Relationship between Oral Glucose Tolerance Test Characteristics and Adverse Pregnancy Outcomes among Women with Gestational Diabetes Mellitus

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Abstract

Background: Hyperglycemia is associated with adverse pregnancy outcomes. However, the relationships between them remain ambiguous. This study aimed to analyze the effect of different oral glucose tolerance test (OGTT) results on adverse perinatal outcomes.

Methods: This retrospective cohort study included data from 15 hospitals in Beijing from June 20, 2013 to November 30, 2013. Women with gestational diabetes mellitus (GDM) were categorized according to the number and distribution of abnormal OGTT values, and the characteristics of adverse pregnancy outcomes were evaluated. Chi-square test and logistic regression analysis were used to determine the associations.

Results: In total, 14,741 pregnant women were included in the study population, 2927 (19.86%) of whom had GDM. As the number of hyperglycemic values in the OGTT increased, the risk of cesarean delivery, preterm births, large-for-gestational age (LGA), macrosomia, and neonatal complications significantly increased. Fasting hyperglycemia had clear associations with macrosomia (odds ratios [ORs]: 1.84, 95% confidence intervals [CI]: 1.39–2.42, P < 0.001), LGA (OR: 1.70, 95% CI: 1.29–2.25, P < 0.001), and cesarean delivery (OR: 1.33, 95% CI: 1.15–1.55, P < 0.001). The associations were stronger as fasting glucose increased. GDM diagnosed by hyperglycemia at OGTT-2 h was more likely to lead to preterm birth (OR: 1.50, 95% CI: 1.11–2.03, P < 0.01).

Conclusions: Various characteristics of OGTTs are associated with different adverse outcomes. A careful reconsideration of GDM with hierarchical and individualized management according to OGTT characteristics is needed.

Key words: Cesarean Delivery; Gestational Diabetes Mellitus; Glucose Tolerance Test; Large-for-gestational Age; Macrosomia; Pregnancy Outcomes; Preterm Births

Introduction

For many years, gestational diabetes mellitus (GDM) has been defined as "any degree of glucose intolerance first recognized during pregnancy".⁰¹ Recently, this definition has been redefined by the American Diabetes Association (ADA) as “hyperglycemia diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes”.⁰² According to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria, the incidence of GDM in China is approximately 17.5%, which is consistent with the epidemic increase in diabetes worldwide.⁰³

Hyperglycemia in pregnancy is independently associated with adverse outcomes for the mother, fetus, and neonate, both in the short- and long-term.⁰⁴ The Hyperglycemia and Adverse Pregnancy Outcome study demonstrated that the...
risk of adverse pregnancy outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation, even with glucose values previously considered normal.\(^9\)

However, the precise relationships between different oral glucose tolerance test (OGTT) characteristics and adverse pregnancy outcomes among GDM patients remain ambiguous. It is unclear whether one, two, or three abnormal glucose values on the OGTT represent a higher risk profile for complications. In addition, it is unclear whether fasting or postload glucose values are more closely related to adverse perinatal outcomes and whether they represent different or specific risks.\(^{14,6,7}\)

Understanding these relationships can facilitate the development of appropriate management strategies for GDM patients with different models of OGTT. Therefore, the aim of the current analysis was to estimate how different OGTT characteristics influenced pregnancy outcomes and to determine which OGTT parameter was best correlated with specific adverse pregnancy outcomes.

**Methods**

**Ethical approval**

The study was approved by the Ethics Committee of Peking University First Hospital (No. 2013[578]). All participants provided written informed consent, and the Ethics Committee approved the consent procedure.

**Study population**

We conducted a retrospective cohort analysis of data from the “Systemic Random Sampling Survey on the Prevalence of Gestational Diabetes Mellitus in Beijing (GDM prevalence survey [GPS])”. In this survey, 15 Beijing hospitals were chosen using systemic cluster sampling, and random seed and sampling intervals were determined and sorted by the number of deliveries in 2012. Pregnant women who delivered from June 20, 2013 to November 30, 2013 were screened. The eligibility criteria include all women delivering from June 20, 2013 to November 30, 2013 who were carrying a singleton fetus and had performed a 75 g OGTT between 24 and 28 weeks of gestation. The exclusion criteria were women who had delivered before 28 weeks of gestation and those with either known prepregnancy diabetes mellitus or overt diabetes diagnosed during pregnancy.

