

# Association between maternal serum lipids during late pregnancy and adverse birth outcomes

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## Research article

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## Abstract

**Background:** Adverse birth outcomes have short- and long-term impacts on maternal and child health. Maternal dyslipidemia during late pregnancy has been found to be associated with increased risk of adverse birth outcomes. However, similar evidence on association between maternal blood lipid levels and adverse birth outcomes is limited in China.

**Methods:** The data were extracted from Guangdong Women and Children Hospital Information System from September 2014 to March 2018. A total of 3951 mother-newborn pairs were included in our study. Logistic regression model and linear trend analysis were conducted to analyze the correlation between maternal blood lipid levels and adverse birth outcomes after controlling potential confounders including gestational age, pre-pregnancy body mass index, fetal sex, and parity.

**Results:** Among the 3951 subjects, the rates of macrosomia, large-for-gestational age (LGA), low birth weight infants (LBW), and preterm birth were 3.9% (154/3951), 8.5% (334/3951), 9.5% (377/3951), and 9.8% (388/3951), respectively. LDL was a risk factor for preterm birth (OR: 1.20; 95% CI: 1.08-1.34) while HDL was a protective factor (OR: 0.73; 95% CI: 0.55-0.96) after adjusting for covariates. As every unit increase in TG, the risk of macrosomia and LGA increased by 25% (adjusted OR: 1.25; 95% CI: 1.12-1.38) and 16% (adjusted OR: 1.16; 95% CI: 1.07-1.26), respectively. However, every unit increase in HDL concentration was associated with decreased risk for LGA (adjusted OR: 0.60; 95% CI: 0.44-0.81) and macrosomia (adjusted OR: 0.64; 95% CI: 0.41-0.99). High LDL concentrations were associated with a decreased risk of macrosomia (adjusted OR: 0.82; 95% CI: 0.68-0.99) and LGA (adjusted OR: 0.86; 95% CI: 0.76-0.98) but an increased risk of LBW (adjusted OR: 1.16; 95% CI: 1.04-1.30). The results of linear trend analysis were similar to those of logistic regression model.

**Conclusions:** Maternal dyslipidemia during the third trimester is closely related to adverse birth outcomes. Monitoring and managing maternal blood lipid levels in an appropriate range may help to reduce the burden of adverse birth outcomes.

## Background

Adverse birth outcomes may have short- and long-term negative impacts on neonates. For example, the mortality rate of premature infants is higher than that of term infants. In addition, premature infants are more susceptible to pneumonia, neonatal respiratory distress syndrome, septicemia and adverse long-term neurodevelopmental and behavioral sequelae[1]. Macrosomia was found to be related to obesity[2] and type 2 diabetes[3] in later life.

For the development of the fetus during pregnancy, intricate changes in maternal lipid metabolism have happened[4]. Lipid levels, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), sharply rise during pregnancy[5, 6]. Many researchers have explored the impacts of increasing maternal serum lipid levels on the fetus. However, controversies exist about the relationships between maternal lipid profiles and adverse birth outcomes. A meta-analysis suggested that maternal dyslipidemia was significantly associated with an increased risk of preterm birth[7]. Elevated TG and TC levels were associated with an increased risk of preterm birth[8–10]. However, a longitudinal study found that TG levels significantly decreased in preterm birth [11]. Jin and colleagues did not observe an association between maternal lipid levels and preterm birth[12]. Another meta-analysis including 46 publications reported that high TG and low HDL-C levels were associated with increased risk of macrosomia and large-for-gestational age (LGA) [13]. Even among the pregnant women with well-controlled GDM, maternal TG was an independent parameter related to LGA[14]. But R Retnakaran, C Ye, AJG Hanley, PW Connelly, M Sermer, B Zinman and JK Hamilton [15] found that TG or HDL had no significant association with LGA or macrosomia.

