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Original Article

Maternal serum lipid levels during late pregnancy and neonatal body size

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Objective: The aim of this study was to determine the predictive value of maternal serum lipid levels during late pregnancy for neonatal body size. **Methods:** This study was conducted from January 1, 2011 to July 31, 2012 at a Maternal and Child Health Hospital. Fasting blood glucose, serum triglyceride, total cholesterol, HDL and LDL were estimated in maternal collected before delivery. Detailed anthropometry of the neonates was performed. **Results:** Women who delivered a large for gestational age baby were older, taller, had a higher pre-pregnancy weight, higher pre-pregnancy BMI, and higher weight gain during pregnancy than women who delivered an appropriate for gestational age infant. After adjusting for maternal age, pre-pregnancy BMI, weight gain during pregnancy, parity, neonatal sex and gestational age at delivery, we found that only maternal HDL level was inverse associated with birth weight, length and head circumference (p<0.05). On logistic regression analysis, the significant metabolic predictors of large for gestational age was HDL (OR 0.57, 95%CI: 0.38-0.84, per 1 mmol/L increase) after adjusting for the confounders. **Conclusions:** Maternal serum HDL level determined in maternal blood taken close to delivery was independently associated with neonatal size and was the independent predictor for large for gestational age.

Key Words: lipids, birth weight, pregnancy, triglycerides, large for gestational age

INTRODUCTION

In recent years there has been a great interest in studying factors influencing fetal growth. Pregnancies with large size infants are associated with increased risk of complications for both the baby and its mother, such as stillbirth, metabolic disorders, and meconium aspiration syndrome, birth asphyxia, increased use of operative deliveries, postpartum hemorrhages and neonatal hypoglycemia.[1,2] In addition, oversized infants may suffer long term effects because of increased risks of cardiovascular disease, obesity, diabetes and cancer.[3-6] Fetal growth is affected by maternal genetic, demographic and metabolic factors.[7] Maternal demographic variables like pre-pregnancy BMI, parity, gestational weight gain (GWG), gestational age at delivery independently predict birth weight.[8,9] Maternal metabolism must satisfy the demands of the developing fetus during pregnancy. Maternal lipid metabolism is specifically altered during pregnancy; total plasma cholesterol (TC) and phospholipids are increased moderately, while plasma triglyceride (TG) levels rise markedly.[10] Both TC and TG are taken up by the placenta and metabolized and transported to the fetus in various forms;[11] this shows that lipids are essential for the fetal development. A number of studies have shown an association between maternal lipids and neonatal body weight,[12-20] but the conclusions were not consistent. In some studies, maternal serum TG levels were positively associated with birth weight,[12,14,16,17,19,20] while some researchers have also reported inverse associations between maternal HDL levels and risk of macrosomia.[15,18]

Therefore, in this study we evaluated the association between maternal lipid profile of the healthy pregnant women close to delivery and large for gestational age (LGA) neonates with normal pregnancies.

MATERIAL AND METHODS

Study population

This study, which was approved by the biomedicine ethical committee of Anhui Medical University, was conducted from January 1, 2011 to July 31, 2012, at Maternal and Child Health (MCH) Hospital of Hefei, China.

Subjects were recruited from participants who would be given birth in MCH centers of Hefei, around 36th-41th gestation week. The informed consent was obtained from the participants. The eligibility criteria included age ≥18 years at the expected date of delivery. Those having gestational diabetes, overt diabetes, hypertension and heart disease were excluded. Women with preterm births (before 37 completed weeks) or multiple pregnancies were

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also excluded. The mothers also were excluded if the medical records were missing or information on birth weight was unavailable. After appropriate exclusion, 1243 women were included as subjects.

