

Association of Pre-pregnancy Body Mass Index and Gestational Blood Lipid Levels with Macrosomia: A Postprint

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Abstract

Background Macrosomia not only poses certain risks to pregnant women and newborns, but may also affect the long-term metabolic health of offspring. Maternal body weight status is closely associated with pregnancy outcomes, and overweight/obese individuals often have dyslipidemia. Abnormal elevation of blood lipids during pregnancy can affect the intrauterine environment and neonatal birth weight.

Objective To analyze the relationship between blood lipid levels during pregnancy and macrosomia in pregnant women with different pre-pregnancy body mass index (BMI).

Methods This was a single-center retrospective study. A total of 5,287 singleton pregnant women who established prenatal care and delivered at the Department of Obstetrics, Beijing Obstetrics and Gynecology Hospital, Capital Medical University between January 2018 and June 2019 and met the inclusion and exclusion criteria were enrolled. According to pre-pregnancy BMI, the pregnant women were divided into underweight, normal weight, and overweight/obese groups. Based on neonatal birth weight, underweight pregnant women were further divided into underweight pregnant women without macrosomia group (Group A, n=731) and underweight pregnant women with macrosomia group (Group B, n=27); normal weight pregnant women were divided into normal weight pregnant women without macrosomia group (Group C, n=3,539) and normal weight pregnant women with macrosomia group (Group D, n=243); overweight/obese pregnant women were divided into overweight/obese pregnant women without macrosomia group (Group E, n=675) and overweight/obese pregnant women with macrosomia group (Group F, n=72). Relevant clinical and laboratory data of the pregnant women were collected for statistical analysis. Binary logistic regression analysis was used to explore the relationship between blood

lipid levels during pregnancy and macrosomia in pregnant women with different pre-pregnancy BMI.

Results The HDL-C level in the third trimester of Group B was lower than that of Group A ($P<0.05$). The total cholesterol (TC) level in the first trimester and triglyceride (TG) level in the third trimester of Group D were higher than those of Group C ($P<0.05$), while HDL-C levels in the second and third trimesters were lower than those of Group C ($P<0.05$). TG levels in the first, second, and third trimesters of Group F were all higher than those of Group E ($P<0.05$), while HDL-C levels in the second and third trimesters were lower than those of Group E ($P<0.05$). Binary logistic regression analysis showed that third-trimester HDL-C [OR=0.256, 95%CI (0.075, 0.871)] was a factor influencing macrosomia delivery in pre-pregnancy underweight pregnant women ($P<0.05$). Second- and third-trimester HDL-C [OR=0.661, 95%CI (0.450, 0.971); OR=0.406, 95%CI (0.271, 0.610)] were factors influencing macrosomia delivery in pre-pregnancy normal weight pregnant women ($P<0.05$). TG levels in the first, second, and third trimesters [OR=1.546, 95%CI (1.070, 2.234); OR=1.399, 95%CI (1.019, 1.758); OR=1.289, 95%CI (1.072, 1.550)] were factors influencing macrosomia delivery in pre-pregnancy overweight/obese pregnant women ($P<0.05$).

Conclusion Low HDL-C levels during pregnancy in pre-pregnancy underweight and normal weight pregnant women were associated with macrosomia, while elevated TG levels during pregnancy in overweight/obese pregnant women were associated with macrosomia. For pregnant women with large-for-date fetuses or high predicted risk of macrosomia during prenatal care, enhanced blood lipid monitoring and control are needed.

Full Text

Association between Blood Lipid Levels and Macrosomia in Pregnant Women with Different Pre-pregnancy Body Mass Index

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Abstract

Background: Macrosomia not only poses immediate risks to pregnant women and newborns but also affects the long-term metabolic health of offspring. Maternal body mass status is closely associated with pregnancy outcomes, as overweight and obese individuals often present with dyslipidemia. Elevated blood lipid levels during pregnancy can affect the intrauterine environment and neonatal birth weight.

Objective: To analyze the association between blood lipid levels during pregnancy and macrosomia in women with different pre-pregnancy body mass index (BMI).