Most previous research was done in Europe and the U.S. while there is a paucity of research available in China. Therefore, our study was aimed to investigate the relationship between maternal lipid levels during late pregnancy and subsequent birth outcomes among Chinese women.

## Methods

### Data source and study population

The data analyzed in this study were sourced from Guangdong Women and Children Hospital Information System. From September 2014 to March 2018, a total of 37193 mother-newborn pairs were recorded. Maternal information on age, pre-pregnancy body mass index (BMI), parity, last menstrual period, delivery date, and fasting blood lipid levels were extracted. We also extracted newborn's information including infant sex, birth weight, and gestational age. Among the 37193 mother-newborn pairs, 19686 mother-newborn pairs have full basic information. Data were recorded anonymously, and no written or oral consent was obtained for this study. The study protocol was approved by the ethics committee of Guangdong Women and Children Hospital.

## Exclusion Criteria

We excluded women whose blood lipid values during late pregnancy were missing. Women who were pregnant with twins or multiple births, stillbirth, birth defects, post-term birth, and birth weight out of range (500–5000 g) were further excluded. Finally, a total of 3951 pregnant women were included in our study.

## Variable And Outcome Definition

According to the diagnostic criteria of the American College of Obstetricians and Gynecologists, infants whose birth weight  $\geq 4000$  g were macrosomia and whose birth weight  $\leq 2500$  g were low birth weight infants (LBW). LGA was defined as newborn birth weight exceed the 90th percentile after adjusting gestational age and sex. Preterm birth was considered as gestational week less than 37 weeks.

## Statistical analysis

The data are expressed as mean  $\pm$  standard deviation (SD) or frequency (percentage). Logistic regression analysis was performed to explore the association between adverse birth outcomes and maternal lipid profiles during late pregnancy with or without adjustment of covariates. The covariates included maternal age, pre-pregnancy BMI, parity, and infant sex. Then, we turned maternal lipid profiles into five categories according to the quintile (Q) of all the measurements to compare the effects of different levels of blood lipids on birth outcomes. The linear trend analysis was conducted using a regression model by taking the median of each group as a continuous variable. Subgroup analysis was also conducted according to pre-pregnancy BMI and infant sex. All statistical analyses were performed using the statistical software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a  $P$  value  $< 0.05$  was considered as statistically significant.

## Results

The demographic characteristics of pregnant women and newborns were shown in Table 1. Of all eligible women, the average age (mean  $\pm$  SD) was  $31.83 \pm 5.00$  years, and mean pre-pregnancy BMI (mean  $\pm$  SD) was  $20.88 \pm 3.08$  kg/m<sup>2</sup>. Primipara accounted for 26.3% among 3951 mothers. Average levels of maternal lipid were also presented in Table 1 that TC is 6.04 mmol/L, TG is 2.94 mmol/L, HDL is 1.78 mmol/L and LDL is 3.18 mmol/L. In our study, 53.9% of newborns were male infants. Mean gestational week (mean  $\pm$  SD) was  $39.13 \pm 1.85$  weeks, and mean birth weight (mean  $\pm$  SD) was  $3146.38 \pm 525.56$  g. The rates of macrosomia, LGA, LBW, and preterm birth were 3.9%, 8.5%, 9.5%, and 9.8%, respectively.

Table 1  
Maternal and Neonatal Characteristics (N = 3951)

Characteristics	Mean (SD)/numbers (%)
Maternal Characteristics	
Age at delivery (years)	31.83 (5.00)
Pre-pregnancy BMI (kg/m <sup>2</sup> )	20.88 (3.08)
Parity (primipara)	1040 (26.3)
Neonatal Characteristics	
Infant sex (male)	2129 (53.9)
Gestational week (weeks)	39.13 (1.85)
Birth weight (g)	3146.38 (525.56)
Lipid levels in the third trimester of pregnancy	
TG (mmol/L)	2.94 (1.23)
HDL (mmol/L)	1.78 (0.40)
LDL (mmol/L)	3.18 (0.94)
TC (mmol/L)	6.04 (1.17)
Birth outcomes	
Preterm birth	388 (9.8)
LGA	334 (8.5)
LBW	377 (9.5)
Macrosomia	154 (3.9)
Note: Data are presented as mean ± SD for normally distributed data or numbers (percentage) for categorical data. BMI, body mass index; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; LGA, large-for-gestational age; LBW, low birth weight; SD, standard deviation.	

