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Association between the glucose pattern in oral glucose tolerance test and adverse pregnancy outcomes among non-diabetic women

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Abstract

Background This study aimed to explore whether the patterns of the oral glucose tolerance test (OGTT) could function as a predictive factor for adverse pregnancy outcomes in pregnant women without gestational diabetes mellitus (GDM).

Methods A retrospective cohort study was carried out, involving a total of 23,577 pregnant women. The participants were classified into three groups according to the area under the curve (AUC) of the OGTT performed between 24 and 28 weeks of gestation. Based on the tertiles of the AUC-OGTT magnitude, three distinct glucose patterns were identified: small AUC (SA) with an AUC-OGTT ≤ 12.26, medium AUC (MA) with an AUC-OGTT between 12.26 and 13.81, and large AUC (LA) with an AUC-OGTT > 13.81. Logistic regression analysis was utilized to assess the association between different AUC-OGTT patterns and the risk of adverse pregnancy outcomes.

Results The incidence of adverse pregnancy outcomes, including preeclampsia, preterm birth, macrosomia, and cesarean delivery, showed a progressive increase from the SA to the MA to the LA pattern. A positive dose-response relationship was observed between the AUC-OGTT and adverse pregnancy outcomes. In the logistic regression analysis, with the SA pattern as the reference, the MA pattern was associated with a higher risk of macrosomia and cesarean delivery (both $P < 0.001$). Even after adjusting for potential covariates, the relative risks for these outcomes were 1.34 (95% CI: 1.14, 1.56) and 1.09 (95% CI: 1.01, 1.16), respectively (both $P < 0.05$). Additionally, the LA pattern was associated with a higher risk of preeclampsia, preterm birth, macrosomia, and cesarean delivery (all $P < 0.01$). After adjusting for potential covariates, the relative risks for preterm birth, macrosomia, and cesarean delivery were 1.20 (95% CI: 1.03, 1.41), 1.68 (95% CI: 1.44, 1.95), and 1.15 (95% CI: 1.07, 1.23), respectively (all $P < 0.05$). Moreover, these risks differed according to maternal age and preconception body mass index (BMI).

Conclusions The present study highlights the relationship between OGTT patterns and adverse pregnancy outcomes in Chinese women without GDM. Identifying the MA and LA patterns as unfavorable factors for adverse

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pregnancy outcomes can provide crucial information for clinicians to develop personalized risk assessment and intervention strategies, which may contribute to improving pregnancy outcomes.

Keywords Glucose pattern, Oral glucose tolerance test, Adverse pregnancy outcomes, Area under the curve, Risk

Introduction

Gestational diabetes mellitus (GDM) is a globally prevalent medical complication of pregnancy [1], exerting a profound impact on the health of millions of women across the world [2]. It has long been firmly associated with a plethora of obstetric and neonatal complications [3, 4]. The current Chinese guidelines for GDM diagnosis, which are grounded in the IADPSG criteria, advocate performing an oral glucose tolerance test (OGTT) with 75-gram glucose [5]. When OGTT results do not satisfy the GDM diagnostic criteria, these results are classified as within the normal range. Typically, women in this group do not continue to monitor their glucose levels in the later stages of pregnancy. This practice is based on the assumption that normal OGTT results imply a low likelihood of the mother and fetus suffering adverse pregnancy outcomes related to high blood glucose [6]. In China, due to its vast territory and large population, the number of GDM-negative women is considerable [7], which elicits significant concerns. Consequently, the timely identification of high-risk groups for adverse pregnancy outcomes among GDM-negative individuals holds great promise for improving maternal and neonatal prognoses.

Previous research has indicated that an abnormal single glucose value or the number of abnormal results in OGTT may predict the risk of adverse pregnancy outcomes [8–10]. These findings provide crucial insights for risk stratification in high-risk pregnancies. However, during OGTT, it is difficult to identify high-risk individuals solely based on a single-time point glucose value, especially for those who do not meet the GDM diagnostic criteria yet are still at high risk. Single glucose measurements, such as fasting glucose, 1-hour post-load glucose, or 2-hour post-load glucose, only capture the blood glucose level at a specific moment. They may fail to represent the overall glucose metabolism pattern throughout the entire OGTT process. Although the number of abnormal OGTT values can, to some extent, reflect the severity of hyperglycemia, this number-based indicator is rather rough and cannot precisely quantify the degree of hyperglycemia. Compared with the number of abnormal OGTT values, the area under the curve (AUC) might be a more comprehensive and representative indicator of the severity of glucose metabolism abnormalities [11]. The AUC, calculated from the time-glucose curve, represents the average blood glucose level at three timepoints during an OGTT. It serves as an integrated index reflecting the severity of maternal hyperglycemia during the OGTT [12].

Previous studies predominantly focused on type 2 diabetes [13], while relatively little research has been conducted on the characteristics and implications of glucose metabolism patterns, such as AUC-OGTT, during pregnancy. Currently, knowledge regarding the demographic characteristics associated with different AUC-OGTT patterns during pregnancy, the relationship between distinct AUC-OGTT patterns and pregnancy outcomes, and the identification of high-risk populations remains limited. Moreover, there were variations in the size and distribution of the study populations, as well as in the design methods for calculating the AUC [14, 15]. Despite progress in understanding OGTT patterns during pregnancy, the understanding of GDM-negative women remains incomplete. Against this background, this study aims to assess the potential value of measuring AUC-OGTT in identifying adverse pregnancy outcomes among GDM-negative women.

Materials and methods

Study design and subjects

This retrospective cohort study encompassed a total of 40,629 pregnant women who received perinatal care and gave birth between January 2018 and December 2019 at the Women's Hospital, Zhejiang University School of Medicine. The study was approved by the ethics committee of the hospital (approval number: IRB-20240021-R). Given the use of anonymous patient records, exemption from informed consent was granted. However, pregnant women meeting the following criteria were excluded from the study: (1) incomplete or duplicated medical records; (2) incomplete OGTTs; (3) under 18 years of age; (4) multiple pregnancies; (5) gestational weeks at delivery ≤ 28 weeks; (6) abortion or stillbirth; (7) diabetes mellitus or chronic hypertension before pregnancy; (8) autoimmune diseases or malignancies; (9) with fetal chromosomal abnormalities; (10) GDM. During the handling of missing data, in the initial data cleaning phase, cases with incomplete or duplicate medical records, as well as those with incomplete OGTTs, were removed. For the remaining dataset, any record that met the predefined exclusion criteria was entirely excluded from the analysis. After applying these exclusion criteria, 23,577 individuals were included in the final analysis (Fig. 1).