Methods: This single-center retrospective study included 5,287 singleton pregnant women who registered for antenatal care and delivered at the Department of Obstetrics, Beijing Obstetrics and Gynecology Hospital, Capital Medical University between January 2018 and June 2019, meeting inclusion and exclusion criteria. Based on pre-pregnancy BMI, women were categorized as underweight, normal weight, or overweight/obese. According to neonatal birth weight, underweight women were divided into underweight non-macrosomia group (Group A, n=731) and underweight macrosomia group (Group B, n=27); normal weight women into normal weight non-macrosomia group (Group C, n=3,539) and normal weight macrosomia group (Group D, n=243); and overweight/obese women into overweight/obese non-macrosomia group (Group E, n=675) and overweight/obese macrosomia group (Group F, n=72). Relevant clinical and laboratory data were collected for statistical analysis. Binary logistic regression was used to explore the relationship between blood lipid levels during pregnancy and macrosomia across different pre-pregnancy BMI categories.

Results: Third-trimester HDL-C levels in Group B were lower than in Group A ($P<0.05$). Group D showed higher first-trimester total cholesterol (TC) and third-trimester triglycerides (TG) compared with Group C ($P<0.05$), while second- and third-trimester HDL-C levels were lower ($P<0.05$). Group F had higher TG levels in all three trimesters compared with Group E ($P<0.05$), and lower second- and third-trimester HDL-C levels ($P<0.05$). Binary logistic regression revealed that third-trimester HDL-C [OR=0.256, 95%CI (0.075, 0.871)] was an influencing factor for macrosomia in underweight women ($P<0.05$). Second- and third-trimester HDL-C [OR=0.661, 95%CI (0.450, 0.971); OR=0.406, 95%CI (0.271, 0.610)] were influencing factors for macrosomia in normal weight women ($P<0.05$). TG levels in all three trimesters [OR=1.546, 95%CI (1.070, 2.234); OR=1.399, 95%CI (1.019, 1.758); OR=1.289, 95%CI (1.072, 1.550)] were influencing factors for macrosomia in overweight/obese women ($P<0.05$).

Conclusion: Low HDL-C levels during pregnancy are associated with macrosomia in underweight and normal weight women, whereas elevated TG levels during pregnancy are associated with macrosomia in overweight/obese women. For pregnant women with large-for-date fetuses or at high risk for macrosomia,

enhanced blood lipid monitoring and control are warranted during prenatal care.

Keywords: Body mass index; Pregnancy; Pregnant women; Blood lipids; Fetal macrosomia; Pregnancy complications; Root cause analysis

Introduction

Macrosomia is defined as an absolute fetal birth weight (BW) $>4,000$ g or $>4,500$ g regardless of gestational age. In China, macrosomia is defined as fetal BW $>4,000$ g at any gestational week. The global incidence of macrosomia is approximately 9%, though this varies considerably between countries. In China, the incidence ranges from 7.3% (4.1%, 13.4%), with significantly higher rates in northern regions (8.5%) compared with southern regions (5.6%). Macrosomia poses risks to both mothers and newborns. For mothers, it can lead to prolonged or arrested labor, increased rates of cesarean delivery, postpartum hemorrhage, and soft tissue birth canal injuries. For newborns, it increases the risk of shoulder dystocia, stillbirth, hypoglycemia, respiratory problems, and significantly elevates the risk of obesity, glucose intolerance, and metabolic syndrome during childhood and beyond.

Maternal body mass status is closely associated with pregnancy outcomes. Studies have shown that maternal obesity and excessive gestational weight gain have surpassed maternal diabetes as risk factors for macrosomia. Overweight and obese individuals often present with dyslipidemia, characterized by elevated triglyceride (TG) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels. Pregnant women with different body mass statuses exhibit significant differences in blood lipid profiles during pregnancy. While altered lipid metabolism represents a normal physiological response in pregnancy, with gradually increasing circulating lipids being essential for fetal growth and development, abnormal elevations in blood lipids can affect the intrauterine environment and fetal outcomes. Therefore, this single-center retrospective study aimed to analyze the relationship between blood lipid levels during pregnancy and macrosomia in women with different pre-pregnancy body mass index (BMI).