**Definitions**

The participating pregnant women were tested for fasting plasma glucose (FPG) during their first prenatal visit using venous blood samples collected after at least 8 h of fasting. Women with FPG ≥7.0 mmol/L were considered to have overt diabetes and were excluded from the study. After 24 weeks of gestation, women received a 75 g OGTT. Women were considered to have GDM if any one of the following OGTT values was met or exceeded: fasting ≥5.10 mmol/L; 1 h ≥10.0 mmol/L; or 2 h ≥8.5 mmol/L. Glucose values above 7.0 mmol/L or 11.1 mmol/L at fasting and 2 h postglucose load, respectively, were considered to indicate overt diabetes.\(^8\) Small for gestational age (SGA) was defined as a birth weight under the 10th percentile, while large for gestational age (LGA) was defined as a birth weight above the 90th percentile based on gender and gestational age.\(^9\) Macrosomia was defined as a birth weight of more than 4000 g.\(^{10}\) Preterm birth was defined as a delivery at gestational age <37 weeks and ≥28 weeks. Neonatal hypoglycemia was defined as glucose values <35 mg/dl by heel stick within 2 h of birth and before the first nonbreastfeeding. Neonatal hyperbilirubinemia was defined as values >95th percentile.\(^{11}\) Hyperinsulinemia was defined as C-peptide levels from cord blood >95th percentile (>1.77 ng/ml).\(^{12}\) Stillbirth was defined as an absence of signs of life at or after birth, and neonatal death was defined as death of a live born neonate during the first 7 days after birth.\(^{13}\)

**Data analysis**

Patients diagnosed with GDM were divided into three groups: Group I, Group II, and Group III, which were divided according to the number of pathological values on the OGTT and consisted of women with one, two, and three pathological glucose values, respectively. The control group comprised pregnant women with normal OGTT results. Further, subgrouping was performed according to OGTT values: patients in Subgroups I\(_1\), I\(_2\), and I\(_1\)+I\(_2\) were diagnosed with GDM according to a single abnormal value for fasting hyperglycemia, 1 h, and 2 h hyperglycemia, respectively (Table 1).

Comparisons were made between groups and subgroups regarding the following adverse pregnancy outcomes: cesarean delivery rate, macrosomia, LGA, SGA, and preterm birth. In addition, neonatal complications were studied and included any of the following: hypoglycemia, hyperbilirubinemia, hyperinsulinemia, admission to the Neonatal Intensive Care Unit, stillbirth, and neonatal death.

**Statistical analysis**

Statistical analysis was conducted with SPSS version 20.0 (IBM, Chicago, IL, USA) software. Categorical variables such as cesarean section, macrosomia, LGA, preterm birth, and neonatal complications were reported as percentages. Pearson’s Chi-square or Fisher’s exact test was also performed using systemic cluster sampling, and random seed and sampling intervals were determined and sorted by the number of deliveries in 2012. Pregnant women who delivered from June 20, 2013 to November 30, 2013 were screened.

**Table 1: Grouping strategies for GDM patients based on 75 g oral glucose tolerance test**

| Groups | Non-GDM | Group I | Group II | Group III |
|--------|---------|---------|----------|-----------|
|        | GDM     |         |          |           |
|        | I\(_2\) | I\(_1\) | I\(_2\)   | I\(_1\)+I\(_2\) |
| Fasting glucose | - | - | - | - |
| 1-h glucose | - | - | - | - |
| 2-h glucose | - | - | - | - |

Group I: GDM patients with one abnormal value on the OGTT; Group II: GDM diagnosed by two abnormal values; Group III: GDM patients with three abnormal values on the OGTT. ↑: Elevated glucose values that meet or exceed the GDM diagnostic criteria; (F): Fasting ≥5.10 mmol/L; (1): 1 h ≥10.0 mmol/L; (2): 2 h ≥8.5 mmol/L; -: Normal glucose value. GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test.
performed. Logistic regression was used in the multivariable analysis to identify the associations between fasting, 1 h, and 2 h hyperglycemia and adverse outcomes. Data were adjusted for gestational age at delivery, maternal age and maternal body mass index at enrollment, and odds ratios (ORs) with 95% confidence intervals (CIs) were computed relative to a control group of women without GDM. A $P < 0.05$ was considered statistically significant.

**Results**

In total, 15,194 pregnant women were included in the initial sample cohort. After excluding 253 women with a multiple pregnancy and 200 women with pregestational or overt diabetes, 14,741 pregnant women were eligible for analysis. The study group consisted of 2927 (19.86%) women with GDM and a control group of 11,814 (80.14%) pregnant women with a normal OGTT.

