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# Is there any association between early trimester Triglyceride–glucose index and incidence of hypertensive disorder of pregnancy and adverse pregnancy outcomes?

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**Background:** Insulin resistance (IR) is a normal feature of pregnancy and plays a crucial role in the pathophysiology of hypertensive disorder of pregnancy (HDP). The triglyceride–glucose index (TyG index) has been shown as a simple and reliable alternative IR marker. This work aimed to investigate the association between the TyG index and the incidence of HDP and adverse pregnancy outcomes.

**Methods:** From January 2016 to December 2018, 289 women with HDP and 861 women without HDP were recruited at Shanghai Fifth People's Hospital, Fudan University to determine the relationship between the TyG index and the incidence of HDP and adverse pregnancy outcomes.

**Results:** In the case-control study, the incidence of HDP was found to be significantly associated with the TyG index. Moreover, logistic regression indicated that the TyG index is an independent risk factor for HDP development and incidence of low birth weight (LBW) and fetal distress. In the cohort study, the results showed that the TyG index increased, there was a stepwise increase in HDP incidence, SBP, and DBP levels one week before delivery as well as in LBW and fetal distress incidence. The early trimester TyG index was positively associated with pre-pregnancy BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) one week before delivery. Spline regression showed that there was a significant linear association between HDP incidence and early trimester TyG index when it was >8.5.

**Conclusions:** This work suggested that the early trimester TyG index was closely associated with the development of HDP and adverse pregnancy outcomes.

## KEYWORDS

triglyceride glucose index, hypertensive disorder of pregnancy, low birth weight, fetal distress, Insulin resistance

## Background

Hypertensive disorder of pregnancy (HDP) is defined as a group of diseases coexisting with pregnancy and hypertension, including gestational hypertension, preeclampsia, eclampsia, chronic hypertension with preeclampsia, and chronic hypertension with pregnancy (1). Except for chronic hypertension, HDP occurred mostly after 20 weeks of gestation and returned to normal within 12 weeks after delivery. Over the past few decades, HDP affect 5%–10% of pregnancies worldwide (2). In China, HDP prevalence has been reported to be 5.55–5.57% in 2011 (3), and with the improvement of living standards and support for multiple births in recent years, the prevalence of HDP has increased to 7.2% in 2021 (4). As a group of common pregnancy complications, HDP can lead to many adverse pregnancy outcomes including preterm delivery, placental abruption, cesarean section, postpartum hemorrhage, and a higher incidence of low birth weight (LBW) and fetal distress (3).

Insulin resistance (IR) is a normal feature of pregnancy and becomes more severe as the pregnancy progresses. Previous studies have shown that IR plays a crucial role in the pathophysiology of HDP (5–9). The triglyceride-glucose index (TyG index), based on fasting glucose and triglycerides, has been shown as a simple and reliable surrogate measure to reflect IR compared with the euglycemic-hyperinsulinemic clamp (10–12), which is the ‘gold standard’ for evaluating IR. Also, compared with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), the TyG index is more accessible in clinical practice. Moreover, recent studies have demonstrated that the TyG index presented a better performance than the HOMA-IR index in identifying patients with IR and was more strongly associated with arterial stiffness in patients with type 2 diabetes mellitus (T2DM) in comparison with the HOMA-IR index (13, 14). In addition, Zheng et al. reported that the TyG index is an independent risk factor for hypertension and has a dose-dependent relationship, which can independently predict hypertension events (15). To the best of our knowledge, the relationship between the TyG index and the incidence of HDP remains unclear. The purpose of this study was to investigate the association between the TyG index and the incidence of HDP and adverse pregnancy outcomes.

## Methods

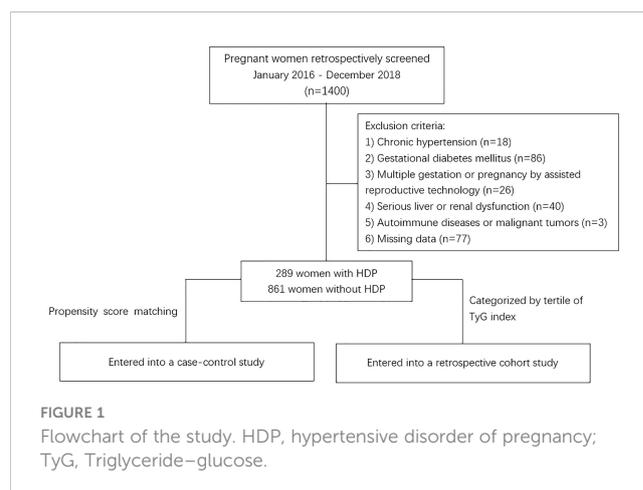
### Study population

In this study, we recruited all women of Obstetrics at Shanghai Fifth People’s Hospital, Fudan University from January 2016 to December 2018, and there were 1400 pregnant women were retrospectively screened at digital medical record systems, the women had no other medical diagnosis at the beginning of pregnancy and were truly representative. Also, all the women were followed up until 12 weeks after delivery. The retrospective analysis process followed the procedure described in Figure 1. Women were excluded from the study for any of the following: (1) had a diagnosis of chronic hypertension before pregnancy or before 20 weeks’ gestation; (2) gestational diabetes mellitus; (3) multiple gestations or pregnancy by assisted reproductive

technology; (4) serious liver dysfunction (alanine transaminase above 2.5 times upper limit) and renal dysfunction (estimated Glomerular Filtration Rate below 90 ml/min/1.73m<sup>2</sup>); (5) autoimmune diseases or malignant tumors; (6) participants with missing TyG index measurements or other data. In total, 1150 women (861 without HDP and 289 with HDP) were finally included in the analysis. The study protocol was approved by the Institutional Review Board of Shanghai Fifth People’s Hospital, Fudan University.

