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Triglyceride-glucose index: A promising biomarker for predicting risks of adverse pregnancy outcomes in Hangzhou, China

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ABSTRACT

Introduction: The triglyceride-glucose (TyG) index has been recommended as an alternative indicator of insulin resistance (IR). However, the association between the TyG index and adverse pregnancy outcomes remains to be elucidated.

Methods: The present retrospective study was conducted at Women's Hospital, Zhejiang University School of Medicine and involved a total of 8,514 participants. Maternal fasting lipid profiles and glucose concentrations were measured. Based on the TyG index, the participants were categorized into quartiles. Logistic regression analysis was used to calculate odds ratios (ORs) for each quartile with reference to the first quartile, while receiver operating characteristic (ROC) curve analysis, Hosmer–Lemeshow test, and calibration curve analysis were employed to evaluate the predictive ability of the TyG index for adverse pregnancy outcomes.

Results: The TyG index was higher in patients with preeclampsia, preterm birth, and macrosomia. On univariate analysis, there was an increased risk of developing adverse pregnancy outcomes with increasing quartiles of the TyG. After adjusting for potential confounders in multivariable logistic regression analysis, a positive independent correlation was found between the TyG index and preeclampsia, preterm birth, and macrosomia. In ROC curve analysis for predicting the risks of preeclampsia, preterm birth, and macrosomia, the area under the curve (AUC) could reach 0.665, 0.588, and 0.606, respectively. These predictive models demonstrated good calibration (all $P > 0.05$).

Conclusions: The TyG index showed a good predictive capacity for assessing the risk of adverse pregnancy outcomes, and it should receive sufficient clinical attention.

1. Introduction

Gestational diabetes mellitus (GDM) is the most common medical complication during pregnancy (Sweeting et al., 2022). In China, the incidence of GDM has reached 14.8 %, with an increasing growth trend (Gao et al., 2019). Pregnancies accompanied by GDM carry an increased risk of experiencing significant complications, including preeclampsia, preterm birth, macrosomia, etc., (Moon and Jang, 2022; Ye et al., 2022), which can profoundly affects the well-being of both pregnant women and fetuses while posing a concealed risk for future ailments (Abokaf et al., 2018; Sellers et al., 2016). Therefore, early identification of pregnancies at risk for these adverse pregnancy outcomes is crucial in preventing negative consequences for both mother and child.

Insulin resistance (IR) is a state in which normal concentrations of insulin fail to elicit a response from target cells, leading to excess insulin secretion due to negative feedback. While physiological IR during pregnancy benefits fetal growth and nutrient supply (Catalano et al., 1993), the degree of IR is significantly higher than that of normal

Abbreviations: TyG, triglyceride-glucose; IR, insulin resistance; OR, odds ratios; ROC, receiver operating characteristic; AUC, area under the curve; GDM, gestational diabetes mellitus; HIEC, hyperinsulinemic-euglycemic clamp; GWG, gestational weight gain; OGTT, oral glucose tolerance test; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; PG, plasma glucose; BMI, body mass index; SD, standard deviation; CI, confidence interval.

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pregnancy and can result in adverse outcomes for both mother and fetus (Sun et al., 2020; Benhalima et al., 2019). Therefore, identifying high-risk populations with adverse pregnancy outcomes through IR may serve as a valuable strategy for intervention. Recently, the triglyceride-glucose (TyG) index has emerged as a convenient and reliable indicator of IR, which can be derived from fasting plasma triglyceride and glucose levels (Tahapary et al., 2022). In comparison to the gold standard for assessing IR - hyperinsulinemic-euglycemic clamp (HIEC), the TyG index offers significant advantages by overcoming issues related to time consumption, cost, and technical complexity.

Currently, the TyG index has demonstrated significant potential in risk stratification for various conditions (Nabipoorashrafi et al., 2022; Liu et al., 2022; Pranata et al., 2021; Wang et al., 2022; Wang et al., 2022; Ling et al., 2022; Behnoush et al., 2024; Shi et al., 2021), rendering it an invaluable tool for diagnosis and outcome prediction. In a systematic review, the TyG index was found to be a sensitive and specific indicator for screening metabolic syndrome [the area under the curve (AUC): 0.87] (Nabipoorashrafi et al., 2022). A meta-analysis revealed that a higher TyG index was associated with the incidence of diabetes mellitus type 2, with an AUC of 0.66 (Pranata et al., 2021). A systematic review revealed that the TyG index exhibited diagnostic capability for obstructive sleep apnea, with a pooled AUC of 0.681 (Behnoush et al., 2024). Meta-analysis findings suggested a potential association between higher TyG index and increased cancer risk (Wang et al., 2022). An investigation implied a link between elevated TyG index and depression (Shi et al., 2021). Another meta-analysis demonstrated that the TyG index accurately diagnosed and predicted patients with metabolic dysfunction-associated fatty liver disease, yielding an AUC value of 0.75 (Wang et al., 2022). The risk of non-alcoholic fatty liver disease escalated with each incremental unit increase in the TyG index, resulting in a summary odds ratio (OR) value of 2.84 (Ling et al., 2022). Given its utility in these above-mentioned diseases, it is imperative to consider the potential implications offered by the TyG index in adverse pregnancy outcomes; however, limited research on this topic is currently available. Consequently, this study aims to examine the correlation between the TyG index and the risk of adverse pregnancy outcomes (preeclampsia, preterm birth, macrosomia).

