sepsis and neonatal death, we defined a composite outcome when any of these events occurred.

Statistical analyses

All the statistical analyses were preformed using Stata, version 16.0. The baseline characteristics were reported as mean ± standard deviation (SD) or frequency with its percentage. Continuous variables with a Gaussian distribution were analyzed by independent sample t tests while categorical variables were analyzed by the Chi-square test or Fisher’s exact test, where appropriate. Propensity score matching (PSM) was utilized to balance the baseline characteristics, including maternal age, ethnicity, BMI, nulliparity, mode of conception and chorionicity, between GDM vs. non-GDM pregnancies. We used 1:1 nearest-neighbor matching without replacement. A caliper width from 1 to 0 was tried until the absolute
standardized mean difference (SMD) was below 0.1 for each covariate. A SMD of < 0.1 was regarded as a balance in the baseline characteristic between the study groups. After the PSM cohort was obtained, unadjusted logistic regressions were performed to evaluate the difference in maternal outcomes between GDM and non-GDM population. For neonatal outcomes, generalized estimating equation (GEE) approach was used to address the intertwin correlation and the models were further adjusted for gestational age at birth, which is a major factor of neonatal outcomes but not considered in PSM process. To ensure the robustness of the study finding, we also performed multivariable logistic regression on the entire cohort. Models for maternal outcomes were adjusted maternal age, BMI, nulliparity, mode of conception and chorianicity while the models for neonatal outcomes were further adjusted for gestational age at birth. Sensitivity analyses were performed by including women had missing information on maternal BMI (n = 874). The models were adjusted for maternal age, use of ART, nulliparity and chorianicity. The results were reported as odds ratio (ORs) and 95% confidence intervals (95% CIs). A two tailed P-value < 0.05 was considered statistical significance.

Results

Baseline characteristics of study population

A total of 2,151 twin pregnancies were included in the study, of which 472 were complicated with GDM with a prevalence of 21.9% (Figure 1). Table 1 shows the characteristics between GDM and non-GDM pregnancies. In general, women diagnosed with GDM were older (32.4 ± 4.3 vs. 30.7 ± 4.2, P < 0.001) and more likely to be overweight or obese than those without GDM (overweight: 22.3 vs. 15.5%; obesity: 9.3 vs. 3.5%). In addition, dichorionic twins (88.1 vs. 83.7%, P = 0.019) and use of ART (77.8 vs. 71.1%, P = 0.004) were more common in GDM pregnancies. The prevalence of chronic hypertension was also higher in GDM pregnant women (1.9 vs. 0.7%, P = 0.012). Other obstetric complications, including ICP, PIH, PE and hepatitis B, were similar between GDM and non-GDM groups. Among GDM women, only a small proportion (6.4%) used insulin during pregnancy. After PSM with a caliper width of 0.05, we obtained a total of 942 pregnancies (471 GDM pregnancies matched 1:1 to 471 non-GDM pregnancies) in the PSM cohort. The baseline characteristics of maternal age, ethnicity, nulliparity, mode of conception, chorianicity and maternal BMI were balanced between the two study groups (SMD < 0.1).

Pregnancy outcomes between GDM and non-GDM twin pregnancies

Overall, the gestational age at delivery was similar between GDM pregnancies and non-GDM pregnancies (36.0 ± 1.8 vs. 35.9 ± 1.8, P = 0.121). After adjustment for confounders, the multivariable logistic regressions on the entire cohort showed no statistical difference in PTB between GDM and non-GDM pregnancies though the incidence of PTB <37 weeks was slightly higher in GDM pregnancies (OR, 1.25; 95% CI: 0.98–1.58; P = 0.082). The rates of cesarean section and PPROM were also similar between two groups. Based on the PSM cohort, there were no difference in the above-mentioned outcomes (Table 2).

Neonatal outcomes between GDM and non-GDM twin pregnancies

In the entire cohort, there were no occurrence of macrosomia. The multivariable logistic models with GEE approach, adjusted for maternal age, BMI, use of ART, nulliparity, chorianicity, and gestational age at birth, showed no significant differences in the birthweight outcomes and other morbidities between GDM twins and non-GDM twins (Table 3). As the incidences of the severe morbidities (i.e, BPD, NEC, HIE, ICH, sepsis and neonatal death) were extremely low, the multivariable models were waived to calculate ORs for each morbidity. Regarding the composite outcome comprising any of these events, there was no difference between GDM and non-GDM (OR, 0.73; 95% CI, 0.38–1.38). Based on the PSM cohort, the models were adjusted for gestational age at delivery. No significant differences were found in abovementioned outcomes between twin newborns with and without maternal GDM.

