Diabetology & Metabolic Syndrome

RESEARCH

Open Access

Serum triglyceride to high density lipoprotein cholesterol ratio in late pregnancy as a potential predictor of adverse birth outcomes: an analysis of real-world data

Bin Zhang[1†], Zhaolong Zhan[1†], Feng Zhang[1], Sijie Xi[1], Xiaosong Yuan[1*] and Zhonghua Shi[2*]

Abstract

Background The association between serum triglyceride to high density lipoprotein cholesterol ratio (THR) in late pregnancy and adverse birth outcomes (ABO) remains controversial because of inconsistent results. The present study assessed the association between maternal serum THR and incidence of ABO [preterm birth (PTB), small and large for gestational age (SGA/LGA), low birth weight (LBW) and macrosomia] in a Chinese population.

Methods A total of 11,553 consecutive participants from a real-world database with data on lipid profiles and birth outcomes were included. Logistic regression models were applied to assess the association between THR and incident ABO. Mediation analysis was performed to investigate the contribution of pregnancy complications [gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy (ICP) and pre-eclampsia (PE)] to this association.

Results Approximately 6.6% (762/11,553), 8.9% (1023/11,553), 15.5% (1792/11,553), 4.3% (494/11,553), and 7.4% (851/11,553) of individuals developed PTB, SGA, LGA, LBW and macrosomia, respectively. Significant trends across the quintiles of THR toward decreasing incidence of SGA and LBW and increasing incidence of LGA and macrosomia were observed. The multivariate-adjusted odds ratios (OR) in the top quintile of serum THR (> 3.16) versus the bottom quintile (< 1.44) were 0.52 for PTB, 0.48 for SGA, 0.64 for LBW, 2.80 for LGA and 3.80 for macrosomia, respectively. A 1-standard deviation (SD) increase in serum THR was associated with decreased risk of PTB [OR = 0.84, 95% confidence interval (CI): 0.76–0.93), SGA (OR = 0.71, 95% CI:0.65–0.78) and LBW (OR = 0.76, 95% CI:0.65–0.90) and increased risk of LGA (OR = 1.40, 95% CI:1.32–1.49) and macrosomia (OR = 1.49, 95% CI:1.38–1.62). In mediation analyses, PE mediated − 19.8%, -10.6% and − 24.6% of THR-associated PTB, SGA and LBW, respectively, GDM accounted for − 3.7%, 6.8% and 4.3% of THR-associated PTB, LGA and macrosomia, respectively, and ICP explained − 1.9% and − 2.1% of THR-associated PTB and LBW, respectively. In addition, incorporating THR to ABO predictive models significantly improved

[†]Bin Zhang and Zhaolong Zhan contributed equally to this work.

*Correspondence:
Xiaosong Yuan
xiaosongyuan@njmu.edu.cn
Zhonghua Shi
Jesse_1982@163.com

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

the area under the curve for SGA (0.743 vs. 0.753, $P<0.001$), LGA (0.734 vs. 0.745, $P<0.001$) and macrosomia (0.786 vs. 0.800, $P<0.001$).

Conclusion Real-world data showed an association between serum THR in late pregnancy and ABO risk, and this association may be partially mediated by prevalent pregnancy complications (PE/GDM/ICP), suggesting a potential role of THR in predicting ABO (SGA/LGA/macrosomia).

Keywords Triglyceride/HDL–C ratio, Adverse birth outcome, Preterm birth, Small for gestational age, Large for gestational age, Macrosomia

Background

Most pregnancies and childbirths are happy experiences. However, they sometimes finish with adverse birth outcomes (ABO), which can disrupt the family situations and result in high personal and societal costs. The etiology of ABO is multifactorial and has not been completely elucidated. There are several common ABO indices, such as preterm birth (PTB), low birth weight (LBW), macrosomia, and small/large for gestational age (SGA/LGA) [1]. PTB (live births < 37 and ≥ 28 completed weeks of gestation) is the leading cause of death in newborns and children younger than five years worldwide and is associated with neurodevelopmental, physiological, and socioeconomic impacts in long-term [2]. LBW (birthweight < 2500 g) and SGA (birthweight < the 10th percentile) are also associated with increased mortality and morbidity in the periods of neonates and infants [3]. The survivors are predisposed to physical and mental problems later in life, including poor neurodevelopment, learning difficulties in adolescence, cardiovascular and metabolic disorders in adulthood [4]. Macrosomia (birthweight > 4000 g) and LGA (birthweight > the 90th percentile) increase the complications risk for both mothers and neonates. Maternal complications include obstructed childbirth, laceration of perineum, uterine hypotonia, abnormal bleeding and caesarean delivery [5]. For neonates these consist of shoulder dystocia, respiratory distress, birth trauma and asphyxia, and hypoglycemia and may also lead to the risk of future hypertension, diabetes, obesity and cardiometabolic disorders [6]. In view of this, it is of great significance to accurately predict and intervene the occurrence of ABO.

Maternal lipids have important implications for fetal growth and development. The effect of abnormal lipid metabolism on pregnancy outcomes has been extensively studied, and dyslipidemia in pregnancy has been related to pregnancy complications and adverse perinatal outcomes [7–12]. Dyslipidemia in peripheral blood is characterized by increased triglyceride and decreased high-density lipoprotein cholesterol (HDL-C) levels, and triglyceride to HDL-C ratio (THR) has been associated with insulin resistance, diabetes mellitus, obesity, metabolic syndrome and cardiovascular disease [13, 14]. Meanwhile, some studied have investigated the association of maternal THR with gestational diabetes mellitus (GDM), pre-eclampsia (PE) and LGA/macrosomia during pre-gestational, the first, second and third trimesters of pregnancy [15–26]. However, the results are inconsistent. For example, two studies observed a significant positive correlation between the early-gestational THR and the risk of LGA birth [18, 21], while another study found no significant difference in the first trimester of THR between appropriate for gestational age (AGA) group and LGA group [25]. In addition, no prior studies to date have explored the association between THR and an extended ABO, including PTB, LBW, macrosomia, SGA and LGA.

The pathophysiologic roles known to increase ABO risk in women with GDM), PE, intrahepatic cholestasis of pregnancy (ICP) and pregnancy-induced hypertension (PIH), suggesting that the impact of THR on ABO might be mediated in part by these pregnancy complications [27–29]. However, to the best of our knowledge, no report to date has investigate the mediating effect of prevalent PE, GDM, ICP, and PIH in the associations between THR and ABO risk. Using real world data from a large-scale public specialized hospital, we aimed (1) to comprehensively explore the association between THR and the risk of ABO and (2) to quantify the intermediary effect of prevalent pregnancy complications as mediators in the impact of THR on ABO risk.

Materials and methods

Study participants

This study utilized 2016–2017 de-identified data from the Changzhou Maternal and Child Health Care Hospital database. A total of 13,275 consecutive individuals were initially enrolled in this observational study. The inclusion criteria were singleton pregnancy and live birth between 28 and 41 weeks of gestation. Pregnant women who presented with multiple gestations, fetal malformation, or had major pre-gestational diseases (including syphilis, diabetes mellitus, hypertension, cardiac, hepatic, renal, thyroid, and immune rheumatic diseases), diseases that affect lipid levels (polycystic ovary syndrome, and Cushing's syndrome), used illicit drugs or alcohol, smoked during pregnancy, or lacked blood lipid profiles and other important parameters were excluded from the

study. A total of 11,553 pregnant women remained for final analysis after excluding 1,722 individuals (lack of lipid profiles: $n=684$, pre-gestational diseases: $n=488$, plural gestations: $n=335$, no mother's height value: $n=119$, and no live birth: $n=96$). Maternal information and neonatal outcomes were retrieved from the perinatal database, including maternal demographic details (age, height, weight, blood pressure, gravidity and parity), medical history, co-existing pregnancy complications, delivery mode, laboratory findings, neonatal sex, gestational weeks, height and weight. All laboratory tests at the time of admission were conducted in the same laboratory at the hospital. The measurements of serum lipid profiles, renal and hepatic function were conducted on an automatic chemistry analyzer with matched detection kits (AU5800, Beckman Coulter, Japan). The concentration of serum high-sensitivity C-reactive protein (hsCRP) was determined by means of particle-enhanced immunonephelometric method using an automated analyzer (BN II System, Siemens Diagnostics, Germany).

The present study received an approval from the Ethics Committee of Changzhou Maternal and Child Health Care Hospital (ZD201803). Written informed consent of each participant was waived because of observational nature and anonymized analysis in this study. The study procedures abide by the Declaration of Helsinki principles.

