Mediating Effects of Maternal Blood Triglycerides on the Relationship between Prepregnancy Body Mass Index and Fetal Macrosomia

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Objective To examine whether the association of prepregnancy body mass index (BMI) with fetal macrosomia is mediated through maternal circulating lipid concentrations during pregnancy.

Study design In this prospective cohort, 3011 eligible pregnant women were enrolled. Information on demographic characteristics were collected using questionnaires, and anthropometrics and laboratory tests were performed at 24 weeks of gestation and before delivery. Macrosomia was defined as birth weight ≥4000 g. Logistic regression and multivariable linear regression, adjusted for age, fetal sex, education, gestational weight gain, fasting blood glucose, gestational diabetes, gestational hypertension, gestational age at delivery, delivery mode, and parity, were used to assess the mediation path between prepregnancy BMI, maternal serum lipids, and fetal macrosomia.

Results A total of 2454 participants with completed records were included in the final analyses. Among the maternal circulating lipid biomarkers, only triglyceride was significantly associated with both prepregnancy BMI and fetal macrosomia risk, adjusting for potential confounders. Mediation analyses demonstrated that the direct effect of prepregnancy BMI on fetal macrosomia was 0.0085 (95% CI, 0.0003-0.018; $P < .05$), the indirect effect mediated through maternal serum triglycerides was 0.0016 (95% CI, 0.0007-0.0029; $P < .001$), and the estimated proportion of mediated effect was 15.7% ($P < .05$).

Conclusions Maternal circulating triglycerides mediate the association of prepregnancy BMI with the risk of fetal macrosomia. *(J Pediatr 2020;226:118-22)*.

Birth weight is an important outcome for evaluating intrauterine growth and predicting short- and long-term morbidities.[1] Fetal macrosomia, defined as birthweight ≥4000 grams irrespective of gestational age, indicates abnormal weight gain in utero.[1] Moreover, macrosomia is also related to rapid weight gain during infancy and a series of adverse health outcomes, including future obesity, hypertension, metabolic disorders, and even cancers.[1-4] The prevalence of fetal macrosomia varies by region, occurring in 6%-10% of Chinese newborns and >10% of newborns in Australia and Canada.[5-8]

Previous studies have found that prepregnancy body mass index (BMI) and weight gain during pregnancy were the most frequently reported predictors of fetal macrosomia.[9,10] Studies have identified maternal lipid levels as strong determinants of fetal growth in women with gestational diabetes mellitus.[11,12] Therefore, it was hypothesized that excessive rise in maternal blood lipids during pregnancy might influence the flux of lipids to the placenta and might play a role in the development of macrosomia.[13,14]

The aims of this study were to evaluate whether higher prepregnancy BMI was associated with altered concentration of blood lipids during pregnancy in our cohort, and to examine whether maternal blood lipids mediated the association, if any, between prepregnancy BMI and fetal macrosomia.

Methods

This study, comprising 2454 pregnant women from the Hangzhou Maternal and Offspring Health Cohort Study (clinical trial registration number ChiCTR1900026149), was conducted in the Hangzhou Women's Hospital (Hangzhou Maternity and Child Health Care Hospital) to investigate the potential effects of environmental exposures on health among pregnant women and

BMI	Body mass index
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
TG	Total triglycerides

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offspring. In brief, pregnant women were registered at a primary care hospital, where they received prenatal examinations until 20-24 weeks of gestation, after which they were transferred to the Hangzhou Women's Hospital and were screened and enrolled in the present study. The enrolled women were followed up via clinic visits twice monthly before 34 weeks of gestation and weekly after 34 weeks of gestation. This study was performed in accordance with the Declaration of Helsinki and approved by the local Ethics Review Board. All participants provided written informed consent.

