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Association between area under the curve of oral glucose tolerance test and the risk of preterm birth among women with gestational diabetes mellitus: a mediation effect of gestational weight gain

Jing Liu[1], Huibin Li[1], Xue Wang[1], Beibei Liu[2], Dan He[1], Gang Zhang[3*] and Yan Gao[1*]

Abstract

Background The risk of preterm birth (PTB) is associated with maternal hyperglycemia but differs by combinations of abnormal oral glucose tolerance test (OGTT) values. However, the potential pathway by which maternal hyperglycemia affects PTB is unclear. This study aimed to investigate the association between OGTT-related measures and PTB and evaluate the mediation effect of gestational weight gain (GWG) on the association between maternal hyperglycemia and the risk of PTB in women with gestational diabetes mellitus (GDM).

Methods This retrospective cohort study included women with GDM from a women's and children's hospital in Chengdu, China, from December 2021 to December 2023. The associations between OGTT-related measures, GWG, and PTB were evaluated by logistic regression analyses. Two-step clustering was used to classify participants by area under the curve (AUC) of the OGTT. SPSS Process Macro was utilized to explore the mediation effect of GWG on the relationship between AUC and PTB.

Results This study included 1860 women with GDM, of whom 694 (37.3%) women had higher AUC (≥ 17 mmol/L·h), 935 (50.3%) women had insufficient GWG, and 132 (7.1%) women had PTB. Multivariable logistic regression analyses showed that only higher AUC was associated with increased odds of PTB (OR:1.47, 95% CI:1.03 to 2.10; $P=0.036$), and no significant associations between other OGTT-related measures and PTB were observed. Besides, GDM women with higher AUC had a higher risk of insufficient GWG (OR:1.23, 95% CI:1.02 to 1.49; $P=0.033$), which was associated with increased odds of PTB (OR:2.15, 95% CI:1.47 to 3.14; $P<0.001$). Mediation analyses revealed that the effect of AUC on PTB was mainly mediated through GWG (indirect effect: 0.15, bootstrapped 95% CI: 0.08 to 0.24).

Conclusions This study found that AUC of the OGTT was positively associated with the occurrence of PTB, and GWG mainly mediated this positive association. Effective intervention strategies for GDM should pay close attention to

*Correspondence:
Gang Zhang
zhanggangcmc@163.com
Yan Gao
gaoyan6596@126.com

Full list of author information is available at the end of the article

avoiding insufficient GWG when managing their blood glucose, especially for those with higher AUC levels, to reduce the impact of maternal hyperglycemia on the risk of PTB.

Keywords Area under the curve, Oral glucose tolerance test, Preterm birth, Gestational diabetes, Gestational weight gain, Mediation effect

Background

Gestational diabetes mellitus (GDM) is a condition that occurs during pregnancy and is characterized by high blood glucose levels that start or are first diagnosed during pregnancy [1]. It affects 7.1 ~ 27.6% of pregnancies worldwide [2] and 14.8% in China [3] and is associated with an increased risk of various adverse outcomes, including preterm birth (PTB) [4, 5]. PTB affects approximately 10% of pregnancies throughout the world, and an estimated 13.4 million preterm neonates are born worldwide every year [6]. Complications of PTB are the leading cause of neonatal death and the second cause of childhood death under the age of five years and cause increased healthcare costs and burden on families [7, 8].

According to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria, women were considered to have GDM if any one of 3 oral glucose tolerance test (OGTT) values was abnormal [9]. Previous studies demonstrated that pregnancy complicated with GDM was at a higher risk of PTB compared to pregnancy with normoglycemia [4, 10, 11]. However, some studies found that the risk of PTB complicated by GDM differs by combination of abnormal OGTT values [10]. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study found that 1-h and 2-h post-load hyperglycemia were correlated with PTB [4]. A retrospective study among Chinese women indicated that only 2-h post-load hyperglycemia was associated with a 1.5-fold increased risk of PTB in GDM women [11]. Another study observed that only fasting glucose was related to an increased risk of PTB among Chinese women with GDM [12]. The inconsistency in these findings suggests the need for further exploration of the associations and potential mechanisms between different OGTT characteristics and the risk of PTB among GDM women.

Gestational weight gain (GWG) is a strong indicator of maternal nutritional status and serves as an important indicator for the health and quality of life of both women and their fetuses. The Institute of Medicine (IOM) recommends specific weight gain ranges based on the mother's pre-pregnancy body mass index (BMI) category [13]. Both insufficient and excessive GWG has been associated with adverse outcomes, including PTB. A meta-analysis of more than 1 million pregnant women by Goldstein et al. showed that 23% had GWG less than IOM recommendations, which was associated with a higher risk of PTB [14]. The proportion is higher among women with GDM, possibly due to the impact of lifestyle management, including medical nutrition therapy and physical activity, which is the primary strategy for managing blood glucose levels in GDM [15]. Gou et al. reported that compared with general pregnant women, women with GDM had a higher rate of insufficient GWG, which increased the incidence of PTB [16]. Chen et al. observed that excessive GWG was also positively associated with PTB in women with GDM [17]. These findings suggest GWG might have a potential role in linking hyperglycemia with PTB. However, it is unknown whether GWG has a mediation effect on the relationship between maternal hyperglycemia and PTB.

Understanding the relationships among OGTT-related measures, GWG, and PTB can improve the development of individualized management strategies for GDM women according to individual OGTT characteristics. Therefore, the aim of our study was (1) to explore the association of OGTT-related measures and the risk of PTB among Chinese women with GDM and (2) to examine whether GWG had a mediation effect on the relationship between OGTT-related measures and PTB.