Definitions

GDM, PE, ICP and PIH were regarded as main complications of pregnancy, and PTB, LBW, macrosomia, SGA and LGA as ABO in this study. Pregnancy complications were diagnosed by obstetricians according to a previous report [30]. Deliveries that occur at less than 37 weeks but have reached at least 28 weeks of gestation were diagnosed as PTB [31]. According to birthweight, newborns were categorized into macrosomia (>4000 g), normal birth weight (NBW, 2500–4000 g) and LBW (<2500 g) [32]. In accordance with the birthweight for gestational weeks and percentiles in Changzhou of China, newborns were stratified into SGA (<10th percentile), AGA (10th −90th percentile) and LGA (>90th percentile) [33].

Statistical analysis

Descriptive statistics for demographic characteristics, pregnancy outcomes and maternal laboratory findings were conducted. Data were presented as mean [standard deviation (SD)] for continuous variables following normal distributions and median [inter-quartile range (IQR)] for those following non-normal distributions as well as percentages for categorical variables. The variables among the quintiles (Q) of serum THR were compared using ANOVA, Kruskal–Wallis and chi-square tests, as appropriate. Spearman's test was performed to examine the correlations of THR with participants' characteristics. Logistic regression analysis was performed to assess the associations between the quintiles of THR and incident ABO (including PTB, SGA, LGA, LBW, and macrosomia). To calculate odds ratios (OR) and 95% confidence intervals (CI) of higher quintiles relative to the lowest quintiles and of one-SD increase in THR, three models were generated with incremental adjustment for potential confounders of ABO: models 1 were unadjusted, models 2 was adjusted for age, BMI, parity, BP, gestational weeks (except for PTB), assisted reproduction and fetal sex, and models 3 were adjusted for same covariates in model 2 and laboratory measurements (total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, creatinine, total cholesterol, LDL–C and hsCRP). Smooth curves were fitted to investigate potential nonlinear relationship of THR with ABO risk. In addition, mediation analysis was used to determine the proportional contribution of co-existing pregnancy complications on the associations between THR and ABO risk. Receiving-operating characteristic (ROC) curves analysis was applied to calculate areas under the curve (AUC) and assess the ability of triglyceride, HDL-C, THR and the two models to discriminate the subjects of ABO.

Statistical analysis in this study was performed using Empower software (version 4.1, X&Y Solutions, USA).A $P<0.05$ presented as statistical significance.

Results

Participant characteristics

Participant characteristics stratified by quintiles of the serum THR are shown in Table 1. Among 11,553 included participants, 6946 (60.12%) were nulliparous, 2330 (20.2%) had prenatal BMI≥30 kg/m^2, and the median age at the time of admission for labor was 28 (IQR 26–31) years. The prevalence of PIH, PE, ICP and GDM were 2.1%, 3.5%, 6.2% and 8.4%, respectively. The ranges of THR for Q 1–5 was <1.44, 1.44–1.88, 1.89–2.38, 2.39–3.16, and >3.16, respectively. Higher THR was associated with older age, elevated prenatal BMI, higher assisted reproduction and cesarean section rate, increased gestational age and neonatal birth height and weight, elevated serum concentrations of total protein and triglyceride, and lower serum concentrations of total bilirubin, direct bilirubin, urea nitrogen, HDL-C, LDL-C and hsCRP. Moreover, pregnant women with higher THR had greater prevalence of PIH, PE, ICP and GDM (all P for trend<0.001, Table 1). The baseline characteristics of the participants, categorized into PTB and full-term birth (FTB) groups, were also summarized in Table S1. Serum THR was positively correlated with maternal age ($r=0.085$, $P<0.001$), BMI ($r=0.132$, $P<0.001$), systolic BP ($r=0.019$, $P=0.039$), diastolic BP ($r=0.023$, $P=0.015$), fetal gestational weeks ($r=0.048$, $P<0.001$), birth length

Table 1 Characteristics of the participants according to the THR quintiles ($n=11,553$)

Characteristics	THR					*P* trend
	Q1 (Bottom) (< 1.44)	Q2 (1.44–1.88)	Q3 (1.89–2.38)	Q4 (2.39–3.16)	Q5 (Top) (> 3.16)	
n	2303	2310	2315	2314	2311	
Maternal age (years)	27.0 (25.0–30.0)	28.0 (26.0–31.0)	28.0 (26.0–31.0)	28.0 (26.0–31.0)	28.0 (26.0–32.0)	< 0.001
< 20	25 (1.1%)	28 (1.2%)	17 (0.7%)	22 (1.0%)	14 (0.6%)	< 0.001
20–34	2065 (89.7%)	2021 (87.5%)	2007 (86.7%)	2056 (88.9%)	1964 (85.0%)	
≥ 35	213 (9.2%)	261 (11.3%)	291 (12.6%)	236 (10.2%)	333 (14.4%)	
BMI (kg/m^2)	26.4 (24.5–28.6)	26.7 (24.7–29.0)	27.0 (25.0–29.2)	27.2 (25.2–29.6)	27.6 (25.6–30.1)	< 0.001
< 25	727 (31.6%)	643 (27.8%)	577 (24.9%)	537 (23.2%)	402 (17.4%)	< 0.001
25–29	1203 (52.2%)	1251 (54.2%)	1296 (56.0%)	1271 (54.9%)	1316 (56.9%)	
≥ 30	373 (16.2%)	416 (18.0%)	442 (19.1%)	506 (21.9%)	593 (25.7%)	
Systolic BP (mmHg)	120 (110–130)	120 (110–130)	120 (110–129)	120 (110–130)	120 (110–130)	< 0.001
Diastolic BP(mmHg)	72 (70–79)	72 (70–80)	72 (70–80)	73 (70–80)	72 (70–80)	0.010
Primipara (%)	1390 (60.4%)	1412 (61.1%)	1339 (57.8%)	1437 (62.1%)	1368 (59.2%)	0.031
Assisted reproduction	31 (1.3%)	45 (1.9%)	54 (2.3%)	68 (2.9%)	71 (3.1%)	< 0.001
Cesarean section	746 (32.4%)	897 (38.8%)	1051 (45.4%)	1049 (45.3%)	1185 (51.3%)	< 0.001
GDM	122 (5.3%)	158 (6.8%)	176 (7.6%)	215 (9.3%)	300 (13.0%)	< 0.001
ICP	116 (5.0%)	141 (6.1%)	105 (4.5%)	159 (6.9%)	190 (8.2%)	< 0.001
PE	41 (1.8%)	54 (2.3%)	84 (3.6%)	86 (3.7%)	134 (5.8%)	< 0.001
PIH	42 (1.8%)	36 (1.6%)	46 (2.0%)	55 (2.4%)	63 (2.7%)	0.048
Gestational age (week)	38.5 ± 1.9	38.7 ± 1.6	38.7 ± 1.6	38.8 ± 1.5	38.8 ± 1.5	< 0.001
Neonatal sex (male)	1241 (53.9%)	1243 (53.8%)	1206 (52.1%)	1193 (51.6%)	1223 (52.9%)	0.415
Neonatal height	49.6 ± 1.8	49.8 ± 1.3	49.9 ± 1.2	49.9 ± 1.1	49.9 ± 1.3	< 0.001
Neonatal weight	3230 (2940–3500)	3325 (3050–3600)	3380 (3090–3660)	3410 (3140–3700)	3470 (3170–3765)	< 0.001
Laboratory findings						
Total Protein (g/L)	62.8 (60.2–65.7)	63.0 (60.3–65.9)	63.2 (60.5–66.0)	63.5 (60.7–66.5)	64.2 (61.4–67.3)	< 0.001
Albumin (g/L)	36.4 (34.9–38.0)	36.3 (34.7–38.0)	36.4 (34.9–38.0)	36.4 (34.9–38.1)	36.3 (34.6–38.0)	0.048
Total bilirubin (μmol/L)	7.5 (6.1–9.3)	7.4 (6.1–9.2)	7.4 (6.1–9.2)	7.3 (5.8–9.1)	7.0 (5.5–8.9)	< 0.001
Direct bilirubin (μmol/L)	1.5 (1.1–2.0)	1.5 (1.1–1.9)	1.5 (1.1–1.9)	1.4 (1.0–1.9)	1.3 (0.8–1.7)	< 0.001
ALT (U/L)	9.0 (8.0–12.0)	9.0 (7.0–12.0)	9.0 (7.0–12.0)	9.0 (7.0–12.0)	9.0 (7.0–12.0)	0.015
AST (U/L)	18.0 (16.0–21.0)	18.0 (16.0–21.0)	18.0 (16.0–21.0)	18.0 (16.0–21.0)	18.0 (16.0–22.0)	0.152
Urea nitrogen (mmol/L)	3.5 (3.0–4.1)	3.4 (2.9–4.1)	3.4 (2.9–4.0)	3.4 (2.8–4.0)	3.4 (2.8–4.1)	< 0.001
Creatinine (μmol/L)	59.7 (54.5–64.8)	59.3 (54.5–64.8)	59.7 (54.5–65.2)	59.7 (54.6–65.0)	59.3 (54.4–64.8)	0.749
Total cholesterol (mmol/L)	6.3 (5.6–7.1)	6.3 (5.6–7.1)	6.4 (5.6–7.2)	6.3 (5.5–7.1)	6.2 (5.4–7.1)	0.005
Triglyceride (mmol/L)	2.3 (2.0–2.6)	3.0 (2.7–3.3)	3.6 (3.2–4.0)	4.3 (3.8–4.9)	5.9 (5.0–7.1)	< 0.001
LDL–C (mmol/L)	3.3 (2.8–4.0)	3.4 (2.9–4.0)	3.4 (2.9–4.1)	3.4 (2.8–4.0)	3.0 (2.4–3.6)	< 0.001
HDL–C (mmol/L)	2.0 (1.8–2.2)	1.8 (1.6–2.0)	1.7 (1.5–1.9)	1.6 (1.4–1.8)	1.4 (1.3–1.6)	< 0.001
hsCRP (mg/L)	3.1 (1.6–5.6)	3.0 (1.7–5.2)	2.8 (1.5–5.0)	2.8 (1.6–4.8)	2.9 (1.6–4.8)	< 0.001