### Data collection

The health cards of all pregnant women were obtained from 9 to 12 weeks’ gestation and included information about age, occupation, last menstruation, method of conception, parity, obstetric history, family history of hypertension, and pre-pregnancy weight. Subsequently, at the first visit, blood pressure (BP), weight, height, blood count (Sysmex XN9000, Japan), biochemistry results (Cobas 8000, Roche, Switzerland), and fasting glucose were recorded. Fasting venous blood samples were performed after at least 8 hours of fast. The Triglyceride–glucose (TyG) index was calculated as  $\ln[\text{triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2]$ . BP was measured with an automated sphygmomanometer (HEM-7124) in the seated position on two occasions 4h apart after resting for at least 5 minutes. The elbow of the arm used to measure BP was supported at heart level. In the presence of raised BP, routine obstetric examination was performed every 2 to 4 weeks in the outpatient clinic until 34 weeks’ gestation and thereafter every week. Each women’s body weight and height were measured in light clothing without shoes. The weighing scale, height meter, and automated sphygmomanometers were calibrated every 6 months and all measurements were taken by the same outpatient nurse. Body mass index (BMI) was calculated as  $\text{weight (kg)} / \text{height (m)}^2$ . After delivery, details including gestational age at delivery, mode of delivery, newborn weight, sex of the neonate and adverse pregnancy outcomes including LBW, macrosomia, preterm birth, placental abruption, postpartum hemorrhage, cesarean section, rupture of membranes, and fetal distress were recorded by medical staff.



## Definitions

HDP is a group of diseases coexisting with elevated blood pressure (systolic blood pressure (SBP)  $\geq 140$  mmHg and/or a diastolic blood pressure (DBP)  $\geq 90$  mmHg on two occasions at least 4h apart) during pregnancy (16). Preterm birth is defined as that occurring after 28 weeks and before 37 completed weeks of gestation (17). Low birth weight (LBW) is defined as that the neonates who were born with birth weights lower than 2500g (18). Macrosomia was defined as birth weight more than 4000g (18). Fetal distress is defined as a non-reassuring fetal status that the baby does not have the adequate amount of oxygen supply before labor, during the labor process or after the period of labor (19). Postpartum hemorrhage is defined as losing more than 500 milliliters of blood 24 hours after vaginal birth, and more than 1000 milliliters of blood after a cesarean birth (20).

## Outcomes

The outcome was the incidence of HDP and adverse pregnancy outcome including LBW, macrosomia, preterm birth, placental abruption, postpartum hemorrhage, cesarean section, rupture of membranes, and fetal distress.

## Statistical analysis

To avoid the confounding effects on BP between women with or without HDP, a propensity score matching (PSM) method was employed to match variables of age, pre-pregnancy BMI, family history of hypertension and parity. Matching tolerance was 0.02. We used Shapiro–Wilk test and the shape of the histogram to check the normality. Proportions (%) were used for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) was used for continuous variables.  $\chi^2$  test, the Student's t-test and Mann-Whitney U test were used to identify the difference between groups. To determine whether TyG index was an independent risk factor, logistic regression analysis was performed with HDP classified in a binary manner (presence/absence) as the dependent variable. Receiver operating characteristic curves were performed to assess the predictability for HDP. To further validate the association of TyG index with HDP and pregnancy outcomes, a cohort study including all subjects was established in which patients were divided into three groups by tertiles of TyG index.  $\chi^2$ , Kruskal-Wallis and *post hoc* test were used to identify the difference in the mean between groups. Linear association between TyG index and pre-pregnancy BMI, SBP and DBP one week before delivery were assessed by simple linear regression analysis. Continuous association of TyG index with HDP incidence was determined by spline regression analysis. All analyses were performed using SPSS 26.0. A two-tailed P value  $< 0.05$  was considered statistically significant.