Methods

Study population and data sources

We conducted a retrospective cohort study using data from the electronic health record (EHR) of Sichuan Provincial Women's and Children's Hospital, Chengdu, China. Pregnant women delivered from December 1, 2021, to December 31, 2023 were screened. The eligibility criteria include all women who were carrying a singleton fetus and diagnosed with GDM by a 75 g OGTT between 24 and 28 weeks of gestation. The exclusion criteria were women who had known pregestational diabetes mellitus (PGDM) or overt diabetes diagnosed during pregnancy, very early preterm birth (< 28 weeks of gestation), thyroid disease during pregnancy, gestational hypertension, polycystic ovary syndrome (PCOS), endometriosis, recurrent pregnancy loss and incomplete data. GDM was considered if any one of the following criteria was met: fasting glucose (OGTT0) ≥ 5.1 mmol/L or 1-h post-load glucose (OGTT1) ≥ 10.0 mmol/L or 2-h post-load glucose (OGTT2) ≥ 8.5 mmol/L, according to the results of a 75 g OGTT by IADPSG criteria [9]. Women with fasting plasma glucose above 7.0 mmol/L during their first prenatal visit or with glucose values above 7.0 mmol/L for OGTT0 or 11.1 mmol/L for OGTT2 were considered to have overt diabetes and were excluded from the study [18].

Main predictors: measurements of OGTT results

The main predictors include OGTT0, OGTT1, OGTT2, and other measures derived from the three OGTT values. The areas under the curve (AUC) of OGTT will be calculated by the trapezoidal rule [19] based on three OGTT values. The incremental areas under the curve (iAUC) will be calculated to exclude all areas below fasting glucose from the calculation of AUC. Post-load excursion of 1-h (1hPE) and 2-h (2hPE) will be calculated by the difference of OGTT1 and OGTT0, OGTT2 and OGTT0, respectively.

Potential mediator: gestational weight gain

GWG was calculated as the difference between the weight measured at the last recorded weight before delivery and the pre-pregnancy weight. The last recorded weight before delivery was measured in the hospital. Participants were classified as adequate, insufficient, or excessive GWG according to IOM recommendations [20]. Insufficient GWG was defined as a total GWG of < 12.5 kg for underweight women, < 11.5 kg for normal women, < 7 kg for overweight women, or < 5 kg for obese women. Excessive GWG was defined as a total GWG of > 18 kg for underweight women, or > 16 kg for normal weight women, or > 11.5 kg for overweight women, or > 9 kg for obese women [20, 21].

Outcome: PTB

This study's outcome was PTB, defined as any delivery at gestational weeks < 37 and ≥ 28 weeks [22, 23]. In this study, gestational age at delivery was determined by maternal report of the last menstrual period or an early ultrasound if the date of the last menstrual period is unknown.

Other variables

Maternal demographics, clinical characteristics, laboratory tests, and infant characteristics, were extracted from the EHR. We collected data regarding maternal age (< 30 years, 30 ≤ age < 35 years, ≥ 35 years), education level (up to high school, or college or above), gravidity (1 or ≥ 2), nulliparity (yes or no), and assisted reproductive technology (yes or no), pre-pregnancy BMI, family history of diabetes (yes or no), fasting glucose levels and blood lipids levels at the first visit before 13 weeks of gestation, gestational age at delivery, birth weight, birth height, low birth weight (LBW, yes or no), macrosomia (yes or no), delivery mode (vaginal delivery or cesarean section). Pre-pregnancy BMI (kg/m^2) was calculated as pre-pregnancy weight in kg divided by height in square meters. Pre-pregnancy weight was self-reported at the initial prenatal examination. The documented weight at the first visit to the hospital (5–6 weeks of gestation) obtained from the EHR was used when the participants could not remember their pre-pregnancy weight [24]. Participants were classified as underweight (BMI < 18.5 kg/m^2), normal (18.5 ≤ BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2), or obese (BMI ≥ 30 kg/m^2) according to pre-pregnancy BMI by the World Health Organization criteria [20]. The Working Group on Obesity in China (WGOC) criteria was also employed to classify BMI [21]. LBW is defined as birth weight < 2,500 g, and macrosomia is defined as birth weight > 4,000 g.

Statistical analysis

Statistical analysis was conducted with SPSS version 25.0 (IBM, Chicago, IL, USA) software. The data for participants' characteristics were presented as the means ± standard deviation (SD) for continuous variables and as frequencies and percentages [n(%)] for categorical variables. Independent sample t-test, Pearson's chi-square test, or Fisher's exact test were performed to analyze the differences in continuous and categorical variables between PTB and non-PTB groups.

We examined the associations between maternal sociodemographic and obstetric characteristics and PTB to screen potential covariates by univariate logistic regression, with $P < 0.2$ used as covariates in the subsequent adjusted model. We then explored the associations of AUC and other OGTT-related measures with PTB. First, unadjusted odds ratios (uOR) with 95% confidence intervals (CIs) were estimated for each factor. Second, we used multivariate logistic regression to estimate the ORs adjusted for potential covariates. Before performing mediation effect analysis, the associations between AUC, GWG, and PTB were confirmed by three logistic regression models. The PROCESS macro (version 4.1) for SPSS was used to analyze the mediation effect [25]. We selected model 4 to conduct the mediation model analysis. The following steps were assessed: (1) the effect of independent variables on mediator (the *a* paths), (2) the effect of mediator on dependent variable (the *b* paths), (3) the effect of independent variables on dependent variable through mediator (i.e., indirect effect, a×b coefficient), (4) the direct effect of independent variables on dependent variable (*c'* paths), and (5) total effect of independent variables on dependent variable (*c* path). Bias-corrected bootstrapped 95% asymmetric confidence intervals (based on 5,000 bootstrap samples) were computed for the indirect effect. The indirect effect is statistically different from zero if the confidence interval does not straddle zero [26]. *P* values less than 0.05 were considered statistically significant.