Notes Variables were expressed as median (IQR), mean ± SD and frequency (percentage)

Abbreviations THR, triglyceride/HDL-C ratio; Q, quintile; BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, pre-eclampsia; PIH, pregnancy induced hypertension; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hsCRP, high sensitive C-reactive protein; IQR, interquartile range; SD, standard deviation

($r=0.111$, $P<0.001$) and birthweight ($r=0.194$, $P<0.001$) and the levels of total protein ($r=0.109$, $P<0.001$) and triglyceride ($r=0.897$, $P<0.001$) and negatively correlated with the levels of total bilirubin (r=-0.079, $P<0.001$), direct bilirubin(r=-0.127, $P<0.001$), ALT (r=-0.021, $P=0.025$), urea nitrogen (r=-0.029, $P=0.002$), total cholesterol(r=-0.019, $P=0.042$), LDL–C (r=-0.142, $P<0.001$), HDL–C (r=-0.596, $P<0.001$) and hsCRP level (r=-0.034, $P<0.001$).

Associations between serum THR and incident ABO

The median birth weight in the present study was 3,360 g with a proportion of 7.4% (854) macrosomia and 4.3% (494) LBW. Of the 11,553 neonates, 1,792 (15.5%) were classified as LGA, 1,023 (8.9%) as SGA and 762 (6.6%) as PTB. Table 2 indicated significant trends across the quintiles of THR toward decreasing incidence of SGA and LBW and increasing incidence of LGA and macrosomia (SGA and LBW: 13.0% and 6.9% in Q1, and decreased to 9.0% and 3.9%, 8.6% and 3.5%, 7.1% and 3.5%, and 6.5% and 3.5% in Q2, Q3, Q4, Q5, respectively; LGA and macrosomia: 8.6% and 3.0% in Q1, and increased

Table 2 Prospective association between the THR and ABO risk in the study population

Characteristics	THR					*P* trend	Per-SD increase in THR
	Q1 (Bottom) (< 1.44)	Q2 (1.44–1.88)	Q3 (1.89–2.38)	Q4 (2.39–3.16)	Q5 (Top) (> 3.16)		
Median	1.19	1.67	2.11	2.71	3.97		
PTB							
No. of cases (percentage)	228 (9.9%)	147 (6.4%)	133 (5.7%)	124 (5.4%)	130 (5.6%)	< 0.001	
Model 1, OR (95% CI)	1.00	0.62 (0.50, 0.77)	0.55 (0.44, 0.69)	0.52 (0.41, 0.65)	0.54 (0.43, 0.68)	< 0.001	0.86 (0.78, 0.93)
Model 2, OR (95% CI)	1.00	0.62 (0.50, 0.77)	0.57 (0.45, 0.71)	0.51 (0.41, 0.65)	0.54 (0.43, 0.68)	< 0.001	0.86 (0.78, 0.94)
Model 3, OR (95% CI)	1.00	0.58 (0.46, 0.73)	0.58 (0.46, 0.73)	0.52 (0.41, 0.66)	0.52 (0.41, 0.67)	< 0.001	0.84 (0.76, 0.93)
SGA							
No. of cases (percentage)	300 (13.0%)	208 (9.0%)	199 (8.6%)	165 (7.1%)	151 (6.5%)	< 0.001	
Model 1, OR (95% CI)	1.00	0.66 (0.55, 0.80)	0.63 (0.52, 0.76)	0.51 (0.42, 0.63)	0.47 (0.38, 0.57)	< 0.001	0.73 (0.67, 0.79)
Model 2, OR (95% CI)	1.00	0.69 (0.57, 0.84)	0.70 (0.58, 0.85)	0.55 (0.45, 0.68)	0.55 (0.45, 0.68)	< 0.001	0.78 (0.71, 0.85)
Model 3, OR (95% CI)	1.00	0.68 (0.56, 0.83)	0.69 (0.56, 0.84)	0.53 (0.43, 0.65)	0.48 (0.38, 0.60)	< 0.001	0.71 (0.65, 0.78)
LGA							
No. of cases (percentage)	199 (8.6%)	298 (12.9%)	379 (16.4%)	402 (17.4%)	514 (22.2%)	< 0.001	
Model 1, OR (95% CI)	1.00	1.57 (1.30, 1.89)	2.07 (1.72, 2.48)	2.22 (1.86, 2.66)	3.02 (2.54, 3.60)	< 0.001	1.34 (1.28, 1.40)
Model 2, OR (95% CI)	1.00	1.56 (1.28, 1.90)	1.98 (1.64, 2.40)	2.19 (1.81, 2.64)	2.74 (2.28, 3.29)	< 0.001	1.29 (1.23, 1.35)
Model 3, OR (95% CI)	1.00	1.60 (1.31, 1.95)	2.03 (1.68, 2.46)	2.27 (1.87, 2.75)	2.80 (2.31, 3.40)	< 0.001	1.40 (1.32, 1.49)
LBW							
No. of cases (percentage)	159 (6.9%)	90 (3.9%)	82 (3.5%)	82 (3.5%)	81 (3.5%)	< 0.001	
Model 1, OR (95% CI)	1.00	0.55 (0.42, 0.71)	0.50 (0.38, 0.65)	0.50 (0.38, 0.65)	0.49 (0.37, 0.64)	< 0.001	0.77 (0.68, 0.86)
Model 2, OR (95% CI)	1.00	0.68 (0.46, 1.02)	0.75 (0.50, 1.13)	0.82 (0.55, 1.23)	0.77 (0.51, 1.17)	0.426	0.86 (0.75, 0.99)
Model 3, OR (95% CI)	1.00	0.62 (0.41, 0.94)	0.71 (0.46, 1.07)	0.81 (0.54, 1.22)	0.64 (0.41, 1.01)	0.152	0.76 (0.65, 0.90)
Macrosomia							
No. of cases (percentage)	69 (3.0%)	119 (5.2%)	178 (7.7%)	198 (8.6%)	287 (12.4%)	< 0.001	
Model 1, OR (95% CI)	1.00	1.75 (1.30, 2.37)	2.67 (2.01, 3.54)	3.01 (2.28, 3.98)	4.53 (3.47, 5.93)	< 0.001	1.38 (1.31, 1.45)
Model 2, OR (95% CI)	1.00	1.59 (1.16, 2.16)	2.46 (1.83, 3.29)	2.50 (1.87, 3.34)	3.75 (2.83, 4.95)	< 0.001	1.34 (1.27, 1.42)
Model 3, OR (95% CI)	1.00	1.59 (1.16, 2.18)	2.50 (1.86, 3.36)	2.52 (1.88, 3.38)	3.80 (2.85, 5.08)	< 0.001	1.49 (1.38, 1.62)

Notes Models 1 were unadjusted. Models 2 were adjusted forage, BMI, parity, BP, gestational age (except for PTB), assisted reproduction and fetal sex. The models 3 were adjusted for covariates in the model 2 and laboratory results (total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, creatinine, total cholesterol, LDL–C and hsCRP)

Abbreviations THR, triglyceride/HDL-C ratio; ABO, adverse birth outcome; Q, quintile; PTB, preterm birth; SGA/LGA, small/large for gestational age; LBW, low birth weight; OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hsCRP, high sensitive C-reactive protein