Table 2 shows the associations between maternal lipid levels during late pregnancy and neonatal adverse birth outcomes. In the crude model, LDL was significantly associated with elevated risk of preterm birth (OR: 1.16; 95% CI: 1.04–1.29), while HDL was significantly associated with decreased risk of preterm birth (OR: 0.72; 95% CI: 0.54–0.94). The associations remained significant after adjustment of covariates. The association between TC and preterm birth became significant in the adjusted model. The risk of macrosomia dramatically increased by 25% as a 1-unit increase of TG when controlling for covariates (adjusted OR: 1.25; 95% CI, 1.12–1.38). HDL reduced the risk of macrosomia by 36% (adjusted OR: 0.64; 95% CI, 0.41–0.99) and LDL (adjusted OR: 0.82; 95% CI, 0.68–0.99) reduced it by 18% after adjusting for covariates. Similar relationships were found in LGA. After adjusting covariates, TG was a risk factor (OR: 1.16; 95% CI: 1.07–1.26) while HDL and LDL were protective factors (HDL: OR: 0.60; 95% CI: 0.44–0.81; LDL: OR: 0.86; 95% CI: 0.76–0.98) for LGA. We also observed significant positive associations of TC and LDL with the risk of LBW.

Table 2  
Associations between maternal third-trimester lipid profiles and adverse birth outcomes

		TG		TC		LDL		HDL	
		OR (95% CI)	<i>P</i> value						
Preterm birth	Model A	1.08 (1.00, 1.17)	0.052	1.09 (1.00, 1.18)	0.062	1.16 (1.04, 1.29)	0.006	0.72 (0.54, 0.94)	0.016
	Model B	1.06 (0.98, 1.15)	0.155	1.11 (1.01, 1.21)	0.025	1.20 (1.08, 1.34)	0.001	0.73 (0.55, 0.96)	0.023
LBW	Model A	1.08 (0.99, 1.17)	0.071	1.11 (1.02, 1.21)	0.022	1.13 (1.02, 1.27)	0.025	0.89 (0.68, 1.17)	0.398
	Model B	1.06 (0.98, 1.16)	0.150	1.11 (1.01, 1.21)	0.025	1.16 (1.04, 1.30)	0.010	0.84 (0.64, 1.10)	0.210
Macrosomia	Model A	1.26 (1.14, 1.39)	< 0.001	0.89 (0.77, 1.03)	0.118	0.77 (0.64, 0.92)	0.005	0.59 (0.38, 0.91)	0.016
	Model B	1.25 (1.12, 1.38)	< 0.001	0.95 (0.82, 1.10)	0.452	0.82 (0.68, 0.99)	0.040	0.64 (0.41, 0.99)	0.045
LGA	Model A	1.20 (1.11, 1.29)	< 0.001	0.89 (0.80, 0.98)	0.020	0.81 (0.71, 0.92)	0.001	0.56 (0.41, 0.75)	< 0.001
	Model B	1.16 (1.07, 1.26)	< 0.001	0.93 (0.84, 1.03)	0.142	0.86 (0.76, 0.98)	0.021	0.60 (0.44, 0.81)	0.001

Note: TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC total cholesterol; LGA, large-for-gestational age; LBW, low birth weight. Model A, crude; Model B, adjusted for maternal age at delivery, pre-pregnancy BMI, infant sex and parity

To evaluate the dose-response relations of maternal lipid profiles and adverse birth outcomes, we divided lipid values into five categories according to their quintiles, as shown in Table 3. The results were similar to those of Table 2. We noted obvious dose-response relations of TG with macrosomia and LGA (TG: *P* for trend < 0.01; LDL: *P* for trend < 0.05). The ORs were decreased with the increasing levels of HDL (*P* for trend < 0.05). It was worth noting that LDL levels had graded associations with all the four adverse birth outcomes (*P* for trend < 0.05).