1. Methods

1.1 Study Participants This study included 5,287 singleton pregnant women who registered for antenatal care and received regular prenatal examinations until delivery at Beijing Obstetrics and Gynecology Hospital, Capital Medical University between January 2018 and June 2019. Inclusion criteria were: age 18-45 years, singleton pregnancy, availability of pre-pregnancy height and weight data, and blood lipid data during pregnancy. Exclusion criteria included: gestational hyperglycemia, hypertensive disorders of pregnancy, thyroid disease; fetal single umbilical artery or other conditions potentially affecting fetal growth; and low

birth weight infants (BW<2,500 g). This study was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital (2018-ky-009-01).

1.2 Grouping Women were first categorized by pre-pregnancy BMI as underweight (BMI<18.5 kg/m²), normal weight (18.5-<24.0 kg/m²), or overweight/obese (BMI≥ 24.0 kg/m²). Based on neonatal birth weight (2,500-4,000 g defined as non-macrosomia, >4,000 g as macrosomia), underweight women were further divided into underweight non-macrosomia group (Group A, n=731) and underweight macrosomia group (Group B, n=27); normal weight women into normal weight non-macrosomia group (Group C, n=3,539) and normal weight macrosomia group (Group D, n=243); and overweight/obese women into overweight/obese non-macrosomia group (Group E, n=675) and overweight/obese macrosomia group (Group F, n=72).

1.3 Research Methods This single-center retrospective study collected maternal clinical data, blood lipid levels during pregnancy, and neonatal birth information to analyze the relationship between blood lipids and macrosomia across different pre-pregnancy BMI categories.

1.3.1 Data Collection Maternal data collected included: age, last menstrual period, gravidity and parity, conception method (including in vitro fertilization-embryo transfer [IVF-ET]), medical history (including diabetes, hypertension, polycystic ovary syndrome [PCOS], thyroid disease), pregnancy complications (including gestational diabetes mellitus, hypertensive disorders of pregnancy, acute fatty liver of pregnancy); physical examination data including height and pre-pregnancy weight for BMI calculation; and laboratory data including blood lipids in early (5-14 weeks), middle (24-28 weeks), and late (32-34 weeks) pregnancy, early and late pregnancy fasting blood glucose (FBG), and oral glucose tolerance test (OGTT) results from the second trimester.

1.3.2 Lipid and Glucose Testing Blood lipid levels were measured in early, middle, and late pregnancy. After fasting for at least 8 hours, fasting venous blood was collected in the morning and analyzed using an ARCHITECT ci16200 automatic biochemical analyzer (Abbott Park, IL, USA) to determine total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), and HDL-C levels. FBG was measured in early and late pregnancy using the same analyzer after an 8-hour fast. A 75 g OGTT was performed in the second trimester, with blood samples collected at 0 h, 1 h, and 2 h after glucose administration. Plasma glucose was measured using the glucose oxidase method, with diagnostic thresholds of 5.1, 10.0, and 8.5 mmol/L; values meeting or exceeding any of these criteria indicated gestational diabetes mellitus.

2. Results

2.1 Comparison Between Underweight Groups (A and B) The study included 758 underweight women, with 731 in Group A and 27 in Group B. As shown in Table 1, no significant differences were observed between Groups A and B in maternal age, pre-pregnancy BMI, multiparity rate, IVF-ET rate, PCOS rate, cesarean delivery rate, neonatal sex ratio, early pregnancy FBG, OGTT results, late pregnancy FBG, or TC, TG, LDL-C, and HDL-C levels across all trimesters ($P>0.05$). However, Group B showed higher gestational weight gain, longer gestational age at delivery, higher neonatal birth weight, and lower third-trimester HDL-C compared with Group A ($P<0.05$).

2.2 Comparison Between Normal Weight Groups (C and D) The study included 3,782 normal weight women, with 3,539 in Group C and 243 in Group D. As shown in Table 2, no significant differences were found between Groups C and D in multiparity rate, IVF-ET rate, PCOS rate, OGTT 2-hour glucose, early pregnancy TG, HDL-C, mid-pregnancy TC and TG, late pregnancy TC, or LDL-C levels across all trimesters ($P>0.05$). Group D had higher maternal age, pre-pregnancy BMI, gestational weight gain, gestational age at delivery, cesarean delivery rate, neonatal birth weight, male neonate ratio, early pregnancy FBG, OGTT glucose values (0 h, 1 h, and AUC), late pregnancy FBG, early pregnancy TC, and late pregnancy TG compared with Group C ($P<0.05$). Mid- and late-pregnancy HDL-C levels were lower in Group D ($P<0.05$).