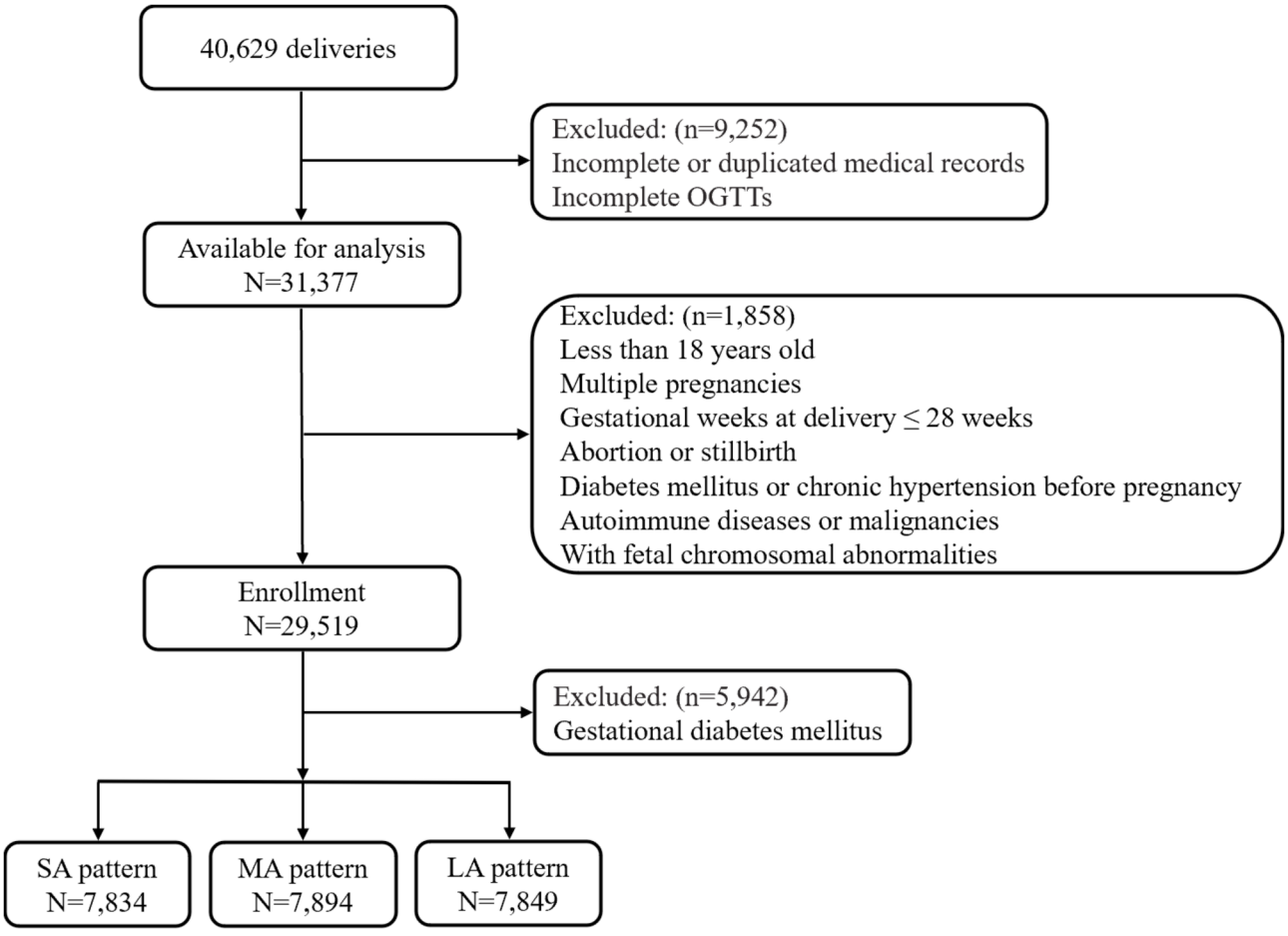

Fig. 1 Flow chart of the study population. The SA, MA, and LA patterns represent three distinct categories based on the area under the curve of OGTT, corresponding to small, medium, and large areas respectively. OGTT, oral glucose tolerance test

Definitions

The small AUC (SA) pattern was defined as an AUC-OGTT ≤ 12.26, which represents the lowest tertile of the total study population. The large AUC (LA) pattern was defined as an AUC-OGTT > 13.82, corresponding to the highest tertile of the total study population. The medium AUC (MA) pattern fell between 12.26 and 13.82.

The AUC of the plasma glucose curve during the OGTT was calculated by summing the areas of two trapezoids. The formula is as follows: (plasma glucose at 0 h + plasma glucose at 1 h) multiplied by 1/2, plus (plasma glucose at 1 h + plasma glucose at 2 h) multiplied by 1/2.

According to the IADPSG guidelines [5], GDM was diagnosed if any of the following values deviated from the normal ranges: fasting plasma glucose (FPG) ≥ 5.1 mmol/L, 1-hour plasma glucose (1 h-PG) ≥ 10.0 mmol/L, or 2-hour plasma glucose (2 h-PG) ≥ 8.5 mmol/L, as determined by a 75-gram glucose OGTT.

Adverse pregnancy outcomes were defined as the occurrence of preeclampsia (characterized by new-onset hypertension and proteinuria or other end-organ damage after 20 weeks of gestation) [16], preterm birth (delivery before 37 weeks of pregnancy) [17], and macrosomia (newborn birth weight ≥ 4000 g) [18].

The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. BMI was classified into underweight, normal-weight, overweight, or obese categories based on values < 18.5, 18.5–23.9, 24.0–28.0, and > 28.0 kg/m^2 respectively [19]. The preconception BMI was determined using the self-reported preconception weight provided by the pregnant women during their OGTT-related antenatal visit and the measured height at our hospital. The height was measured with a standard height-measuring device during this initial antenatal encounter.

Gestational weight gain (GWG) referred to the change in a woman's weight from pre-pregnancy to delivery. It was categorized into three groups: inadequate GWG, adequate GWG, and excessive GWG, according to recommended guidelines. For women with different preconception BMI levels, underweight women were advised to aim for a GWG of 12.5–18.0 kg, normal-weight women

for 11.5–16.0 kg, overweight women for 7.0–11.5 kg, and obese women for 5.0–9.0 kg [20].

OGTT

All study subjects underwent a 75-gram OGTT with venous plasma glucose measurements during outpatient visits between 24 and 28 weeks of gestation. The glucose solution using 75 grams of anhydrous glucose dissolved in 300 mL of water. The subjects were clearly instructed to consume this solution within 5 min. The OGTT was performed following an overnight fast. Subsequently, venous blood samples were systematically collected at 0-hour (fasting), 1-hour, and 2-hour post-glucose ingestion.

Laboratory measurements

In the clinical laboratory department of the hospital, the glucose levels in plasma samples were determined using the hexokinase method on the Architect C16000 chemistry analyzer (Abbott, USA). The instrument underwent daily internal quality control and annual calibration to ensure accurate results. Additionally, the laboratory actively participated in external quality assessments organized by national and provincial clinical laboratories. To maintain test accuracy during internal quality control procedures, the Westgard multi-rule quality control method was employed. All operations strictly adhered to the standard operating procedures for this instrument, with repeatability and within-laboratory coefficient variations maintained at less than 2%.