## Results

### Characteristics of women with and without HDP in all subjects and subjects after PSM

In this study, HDP developed in 289 women (25.13%) among the 1150 subjects, and women with older age ( $P<0.001$ ), higher pre-pregnancy BMI ( $P=0.002$ ) and family history of hypertension ( $P<0.001$ ) were more likely to develop HDP (Table 1). At the first visit, compared with women without HDP, patients with HDP had a much higher level of TG ( $1.83 \pm 0.83$  vs.  $1.62 \pm 0.63$  mmol/L,  $P<0.001$ ), FBG ( $4.20 \pm 0.48$  vs.  $4.04 \pm 0.40$  mmol/L,  $P<0.001$ ), TyG index ( $8.63 \pm 0.41$  vs.  $8.49 \pm 0.36$ ,  $P<0.001$ ) and WBC ( $8.96 \pm 1.82$  vs.  $8.63 \pm 1.98 \times 10^9/L$ ,  $P=0.012$ ), whereas the difference in TC or LDL was not significant. Also, there were no significant differences in SBP, DBP, ALT, AST, and creatin at baseline between the two groups. One week before delivery, women with HDP had a much higher SBP ( $123 \pm 14$  vs.  $121 \pm 13$  mmHg,  $P=0.022$ ), DBP ( $77 \pm 11$  vs.  $75 \pm 11$  mmHg,  $P=0.026$ ), and creatinine ( $50.12 \pm 8.83$  vs.  $46.39 \pm 7.40$   $\mu\text{mol/L}$ ,  $P<0.001$ ). In addition, there were significant differences in weight gain ( $16.93 \pm 4.72$  vs.  $15.79 \pm 4.38$  kg,  $P<0.001$ ) during the whole pregnancy between the two groups. For pregnancy outcome, obviously, mothers with HDP tended to deliver lower-weight newborns ( $3220.3 \pm 619.8$  vs.  $3376.8 \pm 417.5$  g,  $P<0.001$ ), and had a higher rate of fetal distress (10.0% vs. 3.3%,  $P<0.001$ ), cesarean section (59.5% vs. 42.9%,  $P<0.001$ ), preterm (10.7% vs. 3.5%,  $P<0.001$ ), postpartum hemorrhage (11.8% vs. 3.6%,  $P<0.001$ ) and delivering low birth weight infants (10.7% vs. 2.1%,  $P<0.001$ ) than mothers without HDP (Table 1).

To eliminate confounding effects on BP, a PSM method was employed to match variables of age, pre-pregnancy BMI, family history of hypertension, and parity. After matching, there were no significant differences in WBC at the first visit, HDL one week before delivery, and incidence of postpartum hemorrhage between women with and without HDP. Nonetheless, there remained a significantly higher TG ( $P<0.001$ ), FBG ( $P<0.001$ ), and TyG index ( $P<0.001$ ) at baseline, higher SBP ( $P<0.001$ ), DBP ( $P<0.001$ ), and creatinine ( $P<0.001$ ) one week before delivery and higher incidence of LBW ( $P=0.008$ ), fetal distress ( $P=0.010$ ), cesarean section ( $P<0.001$ ) and preterm ( $P=0.032$ ) in women with HDP compared with control subjects (Table 1).

### The early trimester TyG index was an independent risk factor and diagnostic predictive factor for HDP development, LBW and fetal distress

In case-control study, we used multiple logistic regression to analyze the odds ratio (OR) of HDP incidence in each TyG group for all subjects. After adjusted by age, pre-pregnancy BMI, family history of hypertension, parity and weight gain, compared to the

TABLE 1 Characteristics of women with and without HDP in all subjects and subjects after PSM.

	All subjects			After PSM		
	Women without HDP	Women with HDP	<i>P</i>	Women without HDP	Women with HDP	<i>P</i>
<b>n</b>	<b>861</b>	<b>289</b>		<b>230</b>	<b>230</b>	
Age (years)	28.2 ± 5.6	29.7 ± 5.3	<0.001	28.7 ± 6.0	28.7 ± 5.0	0.933
Pre-pregnancy BMI (kg/m <sup>2</sup> )	22.0 ± 3.0	22.7 ± 3.5	0.002	21.5 ± 2.8	21.8 ± 3.0	0.144
<b>Family history of hypertension</b>						
No	772(89.7)	230(79.6)	<0.001	199(86.5)	202(87.8)	0.676
Yes	89(10.3)	59(20.4)		31(13.5)	28(12.2)	
<b>Parity</b>						
Nulliparous	352(40.9)	166(57.4)	<0.001	123(53.5)	113(49.1)	0.351
Parous	509(59.1)	123(42.6)		107(46.5)	117(50.9)	
<b>At the first visit</b>						
SBP (mmHg)	116 ± 9	116 ± 10	0.977	116 ± 8	116 ± 6	0.198
DBP (mmHg)	70 ± 8	71 ± 8	0.458	71 ± 7	71 ± 7	0.840
ALT (units/L)	14.0(10.3-18.0)	15(10.0-22.6)	0.153	14.0(11.0-18.0)	14.3(10.0-22.0)	0.508
AST (units/L)	19.0(15.0-23.0)	19.4(15.0-25.0)	0.146	19.0(15.2-24.0)	19.0(15.0-25.0)	0.585
Creatinine (μmol/L)	44.15 ± 5.74	44.47 ± 6.17	0.421	43.94 ± 5.93	44.19 ± 6.41	0.664
TC (mmol/L)	4.81 ± 0.87	4.70 ± 0.84	0.057	4.80 ± 0.87	4.69 ± 0.87	0.159
TG (mmol/L)	1.62 ± 0.63	1.83 ± 0.83	<0.001	1.46 ± 0.54	1.78 ± 0.72	<0.001
HDL (mmol/L)	1.94 ± 0.43	1.80 ± 0.38	<0.001	1.96 ± 0.42	1.84 ± 0.37	0.001
LDL (mmol/L)	2.73 ± 0.76	2.64 ± 0.72	0.072	2.62 ± 0.78	2.62 ± 0.77	0.927
FBG (mmol/L)	4.04 ± 0.40	4.20 ± 0.48	<0.001	4.05 ± 0.39	4.21 ± 0.49	<0.001
TyG index	8.49 ± 0.36	8.63 ± 0.41	<0.001	8.39 ± 0.35	8.62 ± 0.39	<0.001
WBC (*10 <sup>9</sup> /L)	8.63 ± 1.98	8.96 ± 1.82	0.012	8.73 ± 1.83	8.91 ± 1.83	0.282
<b>One week before delivery</b>						
SBP (mmHg)	121 ± 13	123 ± 14	0.022	120 ± 6	135 ± 12	<0.001
DBP (mmHg)	75 ± 11	77 ± 11	0.026	75 ± 6	88 ± 8	<0.001
ALT (units/L)	8.7(7.0-11.0)	9.0(7.0-12.1)	0.06	9.0(7.0-11.0)	9.0(7.0-12.0)	0.237
Creatinine (μmol/L)	46.39 ± 7.40	50.12 ± 8.83	<0.001	46.82 ± 7.00	50.43 ± 9.04	<0.001
TC (mmol/L)	6.12 ± 1.11	6.16 ± 1.22	0.633	6.12 ± 1.10	6.20 ± 1.25	0.494
TG (mmol/L)	3.04 ± 0.97	3.63 ± 1.26	<0.001	3.02 ± 0.98	3.57 ± 1.20	<0.001
HDL (mmol/L)	1.87 ± 0.38	1.81 ± 0.43	0.035	1.85 ± 0.39	1.83 ± 0.43	0.562
LDL (mmol/L)	3.64 ± 1.04	3.54 ± 1.03	0.252	3.64 ± 1.03	3.58 ± 1.02	0.542
FBG (mmol/L)	4.01 ± 0.47	4.15 ± 0.59	0.001	4.00 ± 0.43	4.13 ± 0.57	0.003
TyG index	9.13 ± 0.34	9.33 ± 0.35	<0.001	9.12 ± 0.34	9.31 ± 0.35	<0.001
WBC (*10 <sup>9</sup> /L)	9.12 ± 2.34	9.09 ± 2.05	0.845	8.92 ± 2.19	9.04 ± 2.09	0.544
Weight gain (kg)	15.79 ± 4.38	16.93 ± 4.72	<0.001	15.82 ± 4.59	16.92 ± 4.59	0.011
	All subjects			After PSM		
	Women without HDP	Women with HDP	<i>P</i>	Women without HDP	Women with HDP	<i>P</i>