2. Materials and methods

2.1. Study population

We conducted this retrospective study from March 2018 to February 2019. The recruitment of pregnant women in this cohort occurred at Women's Hospital, Zhejiang University School of Medicine, where participants received routine prenatal care and delivery. The hospital ethics committee approved the study protocol (approval number: IRB-20220357-R), and an informed consent exemption was applied due to anonymous patient records. Pregnant women with any of the following conditions were excluded: (1) < 18 years old; (2) missing data on triglyceride and glucose; (3) diseases affecting blood glucose levels: hyperthyroidism, Cushing's syndrome, polycystic ovary syndrome, pancreatitis; (4) severe heart, liver and kidney disease; (5) multiple pregnancies; (6) gestational weeks at delivery ≤ 28 weeks; (7) abortion or stillbirth; (8) diabetes mellitus or chronic hypertension before pregnancy; (9) diseases with autoimmune, malignancy. From hospital information system, 9,041 delivery records were retrieved without missing or duplicate medical data. After applying the exclusion criteria, the final analysis included 8,514 individuals (Fig. 1).

2.2. Data collection and measurements

Maternal characteristics and pregnancy outcome was extracted from the hospital information system, and data related to laboratory tests were extracted from the laboratory information system. The demographic and medical information comprised maternal age, preconception weight, height, gestational weight gain (GWG), gestational age, birth weight, delivery method, gravidity, parity, and pregnancy complications.

Adverse pregnant outcomes were defined, including preeclampsia (the presence of new-onset hypertension and proteinuria or other end-organ damage occurring after 20 weeks gestation), preterm birth (<37 weeks of pregnancy), and macrosomia (newborn birth weight ≥4000 g). At 24–28 weeks of gestation, the 75 g oral glucose tolerance test (OGTT), total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c) and hemoglobin A1c (HbA1c) were performed in all participants after an overnight fast. The diagnosis of GDM using the IADPSG/ WHO criteria that one or more 75 g OGTT had glucose values equal to or above the following thresholds: fasting plasma glucose (FPG) 5.1 mmol/L, 1-h plasma glucose (1-h PG) 10.0 mmol/L, and 2-h plasma glucose (2-h PG) 8.5 mmol/L (D. International Association of, P. Pregnancy Study Groups Consensus, 2010).

2.3. Laboratory analysis

Maternal FPG, 1-h PG, 2-h PG, TC, TG, HDL-c, and LDL-c were analyzed by the Architect c16000 chemistry analyzer (Abbott, USA), and HbA1c was performed in HLC-723-G8 (Tosoh, Japan) in the hospital's clinical laboratory department which performed internal quality

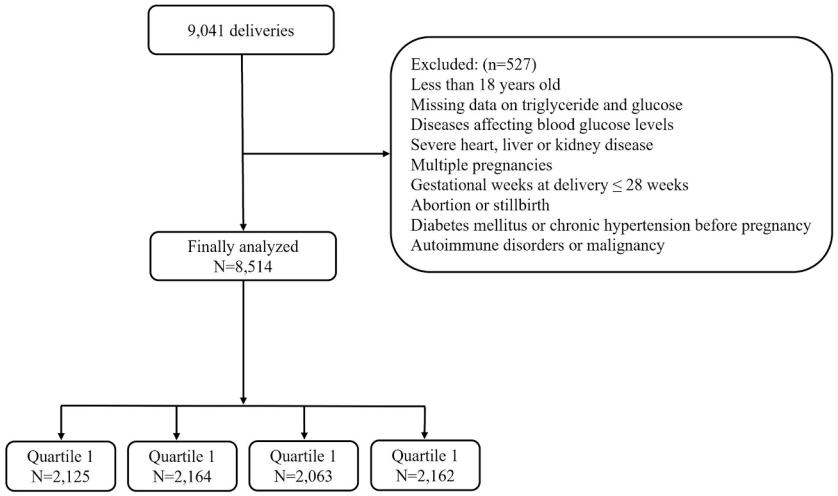

Fig. 1. Flowchart of participant enrollment and group assignment in Hangzhou, China, from March 2018 to February 2019.

controls daily and calibrated the instrument annually. In addition, the laboratory participated in and passed the external quality assessments organized by the national and provincial for clinical laboratories to guarantee the accuracy of the tests. The Westgard multi-rule quality control method was used throughout the testing process for internal quality control. All operations were performed in strict accordance with the standard operating procedures of the instrument.

