A new classification method for gestational diabetes mellitus: a study on the relationship between abnormal blood glucose values at different time points in oral glucose tolerance test and adverse maternal and neonatal outcomes in pregnant women with gestational diabetes mellitus

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BACKGROUND: Gestational diabetes mellitus (GDM) can lead to various adverse pregnancy outcomes for both mothers and infants, including gestational hypertension, premature rupture of membranes, preterm birth, macrosomia, large for gestational age (LGA) infants, and neonatal hypoglycemia. Previous studies have mainly focused on the overall risk of GDM for adverse maternal and neonatal outcomes, but there has been limited research specifically investigating the relationship between different patterns of abnormal oral glucose tolerance test (OGTT) results and adverse maternal and neonatal outcomes.

OBJECTIVE: The study aimed to analyze the maternal and neonatal outcomes among GDM women with different OGTT patterns and to explore a new classification method capable of stratifying GDM into high-risk (GDM-HR) and low-risk subtypes based on OGTT results.

STUDY DESIGN: We conducted a retrospective cohort study at the Women's Hospital, School of Medicine, Zhejiang University, spanning from November 1, 2015, to April 30, 2018. During the study period, a total of 3268 cases of GDM were enrolled. Based on the results of the OGTT, these GDM cases were classified into 7 subtypes, and the composition ratio of each subtype and their maternal and neonatal outcomes were analyzed. Innovatively, we proposed to categorize GDM-HR (characterized by elevated fasting blood glucose [FBG] levels, including T0, T0+1, T0+2, and T0+1+2) and low-risk GDM (GDM-LR, without elevated FBG, including T1, T2, and T1+2) and compared the maternal and neonatal outcomes between the two subtypes.

RESULTS: (1) In this cohort of 3268 GDM cases, the composition ratios of the 7 GDM subtypes were as follows: T0 (7.9%, *n*=260), T1 (24.2%, *n*=791), T2 (27.4%, *n*=897), T0+1 (5.4%, *n*=175), T0+2 (1.7%, *n*=56), T1+2 (26.2%, *n*=855), and T0+1+2 (7.2%, *n*=234). (2) GDM subtypes with elevated FBG levels (GDM-HR) exhibit more severe adverse prognostic outcomes compared to those without elevated FBG levels (GDM-LR). (3) Multiple logistic regression analysis revealed that compared to the GDM-LR group, the GDM-HR group showed increased fetal birth weight (by approximately 150 grams), and had higher rates of cesarean section (adjusted odds ratio [aOR]: 1.45, 95% confidence interval [CI]: 1.19−1.76), hypertensive disorders of pregnancy (aOR: 1.78, 95% CI: 1.35−2.35), preterm birth (aOR: 1.59, 95% CI: 1.17−2.16), macrosomia (aOR: 2.66, 95% CI: 2.07−3.43), LGA infants (aOR: 2.46, 95% CI: 2.05−2.97), and neonatal hypoglycemia (aOR: 2.00, 95% CI: 1.37−2.91). Partial correlation analysis shows a positive correlation between fetal birth weight and FBG levels, with r=0.222, P<.001. Multiple linear regression indicates that for every 1 mmol/L increase in FBG, the fetal weight is estimated to increase by approximately 188 grams.

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Tweetable Statement: Subdividing GDM into GDM high-risk subtype (GDM-HR) with elevated FBG levels and GDM low-risk subtype (GDM-LR) without elevated FBG levels may better differentiate and individualize the management of GDM.

Conflicts of interest: All authors report no conflicts of interest.

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CONCLUSION: The composition ratio of GDM subtypes with elevated FBG (GDM-HR) is relatively low within GDM cases, yet it presents with a higher risk of adverse outcomes compared to subtypes without elevated FBG (GDM-LR), warranting increased attention from obstetricians. Applying this new classification method in clinical practice enables better differentiation and individualized management of GDM.

Key words: classification, fasting blood glucose, gestational diabetes mellitus, oral glucose tolerance test, outcomes

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Why was this study conducted?

The existing classification of GDM (A1/A2), relying on blood glucose control and medication, may face challenges in monitoring and compliance. Our study investigates oral glucose tolerance test (OGTT) patterns in GDM women to pinpoint a high-risk subtype associated with adverse maternal and neonatal outcomes. This study aims to stratify GDM into high-risk (GDM-HR) and low-risk (GDM-LR) categories, facilitating personalized care, especially vital in resource-limited or economically disadvantaged regions.

Key findings

GDM subtypes with elevated fasting blood glucose (FBG) levels exhibit more severe adverse maternal and neonatal outcomes, including preterm birth, hypertensive disorders of pregnancy (HDP), increased cesarean section rates, macrosomia, large for gestational age (LGA) infants, and neonatal hypoglycemia.

What does this add to what is known?

Defining GDM with elevated FBG levels as high-risk GDM (GDM-HR) and those without elevated FBG levels as low-risk GDM (GDM-LR) can simplify and facilitate the differentiation and individualized management of GDM.

Introduction

Gestational diabetes mellitus (GDM) is one of the most common complications during pregnancy. In 2019, according to the International Diabetes Federation, it was estimated that approximately one-sixth (about 16.7%) of live births worldwide were from mothers with GDM, with over 90% of gestational hyperglycemia cases occurring in low- and middle-income countries.[1] If left untreated, gestational hyperglycemia may lead to complications during pregnancy such as macrosomia, preterm birth, stillbirth, neonatal asphyxia, and neonatal respiratory distress.[2] Infants born to women with GDM have an increased risk of developing heart disease, obesity, or type 2 diabetes.[3] The etiology of GDM is complex, but maternal insulin resistance, low-grade inflammation, and endothelial dysfunction are three core features of GDM.[4]

According to the guidelines of the American College of Obstetricians and Gynecologists, GDM can be classified into two types: Class A1 GDM and Class A2 GDM.[5] Class A1 GDM is a milder form that can typically be managed through diet control and lifestyle modifications, while Class A2 GDM is more severe and requires medication for blood glucose control. However, these classifications are primarily based on the ease of blood glucose control, with Class A1 being relatively easier to manage than Class A2. Obstetricians determine a woman's classification based on her blood glucose levels. However, this classification method assumes optimal outpatient follow-up and strict blood glucose monitoring, which may not be feasible in some low- and middle-income countries or economically disadvantaged areas. In such cases, pregnant women with poor access to care or inadequate monitoring may be overlooked, potentially leading to adverse maternal and neonatal outcomes.

Clinical observations suggest that women diagnosed with GDM may have different prognostic outcomes.[6,7] Therefore, GDM may be a heterogeneous condition and should be classified into different subtypes. According to the diagnostic criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and abnormal values at different time points in the 75g-oral glucose tolerance test (OGTT), GDM can be classified into the following 7 subtypes: T0 (elevated fasting blood glucose [FBG] only), T1 (elevated blood glucose at 1 hour in OGTT), T2 (elevated blood glucose at 2 hours in OGTT), T0+1 (elevated fasting and 1-hour blood glucose in OGTT), T0+2 (elevated fasting and 2-hour blood glucose in OGTT), T1+2 (elevated 1- and 2-hour blood glucose in OGTT), and T0+1+2 (elevated fasting, 1-, and 2-hour blood glucose in OGTT). We hypothesize that different types of GDM subtypes based on different OGTT results may represent different prognostic outcomes. Recent studies have shown that among GDM women, those exhibiting elevated FBG levels in the OGTT results experience worse maternal and neonatal outcomes, including increased rates of macrosomia, higher rates of large for gestational age (LGA), elevated rates of cesarean section, and increased usage of insulin.[6–8] Additionally, this group of pregnant women with elevated FBG levels have a significantly increased risk of developing type 2 diabetes mellitus in the future.[9]

Distinguishing between GDM with elevated FBG levels and those without this elevation can be easily accomplished clinically. Such differentiation allows for individualized clinical management, thereby enhancing the convenience and efficacy of GDM management. Hence, our team is

contemplating further subclassifying GDM into two types: high-risk GDM with elevated FBG (GDM-HR type, including four subtypes from the OGTT: T0, T0+1, T0+2, T0+1+2) and low-risk GDM without elevated FBG (GDM-LR type, including three subtypes from the OGTT: T1, T2, T1+2).