The AUC of the 75 g OGTT was adopted to evaluate the severity of maternal hyperglycemia based on the trapezoidal approximation of glucose levels at three time points between 0 and 120 min [27, 28]. Glucose levels

at baseline, 60, and 120 min were defined as OGTT0, OGTT1, and OGTT2. AUC was calculated as follows:

$$\mathrm{AUC\,(mmol/L \cdot h)} = (\mathrm{OGTT0} + \mathrm{OGTT1})/2 + (\mathrm{OGTT1} + \mathrm{OGTT2})/2$$

Two-step clustering analysis, i.e., pre-clustering followed by hierarchical clustering, was applied to automatically identify the optimal clustering number based on the silhouette width. The distance was calculated using the log-likelihood and clustering by Schwarz's Bayesian criterion. We performed a two-step clustering analysis based on OGTT criteria and AUC values to produce OGTT patterns in GDM women. Sevent clusters were identified (Table S1), the clustering effect is excellent (silhousette = 0.9), and the importance of predictive variables is equal. Among the seven clusters, OGTT patterns in clusters 3, 4, and 6 were characteristic with two or three abnormal glucose values meeting the OGTT criteria and having the highest AUC values among the seven clusters. The AUC in cluster 5 and 7 were in the middle. Considering the practical application in clinical settings, the AUC value of the third quartile in cluster 5 (16.98 mmol/L.h) and 7 (16.99 mmol/L·h) were chosen as the cut-point to classify GDM women into two groups, i.e., higher AUC (≥ 17 mmol/L·h) and lower AUC (< 17 mmol/L·h).

Given that WGOC criteria has been widely used to classify BMI in Chinese population, we performed sensitivity analysis utilizing WGOC criteria for pre-pregnancy BMI and GWG classification. Furthermore, considering the complications associated with PTB are primarily linked to the risk of very preterm birth (≥ 28 weeks and < 32 weeks), we also conducted sensitivity analysis for PTB excluding very preterm birth. To explore the underlying mechanisms of PTB in current study, we performed additional subgroup analysis for PTB by pregnancies with or without PROM.

Results

General characteristics of the study population

In total, 12,424 pregnant women who performed OGTT between 24 and 28 weeks of gestation were included in the initial sample. Women with normal OGTT values were excluded first. After excluding women with pre-gestational or overt diabetes, twin, very early preterm birth, thyroid disease during pregnancy, gestational hypertension, PCOS, endometriosis, recurrent pregnancy loss and incomplete data, 1860 women with GDM were eligible for final analysis. The flow chart of the inclusion and exclusion of participants is shown in Fig. 1.

Participant characteristics are shown in Table 1. Among 1860 women with GDM, 132 (7.1%) had PTB, higher than those without GDM in our cohort (3.8%, Table S2). The mean age of participants was 30.32 years, and the mean pre-pregnancy BMI was 21.76 kg/m^2. Compared with the non-PTB group, the PTB group had a non-significantly higher maternal age ($P = 0.097$), and more women in the PTB group were nulliparous ($P = 0.028$). The proportion of women receiving ART was significantly higher in the PTB group than in the non-PTB group ($P = 0.014$). No difference in pre-pregnancy BMI between the two groups was observed. Compared with the non-PTB group, the PTB group had a significantly higher proportion of PROM and lower birth weight and birth height, with no significant difference observed in the proportion of cesarean delivery and macrosomia between the two groups.

Among all participants with GDM, only 21.2% had abnormal OGTT0, about half (53.3%) had abnormal OGTT1, and most had abnormal OGTT2 (70.0%). OGTT2 level was close to being significantly higher among the PTB group than among the non-PTB group ($P = 0.062$), while there were no significant differences in OGTT0 and OGTT1 levels between PTB and non-PTB groups. The mean GWG was 9.31 ± 3.99 kg among the PTB group, significantly lower than that among the non-PTB group (11.40 ± 4.06 kg). When using WHO criteria, about half of the GDM women's GWG was below IOM recommendations (50.3%), higher than that among non-GDM women in our cohort (26.6%, Table S2), with the highest rate of insufficient GWG in PTB group (68.2%). Excessive GWG was less prevalent among the PTB group (4.5%) than the non-PTB group (14.5%). According to WGOC classification criteria (Table S3), there are more women classified into overweight (17.6%) or obesity (2.8%)(Table S4), accordingly higher rate of excessive GWG (24.9%) and lower rate of insufficient GWG (20.9%) were observed among all GDM women than WHO criteria (Table S5).

Relationship of OGTT-related measures and PTB

The relationship between OGTT-related measures and PTB is shown in Table 2. When used as continuous variables, only the associations of OGTT2, AUC, and PTB approached near significance in unadjusted models. When taken as categorized variables, only higher AUC (≥ 17 mmol/L·h) was associated with increased odds of PTB among GDM women in the unadjusted model (OR:1.54, 95% CI: 1.08 to 2.19; $P = 0.018$) and after adjusting for covariates (OR:1.47, 95% CI:1.03 to 1.88; $P = 0.036$). Covariates screening for PTB is shown in Table S6. We found no associations between other OGTT-related measures and PTB in unadjusted and adjusted models (Table 2).

GDM patients with three abnormal glucose values had a higher rate of PTB (8.2%) than those with one (6.9%) and two (7.2%) abnormal glucose values, but no statistical significance was observed (Table 2). We further compared the distribution characteristics of abnormal OGTT