2.4. Definition of index

The formulas for calculating the indexes:

Body mass index (BMI) was defined as body weight (kg) divided by the square of height in meters (Jastreboff et al., 2022);

TyG was calculated as TyG = Ln [TG (mg/dl) × FPG (mg/dl)/2] (Simental-Mendia et al., 2008).

2.5. Statistical analysis

Continuous variables were presented as mean with standard deviation (SD), and categorical variables were described as frequency or percentage. Continuous variables in multiple groups were compared using a one-way analysis of variance, and the independent-sample *t*-test was performed in two groups. The statistical differences between categorical variables were compared using Pearson's chi-square test. Additionally, the nonlinearity of the dose–response curve was assessed to investigate the association between the TyG index and the risk of adverse pregnancy outcomes. Five knots were created at the ≤8.5, 8.6–9.0, 9.1–9.5, 9.6–10.0 and >10.0, with the TyG index ≤8.5 as the reference point. Logistic regression analyses were performed to determine the ORs and 95 % confidence intervals (CIs) according to respective quartiles with adjusting for potential covariates. The ORs for each quartile were calculated using the 1st quartile of TyG index as the reference. The statistical analysis was performed using SPSS 20.0 software (IBM, USA).

Receiving operating characteristic (ROC) curves and AUC were applied to evaluate the ability of these indices to detect adverse pregnancy outcomes. The predictive model was evaluated using the bootstrap resampling method (1000 bootstrap resamples). The performance of the models was assessed by conducting the Hosmer-Lemeshow test and calibration curve. The calibration curves were generated using the R programming language. A two-sided $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

A total of 8,514 pregnant women were enrolled, out of which 1,738 (20.41 %) women were diagnosed with GDM. Table 1 showed the baseline characteristics according to the TyG index's quartiles. The ranges of TyG index for the 1st, 2nd, 3rd, and 4th quartiles were as follows: 7.81–8.63, 8.64–8.86, 8.87–9.09, and 9.10–10.83 respectively. The mean age, preconception BMI, GWG, gestational age, birth weight, cesarean section rate, TC, TG, LDL-c, HbA1c, FPG, 1-h PG, and 2-h PG of the pregnant women exhibited significant changes with increasing TyG index levels (all $P < 0.05$). Patients in higher TyG index quartiles showed a lower level of HDL-c ($P < 0.001$).

Table 1
Characteristics of participants based on the TyG index quartiles in Hangzhou, China, from March 2018 to February 2019.

Variables	Q1	Q2	Q3	Q4	*P*-values
N (number)	2,125	2,164	2,063	2,162	
Maternal age (years)	30.1 ± 4.0	30.7 ± 4.2	31.3 ± 4.3	31.8 ± 4.4	<0.001[a]
Preconception BMI (kg/m^2)	19.98 ± 2.37	20.53 ± 2.52	21.11 ± 2.79	21.87 ± 2.96	<0.001 [a]
Gestational weight gain (kg)	14.04 ± 4.37	13.92 ± 4.33	13.93 ± 4.86	13.63 ± 4.72	0.027 [a]
Gestational age (week)	39.41 ± 1.36	39.24 ± 1.37	39.21 ± 1.37	38.99 ± 1.57	<0.001 [a]
Birth weight (g)	3262 ± 417	3286 ± 421	3321 ± 432	3351 ± 482	<0.001 [a]
Cesarean section (n, %)	675 (31.76)	823 (38.03)	890 (43.14)	1,010 (46.72)	<0.001[b]
Gravidity (n, %)					
1	966 (45.46)	883 (40.81)	715 (34.66)	690 (31.91)	
2	616 (28.99)	640 (29.57)	637 (30.88)	684 (31.64)	
≥3	543 (25.55)	641 (29.62)	711 (34.46)	788 (36.45)	
Parity (n, %)					
0	1,415 (66.59)	1,359 (62.80)	1,159 (56.18)	1,182 (54.67)	
1	681 (32.05)	777 (35.91)	864 (41.88)	936 (43.29)	
≥2	29 (1.36)	28 (1.29)	40 (1.94)	44 (2.04)	
TC (mmol/L)	5.63 ± 0.89	5.93 ± 0.94	6.03 ± 1.02	6.03 ± 1.05	<0.001 [a]
TG (mmol/L)	1.41 ± 0.24	1.87 ± 0.17	2.26 ± 0.24	3.19 ± 0.77	<0.001 [a]
HDL-c (mmol/L)	2.04 ± 0.36	1.99 ± 0.35	1.90 ± 0.36	1.77 ± 0.34	<0.001 [a]
LDL-c (mmol/L)	2.68 ± 0.67	2.88 ± 0.70	2.94 ± 0.78	2.77 ± 0.82	<0.001 [a]
HbA1c (%)	4.87 ± 0.27	4.92 ± 0.27	4.97 ± 0.29	5.04 ± 0.33	<0.001 [a]
FPG (mmol/L)	4.24 ± 0.30	4.34 ± 0.30	4.40 ± 0.33	4.57 ± 0.46	<0.001 [a]
1-h PG (mmol/L)	7.77 ± 1.57	7.98 ± 1.59	8.14 ± 1.62	8.63 ± 1.77	<0.001 [a]
2-h PG (mmol/L)	6.68 ± 1.28	6.96 ± 1.33	7.10 ± 1.38	7.46 ± 1.51	<0.001 [a]
TyG index	8.46 ± 0.15	8.76 ± 0.07	8.98 ± 0.07	9.33 ± 0.21	<0.001 [a]