Statistical analysis

Statistical analyses were performed using IBM SPSS 20.0 (Chicago, USA) for data analysis and GraphPad Prism 8.0 (California, USA) for figure generation. Continuous variables were presented as mean ± standard deviation and compared using an independent sample t-test. Categorical variables were expressed as proportions (%) and compared using the chi-square test. Furthermore, to explore the association between the AUC-OGTT and the risk of adverse pregnancy outcomes, we evaluated the nonlinearity of the dose-response curve. Three cut-off points were defined: at the ≤ 33.3rd percentile (≤ 12.26), between the 33.3rd and 66.7th percentiles (12.26–13.81), and at the > 66.7th percentile (> 13.81), with the AUC-OGTT value at the ≤ 33.3rd percentile (≤ 12.26) serving as the reference. Logistic regression analyses were conducted to determine the relative risks (RRs) and 95% confidence intervals (CIs) for each model, both in the unadjusted and adjusted scenarios for potential covariates. The potential covariates included maternal age, preconception BMI, ethnicity, smoking history, drinking history, education, gestational weight gain, gravidity, parity, in-vitro fertilization (IVF) status, history of abortion, and history of preterm birth. A significance level of $P < 0.05$ was considered statistically significant.

Results

Features of three AUC-OGTT patterns

The final analysis incorporated 23,577 individuals, including 7,834 cases with SA pattern, 7,894 with MA pattern, and 7,849 cases with LA pattern. The LA pattern, accounting for 33.29% of the participants, was characterized by the highest plasma glucose levels. Medium plasma glucose levels were observed in 33.48% of the participants with the MA pattern. In contrast, the remaining group with the SA pattern, which made up 33.23% of the participants, exhibited the lowest plasma glucose levels. Figure 2 illustrated the average AUC-OGTT sizes for the three groups.

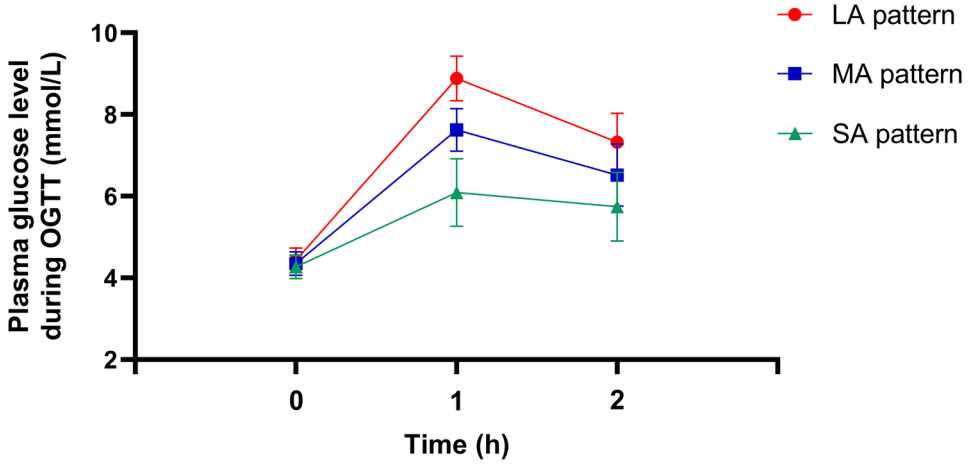

Fig. 2 Participants with different AUC patterns of OGTT during 24–28 weeks of gestation. The SA, MA, and LA patterns represent three distinct categories based on the area under the curve of OGTT, corresponding to small, medium, and large areas respectively

Baseline characteristics of three AUC-OGTT patterns

Maternal age demonstrated a gradual increase from the SA to the MA and the LA pattern. The mean ages were 29.9 years, 30.8 years, and 31.6 years, respectively. The differences between the MA and SA patterns and between the LA and SA patterns were highly significant (both $P<0.001$). Similarly, preconception BMI also showed an increasing trend. The mean preconception BMIs were 20.2 kg/m^2, 20.7 kg/m^2, and 21.0 kg/m^2, respectively, with highly significant differences for both comparisons ($P<0.001$).

Regarding lifestyle-related factors, there were no notable differences in ethnicity, smoking history, and drinking history across the groups. In terms of educational attainment, there was no significant difference between the SA and MA groups ($P>0.05$). However, a highly significant difference was observed between the LA and SA patterns ($P<0.001$).

Gestational weight gain varied among the groups. There was no significant difference between the SA and MA groups ($P>0.05$), but a significant difference was found between the LA and SA patterns ($P<0.001$). Gravidity, parity, the proportion of IVF cases, and the history of abortion all demonstrated highly significant differences (all $P<0.001$) when comparing the MA and LA patterns with the SA pattern. There was no significant variation in the history of preterm birth among the groups (both $P>0.05$).

Concerning the OGTT results, fasting plasma glucose (FPG), 1-hour plasma glucose (1 h-PG), and 2-hour plasma glucose (2 h-PG) levels all increased significantly from the SA pattern to the MA and the LA patterns. All comparisons yielded highly significant results (all $P<0.001$) (Table 1).

Maternal and neonatal outcomes of different AUC-OGTT patterns

The mean gestational ages were 39.3 weeks, 39.2 weeks, and 39.1 weeks for the SA, the MA, and the LA pattern, respectively. Highly significant differences were observed when comparing the MA and LA patterns with the SA pattern (both $P<0.001$). Conversely, birth weight presented an upward trend. The mean birth weights were 3,283 g, 3,311 g, and 3,344 g for the SA, the MA, and the LA patterns, respectively. The differences in birth weight for both comparisons were highly significant (both $P<0.001$) (Table 2).

Relative to the SA pattern, the MA pattern showed a significantly higher incidence of macrosomia and caesarean delivery (both $P<0.001$). However, there was no statistically significant difference between the two patterns in terms of the incidence of preeclampsia and preterm birth (both $P>0.05$). Compared to the SA pattern, the LA pattern had higher incidences of preeclampsia, preterm birth, macrosomia, and cesarean delivery (all $P<0.001$) (Fig. 3). Moreover, the Supplementary Fig. 1 illustrated the dose-response relationship between the AUC-OGTT and adverse pregnancy outcomes. The results indicated a positive dose-response relationship between the AUC-OGTT and preeclampsia, preterm birth, macrosomia, and cesarean delivery across the entire study population.