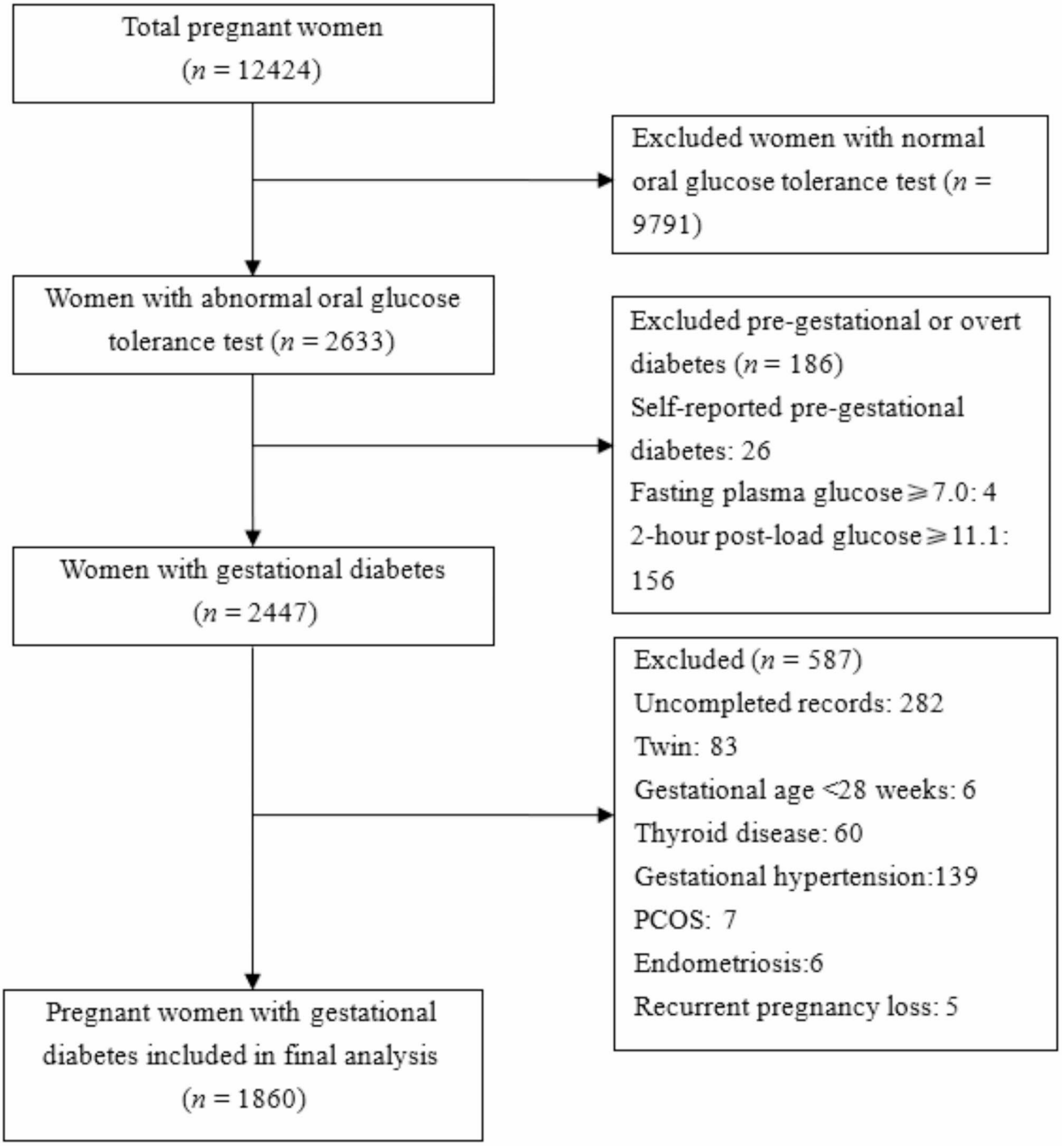

Fig. 1 Flow chart of participants screening

numbers by AUC level, which were categorized into two groups using the cut-point 17 mmol/L·h from a two-step clustering analysis (Table S7). Our findings showed that the proportion of GDM women with three abnormal OGTT values was only 5.9% (110/1860), much less than that of higher AUC (37.3%, 694/1860). Among GDM women with higher AUC, the proportions of women with different numbers of abnormal OGTT values were 15.9% for one, 68.3% for two, and 15.8% for three abnormal OGTT values, respectively.

Mediation effect of GWG on the association between AUC and PTB

As shown in Table S8, compared with women without insufficient GWG, the risk of PTB was significantly higher among women with insufficient GWG (OR:2.24,

Table 1 Characteristics of GDM patients with and without PTB

Variables	Total *n* = 1860	Non-PTB *n* = 1728	PTB *n* = 132	*P*
Maternal age, years, Mean ± SD	30.32 ± 3.77	30.28 ± 3.77	30.84 ± 3.69	0.097
Age group, n (%)				0.179
< 30	863(46.4)	812(47.0)	51(38.6)	
30–35	728(39.1)	669(38.7)	59(44.7)	
≥ 35	269(14.5)	247(14.3)	22(16.7)	
Education, n (%)				0.663
Up to high school	381(20.5)	352(20.4)	19(22.0)	
College or higher	1478(79.5)	1375(79.6)	103(78.0)	
Gravidity, n (%)				0.145
1	817(43.9)	751(43.5)	66(50.0)	
≥ 2	1043(56.1)	977(56.5)	66(50.0)	
Nulliparity, n (%)				0.028
No	642(34.5)	608(35.2)	34(25.7)	
Yes	1218(66.5)	1120(64.8)	98(74.3)	
DM Family history, n (%)				0.257
No	1661(89.3)	1547(89.5)	114(86.4)	
Yes	199(10.7)	181(10.5)	18(13.6)	
Pre-pregnancy BW, kg, Mean ± SD	55.01 ± 7.80	55.05 ± 7.80	54.44 ± 7.79	0.389
Pre-pregnancy BMI, kg/m^2, Mean ± SD	21.76 ± 2.80	21.76 ± 2.81	21.68 ± 2.73	0.742
Pre-pregnancy BMI group, n (%) [a]				0.702
Underweight	195(10.5)	183(10.6)	12(9.1)	
Normal weight	1424(76.5)	1319(76.3)	105(79.5)	
Overweight or obesity	241(13.0)	226(13.1)	15(11.4)	
TC, mmol/L, Mean ± SD	4.42 ± 0.78	4.42 ± 0.78	4.48 ± 0.79	0.372
HDL-c, mmol/L, Mean ± SD	1.70 ± 0.37	1.70 ± 0.37	1.73 ± 0.37	0.381
LDL-c, mmol/L, Mean ± SD	2.19 ± 0.57	2.19 ± 0.57	2.19 ± 0.58	0.865
TG, mmol/L, Mean ± SD	1.37 ± 0.61	1.37 ± 0.61	1.43 ± 0.63	0.233
Early FPG, mmol/L, Mean ± SD	4.67 ± 0.38	4.67 ± 0.38	4.64 ± 0.38	0.301
Gestational age for OGTT, weeks, Mean ± SD	25.75 ± 1.05	25.76 ± 1.06	25.64 ± 0.96	0.186
OGTT0, mmol/L, Mean ± SD	4.70 ± 0.46	4.70 ± 0.46	4.77 ± 0.51	0.095
OGTT1, mmol/L, Mean ± SD	9.85 ± 1.35	9.84 ± 1.33	9.98 ± 1.56	0.265
OGTT2, mmol/L, Mean ± SD	8.74 ± 1.18	8.72 ± 1.19	8.92 ± 1.13	0.062
OGTT0 group, n (%)				0.664
< 5.1	1465(78.8)	1363(78.9)	101(77.3)	
≥ 5.1	395(21.2)	365(21.1)	30(22.7)	
OGTT1 group, n (%)				0.547
< 10	869(46.7)	804(46.5)	65(49.2)	
≥ 10	991(53.3)	924(53.5)	67(50.8)	
OGTT2 group, n (%)				0.365
< 8.5	558(30.0)	523(30.3)	35(26.5)	
≥ 8.5	1302(70.0)	1205(69.7)	110(73.5)	
GWG, kg, Mean ± SD	11.25 ± 4.09	11.40 ± 4.06	9.31 ± 3.99	< 0.001
GWG group, n (%)				< 0.001
Adequate	668(35.9)	632(36.6)	36(27.3)	
Insufficient	935(50.3)	845(48.9)	90(68.2)	
Excessive	257(13.8)	251(14.5)	6(4.5)	
ART, n (%)				0.014
No	1772(95.3)	1652(95.6)	120(90.9)	
Yes	88(4.7)	76(4.4)	12(9.1)	
Delivery mode, n (%)				0.108
Vaginal delivery	1082(58.2)	1014(58.7)	68(51.5)	
Cesarean Delivery	778(41.8)	714(41.3)	64(48.5)	