Sensitivity analyses

The baseline characteristics were compared between those with missing information on maternal BMI vs. those without. Maternal age, nulliparity, mode of conception, chorianicity, chronic hypertension, hepatitis B and PIH or PE were found to be different between these population (Supplementary Table S1). After including those with first prenatal visit after 14 weeks of gestation, an increased aOR for PTB <34 weeks (aOR, 1.40; 95% CI: 1.08–1.81) was found (Supplementary Table S2). No other significant aORs were found in the sensitivity analysis including women who had their first visit after 14 weeks of gestational age (Supplementary Table S3).
TABLE 1  Baseline characteristics of the study population.

| Characteristics          | Entire cohort | PSM cohort |
|--------------------------|---------------|------------|
|                          | Non-GDM (n = 1679) | GDM (n = 472) | P-value | SMD | Non-GDM (n = 471) | GDM (n = 471) | P-value | SMD |
| Maternal age, year       | 30.7 ± 4.2     | 32.4 ± 4.3 | <0.001 | 0.381 | 32.4 ± 4.4     | 32.3 ± 4.2 | 0.682 | 0.027 |
| Ethnicity                |               |            |        |      |               |            |        |      |
| Han                      | 1649 (98.2)    | 463 (98.1) | 0.846 | 0.009 | 466 (98.9)    | 462 (98.1) | 0.281 | 0.063 |
| Others                   | 30 (1.8)       | 9 (1.9)    |        |      | 5 (1.1)       | 9 (1.9)    |        |      |
| Married                  |               |            |        |      |               |            |        |      |
| Yes                      | 1620 (96.5)    | 448 (94.9) | 0.118 |      | 461 (97.9)    | 447 (94.9) | 0.014 |      |
| No                       | 59 (3.5)       | 24 (5.1)   |        |      | 10 (2.1)      | 24 (5.1)   |        |      |
| Nulliparity              |               |            |        |      |               |            |        |      |
| Yes                      | 1165 (69.4)    | 324 (68.6) | 0.758 | 0.016 | 313 (66.5)    | 323 (68.6) | 0.487 | 0.046 |
| No                       | 514 (30.6)     | 148 (31.4) |        |      | 158 (33.6)    | 148 (31.4) |        |      |
| Mode of conception       |               |            |        |      |               |            |        |      |
| Spontaneous              | 485 (28.9)     | 105 (22.3) | 0.004 | 0.153 | 102 (21.7)    | 105 (22.3) | 0.813 | 0.015 |
| ART                      | 1194 (71.1)    | 367 (77.8) |        |      | 369 (78.3)    | 366 (77.7) |        |      |
| Chorionicity             |               |            |        |      |               |            |        |      |
| Dichorionic              | 406 (83.7)     | 416 (88.1) | 0.019 | 0.127 | 420 (89.2)    | 415 (88.1) | 0.608 | 0.031 |
| Monochorionic            | 273 (16.3)     | 56 (11.9)  |        |      | 51 (10.8)     | 56 (11.9)  |        |      |
| Maternal BMI             |               |            |        |      |               |            |        |      |
| Underweight              | 278 (16.6)     | 36 (7.6)   | <0.001 | 0.226 | 283 (60.1)    | 287 (60.9) | 0.514 | 0.024 |
| Normal weight            | 1083 (64.5)    | 287 (60.8) |        |      | 47 (10)       | 36 (7.6)   |        |      |
| Overweight               | 260 (15.5)     | 105 (22.3) |        |      | 105 (22.3)    | 104 (22.1) |        |      |
| Obese                    | 58 (3.5)       | 44 (9.3)   |        |      | 36 (7.6)      | 44 (9.3)   |        |      |
| Use of insulin           |               |            |        |      |               |            |        |      |
| Yes                      | -              | 30 (6.4)   |        |      | -             | 30 (6.4)   |        |      |
| No                       | -              | 442 (93.6) |        |      | -             | 442 (93.6) |        |      |
| Chronic hypertension     |               |            |        |      |               |            |        |      |
| Yes                      | 11 (0.7)       | 9 (1.9)    | 0.012 |      | 7 (1.5)       | 9 (1.9)    | 0.614 |      |
| No                       | 1668 (99.3)    | 463 (98.1) |        |      | 464 (98.5)    | 462 (98.1) |        |      |
| Hepatitis B              |               |            |        |      |               |            |        |      |
| Yes                      | 112 (6.7)      | 40 (8.5)   | 0.177 |      | 44 (9.3)      | 40 (8.5)   | 0.647 |      |
| No                       | 1567 (93.3)    | 432 (91.5) |        |      | 427 (90.7)    | 431 (91.5) |        |      |
| ICP                      |               |            |        |      |               |            |        |      |
| Yes                      | 45 (2.7)       | 13 (2.8)   | 0.930 |      | 16 (3.4)      | 13 (2.8)   | 0.571 |      |
| No                       | 1634 (97.3)    | 459 (97.3) |        |      | 455 (96.6)    | 458 (97.2) |        |      |
| PIH or PE                |               |            |        |      |               |            |        |      |
| Yes                      | 168 (10.0)     | 55 (11.7)  | 0.300 |      | 56 (11.9)     | 54 (11.5)  | 0.839 |      |
| No                       | 1511 (90.0)    | 417 (88.4) |        |      | 415 (88.1)    | 417 (88.5) |        |      |
| Fetal sex                |               |            |        |      |               |            |        |      |
| Male-male                | 558 (33.2)     | 152 (32.2) | 0.375 |      | 159 (33.8)    | 151 (32.1) | 0.855 |      |
| Female-female            | 481 (28.7)     | 124 (26.3) |        |      | 120 (25.5)    | 124 (26.3) |        |      |
| Male-female              | 640 (38.1)     | 196 (41.5) |        |      | 192 (40.8)    | 196 (41.6) |        |      |