(Continued)

TABLE 1 Continued

	All subjects			After PSM		
	Women without HDP	Women with HDP	<i>P</i>	Women without HDP	Women with HDP	<i>P</i>
n	861	289		230	230	
n	861	289		230	230	
<b>Pregnancy outcome</b>						
Fetus sex (female)	422(49.9)	156(54.0)	0.229	117(50.9)	127(55.2)	0.350
Newborn weight (g)	3376.8 ± 417.5	3220.3 ± 619.8	<0.001	3384.8 ± 395.4	3158.4 ± 623.2	<0.001
LBW	18(2.1)	31(10.7)	<0.001	10(4.3)	25(10.9)	0.008
Macrosomia	47(5.5)	18(6.2)	0.624	9(3.9)	10(4.3)	0.815
Fetal distress	28(3.3)	29(10.0)	<0.001	9(3.9)	23(10.0)	0.010
Cesarean section	363(42.9)	172(59.5)	<0.001	93(40.4)	128(55.7)	<0.001
Preterm	30(3.5)	31(10.7)	<0.001	11(4.8)	23(10.0)	0.032
Rupture of membranes	102(11.8)	22(7.6)	0.058	23(10.0)	16(7.0)	0.241
Placental abruption	3(0.4)	4(1.4)	0.071	0.0(0.0)	3(1.3)	0.247
Postpartum hemorrhage	31(3.6)	34(11.8)	<0.001	21(9.1)	26(11.3)	0.441

Data are means ± SD, median (IQR), or n (%). \*Log-transformed for t test. Boldface P values are statistically significant ( $P < 0.05$ ).

DBP, diastolic blood pressure; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase;

TC, cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; FBG, Fasting glucose; TyG, Triglyceride-glucose; WBC, white blood cell; LBW, low birth weight; PSM, propensity score matching.

PSM to even the variables of age, pre-pregnancy BMI, family history of hypertension and parity, match tolerance was 0.02.

lowest tertile of the TyG index, the OR for subjects in tertile 2 and tertile 3 were 1.46 (95%CI: 1.02-2.09;  $P=0.040$ ) and 2.44 (95%CI: 1.71-3.48;  $P < 0.001$ ) respectively (Table 2). The same results were showed in the logistic regression for the subjects after PSM (Supplementary Table 1). All of these showed that early trimester TyG index as an independent risk factor was closely correlated with the development of HDP. The ROC curves of the TyG index as a marker to predict the incidence of HDP are illustrated in Figure 2. Clinical model include age, pre-pregnancy BMI, family history of hypertension, and parity. The AUC of the TyG index for predicting the occurrence of HDP was 0.684 (95% CI: 0.647-0.721), but the clinical model without TyG index for predicting was 0.657 (95% CI: 0.620-0.695), adding TyG index to the model significantly increased its discriminatory capacity (AUC: 0.725; 95% CI: 0.690-0.760).