At registration for pregnancy, the information on maternal demographic characteristics (eg, age, education, occupation), anthropometrics (eg, body weight, height, blood pressure), and clinical history (eg, parity, disease history) were recorded. Dietary supplements were collected at 24 weeks of gestation with questionnaires. Fasting blood sample collection and laboratory tests (eg, blood routine examination and blood biochemistry examination including blood lipids, glucose) were undertaken twice, first at 24 weeks of gestation and then at hospitalization for delivery. Anthropometric measurements and laboratory tests were conducted again at hospitalization for delivery. The clinical records (eg, delivery mode, birth weight, sex, Apgar score) for delivery were retrieved. Participants were asked to wear light clothing for height and weight measurements, and BMI was calculated as body weight in kilograms divided by height in meters squared. Sitting blood pressure was examined after at least 10 minutes of break. Fetal macrosomia was defined as birth weight ≥4000 g, irrespective of gestational age.[1]

The general baseline characteristics, laboratory test results during pregnancy, and pregnancy outcomes are described as mean (SD), median (IQR), or percentage, as appropriate. We hypothesized that circulating lipid concentration (total triglycerides [TG], total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], and low-density lipoprotein cholesterol [LDL-C]) during pregnancy may mediate the association between prepregnancy BMI and fetal macrosomia risk. A mediator is related to both the exposure and the outcomes of interest.[15] We evaluated the association of serum lipid levels (at 24 weeks of gestation) with the risk of fetal macrosomia using logistic regression and examined the relationship between serum lipids (at 24 weeks of gestation) and prepregnancy BMI using multivariable linear regression. In the logistic regression model, TG, TC, HDL-C, and LDL-C are mutually adjusted for one another and further adjusted for potential confounders, including age, fetal sex, education level, gestational weight gain, fasting blood glucose concentration, gestational diabetes, gestational hypertension, gestational age at delivery, delivery mode, and parity. Only the circulating lipid biomarkers showing significant association with fetal macrosomia risk are sequentially included in the further multivariable linear regression model, to investigate the associations with prepregnancy BMI, adjusting for age, fetal sex, education level, fasting blood glucose concentration, and gestational diseases. The Bonferroni method was used to adjust for multiple comparisons when multiple circulating lipid biomarkers were included.

To determine whether circulating lipids may mediate the relationship between prepregnancy BMI and fetal macrosomia risk, maternal circulating lipid biomarkers that are significantly associated with both prepregnancy BMI and fetal macrosomia were used for further mediation analysis. The direct, indirect, and total effects were calculated using the mediation package in R, with uncertainty estimated using a quasi-Bayesian Monte Carlo method with 2000 simulations based on a normal approximation.[16] The total effect is the effect of prepregnancy BMI on the fetal macrosomia, and the indirect effect indicates the effect mediated through maternal circulating lipids. The mediation proportion is calculated as the value of indirect effect divided by the total effect.

The interclass correlation analysis was performed to test the correlation of TG levels measured at different time points, and sensitivity analyses were performed by replacing the maternal serum lipids at 24 weeks of gestation with those examined when the participants were hospitalized for delivery, to test the consistency. All statistical analyses are conducted using Stata version 15 (StataCorp, College Station, Texas) or R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed P value <.05 was considered to indicate statistical significance.

Results

Of the 3011 pregnant women enrolled in the study, 2982 gave birth to singletons. Another 528 participants were excluded owing to incomplete records (eg, prepregnancy weight, gestational weight gain) and missing data on laboratory tests (eg, serum levels of TG, TC, and HDL-C), resulting in 2454 participants in the final analyses (**Figure 1**). The general characteristics of the participants are presented in **Table I**.

With mutual adjustment among the 4 circulating lipid biomarkers, only maternal serum TG showed a significant association with fetal macrosomia risk, with a 44% higher risk of fetal macrosomia per 1 mmol/L increment of maternal serum TG concentration (95% CI, 1.19-1.75; $P < .001$). Further adjusting for covariates including age, fetal sex, prepregnancy BMI, education status, gestational weight gain, gestational age, fasting blood glucose, delivery mode, and parity did not substantially change the effect of TG level, and each 1-mmol/L increment in TG concentration was associated with a 46% higher risk of fetal macrosomia (95% CI, 1.17-1.81; $P < .01$). Other lipid biomarkers did not show any significant associations with fetal macrosomia risk.