Table 3  
Associations between quintiles of maternal third-trimester lipid profiles and adverse birth outcomes\*

		<b>Preterm Birth</b>	<b>LBW</b>	<b>Macrosomia</b>	<b>LGA</b>
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
TG	Q1(reference)	1.00	1.00	1.00	1.00
	Q2	1.06 (0.75,1.50)	0.92 (0.66,1.30)	1.05 (0.56,1.94)	1.15 (0.76,1.73)
	Q3	1.08 (0.77,1.52)	0.97 (0.69,1.35)	1.56 (0.88,2.75)	1.30 (0.87,1.92)
	Q4	0.91 (0.64,1.30)	0.87 (0.62,1.22)	1.30 (0.72,2.32)	1.35 (0.91,2.00)
	Q5	1.33 (0.95,1.84)	1.05 (0.75,1.46)	2.16 (1.26,3.71)	1.82 (1.25,2.64)
	<i>P</i> for trend	0.127	0.749	0.001	0.001
TC	Q1(reference)	1.00	1.00	1.00	1.00
	Q2	1.58 (1.10,2.26)	1.38 (0.97,1.96)	1.22 (0.75,1.97)	0.84 (0.60,1.18)
	Q3	1.81 (1.27,2.57)	1.26 (0.88,1.80)	0.81 (0.47,1.38)	0.74 (0.52,1.06)
	Q4	1.54 (1.07,2.21)	1.33 (0.93,1.90)	1.34 (0.82,2.18)	0.88 (0.62,1.25)
	Q5	1.59 (1.11,2.28)	1.39 (0.98,1.97)	0.75 (0.43,1.31)	0.69 (0.48,0.99)
	<i>P</i> for trend	0.043	0.127	0.463	0.081
LDL	Q1(reference)	1.00	1.00	1.00	1.00
	Q2	1.14 (0.80,1.62)	1.16 (0.81,1.65)	0.79 (0.49,1.28)	0.77 (0.55,1.08)
	Q3	1.27 (0.90,1.80)	1.13 (0.79,1.62)	0.791 (0.49,1.28)	0.68 (0.48,0.96)
	Q4	1.41 (1.00,1.98)	1.36 (0.96,1.93)	0.72 (0.44,1.19)	0.60 (0.42,0.86)
	Q5	1.49 (1.06,2.10)	1.40 (0.99,1.97)	0.58 (0.34,0.99)	0.68 (0.47,0.97)
	<i>P</i> for trend	0.010	0.037	0.044	0.013
HDL	Q1(reference)	1.00	1.00	1.00	1.00
	Q2	0.88 (0.64,1.22)	0.82 (0.59,1.14)	0.73 (0.45,1.19)	0.85 (0.61,1.19)
	Q3	0.91 (0.66,1.25)	0.74 (0.53,1.03)	0.81 (0.50,1.31)	0.73 (0.51,1.03)
	Q4	0.79 (0.56,1.10)	0.66 (0.47,0.93)	0.73 (0.45,1.20)	0.75 (0.53,1.06)
	Q5	0.74 (0.53,1.04)	0.78 (0.56,1.09)	0.52 (0.30,0.90)	0.51 (0.35,0.75)
	<i>P</i> for trend	0.061	0.087	0.030	0.001
Note: Q, quintile; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC total cholesterol; LGA, large-for-gestational age; LBW, low birth weight.					
* Adjusted for maternal age at delivery, infant sex, and parity.					