The risks of adverse pregnant outcomes with three different AUC-OGTT patterns

The risks of preeclampsia, preterm birth, macrosomia, and cesarean delivery were evaluated among individuals with three different AUC-OGTT patterns, with the SA pattern serving as the reference group. Regression analysis was employed to assess these risks (Table 3). In the unadjusted crude model, individuals with an MA pattern exhibited an elevated risk of macrosomia [1.41 (1.21, 1.64), $P<0.001$] and cesarean delivery [1.22 (1.15, 1.31), $P<0.001$]. Nevertheless, no significant associations were observed between the MA pattern and preeclampsia [1.27 (0.97, 1.66), $P>0.05$], nor with preterm birth [1.12 (0.96, 1.31), $P>0.05$]. Conversely, those with an LA pattern faced a heightened risk of all four adverse pregnancy outcomes: preeclampsia [1.61 (1.25, 2.08), $P<0.001$], preterm birth [1.28 (1.10, 1.48), $P<0.01$], macrosomia [1.87 (1.62, 2.16), $P<0.001$], and cesarean delivery [1.41 (1.32, 1.50), $P<0.001$]. Even after adjusting for fundamental characteristics including maternal age, preconception BMI, ethnicity, smoking history, drinking history, education, gestational weight gain, gravidity, parity, IVF status, history of abortion, and history of preterm birth, the increased risks associated with the MA pattern persisted. Specifically, individuals with an MA pattern still had a higher risk of macrosomia [1.34 (1.14, 1.56), $P<0.001$] and cesarean delivery [1.09 (1.01, 1.16), $P<0.05$], while maintaining no significant associations with preeclampsia [1.17 (0.89, 1.54), $P>0.05$] and preterm birth [1.10 (0.94, 1.28), $P>0.05$]. Following these adjustments, individuals with an LA pattern continued to have an elevated risk of three adverse pregnancy outcomes: preterm birth [1.20 (1.03, 1.41), $P<0.05$], macrosomia [1.68 (1.44, 1.95), $P<0.001$], and cesarean delivery [1.15 (1.07, 1.23), $P<0.01$]. However, there was no significant association with preeclampsia [1.29 (0.99, 1.68), $P>0.05$].

Association between AUC-OGTT patterns and adverse outcomes in different maternal age groups

The risk of adverse pregnancy outcomes was evaluated among individuals with different AUC-OGTT patterns across various maternal age groups, with the SA pattern serving as the reference group (Table 4). Among women younger than 30 years old, compared with the SA pattern, the MA and LA patterns presented non-significant trends of an increased risk of preeclampsia, preterm

Table 1 Baseline characteristics of the participants with different AUC-OGTT patterns during 24–28 weeks of gestation

Variables	SA pattern	MA pattern	LA pattern	*P*-value [a]	*P*-value [b]
N (number)	7,834	7,894	7,849		
Maternal age (years)	29.9 ± 4.0	30.8 ± 4.1	31.6 ± 4.2	< 0.001	< 0.001
< 30	3,951 (50.43)	3,287 (41.64)	2,796 (35.62)		
30–34	2,831 (36.14)	3,087 (39.11)	3,093 (39.41)		
≥ 35	1,052 (13.43)	1,520 (19.25)	1,960 (24.97)		
Preconception BMI (kg/m^2)	20.2 ± 2.4	20.7 ± 2.6	21.0 ± 2.7	< 0.001	< 0.001
Underweight	1,932 (24.66)	1,541 (19.52)	1,257 (16.01)		
Normal-weight	5,390 (68.80)	5,513 (69.84)	5,584 (71.15)		
Overweight and obese	512 (6.54)	840 (10.64)	1008 (12.84)		
Han ethnic group (n, %)	7,799 (99.55)	7,856 (99.52)	7,821 (99.64)	0.750	0.373
Smoking history (n, %)				0.359	0.205
Yes	7 (0.09)	4 (0.05)	3 (0.04)		
No	7,827 (99.91)	7,890 (99.95)	7,846 (99.96)		
Drinking history (n, %)				0.314	0.316
Yes	3 (0.04)	1 (0.01)	1 (0.01)		
No	7,831 (99.96)	7,893 (99.99)	7,848 (99.99)		
Education (n, %)				0.053	< 0.001
Primary or below	24 (0.31)	28 (0.35)	24 (0.30)		
Middle school	1,111 (14.18)	1,017 (12.88)	940 (11.98)		
College or above	6,699 (85.51)	6,849 (86.77)	6,885 (87.72)		
Gestational weight gain (kg)	14.4 ± 4.4	14.3 ± 4.3	14.1 ± 4.2	0.088	< 0.001
Adequate	3,591 (45.84)	3,594 (45.53)	3,605 (45.93)		
Inadequate	1,907 (24.34)	1,911 (24.21)	1,860 (23.70)		
Excess	2,336 (29.82)	2,389 (30.26)	2,384 (30.37)		
Gravidity (n, %)				< 0.001	< 0.001
0	3,576 (45.65)	3,293 (41.72)	3,004 (38.27)		
1	2,304 (29.41)	2,404 (30.45)	2,455 (31.28)		
≥ 2	1,954 (24.94)	2,197 (27.83)	2,390 (30.45)		
Parity (n, %)				< 0.001	< 0.001
Nullipara	5,171 (66.01)	4,893 (61.98)	4,590 (58.48)		
Multipara	2,663 (33.99)	3,001 (38.02)	3,259 (41.52)		
IVF (n, %)	236 (3.01)	348 (4.41)	405 (5.16)	< 0.001	< 0.001
History of abortion (n, %)				< 0.001	< 0.001
0	4,779 (61.00)	4,607 (58.36)	4,382 (55.83)		
1	2,004 (25.58)	2,072 (26.25)	2,192 (27.93)		
≥ 2	1,051 (13.42)	1,215 (15.39)	1,275 (16.24)		
History of preterm birth (n, %)				0.585	0.261
Yes	132 (1.68)	142 (1.80)	151 (1.92)		
No	7,702 (98.32)	7,752 (98.20)	7,698 (98.08)		
OGTT (mmol/L)					
FPG	4.27 ± 0.29	4.35 ± 0.29	4.43 ± 0.30	< 0.001	< 0.001
1 h-PG	6.07 ± 0.83	7.61 ± 0.52	8.88 ± 0.55	< 0.001	< 0.001
2 h-PG	5.74 ± 0.84	6.52 ± 0.76	7.32 ± 0.71	< 0.001	< 0.001

Continuous variables were presented as mean ± standard deviation and compared using the independent sample t-test. Categorical variables were expressed as proportions (%) and compared using the chi-square test. The SA, MA, and LA patterns represent three distinct categories based on the AUC of OGTT, corresponding to small, medium, and large areas respectively

P-value [a], MA pattern vs. SA pattern; *P*-value [b], LA pattern vs. SA pattern

AUC, area under the curve; OGTT, oral glucose tolerance test; BMI: body mass index; IVF, in vitro fertilization; FPG: fasting plasma glucose; 1 h-PG, 1-hour plasma glucose; 2 h-PG, 2-hour plasma glucose

birth, and cesarean delivery (all $P > 0.05$). Nevertheless, both the MA pattern [1.42 (1.13, 1.78), $P < 0.01$] and the LA pattern [1.60 (1.26, 2.01), $P < 0.001$] had a significantly higher risk of macrosomia. In 30-34-year-old women, neither the MA nor the LA pattern was significantly associated with preeclampsia (both $P > 0.05$). However, the LA pattern significantly increased the risk of preterm birth [1.33 (1.04, 1.71), $P < 0.05$]. The risks of

Table 2 Pregnancy delivery and neonatal outcomes with different AUC-OGTT patterns during 24–28 weeks of gestation