Continuous variables are presented as means ± SD. Categorical data are presented as frequencies (percentages). [a] *P*-values were obtained through one-way analysis of variance; [b] *P*-value was obtained through Pearson's chi-square test. TyG index, triglyceride-glucose index; Q, quartiles; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; PG, plasma glucose.

3.2. The characteristics of participants according to adverse pregnancy outcomes

The fundamental characteristics of participants across different pregnancy outcomes were presented in Supplementary Table 1. The incidence of preeclampsia, preterm birth, and macrosomia among participants were 1.80 % (153/8,514), 4.92 % (419/8,514), and 5.34 % (455/8,514), respectively. Moreover, cases of preeclampsia, preterm birth, and macrosomia exhibited significantly higher TyG index values, preconception BMI levels, and GDM rates compared to the control group (all $P < 0.05$). Pregnant women with preeclampsia demonstrated increased GWG and earlier gestational age as well as differences in gravidity and parity when compared to non-preeclamptic pregnant women (all $P < 0.01$). Pregnant women who delivered prematurely were older with lower GWG during pregnancy and delivered at an earlier gestational age; they also showed differences in gravidity and parity when compared to full-term pregnant women (all $P < 0.01$). Furthermore, pregnant women who gave birth to macrosomia exhibited higher GWG and later gestational age compared to those who gave birth to infants with normal weight (all $P < 0.001$); a disparity in gravidity was also observed ($P < 0.05$).

3.3. Univariate analysis

The association between the TyG index and adverse pregnancy outcomes was demonstrated in Fig. 2 and Fig. 3. The findings depicted in Fig. 2 revealed a positive dose–response relationship between the TyG index and adverse pregnancy outcomes (preeclampsia, preterm birth, and macrosomia) within the entire study population. Furthermore, on univariate analysis, compared with the first quartile of the TyG index, higher levels of TyG index (2nd, 3rd, and 4th quartiles) were associated with an increased risk of adverse outcomes: preeclampsia (OR: 1.28; 1.82; 3.63), preterm birth (OR: 1.17; 1.31; 2.12), and macrosomia (OR: 1.39; 1.80; 2.68) (Fig. 3).

3.4. Multivariable analysis

Two models were established to verify the relationship stability under different conditions. First, Model 1 was adjusted for basic characteristics, including maternal age, preconception BMI, GWG, gestational age, gravidity, and parity. Compared to pregnant women in the first quartile of TyG index, those in the highest quartile (4th quartile) exhibited significantly higher adjusted ORs for preeclampsia [2.16 (1.28, 3.64)] ($P < 0.01$) and preterm birth [2.03 (1.51, 2.72)] ($P < 0.001$). Furthermore, there was a progressive increase in adjusted ORs for macrosomia across TyG index quartiles [Q2: 1.42 (1.02, 2.27); Q3: 1.66 (1.21, 2.27); Q4:2.48 (1.83, 3.35)] (all $P < 0.05$). Subsequently, to account for the influence of diabetes-related factors in this model, GDM was included as a covariate in Model 2. The results obtained from this model were consistent with those observed previously (Table 2).

3.5. ROC curve analyses of TyG index to predict adverse pregnancy outcomes

To assess the predictive value of the TyG index, we employed ROC curve analysis to evaluate sensitivity and specificity (Table 3). The AUC values for preeclampsia [0.665 (0.619, 0.711)], preterm birth [0.588 (0.559, 0.618)], and macrosomia [0.606 (0.580, 0.633)] demonstrated significant AUC (all $P < 0.001$, data were not shown), indicating considerable accuracy and specificity as depicted in Fig. 4 and Table 3 respectively. At a cut-off of 8.96, optimal sensitivity and specificity were observed for preeclampsia at levels of 64.71 % and 61.95 % respectively; while at a cut-off point of 8.98, sensitivity and specificity for preterm birth were found to be 50.12 % and 64.45 %. Similarly, at the cut-off of 8.97, sensitivity and specificity for macrosomia were 53.63 % and 63.44 % respectively. Furthermore, the results indicated that the TyG index exhibited a considerable NPV value and diagnostic efficiency.