Among the 3951 mothers, about 14% of the subjects were overweight or obese according to pre-pregnancy BMI. In the group of women with pre-pregnancy BMI < 24 kg/m<sup>2</sup>, the associations between LDL and HDL levels and preterm birth were similar to the results shown in Table 2. The relationship between maternal lipid profiles and LGA was also analogous to the general results shown in Table 2. In the group of women with pre-pregnancy BMI ≥ 24 kg/m<sup>2</sup>, we found a significant association between LDL and premature infants. Increased TG level was related to an increased risk of macrosomia regardless of pre-pregnancy BMI categories, whereas the effect of LDL and HDL became unapparent in the both groups. HDL remained a protective factor for LGA and LDL remained a risk factor for LBW in the overweight/obese group (shown in Table 4).

Table 4  
Associations between maternal third-trimester lipid profiles and adverse birth outcomes, stratified by maternal pre-pregnancy BMI\*

		TG		TC		LDL		HDL	
		OR (95%CI)	P value						
BMI < 24 kg/m <sup>2</sup> (N = 3389)	Preterm birth	1.07(0.97,1.17)	0.164	1.10(1.00,1.21)	0.060	1.17(1.04,1.32)	0.011	0.65(0.48,0.88)	0.005
	LBW	1.06(0.97,1.16)	0.233	1.10(1.00,1.21)	0.055	1.11(0.99,1.26)	0.080	0.86(0.64,1.16)	0.326
	Macrosomia	1.26(1.11,1.42)	< 0.001	0.97(0.82,1.15)	0.741	0.81(0.65,1.01)	0.058	0.70(0.42,1.15)	0.158
	LGA	1.18(1.08,1.29)	< 0.001	0.93(0.82,1.04)	0.188	0.83(0.72,0.96)	0.014	0.62(0.44,0.88)	0.007
BMI ≥ 24 kg/m <sup>2</sup> (N = 562)	Preterm birth	1.05(0.87,1.26)	0.634	1.17(0.94,1.46)	0.158	1.38(1.05,1.81)	0.021	1.28(0.67,2.42)	0.453
	LBW	1.09(0.88,1.34)	0.443	1.18(0.93,1.50)	0.179	1.48(1.10,2.00)	0.009	0.77(0.38,1.58)	0.473
	Macrosomia	1.25(1.02,1.53)	0.035	0.86(0.64,1.16)	0.310	0.84(0.58,1.21)	0.341	0.53(0.23,1.25)	0.148
	LGA	1.15(0.97,1.37)	0.104	0.90(0.72,1.12)	0.338	0.91(0.69,1.19)	0.480	0.51(0.27,0.96)	0.038

Note: \* Adjusted for maternal age at delivery, infant sex, and parity

## Discussion

In the present study, we comprehensively explored the associations between maternal fasting blood lipids during late pregnancy and adverse birth outcomes. Maternal lipid profiles were closely linked to adverse birth outcomes.

We found that maternal TG levels in late pregnancy were associated with increased risk of macrosomia and LGA, in line with previous cohort studies conducted at home and abroad[12, 16–18] where TG was found to be an independent risk factor for macrosomia and LGA. We found no association between TG levels and preterm birth, as also reported by other research[12]. However, W Zheng, W Huang, L Zhang, Z Tian, T Wang, T Zhang, Z Zhang, W Zhang and G Li [19] reported that higher TG levels were associated with an increased risk of preterm birth. Participants were healthier in their study as women with chronic conditions excluded from their analysis, which may explain the heterogeneity of the results. Similar positive association was also reported by a meta-analysis[7], but it only included studies with blood samples taken in the first two trimesters and the definition of preterm birth varied among studies.