**Adverse pregnancy outcomes among gestational diabetes mellitus patients**

Table 2 illustrates the relationship of maternal GDM with adverse pregnancy outcomes. Compared to non-GDM women, GDM patients had a higher risk of cesarean delivery, macrosomia, LGA infants, preterm birth, and neonatal complication, but a lower risk of SGA infants.

GDM patients were also divided into three groups: Group I, Group II, and Group III which consisted of patients with one, two, and three abnormal glucose values, respectively [Table 3]. More cesarean deliveries, preterm births, and neonatal complications were observed in Group II than those in Group I ($P < 0.001$). The prevalence of cesarean delivery, macrosomia, LGA, preterm birth, and neonatal complications was higher in Group III than those in Group II ($P < 0.001$) [Table 3]. The ORs, relative to the non-GDM group, were presented in Supplementary Table 1. As the number of abnormal glucose parameters increased, the associations with adverse pregnancy outcomes became stronger, with the strongest association in Group III.

**Relationship between fasting glucose and adverse outcomes**

GDM patients in each group were further subclassified, and the rates of adverse outcomes by OGTT subgroup were shown in Table 4. In Subgroup I,, in which a single abnormal fasting OGTT value served as the GDM diagnostic criteria, significantly more macrosomia and LGA were detected than in Subgroups I and I, in which 1 h or 2 h glucose values were abnormal, respectively. In Group II, which had two abnormal OGTT values, Subgroups II, and II, which had abnormal fasting glucose and one of the postload values over the threshold, demonstrated significantly higher rates of macrosomia and LGA than in GDM patients with both postload glucose values but a normal fasting glucose (Subgroup II,). Similar trends were observed for operative delivery [Table 4].

The ORs are shown in Table 5 and Supplementary Table 1. Fasting hyperglycemia had the strongest association with macrosomia (OR: 1.84, 95% CI: 1.39–2.42, $P < 0.001$), LGA (OR: 1.70, 95% CI: 1.29–2.25, $P < 0.001$), and cesarean delivery (OR: 1.33, 95% CI: 1.15–1.55, $P < 0.001$).

**Relationship between 2 h oral glucose tolerance test and adverse outcomes**

GDM mothers with abnormal 2 h OGTT were more likely to have preterm birth [Table 4]. For GDM patients with

| Parameters                  | Non-GDM ($n = 11,814$) | GDM ($n = 2927$) | OR | 95% CI | $\chi^2$ | $P$  |
|-----------------------------|-------------------------|-----------------|----|--------|----------|------|
| Cesarean section            | 4790 (40.55)            | 1435 (49.05)    | 1.41 | 1.3–1.53 | 68.99    | <0.001|
| Macrosomia                  | 861 (7.29)              | 283 (9.67)      | 1.36 | 1.18–1.57 | 18.57    | <0.001|
| LGA                         | 694 (5.87)              | 273 (9.33)      | 1.65 | 1.42–1.91 | 45.62    | <0.001|
| Preterm birth               | 588 (4.98)              | 184 (6.29)      | 1.28 | 1.08–1.52 | 8.10     | 0.004 |
| Neonatal complication       | 1314 (11.12)            | 386 (13.19)     | 1.21 | 1.07–1.37 | 9.74     | 0.002 |
| SGA                         | 611 (5.17)              | 115 (3.93)      | 0.75 | 0.61–0.92 | 7.74     | 0.005 |

Data were presented as $n$ (%). GDM: Gestational diabetes mellitus; LGA: Large for gestational age; SGA: Small for gestational age; CI: Confidence interval; OR: Odds ratio.

| Adverse pregnancy outcomes | Non-GDM ($n = 11,814$) | GDM | Group I ($n = 2182$) | Group II ($n = 544$) | Group III ($n = 201$) |
|----------------------------|-------------------------|-----|---------------------|----------------------|----------------------|
| Cesarean delivery          | 4790 (40.6)             | 1014 (47.8)$^*$ | 282 (51.9)$^{*+}$ | 112 (56.0)$^{*+}$ |
| Macrosomia                 | 861 (7.3)               | 210 (9.6)$^*$  | 49 (9.0)            | 24 (12.0)$^{*+}$   |
| LGA                        | 694 (5.9)               | 202 (9.3)$^*$  | 47 (8.6)$^*$        | 24 (12.0)$^{*+}$   |
| Preterm birth              | 588 (5.0)               | 124 (5.7)     | 39 (7.2)$^{*+}$     | 21 (10.5)$^{*+}$   |
| Neonatal complication      | 1314 (11.2)             | 283 (13.1)$^*$ | 75 (13.9)$^*$       | 28 (14.2)$^*$      |
| SGA                        | 611 (5.2)               | 90 (4.1)$^*$  | 16 (2.9)$^*$        | 9 (4.5)             |