3.6. Evaluation of the predictive models of adverse pregnancy outcomes

The Hosmer-Lemeshow test was employed to calibrate the predictive models for adverse pregnancy outcomes. The results indicated that all three models were well calibrated (preeclampsia: $\chi2 = 9.802$; preterm birth: $\chi2 = 11.800$; macrosomia: $\chi2 = 6.426$, all $P > 0.05$). Bootstrap resampling validated the predictive accuracy of the models, and calibration curves demonstrated a high level of consistency between predicted and actual probabilities for risks below 15 % (Supplementary Fig. 1).

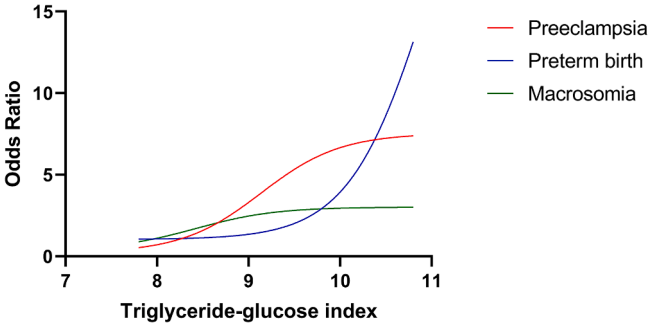

Fig. 2. Dose-response relationship between the TyG index and adverse pregnancy outcomes in Hangzhou, China, from March 2018 to February 2019. TyG index, triglyceride-glucose index.

4. Discussion

This study comprehensively evaluates the associations between maternal TyG index and adverse pregnancy outcomes. The study included 8,514 pregnant women, among whom 153 (1.80 %) developed preeclampsia, 419 (4.92 %) experienced preterm delivery, and 455 (5.34 %) had macrosomia. Our findings confirm a significant positive association and dose–response relationship between the TyG index and the incidence of preeclampsia, preterm birth, and macrosomia in a large sample size. Even after adjusting for various confounding factors, individuals in higher quartiles of the TyG index exhibited significantly increased risks of adverse pregnancy outcomes compared to those in the first quartile. Based on ROC analysis, we observed significant areas under the ROC curve for preeclampsia, preterm birth, and macrosomia when using the TyG index as a predictor; these results were further validated by Hosmer-Lemeshow test and calibration curve. These findings suggested that the TyG index was a valuable predictor for adverse pregnancy outcomes.

Impaired insulin secretion or sensitivity is commonly referred to as the primary pathophysiology of various conditions, and women with dominant IR are at a higher risk for adverse pregnancy outcomes. Therefore, early identification of pregnant women with unfavorable pregnancy outcomes is crucial. Numerous observations suggest that the TyG index serves as a potentially valuable indicator of IR and demonstrates its significance in predicting a wide range of morbidity and development. Considering that the TyG index is a simple method for assessing IR, utilizing it to identify high-risk women may be an advantageous alternative to identifying populations prone to adverse pregnancy outcomes in general.

Epidemiological studies have demonstrated that IR plays a pivotal role in the occurrence of numerous adverse pregnancy outcomes (Sun et al., 2020; Benhalima et al., 2019; Cosson et al., 2022; Lin et al., 2021). Preeclampsia is a multisystem disorder that typically affects 2 %–5 % of pregnant women and stands as one of the primary causes of maternal morbidity and mortality (Poon et al., 2019). A retrospective study revealed a significant association between IR and an increased risk of hypertensive disorders during pregnancy (Lin et al., 2021). The underlying mechanisms can be elucidated as follows: Insulin resistance is a physiological characteristic of pregnancy, which progressively intensifies to support normal fetal development and growth. However, elevated steroid hormones like progesterone and corticosteroids (Vejrazkova et al., 2014), along with certain placenta-secreted cytokines and hormones such as leptin and TNFα (Lacroix et al., 2013), may exacerbate insulin resistance during pregnancy. Nevertheless, excessive activation of insulin resistance stimulates the sympathetic nervous system, elevates vascular resistance, augments sodium reabsorption in the distal glomerulus, ultimately leading to endothelial dysfunction and potentially contributing to elevated blood pressure during pregnancy (Pan et al., 2023). Preterm birth, the leading cause of neonatal mortality, can result in various lifelong morbidities (Howson et al., 2013; Goldenberg et al., 2008). The condition of IR is characterized by elevated blood glucose levels, which in turn triggers inflammation, oxidative stress, and dysfunction of the endothelial cells (Monnier and Colette, 2015; Ceriello et al., 2008). A substantial body of evidence from both mouse models and human studies now supports the notion that preterm birth occurs due to a breakdown in fetal-maternal tolerance coupled with excessive premature inflammation (Green and Arck, 2020). The placenta is responsible for providing oxygenation and nutrition to the fetus. During