Besides, TyG index was also an independent risk factor for the incidence of LBW and fetal stress. After adjusted by age, pre-pregnancy BMI, family history of hypertension, parity and weight gain, compared to the lowest tertile of the TyG index, the OR for incident LBW and fetal distress in tertile 3 were 2.59 (95%CI: 1.25-5.33;  $P=0.010$ ) and 2.92 (95%CI: 1.40-6.10;  $P=0.004$ ) (Supplementary Table 2).

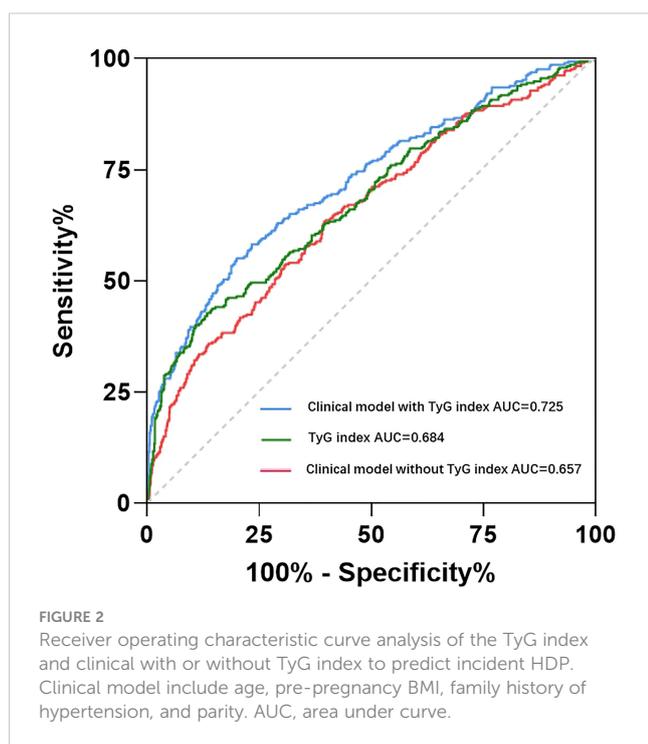
## Comparison of parameters during pregnancy among three groups categorized by tertiles of the early trimester TyG index in the cohort study

All subjects were divided into three groups according to tertiles of the early trimester TyG index: lowest group ( $< 8.35$ ), middle group (8.35-8.70), and highest group ( $> 8.70$ ). There was a stepwise increase in the incidence of HDP (18.9%, 23.6%, and 33.4%;  $P < 0.001$ ), age ( $28.1 \pm 4.8$  vs.  $28.6 \pm 5.3$  vs.  $29.1 \pm 5.3$  years;  $P=0.038$ ), pre-pregnancy BMI ( $21.5 \pm 2.9$  vs.  $22.1 \pm 3.0$  vs.  $22.8 \pm 3.3$  kg/m<sup>2</sup>;  $P < 0.001$ ), DBP ( $70 \pm 8$  vs.  $70 \pm 8$  vs.  $71 \pm 7$  mmHg;  $P=0.003$ ), TC ( $4.54 \pm 0.78$  vs.  $4.77 \pm 0.81$  vs.  $5.05 \pm 0.93$  mmol/L;  $P < 0.001$ ), TG ( $1.10 \pm 0.19$  vs.  $1.55 \pm 0.20$  vs.  $2.41 \pm 0.70$  mmol/L;  $P < 0.001$ ), HDL ( $2.00 \pm 0.41$  vs.  $1.93 \pm 0.41$  vs.  $1.77 \pm 0.41$  mmol/L;  $P < 0.001$ ), LDL ( $2.49 \pm 0.65$  vs.  $2.69 \pm 0.70$  vs.  $2.95 \pm 0.83$  mmol/L;  $P < 0.001$ ), FBG ( $3.98 \pm 0.39$  vs.  $4.10 \pm 0.40$  vs.  $4.18 \pm 0.47$  mmol/L;  $P < 0.001$ ) and WBC ( $8.40 \pm 1.87$  vs.  $8.65 \pm 2.01$  vs.  $9.12 \pm 1.90$   $\times 10^9/L$ ;  $P < 0.001$ ) at the first visit, level of SBP ( $116 \pm 12$  vs.  $118 \pm 9$  vs.  $132 \pm 13$  mmHg;  $P < 0.001$ ), DBP ( $70 \pm 9$  vs.  $73 \pm 8$  vs.  $85 \pm 10$  mmHg;  $P < 0.001$ ), TG ( $2.85 \pm 0.94$  vs.  $3.26 \pm 0.96$  vs.  $3.89 \pm 1.30$  mmol/L;  $P < 0.001$ ), HDL ( $1.93 \pm 0.42$  vs.  $1.84 \pm 0.40$  vs.  $1.75 \pm 0.37$

TABLE 2 Logistic regression analysis with enter selection for presence/absence HDP.