Data are presented as $n$ (%). $^*P<0.05$ versus non-GDM Group; $^*P<0.001$ versus Group I; $^+P<0.01$ versus Group II. Group I: GDM patients with one abnormal value on the OGTT; Group II: GDM diagnosed by two abnormal values; Group III: GDM patients with three abnormal values on the OGTT. GDM: Gestational diabetes mellitus; LGA: Large for gestational age; SGA: Small for gestational age; OGTT: Oral glucose tolerance test.
Table 4: Adverse pregnancy outcomes in different OGTT subgroups

| Groups                  | Non-GDM (n = 11,814) | Group I (n = 1370) | Group II (n = 161) | Group III (n = 288) |
|-------------------------|----------------------|--------------------|--------------------|--------------------|
|                         | [L₁ (n = 1370)] L₂ (n = 427) | [L₁ (n = 161)] L₂ (n = 95) | [L₁ (n = 201)] |
| Cesarean delivery       | 4790 (40.6)          | 683 (50.0)*        | 186 (43.6)         | 133 (46.3)         |
| Macrosomia              | 861 (7.3)            | 149 (10.9)*        | 29 (6.8)*          | 12 (4.2)*          |
| LGA                     | 694 (5.9)            | 143 (10.5)*        | 25 (5.8)*          | 5 (5.2)*           |
| Preterm birth           | 588 (5.0)            | 74 (5.4)           | 30 (7.0)           | 21 (7.3)           |
| Neonatal complications  | 1314 (11.2)          | 177 (13.0)*        | 60 (14.2)          | 40 (14.0)          |
| SGA                     | 611 (5.2)            | 50 (3.7)*          | 25 (5.8)*          | 9 (3.1)*           |

Data are presented as n (%). *P<0.05 versus non-GDM Group; †P<0.001 versus Group IF; §P<0.001 versus Group II; ‡P<0.001, versus Group II; §P<0.001 versus Group II. Group I: GDM patients with one abnormal value on the OGTT; Subgroups L₁ and L₂ were diagnosed as GDM according to a single abnormal value for fasting hyperglycemia, 1-h and 2-h hyperglycemia, respectively; Group II: GDM diagnosed by two abnormal values; Group III: GDM patients with three abnormal values on the OGTT. GDM: Gestational diabetes mellitus; LGA: Large for gestational age; SGA: Small for gestational age; OGTT: Oral glucose tolerance test.

Table 5: ORs of adverse pregnancy outcomes for hyperglycemia (n = 14,741)

| Outcomes                  | OR  | 95% CI  | P     |
|---------------------------|-----|---------|-------|
| Cesarean section          |     |         |       |
| Fasting glucose 1 h       | 1.33| 1.15–1.55| <0.001|
| OGTT 1 h                  | 1.02| 0.88–1.19| 0.755 |
| OGTT 2 h                  | 0.95| 0.81–1.10| 0.475 |
| Macrosomia                |     |         |       |
| Fasting glucose 1 h       | 1.84| 1.39–2.42| <0.001|
| OGTT 1 h                  | 0.83| 0.63–1.07| 0.152 |
| OGTT 2 h                  | 0.74| 0.56–0.97| 0.028 |
| LGA                       |     |         |       |
| Fasting glucose 1 h       | 1.70| 1.29–2.25| <0.001|
| OGTT 1 h                  | 0.88| 0.67–1.14| 0.323 |
| OGTT 2 h                  | 0.77| 0.58–1.01| 0.057 |
| Preterm birth             |     |         |       |
| Fasting glucose 1 h       | 0.90| 0.68–1.26| 0.739 |
| OGTT 1 h                  | 0.55| 0.40–0.74| 0.0001|
| OGTT 2 h                  | 0.53| 0.40–0.73| 0.0001|
| Neonatal complications    |     |         |       |
| Fasting glucose 1 h       | 0.99| 0.80–1.24| 0.944 |
| OGTT 1 h                  | 0.16| 0.07–1.21| 0.789 |
| OGTT 2 h                  | 0.11| 0.08–1.42| 0.251 |
| SGA                       |     |         |       |
| Fasting glucose 1 h       | 0.81| 0.60–1.11| 0.267 |
| OGTT 1 h                  | 0.86| 0.58–1.29| 0.471 |
| OGTT 2 h                  | 1.28| 0.87–1.87| 0.210 |