This study retrospectively analyzed the characteristics of GDM cases in our hospital and classified them into 7 subtypes based on OGTT results. We analyzed the composition ratio of these 7 subtypes within the GDM cohort and the occurrence rate of adverse maternal and neonatal outcomes. Subsequently, we further categorized GDM cases into GDM-HR type and GDM-LR type based on whether FBG level elevation was combined in the OGTT results. We explored the effectiveness of this new classification method in distinguishing adverse maternal and neonatal outcomes in GDM cases, providing a theoretical basis for individualized management and treatment of GDM.

Materials and methods

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University (*Ethical NO.: IRB-20240160-R*). As this was a retrospective study, written informed consents were not obtained, but all patients' records/information were anonymized before analysis.

Patients

During the study period, a total of 35,783 pregnant women underwent standardized antenatal care at our hospital and underwent testing for GDM using a 75-g OGTT at gestational weeks 24 to 28. Through this test, 5991 pregnant women were diagnosed with hyperglycemia in pregnancy. Ultimately, 3268 cases of pregnant women with GDM who met the inclusion criteria were included in our study.

Selection criteria

This retrospective cohort study included all women who had a live singleton hospital birth and underwent testing for GDM using a 75-g OGTT at our hospital between November 1, 2015, and April 30, 2018. The following cases were excluded: (1) Women with other obstetric indications for surgery (eg, scarred uterus, as scarred uterus cases significantly affected the gestational age at delivery and mode of delivery), breech or transverse presentation; placenta previa, vasa previa, twin/multiple pregnancy, (2) pregnancy associated with stillbirth, (3) uterine anomalies, (4) pregnancy complicated by chronic hypertension, (5) pregnancy complicated by severe maternal diseases (eg, renal disease, heart disease), (6) pregnancy complicated by thyroid dysfunction, (7) pregnancy complicated by tumors, (8) pregnancy complicated by a history of pelvic fractures, (9) pregnancy complicated by retinopathy, (10) cesarean section requested by the patient without obstetric indications, (11) incomplete data, (12) pregestational diabetes, (13) birth occurring before 28 weeks of gestation, (14) pregnancy complicated by cervical insufficiency. (Inclusion and exclusion criteria are shown in Figure 1.)

Diagnostic criteria for GDM

The diagnosis of GDM is made by performing a 75g-OGTT between 24 to 28 weeks of gestation, which is routine screening for gestational diabetes in pregnant women.[10] The revised diagnostic criteria proposed by IADPSG and endorsed by the World Health Organization include the following parameters for diagnosis: fasting plasma glucose 5.1 to 6.9 mmol/L, 1-hour postload glucose ≥10.0 mmol/L, and 2 hours postload glucose 8.5 to 11.0 mmol/L following 2 hours 75 g-OGTT.[10–12]

Diagnostic criteria for pregestational diabetes mellitus (PGDM)

In this study, the diagnostic criteria for PGDM included any of the following[11]: (1) fasting glucose ≥7.0 mmol/L, (2) a 2-hour result in a 75-g OGTT ≥11.1 mmol/L, (3) random glucose ≥11.1 mmol/L, or (4) glycosylated hemoglobin (HbA1c) ≥6.5%.

Statistical analyses

Study data were collected from delivery information that was recorded by the research team. Baseline maternal data and neonatal outcomes were recorded for descriptive and multivariate analyses. Outcome data are presented as percentages (*n* (%), median) (interquartile range) and mean±SD. The comparison between the seven types of GDM subtypes was conducted using univariate unordered multicategory logistic regression analysis, calculating the odds ratio (OR) and 95% confidence interval (CI) of each GDM subtype's characteristics relative to the reference group. For comparisons between the two reclassified GDM subtypes, specifically (GDM-HR vs GDM-LR), both univariate and multivariate logistic regression analyses were used to calculate the OR and 95% CI for GDM-HR compared to GDM-LR. Pearson correlation and partial correlation analyses and was used to analyze the relationship between FBG and fetal birth weight. Multiple linear regression analysis was used to evaluate the relationship between increases in FBG and changes in fetal weight. IBM SPSS Statistics 27.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA) was used for statistical analyses and calculations. A P value $<.05$ was considered statistically significant.

Results

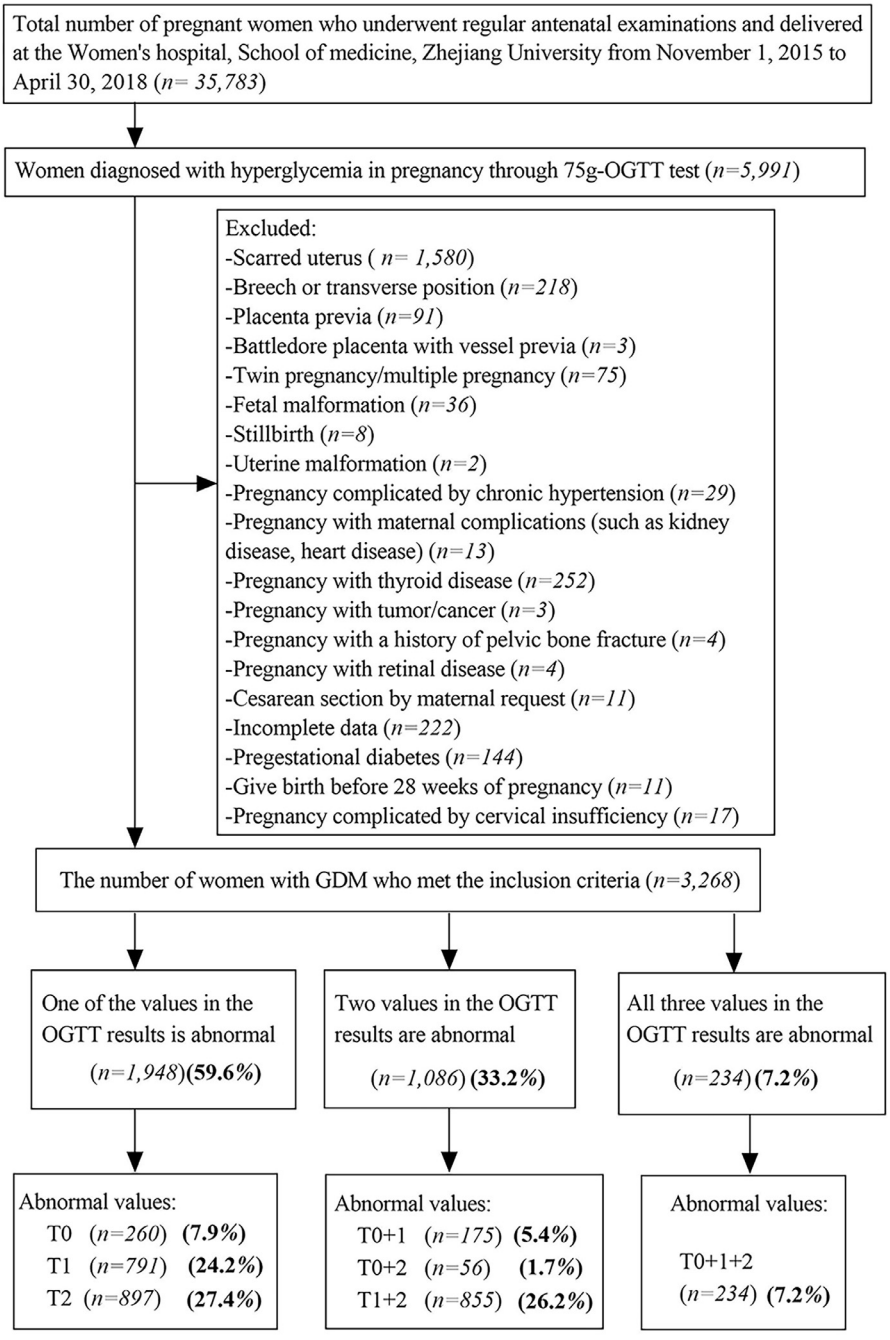
Recruitment and baseline data

During the study period, a total of 5991 women were diagnosed with hyperglycemia in pregnancy. However, 2723 pregnant women were excluded for not meeting the selection criteria. Ultimately, 3268 cases of GDM were included in our study. There were no losses to follow-up, and complete information was available for all cases (Figure 1).