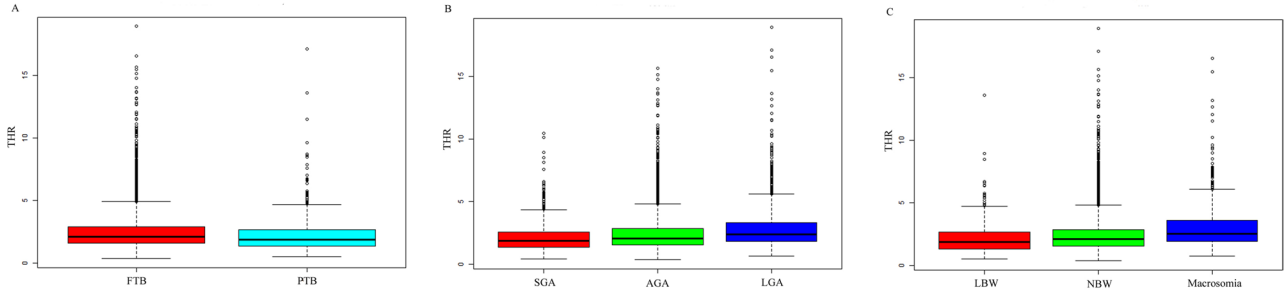

Fig. 1 Serum triglyceride to HDL-C ratio among women who delivered PTB and FTB, SGA, AGA and LGA, and LBW, NBW and macrosomia (PTB/FTB: 2.26 ± 1.47 vs. 2.45 ± 1.39; SGA/AGA/LGA: 2.14 ± 1.17 vs. 2.38 ± 1.33 vs. 2.86 ± 1.72; LBW/NBW/macrosomia: 2.17 ± 1.28 vs. 2.40 ± 1.35 vs. 3.03 ± 1.77; all $P < 0.001$)

to 12.9% and 5.2%, 16.4% and 7.7%, 17.4% and 8.6%, and 22.2% and 12.4 in Q2, Q3, Q4, Q5, respectively; all *P* for trend < 0.001). There were significant differences in serum THR among the participants who delivered PTB/FTB, SGA/AGA/LGA, and LBW/NBW/macrosomia newborns (PTB/FTB: 2.26 ± 1.47 vs. 2.45 ± 1.39; SGA/AGA/LGA: 2.14 ± 1.17 vs. 2.38 ± 1.33 vs. 2.86 ± 1.72; LBW/NBW/macrosomia: 2.17 ± 1.28 vs. 2.40 ± 1.35 vs. 3.03 ± 1.77; all $P < 0.001$; Fig. 1). Significant differences in serum triglyceride and HDL-C concentrations were

also observed among these participants (Fig S1 and Fig S2). In crude logistic regression analyses, both higher triglyceride and THR were associated with decreased risk of PTB, SGA, and LBW and increased risk of LGA and macrosomia, and these associations also persisted significantly after correcting for sociodemographic factors and laboratory findings, with the exception of LBW (Table 2 and Table S2). The multi variables-adjusted OR (95% CI) in the top quintile of THR (>3.16) versus the bottom quintile (<1.44) were 0.52 (0.41, 0.67) for PTB, 0.48 (0.38, 0.60) for SGA, 0.64 (0.41, 1.01) for LBW, 2.80 (2.31, 3.40) for LGA and 3.80 (2.85, 5.08) for macrosomia, respectively. In addition, higher HDL-C was associated with decreased risks of PTB, LGA, and macrosomia; the adjusted OR (95% CI) were 0.64 (0.45, 0.90), 0.72 (0.56, 0.91), and 0.64 (0.45, 0.90), respectively (Table S3). Each one standard deviation (SD) increment in serum THR was associated with 16%, 29%, and 24% decrease risk of PTB, SGA, and LBW and 40% and 49% increase risk of LGA and macrosomia, respectively. Similar results were observed in sensitivity analyses among individuals without advance age (Table S4), obesity (Table S5), multipara (Table S6) and PTB (for SGA/LGA/LBW/macrosomia, Table S7). In addition, multivariate-adjusted smooth curve fitting analyses indicated nonlinear associations of ABO with triglyceride, HDL-C and THR (Fig. 2. and Fig S3).

Mediation analysis

Serum THR at the time of admission was significantly higher in women with pregnancy complications than those with non-pregnancy complications (NPC) (GDM/ICP/PE/PIH vs. NPC: 2.92±1.76/2.74±1.73/2.89±1.45/2.60±1.36 vs. 2.36±1.34; all $P<0.001$; Fig. 3). In mediation analyses (Table 3), PE explained −19.8%, -10.6% and −24.6% of the association of THR with PTB, SGA and LBW, respectively. The proportions mediated by GDM were −3.7%, 6.8% and 4.3% for the association of THR with PTB, LGA and macrosomia, respectively. ICP also had a slight mediating effect of THR on incident PTB and LBW (proportions mediated: -1.9% and −2.1%, respectively).

Predicting ABO with THR and related models

ROC curves were constructed to evaluate sensitivity and specificity of triglycerides, HDL-C and THR separately in predicting ABO (Fig. 4). THR had shown better power in detecting SGA, LGA and macrosomia than using either triglycerides or HDL-C alone, which was determined by area under the curve (AUC) calculated in ROC analysis (SGA: 0.580 vs. 0.567/0.559; LGA: 0.604 vs. 0.587/0.582; macrosomia: 0.636 vs. 0.614/0.605; all $P<0.001$, Table 4). The optimal THR cutoff values for detecting SGA, LGA, and macrosomia were 1.76, 2.13, and 2.14, respectively. To establish the predictive models of ABO at the time of admission, prenatal characteristics and laboratory findings were included. Compared with the models without THR, the addition of THR increased the AUC of SGA, LGA, and macrosomia from 0.743 to 0.753, 0.734 to 0.745, and 0.786 to 0.800, respectively (all $P<0.001$, Table 4).

Discussion

Main findings

In the present real-world study using a single central dataset, women in the top quintile of serum THR (>3.16) measured at admission for delivery had higher risk of LGA and macrosomia and lower risk of PTB, SGA, and LBW compared with those in the bottom quintile (<1.44). Except for the association of LBW, the remaining associations were still statistically significant after adjustment for potential confounders. The observed associations were partially mediated by the prevalence of PE, GDM and ICP. In addition, THR was superior to triglycerides and HDL-C for predicting SGA, LGA and macrosomia, and adding THR to ABO predictive models could improve the predictive efficiency for these outcomes in this real-world analysis. These findings reveal serum THR measured at admission for delivery could be a potential predictor of ABO (SGA, LGA and macrosomia).

Interpretation

Serum triglyceride level increases gradually with the gestational progress and reaches a peak in the third trimester of pregnancy, while the level of HDL-C increases from the first trimester and decreased slightly in the second and third trimesters [34]. Gestational dyslipidemia, characterized by a high THR, has been demonstrated in women with GDM at the time of oral glucose tolerance test and those who developed GDM in pre-pregnancy and early pregnancy, representing THR as a reliable index for predicting GDM (15–19,21,23,24,26]. In addition, Arbib et al. in Israel reported that a high THR (≥3) before pregnancy (up to 52 weeks) was associated with increased risk of PE [23]. Another longitudinal study from Colombia observed a significant elevation in maternal THR as pregnancy progressed with no significant difference between PE and healthy women [20]. The present study revealed that THR was significantly higher in women with GDM, PE, PIH and ICP compared to those without pregnancy complications in late gestation. To the best of our knowledge, this is the first cohort study comparing serum late-gestational THR between ICP and NPC women. Therefore, these findings draw one hypothesis that gestational dyslipidemia might contribute to the development of pregnancy complications in the mechanism, which has been demonstrated in a mouse model of GDM and the placenta of PE women [35, 36].