Variables	SA Pattern (*n* = 7,834)	MA pattern (*n* = 7,894)	LA pattern (*n* = 7,849)	*P*-value [a]	*P*-value [b]
Preeclampsia (n, %)	98 (1.25)	125 (1.58)	157 (2.00)	0.078	< 0.001
Gestational age (weeks)	39.3 ± 1.4	39.2 ± 1.5	39.1 ± 1.5	< 0.001	< 0.001
Preterm birth (n, %)	321 (4.10)	361 (4.57)	406 (5.17)	0.143	0.001
Birth weight (g)	3,283 ± 415	3,311 ± 431	3,344 ± 460	< 0.001	< 0.001
Macrosomia (n, %)	297 (3.79)	416 (5.27)	538 (6.85)	< 0.001	< 0.001
Caesarean delivery (n, %)	2,585 (33.00)	2,966 (37.57)	3,216 (40.97)	< 0.001	< 0.001

Continuous variables were presented as mean ± standard deviation and compared using the independent sample t-test. Categorical variables were expressed as proportions (%) and compared using the chi-square test. The SA, MA, and LA patterns represent three distinct categories based on the AUC of OGTT, corresponding to small, medium, and large areas respectively

P-value [a], MA pattern vs. SA pattern; *P*-value [b], LA pattern vs. SA pattern

AUC, area under the curve; OGTT, oral glucose tolerance test

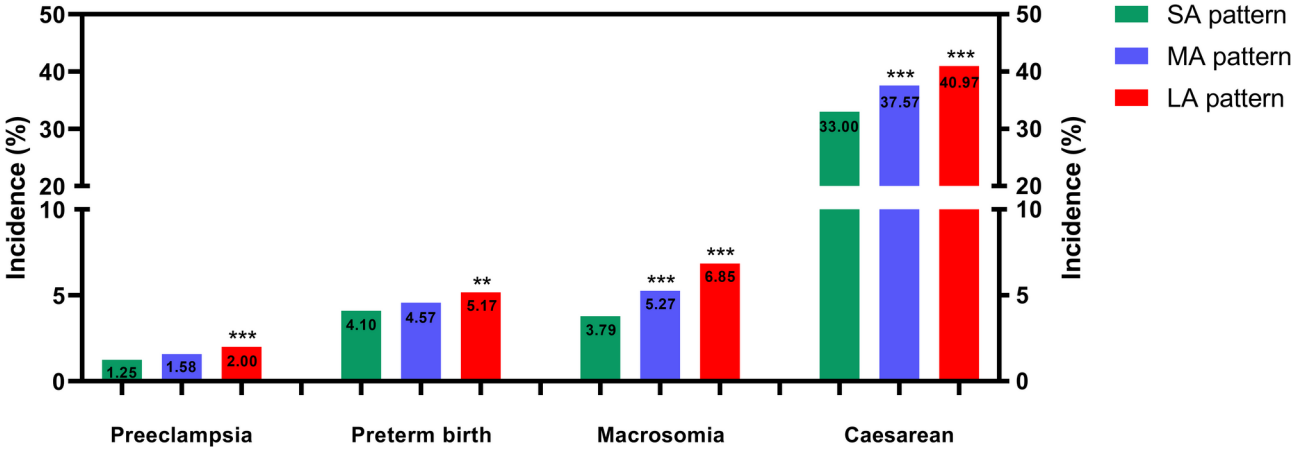

Fig. 3 The incidence of adverse pregnancy outcomes. The SA, MA, and LA patterns represent three distinct categories based on the area under the curve of OGTT, corresponding to small, medium, and large areas respectively. $^{**}P < 0.01$; $^{***}P < 0.001$. *P*-values were calculated using the chi-square test and compared against the SA pattern

Table 3 Relative risks and 95% CIs for adverse pregnant outcomes with different AUC-OGTT patterns during 24–28 weeks of gestation

Outcomes	*N* (%)	Relative risks (95% CI)			
		Crude [a]	*P*-value	Adjusted [b]	*P*-value
Preeclampsia					
SA pattern	98 (1.25)	Reference		Reference	
MA pattern	125 (1.58)	1.27 (0.97, 1.66)	0.078	1.17 (0.89, 1.54)	0.262
LA pattern	157 (2.00)	1.61 (1.25, 2.08)	< 0.001	1.29 (0.99, 1.68)	0.061
Preterm birth					
SA pattern	321 (4.10)	Reference		Reference	
MA pattern	361 (4.57)	1.12 (0.96, 1.31)	0.143	1.10 (0.94, 1.28)	0.250
LA pattern	406 (5.17)	1.28 (1.10, 1.48)	0.001	1.20 (1.03, 1.41)	0.020
Macrosomia					
SA pattern	297 (3.79)	Reference		Reference	
MA pattern	416 (5.27)	1.41 (1.21, 1.64)	< 0.001	1.34 (1.14, 1.56)	< 0.001
LA pattern	538 (6.85)	1.87 (1.62, 2.16)	< 0.001	1.68 (1.44, 1.95)	< 0.001
Caesarean					
SA pattern	2,585 (33.00)	Reference		Reference	
MA pattern	2,966 (37.57)	1.22 (1.15, 1.31)	< 0.001	1.09 (1.01, 1.16)	0.018
LA pattern	3,216 (40.97)	1.41 (1.32, 1.50)	< 0.001	1.15 (1.07, 1.23)	0.002

[a] unadjusted; [b] adjusted for maternal age, preconception BMI, ethnicity, smoking history, drinking history, education, gestational weight gain, gravidity, parity, IVF, history of abortion, and history of preterm birth. The SA, MA, and LA patterns represent three distinct categories based on the AUC of OGTT, corresponding to small, medium, and large areas respectively. Relative risks and 95% CIs were calculated using the logistic regression analyses and compared against the SA pattern

CI, confidence interval; AUC, area under the curve; OGTT, oral glucose tolerance test

Table 4 Association between AUC-OGTT patterns and adverse pregnancy outcomes in different maternal age groups

Maternal age	SA pattern (*n* = 7,834)	MA pattern (*n* = 7,894)	*P*-value	LA pattern (*n* = 7,849)	*P*-value
< 30 years (*n* = 10,034)					
Preeclampsia	Reference	1.40 (0.95, 2.05)	0.089	1.40 (0.94, 2.08)	0.100
Preterm birth	Reference	1.05 (0.82, 1.34)	0.699	1.07 (0.83, 1.39)	0.601
Macrosomia	Reference	1.42 (1.13, 1.78)	0.003	1.60 (1.26, 2.01)	< 0.001
Caesarean	Reference	1.09 (0.98, 1.22)	0.107	1.12 (1.00, 1.25)	0.059
30–34 years (*n* = 9,011)					
Preeclampsia	Reference	1.10 (0.69, 1.75)	0.697	1.18 (0.74, 1.86)	0.491
Preterm birth	Reference	1.10 (0.85, 1.42)	0.481	1.33 (1.04, 1.71)	0.023
Macrosomia	Reference	1.37 (1.06, 1.78)	0.016	1.75 (1.36, 2.24)	< 0.001
Caesarean	Reference	1.08 (0.97, 1.21)	0.146	1.12 (1.01, 1.26)	0.037
≥ 35 years (*n* = 4,532)					
Preeclampsia	Reference	0.75 (0.38, 1.48)	0.748	1.37 (0.76, 2.46)	0.297
Preterm birth	Reference	1.18 (0.83, 1.68)	0.358	1.21 (0.86, 1.70)	0.274
Macrosomia	Reference	1.07 (0.73, 1.57)	0.748	1.81 (1.28, 2.57)	0.001
Caesarean	Reference	1.03 (0.88, 1.21)	0.728	1.12 (0.96, 1.31)	0.153