GDM patients diagnosed according to a 2 h glucose ≥8.50 mmol/L in the OGTT had less macrosomia, LGA, and cesarean delivery, whether in Group I or Group II [Table 4]. Moreover, it is worth noting that although GDM diagnosis did not increase the rate of SGA infants according to our data, some differences were observed in the SGA distribution of different OGTT models. After comparing the prevalence of SGA, Subgroup I, which included GDM patients with elevated 2 h OGTT as the diagnostic criteria had the highest rate of SGA (5.8%). Patients with abnormal 2 h OGTT exhibited a nonsignificant trend for having more SGA infants than patients with normal 2 h OGTT. In Subgroups I₁ and I₂, in which abnormal 2 h OGTT was one of the diagnostic thresholds, there were more SGA infants than in Subgroup I₁, which had normal 2 h OGTT, with rates of 3.1% and 3.2% compared to 2.5%, respectively (P = 0.002) [Table 4]. Based on this finding, it seemed that there might have been an association between 2 h OGTT glucose and fetal growth restriction in GDM patients, with an OR of 1.28 (95% CI: 0.87–1.88, P = 0.210) for SGA and 0.74 (95% CI: 0.56–0.97, P = 0.028) for macrosomia [Table 5].

Association between fasting hyperglycemia and adverse pregnancy outcomes

Fasting hyperglycemia was associated with perinatal outcomes, including macrosomia, LGA, and cesarean delivery. The fasting glucose on the OGTT were further stratified into 0.5-unit increments [Table 6]. Among pregnant women, the group with a fasting glucose level of 4.60 to 6.59 mmol/L was associated with macrosomia, LGA, and cesarean delivery (P < 0.001) when compared against the group with fasting glucose <4.1 mmol/L. As fasting glucose increased, the risk of adverse pregnancy outcomes was higher. The ORs of macrosomia (up to 5.36 folds), LGA (up to 5.74 folds), and cesarean delivery (up to 2.94 folds) were higher in subgroups with higher fasting glucose levels. However, the subgroup with values in the 6.60 to 6.99 mmol/L range did not show statistical significance for macrosomia, LGA, or cesarean delivery.
Table 6: ORs of pregnancy outcomes according to different ranges of fasting glucose in the 75 g OGTT

| Outcomes      | n (%) | OR    | 95% CI     | P     |
|---------------|-------|-------|------------|-------|
| Macrosomia    |       |       |            |       |
| <4.10         | 1749 (12.67) | 1.00 | <0.001     |       |
| 4.10–4.59     | 5586 (40.45) | 1.17 | 0.93–1.48 | 0.185 |
| 4.60–5.09     | 4909 (35.55) | 1.77 | 1.49–2.58 | <0.001|
| 5.10–5.59     | 1286 (9.31)  | 1.96 | 1.49–2.58 | <0.001|
| 5.60–6.09     | 208 (1.51)   | 3.28 | 2.15–5.03 | <0.001|
| 6.10–6.59     | 51 (0.37)    | 5.36 | 2.72–10.57| <0.001|
| 6.6–6.99      | 19 (0.14)    | 0.97 | 0.13–7.32 | 0.974 |
| LGA           |       |       |            |       |
| <4.10         | 1749 (12.67) | 1.00 | <0.001     |       |
| 4.10–4.59     | 5586 (40.45) | 1.40 | 1.06–1.85 | 0.019 |
| 4.60–5.09     | 4909 (35.55) | 2.35 | 1.79–3.08 | <0.001|
| 5.10–5.59     | 1286 (9.31)  | 2.78 | 2.03–3.80 | <0.001|
| 5.60–6.09     | 208 (1.51)   | 4.69 | 2.97–7.40 | <0.001|
| 6.10–6.59     | 51 (0.37)    | 5.74 | 2.68–12.29| <0.001|
| 6.6–6.99      | 19 (0.14)    | 1.49 | 0.20–11.31| 0.702 |
| Cesarean delivery |      |       |            |       |
| <4.10         | 1749 (12.67) | 1.00 | <0.001     |       |
| 4.10–4.59     | 5586 (40.45) | 1.03 | 0.93–1.16 | 0.552 |
| 4.60–5.09     | 4909 (35.55) | 1.28 | 1.15–1.43 | <0.001|
| 5.10–5.59     | 1286 (9.31)  | 1.56 | 1.20–2.04 | <0.001|
| 5.60–6.09     | 208 (1.51)   | 2.23 | 1.67–2.99 | <0.001|
| 6.10–6.59     | 51 (0.37)    | 2.94 | 1.64–5.27 | <0.001|
| 6.6–6.99      | 19 (0.14)    | 1.17 | 0.47–2.92 | 0.741 |

LGA: Large for gestational age; CI: Confidence interval; ORs: Odds ratios; OGTT: Oral glucose tolerance test.