Data collection and variables

Maternal demographic and health characteristics were collected by questionnaire upon entry into the study and the review of medical records. Maternal pre-pregnancy weight and height were collected by self-report at the initial visit. Pre-pregnancy BMI was calculated as pre-pregnancy weight (kg) / height^2 (m^2). Gestational weight gain (GWG) during pregnancy was calculated as pre-pregnancy weight subtracted from the measured weight recorded at the last prenatal visit before delivery. The gestational age was estimated by last menstrual period, confirmed by ultrasonography. In addition, the following parameters were collected: the mother's age, parity, fasting blood glucose (FBG), serum TG, TC, HDL, LDL concentration upon entry into the study. The metabolic parameters measured in maternal blood taken close to delivery (between 36 and 41 weeks of gestation, in most cases 1 week to delivery). Pregnancy outcome (delivery method, birth weight, birth length, head circumference, gestational age, gender of the baby, Apgar score at 1 and 5 minutes after delivery) were retrieved from medical records after delivery. Infants with birth weight>90th percentile for local population after adjusting for gestational age and sex were classified as LGA, and small for gestational age (SGA) was defined as the lowest 10th percentile, those having weight between 10th and 90th percentile were appropriate for gestational age (AGA).

Statistical analysis

Statistical analysis was performed using SPSS 16.0 for Windows software. Data were expressed as means± standard deviations (SD) or number (percentage). Differences between groups were analyzed using ANOVA. Multiple linear regression analysis of infant birth weight, length and head circumference were performed, with adjustment for the following covariates: maternal age, pre-pregnancy BMI, weight gain during pregnancy, parity, FBG, neonatal sex and gestational age at delivery. Logistic regression analysis of the dependent variables (SGA and LGA) was performed with use of the same covariates as in the multiple linear regression analysis, except for neonatal sex and gestational age at delivery because both of these variables are considered when defining SGA and LGA. All statistical tests were two-tailed, and a p value <0.05 was considered significant.

RESULTS

The pregnant women in this study had a mean (SD) age of 27.9 (4.3) years, 81% were nulliparous. The mean pre-pregnancy BMI, weight gain during pregnancy and gestational age at delivery were 20.5±2.5 kg/m^2, 17.2±5.1 kg, and 39.6±1.0 weeks, respectively. There were thirty nine cases (3.1%) with SGA, 331 cases (26.6%) with LGA, and 760 cases (60.1%) with caesarean section. The mean neonatal birth weight, length and head circumference were 3429±424 g, 50.7±1.6 cm and 34.4±1.5 cm, respectively. Maternal FBG, TG, TC, HDL and LDL levels close to delivery are shown in Table 1.

Women who delivered a LGA baby were older, taller, had a higher pre-pregnancy weight, higher pre-pregnancy BMI, and higher weight gain during pregnancy than women who delivered an AGA infant. Moreover, cesarean delivery was more frequent among women delivering a LGA baby than in women giving birth to an AGA baby (71.6% compared with 57.6%, p<0.001). The mothers of SGA babies had less weight gain during pregnancy (-13.0%, p<0.05) than mothers of AGA babies (Table 2).

In this study, we found that serum TG was higher and HDL-cholesterol was lower in women with LGA babies compared with women with AGA infants. However, we found no statistically significant difference in maternal serum FBG, TC and LDL levels between LGA and AGA. In addition, there was no difference in maternal serum glucose and lipids between SGA and AGA (Table 2).

Table 3 presents estimated associations between maternal glucose and lipids during late pregnancy and three neonatal growth parameters (body weight, length and head circumference). In model 1, after adjusting for maternal age, pre-pregnancy BMI, weight gain during pregnancy, parity, neonatal sex and gestational age at delivery, we found that increases in maternal TG and LDL levels, but decreases in maternal HDL levels were associated with increases in birth weight and length. When maternal lipids and glucose are entered together in the model (Model 2), only maternal HDL level was inverse associated with birth weight, length and head circumference. Every 1 mmol/L increase of HDL was associated with a 99.7-g (95% CI: -159, -40) decrease in birth weight, a