Values are reported as relative risks (95% CIs), and the relative risks were adjusted for maternal age, preconception BMI, ethnicity, smoking history, drinking history, education, gestational weight gain, gravidity, parity, IVF, history of abortion, and history of preterm birth. The SA, MA, and LA patterns represent three distinct categories based on the AUC of OGTT, corresponding to small, medium, and large areas respectively

AUC, area under the curve; OGTT, oral glucose tolerance test; CI, confidence interval; BMI: body mass index; IVF, in vitro fertilization

Table 5 Association between AUC-OGTT patterns and adverse pregnancy outcomes in different preconception BMI groups

Preconception BMI	SA pattern (*n* = 7,834)	MA pattern (*n* = 7,894)	*P*-value	LA pattern (*n* = 7,849)	*P*-value
Normal-weight (*n* = 16,487)					
Preeclampsia	Reference	1.09 (0.78, 1.51)	0.620	1.09 (0.79, 1.51)	0.614
Preterm birth	Reference	1.09 (0.90, 1.31)	0.393	1.12 (0.93, 1.35)	0.232
Macrosomia	Reference	1.37 (1.14, 1.65)	0.001	1.67 (1.39, 1.99)	< 0.001
Caesarean	Reference	1.05 (0.97, 1.14)	0.256	1.13 (1.04, 1.23)	0.004
Underweight (*n* = 4,730)					
Preeclampsia	Reference	3.25 (1.33, 7.96)	0.010	2.65 (1.03, 6.80)	0.043
Preterm birth	Reference	1.04 (0.74, 1.47)	0.816	1.32 (0.92, 1.87)	0.128
Macrosomia	Reference	1.77 (1.17, 2.70)	0.008	1.80 (1.16, 2.78)	0.008
Caesarean	Reference	1.08 (0.93, 1.26)	0.306	1.03 (0.88, 1.22)	0.716
Overweight and Obese (*n* = 2,360)					
Preeclampsia	Reference	0.78 (0.42, 1.45)	0.434	1.49 (0.86, 2.58)	0.153
Preterm birth	Reference	1.22 (0.68, 2.19)	0.505	1.69 (0.97, 2.94)	0.062
Macrosomia	Reference	0.91 (0.59, 1.38)	0.644	1.66 (1.13, 2.44)	0.011
Caesarean	Reference	1.24 (0.99, 1.56)	0.066	1.20 (0.96, 1.51)	0.113

Values are reported as relative risks (95% CIs), and the relative risks were adjusted for maternal age, preconception BMI, ethnicity, smoking history, drinking history, education, gestational weight gain, gravidity, parity, IVF, history of abortion, and history of preterm birth. The SA, MA, and LA patterns represent three distinct categories based on the AUC of OGTT, corresponding to small, medium, and large areas respectively

AUC, area under the curve; OGTT, oral glucose tolerance test; BMI: body mass index; CI, confidence interval; IVF, in vitro fertilization

macrosomia were elevated in both the MA pattern [1.37 (1.06, 1.78), $P < 0.05$] and the LA pattern [1.75 (1.36, 2.24), $P < 0.001$]. Additionally, the LA pattern significantly increased the risk of cesarean delivery [1.12 (1.01, 1.26), $P < 0.05$]. Among mothers 35 years old or older, neither the MA nor the LA pattern was significantly associated with preeclampsia, preterm birth, or cesarean delivery (all $P > 0.05$). However, the LA pattern had a significantly higher risk of macrosomia [1.81 (1.28, 2.57), $P < 0.01$], while the MA pattern did not ($P > 0.05$).

Association between AUC-OGTT patterns and adverse outcomes in different preconception BMI groups

The risk of adverse pregnancy outcomes was evaluated among individuals with different AUC-OGTT patterns across distinct preconception BMI groups, with the SA pattern designated as the reference group (Table 5). In the normal-weight group, neither the MA nor the LA pattern exhibited a significant association with preeclampsia and preterm birth (all $P > 0.05$). Nevertheless, the risk of macrosomia was significantly elevated in both

the MA [1.37 (1.14, 1.65), $P<0.01$] and LA pattern [1.67 (1.39, 1.99), $P<0.001$]. Moreover, the LA pattern significantly increased the risk of cesarean delivery [1.13 (1.04, 1.23), $P<0.01$], while the MA pattern did not show such a significant increase ($P>0.05$). Among underweight women, both the MA [3.25 (1.33, 7.96), $P<0.05$] and LA pattern [2.65 (1.03, 6.80), $P<0.05$] were significantly associated with an augmented risk of preeclampsia. However, there was no significant association between these patterns and preterm birth or cesarean delivery (all $P>0.05$). The risks of macrosomia were significantly higher for both the MA [1.77 (1.17, 2.70), $P<0.01$] and LA pattern [1.80 (1.16, 2.78), $P<0.01$]. In the overweight and obese group, neither the MA nor the LA pattern was significantly associated with preeclampsia, preterm birth, or cesarean delivery (all $P>0.05$). Notably, the LA pattern had a significantly higher risk of macrosomia [1.66 (1.13, 2.44), $P<0.05$], whereas the MA pattern did not present a significant risk increase ($P>0.05$).

Discussion

The primary aim of this study was to evaluate the characteristics of pregnant women presenting with different OGTT-derived AUC sizes and to explore the potential associations between these AUC sizes and adverse pregnancy outcomes in GDM-negative women. A total of 23,577 pregnant women were enrolled in this investigation. Based on our results, we identified three distinct glucose patterns (SA, MA, and LA pattern) within normal OGTT results at 24–28 weeks of gestation, categorized according to AUC sizes. These patterns exhibited statistically significant differences in demographic and obstetric characteristics. Maternal age and preconception BMI showed a progressive increase from the SA to the MA to the LA pattern, with highly significant differences (both $P<0.001$). Furthermore, our research indicated that as the AUC-OGTT increased, the incidences of preeclampsia, preterm birth, macrosomia, and cesarean delivery also rose. Our findings, based on a large sample size, confirm a significant positive association and dose-response relationship between the AUC-OGTT and the incidence of these adverse pregnancy outcomes. Logistic regression analysis, using the SA pattern as the reference, revealed that after adjusting for multiple confounding factors, including maternal age, preconception BMI, ethnicity, smoking history, drinking history, education, gestational weight gain, gravidity, parity, IVF status, history of abortion, and history of preterm birth, the MA pattern was associated with an elevated risk of macrosomia and cesarean delivery (both $P<0.05$). Similarly, the LA pattern was associated with preterm birth, macrosomia, and cesarean delivery (all $P<0.05$) after accounting for these confounding factors. These findings emphasize the importance of considering the AUC value when comprehensively interpreting OGTT results. Incorporating the AUC can significantly improve the prediction of adverse pregnancy outcomes in GDM-negative pregnant women, highlighting the need for intensive intervention during pregnancy to mitigate these risks.