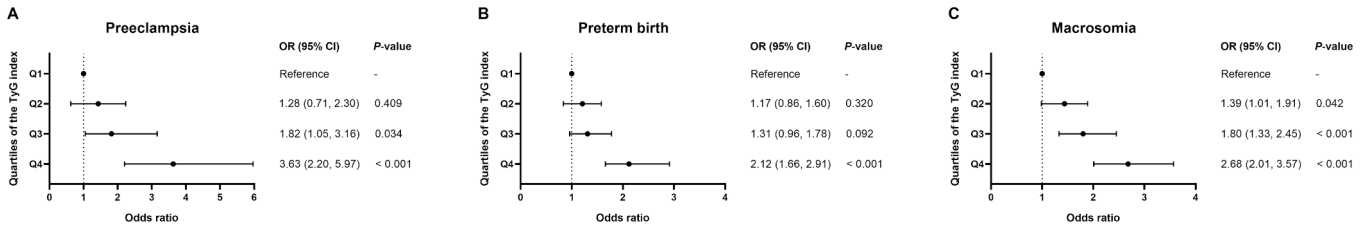

Fig. 3. The TyG index and the risk of adverse pregnancy outcomes in Hangzhou, China, from March 2018 to February 2019. (A) The association between quartiles of the TyG index and the risk of preeclampsia; (B) The association between quartiles of the TyG index and the risk of preterm birth; (C) The association between quartiles of the TyG index and the risk of macrosomia. The risk was assessed using logistic regression analysis, with the first quartile serving as the reference point. TyG, triglyceride-glucose; Q, quartile; OR, odds ratio.

Table 2
Multivariable logistic regression analysis of various indices for adverse pregnancy outcomes in Hangzhou, China, from March 2018 to February 2019.

Variables	Q1	Q2		Q3		Q4	
		OR (95 % CI)	*P*-values	OR (95 % CI)	*P*-values	OR (95 % CI)	*P*-values
Preeclampsia							
Model 1	Reference	1.11 (0.61, 2.03)	0.723	1.38 (0.78, 2.45)	0.264	2.16 (1.28, 3.64)	0.004
Model 2	Reference	1.09 (0.60, 1.99)	0.768	1.35 (0.76, 2.38)	0.309	2.01 (1.18, 3.41)	0.010
Preterm birth							
Model 1	Reference	1.14 (0.83, 1.57)	0.415	1.22 (0.89, 1.67)	0.229	2.03 (1.51, 2.72)	<0.001
Model 2	Reference	1.14 (0.83, 1.56)	0.420	1.21 (0.88, 1.67)	0.234	2.02 (1.50, 2.71)	<0.001
Macrosomia							
Model 1	Reference	1.42 (1.02, 2.27)	0.036	1.66 (1.21, 2.27)	0.002	2.48 (1.83, 3.35)	<0.001
Model 2	Reference	1.41 (1.02, 1.95)	0.038	1.64 (1.19, 2.25)	0.002	2.35 (1.74, 3.19)	<0.001

Model 1: adjusted for maternal age, preconception BMI, gestational weight gain, gestational age, gravidity, parity; Model 2: adjusted for GDM, maternal age, preconception BMI, gestational weight gain, gestational age, gravidity, parity. Gestational age was not included as an adjusted variable for preterm birth. Q, quartiles; OR, odds ratio; CI, confidence interval.

Table 3
ROC analysis of the TyG index for predicting adverse pregnancy outcomes in Hangzhou, China, from March 2018 to February 2019.

Variables	Preeclampsia	Preterm birth	Macrosomia
AUC (95 % CI)	0.665 (0.619, 0.711)	0.588 (0.559, 0.618)	0.606 (0.580, 0.633)
Cutoff value	8.96	8.98	8.97
Sensitivity, %	64.71	50.12	53.63
Specificity, %	61.95	64.45	63.44
PPV, %	3.02	7.18	7.65
NPV, %	98.97	96.26	96.04
Diagnostic efficiency, %	62.00	65.64	62.92