**Discussion**

In 2011, based on the IADPSG guidelines, the ADA recommended for the first time that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation. The National Health and Family Planning Commission of China adopted testing and diagnostic criteria based on the IADPSG guidelines. Through these guidelines, single abnormal blood glucose levels can be diagnosed, which means more pregnant women are included as having GDM. Moreover, these GDM patients have different hyperglycemia characteristics, which may lead to different pregnant outcomes.

First, GDM results in further adverse maternal, fetal, and neonatal outcomes, including cesarean deliveries, macrosomia, LGA, preterm birth, and neonatal complications. Moreover, in addition to the plasma glucose levels in OGTT, the number of abnormal OGTT parameters also identified different degrees of maternal hyperglycemia and maternal/fetal risk. We found consistent trends between the number of abnormal glucose parameters and frequencies of adverse outcomes, such as cesarean delivery, premature delivery, and neonatal complications. Increasing numbers of abnormal parameters in the OGTT were associated with higher odds of the incidence of adverse perinatal outcomes. This association may warrant a tailored management strategy for GDM. Compared with one hyperglycemic value, patients with two or more elevated glucose values may have a more severe disruption in glucose metabolic balance and insulin sensitivity. This finding should be taken into account during pregnancy follow-up and management of hyperglycemia with stricter glucose control, including regulation of diet and exercise and administration of insulin, to attain satisfactory glycemic control.

Not all abnormal glucose OGTT values resulted in the same adverse outcomes or in the same risk of a specific adverse outcome. The metabolic physiology of pregnancy is characterized by fasting hypoglycemia due to insulin-independent glucose uptake by the placenta, postprandial hyperglycemia, and carbohydrate intolerance as a result of diabetogenic placental hormones. In addition, insulin resistance increases exponentially during the second trimester and levels off toward the end of the third trimester. For GDM patients, fasting hyperglycemia may mean that glucose metabolic abnormalities are more prone to causing adverse perinatal outcomes. However, the associations between fasting hyperglycemia and adverse perinatal outcomes seem more obvious in regard to fetal growth, as GDM is characterized by increased risk of macrosomia, without a risk threshold. Previous studies have suggested that fasting glucose levels are associated with neonatal adiposity including body fat percentage and increased skinfold thickness in neonates born to women with both diet- and insulin-treated gestational diabetes. Consistent with those reports, our data also showed positive associations of fasting hyperglycemia with macrosomia and LGA. Higher fasting glucose levels have been associated with macrosomia and LGA. Consistent with these guidelines, our data also showed positive associations of fasting hyperglycemia with macrosomia and LGA. Moreover, the association was stronger with increases in fasting glucose, although the highest risk was not observed in the 6.60–6.99 mmol/L group, likely due to the limited samples available for the analysis. Moreover, it was worth noting that these results were in contrast to those reported in studies by de Veciana et al. and Combs et al., who described a consistent association between postprandial glucose values and birth weight, frequency of LGA, and macrosomia.

Macrosomia and LGA indicated a greater likelihood of operative delivery. Our data presented a similar distribution between cesarean delivery and macrosomia and LGA. More GDM patients diagnosed by fasting OGTT ≥5.1 mmol/L received a cesarean section. However, it should be considered that the diagnosis of GDM itself shifts obstetric practice toward operative delivery because of its association with macrosomia. Meanwhile, some confounders, such as previous GDM, previous macrosomia, and social psychological factors, may also influence clinical decisions regarding the mode of delivery. In addition to this increase in operative delivery, macrosomic infants are at risk for a variety of perinatal complications, including higher rates of shoulder dystocia and birth trauma. Moreover, longitudinal population studies have documented that macrosomia and LGA confer high risks for infants’ long-term health. Fetal overgrowth and increased neonatal fat mass have
been linked to the development of obesity and metabolic syndrome in childhood and adolescence.[18,19] Given the close relationship of fasting glucose with macrosomia and LGA, the normalization of fasting glucose in GDM has immediate benefits and could potentially improve long-term health outcomes for mothers and neonates.