Analysis of the composition ratio of the 7 types of GDM subtypes

A total of 3268 GDM patients who met the inclusion criteria were classified into seven types based on their OGTT results. The specific types and proportions are shown in Figure 2. The composition ratio from lowest to highest is

FIGURE 1
Enrollment flow diagram



GDM, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test.

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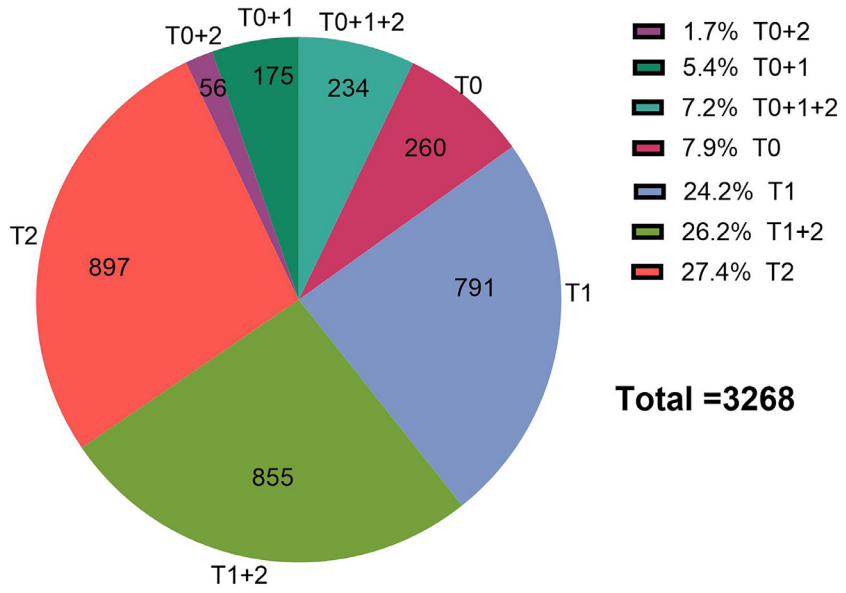
as follows: T0+2, T0+1, T0+1+2, T0, T1, T1+2, and T2. Interestingly, the four GDM subtypes that involve elevated FBG levels (ie, T0+2, T0+1, T0+1+2, and T0) are exactly located in the first quadrant of the composition ratio circle (total proportion of 22.2%, 725 out of 3268).

Comparison of basic characteristics among the 7 subtypes of GDM patients

In this study, we used the basic characteristics of T2 GDM subtype as the reference, as we found that compared to other GDM subtypes, T2 GDM had the highest composition ratio, yet its incidence of adverse maternal and neonatal outcomes was relatively low. Univariate unordered multiclass logistic regression analysis was used to assess the comparison of basic characteristics for different GDM subtypes relative to the T2 GDM subtype. (Table 1 displays the basic characteristics of the seven

FIGURE 2
The composition ratios of the 7 subtypes of GDM based on their OGTT results



T0 (elevated FBG only), T1 (elevated blood glucose at 1 hour in OGTT), T2 (elevated blood glucose at 2 hours in OGTT), T0+1 (elevated fasting and 1-hour blood glucose in OGTT), T0+2 (elevated fasting and 2-hour blood glucose in OGTT), T1+2 (elevated 1- and 2-hour blood glucose in OGTT), and T0+1+2 (elevated fasting, 1-, and 2-hour blood glucose in OGTT).

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subtypes of GDM, while the ORs and 95% CI relative to the T2 group are shown in Figure 3 [forest plot]. In the plot, red bars indicate an OR >1 with $P<.05$; green bars indicate an OR <1 with $P<.05$.)

Comparison of delivery outcomes among the 7 subtypes of GDM patients

Table 2 presents the maternal and neonatal outcomes for the seven different GDM subtypes, while Figure 4 shows the comparison of maternal and neonatal outcomes for the different GDM subtypes relative to the T2 GDM subtype.

The development of a new classification system for GDM subtypes based on distinct prognostic outcomes

The results previously mentioned indicate that GDM types with elevated FBG levels (including T0, T0+1, T0+2, and T0+1+2) exhibit more severe adverse prognostic outcomes compared to those without elevated FBG levels (including T1, T2, and T1+2). These outcomes include an increased rate of cesarean delivery, a higher incidence of hypertensive disorders of pregnancy (HDP), increased fetal birth weight, and increased rates of macrosomia and LGA infants (Figure 4, C, E, I, M, N). This suggests that GDM should not be viewed as a homogenous condition but should be classified into different subtypes. In particular, subtypes with elevated FBG levels warrant more attention. Therefore, we propose defining the former group (T0, T0+1, T0+2, and T0+1+2) as high-risk GDM (GDM-HR subtype), and the latter (T1, T2, T1+2) as low-risk GDM (GDM-LR subtype). The composition ratio is 22.2% (725 out of 3268) for GDM-HR subtype, and 77.8% (2543 out of 3268) for GDM-LR subtype (Figure 5).

Comparison of clinical basic characteristics between the two newly classified subtypes of GDM (GDM-HR and GDM-LR)

Compared to the GDM-LR group, the GDM-HR group exhibited lower parity, reduced gestational ages, higher GWG, taller maternal height, higher predelivery weight, higher predelivery BMI, and higher prepregnancy BMI, all $P<.05$. However, there were no statistically significant differences in maternal age and gravidity between the two groups, both $P>.05$ (Figure 6).

Comparison of the delivery outcomes between GDM-HR and GDM-LR subtypes

Univariate logistic regression analysis revealed that compared to the GDM-LR group, the GDM-HR group had higher fetal weights, and exhibited higher rates of PROM, cesarean section, HDP, preterm birth, macrosomia, LGA infants, and neonatal hypoglycemia, all $P<.05$. However, there were no significant differences between the groups in terms of the rates of ART, ICP, shoulder dystocia, PPH, and OVD, as well as newborn 1- and 5-minute Apgar scores, newborn blood glucose levels, and the rate of SGA infants, all $P>.05$.

After adjusting for potential confounders, including maternal age, parity, gestational age, and GWG, the GDM-HR group still exhibited increased fetal birth weight (by approximately 150 grams) and higher rates of cesarean section (adjusted odds ratio [aOR]: 1.45, 95% CI: 1.19−1.76), HDP (aOR: 1.78, 95% CI: 1.35−2.35), preterm birth (aOR: 1.59, 95% CI: 1.17−2.16), macrosomia (aOR: 2.66, 95% CI: 2.07−3.43), LGA infants (aOR: 2.46, 95% CI: 2.05−2.97), and neonatal hypoglycemia (aOR: 2.00, 95% CI: 1.37−2.91). However, the rate of PROM showed no statistical difference after adjusting for confounders ($P=.171$) (Figure 7).