ROC, receiver operating characteristic; TyG, triglyceride-glucose; AUC, the area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

these processes, certain by-products of oxygen have been shown to induce oxidative stress and cause cellular damage. This leads to premature aging of the placenta. Premature aging along with degenerative changes may reduce its functional capacity resulting in abnormal pregnancy outcomes such as preterm birth (Sultana et al., 2017). The vascular endothelium plays a critical role in regulating fetal growth and development. In pregnancies with preterm birth, inadequate trophoblast invasion combined with insufficient remodeling of uterine spiral arteries leads to placental malperfusion and ischemia - key mechanisms underlying preterm birth (Lane-Cordova et al., 2019). Therefore, insulin directly or indirectly promotes the occurrence of premature birth through inflammation, oxidative stress, and endothelial dysfunction. Furthermore, several epidemiological studies have observed associations between insulin resistance and macrosomia (Kc et al., 2015; Yamashita et al., 2014). Maternal hyperglycemia can pass through the placenta and stimulate excessive insulin secretion from the fetal pancreas. This excess insulin promotes storage of fetal adipose tissues and growth (Kc et al., 2015). Therefore, during pregnancy insulin resistance or beta cell dysfunction plays an important role in fetal overgrowth. This enabled us to elucidate the heightened TyG index, a marker of insulin resistance, in preeclampsia, preterm birth, and macrosomia patients. Even after conducting univariate analysis, the data further demonstrated that the TyG index is linked with these adverse pregnancy outcomes during pregnancy and these correlation remains statistically significant even after adjusting for potential confounding variables.

Given the potential mechanism by which the TyG index may contribute to adverse pregnancy outcomes, there is a limited number of relevant articles available. Pazhohan et al. (Pazhohan et al., 2019) assessed the association between maternal TyG index and the likelihood of having large for gestational age (LGA) infants in Iranian mothers. The findings demonstrated a significant correlation between an increase in TyG index and an elevated risk of LGA infants. Similarly, Liu et al. (Liu et al., 2020) investigated the predictive ability of first-trimester TyG index for identifying Chinese women at risk for delivering LGA neonates. After adjusting for confounding factors, it was observed that women in the highest tertile of TyG had a significantly higher probability of giving birth to LGA infants compared to those in the lowest tertile. Pan et al.'s study revealed that early trimester TyG index independently contributed as a risk factor for developing hypertensive disorders during pregnancy. Although they found an increased incidence of preterm birth with rising TyG index values, they did not conduct an extensive analysis (Pan et al., 2023). Conversely, Li et al. (2022) found that although an increased TyG index was associated with a higher risk of gestational hypertension and preeclampsia according to univariate logistic regression analysis, no significant association was observed after comprehensive adjustment. In Latin American women, similar results were obtained as no significant

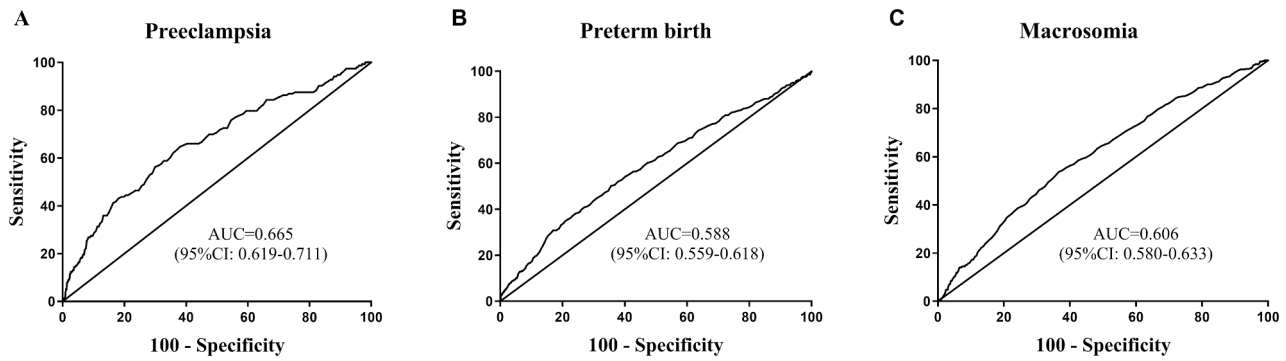

Fig. 4. ROC curves of the TyG index for predicting adverse pregnancy outcomes in Hangzhou, China, from March 2018 to February 2019. (A) ROC curve of the TyG index for predicting preeclampsia; (B) ROC curve of the TyG index for predicting preterm birth; (C) ROC curve of the TyG index for predicting macrosomia. ROC, receiver operative characteristic curves; TyG, triglyceride-glucose; AUC, area under the curve; CI, confidence interval.

differences were found between high and low TyG indices regarding preeclampsia incidence, preterm birth rates or occurrence of LGA infants (Sanchez-Garcia et al., 2020). Although the existing literature suggests that the TyG index is a risk factor for adverse pregnancy outcomes in univariate regression analyses, inconsistencies in the results were observed after adjusting for various factors. We have identified several reasons contributing to this discrepancy: (1) geographic variations among populations; (2) differences in the timing of testing this index, as we conducted it during in the second trimester while some studies tested it during first trimester; and (3) discrepancies in calibrating factors used in regression analyses. Additionally, sample sizes and variations in grouping methods also played a potential role. It is crucial for future studies to acknowledge these inconsistencies and explore potential explanations for conflicting findings.