	B	OR	95%CI	P
TyG index (At first visit)				
Tertile 1	Reference			
Tertile 2	0.38	1.46	1.02-2.09	<b>0.040</b>
Tertile 3	0.89	2.44	1.71-3.48	<b>&lt;0.001</b>
Age	0.06	1.06	1.03-1.10	<b>&lt;0.001</b>
Pre-pregnancy BMI	0.06	1.06	1.01-1.11	<b>0.010</b>
Family history of hypertension	0.79	2.20	1.51-3.23	<b>&lt;0.001</b>
Parity	-1.08	0.34	0.24-0.47	<b>&lt;0.001</b>
Weight gain	0.05	1.05	1.02-1.10	<b>0.001</b>

TyG, Triglyceride-glucose. The bold values means statistically significant.



mmol/L;  $P<0.001$ ) and FBG ( $3.98 \pm 0.44$  vs.  $4.11 \pm 0.51$  vs.  $4.15 \pm 0.63$  mmol/L;  $P=0.002$ ) one week before delivery. Likewise, the incidence of LBW (3.1%, 3.1%, and 6.8%,  $P=0.014$ ), fetal distress (2.8%, 5.1%, and 7.1%;  $P=0.025$ ), cesarean section (29.4%, 46.5%, and 67.8%,  $P<0.001$ ), preterm (4.8%, 3.6% and 7.6%,  $P=0.042$ ) and placental abruption (0.0%, 0.5% and 1.4%,  $P=0.028$ ) increase as TyG index increased (Table 3).

### The early trimester TyG index was closely associated with pre-pregnancy BMI, SBP and DBP one week before delivery

To investigate the correlation between the early trimester TyG index and pre-pregnancy BMI, SBP or DBP one week before

delivery, correlation analysis was performed. Simple linear regression analyses were performed to determine the association of the early trimester TyG index with pre-pregnancy BMI, SBP and DBP one week before delivery. There was a significant and moderate linear association for TyG index with pre-pregnancy BMI [ $\beta=0.18$ ;  $t=6.35$ ;  $P<0.001$ ] (Figure 3A), SBP [ $\beta=0.47$ ;  $t=17.78$ ;  $P<0.001$ ] (Figure 3B), and DBP [ $\beta=0.51$ ;  $t=20.00$ ;  $P<0.001$ ] (Figure 3C).

### The early trimester TyG index was closely associated with the incidence of HDP

After adjusting for age, pre-pregnancy BMI, family history of hypertension and parity, a spline model showed a significant relationship between continuous early trimester TyG index and incidence of HDP. We found an increasing trend of incidence of HDP with a higher TyG index despite the lack of a linear relationship between the TyG index and the incidence of HDP. The risk of developing HDP increased when the TyG index was greater than 8.5 (Figure 4).

## Discussion

This retrospective study is the one to confirm the significant positive association and a dose-response relation between the early trimester TyG index and the incidence of HDP in a large sample size. Furthermore, the results provide evidence that the early trimester TyG index is independently associated with the incidence of LBW and fetal distress. This study elucidated the substantial role of TyG index in predicting the development of HDP and adverse pregnancy outcome.

Pregnancy is characterized by a number of metabolic adaptations. Insulin resistance (IR) is a normal characteristic of pregnancy and increases physiologically as the pregnancy progresses to support the normal fetal development and growth (21). Some studies demonstrated the mechanism of IR in pregnancy, Daniela et al. showed that some steroid hormones

TABLE 3 Comparison of parameters during pregnancy among three groups categorized by tertiles of TyG index at the first visit in the cohort study.

	Tertile 1	Tertile 2	Tertile 3	P
TyG index range	<8.35	8.35-8.70	>8.70	
N	392	390	368	
Women with HDP	74(18.9)	92(23.6)	123(33.4)	<0.001
Age (years)	28.1 ± 4.8	28.6 ± 5.3	29.1 ± 5.3†	0.038
Pre-pregnancy BMI (kg/m <sup>2</sup> )	21.5 ± 2.9	22.1 ± 3.0*	22.8 ± 3.3†#	<0.001
Family history of hypertension	30(7.6)	51(13.1)	72(20.5)	<0.001
Parity (Nulliparous)	211(53.8)	169(43.3)	138(37.5)	<0.001
<b>At the first visit</b>				
SBP (mmHg)	116 ± 11	115 ± 10	116 ± 7	0.115
DBP (mmHg)	70 ± 8	70 ± 8	71 ± 7†	0.003
ALT (units/L)	13.2(10.0-18.8)	14.0(10.0-20.9)	13.1(9.0-20.8)	0.507
AST (units/L)	18.0(15.0-23.0)	19.0(15.0-24.0)	19.0(15.0-24.0)	0.471
Creatinine (μmol/L)	43.99 ± 5.69	44.39 ± 6.09	44.32 ± 5.76	0.754
TC (mmol/L)	4.54 ± 0.78	4.77 ± 0.81*	5.05 ± 0.93†#	<0.001
TG (mmol/L)	1.10 ± 0.19	1.55 ± 0.20*	2.41 ± 0.70†#	<0.001
HDL (mmol/L)	2.00 ± 0.41	1.93 ± 0.41	1.77 ± 0.41†#	<0.001
LDL (mmol/L)	2.49 ± 0.65	2.69 ± 0.70*	2.95 ± 0.83†#	<0.001
FBG (mmol/L)	3.98 ± 0.39	4.10 ± 0.40*	4.18 ± 0.47†#	<0.001
WBC (*10 <sup>9</sup> /L)	8.40 ± 1.87	8.65 ± 2.01	9.12 ± 1.90†#	<0.001
<b>One week before delivery</b>				
SBP (mmHg)	116 ± 12	118 ± 9*	132 ± 13†#	<0.001
DBP (mmHg)	70 ± 9	73 ± 8*	85 ± 10†#	<0.001
ALT (units/L)	11.0(8.0-18.0)	11.0(7.7-19.3)	11.0(7.7-19.0)	0.928
Creatinine (μmol/L)	47.42 ± 8.01	47.32 ± 7.84	47.23 ± 8.03	0.876
TC (mmol/L)	6.12 ± 1.17	6.12 ± 1.08	6.18 ± 1.16	0.840
TG (mmol/L)	2.85 ± 0.94	3.26 ± 0.96*	3.89 ± 1.30†#	<0.001
HDL (mmol/L)	1.93 ± 0.42	1.84 ± 0.40	1.75 ± 0.37†#	<0.001
LDL (mmol/L)	3.66 ± 0.99	3.59 ± 1.04	3.52 ± 1.07	0.389
FBG (mmol/L)	3.98 ± 0.44	4.11 ± 0.51*	4.15 ± 0.63†	0.002
WBC (*10 <sup>9</sup> /L)	9.19 ± 2.25	9.01 ± 2.39	9.14 ± 2.16	0.500
Weight gain	16.42 ± 4.36	15.82 ± 4.58	16.07 ± 4.50	0.166
<b>Pregnancy outcome</b>				
Fetus sex (female)	197(49.9)	183(47.0)	185(52.7)	0.306
Newborn weight (g)	3314.7 ± 433.2	3356.6 ± 440.3	3337.6 ± 558.4	0.327
LBW	12(3.1)	12(3.1)	25(6.8)	0.014
Macrosomia	15(3.8)	21(5.4)	29(7.9)	0.052
Fetal distress	11(2.8)	20(5.1)	26(7.1)	0.025
Cesarean section	116(29.4)	181(46.5)	238(67.8)	<0.001
Preterm	19(4.8)	14(3.6)	28(7.6)	0.042