Exploration of optimal gestational weeks for delivery in the newly classified GDM subgroups—GDM-HR and GDM-LR

Through the above results, we found that the GDM-HR group exhibited

TABLE 1
The basic characteristics of the 7 subtypes of GDM cases

Groups Factors	Maternal age (y)	Gravidity	Parity	GA (wk)	GWG (kg)	Maternal height (cm)	Predelivery weight (kg)	Predelivery BMI (kg/m^2)	Prepregnancy BMI (kg/m^2)	Fast glucose (mM)	OGTT-1h (mM)	OGTT-2h (mM)
T2	31.7 ± 4.2	2 (1–2)	0 (0–1)	39.6 (38.7–40.4)	12.5 (10–15)	160.5 ± 4.6	65 (60–70.5)	25.4 ± 3.2	20.5 ± 3.1	4.4 (4.2–4.7)	9.2 (8.5–9.6)	9.0 (8.7–9.4)
T0	30.6 ± 4.3	2 (1–2)	0 (0–1)	39.4 (38.6–40.3)	15 (12–16)	161.7 ± 5.3	72 (66–78)	27.7 ± 3.5	22.0 ± 3.5	5.3 (5.2–5.4)	8.5 (7.5–9.3)	7.1 (6.5–7.7)
T1	31.4 ± 4.3	2 (1–3)	0 (0–1)	39.4 (38.6–40.3)	13 (10.5–15)	160.7 ± 5.9	67.5 (61.5–73.5)	26.5 ± 6.2	21.2 ± 4.9	4.6 (4.4–4.8)	10.5 (10.2–10.9)	7.5 (6.9–8.1)
T0+1	32.2 ± 4.8	2 (1–3)	0 (0–1)	39.3 (38.1–40.1)	13.5 (10–15)	160.4 ± 4.8	71 (66–78)	28.3 ± 3.7	23.1 ± 3.6	5.3 (5.2–5.6)	10.8 (10.3–11.5)	7.67 (7.15–8.06)
T0+2	31.7 ± 4.6	2 (1–3)	0 (0–1)	39.4 (38.3–40.3)	12.3 (10–15)	161.0 ± 4.6	71.5 (64.3–76.8)	27.6 ± 3.2	22.7 ± 3.5	5.3 (5.2–5.4)	9.4 (8.8–9.7)	9.1 (8.8–9.7)
T1+2	32.0 ± 4.3	2 (1–3)	0 (0–1)	39.4 (38.4–40.3)	12 (10–15)	159.9 ± 4.7	71.5 (64.3–76.8)	25.5 ± 3.0	20.6 ± 2.8	4.5 (4.3–4.7)	10.7 (10.3–11.2)	9.4 (8.9–9.9)
T0+1+2	32.3 ± 4.2	2 (1–3)	0 (0–1)	39.3 (38.4–40.3)	12 (10–15)	160.6 ± 4.9	65 (60–70)	28.1 ± 3.5	23.3 ± 3.4	5.4 (5.2–5.7)	11.4 (10.7–12.3)	9.5 (9.0–10.2)

BMI, body mass index; mM:mmol/L; *GA*, gestational age; *GWG*, gestational weight gain; *OGTT*, oral glucose tolerance test.

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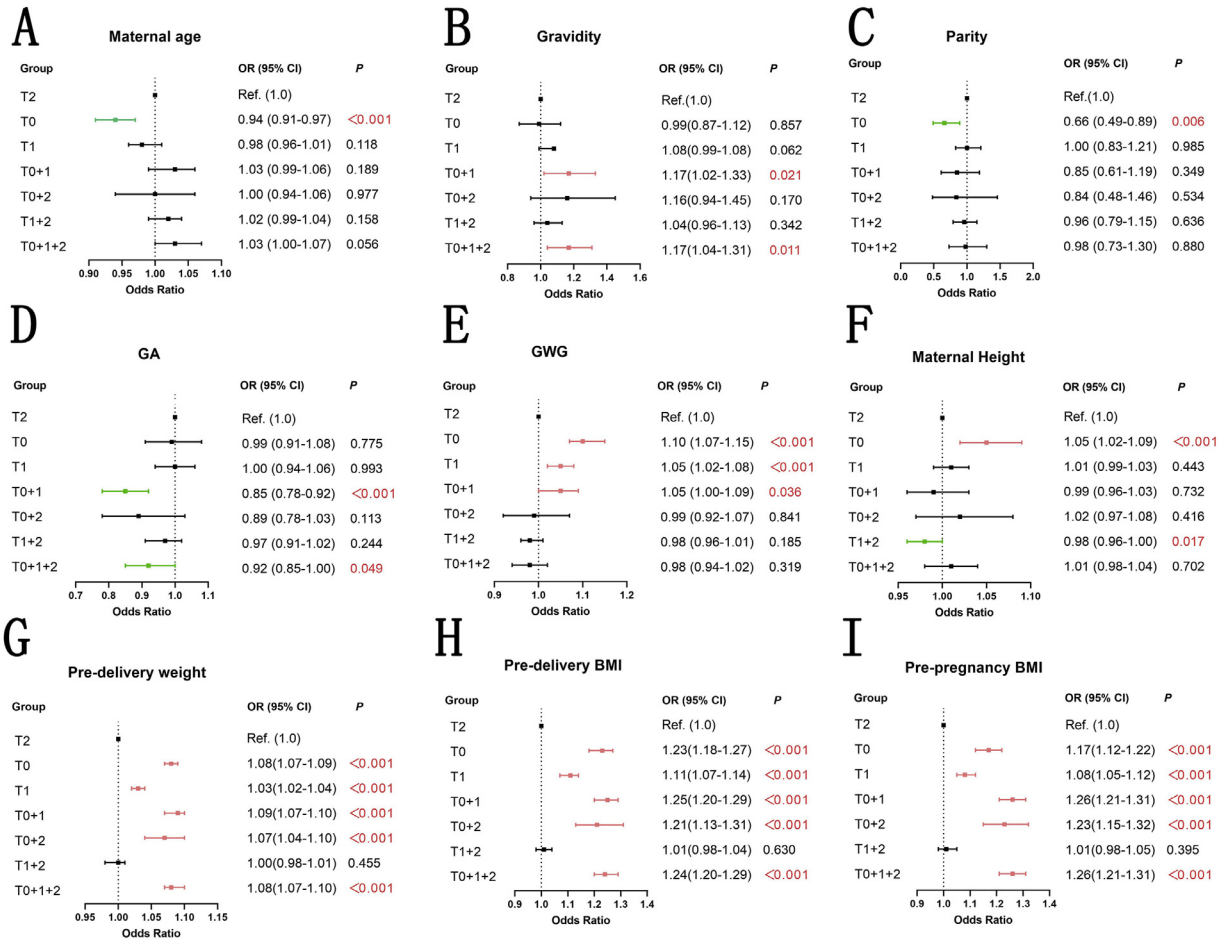
higher fetal birth weight, increased cesarean section rate, and elevated rates of macrosomia and LGA. These indicators all suggest that the GDM-HR subtype may require delivery at an earlier gestational weeks to reduce these risks. Therefore, next, we attempted to explore the optimal gestational weeks for delivery in GDM subtypes by calculating the cumulative rates of macrosomia for the seven GDM subtypes before reclassification and the two GDM subtypes after reclassification.

As shown in Figure 8, A, the cumulative incidence rates of macrosomia for the 7 GDM subtypes gradually increase with advancing gestational weeks. (1) At gestational weeks $\geq 41^{+0}$, the cumulative incidence rates of macrosomia from highest to lowest are T0+2, T0+1+2, T0, T0+1, T1, T2, and T1+2, where the first four subtypes precisely represent the GDM-HR subtype characterized by elevated FBG levels. The cumulative incidence rates of macrosomia for these subtypes are all significantly higher than 10%, ranging from 26.8% to 13.1%. In contrast, the cumulative incidence rates of macrosomia for the T1, T2, and T1+2 subtypes (GDM-LR subtype) do not exceed 10%, ranging from 8.5% to 6.7%. (2) Between gestational weeks 40^{+0} and 40^{+6}, the cumulative incidence rates of macrosomia for the GDM-HR subtype are 23.2%, 12.7%, 12.0%, and 11.1%, all exceeding 10%. (3) At gestational weeks 39^{+0} to 39^{+6}, the cumulative incidence rates of macrosomia for the GDM-HR subtype are 10.7%, 9.1%, 5.0%, and 3.8%, with only the T0+2 subtype exceeding 10% at 10.7%.