Adverse pregnancy outcomes remain a major concern in the context of GDM. The growing prevalence of GDM and its associated adverse pregnancy outcomes has imposed substantial socio-economic and health burdens at both the population and individual levels. Over the past few decades, the incidence of GDM has experienced a remarkable increase, emerging as a serious global health issue [21]. Although healthcare providers can manage GDM complications effectively through personalized treatment plans, including dietary control, regular exercise, and insulin intervention, there is a tendency to overlook GDM-negative women. Given that China's seventh national population census reported over 300 million women of childbearing age, the majority of whom are GDM-negative pregnant women, failure to recognize hyperglycemia in this group can pose significant risks for adverse pregnancy outcomes. Findings from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study indicated that the risk of adverse pregnancy outcomes increased with maternal blood glucose levels [22]. Significantly, these risks are also elevated in women with OGTT blood glucose levels below the GDM diagnostic thresholds [6]. Thus, identifying high-risk GDM-negative women has significant clinical value, as appropriate management can improve maternal and fetal outcomes.

Previous research has established associations between abnormal OGTT values and adverse pregnancy outcomes [8, 23–26]. However, during OGTT, it is difficult to identify high-risk individuals based solely on a single-time-point glucose value, especially for those who do not meet the GDM diagnostic criteria yet are still at risk. The number of abnormal OGTT values can reflect the severity of hyperglycemia to some extent, but it is a qualitative measure that cannot precisely quantify the degree of hyperglycemia. In contrast, the AUC-OGTT may be a more comprehensive and representative indicator of glucose metabolism abnormalities [11, 12]. Developed to quantify total glucose exposure after OGTT, it is mainly used in diabetes patients [13]. Currently, research on glucose patterns during pregnancy OGTT is limited. Our study focuses on the glucose patterns of normal OGTT values during pregnancy. Fasting blood glucose reflects glucose metabolism under baseline conditions, often associated with steady-state β-cell dysfunction and low β-cell mass [6]. Conversely, 1- and 2- hour glucose levels measure post-glucose-load metabolism and are more closely related to environmental factors like physical activity and diet [27, 28]. In our study, significant differences were observed in FBG, 1-hour, and 2-hour glucose

levels among the three patterns. This indicates disparities in β-cell function and environmental factors among the patterns. Thus, relying solely on a single abnormal blood glucose value for assessment is insufficient. Evaluating the entire glucose excursion provides more comprehensive information on glucose tolerance. Several prior studies have explored the correlation between different AUC-OGTTs and pregnancy outcomes. For instance, Kim et al. [29] found that an elevated AUC-OGTT in the OGTT was associated with an increased risk of large-for-gestational-age infants in GDM cases. Another study demonstrated that a higher AUC in the OGTT was linked to adverse pregnancy outcomes such as hypertensive disease and macrosomia among all pregnant women [14]. Kim et al. [12]. further supported these findings, suggesting that the AUCs of the OGTT curves can also distinguish patients at risk of adverse pregnancy outcomes across all pregnant women: generally, a larger AUC corresponds to a higher risk. However, it is important to note that the authors discussed composite adverse pregnancy outcomes collectively without performing separate analyses. Another study [15] indicated that participants with a high-glucose pattern in normal OGTT during 24–28 gestational weeks were more likely to develop late-onset GDM and had an increased risk of other adverse pregnancy outcomes, like cesarean delivery, macrosomia, preterm birth, and large-for-gestational-age infants. This aligns with our results, but their AUC calculation was complex, limiting clinical application. Similarly, Kim et al.. adopted the AUC of 100-gram OGTT as a quantitative method of GDM [29], yet their formula was complex and not easily applicable in clinical practice. Although pregnant women with any OGTT indicator above the critical value are diagnosed with GDM and receive interventions like diet control, exercise, and insulin, our research highlights the need to pay special attention to pregnant women with MA and LA patterns. These women have relatively high blood glucose levels at all time points despite normal OGTT results. Moreover, 13.5–18.3% of OGTT-negative pregnant women develop GDM in the third trimester [15]. Delayed diagnosis may cause them to miss management and intervention opportunities. Therefore, these women should monitor their blood glucose levels 24–28 weeks after OGTT and adjust their diet and exercise to prevent late-onset GDM and adverse pregnancy outcomes.

The relationship between hyperglycemia and adverse pregnancy outcomes has been firmly established [30]. The HAPO multicenter study demonstrated a significant correlation between hyperglycemia and various negative birth outcomes [31]. Extensive research has been carried out to explore the potential mechanisms underlying the link between hyperglycemia and adverse pregnancy outcomes. Strong evidence shows a positive linear correlation between maternal glucose concentrations and neonatal birth weight [32]. When mothers have hyperglycemia, it causes fetal β-cell hyperplasia and boosts the endogenous production of insulin and insulin-like growth factor (IGF) 1 [33], which stimulate growth-promoting pathways in developing muscles, connective tissues, and adipose tissue [34]. Consistent with this, our results show that as the AUC increases, fetal birth weight rises, and the likelihood of macrosomia also increases. Simultaneously, maternal hyperglycemia also disrupts placental blood vessel development and function. It damages vascular endothelial cells, constricting blood vessels and reducing blood flow, thus limiting oxygen and nutrient supply to the fetus [35]. Additionally, hyperglycemia activates the body's inflammatory response. Inflammatory factors affect uterine smooth muscle stability, increasing the risk of preterm birth. They can also compromise fetal membrane integrity, raising the risk of premature rupture of membranes [36]. Hyperglycemia further increases oxidative stress, which impacts the uterine environment and stimulates uterine contractions, also contributing to preterm birth [2]. Our data show that as the AUC increases, gestational age shortens, and the incidence of preterm birth rises, reflecting these mechanisms. Hyperglycemia and insulin resistance are intertwined, forming a vicious cycle. Insulin resistance is a crucial factor in pregnancy-related metabolic dysfunction. It promotes endothelial dysfunction, oxidative stress, and systemic inflammation, which are key in the development of gestational hypertension diseases [37]. In line with this, our research shows that as the AUC increases, infant birth weight, the risk of macrosomia, and the incidence of preeclampsia all increase, potentially leading to a higher cesarean section rate. These factors may partly explain the elevated risk of adverse pregnancy outcomes in participants with MA and LA patterns during pregnancy. Given the potential link between AUC-OGTT and adverse pregnancy outcomes, along with the limited research in this area, our study enriches this field. Since many individuals with MA or LA patterns are at a higher risk of adverse pregnancy outcomes, it is both interesting and clinically valuable to investigate whether interventions like lifestyle changes or insulin therapy can modify the OGTT pattern, with the aim of reversing or preventing adverse pregnancy outcomes.