PSM, propensity score matching; ART, assisted reproductive technology; BMI, body mass index; ICP, intrahepatic cholestasis of pregnancy; PIH, pregnancy-induced hypertension; PE, preeclampsia.

**Discussion**

In the current study, we compared the perinatal outcomes between twin pregnancies with vs. without GDM. Overall, the prevalence of GDM in twin pregnancies was 21.9%. Both of the PSM and the entire cohort revealed that the maternal and neonatal outcomes were comparable between GDM and non-GDM twin pregnancies.
The prevalence of GDM depends on the use of screening methods, population characteristics and diagnostic criteria. Based on the IADPSG criteria, we obtained a prevalence similar to that reported in another Chinese population with twin pregnancies (20.4%) (30). In line with previous reports (14, 15, 23, 31), women with GDM were of advanced age and higher BMI. Conversely, our finding, that the incidence of PIH or PE between GDM and non-GDM women was similar, was conflicting with previous studies, which reported a relationship between GDM and HDP in both singleton and twin pregnancies (15, 21, 32). We also found that GDM pregnancies were more likely to be assisted conception, which might be affected by maternal age and BMI because women with advanced age or obesity are likely to be in need of fertility treatment (33).

Regarding the maternal outcomes, we did not observe an increased risk of preterm birth among GDM twin pregnancies, whether in the PSM or the entire cohort. This finding supported previous findings (14, 17, 20) but that of Hiersch et al. (23). The lack of association could be partially explained by the similar incidence of PIH and PE and PPROM in both groups. Also, since this study was performed at a tertiary hospital, pregnancies included in this study were more likely to be high-risk, resulting in iatrogenic preterm delivery, even in the non-GDM group. Not unexpectedly, different from singleton pregnancies, the rate of cesarean section was much lower. This finding supported the recommendation of IADPSG criteria (17) that a women with GDM in twin pregnancies should be offered assisted conception by assisted reproductive technique (ART) as appropriate. The prevalence of cesarean section was lower than previous reports (14, 21, 32), but the incidence of PPROM and PTB was similar to previous reports (15, 21, 32).