Table 1 (continued)

Variables	Total *n* = 1860	Non-PTB *n* = 1728	PTB *n* = 132	*P*
PROM				< 0.001
No	1424(76.6)	1366(79.1)	58(43.9)	
Yes	436(23.4)	362(20.9)	74(56.1)	
Birth height, cm, Mean ± SD	48.83 ± 2.61	49.10 ± 2.31	45.30 ± 3.58	< 0.001
Birth weight, g, Mean ± SD	3179.62 ± 447.15	3234.60 ± 396.62	2459.81 ± 449.02	< 0.001
Macrosomia, n (%)				0.103
No	1813(97.5)	1681(97.5)	132(100.0)	
Yes	47(2.5)	47(2.7)	0(0.0)	
LBW, n (%)				< 0.001
No	1760(94.6)	1685(97.5)	75(56.8)	
Yes	100(5.4)	43(2.5)	57(43.2)	

Abbreviations: GDM, gestational diabetes mellitus; PTB, preterm birth; DM, diabetes mellitus; BW, body weight; BMI, body mass index; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; Early FPG, fasting plasma glucose before 13 weeks of gestation; OGTT, oral glucose tolerance test; GWG, gestational weight gain; ART, assisted reproductive technology; LBW, low birth weight

[a] Underweight (BMI < 18.5 kg/m^2), Normal weight (18.5 ≤ BMI < 25 kg/m^2), Overweight or obesity (BMI ≥ 25 kg/m^2)

Table 2 OGTT-related measures as associated factors of PTB

Variables	Row%	uOR(95%CI)	*P*	aOR(95%CI)	*P*
OGTT values					
0	NA	1.37(0.95–1.98)	0.096	1.38(0.95–2.01)	0.095
1 h	NA	1.08(0.94–1.23)	0.265	1.06(0.93–1.22)	0.385
2 h	NA	1.16(0.99–1.36)	0.062	1.14(0.97–1.34)	0.108
OGTT0 group					
< 5.1	7.0	1.00		1.00	
≥ 5.1	7.6	1.10(0.72–1.68)	0.664	1.12(0.73–1.72)	0.589
OGTT1 group					
< 10	7.5	1.00		1.00	
≥ 10	6.8	0.90(0.63–1.28)	0.547	0.86(0.60–1.23)	0.419
OGTT2 group					
< 8.5	6.3	1.00		1.00	
≥ 8.5	7.5	1.20(0.81–1.79)	0.365	1.17(0.78–1.75)	0.450
1hPE	NA	1.03(0.90–1.17)	0.698	1.01(0.89–1.15)	0.884
2hPE	NA	1.08(0.94–1.23)	0.294	1.06(0.92–1.22)	0.417
1hPE group					
< 6.5	7.0	1.00		1.00	
≥ 6.5	8.1	1.18(0.71–1.95)	0.528	1.11(0.66–1.84)	0.701
2hPE group					
< 5	7.1	1.00		1.00	
≥ 5	7.1	0.99(0.65–1.51)	0.972	0.95(0.62–1.45)	0.807
iAUC	NA	1.04(0.94–1.16)	0.467	1.02(0.92–1.14)	0.663
AUC	NA	1.11(0.99–1.24)	0.062	1.09(0.98–1.22)	0.118
AUC group					
Lower(< 17)	6.0	1.00		1.00	
Higher(≥ 17)	8.9	1.54(1.08–2.19)	0.018	1.47(1.03–2.10)	0.036
Number of diagnostic criteria					
1	6.9	1.00		1.00	
2	7.2	1.05(0.72–1.54)	0.804	1.01(0.68–1.48)	0.973
3	8.2	1.20(0.58–2.46)	0.621	1.15(0.56–2.38)	0.708

Abbreviations: OGTT, oral glucose tolerance test; PTB, preterm birth; PE, post-load excursion; iAUC, increased area under the curve of the OGTT; AUC, area under the curve of the OGTT; uOR, unadjusted odds ratios; aOR, adjusted odds ratios; 95%CI, 95% confidence interval

aOR: Adjusted for all variables with $p < 0.2$ in the univariate analysis listed in Table S6, including maternal age, nulliparity, gravidity, ART and gestational weeks for OGTT

95% CI:1.53 to 3.27; $P<0.001$), the results remained unchanged in different AUC categories.