Offspring of diabetic mothers may be macrosomic, SGA, or of normal birth weight, depending on the severity of the mother’s diabetes, presence or absence of complications, and the degree of diabetic control.[20] In poorly controlled diabetes without severe complications, newborn infants will often be overweight and macrosomic.[21] Improved glycemic control would normalize fetal growth, while severe diabetes or overly strict control may often result in SGA offspring.[22]

Our study demonstrated no association between GDM and SGA. This lack of association might be because our population included GDM patients who had received interventions such as diet, exercise, and insulin treatment after diagnosis, and these interventions might have resulted in good control without deterioration to severe uncontrolled diabetes. However, it is worth noting that GDM patients with abnormal 2 h OGTT values had a trend toward more SGA infants than GDM women with normal 2 h OGTT. A clear difference was observed in GDM patients with one abnormal glucose parameter; when combined with elevated 0 h or 1 h glucose, the effect of 2 h hyperglycemia on SGA seemed to be attenuated. As SGA is a risk factor for a variety of diseases including hypertension, cardiovascular disease, and diabetes, these results suggest that more attention is needed for SGA prevention in GDM mothers, especially if they show an abnormal 2 h OGTT value.[21,23]

Preterm delivery was also associated with GDM.[24] Furthermore, it appeared to be more closely related to elevated postload glucose than abnormal fasting values, with the highest risks of preterm delivery observed among women with normal fasting and two elevated postload glucose values.[16] Our data demonstrate a trend toward more preterm infants in mothers with hyperglycemia in the 2 h OGTT. Further research efforts should determine the precise influence of 2 h OGTT values on premature birth.

There were several limitations to this study. First, it was worth noting that the patients investigated in this study accepted some form of intervention, including diet, exercise, and insulin treatment. It was reasonable to speculate that, if not treated, GDM mothers and their offspring would have had worse adverse outcomes and that the links between different parameters of OGTT and adverse perinatal outcomes would thus be more severe. In addition, participants’ nutritional status could affect fetal growth and other perinatal outcomes, but we did not have data on these variables.

In conclusion, our study indicated the following: first, as the number of hyperglycemic values in the OGTT increased, there was a significant increase in cesarean delivery, preterm birth, LGA infants, macrosomia, and neonatal complications. In addition, fasting hyperglycemia was associated with more macrosomia, LGA, and cesarean delivery, and the association was stronger for higher glucose values. Finally, hyperglycemia according to the 2 h OGTT was associated with a greater possibility of preterm birth and SGA.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilsrb LC, Wenstrom KD. Williams Obstetrics. New York: McGraw Hill; 2005. p. 3.
2. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015;38 Suppl 1:58-16. doi: 10.2337/dc15-S005.
3. Zhu WW, Yang HX, Wei YM, Yan J, Wang ZL, Li XL, et al. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. Diabetes Care 2013;36:586-90. doi: 10.2337/dc12-1157.
4. Landon MB, Mele L, Spong CY, Carpenter MW, Ramin SM, Casey B, et al. The relationship between maternal glycemia and perinatal outcome. Obstet Gynecol 2011;117(2 Pt 1):218-24. doi: 10.1097/AOG.0b013e318203ef09.
5. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarin U, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002. doi: 10.1056/NEJMoa0707943.
6. Durwald CP, Mele L, Spong CY, Ramin SM, Varner MW, Rouse DJ, et al. Glycemic characteristics and neonatal outcomes of women treated for mild gestational diabetes. Obstet Gynecol 2011;117:819-27. doi: 10.1097/AOG.0b013e318206fecf.
7. Combs CA, Gundersen E, Kitzmiller JL, Gavin LA, Main EK, Daniel R. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. Diabetes Care 1992;15:1251-7. doi: 10.2337/diabetes.38.8.1888.
8. Yang HX. Diagnostic criteria for gestational diabetes mellitus (WS 331-2011). Chin Med J 2012;125:122-3.
9. Hill MDH, Himes JH. 1994-1996 U.S. singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender. Matern Child Health J 1999;3:225-31.
10. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999;103:6-14. doi: 10.1542/peds.103.1.6.
11. Landon MB, Spong CY, Thoms E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339-48. doi: 10.1056/NEJMoa0909240.
12. Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Hofmna BL, et al. Williams Obstetrics. 24th ed. New York: McGraw-Hill Education; 2014.
13. Baseri V, Di Mario S, Morciano C, Nonino F, Magrini N. Comment on: American Diabetes Association. Standards of medical care in diabetes-2011. Diabetes Care 2011;34:S11-61. doi: 10.2337/dc11-0174.
14. Uvena-Celebrezze J, Fung C, Thomas AJ, Hoty A, Huston-Presley L, Amini SB, et al. Relationship of neonatal body composition to
maternal glucose control in women with gestational diabetes mellitus. J Matern Fetal Neonatal Med 2002;12:396-401. doi: 10.1080/jmf.12.6.396.401.