Although there are limited reports regarding the predictive ability of the TyG index for adverse pregnancy outcomes, most studies demonstrate comparable predictive values for this index. Among them, Li et al. (Li et al., 2022) reported an AUC value of 0.5619 (0.5187, 0.6052) for preeclampsia using the TyG index, with an optimal cut-off point of 8.560, sensitivity of 51.5 %, and specificity of 61.4 %. Lin et al. (2023) found a positive association between the TyG index and risk of LGA after stratification analysis, with an AUC value of 0.584 (0.569, 0.600) in the entire study population and a threshold value of 8.34, sensitivity of 74 %, and specificity of 38 %. Our findings demonstrated that the predictive performance of the TyG index for adverse pregnancy outcomes was consistent with previously reported values. The TyG index exhibited superior discriminative ability (AUC: 0.665) for preeclampsia, with a sensitivity of 64.71 % and a specificity of 61.95 %. Although its predictive capability for preterm birth and macrosomia is slightly weaker compared to preeclampsia, it still demonstrates significant predictive value as evidenced by AUC values of 0.588 (0.559, 0.618) and 0.606 (0.580, 0.633), along with sensitivities and specificities of 50.12 % and 64.45 % for preterm birth, as well as 53.63 % and 64.45 % for macrosomia respectively.

Furthermore, to enhance the credibility of the prediction results, we conducted model calibration. The findings demonstrated a high consistency between the predicted and actual probabilities of the models in predicting a risk of less than 15 %. Considering that the incidence rate of these adverse pregnancy outcomes was below 6 %, in addition to TyG serving as an indicator of conversion to ln, which could result in a more concentrated representation of previously scattered data. Therefore, we could conclude that a satisfactory agreement within an incidence rate of 15 % indicates acceptability. In summary, these findings validated the efficacy of TyG index as additional reliable biomarkers for predicting adverse pregnancy outcomes.

Preeclampsia, preterm birth and macrosomia represent common and dangerous complications during pregnancy whose underlying mechanisms remain largely unknown; due to our limited comprehension regarding this pathology's biology thus far we have not yet identified any effective preventative measures. However, the TyG index provides us with a novel and simple approach towards addressing these issues. To the best of our knowledge, the present study appears to be the first to comprehensively report TyG index is independently associated with an increased likelihood of preeclampsia, preterm birth, and macrosomia. However, some limitations of our study must be considered. Firstly, we did not collect adequate information regarding the lifestyle status of our participants, such as dietary and physical activity factors which could act as confounders. Secondly, we lack data on TyG index in the first trimester or even before pregnancy, which would allow early detection of abnormal TyG index, and timely intervention could provide to prevent or reduce the occurrence of adverse pregnancy outcomes. This is partly because most prepregnant and early pregnant examinations of women are completed in community hospitals. Thirdly, although we also collected other adverse pregnancy outcomes, such as polyhydramnios, shoulder dystocia, neonatal hypoglycemia, neonatal respiratory distress, congenital anomaly, etc., they were not included in the statistical analysis in this paper, considering that the number is small and could easily make the results prone to false bias. Fourthly, the analysis was conducted on a small sample with population and single-center limitations, which may make the results unrepresentative. Finally, we could not compare the TyG index with hyperinsulinemic-euglycemic clamp or HOMA-IR as an independent risk factor for GDM because the above two tests are not included in regular prenatal health care.

5. Conclusion

Our findings suggest that the TyG index possesses a certain level of predictive capability in evaluating the risk associated with adverse pregnancy outcomes. Moreover, the TyG index is independently associated with preeclampsia, preterm birth, and macrosomia, regardless of whether the pregnant woman has GDM or not. Therefore, it can be used as alternative indices in evaluating the risk of complications during pregnancy.

Ethical approval

The ethics committee of Women's Hospital, Zhejiang University School of Medicine approved the study protocol (approval number: IRB-20220357-R).

Informed consent

Due to the retrospective nature of the study, an informed consent exemption was applied.

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CRediT authorship contribution statement

Jinghua Zhang: Supervision, Formal analysis, Data curation, Conceptualization. **Binbin Yin:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Ya Xi:** Software, Methodology, Formal analysis. **Yongying Bai:** Writing – review & editing, Writing – original draft, Supervision, Software, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Consent for publication

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The manuscript is not under publication or consideration for publication elsewhere.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102683.

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