(Continued)

TABLE 3 Continued

	Tertile 1	Tertile 2	Tertile 3	P
Rupture of membranes	47(12.0)	40(10.3)	37(10.1)	0.635
Placental abruption	0(0.0)	2(0.5)	5(1.4)	<b>0.028</b>
Postpartum hemorrhage	23(5.9)	15(3.8)	27(7.3)	0.112

Data are means  $\pm$  SD, median (IQR), or n (%). \*Log-transformed for t test. Boldface P values are statistically significant ( $P < 0.05$ ).

DBP, diastolic blood pressure; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase;

TC, cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; FBG, Fasting glucose; TyG, Triglyceride-glucose; WBC, white blood cell; LBW, low birth weight.

\*Middle group vs. lowest group,  $P < 0.05$ . †Highest

group vs. lowest group,  $P < 0.05$ . #Highest group vs. middle group,  $P < 0.05$ . z

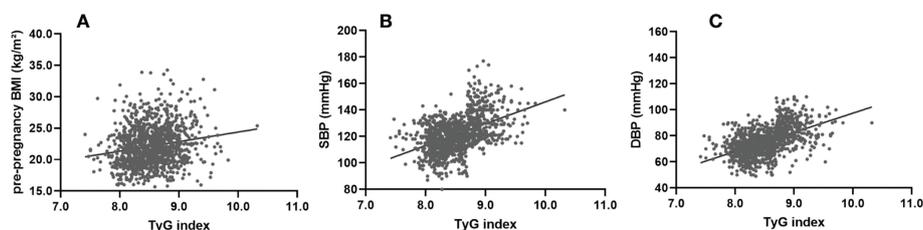


FIGURE 3

Simple linear regression analysis between the TyG index at first visit and pre-pregnancy BMI, SBP and DBP one week before delivery. The TyG index showed a significant and moderate linear association with pre-pregnancy BMI ( $\beta = 0.31$ ;  $F = 65.21$ ; adjusted  $R^2 = 0.09$ ;  $P < 0.001$ ) (A), SBP ( $\beta = 0.25$ ;  $F = 41.48$ ; adjusted  $R^2 = 0.06$ ;  $P < 0.001$ ) (B), and DBP ( $\beta = 0.38$ ;  $F = 106.11$ ; adjusted  $R^2 = 0.14$ ;  $P < 0.001$ ) (C). SBP, systolic blood pressure; DBP, diastolic blood pressure.

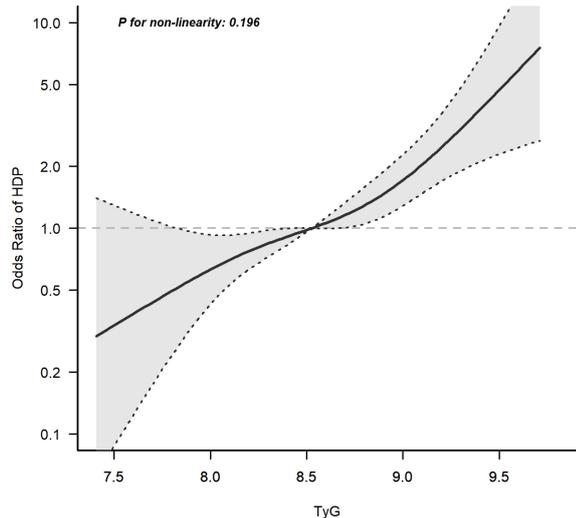


FIGURE 4

Continuous association of the TyG index at the first visit with the incidence of HDP. Adjusted for age, pre-pregnancy BMI, family history of hypertension and parity. The risk of developing HDP increased when the TyG index was greater than 8.5.