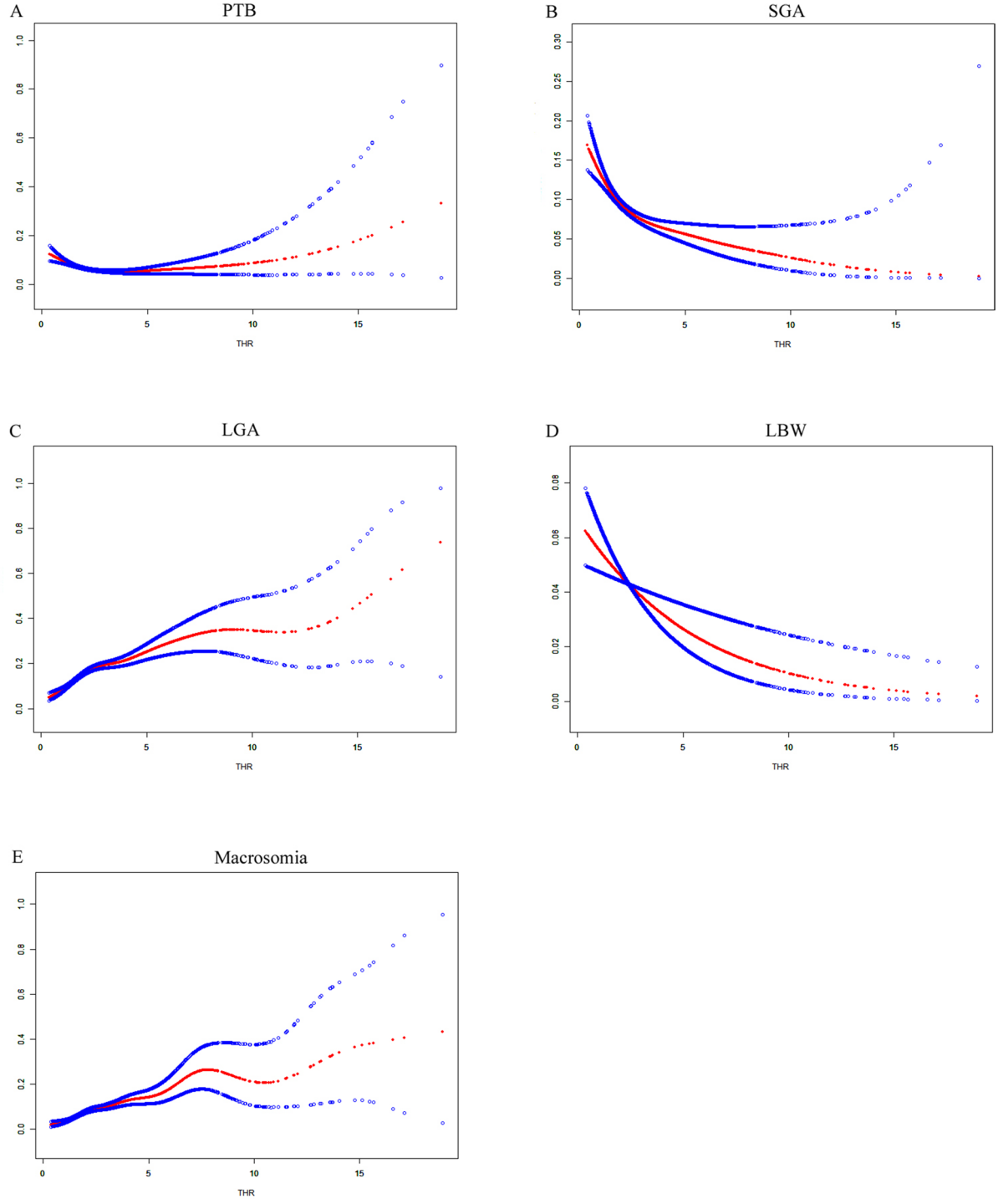

Fig. 2 Smooth curve fitting analysis of THR with ABO risk. Adjusted for age, BMI, parity, BP, gestational age (except for PTB), assisted reproduction, fetal sex and laboratory results (total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, creatinine, total cholesterol, LDL-C and hsCRP)

Several studies have reported a significant positive correlation of maternal THR with neonatal birthweight and the risk of LGA or macrosomia during early, mid and late pregnancies among women with/without GDM [16, 21, 22, 24]. However, Wang et al. in China argued that only apolipoprotein B/A1 ratio (not THR) in the first trimester was significant impact factor for the prevalence of LGA neonates. In the current study, THR in top quintile (compared with bottom quintile) in late pregnancy was significantly associated with increased risk of LGA and macrosomia and decreased risk of PTB and SGA, but not with decreased risk of LBW (LGA: adjusted OR=2.80,

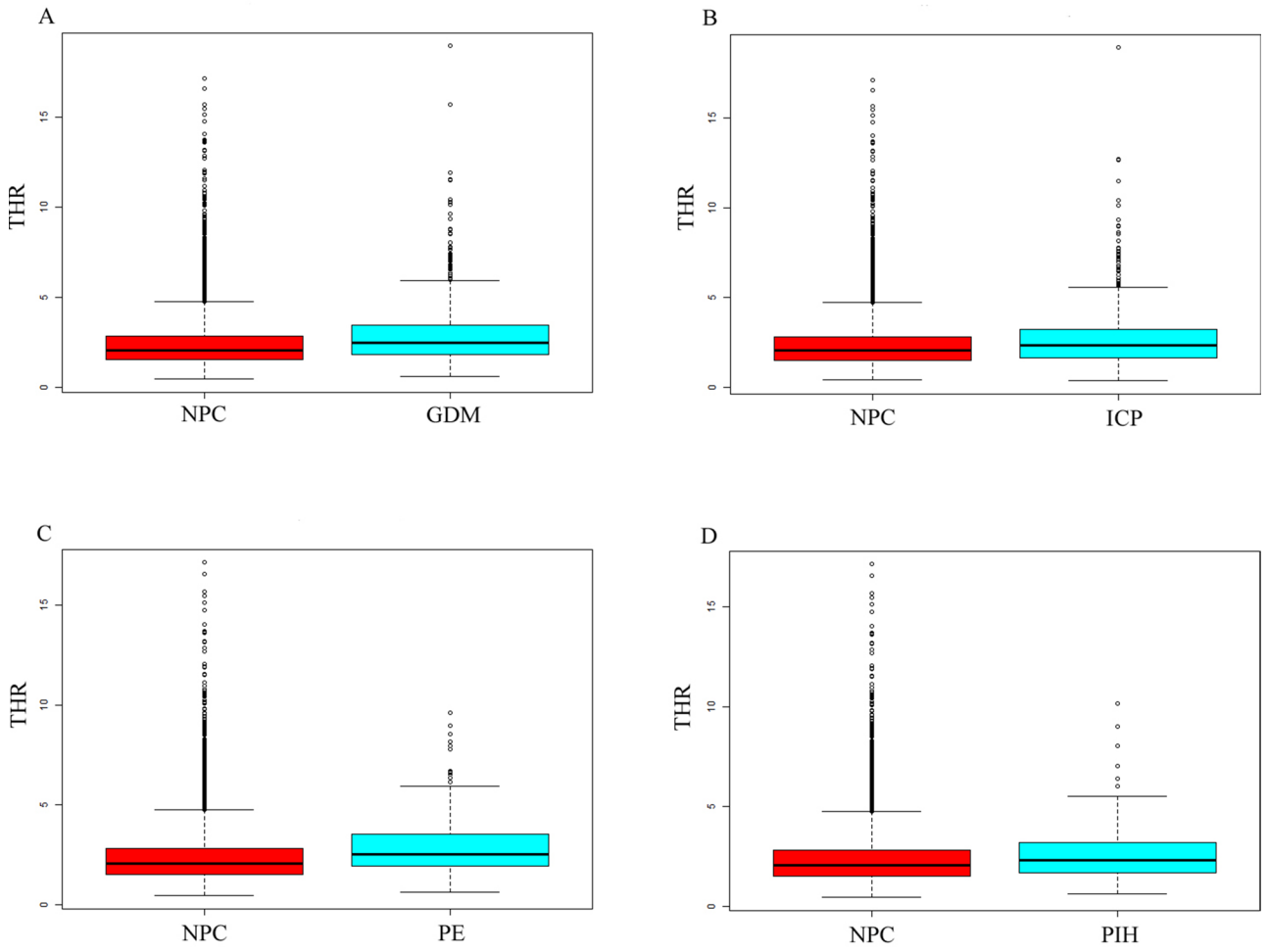

Fig. 3 Serum triglyceride to HDL-C ratio in women with and with pregnancy complications (GDM/ICP/PE/PIH vs. NPC: 2.92 ± 1.76/2.74 ± 1.73/2.89 ± 1.45 /2.60 ± 1.36 vs. 2.36 ± 1.34; all $P < 0.001$)

$P<0.001$; macrosomia: adjusted OR = 3.80, $P<0.001$; PTB: adjusted OR = 0.52, $P<0.001$; SGA: adjusted OR = 0.48, $P<0.001$; LBW: adjusted OR = 0.64, $P=0.152$). Additionally, the present study confirmed that THR is a more effective indicator than separately using triglycerides or HDL-C when predicting the delivery of SGA/LGA neonates and macrosomia. ROC analysis demonstrated that the AUC of the best cut-point of >2.14 for macrosomia is higher than those of the cut-points of >2.13 for LGA and <1.76 for SGA (0.636 vs. 0.604 vs. 0.580). The AUC of the optimal cut-points for ABO is relatively weak, suggesting that it is necessary to develop prediction models to improve the predictive efficiency. Based on maternal antenatal parameters and laboratory findings, this study established two types of prediction models (models 1 excluded THR and models 2 included THR), suggesting that incorporating THR to the models promoted the ability of predicting these outcomes (for macrosomia: 0.800 vs. 0.786; for LGA: 0.745 vs. 0.734; for SGA: 0.753 vs. 0.743; all $P<0.001$). However, THR did not improve the predictive power of the modes 1 for PTB and LBW (for PTB: 0.749 vs. 0.745, $P=0.052$; for LBW: 0.958 vs. 0.957, $P=0.280$). Interestingly, the AUC of the best thresh hold of <-0.315 in the model 1 for LBW was up to 0.957, with sensitivity and specificity of 87.9% and 91.7%, respectively. Multiple-center prospective studies with large sample size are necessary to confirm these finding in the present study.