Table 1. Basic characteristics of 1243 mothers and their neonates

Characteristics	Mean±SD or n (%)
Maternal Characteristics	
Age (years)	27.9±4.3
Height (cm)	161±4
Weight before pregnancy (kg)	53.2±7.0
Weight gain during pregnancy (kg)	17.2±5.1
BMI before pregnancy (kg/m^2)	20.5±2.5
Parity (one)	1012 (81.4)
FBG (mmol/L)	4.4±0.8
TC (mmol/L)	6.6±1.4
TG (mmol/L)	2.9±1.2
HDL (mmol/L)	2.4±0.5
LDL (mmol/L)	3.3±0.8
Neonatal Characteristics	
Gestational age at delivery (weeks)	39.6±1.0
Gender (male)	665 (53.5)
Birth weight (g)	3429±424
Length (cm)	50.7±1.6
Head circumference (cm)	34.4±1.5
Apgar score at 1 min	8.9±0.4
Apgar score at 5 min	10.0±0.2
Cesarean delivery	760 (60.1)
SGA	39 (3.1)
LGA	331 (26.6)

All data were expressed as number (percentage) or means±SD. BMI: body mass index, FBG: fasting blood glucose, TG: serum triglyceride, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, SGA: small for gestational age, LGA: large for gestational age.

Table 2. Maternal and neonatal characteristics in SGA, AGA and LGA groups

Characteristics	SGA (n=39)	AGA (n=873)	LGA (n=331)	*p* value
Maternal Characteristics				
Age (years)	26.6±4.1	27.6±4.2	28.8±4.5**	<0.001
Height (cm)	159±5	161±4	162±4**	<0.001
Weight before pregnancy (kg)	50.2±5.4	52.4±6.8	55.6±7.1**	<0.001
Weight gain during pregnancy (kg)	14.5±4.8**	16.7±4.8	18.8±5.3**	<0.001
BMI before pregnancy (kg/m^2)	19.7±2.0	20.2±2.4	21.2±2.5**	<0.001
Parity (one)	35 (89.7)	730 (83.6)	247 (74.6)**	0.001
FBG (mmol/L)	4.4±0.9	4.4±0.8	4.5±0.9	0.867
TC (mmol/L)	6.5±1.5	6.6±1.4	6.6±1.3	0.864
TG (mmol/L)	2.5±0.7	2.9±1.2	3.1±1.2**	0.001
HDL-C (mmol/L)	2.5±0.5	2.4±0.5	2.3±0.5**	0.008
LDL-C (mmol/L)	3.1±0.9	3.3±0.8	3.4±0.8	0.101
Neonatal Characteristics				
Gestational age at delivery (weeks)	39.3±1.0	39.5±1.1	39.6±1.0	0.110
Gender (male)	12 (30.8)**	439 (50.3)	214 (64.7)**	<0.001
Birth weight (g)	2539±227**	3273±265	3944±244**	<0.001
Length (cm)	48.4±1.2**	50.2±1.2	52.1±1.6**	<0.001
Head circumference (cm)	32.5±1.5**	34.1±1.2	35.7±1.5**	<0.001
Apgar score at 1 min	8.9±0.4	8.9±0.5	9.0±0.3	0.378
Apgar score at 5 min	10.0±0.2	10.0±0.2	10.0±0.1	0.219
Cesarean delivery	20 (51.3)	503 (57.6)	237 (71.6)**	<0.001

All data were expressed as number (percentage) or means±SD. *p<0.05, **p<0.01 as compared with AGA. BMI: body mass index, FBG: fasting blood glucose, TG: serum triglyceride, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, SGA: small for gestational age, LGA: large for gestational age, AGA: appropriate for gestational age.