In contrast, the neonatal outcomes were similar between GDM and non-GDM pregnancies. This finding supported previous reports (14, 17, 20, 23). The lack of association could be explained by the similar incidence of PIH and PE in both groups. Also, since this study was performed at a tertiary hospital, neonates included in this study were more likely to be high-risk, resulting in iatrogenic preterm delivery, even in the non-GDM group.
higher among twin gestations. Apart from common growth retardation and breech presentation among twins, the high rate of cesarean section in current study population could be attributed to maternal inclination to deliver babies by cesarean section ahead of expected date since vaginal delivery is thought to be risky. In this regard, the observed difference in cesarean section rate between GDM and non-GDM twin pregnancies was blunted.

Accumulated evidence that GDM pregnancies are at risk of accelerated fetal growth are well established in singletons (34–37). For twin pregnancies, whereas, the situation might be different. In the current study, no macrosomia was found in both GDM and non-GDM pregnancies, mainly due to the generally earlier delivery and slower growth among twin pregnancies compared with singleton pregnancies. We did not observe difference in neither LGA nor SGA between GDM and non-GDM pregnancies, which was consistent with previous findings (14, 17, 19, 20). Ashwal et al. (38) recently reported that the longitudinal fetal growth was different between GDM and non-GDM singleton fetuses but comparable between GDM and non-GDM twin fetuses. In this regard, the fetal overgrowth in GDM twin pregnancies might be counteracted by the inherent nature of decreased fetal growth velocity in the third trimester and increased predisposition to fetal growth restriction. Similarly, there was no relationship between neonatal respiratory morbidities and GDM among our study population, consistent with previous reports (17, 20, 23). Maternal diabetes, including GDM and pre-existing diabetes, is reported to be associated with delayed fetal lung maturation, which causes neonatal respiratory morbidities (39–41). This evidence came from singleton pregnancies. Nevertheless, twins showed more rapid fetal lung development than singletons, as reported by Tsuda et al. (42). Further evidence is necessary to clarify different roles of GDM in the lung maturation between GDM twins and singletons.

Luo et al. (24) speculated that the prolong elevated glucose level might play a protective role in multiple pregnancies, which are higher energy and nutrient demanded. The finding of similar neonatal outcomes between GDM and non-GDM twin pregnancies could suggest different clinical implications of GDM for twins and singletons. It also raised our rethinking, whether the diagnostic criteria and prenatal management for GDM should be individualized for twin pregnancies.

The main strength of the present study was the relatively large study population. Furthermore, in the analysis, we adopted PSM method and the results were similar to those obtained from the multivariable models on the entire cohort, which increased the robustness of our finding. Several limitations should be aware of when interpreting the current results, however. First, this study was based on a single center in China, which would limit the generalization of our results to other populations. Furthermore, due to the retrospective design, this database did not include information on oral glucose tolerance test (OGTT) and degree of glycemic control during gestation, which limited the interpretation of the findings. A previous study reported that accelerated fetal growth was found in medically-treated GDM but not diet-treated GDM twin pregnancies, compared with non-GDM pregnancies (38). In the current study, only a small proportion of GDM women used insulin, which may indicate relatively good glycemic control in our study population. Other information, such as maternal smoking status, gestational weight gain, Apgar score, was not available or incomplete in our database. These residual confounding cannot be rule out. In this study, we used the measured weight at the first prenatal visit before 14 weeks to calculate the maternal BMI, which may introduce bias, despite its satisfying correlation with pre-pregnancy weight (32). At last, selection bias could be caused by excluding pregnant women with their first visit after 14 weeks of gestations to ensure information completeness of maternal BMI. The main sample who attended their prenatal visit before 14 weeks of gestations would have higher adequacy of prenatal care or better adherence to prenatal care. Our sensitivity analyses revealed an increased risk of PTB < 34 weeks in GDM pregnancies after including those with their first visit after 14 weeks of gestations. This result might also stress the important role of timing of initial antenatal care in GDM twin pregnancies.

In conclusion, we found that, GDM twin pregnancies with adequate prenatal care have similar outcomes to non-GDM pregnancies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Southern Medical University Affiliated Maternal and Child Health Hospital of Foshan. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

DLin and ZL: concept and design. HZ, JR, ZZ, JF, DLu, LW, SL, and CL: acquisition, analysis, and interpretation of data. D Lin, GC, and PL: statistical analysis. D Lin and DF: drafting of the manuscript. XL, XG, HM, and ZL: critical revision of the manuscript. All authors contributed to the article and approved the submitted version.
Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.946186/full#supplementary-material

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