The direct associations between AUC and GWG, GWG and PTB, and AUC and PTB were confirmed by logistic regression (Table 3). Higher AUC was associated with increased odds of insufficient GWG (OR:1.23, 95% CI: 1.02 to 1.49; $P=0.033$) (Model 2). Insufficient GWG was observed to be associated with increased odds of PTB (OR:2.15, 95% CI:1.47 to 3.14; $P<0.001$) (Model 2). Higher AUC was associated with increased odds of PTB (OR:1.47, 95% CI:1.03 to 2.11; $P=0.036$) (Model 2). The relationship between AUC and PTB was attenuated when GWG was added to model 2 (OR 1.47 to 1.40) (Model 3).

Given the above results, we performed a mediation analysis to examine the mediation effect of GWG on the relationship between AUC and PTB. Figure 2 shows the mediation structural model of GWG regarding the mediation effect on AUC and PTB. GWG significantly mediated the association between AUC and PTB (indirect effect: 0.15, 95% CI: 0.08 to 0.24) after controlling for covariates (Fig. 2).

Sensitivity analysis and subgroup analysis

For the associations of GWG with AUC and PTB, sensitivity analysis using the WGOC criteria for BMI classification suggested that pregnancies with higher AUC had an even greater increased risk of insufficient GWG (aOR:1.83, 95%CI:1.45–2.29; $P<0.001$), which was associated with greater increased risk of developing PTB (aOR:2.47, 95%CI:1.70–3.59; $P<0.001$) (Table S9), than observed in the primary analyses using WHO criteria. The PTB sensitivity analysis which excluded pregnancies with very preterm birth ($n=8$) showed similar results to the primary analysis (Table S10).

Subgroup analysis showed a significant effect of insufficient GWG on the incidence of PTB in pregnancies with and without PROM, which is consistent with the main analysis. However, there is no significant effect of higher AUC on the incidence of PTB within each subgroup, only with a tendency toward statistical significance ($P=0.062$) in subgroup without PROM observed in unadjusted model. Although the effect of higher AUC (P for interaction = 0.509) and insufficient GWG (P for interaction = 0.636) on PTB is consistent across pregnancies with and without PROM, the association of AUC, GWG and PTB is slightly stronger in pregnancies without PROM than with PROM (Table S11).

Discussion

We reported three key findings in this retrospective cohort study involving Chinese GDM women. First, AUC, rather than other OGTT-related measures, was significantly associated with PTB after adjusting for covariates. Second, higher AUC was related to an increased risk of insufficient GWG. Third, an important finding of our study was that GWG mediated the association between AUC and the risk of PTB.

Maternal hyperglycemia has been demonstrated to be associated with a higher risk of PTB [4, 29], which may differ according to whether GDM diagnosis under IADPSG criteria is based on high fasting or high post-load glucose values during OGTT [30]. Some studies reported that women with high fasting and post-load glucose values [4, 11, 30, 31] or with isolated elevated post-load glucose values [10] had the highest rate for PTB, whereas several others showed similar rates of PTB across different OGTT subtypes [32, 33]. Inconsistent results from these studies may indicate that three OGTT values did not show the total rise in blood glucose levels [27], suggesting that a more thorough interpretation of OGTT results should be made at the time of GDM diagnosis [34]. Therefore, in addition to OGTT values and

Table 3 Associations between AUC and GWG, GWG and PTB, and AUC and PTB

	Model 1		Model 2		Model 3	
	OR(95% CI)	*P*	OR(95% CI)	*P*	OR(95% CI)	*P*
AUC and GWG						
AUC						
Lower	1		1			
Higher	1.25(1.03–1.51)	0.021	1.23(1.02–1.49)	0.033		
GWG and PTB						
GWG						
Adequate or Excessive	1		1			
Insufficient	2.24(1.53–3.27)	< 0.001	2.15(1.47–3.14)	< 0.001		
AUC and PTB						
AUC						
Lower	1		1		1	
Higher	1.54(1.08–2.19)	0.018	1.47(1.03–2.11)	0.036	1.40(0.98–2.02)	0.066

Abbreviations: AUC, area under the curve of the OGTT; OGTT, oral glucose tolerance test; GWG, gestational weight gain; PTB, preterm birth

Model 1: unadjusted univariate model. Model 2: adjusted for all variables with $p<0.2$ in the univariate analysis listed in Table S6, including maternal age, multiparous, ART, gravidity, and gestational weeks for OGTT. Model 3: GWG was added to Model 2