As illustrated in Figure 8, B, after categorizing GDM into GDM-HR and GDM-LR subtypes: (1) At gestational weeks $\geq 41^{+0}$, the cumulative incidence rate of macrosomia for GDM-HR is 17.0%, whereas for GDM-LR subtype, it is only 7.7%. (2) Between gestational weeks 40^{+0} and 40^{+6}, the cumulative incidence rate of macrosomia for GDM-HR subtype is 12.8%, while for GDM-LR subtype, it is only 6.7%. (3) At gestational weeks 39^{+0} to 39^{+6}, the cumulative incidence rates

FIGURE 3
Comparison of maternal basic characteristics among 7 subtypes of GDM



A–I represent the basic maternal characteristics among the 7 subtypes of women with GDM, including maternal age (A), gravidity (B), parity (C), GA (D), GWG (E), maternal height (F), pre-delivery weight (G), pre-delivery BMI (H), and pre-pregnancy BMI (I).

BMI, body mass index; *CI*, confidence interval; *GA*, gestational age; *GWG*, gestational weight gain; *OR*, odd ratio.

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of macrosomia for both groups are 6.1% and 3.0%, respectively.

Based on the aforementioned findings, in an effort to mitigate adverse maternal and neonatal outcomes associated with GDM and to tailor GDM management individually, we advocate for an innovative strategy: When considering a cumulative incidence rate of macrosomia not surpassing 10% as a precautionary threshold, induction of labor should be considered for GDM-HR subtype pregnancies between gestational weeks 39^{+0} and 39^{+6}, whereas for GDM-LR subtype pregnancies, induction could be considered between gestational weeks 40^{+0} and 40^{+6}.

The relationship between blood glucose values in OGTT and fetal weight, as well as the risk of macrosomias

Pearson correlation regression analysis indicates a positive correlation between FBG levels and fetal weight, with r=0.164, P<.001. OGTT-2h blood glucose level shows a weak negative correlation with fetal weight, with r=−0.062, P<.001; whereas OGTT-1h blood glucose level shows no correlation with fetal weight, with P>.05 (Figure S1, A–C). Partial correlation regression analysis showed that after controlling for maternal age, parity, GA, and GWG, FBG levels remained positively correlated with fetal weight, r=0.222, P<.001. (Data not shown.)

Due to various factors that may affect fetal weight, we included indicators such as maternal age, GA, FBG levels, OGTT-2h blood glucose, and GWG in a multiple linear regression analysis (using stepwise regression). The regression model obtained is as follows:

$$Y(Fetal\ weight) = -4589 + 169.3 * GA + 188.0 * FBG + 20.8 * GWG + 93.8 * parity + 4.0 * maternal\ age$$

The variable of OGTT-2h blood glucose was eliminated from the stepwise

TABLE 2
The delivery outcomes among the 7 subtypes of GDM patients

Groups Maternal outcomes	ART (*n*, %)	PROM (*n*, %)	CS rate (*n*, %)	ICP (*n*, %)	HDP (*n*, %)	Shoulder dystocia (*n*, %)	PPH (*n*, %)	OVD (*n*, %)
T2	26 (2.9)	232 (25.9)	168 (18.7)	28 (3.1)	42 (4.7)	5 (0.6)	42 (4.7)	33 (3.7)
T0	10 (3.8)	70 (26.9)	80 (30.8)	8 (3.1)	27 (10.4)	3 (1.2)	14 (5.4)	8 (3.1)
T1	58 (7.3)	212 (26.8)	174 (22.0)	21 (2.7)	69 (8.7)	10 (1.3)	60 (7.6)	27 (3.4)
T0+1	7 (4.0)	52 (29.7)	52 (29.7)	6 (3.4)	24 (13.7)	1 (0.6)	11 (6.3)	9 (5.1)
T0+2	1 (1.8)	18 (32.1)	14 (25.0)	1 (1.8)	9 (16.1)	1 (1.8)	3 (5.4)	2 (3.6)
T1+2	29 (3.4)	205 (24.0)	190 (22.0)	23 (2.7)	59 (6.9)	1 (0.1)	38 (4.4)	20 (2.3)
T0+1+2	10 (4.3)	72 (30.8)	64 (27.4)	8 (3.4)	28 (12)	3 (1.3)	12 (5.1)	11 (4.7)
Groups Neonatal outcomes	Fetal weight (g)	1-min Apgar score	5min-Apgar score	Preterm birth (*n*, %)	Macrosomia (*n*, %)	LGA (*n*, %)	SGA (*n*, %)	Neonatal hypoglycemia (*n*, %)
T2	3312.0 ± 527	10 (10−10)	10 (10−10)	46 (6.4)	71 (7.9)	162 (18.1)	38 (4.2)	31 (3.5)
T0	3521.0 ± 533.7	10 (10−10)	10 (10−10)	15 (5.8)	40 (15.4)	91 (35.0)	3 (1.2)	9 (3.5)
T1	3359.5 ± 481.5	10 (10−10)	10 (10−10)	46 (5.8)	69 (8.7)	158 (20)	21 (2.7)	30 (3.8)
T0+1	3394.0 ± 565.9	10 (10−10)	10 (10−10)	21 (12)	22 (12.6)	57 (32.6)	13 (7.4)	9 (5.1)
T0+2	3498.4 ± 571.0	10 (10−10)	10 (10−10)	7 (12.5)	13 (23.2)	22 (39.3)	3 (5.4)	2 (3.6)
T1+2	3306.9 ± 474.6	10 (10−10)	10 (10−10)	49 (5.7)	58 (6.8)	176 (20.6)	12 (1.4)	31 (3.6)
T0+1+2	3497.8 ± 621.8	10 (10−10)	10 (10−10)	21 (9.0)	49 (20.9)	95 (40.6)	11 (4.7)	14 (6.0)

ART, assisted reproductive technology; *CS*, cesarean section; *HDP*, hypertensive disorders of pregnancy; *ICP*, intrahepatic cholestasis of pregnancy; *LGA*, large for gestational age; *OVD*, operative vaginal delivery; PPH, postpartum hemorrhage; *PROM*, premature rupture of membrane; *SGA*, small for gestational age.

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regression model due to its *P* value >.10. The equation's multiple correlation coefficient is *R*=0.618, and the coefficient of determination *R*2=0.382. The results indicate that for every 1 mmol/L increase in FBG, the fetal weight is estimated to increase by approximately 188 grams (Table S1).

Univariate analysis indicated that for every 1 mmol/L increase in FBG level, the risk of macrosomia increased by 1.77-fold (OR: 2.77, 95% CI: 2.23−3.45), *P*<.001; while there was no significant correlation between OGTT-1h and OGTT-2h blood glucose levels and the occurrence of macrosomia. After adjusting for maternal age, parity, gestational weeks, and GWG, for every 1 mmol/L increase in FBG level, the risk of macrosomia increased by 2.29-fold (adjusted OR: 3.29, 95% CI: 2.59−4.18), *P*<.001 (Table S2).