Up to date, the exact mechanism leading to the association of THR with fetal growth-related ABO remains unclear. Prior studies have shown that the importance of pregnancy complications including PE, GDM, ICP and PIH in modulating fetal growth, adversely impacted fetal gestational age and birthweight in pregnant women [27–29]. Another interesting finding of this study is that PE, GDM, and ICP make substantial mediating contributions in the association between THR and ABO, which has never been reported previously to our knowledge. This finding reinforces the importance of developing effective comprehensive interventions for these complications

Table 3 Mediation analysis to investigate whether prevalent pregnancy complications mediated the association between THR and APO risk [a]

	PTB	*P*	SGA	*P*	LGA	*P*	LBW	*P*	Macrosomia	*P*
Mediation: GDM										
Total effects (95% CI)	-0.020 (-0.027, -0.013)	< 0.001	-0.030 (-0.037, -0.022)	< 0.001	0.063 (0.054, 0.073)	< 0.001	-0.015 (-0.021, -0.010)	< 0.001	0.043 (0.037, 0.050)	< 0.001
Direct effects (95% CI)	-0.021 (-0.028, -0.014)	< 0.001	-0.029 (-0.036, -0.021)	< 0.001	0.059 (0.050, 0.069)	< 0.001	-0.015 (-0.021, -0.010)	< 0.001	0.042 (0.036, 0.048)	< 0.001
Mediated effects (95% CI)	0.001 (0.000, 0.001)	0.044	-0.001 (-0.002, -0.001)	< 0.001	0.004 (0.003, 0.006)	< 0.001	-0.000 (-0.001, 0.000)	0.474	0.002 (0.001, 0.003)	< 0.001
Mediated Proportion (%)	-3.69		3.85		6.79		1.08		4.25	
Mediation: ICP										
Total effects (95% CI)	-0.020 (-0.027, -0.013)	< 0.001	-0.030 (-0.037, -0.022)	< 0.001	0.063 (0.054, 0.073)	< 0.001	-0.015 (-0.021, -0.010)	< 0.001	0.043 (0.037, 0.050)	< 0.001
Direct effects (95% CI)	-0.020 (-0.027, -0.014)	< 0.001	-0.030 (-0.038, -0.022)	< 0.001	0.063 (0.054, 0.073)	< 0.001	-0.016 (-0.021, -0.011)	< 0.001	0.043 (0.037, 0.050)	< 0.001
Mediated effects (95% CI)	0.000 (0.000, 0.001)	0.008	0.000 (0.000, 0.001)	0.036	-0.000 (-0.001, 0.000	0.654	0.000 (0.000, 0.001)	0.002	-0.000 (-0.000, 0.000)	0.334
Mediated Proportion	-1.86		-0.87		0.09		-2.09		-0.21	
Mediation: PE										
Total effects (95% CI)	-0.020 (-0.027, -0.013)	< 0.001	-0.030 (-0.037, -0.022)	< 0.001	0.063 (0.054, 0.073)	< 0.001	-0.015 (-0.021,-0.010)	< 0.001	0.043 (0.037, 0.050)	< 0.001
Direct effects (95% CI)	-0.024 (-0.031, -0.017)	< 0.001	-0.033 (-0.040, -0.025)	< 0.001	0.064 (0.055, 0.074)	< 0.001	-0.019 (-0.025, -0.014)	< 0.001	0.043 (0.038, 0.050)	< 0.001
Mediated effects (95% CI)	0.004 (0.003, 0.006)	< 0.001	0.003 (0.002, 0.005)	< 0.001	-0.000 (-0.001, 0.000)	0.416	0.004 (0.003, 0.006)	< 0.001	-0.000 (-0.001, 0.000)	0.398
Mediated Proportion (%)	-19.77		-10.61		-0.33		-24.57		-0.41	
Mediation: PIH										
Total effects (95% CI)	-0.020 (-0.027, -0.013)	< 0.001	-0.030 (-0.037, -0.022)	< 0.001	0.063 (0.054, 0.073)	< 0.001	-0.015 (-0.021,-0.010)	< 0.001	0.043 (0.037, 0.050)	< 0.001
Direct effects (95% CI)	-0.020 (-0.027, -0.013)	< 0.001	-0.030 (-0.037, -0.022)	< 0.001	0.063 (0.054, 0.073)	< 0.001	-0.015 (-0.021, -0.010)	< 0.001	0.043 (0.037, 0.050)	< 0.001
Mediated effects (95% CI)	-0.000 (-0.000, 0.000)	0.686	0.000 (-0.000, 0.000)	0.804	0.000 (-0.000, 0.001)	0.134	0.000 (-0.000, 0.000)	0.236	0.000 (0.000, 0.001)	0.044
Mediated Proportion (%)	0.14		-0.06		0.29		-0.56		0.56	

Notes[a] adjusted forage, BMI, parity, BP, gestational age (except for PTB), assisted reproduction, fetal sex and laboratory results (total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, creatinine, total cholesterol, LDL–C and hsCRP)

Abbreviations THR, triglyceride/HDL-C ratio; ABO, adverse birth outcome; CI, confidence interval; PTB, preterm birth; SGA/LGA, small/large for gestational age; BMI, body mass index; LBW, low birth weight; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, pre-eclampsia; PIH, pregnancy induced hypertension; BP, blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-C, low density lipoprotein cholesterol; hsCRP, high sensitive C-reactive protein

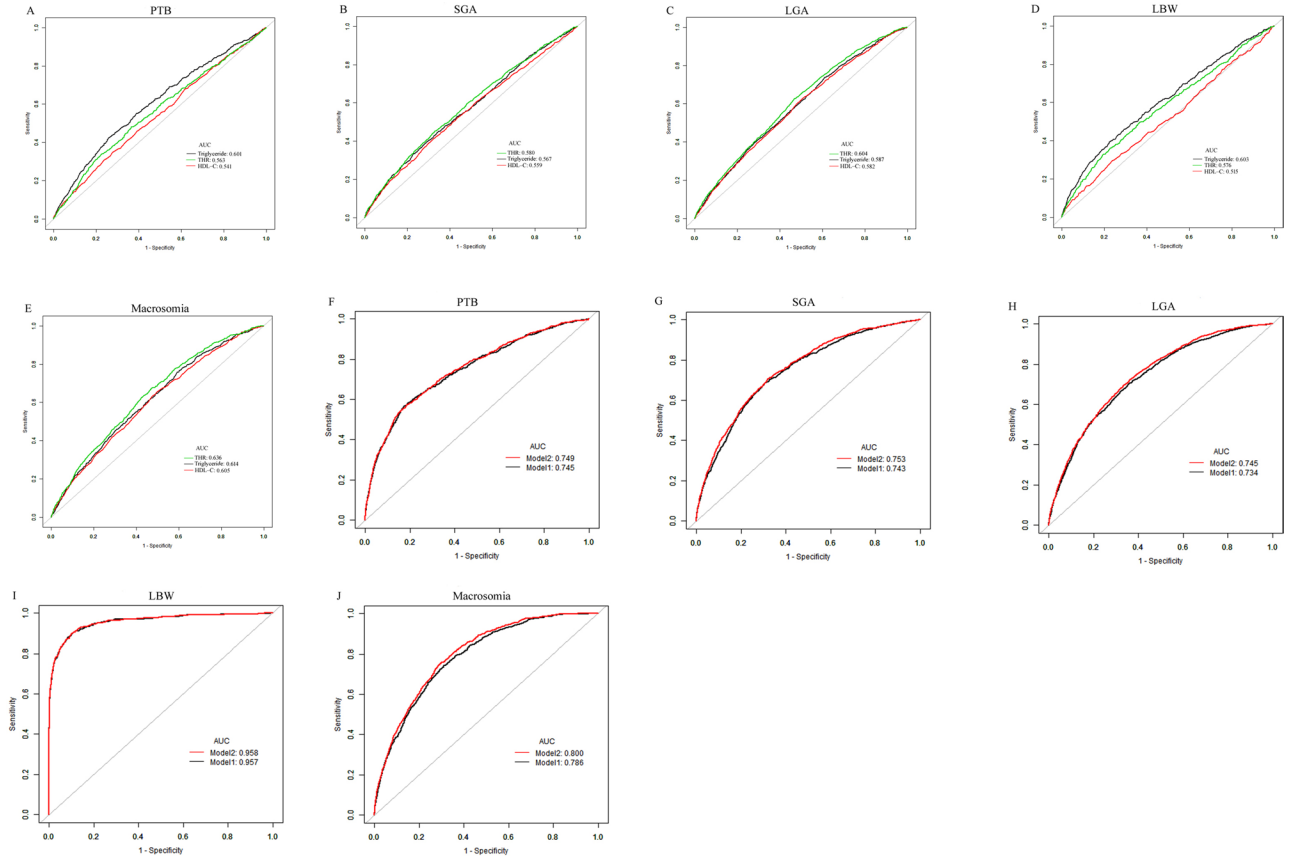

Fig. 4 ROC curves analysis to compare triglyceride, HDL-C, THR and the predictive models for ABO. Model 1 included age, BMI, parity, BP, gestational age (except for PTB), assisted reproduction, fetal sex and laboratory results (total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, creatinine, hsCRP, total cholesterol, and LDL-C. Model 2, Model 1 plus THR

as a means of preventing ABO among individuals with dyslipidemia.