2.3 Comparison Between Overweight/Obese Groups (E and F) The study included 747 overweight/obese women, with 675 in Group E and 72 in Group F. As shown in Table 3, no significant differences were observed between Groups E and F in maternal age, pre-pregnancy BMI, gestational weight gain, multiparity rate, PCOS rate, early pregnancy FBG, OGTT 2-hour glucose, early pregnancy TC and HDL-C, or mid- and late-pregnancy TC and LDL-C ($P>0.05$). Group F had higher IVF-ET rate, gestational age at delivery, cesarean delivery rate, neonatal birth weight, male neonate ratio, OGTT glucose values (0 h, 1 h, and AUC), late pregnancy FBG, and TG levels across all three trimesters compared with Group E ($P<0.05$). Mid- and late-pregnancy HDL-C levels were lower in Group F ($P<0.05$).

2.4 Binary Logistic Regression Analysis of Blood Lipid Levels and Macrosomia Normally distributed continuous variables are expressed as ($\bar{x}\pm s$) and compared using independent samples t-tests; non-normally distributed variables are expressed as M(P25,P75) and compared using non-parametric tests; categorical data are expressed as percentages and compared using χ^2 tests. Blood lipid indicators showing significant differences in univariate analysis (TG, LDL-C, HDL-C) were included in binary logistic regression analysis to examine their relationship with macrosomia across

different pre-pregnancy BMI categories, with $P < 0.05$ considered statistically significant.

Results showed that third-trimester HDL-C was an influencing factor for macrosomia in underweight women [OR=0.196, 95%CI (0.060, 0.645), $P=0.007$]. After adjusting for gestational age at delivery, neonatal sex, maternal age, pre-pregnancy BMI, gestational weight gain, and FBG, the association remained significant [OR=0.256, 95%CI (0.075, 0.871)] ($P=0.029$). No association was found between TG or LDL-C levels in any trimester and macrosomia in this group.

Second- and third-trimester HDL-C were influencing factors for macrosomia in normal weight women [OR=0.598, 95%CI (0.412, 0.868); OR=0.406, 95%CI (0.271, 0.610)] ($P < 0.05$). After adjusting for gestational age at delivery, neonatal sex, maternal age, pre-pregnancy BMI, gestational weight gain, and FBG, the associations remained significant [OR=0.661, 95%CI (0.450, 0.971); OR=0.406, 95%CI (0.271, 0.610)] ($P < 0.05$). No association was observed between TG or LDL-C levels and macrosomia in this group.

TG levels in all three trimesters were influencing factors for macrosomia in overweight/obese women [OR=1.501, 95%CI (1.044, 2.160); OR=1.355, 95%CI (1.052, 1.745); OR=1.260, 95%CI (1.065, 1.490)] ($P < 0.05$). After adjusting for gestational age at delivery, neonatal sex, maternal age, pre-pregnancy BMI, gestational weight gain, and FBG, the associations persisted [OR=1.546, 95%CI (1.070, 2.234); OR=1.399, 95%CI (1.019, 1.758); OR=1.289, 95%CI (1.072, 1.550)] ($P < 0.05$). No association was found between HDL-C or LDL-C levels and macrosomia in this group.

Discussion

Pregnant women with different body mass statuses exhibit significant differences in blood lipid levels during pregnancy, with overweight/obese individuals typically showing elevated TG and/or reduced HDL-C levels. Maternal lipid metabolism during pregnancy is crucial for fetal growth and development. Numerous studies have examined the relationship between blood lipid levels during pregnancy and macrosomia, large-for-gestational-age (LGA) infants, or neonatal birth weight, but most have not stratified analyses by maternal body weight. Kong et al. analyzed 27,152 pregnant women from 15 Beijing hospitals and found that women delivering macrosomic infants had significantly higher TG levels across all trimesters and lower HDL-C levels compared with those delivering normal-weight infants. Another study investigating the predictive value of mid-pregnancy maternal lipid levels for macrosomia found that low HDL-C at 20 weeks gestation was an independent risk factor [OR=1.67, 95%CI (1.06, 2.64), $P=0.026$].