Comment

Principal findings

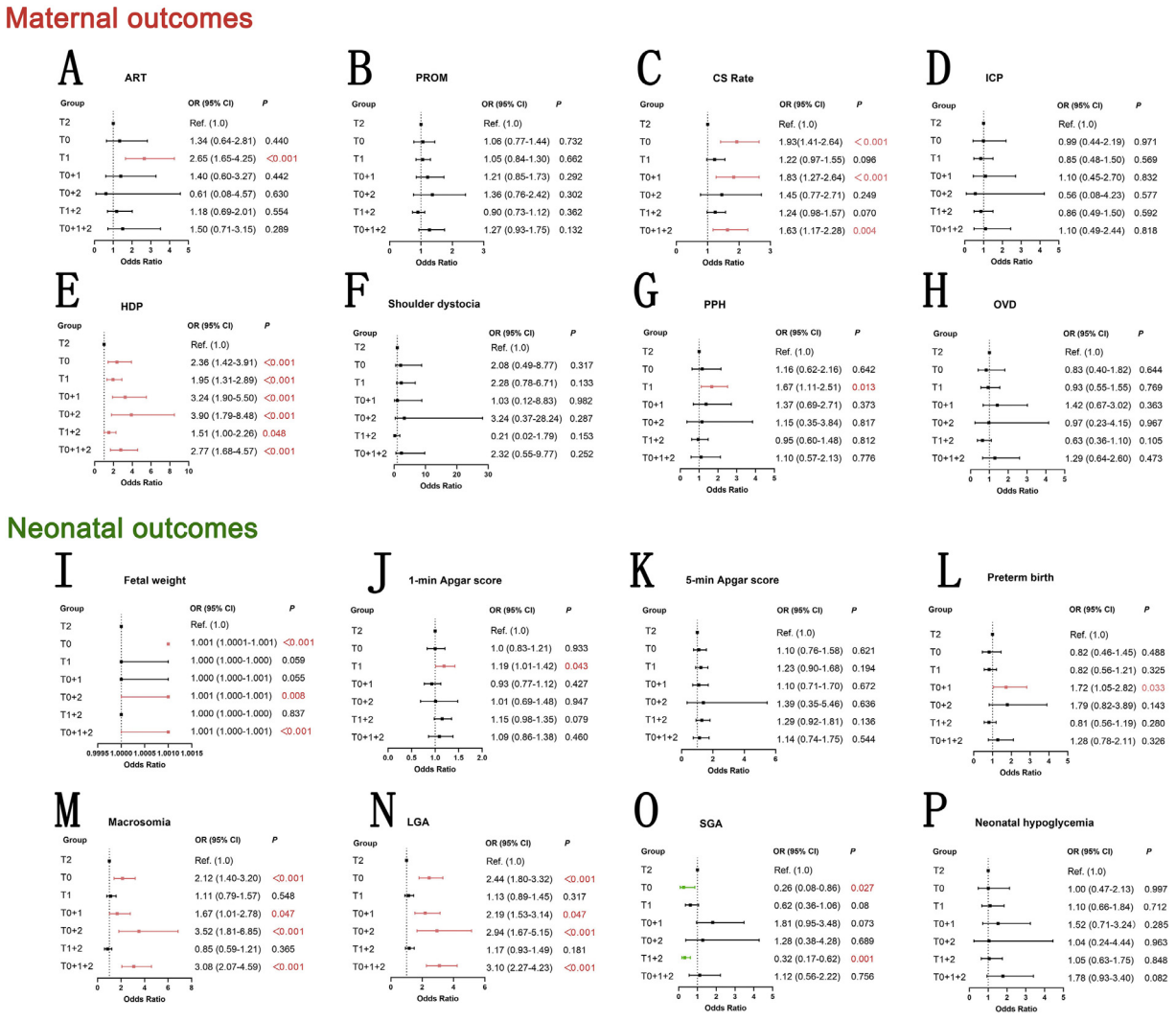
In this retrospective cohort study, we classified GDM into two subtypes based on whether elevated FBG levels were present in the OGTT results: GDM-HR (GDM with elevated FBG levels) and GDM-LR (GDM without elevated FBG levels). We found that GDM-HR subtype had more adverse prognostic outcomes, including increased fetal birth weight (by approximately 150 grams), higher rates of cesarean section (aOR: 1.45), HDP (aOR: 1.78), preterm birth (aOR: 1.59), macrosomia (aOR: 2.66), LGA infants (aOR: 2.46), and neonatal hypoglycemia (aOR: 2.00). We determined through multiple linear regression that for every 1 mmol/L increase in FBG, the fetal birth weight increases by approximately 188 grams.

We further explored the timing of induction of labor for GDM-HR and GDM-LR subtypes. If the cumulative incidence of macrosomia is maintained below 10% as a cautionary threshold, induction of labor should be considered for GDM-HR subtype pregnancies between gestational weeks 39^{+0} and 39^{+6}, whereas for GDM-LR subtype pregnancies, induction could be considered between gestational weeks 40^{+0} and 40^{+6}. These findings provide valuable clinical insights and may serve as a theoretical basis for personalized management and treatment of GDM.

Results in the context of what is known

In our current research, we found that GDM subtypes with elevated FBG levels had more adverse outcomes for both mothers and infants, including higher birth weight, cesarean rates, macrosomia, LGA, and HDP. Elevated maternal blood glucose stimulates fetal insulin secretion, causing excess nutrient absorption and fetal fat accumulation, leading to macrosomia/LGA. Isolated impaired glucose tolerance represents transient elevation of postprandial blood glucose levels, while elevated FBG levels indicate that the mother has been in a state of high blood glucose levels for a prolonged period, exacerbating fetal insulin overproduction.[8,9] Maternal factors like obesity and excessive GWG worsen insulin resistance.[13]

FIGURE 4
Comparison of delivery outcomes among the 7 subtypes of GDM



The maternal outcomes for the 7 subtypes of GDM women are represented by A–H, including the rates of ART (A), PROM (B), CS (C), ICP (D), HDP (E), shoulder dystocia (F), PPH (G), and OVD (H). Neonatal outcomes are represented by I–P, including fetal weight (I), 1-min Apgar score (J), 5-min Apgar score (K), rate of preterm birth (L), macrosomia (M), LGA (N), SGA (O), and neonatal hypoglycemia (P).

ART, assisted reproductive technology; *PROM*, premature rupture of membrane; *CS*, cesarean section; *ICP*, intrahepatic cholestasis of pregnancy; *HDP*, hypertensive disorders of pregnancy; *PPH*, postpartum hemorrhage; *OVD*, operative vaginal delivery; *LGA*, large for gestational age; *SGA*, small for gestational age.

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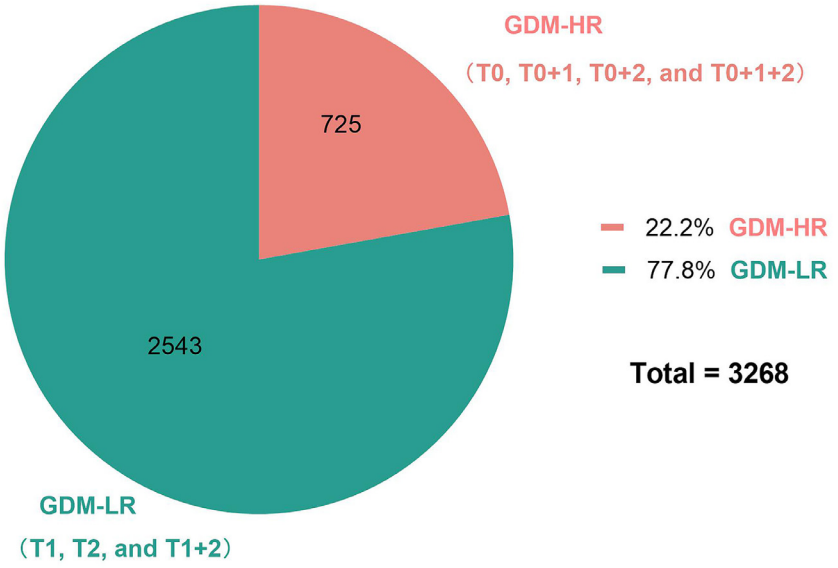
Among the cases observed in this study, women with elevated FBG levels had significantly higher prepregnancy or predelivery weights and higher BMI compared to those with impaired glucose tolerance (Figure 3, G–I). Black et al[14] conducted a retrospective study involving 8711 pregnant women in the United States who underwent a 75g-OGTT. They also found that women with elevated FBG levels had a two-fold increase in the risk of having LGA infants compared to those with normal OGTT patterns, while those with elevated blood glucose levels at 1 hour and/or 2 hours OGTT values did not show a significant increase in the risk of LGA. This conclusion is consistent with the findings of our study.

Our research also found that GDM with elevated FBG levels is more prone to developing HDP. Current studies suggest that the etiology of GDM-induced HDP is primarily associated with hyperinsulinemia leading to maternal weight gain and renal sodium retention.[15,16] Additionally, pregnant women with GDM who are exposed to prolonged high-glucose environments are associated with increased inflammation and oxidative stress, which may impair endothelial cell function and contribute to the occurrence of HDP.[17]

FIGURE 5
New classification method and composition ratios of GDM



GDM-HR, high-risk GDM (including four subtypes: T0, T0+1, T0+2, and T0+1+2); *GDM-LR*, low-risk GDM (including four subtypes: T1, T2, and T1+2).