Table 3. Associations of maternal lipid levels during late pregnancy with neonatal body weight, length and head circumference

	Body weight (g)	Length (cm)	Head circumference (cm)
Model 1			
TG (mmol/L)	25.2 (7.9, 42.6)*	0.690 (0.000, 0.138)*	0.061 (-0.007, 0.128)
TC (mmol/L)	9.1 (-6.4, 24.6)	0.031 (-0.031, 0.093)	0.031 (-0.030, 0.090)
HDL (mmol/L)	-69.5 (-110, -28.2)*	-0.230 (-0.394, -0.065)*	-0.126 (-0.287, 0.034)
LDL (mmol/L)	35.4 (10.1, 60.8)*	0.135 (0.034, 0.236)*	0.076 (-0.023, 0.174)
Model 2			
TG (mmol/L)	17.9 (-0.7, 36.6)	0.043 (-0.031, 0.118)	0.041 (-0.032, 0.113)
TC (mmol/L)	17.6 (-18.2, 53.3)	0.033 (-0.110, 0.176)	0.072 (-0.067, 0.211)
HDL (mmol/L)	-99.7 (-159, -40.1)*	-0.303 (-0.542, -0.064)*	-0.232 (-0.463, 0.000)*
LDL (mmol/L)	13.7 (-34.3, 61.6)	0.099 (-0.093, 0.291)	-0.014 (-0.201, 0.173)

Values are regression coefficients (β) (95% CI). Maternal lipids are entered respectively in model 1 and entered together in model 2. All models were adjusted for maternal age, pre-pregnancy BMI, weight gain during pregnancy, parity, FBG, neonatal sex and gestational age at delivery. BMI: body mass index; FBG: fasting blood glucose; TG: serum triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein. *p<0.05.

0.30-cm (95% CI: -0.54, -0.06) decrease in birth length and a 0.23-g (95% CI: -0.46, 0.00) decrease in head circumference.

On logistic regression analysis, the significant predictors of having a LGA infant, after adjustment for maternal age, pre-pregnancy BMI, weight gain during pregnancy, parity and FBG, were TG (OR 1.15, 95% CI: 1.03-1.27, per 1 mmol/L increase), HDL (OR 0.62, 95% CI: 0.47-0.82, per 1 mmol/L increase) and LDL (OR 1.25, 95% CI: 1.06-1.47, per 1 mmol/L increase). When maternal lipid levels were entered together in the model, we found that maternal HDL (OR 0.57, 95%CI: 0.38-0.84, per 1 mmol/L increase) level was the independent predictor of having a LGA infant. In addition, it could be seen that maternal lipid levels had no association with the risk of having a SGA infant (Table 4).

DISCUSSION

Maternal BMI and weight, which are the indicators of maternal nutrition, have been proved to be directly correlated with birth weight.[8,21] Chiba reported that the factors influencing birth weight may be different for primiparous and multiparous female.[22] In fact, gestational age at delivery is an important determinant of birth weight.[23] In addition, maternal blood glucose also exhibited a positive correlation with birth weight in several studies.[13,24] Therefore, when exploring the relationship between maternal lipids and neonatal body size and the independent predictors of SGA and LGA, we adjusted for the above parameters.

Maternal triglycerides determined in the last trimester of gestation have been shown to be independently associated with neonatal birth weight in women with normal glucose tolerance,[16] whereas there is a negative correlation for HDL.[25] In women with GDM, HDL was also the independent predictor for LGA.[15] Our findings were similar with the above. We found that maternal serum HDL was independently associated with neonatal body size and

Table 4. Odds ratios for the association between maternal lipid levels during late pregnancy and SGA and LGA

	SGA	AGA	LGA
Model 1			
TC (mmol/L)	0.94 (0.74, 1.20)	1.00 (referent)	1.04 (0.94, 1.15)
TG (mmol/L)	0.69 (0.47, 1.03)	1.00 (referent)	1.15 (1.03, 1.27)*
HDL (mmol/L)	1.57 (0.87, 2.83)	1.00 (referent)	0.62 (0.47, 0.82)*
LDL (mmol/L)	0.75 (0.50, 1.14)	1.00 (referent)	1.25 (1.06, 1.47)*
Model 2			
TC (mmol/L)	1.03 (0.55, 1.94)	1.00 (referent)	1.03 (0.82, 1.30)
TG (mmol/L)	0.71 (0.46, 1.09)	1.00 (referent)	1.11 (0.99, 1.25)
HDL (mmol/L)	1.68 (0.65, 4.38)	1.00 (referent)	0.57 (0.38, 0.84)*
LDL (mmol/L)	0.76 (0.33, 1.76)	1.00 (referent)	1.27 (0.88, 1.65)