Gestational hyperglycemia is an important risk factor for macrosomia, but re-

search has shown that in diabetic women with well-controlled blood glucose, maternal lipid levels during pregnancy are strong predictors of fetal size, potentially explaining why macrosomia or LGA rates remain high in diabetic pregnancies despite strict glycemic control. In women with normal glucose tolerance, blood lipid levels during pregnancy are also associated with birth weight and macrosomia risk. One study found that each 1 mmol/L increase in third-trimester TG increased macrosomia risk by 27%, while each 1 mmol/L increase in HDL-C decreased risk by 37%; women with high TG combined with low HDL-C had higher macrosomia risk than those with either abnormality alone. A meta-analysis of 46 studies including 31,402 pregnant women demonstrated that elevated TG and low HDL-C levels throughout pregnancy were associated with increased birth weight, LGA risk, and reduced small-for-gestational-age (SGA) risk, with stronger associations in overweight/obese women.

Overweight/obese individuals frequently present with dyslipidemia characterized by elevated TG and reduced HDL-C levels. This study stratified women by pre-pregnancy BMI and analyzed the relationship between blood lipids and macrosomia within each category. Results showed differences in lipid profiles between macrosomic and non-macrosomic groups across all BMI categories. Binary logistic regression revealed that low HDL-C was associated with macrosomia in underweight and normal weight women, while elevated TG was associated with macrosomia in overweight/obese women.

Mediation analyses of the relationship between overweight/obesity and macrosomia have shown that high TG levels mediated 11.1% of the total effect of overweight on macrosomia and 3.8% of the total effect of obesity. However, other studies have reported conflicting results regarding TG effects in different BMI groups, with some finding significant associations between early pregnancy TG and LGA risk only in non-obese women, while others found significant negative correlations between HDL-C and birth weight only in overweight/obese women.

Mechanistically, non-esterified fatty acids generated from maternal TG lipolysis mediated by lipoprotein lipase enter the placenta via fatty acid transport proteins or fatty acid translocase CD36. Insulin activates abundant insulin receptors on the maternal side of syncytiotrophoblast cells, inducing free fatty acid esterification into TG through the AKT signaling pathway. These TG are stored in trophoblast cells, and hydrolysis releases free fatty acids that diffuse into fetal circulation, providing energy for fetal growth. Overweight/obese women often have insulin resistance, and maternal hyperinsulinemia induces placental TG storage. Increased hydrolysis by placental lipoprotein lipase releases more free fatty acids to the fetus, partially explaining why maternal hypertriglyceridemia increases macrosomia risk.

HDL-C plays important roles in cholesterol transport and homeostasis. Animal studies have confirmed that maternal HDL-C participates in fetal metabolism and growth. In mouse models lacking HDL-C, increased placental sterol synthesis rates or altered placental metabolism allow more cholesterol transport to

the fetus to compensate for inadequate cholesterol uptake and delivery, which may partially explain the association between low HDL-C and macrosomia.

In conclusion, this study demonstrates that low HDL-C during pregnancy is associated with macrosomia in underweight and normal weight women, while elevated TG is associated with macrosomia in overweight/obese women. Therefore, for pregnant women with large-for-date fetuses or at high risk for macrosomia, enhanced blood lipid monitoring and control are essential during prenatal care, focusing not only on elevated TG but also on low HDL-C to improve adverse pregnancy outcomes. However, unified reference standards for blood lipid levels during pregnancy are currently lacking, necessitating multi-center, large-scale epidemiological studies to establish standardized diagnostic criteria for dyslipidemia in pregnancy.

Author Contributions: YUAN Xianxian contributed to study design, implementation, data analysis, and manuscript writing; WANG Jia, ZHANG Kexin, and YANG Ruihua contributed to data organization; ZHENG Wei contributed to manuscript revision; LI Guanghui contributed to study design supervision and manuscript revision.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.

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