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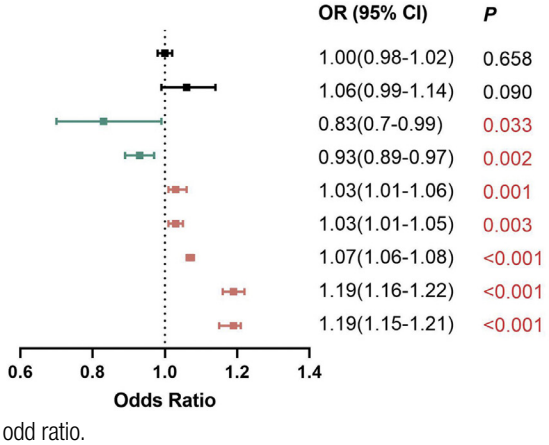
Liang et al found that elevated maternal blood glucose levels were associated with an increased risk of subsequent hypertension. Among those who underwent an OGTT, the combined group (elevated fasting and postload glucose) had the highest risk of developing hypertension (HR: 2.65, 95% CI: 2.33−3.01), followed by elevated fasting glucose (HR: 2.02, 95% CI: 1.70−2.40), and then isolated postload glucose elevation (HR: 1.83, 95% CI: 1.68−2.00). They emphasized that elevated FBG levels in OGTT were associated with a higher risk for hypertension compared with isolated postload glucose elevation.[18] This aligns with the conclusions drawn in our study.

Our study also uncovered that GDM with elevated FBG levels had a higher incidence of preterm birth. In a retrospective cohort study conducted by Li et al,[19] maternal GDM increased the risk of preterm birth in both nulliparous (aOR=1.28, 95% CI: 1.14−1.45) and multiparous women (aOR=1.26, 95% CI: 1.14−1.40). However, in their study, GDM women were analyzed as a whole without subgroup analysis based on OGTT results. Another study from China suggests that elevated maternal FBG levels before pregnancy increases the risk of preterm birth. Compared to women with normal blood glucose levels, those with impaired fasting glucose before pregnancy had a 7.0% higher risk of preterm birth (aOR, 1.07, 95% CI: 1.02−1.12).[20] This evidence is consistent with our research findings.

Furthermore, our investigation revealed a link between elevated FBG levels in the GDM-HR subtype and an increased rate of neonatal hypoglycemia. Neonatal hypoglycemia arises from fetal hyperinsulinemia triggered by exposure to elevated glucose levels from the mother.[21] In the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, neonatal hypoglycemia occurred in 2.1% of participants, consistent with our findings. Elevated OGTT-1h and OGTT-2h glucose levels were associated with increased odds of neonatal hypoglycemia, whereas FBG alone showed a weaker association (OR: 1.08, 95% CI: 0.98−1.19).[22] However, the HAPO study did not comprehensively analyze all types of combined FBG elevation (T0, T0+1, T0+2, and T0+1+2) merged with noncombined FBG elevation in GDM (T1, T2, and

FIGURE 6
Comparison of clinical basic characteristics between the two newly classified subtypes of GDM

Characteristics	GDM-HR group	GDM-LR group	OR (95% CI)	*P*
Maternal age (years)	31(28-34)	31.7(29-35)	1.00(0.98-1.02)	0.658
Gravidity	2(1-3)	2(1-3)	1.06(0.99-1.14)	0.090
Parity	0(0-1)	0(0-1)	0.83(0.7-0.99)	0.033
GA (weeks)	39.3(38.3-40.3)	39.4(38.6-40.3)	0.93(0.89-0.97)	0.002
GWG (kg)	13(10.25-15)	12.5(10-15)	1.03(1.01-1.06)	0.001
Maternal height (cm)	160(158-164)	160(158-163)	1.03(1.01-1.05)	0.003
Pre-delivery weight (kg)	72(66-78)	65.5(60-71.5)	1.07(1.06-1.08)	<0.001
Pre-delivery BMI (kg/m^2)	27.6(25.8-30.05)	25.5(23.6-27.6)	1.19(1.16-1.22)	<0.001
Pre-pregnancy BMI (kg/m^2)	22.5(20.5-24.7)	20.6(18.9-22.4)	1.19(1.15-1.21)	<0.001



CI, confidence interval; *GA*, gestational age; *GWG*, gestational weight gain; *OR*, odd ratio.

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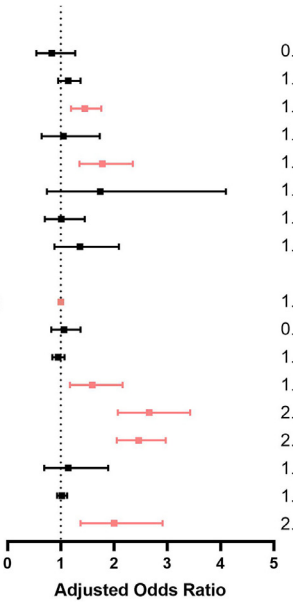
FIGURE 7
Comparison of maternal and neonatal outcomes between the two new classifications of GDM subtypes

Outcomes	GDM-HR group (n=725)	GDM-LR group (n=2543)	aOR（95%CI）	Adjusted *P*-value
Maternal outcomes				
ART (n,%)	28(3.9)	113(4.4)	0.83(0.54-1.27)	0.385
PROM (n,%)	212(29.2)	649(25.5)	1.14(0.95-1.37)	0.171
CS Rate (n,%)	210(29.0)	532(20.9)	1.45(1.19-1.76)	<0.001
ICP (n,%)	23(3.2)	72(2.8)	1.05(0.64-1.73)	0.840
HDP (n,%)	88(12.1)	170(6.7)	1.78(1.35-2.35)	<0.001
Shoulder dystocia (n,%)	8(1.1)	16(0.6)	1.74(0.74-4.10)	0.206
PPH (n,%)	40(5.5)	140(5.5)	1.01(0.70-1.45)	0.980
OVD (n,%)	30(4.1)	80(3.1)	1.36(0.88-2.09)	0.168
Neonatal outcomes				
Fetal weight (g)	3490(3140-3850)	3340(3040-3620)	1.001(1.001-1.001)	<0.001
1-min Apgar score	10(10-10)	10(10-10)	0.95(0.84-1.07)	0.306
5-min Apgar score	10(10-10)	10(10-10)	1.06(0.82-1.37)	0.663
Preterm birth (n,%)	64(8.8)	152(6.0)	1.59(1.17-2.16)	0.003
Macrosomia (n,%)	124(17.1)	198(7.8)	2.66(2.07-3.43)	<0.001
LGA (n,%)	265(36.6)	496(19.5)	2.46(2.05-2.97)	<0.001
SGA (n,%)	30(4.1)	71(2.8)	1.14(0.69-1.89)	0.599
Neonatal blood glucose level (mM)	3.3(2.9-3.9)	3.3(2.8-3.9)	1.02(0.93-1.12)	0.648
Neonatal hypoglycemia (n,%)	45(6.2)	81(3.2)	2.00(1.37-2.91)	<0.001



aOR, adjusted odds ratio; adjusted for maternal age, parity, gestational age, and gestational weight gain; *ART*, assisted reproductive technology; *CS*, cesarean section; *HDP*, hypertensive disorders of pregnancy; *ICP*, intrahepatic cholestasis of pregnancy; *LGA*, large for gestational age; *OVD*, operative vaginal delivery; *PPH*, postpartum hemorrhage; *PROM*, premature rupture of membrane; *SGA*, small for gestational age.