Univariable linear regression indicated that prepregnancy BMI was significantly associated with maternal serum TG concentration with a β coefficient of 0.054 (95% CI, 0.042-0.066; $P < .001$). After adjustment for confounders, including age, fetal sex, prepregnancy BMI, education status, gestational weight gain, gestational age, fasting blood glucose, delivery mode, and parity, in the multivariable linear

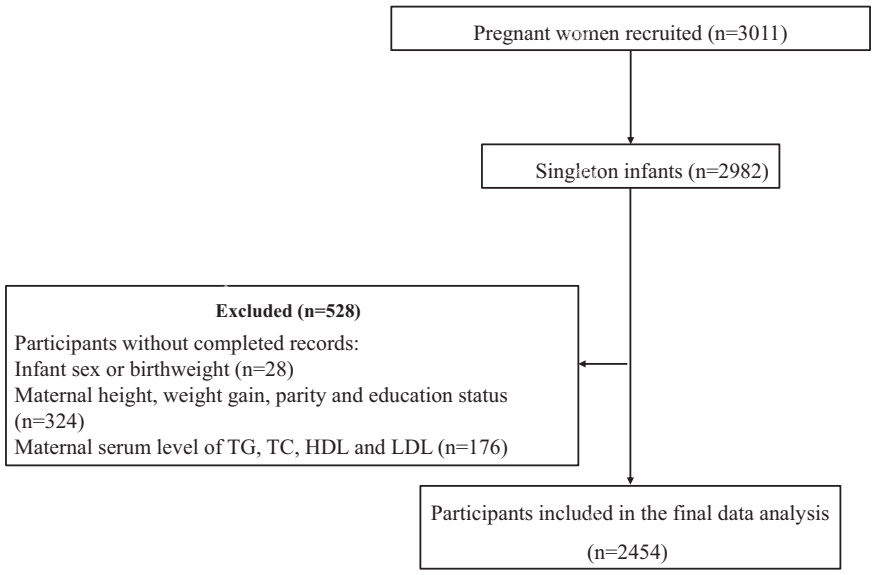

Figure 1. Flow chart of the inclusion of study participants.

regression, the significant association persisted. The β coefficient was 0.037 (95% CI, 0.025-0.049; $P < .001$).

Among the 4 maternal circulating lipid biomarkers, only TG level was significantly associated with both prepregnancy BMI and fetal macrosomia risk. Therefore, mediation analysis was performed to evaluate whether serum TG level mediated the relationship of prepregnancy BMI with fetal macrosomia. After controlling for the influence of all covariates except TG, prepregnancy BMI was significantly associated with fetal macrosomia (OR, 1.09; 95% CI, 1.01-1.17; $P < .05$), indicating a significant total effect. This statistical significance persisted (OR, 1.08; 95% CI, 1.00-1.16; $P = .05$) when TG was included as a mediator, implying a significant direct effect of prepregnancy BMI on macrosomia controlling for the mediation.

Table I. General characteristics of the study population (N = 2454)

Characteristics	Value
Age, y, mean (SD)	30.1 (3.8)
Education level, n (%)	
<High school	136 (5.5)
High school	260 (10.6)
>High school	2058 (83.9)
Prepregnancy weight, kg, mean (SD)	54.0 (7.6)
Height, cm, mean (SD)	160.6 (4.9)
Pre-pregnancy BMI, kg/m^2, mean (SD)	20.9 (2.7)
Calcium supplements, n (%)	1428 (58.2)
Folate acid supplements, n (%)	1571 (64.0)
Ferron supplements, n (%)	535 (21.8)
DHA supplements, n (%)	1101 (44.9)
Gestational diabetes mellitus, n (%)	335 (13.7)
Gestational hypertension, n (%)	59 (2.4)
Gestational hypothyroidism, n (%)	334 (13.6)
Gestational weight gain, kg, mean (SD)	13.0 (4.1)
Parity: multiparous, n (%)	878 (35.8)
Gestational age at delivery, wk, mean (SD)	38.8 (1.6)
Cesarean delivery, n (%)	830 (33.8)
Birthweight, g, mean (SD)	3284.5 (459.8)
Fetal macrosomia, n (%)	108 (4.4)
Male sex, n (%)	1294 (52.7)