Strengths and limitations

Several crucial strengths of this study are worth mentioning. Firstly, for the first time, the present study demonstrated significant associations between high THR and decreased risk of PTB and SGA based on an analysis of real-world data including a large number of clinical and laboratory data on pregnant women. Sensitivity analysis was performed to ensure robustness of the findings. Secondly, this study further revealed the first evidence of underlying mechanism of THR-associated ABO risk. Significant mediating effect of co-existing pregnancy complications (PE/GDM/ICP) on the associations between serum THR and ABO risk provided crucial clues for further studies on mechanism. Thirdly, lipid profiles and other biochemical indicators were retrieved from routine laboratory tests. The measurements are objective, reliable, accurate and free from the influence of observer bias. The levels of these indicators are closer to pathology, potentially providing mechanistic insights. Therefore, some indicators are widely accepted and become an important part of real-world datasets. Lastly, the potential confounding factors were comprehensively controlled in the statistical analysis of this study, including maternal demographics and other biochemical parameters.

Some limitations of this study should also be acknowledged. Firstly, in view of the observational nature of this study, residual confounding effects could not be completely excluded. The maternal, demographic, and medical history data were obtained from the database without direct confirmation. Additionally, some important confounding factors, such as education, family income, history of adverse pregnancy outcomes, and gestational weight gain (GWG), could not be controlled due to a lack of this information in the current real-world datasets. Secondly, this is a single-center study conducted at a large-scale public specialized hospital, which has a relatively high proportion of high-risk pregnant women. In the statistical analysis, we adjusted for prenatal BMI rather than pre-gestational BMI, as pre-gestational weight values were not available. More than 20% (2,030) of the participants were obese, and 54% (6,337) were overweight. Although a sensitivity analysis was performed among pregnant women without obesity, caution

Table 4 Accuracy of triglyceride, HDL–C, THR and models to predict ABO

	AUC	95% CI	*P* value	Best threshold	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
PTB								
Triglyceride (mmol/L)	0.601	0.579, 0.622	< 0.001	2.89	73.58	42.91	10.29	94.81
HDL-C (mmol/L)	0.541	0.520, 0.563	< 0.001	1.48	76.62	30.18	8.35	93.95
THR	0.563	0.541, 0.585		1.82	63.46	47.77	8.45	94.51
Model 1	0.745	0.725, 0.764	0.052	-2.32	82.58	56.57	18.68	96.41
Model 2	0.749	0.730, 0.768		-2.35	81.52	57.24	17.97	96.42
SGA								
Triglyceride (mmol/L)	0.567	0.548, 0.586	< 0.001	2.96	70.96	39.20	11.59	92.32
HDL–C (mmol/L)	0.559	0.540, 0.578	< 0.001	1.89	70.23	39.10	11.32	92.23
THR	0.580	0.562, 0.599		1.76	67.14	45.26	11.80	92.66
Model 1	0.743	0.727, 0.759	< 0.001	-2.29	69.33	68.69	17.81	95.81
Model 2	0.753	0.738, 0.769		-2.33	68.03	70.58	17.60	95.98
LGA								
Triglyceride (mmol/L)	0.587	0.572, 0.601	< 0.001	3.17	38.72	73.83	18.11	88.96
HDL–C (mmol/L)	0.582	0.568, 0.596	< 0.001	1.73	49.77	62.56	18.61	87.86
THR	0.604	0.590, 0.618		2.13	53.23	62.50	19.70	88.55
Model 1	0.734	0.722, 0.746	< 0.001	-1.80	63.91	70.53	26.43	92.18
Model 2	0.745	0.733, 0.757		-1.77	66.36	69.68	27.58	92.25
LBW								
Triglyceride (mmol/L)	0.603	0.576, 0.630	< 0.001	2.74	77.60	39.07	7.23	96.61
HDL–C (mmol/L)	0.515	0.487, 0.542	< 0.001	1.48	76.41	29.15	5.23	96.02
THR	0.576	0.549, 0.603		1.51	77.28	35.83	6.58	96.42
Model 1	0.957	0.947, 0.968	0.280	-0.315	91.70	87.91	33.91	99.37
Model 2	0.958	0.948, 0.969		-0.349	89.13	90.57	28.78	99.49
Macrosomia								
Triglyceride (mmol/L)	0.614	0.595, 0.633	< 0.001	3.25	40.67	75.79	9.22	95.48
HDL–C (mmol/L)	0.605	0.586, 0.625	< 0.001	1.72	50.27	65.69	9.51	94.85
THR	0.636	0.618, 0.655		2.14	52.57	67.69	10.19	95.34
Model 1	0.786	0.772, 0.801	< 0.001	-2.58	68.79	74.44	16.03	97.11
Model 2	0.800	0.786, 0.814		-2.58	70.10	75.74	16.86	97.30

Notes Model 1 included age, BMI, systolic and diastolic BP, parity, gestational age (except for PTB), pregnancy complications, assisted reproduction, fetal sex and laboratory results (total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, creatinine, total cholesterol, LDL–C and hsCRP). Model 2, model 1 plus THR. *P* values indicated the significance of differences between THR and triglyceride /HDL-C or between Model 1 and Model 2

Abbreviations AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; PTB, preterm birth; SGA/LGA, small/large for gestational age; HDL-C, high density lipoprotein cholesterol; THR, triglyceride/HDL-C ratio; ABO, adverse birth outcome; BMI, body mass index; BP, blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-C, low density lipoprotein cholesterol; hsCRP, high sensitive C-reactive protein

should be exercised when generalizing the current results to general population. Thirdly, the present study focuses on the association between THR and ABO only in late pregnancy, and its application value is limited due to less time for clinical intervention. Longitudinal studies may be combined with findings of the first and second trimesters to promote the predictive power. Finally, sample collection for this study was conducted at the time of admission for delivery (28–41 weeks of gestation) rather than at a uniform gestational week. Although we adjusted for gestational age in the statistical analyses and performed a sensitivity analysis among non-PTB participants, the influence of gestational age on the association between THR and ABO (particularly for PTB and LBW) cannot be entirely ruled out. Large-scale, well-designed prospective studies are needed to confirm our findings.

Conclusion

Real-world evidence showed an association between serum THR in late pregnancy and ABO risk, after adjusting for potential confounders. This association may be partially mediated by the prevalence of PE, GDM and ICP. In addition, adding THR to the designed predictive models may improve the prediction ability of ABO (SGA/LGA/macrosomia). These results from real world data indicated that serum THR at the time of admission for delivery may be a potential predictor of ABO risk, representing a simple marker to consider when studying fetal growth-related outcomes.

Abbreviations

HDL-C	High-density lipoprotein cholesterol
THR	Triglyceride/HDL-C ratio
ABO	Adverse birth outcomes
PTB	Preterm birth

SGA/AGA/LGA	Small/appropriate/large for gestational age
LBW	Low birthweight
GDM	Gestational diabetes mellitus
ICP	Intrahepatic cholestasis of pregnancy
PE	Preeclampsia
PIH	Pregnancy-induced hypertension
PTB	Preterm birth
LDL-C	Low-density lipoprotein cholesterol
hsCRP	High-sensitive C-reactive protein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01503-9.

Supplementary Material 1

Acknowledgements
The authors appreciate the contributions of all members of laboratory and medical record section in Changzhou Maternal and Child Health Care Hospital.

Author contributions
B Z, and Z S conceived and designed this study. X Y wrote the manuscript. Z Z collected the data. F Z and S X analyzed and interpreted data. All authors reviewed and approved the final manuscript.

Funding
This study was supported by General project of Jiangsu Provincial Health Commission (H2023131), Changzhou Medical Center of Nanjing Medical University (CMCC202219), and Top Talent of Changzhou "The 14th Five-Year Plan" High-Level Health Talents Training Project.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The protocol of this study was permitted by Ethics Committee of Changzhou Maternal and Child Health Care Hospital. Anonymous data were analyzed and written informed consents for observational subjects were waived in the present study.