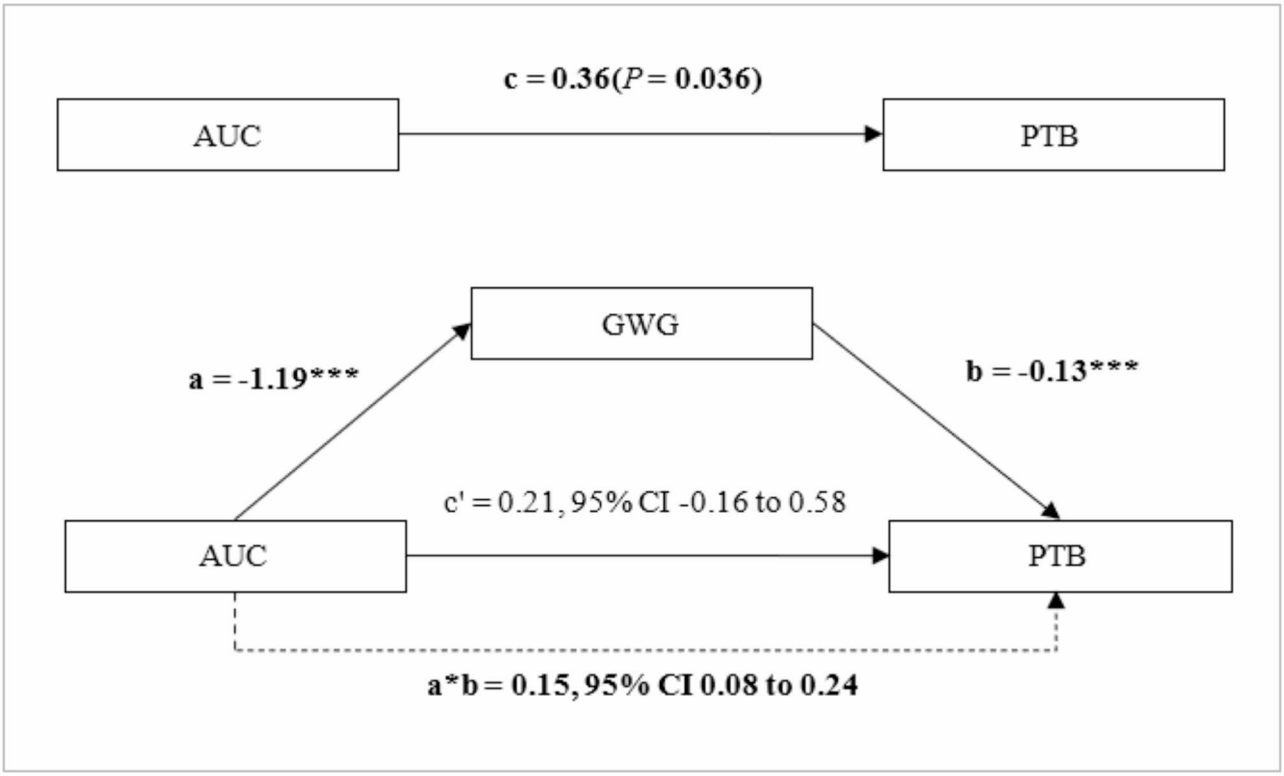

Fig. 2 Mediation of GWG on the effect of AUC on PTB. The model is adjusted for maternal age, ART, gestational weeks for OGTT, and nulliparity. *$P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. c: total effect; c': direct effect; a*b: indirect effect. Bold indicates significant values. AUC: area under the curve of the 75 g oral glucose tolerance test, PTB: preterm birth, GWG: gestational weight gain

the number of abnormal OGTT values, we also explored the relationship between several other OGTT-related measures and PTB, including 1hPE, 2hPE, iAUC, and AUC. The first three indicators reflect post-load glucose excursion and increased glucose exposure. AUC is an integrated index reflecting the severity of maternal hyperglycemia during the OGTT [34]. It has been developed to quantify the total glucose exposure following OGTT, mainly applied in patients with type 2 diabetes [27] and a few in pregnant women [35, 36]. In this study, most OGTT-related measures, including OGTT0, OGTT1, OGTT2, 1hPE1h, 2hPE, and iAUC, whether as continuous or categorized variables, were not significantly associated with risk for PTB. Only higher AUC was associated with increased odds of PTB among GDM women after adjusting for covariates. Similar results were reported in a previous study that found a rising trend of PTB with AUC increasing, although not statistically significant among GDM women [35]. Our findings indicated that AUC may reflect the severity of maternal hyperglycemia more accurately and increase the risk of PTB. The pathophysiological changes in insulin resistance might explain it. Sun et al. demonstrated that the AUC of OGTT increased with insulin resistance, which was significantly associated with PTB in women with GDM [36].

Several studies explored the relationship of the number of abnormal OGTT values with the risk of PTB and reported that the risk of PTB significantly increased as the number of abnormal values during the OGTT increased [11, 17]. A similar trend was found in our study that GDM women with three abnormal OGTT values had a higher rate of PTB than those with one or two abnormal OGTT values, but no statistical significance was observed. These findings suggest that the number of abnormal OGTT values may reflect the severity of hyperglycemia to some extent, but it is a qualitative indicator that cannot accurately quantitatively reflect the degree of hyperglycemia. Moreover, we compared the distribution of abnormal OGTT numbers by AUC group, and the results showed that the proportion of GDM women with three abnormal OGTT values was only 5.9%, similar to findings reported by previous studies (6.8%~8.8%) [11]. However, GDM women with higher AUC accounted for 37.3%, which included 15.8% with three abnormal OGTT values, 68.3% with two, and 15.9% with one abnormal item. This finding suggests that AUC may be a more comprehensive and representative index in reflecting the severity of glucose metabolic abnormality in GDM

women, who are more prone to causing PTB, compared to the number of abnormal OGTT values. Therefore, AUC might be the strongest predictor among OGTT-related measures, which warrants a tailored management strategy for GDM.

A systematic review and meta-analysis indicated that GDM women with insufficient GWG had a higher risk of PTB than GDM women with adequate GWG [37, 38], which aligns with our study. This may be related to nutritional deficiencies, unfavorable uterine environment, and poor placental functions [39, 40]. Surprisingly, insufficient GWG using WHO criteria occurred in 50.3% of GDM women in this present study, which was higher than that previously reported among GDM women (29.6%~44.1%) [16, 17] and general pregnant women (12.5%~25%) [41, 42]. Therefore, medical staff should pay close attention to the weight management of women with GDM during pregnancy while concentrating on achieving satisfactory glycemic control [37]. Regarding the relationship between maternal hyperglycemia and GWG, previous studies have focused mainly on preventing excessive GWG among GDM women to reduce the risk for adverse pregnancy outcomes [14, 43]. However, some recent studies have found that GWG differs from OGTT patterns [16, 35]. Some research indicated that fasting plasma glucose was lower, but post-load glucose was higher in the insufficient GWG group than in the excessive GWG group [16]. Zhang et al. reported a downward trend of GWG with AUC increasing, although it was not statistically significant [35]. Our results showed that higher AUC was associated with an increased risk of insufficient GWG, which was related to increased risk for PTB. Sensitivity analysis using WGOC criteria for BMI classification suggested that the association between insufficient GWG and PTB appeared to be stronger than using the WHO criteria, although the proportion of GDM women with insufficient GWG was much lower when using WGOC criteria. This suggested that the WGOC criteria may underestimate insufficient GWG. The optimal GWG recommendations for Chinese women with GDM and the investigation of the reasons for insufficient GWG are worthy of further study.