In addition to the overall relationship between AUC-OGTT and adverse pregnancy outcomes, it is also essential to explore how these associations vary among different subgroups. To date, numerous risk factors, such as maternal age and preconception BMI, have been linked to adverse pregnancy outcomes [38, 39]. Integrating OGTT patterns with these well-established risk factors can help identify pregnant women at high risk of adverse pregnancy outcomes at an early stage. This

enables timely intervention to safeguard maternal and infant health. Therefore, we performed a stratified analysis based on maternal age and preconception BMI. In our subgroup analysis by maternal age, no statistically significant graded association between AUC sizes and preeclampsia was found. However, after controlling for confounding variables, our results showed that regardless of maternal age, the risk of macrosomia was significantly higher in the LA pattern group compared to the SA pattern group. Similarly, when adjusting for confounding factors, the risk of macrosomia was significantly higher in the LA pattern group than in the SA pattern group, regardless of maternal BMI status. Interestingly, in the low BMI group, the risks of preeclampsia in the MA and LA groups were higher than in the SA group, even after adjusting for various factors. This was not observed in other groups. Potential explanations include that underweight pregnant women often have multiple micronutrient deficiencies. Maintaining appropriate levels of these nutrients during pregnancy can reduce the risk of complications like hypertension, preeclampsia, and low birth weight [40–42]. Additionally, underweight status may be associated with abnormal hormonal profiles, particularly disruptions in the IGF axis. Reduced IGF-1 levels can increase the risk of adverse outcomes [43]. Although being underweight has the potential to trigger adverse pregnancy outcomes, the risks related to high blood glucose are likely to exceed those associated with underweight. Overall, the impact of AUC-OGTT patterns on adverse pregnancy outcomes varies across different maternal age and preconception BMI groups. This suggests that maternal age and preconception BMI are important factors influencing the relationship between AUC-OGTT patterns and adverse pregnancy outcomes. Thus, when assessing pregnancy risks, it is essential to consider maternal age, preconception BMI, and AUC-OGTT patterns comprehensively for more accurate prediction and management of adverse pregnancy outcomes.

These subgroup analysis results not only deepen our understanding of the complex relationship between AUC-OGTT patterns and adverse pregnancy outcomes, but also have important implications for clinical practice. Clinicians can use our findings to identify pregnant women at higher risk of adverse pregnancy outcomes, even among those without GDM. This information can help clinicians prioritize patients for more intensive monitoring. By combining AUC-OGTT patterns with other clinical factors such as maternal age, preconception BMI, clinicians can create more personalized risk profiles for each patient. This individualized approach allows for more targeted prenatal care. For women with MA or LA patterns, clinicians can recommend early diet and lifestyle interventions. Implementing these interventions early may reduce the risk of adverse outcomes. Intervention strategies may include dietitian-supervised pregnancy management, regular blood glucose monitoring, healthy eating, using supplements to lower blood glucose, and consuming functional foods for glucose regulation. Clinicians can also use our findings to educate patients about the significance of their glucose metabolism during pregnancy.

In addition to its clinical utility, the use of AUC-OGTT is cost-effective. Calculating the AUC-OGTT is a simple mathematical operation based on existing glucose values. There is no need for additional blood draws, laboratory tests, or specialized equipment solely for this purpose. Early detection of high-risk women through AUC-OGTT analysis facilitates the implementation of appropriate interventions. These early-stage interventions can effectively lower the probability of adverse pregnancy outcomes. Avoiding such adverse outcomes has far-reaching economic ramifications. It contributes to improving the long-term health of both the mother and the child, which is crucial for their well-being and can also lead to a reduction in future healthcare costs.

However, the use of AUC-OGTT has certain limitations. Although calculating the AUC values is easy in highly informatized laboratories, there are several issues. Test protocols can vary: different clinical guidelines may recommend different glucose loads, such as 75-gram or 100-gram glucose solutions. The number and timing of blood samples during the OGTT also vary. Standard OGTTs usually involve sampling at fasting, 1- hour, and 2- hour intervals after glucose ingestion, but some protocols deviate from this standard, which can impact the calculated AUC-OGTT. Analytical methods for measuring blood glucose levels can differ between laboratories, leading to differences in accuracy and precision. Additionally, co-morbidities and medications in pregnant women can confound the measured AUC-OGTT. When interpreting results, these limitations should be considered.

Despite these limitations in the use of AUC-OGTT, it is important to also assess the overall strengths and weaknesses of our study to fully understand the significance and applicability of our findings. Our study benefits from a substantial sample size of pregnant women who underwent a 75-gram OGTT during pregnancy. This large cohort provides a more comprehensive representation of the population under study, reducing the potential for sampling bias. Additionally, the unified pregnancy surveillance and management in a single center offer several advantages. It ensures consistency in data collection, diagnostic procedures, and patient care, which is crucial for the reliability of the results. However, our study also has several limitations. First, we were unable to collect sufficient information on other forms of management, such as diet, exercise, socioeconomic status etc. Thus, we could not clarify these potential confounding effects

on adverse pregnancy outcomes, which may affect the reliability of the results. Second, although we also collected data on other adverse pregnancy outcomes, such as shoulder dystocia, neonatal hypoglycemia, neonatal respiratory distress, and congenital anomalies, they were not included in the statistical analysis of this paper due to the small number of cases, which could easily introduce false bias into the results. Third, during the analysis using logistic regression models, we adjusted for numerous potential variables in an attempt to minimize confounding effects. However, there may still be unobservable and unmeasured confounders not accounted for in our analysis, which may affect the reliability of the results. Fourth, while the exclusion criteria were comprehensive, they were necessary to minimize the confounding effects of factors such as pre-existing medical conditions, multiple pregnancies, and incomplete data, which could have obscured the relationship and partly influencing the representativeness of the general pregnant population. Finally, the basic pregnancy information was calculated based on self-reported data during the first antenatal visit. Although this method is widely used and validated in clinical research, it may introduce recall bias.

In conclusion, the identification of high-risk pregnancies remains a significant challenge in modern obstetrics. This study demonstrates that the use of the OGTT, a well-established prenatal diagnostic tool, allows for the easy calculation of AUC-OGTT using measured OGTT values without incurring additional costs. As a result, clinicians can not only identify women with GDM but also recognize those at an elevated risk of adverse pregnancy outcomes among GDM-negative individuals. Detecting this previously unrecognized risk group enables more rigorous monitoring during pregnancy when necessary, potentially leading to a reduction in these complications.

Supplementary Information

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Supplementary Material 1

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Author contributions
FZ, YX and YB contributed to the study concept and design. FZ and YB performed the data analysis. FZ, BY and JZ were involved in the interpretation of the data and the drafting of the manuscript. FZ, YX, BY, JZ and YB were involved in the critical revision. FZ and YB were involved in the interpretation of the data, critical revision of the manuscript, and study supervision. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the ethics committee of Women's Hospital, Zhejiang University School of Medicine (approval number: IRB-20240021-R; approval date: January 22, 2024), and an informed consent exemption was granted due to the use of anonymous participants' records.

Consent for publication
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Competing interests
The authors declare no competing interests.

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