Human Ethics and Consent to Participate
The Ethics Committee of Changzhou Maternal and Child Health Care Hospital approved this study (approval reference ZD201803).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Medical Genetics, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Changzhou, China
[2]Department of Obstetrics, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Changzhou, China

Received: 11 June 2024 / Accepted: 29 October 2024
Published online: 05 November 2024

References

1. Yuan X, Gao Y, Zhang M, Long W, Liu J, Wang H, et al. Association of maternal D-dimer level in late pregnancy with birth outcomes in a Chinese cohort. Clin Chim Acta. 2020;501:258–63.
2. Ohuma EO, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. Lancet. 2023;402(10409):1261–71.
3. Hazel EA, Erchick DJ, Katz J, Lee ACC, Diaz M, Wu LSF et al. Neonatal mortality risk of vulnerable newborns by fine stratum of gestational age and birthweight for 230 679 live births in nine low- and middle-income countries, 2000–2017. BJOG. 2024 Jan 16.
4. Ashorn P, Ashorn U, Muthiani Y, Aboubaker S, Askari S, Bahl R, UNICEF–WHO Low Birthweight Estimates Group, et al. Small vulnerable newborns-big potential for impact. Lancet. 2023;401(10389):1692–706.
5. Chandrasekaran N. Induction of labor for a suspected large-for-gestational-age/macrosomic fetus. Best Pract Res Clin Obstet Gynaecol. 2021;77:110–8.
6. Viswanathan S, McNelis K, Makker K, Calhoun D, Woo JG, Balagopal B. Childhood obesity and adverse cardiometabolic risk in large for gestational age infants and potential early preventive strategies: a narrative review. Pediatr Res. 2022;92(3):653–61.
7. Jin WY, Lin SL, Hou RL, Chen XY, Han T, Jin Y, et al. Associations between maternal lipid profile and pregnancy complications and perinatal outcomes: a population-based study from China. BMC Pregnancy Childbirth. 2016;16:60.
8. Wang C, Zhu W, Wei Y, Su R, Feng H, Hadar E, et al. The associations between early pregnancy lipid profiles and pregnancy outcomes. J Perinatol. 2017;37(2):127–33.
9. Xi F, Chen H, Chen Q, Chen D, Chen Y, Sagnelli M, et al. Second-trimester and third-trimester maternal lipid profiles significantly correlated to LGA and macrosomia. Arch Gynecol Obstet. 2021;304(4):885–94.
10. Zhu SM, Zhang HQ, Li C, Zhang C, Yu JL, Wu YT, et al. Maternal lipid profile during early pregnancy and birth weight: a retrospective study. Front Endocrinol (Lausanne). 2022;13:951871.
11. Wang X, Zhang E, Tian Z, Zhao R, Huang K, Gao S, et al. The association between dyslipidaemia in the first trimester and adverse pregnancy outcomes in pregnant women with subclinical hypothyroidism: a cohort study. Lipids Health Dis. 2024;23(1):13.
12. Zhang B, Xi S, Liu R, Han X, Long W, Yuan X, et al. Maternal fibrinogen/fibrin degradation products to high density lipoprotein cholesterol ratio for predicting delivery of small and large for gestational age infants: a pilot study. Lipids Health Dis. 2023;22(1):221.
13. Chen Z, Hu H, Chen M, Luo X, Yao W, Liang Q, et al. Association of Triglyceride to high-density lipoprotein cholesterol ratio and incident of diabetes mellitus: a secondary retrospective analysis based on a Chinese cohort study. Lipids Health Dis. 2020;19(1):33.
14. Che B, Zhong C, Zhang R, Pu L, Zhao T, Zhang Y, et al. Triglyceride-glucose index and triglyceride to high-density lipoprotein cholesterol ratio as potential cardiovascular disease risk factors: an analysis of UK biobank data. Cardiovasc Diabetol. 2023;22(1):34.
15. dos Santos-Weiss IC, Réa RR, Fadel-Picheth CM, Rego FG, Pedrosa Fde O, Gillery P, et al. The plasma logarithm of the triglyceride/HDL-cholesterol ratio is a predictor of low risk gestational diabetes in early pregnancy. Clin Chim Acta. 2013;418:1–4.
16. Wang D, Xu S, Chen H, Zhong L, Wang Z. The associations between triglyceride to high-density lipoprotein cholesterol ratios and the risks of gestational diabetes mellitus and large-for-gestational-age infant. Clin Endocrinol (Oxf). 2015;83(4):490–7.
17. Wang C, Zhu W, Wei Y, Su R, Feng H, Lin L, et al. The Predictive effects of early pregnancy lipid profiles and fasting glucose on the risk of gestational diabetes Mellitus Stratified by Body Mass Index. J Diabetes Res. 2016;2016:3013567.
18. Pazhohan A, Rezaee Moradali M, Pazhohan N. Association of first-trimester maternal lipid profiles and triglyceride-glucose index with the risk of gestational diabetes mellitus and large for gestational age newborn. J Matern Fetal Neonatal Med. 2019;32(7):1167–75.
19. Barat S, Ghanbarpour A, Bouzari Z, Batebi Z. Triglyceride to HDL cholesterol ratio and risk for gestational diabetes and birth of a large-for-gestational-age newborn. Casp J Intern Med. 2018;9(4):368–75.
20. Poveda NE, Garcés MF, Darghan AE, Jaimes SAB, Sánchez EP, Díaz-Cruz LA, et al. Triglycerides/Glucose and Triglyceride/High-Density Lipoprotein Cholesterol Indices in normal and preeclamptic pregnancies: a longitudinal study. Int J Endocrinol. 2018;2018:8956404.
21. Liu PJ, Liu Y, Ma L, Yao AM, Chen XY, Hou YX, et al. The Predictive ability of two triglyceride-Associated Indices for Gestational Diabetes Mellitus and large

for gestational age infant among Chinese pregnancies: a preliminary Cohort Study. Diabetes Metab Syndr Obes. 2020;13:2025–35.
22. Yu M, Wang W, Wang H. The late-gestational triglyceride to high-density lipoprotein cholesterol ratio is Associated with neonatal Macrosomia in women without Diabetes Mellitus. Int J Endocrinol. 2020;2020:7250287.
23. Arbib N, Pfeffer-Gik T, Sneh-Arbib O, Krispin E, Rosenblat O, Hadar E. The pre-gestational triglycerides and high-density lipoprotein cholesterol ratio is associated with adverse perinatal outcomes: a retrospective cohort analysis. Int J Gynaecol Obstet. 2020;148(3):375–80.
24. Rao C, Ping F. Second-trimester maternal lipid profiles rather than glucose levels predict the occurrence of neonatal macrosomia regardless of glucose tolerance status: a matched cohort study in Beijing. J Diabetes Complications. 2021;35(8):107948.
25. Wang Z, Peng Y, Mao S, Zhang L, Guo Y. The correlation between blood-lipid ratio in the first trimester and large-for-gestational-age infants. Lipids Health Dis. 2023;22(1):18.
26. You Y, Hu H, Cao C, Han Y, Tang J, Zhao W. Association between the triglyceride to high-density lipoprotein cholesterol ratio and the risk of gestational diabetes mellitus: a second analysis based on data from a prospective cohort study. Front Endocrinol (Lausanne). 2023;14:1153072.
27. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. BMJ. 2022;377:e067946.
28. Terrault NA, Williamson C. Pregnancy-Associated Liver diseases. Gastroenterology. 2022;163(1):97–e1171.
29. Battarbee AN, Sinkey RG, Harper LM, Oparil S, Tita ATN. Chronic hypertension in pregnancy. Am J Obstet Gynecol. 2020;222(6):532–41.
30. Yuan X, Zhou L, Zhang B, Wang H, Jiang J, Yu B. Early second-trimester plasma cell free DNA levels with subsequent risk of pregnancy complications. Clin Biochem. 2019;71:46–51.
31. Yuan X, Han X, Jia C, Zhou W, Yu B. Low fetal fraction of cell free DNA at non-invasive prenatal screening increases the subsequent risk of Preterm Birth in Uncomplicated Singleton pregnancy. Int J Womens Health. 2022;14:889–97.
32. Yuan X, Gao Y, Zhang M, Long W, Liu J, Wang H, et al. Fibrin/fibrinogen degradation products in late pregnancy promote macrosomia prediction in normal uncomplicated pregnancy. Placenta. 2020;96:27–33.
33. Yuan X, Hu H, Zhang M, Long W, Liu J, Jiang J, et al. Iron deficiency in late pregnancy and its associations with birth outcomes in Chinese pregnant women: a retrospective cohort study. Nutr Metab (Lond). 2019;16:30.
34. Roland MCP, Lekva T, Godang K, Bollerslev J, Henriksen T. Changes in maternal blood glucose and lipid concentrations during pregnancy differ by maternal body mass index and are related to birthweight: a prospective, longitudinal study of healthy pregnancies. PLoS ONE. 2020;15(6):e0232749.
35. Furse S, Fernandez-Twinn DS, Chiarugi D, Koulman A, Ozanne SE. Lipid metabolism is dysregulated before, during and after pregnancy in a mouse model of gestational diabetes. Int J Mol Sci. 2021;22(14):7452.
36. Khaire AA, Thakar SR, Wagh GN, Joshi SR. Placental lipid metabolism in pre-eclampsia. J Hypertens. 2021;39(1):127–34.

Publisher's note