The mediation analyses found a total effect of prepregnancy BMI on fetal macrosomia of 0.0101 (95% CI, 0.002-0.020; $P < .05$), including a direct effect of 0.0085 (95% CI, 0.0003-0.018; $P < .05$) (Table II). A significant positive indirect effect of prepregnancy BMI associated with fetal macrosomia (mean indirect effect, 0.0016; 95% CI, 0.0007-0.0029; $P < .001$) through maternal serum TG level was observed, and the estimated proportion of mediated effect was 15.7% ($P < .05$).

The interclass correlation analysis showed a coefficient of 0.65 ($P < .001$) between TG levels measured at different time points, indicating the levels were relatively stable. Sensitivity analyses showed that repeating the logistic regression analysis using maternal circulating TG concentration collected close to the time of delivery (when participants were hospitalized for delivery) did not substantially change the association. With mutual adjustment among the 4 circulating lipid biomarkers, a 1 mmol/L increase in the delivery measure of TG concentration was associated with a 45% higher risk of fetal macrosomia (95% CI, 1.18-1.79; $P < .001$). Additional adjustment for covariates including age, fetal sex, prepregnancy BMI, gestational weight gain, and fasting blood glucose indicated a 45% higher risk of fetal macrosomia per 1 mmol/L increment of the delivery measure of TG concentration (95% CI, 1.16-1.82; $P < .001$). We also repeated the mediation analysis using the maternal serum TG concentration at this time point as the mediator. As shown in Figure 2 (available at www.jpeds.com), significant indirect effects of prepregnancy BMI associated with fetal macrosomia through maternal blood TG concentration at

Table II. Mediation effects of maternal serum TG concentration on the association between prepregnancy BMI and fetal macrosomia (N = 2454)

Mediator	Total effect (95% CI)	Direct effect (95% CI)	Indirect effect (95% CI)	Estimated mediated, %
Maternal serum TG	0.0101 (0.002-0.020)*	0.0085 (0.0003-0.018)*	0.0016 (0.0007-0.0029)†	15.7

*$P < .05$.
†$P < .01$.

this time point were also found, and the estimated proportion of mediated effect was 5.8% ($P < .05$).

Discussion

Higher prepregnancy BMI was significantly associated with higher serum concentration of maternal TG, which was subsequently demonstrated to be significantly associated with an increased risk of fetal macrosomia. Both primary analyses and sensitivity analyses demonstrated that maternal serum TG mediated significant and positive indirect effects of prepregnancy BMI on fetal macrosomia, which highlights the importance of the role that maternal circulating TG during pregnancy played in the development of fetal macrosomia.

Previous studies have shown that accumulation of fat in maternal depots that occurs during early pregnancy and later development of hyperlipidemia are 2 principal changes in lipid metabolism during pregnancy.[17,18] Specifically, the increased tissue lipoprotein lipase activity during the early stage of pregnancy catalyze the hydrolysis of circulating TG, and the hydrolytic products are mostly taken up by tissue, which facilitates the accumulation of lipids in maternal depots. Thereafter, during late pregnancy, the accumulation of fat stops and even declines due to increased lipolysis, mobilization of TG stored in adipose tissue and decreased activity of adipose tissue lipoprotein lipase.[17,19] Whether the prepregnancy BMI may act as a negative feedback for accumulation of lipids during early stage of pregnancy is not well understood, but our study did indicate that the prepregnancy BMI was negatively associated with gestational weight gain rate, which was consistent with previous studies across different cohorts.[20,21] Maternal circulating lipid concentrations during pregnancy differed by maternal BMI[13]; therefore, whether the lipoprotein lipase activity and related hydrolysis of circulating TG is affected by prepregnancy BMI and subsequently involved in the positive association between prepregnancy BMI and blood TG concentration during middle and late pregnancy merits further investigation.