The associations between increased HDL levels and decreased risks of preterm birth, macrosomia, and LGA were also observed in this study. A retrospective cohort study including 5,407 healthy women also found that maternal HDL in late pregnancy was a protective factor for macrosomia and this association was dose-dependent[16]. Previous research also reported that HDL was an independent predictor for LGA[20–22]. Furthermore, most results with regard to a decreased risk for preterm birth was found for high HDL levels[7, 23–25], and the present study confirmed this association. But no relationship between HDL and preterm birth was found in a cohort study conducted in China[12]. Although the maternal characteristics were comparable, the discrepancy in the results might be explained by the fact that our sample was larger with higher prevalence rate of preterm birth. The protective effect of HDL on these birth outcomes may relate to its anti-inflammatory, anti-oxidant, anti-thrombotic, and vasodilator functions[26].

A striking finding in the present study was that high LDL concentrations during the third trimester were associated with a decreased risk of macrosomia and LGA but an increased risk of LBW. Analogous association between LDL concentrations during the third trimester and macrosomia was also found in a cohort study including 10,366 pregnant women[19]. Similarly, R-J Hou, et al[27] proposed that LDL-C concentrations of pregnancy women who gave birth to LGA newborns were lower than those who gave birth to appropriate-for-gestational age (AGA) newborns. However, meta-analysis[13] and other research [12, 15, 16] failed to observe the relationships. The differences in maternal LDL levels, maternal basic characteristics, and covariates may explain the inconsistency of the findings.

The fetus mainly relies on the placenta to obtain nutrition from the mother. The normal physiological structure and function of the placenta are crucial to the growth and development of the fetus[28]. However, abnormal maternal lipid levels during pregnancy will affect the normal transport function of the placenta[29, 30], thus damaging the intrauterine development of the fetus and increasing the risk of adverse birth outcomes. Over the course of pregnancy, due to the enrichment of triglycerides and the decrease of liver lipase activity, the particles of LDL

become smaller and denser, which are more easily oxidized into oxidized LDL (Ox-LDL)[31]. Moreover, pregnancy is associated with a decrease in total antioxidant capacity (TAC), making it an inflammatory state[31, 32]. This may exacerbate changes in LDL particles. Ox-LDL may increase the risk of endothelial damage[33, 34] and the smaller, denser particle is an independent predictor of smaller birth weight[35]. These changes during pregnancy may be responsible for the associations between maternal serum lipids and adverse birth outcomes. However, the potential mechanisms still deserve further exploration.

Some limitations should be noted. First, the study population was only from Guangdong province, limiting the generalization of conclusions. Second, the results of the sample analysis were extracted only once, thus the dynamic changes of the indicators cannot be observed. Finally, we cannot exclude the effects of potential confounding factors on the results, such as the dietary structure and supplementation of nutrients during pregnancy, weight gain and exercise during pregnancy. Therefore, more in-depth and detailed research on the influencing factors of birth outcomes is needed.

## Conclusion

In conclusion, this study found that dyslipidemia in Chinese pregnant women during late pregnancy was associated with increased risks of adverse birth outcomes. Blood lipid levels during pregnancy should be monitored and controlled at an appropriate level to prevent adverse birth outcomes.

## Abbreviations

LGA: Large-for-Gestational Age

LBW: Low Birth Weight infants

TC: Total Cholesterol

TG: Triglycerides,

HDL: High-density Lipoprotein

LDL: Low-density Lipoprotein

BMI: Body Mass Index

GDM: Gestational Diabetes Mellitus

Q: Quintile

CI: Confidence Intervals

SD: Standard Deviation

## Declarations

### Ethics approval and consent to participate

The data were recorded anonymously, and no written or oral consent was obtained for this study. The study protocol was approved by the ethics committee of Guangdong Women and Children Hospital.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to other ongoing studies, but are available from the corresponding author on reasonable request.

### Competing interests

The authors have no competing interests to report.

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## Authors' contributions

MYD participated in study design, literature search and drafted the manuscript. LLW participated in study design, analyzed and interpreted the data and carried out the statistical analysis. YTW, HL, JHX, LW participated in the design of the study and the collection of the data. YHT conceived of the study, and critically reviewed and edited the manuscript. All the authors read and approved the final manuscript.

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