16. Black MH, Sacks DA, Xiang AH, Lawrence JM. Clinical outcomes of pregnancies complicated by mild gestational diabetes mellitus differ by combinations of abnormal oral glucose tolerance test values. Diabetes Care 2010;33:2524-30. doi: 10.2337/dc10-1445.

17. de Veciana M, Major CA, Morgan MA, Asrat T, Tooshey JS, Lien JM, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N Engl J Med 1995;333:1237-41. doi: 10.1056/NEJM199511093331901.

18. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics 2003;111:e221-6. doi: 10.1542/peds.111.3.e221.

19. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: Association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115:e290-6. doi: 10.1542/peds.2004-1808.

20. Ergaz Z, Avgil M, Ornoy A. Intrauterine growth restriction-etiology and consequences: What do we know about the human situation and experimental animal models? Reprod Toxicol 2005;20:301-22. doi: 10.1016/j.reprotox.2005.04.007.

21. Ornoy A. Prenatal origin of obesity and their complications: Gestational diabetes, maternal overweight and the paradoxical effects of fetal growth restriction and macrosomia. Reprod Toxicol 2011;32:205-12. doi: 10.1016/j.reprotox.2011.05.002.

22. Eriksson UI, Cedergren J, Wentzel P. Congenital malformations in offspring of diabetic mothers – Animal and human studies. Rev Endocr Metab Disord 2003;4:79-93.

23. Ornoy A, Reece EA, Pavlinkova G, Kappen C, Miller RK. Effect of maternal diabetes on the embryo, fetus, and children: Congenital anomalies, genetic and epigenetic changes and developmental outcomes. Birth Defects Res C Embryo Today 2015;105:53-72. doi: 10.1002/bdrc.21090.

24. Aktün HL, Uyan D, Yorgunlar B, Acet M. Gestational diabetes mellitus screening and outcomes. J Turk Ger Gynecol Assoc 2015;16:25-9. doi: 10.5152/jtgga.2015.15081.
### Supplementary Table 1: ORs of adverse pregnancy outcomes in different GDM groups

| Groups  | Cesarean delivery | Macrosomia | LGA     | Preterm birth | Neonatal complication | SGA     |
|---------|-------------------|------------|---------|---------------|-----------------------|---------|
| Group I |                   |            |         |               |                       |         |
| Iₚ (n = 1370) | 1.34 (1.22–1.47) | 1.36 (1.16–1.59) | 1.64 (1.39–1.93) | 1.15 (0.94–1.41) | 1.19 (1.04–1.37) | 0.79 (0.63–0.99) |
| I₁ (n = 385)   | 1.23 (1.09–1.38) | 1.46 (1.21–1.77) | 1.61 (1.32–1.95) | 1.09 (0.85–1.40) | 1.19 (1.00–1.40) | 0.76 (0.56–1.02)  |
| I₂ (n = 427)   | 0.90 (0.74–1.10) | 1.02 (0.69–1.51) | 0.97 (0.64–1.47) | 1.44 (0.98–2.11) | 1.31 (0.99–1.73) | 1.21 (0.80–1.84)  |
| Group II      |                   |            |         |               |                       |         |
| IIₚ₁ (n = 161) | 1.58 (1.33–1.88) | 1.26 (0.93–1.70) | 1.52 (1.11–2.06) | 1.48 (1.05–2.06) | 1.28 (0.99–1.64) | 0.56 (0.34–0.92)  |
| IIₚ₂ (n = 95)  | 1.43 (1.03–1.98) | 1.74 (1.08–2.83) | 1.38 (0.81–2.34) | 1.27 (0.66–2.41) | 1.14 (0.71–1.83) | 0.55 (0.20–1.49)  |
| IIₚ₃ (n = 288) | 1.26 (0.83–1.92) | 2.73 (1.55–4.81) | 2.68 (1.55–4.66) | 1.76 (0.85–3.64) | 1.48 (0.85–2.58) | 0.72 (0.23–2.28)  |
| Group III     |                   |            |         |               |                       |         |
| III (n = 200)  | 1.86 (1.41–2.47) | 1.74 (1.13–2.67) | 2.19 (1.42–3.37) | 2.24 (1.42–3.55) | 1.31 (0.88–1.96) | 0.86 (0.44–1.70)  |

Data are presented as OR (95% CI). Group I: GDM patients with one abnormal value at the OGTT; Group II: GDM diagnosed by two abnormal values; Group III: GDM patients with three abnormal values at the OGTT. CI: Confidence interval; ORs: Odds ratios; GDM: Gestational diabetes mellitus; LGA: Large for gestational age; SGA: Small for gestational age; OGTT: Oral glucose tolerance test.