Values are OR (95% CI). Maternal lipids are entered respectively in model 1 and entered together in model 2. All models were adjusted for maternal age, pre-pregnancy BMI, weight gain during pregnancy, parity, FBG. BMI: body mass index; FBG: fasting blood glucose; TG: serum triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SGA: small for gestational age; LGA: large for gestational age; AGA: appropriate for gestational age. *$p<0.05$.

was the independent predictor of LGA . Birth weight was positive associated with TG and negative correlated with LDL after adjusting for maternal age, pre-pregnancy BMI, weight gain during pregnancy, parity, neonatal sex and gestational age at delivery. But when other lipid profiles were also adjusted, the association disappeared. In our study, we also explored the predictors of SGA. There was no correlated relationship between maternal lipids and SGA after adjustment for confounders. Our findings are inconsistent with Kramer's study,[26] but was consistent with Tanja's research.[20]

The mechanisms through which maternal HDL may influence birth weight are poorly understood. However, HDL has an important role in cholesterol transport and homeostasis which may have an influence on fetal development. McConihay et al[27] reported that a difference in maternal HDL-C concentration or composition can affect the size of the fetus and sterol metabolism of the yolk sac and placenta in the mouse. Although HDL does not cross the placenta, HDL could affect fetal metabolism and growth via its effect on the metabolic function of extra-embryonic fetal tissues.[27] Additionally, HDL has anti-inflammatory, antioxidant, and antithrombotic properties[28] that may influence placental circulation and fetal growth. Much work is still needed to explain clearly how maternal lipids influence body size.

As with every study, our study also had few limitations. Firstly, calculation of maternal pre-pregnancy BMI was obtained by self-report which could threaten the validity of the data. Generally, individuals tend to slightly underestimate their weight by a few kilograms. However, self-reported and clinically measured pre-pregnancy weights have been found to be highly correlated ($r=0.98$, $p<0.001$).[29,30] Secondly, some factors affecting neonatal birth weight like maternal nutrition and physical activity were not considered in this study. Finally, the sample size was not large, which may limit the power of the finding. Further study should be done in a prospective cohort study with larger sample.

In conclusion, maternal serum HDL level determined in maternal blood taken close to delivery was independently associated with neonatal size and was the independent predictor for LGA. Additional studies are needed to evaluate whether elevating HDL levels by means of lifestyle programs (e.g. physical activity and diet) is beneficial in reducing the risk of LGA.

AUTHOR DISCLOSURES

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Original Article

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妊娠晚期母体的血脂水平与新生儿体重的关系

目的：是探讨妊娠晚期母体的血脂水平对新生儿出生体重的预测价值。**方法：**本研究是从 2011 年 1 月到 2012 年 7 月在一个妇幼保健院实施的，在孕妇分娩前测定母体的空腹血糖、甘油三酯、胆固醇、高密度脂蛋白和低密度脂蛋白水平，并测量新生儿的人体学资料。**结果：**大于胎龄儿的母亲与正常母亲相比，年龄更大、身高更高、妊娠前体重和体质指数更高。在调整了母亲的年龄、妊娠前体质指数、孕期增重、产次、新生儿性别和分娩孕周后，妊娠晚期母体的高密度脂蛋白水平与新生儿的出生体重、身长和头围成负相关($p<0.05$). Logistic 回归分析发现，在调整混杂因素后，大于胎龄儿的预测因子是妊娠晚期母体高密度脂蛋白水平(OR 0.57, 95% CI: 0.38-0.84)。**结论：**我们认为母体妊娠晚期的高密度脂蛋白水平与新生儿出生体重独立相关，是大于胎龄儿的独立预测因子。

关键词：血脂、出生体重、孕期、甘油三酯、大于胎龄儿