which are elevated in pregnancy, such as progesterone and corticosteroids, contribute to impaired insulin sensitivity and glucose tolerance (22). Marilyn et al. showed that some cytokines and hormones secreted by the placenta including leptin and TNF $\alpha$  could be implicated in IR during pregnancy (21). Some markers

correlate with IR, such as triglycerides, free fatty acids, small dense LDL particles and PAI-1, increase as normal pregnancy and associated IR progress (23, 24). Moreover, a growing number of studies have described the central role of IR in development of HDP. In a study using the euglycemic clamp technique, compared with controls, women with gestational hypertension exhibited approximately 40% lower steady-state insulin sensitivity index and approximately 33% higher mean plasma TG (25). IR may increase gestational blood pressure through activation of the sympathetic nervous system (8, 26), sodium reabsorption by the distal nephron segments (6), enhanced vascular resistance and endothelial dysfunction (26, 27). Furthermore, the recognition that features of insulin resistance persists many years after pregnancy among women which raises the risk for future cardiovascular disease (28–30). These observations suggest that interventions to reduce insulin resistance may reduce the risk of both hypertension in pregnancy and later life cardiovascular complications.

The TyG index, the product of fasting glucose and triglycerides, which has high sensitivity (96.5%) and specificity (85.0%; AUC: 0.858) for diagnosis of IR (31), is a simple, reliable and early marker of IR, and can be widely used in clinical practice especially in primary hospital because all clinical laboratories can measure triglycerides and glucose and quantification of insulin levels is not required. Besides, Ana Carolina et al. showed that the TyG index had a slightly better performance compared with the HOMA-IR in identifying patients with IR (13). Although there were few studies on the relationship between the TyG index and HDP, in the study of

the TyG index and hypertension, Yi Wang et al. showed that compared with those with the lowest category of TyG index, subjects with the highest category of TyG index were associated with higher odds of hypertension (32), the reason for its lower risk ratio than in our study may be that the degree of IR is more pronounced during pregnancy. In addition, in a longitudinal population-based study, Zheng et al. revealed that the TyG index can predict the incidence of hypertension among the Chinese population (15), after 9 years follow up, compared with the lowest TyG group, the hazard ratios for subjects in quartile 2, quartile 3 and quartile 4 increased, and were statistically significant. And numerous studies have also found that the TyG index was closely associated with hypertension (33–35). A retrospective cohort study showed that High maternal triglyceride level had higher risks of HDP in all maternal FPG strata, and both the early-pregnancy FPG and mTG levels should be screened among overall population including the low-risk population to reduce the incidence of pregnancy complications (36). The TyG index, which is the product of FBG and TG, may have a more obvious association with HDP.

In our investigation, to avoid confounding, a PSM method was applied and revealed that women with HDP had a much higher level of the early trimester TyG index. We also confirmed that the TyG index was independently associated with the incidence of HDP and was a diagnostic predictive factor for HDP development in case-control study. Further analysis of the relationship between the early trimester TyG index and HDP was performed in the cohort study. We found the incidence of HDP increased progressively with the increase of the early trimester TyG index and the risk of developing HDP increased when the TyG index was greater than 8.5. All of these indicated a close relation between the early trimester TyG index and HDP development.

Another finding in our study was that the TyG index was also associated with adverse pregnancy outcome. In the case-control study, we found that a higher TyG index was an independent risk factor for LBW and fetal distress. In the cohort study, women with the highest tertile of the TyG index had the highest risk for cesarean section, preterm and placental abruption. Maternal hyperglycemia and obesity predispose offspring to metabolic dysfunction (37), although the underlying mechanism is elusive, and the fetal hyperglycemia and IR disrupt normal surfactant synthesis and function, which may lead to adverse outcome in neonates (38). In addition, the women with higher blood pressure have decreased uteroplacental blood flow, which obstructs fetal growth and exacerbates fetal hypoxia and ischemia (39), thereby increases the risk of fetal distress and the need for timely termination of pregnancy.

There were some limitations to our study. First, all subjects were derived from one center, which may have led to biased results. Second, we did not measure dietary sodium intake and physical activity which may affect the blood pressure or lipids. Third, this is a

retrospective study, due to the lack of information, fasting insulin was not obtained. Also, the TyG index is associated with gestational diabetes and the incidence of post-partum diabetes in women, and we are collecting data on women with gestational diabetes, we would like to explore the relationship between gestational diabetes and HDP once we have data. Despite these limitations, this study first demonstrated the association between the TyG index and HDP development.

## Conclusions

In conclusion, our study suggested that the early trimester TyG index was closely associated with HDP development and adverse pregnancy outcomes. Besides, the TyG index could be a novel and clinically effective indicator for identifying the risk of HDP especially in primary hospital.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Shanghai Fifth People's Hospital Affiliated to Fudan University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

YP and GZ designed the study. YP, SZ, ZW, CY and XW collected the data. YP, RD and HG analyzed the data. YP wrote the main manuscript text. GZ and YX contributed to the refinement of the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2023.1093991/full#supplementary-material>

### SUPPLEMENTARY TABLE 1

Logistic regression analysis for presence/absence HDP in subjects after PSM

### SUPPLEMENTARY TABLE 2

Logistic regression analysis to determine the risk factor for LBW/fetal distress

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