The mechanisms linking hyperglycemia and insufficient GWG are poorly understood, and whether GWG plays a mediating role in the relationship between AUC and PTB remains unclear. Based on the relationship between AUC, GWG, and PTB, further analysis found that GWG had a significant mediation effect on AUC and PTB in GDM women, which indicated that the increased risk of PTB associated with maternal hyperglycemia, as indicated by a higher AUC, could be explained mainly by the insufficient GWG. Our study's negative association between AUC and GWG suggested that GDM women with more severe glucose exposure were prone to developing insufficient GWG. We further compared the OGTT characteristics among GDM women with and without insufficient GWG, and the results showed that women with insufficient GWG had significantly higher levels of OGTT2, while OGTT0 was significantly lower than those without insufficient GWG (Table S12). Medical nutritional therapy is the first-line treatment to control blood glucose after GDM diagnosis, recommended by guidelines in China and worldwide [44, 45]. GDM women with higher post-load glucose values might take more strict diet control to achieve the ideal glucose target, which potentially leads to insufficient GWG. Although 2-hour postprandial blood glucose lower than 6.7 mmol/L and fasting glucose lower than 5.3 mmol/L are regularly recommended targets [44, 45], the effect of restricting dietary carbohydrate intake on reducing postprandial blood glucose is more pronounced and immediate compared to the reduction of fasting glucose. Moreover, this effect can be immediately reflected through self-monitoring of blood glucose. According to the Common-Sense Model of Self-Regulation (CSM-SR) theory by Leventhal et al. [46, 47], coping behaviors that receive immediate feedback on the effect can reinforce the patient's adherence to such actions. However, if patients overlimit their diet to achieve blood glucose target to avoid insulin therapy, it may lead to suboptimal nutritional intake and insufficient weight gain. Future research is needed to explore potential behavioral mechanisms between maternal hyperglycemia and GWG. The public health and clinical implication of the mediating effects of GWG between AUC and PTB suggests that nutritional interventions aimed at achieving ideal glycemic control should also pay close attention to prevent insufficient GWG in GDM women, particularly with higher AUC, to mitigate the adverse effect of hyperglycemia on risk of PTB.

The strength of our study is the use of a composite index of AUC exploring the relationship between maternal hyperglycemia and the risk of PTB among GDM women. In addition, the mediation effect analysis could add more evidence for the association between maternal hyperglycemia, GWG, and PTB, which were helpful for tailored GDM management. To our knowledge, this is the first study to report this finding. However, several limitations should be considered in this study. First, the nutritional status and dietary behavior modifications of GDM women could affect glycemic control, GWG, fetal growth, and other perinatal outcomes, and we did not collect data on these variables, which should be investigated in further studies. Second, self-monitoring of blood glucose data was unavailable after GDM diagnosis to reflect glycemic control during pregnancy. Third, the index AUC calculated from three values of the OGTT in this study is relatively imprecise. In the future, continuous glucose monitoring can be used to obtain a more

accurate AUC index for exploring maternal hyperglycemia's impact on PTB. Fourth, we only collected information of pregnancies with or without PROM in this study, different categories of PTB, e.g., spontaneous or induced preterm labor, could not be differentiated by searching discharge records. This may be an important reason for the non-significant effects of AUC on the PTB in subgroup analysis by pregnancies with and without PROM, in addition to the potentially small sample size. It would be valuable to perform an in-depth analysis with a larger sample size in future studies whether PTB was due to different causes or conditions, may help to identify the mechanisms and pathways between glucose metabolism disorders, GWG and PTB, offer insights into potential intervention points and assist in contextualizing our findings. Lastly, given that several pre-existing conditions, e.g., PCOS, endometriosis and recurrent pregnancy loss, may not be collected completely in discharge records, these conditions could mediate the effect observed in present study. A more thorough collection of the medical history of pregnant women in future studies will facilitate a more in-depth analysis of the relationship between abnormal glucose metabolism and preterm birth.

Conclusions

In summary, this study found that in GDM women, AUC of the OGTT was positively associated with the occurrence of PTB, and this positive association was mediated by GWG, suggesting that GDM women with higher AUC should pay close attention to prevent insufficient GWG when managing their blood glucose. Further studies are needed to determine the mechanisms by which AUC affects insufficient GWG so that interventions to prevent insufficient GWG can be developed to reduce the impact of maternal hyperglycemia on the risk of PTB.

Abbreviations

1hPE	1-hour post-load glucose excursion
2hPE	2-hour post-load glucose excursion
ART	Assisted reproductive technology
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
EHR	Electronic Health Record
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GWG	Gestational weight gain
IADPSG	International Association of Diabetes and Pregnancy Study Groups
iAUC	Increased area under the curve
IOM	Institute of Medicine
LBW	Low birth weight
OGTT	Oral glucose tolerance test
OR	Odds ratio
PGDM	Pregestational diabetes mellitus
PROM	Premature rupture of membranes
PTB	Preterm birth
SD	Standard deviation
WGOC	Working Group on Obesity in China
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

G.Z. and Y.G. designed the study and interpreted the results. H.L., X.W., B.L., and D.H. collected data. J.L. conducted analyses. J.L. and H.L. wrote the manuscript. G.Z., Y.G., and B.L. contributed to the revision of the manuscript. All authors read and approved the final version of our manuscript.

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Data availability

The data supporting this study's findings are available upon reasonable request from the first author, JL.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Sichuan Provincial Women's and Children's Hospital (No. 20231205-315) and conducted following the 1964 Declaration of Helsinki and its later amendments. Given the retrospective nature of this study with de-identified information downloaded from the EHR database, the need for informed consent to participate was waived by the Ethics Committee of Sichuan Provincial Women's and Children's Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Obstetrics, Sichuan Provincial Women's and Children's Hospital, The Affiliated Women's and Children's Hospital of Chengdu Medical College, Chengdu, Sichuan, China
[2]Department of Neonatology, Sichuan Provincial Women's and Children's Hospital, The Affiliated Women's and Children's Hospital of Chengdu Medical College, Chengdu, Sichuan, China
[3]Department of Hepatobiliary and Vascular Surgery, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, China

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