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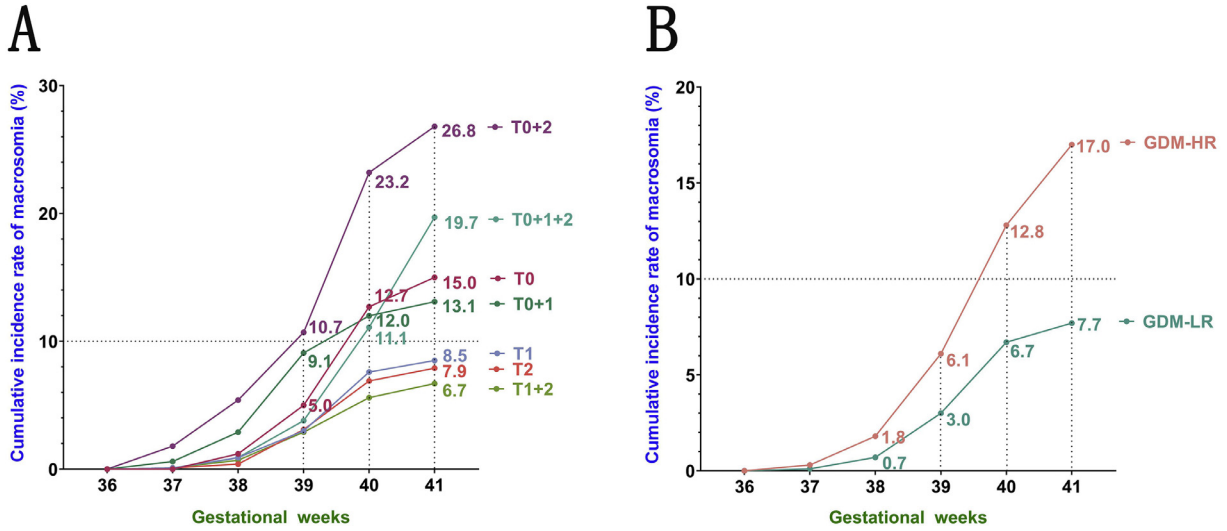
FIGURE 8
As gestational weeks increase, the cumulative incidence rate of macrosomia corresponding to the two classification methods of GDM



The threshold is set at a cumulative incidence rate of macrosomia=10%. (**A**) GDM is classified into 7 subtypes based on their OGTT results. (**B**) GDM is classified into 2 types based on whether FBG elevation is present (GDM-HR and GDM-LR types).

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T1+2). Similarly, in our study, no statistically significant differences were observed in the rate of neonatal hypoglycemia among the seven subgroups during univariate analysis. However, after categorizing into GDM-HR and GDM-LR types, our study found a higher rate of neonatal hypoglycemia in the GDM-HR group, suggesting that this classification method may offer clinical guidance for managing neonatal hypoglycemia.

Moreover, our research highlighted that as gestational weeks at delivery increased, the incidence of macrosomia gradually rises, especially among pregnant women in the GDM-HR group. Through our analysis, we propose for the first time that when considering a cumulative incidence rate of macrosomia not exceeding 10% as a precautionary threshold, induction of labor should be considered for GDM-HR subtype pregnancies between gestational weeks 39^{+0} and 39^{+6}, whereas for GDM-LR subtype pregnancies, induction could be considered between gestational weeks 40^{+0} and 40^{+6}. This conclusion has not been reported in the current literature and provides additional clinical evidence for personalized clinical management of these GDM women, aiming to reduce maternal and neonatal complications.

Finally, our study demonstrated a positive correlation between fetal weight and FBG levels. Moreover, for every 1 mmol/L increase in FBG, fetal birth weight increased by approximately 188 grams. Furthermore, after controlling for potential confounding factors, elevated FBG levels were associated with an increased rate of macrosomia (aOR: 3.29). In a retrospective cohort study involving 3211 singleton GDM pregnancies, Wei et al[23] also came to the same conclusion as ours, that FBG levels are associated with fetal birth weight and the occurrence of macrosomia. This further emphasizes the importance of focusing on FBG in the management of GDM.

Clinical and research implications

Our research indicates that GDM is not a homogeneous condition but should be classified into different subtypes. Firstly, in terms of clinical outcomes, GDM-HR subtype shows poorer maternal and neonatal outcomes compared to GDM-LR subtype. Secondly, in terms of pathophysiology, women with elevated FBG levels (GDM-HR subtype) are more likely to exhibit stable β-cell dysfunction, chronic reduction in β-cell mass, decreased hepatic insulin sensitivity, and a predisposition to type 2 diabetes, while those with impaired glucose tolerance (GDM-LR subtype) are more likely to display decreased peripheral insulin sensitivity, possibly associated with environmental factors such as lack of physical activity and unhealthy diet. Thus, elevated FBG levels likely indicate more severe β-cell dysfunction.[9] Therefore, whether from the perspective of delivery outcomes or pathological mechanisms, GDM should be classified into distinct subtypes. According to OGTT results, based on the presence of elevated FBG levels, GDM can be simply classified into high-risk GDM (GDM-HR subtype) and low-risk GDM (GDM-LR subtype), facilitating personalized management and counseling for GDM patients.

In clinical practice, closer monitoring is required for women with GDM-HR subtype, focusing on blood glucose monitoring, preventing excessive GWG, and paying special attention to the risks of preterm birth and HDP. Additionally, the timing of delivery may need to be earlier than for those with GDM-LR subtype, and greater attention should be given to neonatal hypoglycemia after birth.

After classifying GDM into GDM-HR and GDM-LR types, future research avenues include exploring the pathophysiological mechanisms, genetic and epigenetic factors, tailored lifestyle interventions or treatments for each subtype, and evaluating their long-term maternal and neonatal outcomes. This opens new directions for refining risk assessment, improving clinical management, and deepening our understanding of GDM's heterogeneity.

Strengths and limitations

Our present study provides valuable insights into the relationship between blood glucose levels at different time points of OGTT and adverse prognostic outcomes in GDM. Additionally, we propose for the first time to classify GDM into GDM-HR (with elevated FBG levels) and GDM-LR (without elevated FBG levels) and confirmed that GDM-HR is associated with worse maternal and neonatal outcomes, including macrosomia, LGA, preterm birth, HDP, and neonatal hypoglycemia. We also discussed the differing pathological mechanisms between these two types of GDM subtypes. In terms of clinical guidance, to reduce the risk of macrosomia, we suggest for the first time that induction of labor can be performed at gestational weeks 39^{+0} to 39^{+6} for GDM-HR and at gestational weeks 40^{+0} to 40^{+6} for GDM-LR. Furthermore, we found a positive correlation between elevated FBG levels and increased fetal birth weight and the occurrence of macrosomia, emphasizing the importance of monitoring FBG levels for the clinical management of GDM.

However, our study still has several limitations. Firstly, it is a retrospective study, meaning that we cannot rule out biases introduced during the data collection process. Secondly, this is a single-center study, and the conclusions drawn are more applicable to the Chinese population; further research from multiple centers is needed to confirm our findings. Thirdly, when discussing the optimal timing for induction of labor for GDM-HR and GDM-LR subtypes, we chose a threshold with a cumulative incidence rate of fetal macrosomia <10%. However, the selection of this optimal threshold still requires further exploration through additional research. Fourthly, while this study only proposes subclassifying GDM into GDM-HR and GDM-LR based on the risk values of maternal and neonatal outcomes and only explores recommendations for gestational weeks at delivery and emphasizes the importance of monitoring FBG levels in clinical management, additional research is required to explore subsequent details of management, such as the frequency of blood glucose monitoring, the level of blood glucose control, guidance on diet and exercise, optimal gestational weight gain, and insulin usage.

Conclusions

The proportion of GDM subtypes with elevated FBG (GDM-HR) is relatively low within GDM cases, yet it presents with a higher risk of adverse outcomes compared to subtypes without elevated FBG (GDM-LR), warranting increased attention from obstetricians. Applying this classification method in clinical practice enables better differentiation and individualized management of GDM. ■

CRediT authorship contribution statement

Yongqing Zhang: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Luping Chen:** Investigation, Data curation, Conceptualization. **Yinluan Ouyang:** Software, Data curation, Conceptualization. **Xiaoyan Wang:** Supervision, Resources, Data curation. **Tiantian Fu:** Software, Data curation, Conceptualization. **Guohui Yan:** Methodology, Formal analysis, Data curation, Conceptualization. **Zhaoxia Liang:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Danqing Chen:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization.

Patient Consent Statement

As this was a retrospective study, written informed consents were not obtained, but all patients' records/information were anonymized before analysis. The study was conducted in accordance with the *Declaration of Helsinki* and was approved by Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University *(Ethical NO.: IRB-20240160-R)*.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2024.100390.

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