Maternal blood glucose has been extensively studied and is believed to be the substrate transferred to fetus in the greatest quantities.[22] In both healthy women and women with diabetes, maternal blood glucose concentration is associated with fetal growth.[22-24] Nevertheless, other factors, such as maternal circulating lipids, also may play important roles in fetal growth, given that no significant correlation between maternal blood glucose and fetal overgrowth has been consistently found.[12,25] In addition, the availability of substrate in the fetus depends on the concentration in the maternal circulation. We believe that a high concentration of maternal circulating TG facilitates the availability of lipids to the fetus, despite the difficulties in transportation across the placenta. Moreover, hypertriglyceridemia in gestational diabetes mellitus has been associated with an elevated risk of having neonates large for gestational age and circulating concentration of TG in diabetic women has been considered a strong predictor of birth weight.[12] Our study shows that after adjusting for fasting glucose concentration and gestational diabetes, there are still significant positive associations between maternal circulating TG concentrations and the risk of fetal macrosomia.

A previous study evaluating dynamic changes in maternal circulating lipid profile during pregnancy found that the dynamics in pregnant women differed by BMI.[13] Consistent with our results, they found a higher circulating TG concentration in late pregnancy in mothers who gave birth to infants with macrosomia. Our mediation analyses clarified that the positive association between prepregnancy BMI and fetal macrosomia risk was partially mediated by maternal circulating TG concentration, after controlling for gestational weight gain, maternal blood glucose, and gestational diabetes. This finding implies that pregnant women who had been overweight or obese before pregnancy might benefit from management of circulating TG for prevention of overgrowth of the fetus.

This study has some limitations. First, detailed dietary information was not collected, which together with other potential contributors to changes in birth weight might have confounded our results. Second, the blood glucose and lipid profiles of offspring were not examined, which may be important to help explain the proposed association between maternal circulating TG concentration and fetal macrosomia.

Our results have potential public health implications for prevention of fetus overgrowth among pregnant women who are overweight or obese before pregnancy. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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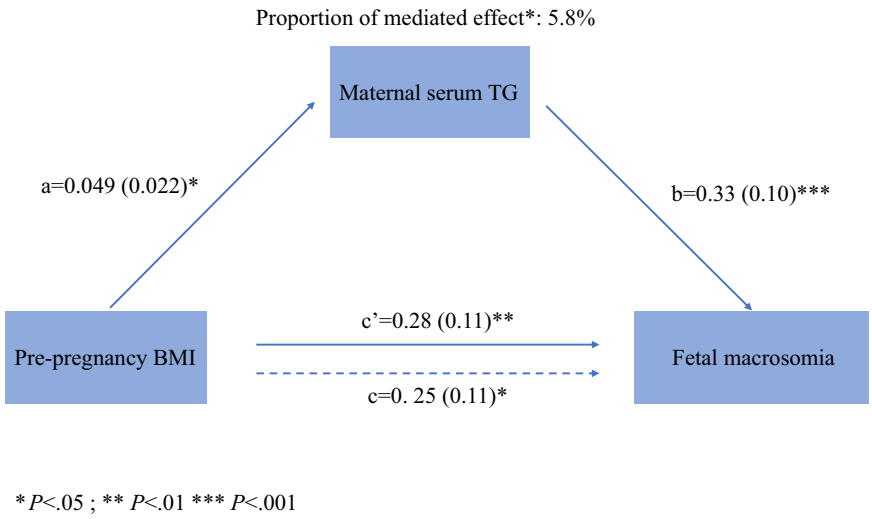

Figure 2. Sensitivity analysis for the mediating effects of maternal serum TG concentration on the association between prepregnancy BMI and fetal macrosomia (n = 2191). Maternal serum TG concentration examined at the time point closest to delivery was used. The dotted line represents the association of prepregnancy BMI with fetal macrosomia when the mediating variable (maternal serum TG concentration the time point close to deliver) is included in the model. Coefficients derived from generalized linear regression are reported in the paths.