Effect of maternal lipid profile, C-peptide, insulin, and HbA$_1c$ levels during late pregnancy on large-for-gestational age newborns

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**Background:** Large-for-gestational age (LGA) newborns can increase the risk of metabolic syndrome. Previous studies have shown that the levels of maternal blood lipids, connecting peptide (C-peptide), insulin and glycosylated hemoglobin (HbA$_1c$) were significantly different between LGA and appropriate-for-gestational age (AGA) newborns. This study aimed to determine the effect of the levels of maternal lipids, C-peptide, insulin, and HbA$_1c$ during late pregnancy on LGA newborns.

**Methods:** This study comprised 2790 non-diabetic women in late pregnancy. Among their newborns, 2236 (80.1%) newborns were AGA, and 554 (19.9%) newborns were LGA. Maternal and neonatal characteristics were obtained from questionnaires and their case records. The levels of maternal fasting serum apolipoprotein A1 (ApoA1), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), C-peptide, insulin and blood HbA$_1c$ were measured. The chi-square and Mann-Whitney U test were used to analyze categorical variables and continuous variables between the AGA and LGA groups, respectively. Binary logistic regression analysis was made to determine the independent risk factors for LGA newborns.

**Results:** Maternal TG, C-peptide, insulin and HbA$_1c$ levels were significantly higher in the LGA group than in the AGA group ($P<0.05$). The LGA group had significantly lower levels of maternal TC, HDL-C and LDL-C than the AGA group ($P<0.05$). After adjustment for confounding variables, including maternal age, pre-pregnancy body mass index, education, smoking, annual household income, amniotic fluid volume, gestational hypertension, newborn gender and gestational age at blood collection, high maternal TG levels remained significantly associated with LGA newborns ($P<0.05$).

**Conclusion:** High maternal TG level during late pregnancy is significantly associated with LGA newborns.

**Key words:** large-for-gestational-age newborns; late pregnancy; maternal lipid profile; triglyceride

**Introduction**

Fetal growth and development is determined by a combination of genetic and environmental factors. As environmental factors, maternal nutritional status and metabolism are critical to fetal growth. Adverse intrauterine environment could lead to abnormal birth weight. There are increasing evidences indicating that large-for-gestational age (LGA) is associated with metabolic syndrome (MS), such as cardiovascular disease and type 2 diabetes mellitus\[1,2\]. The prevalence of MS is particularly high in the obese pediatric population born with LGA\[3,4\]. Maternal lipids increase during gestation compared with pre-pregnancy\[5-9\]. Hyperlipidemia during pregnancy can result in fetal overgrowth. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDLC) and apolipoprotein A1 (ApoA1) in the LGA group are significantly lower than in the appropriate-for-gestational age (AGA) group. Maternal triglyceride (TG) levels during pregnancy are positively associated with birth weight, which result in a higher occurrence of LGA infants\[10-13\]. Previous studies\[14,15\] have suggested that cord connecting peptide (C-peptide) levels are positively correlated with birth weight. C-peptide and insulin levels are higher in the LGA group than in the AGA group\[15,16\]. Maternal lipids metabolism...
is important and complex in the process of fetal development. However, the effect of maternal lipids metabolism on fetal development has not been fully elucidated yet. It is well-known that gestational diabetes can significantly affect maternal lipids levels and cause adverse birth weight outcomes. Studies on the relationship between C-peptide levels and birth weight were mostly carried out in cord blood. And few studies have eliminated the effect of confounding variables that may affect fetal growth and birth weight. To our knowledge, studies of the relationship between maternal blood markers in late pregnancy and LGA newborns rarely focused on maternal lipids, C-peptide, insulin and glycosylated hemoglobin (HbA1c). Therefore, the present study aimed to determine the effect of the levels of maternal lipids, C-peptide, insulin and HbA1c during late pregnancy on LGA newborns in the non-diabetic population, independent of other confounding variables.

Methods
Study population
Pregnant women during 28-37 weeks' gestation were enrolled into this study. Before enrollment, written informed consent was signed. These women were asked to complete a questionnaire with items of maternal age, height, pre-pregnancy weight, smoking, maternal education level and annual household income. Information about diabetes, abnormal glucose tolerance, gestational hypertension and amniotic fluid were collected. At the same time, overnight fasting blood was collected. The women were followed up from enrollment to delivery, and data on gestational age, Apgar score and birth weight were recorded by the doctor upon delivery. Inclusion criteria of pregnant women were as follows: pregnancy at 28-37 weeks' gestation, conceiving naturally and singleton pregnancy. Exclusion criteria of pregnant women were as follows: diabetes, abnormal glucose tolerance, chromosomal abnormality, inherited metabolic diseases, thyroid disease, and risk for fetal chromosomal abnormality. Exclusion criterion of newborns was full term birth. Exclusion criteria of newborns included inherited metabolic diseases, congenital abnormalities and congenital heart diseases. In 3111 women enrolled, 127 pregnant women were diagnosed with abnormal glucose tolerance, and 22 with diabetes. In their newborns, there were 83 SGA, 2236 AGA, 554 LGA, 82 preterm and 7 post-term. The present study aimed to investigate the effect of blood markers on LGA newborns; therefore, the SGA newborns were also excluded. Based on the criteria above, 2790 women were finally included. This study was approved by the Ethics Committee of the hospital.

Biochemical analyses
Venous blood after overnight fasting was taken from the women, put in a separation tube and then centrifuged. Serum was collected and assayed for ApoA1, C-peptide, HbA1c, insulin, total cholesterol (TC), HDL-C, LDL-C and TG according to the protocols. Blood collected with a sodium fluoride anticoagulant tube was used for HbA1c measurement. ApoA1 and HbA1c levels were measured with an immunoturbidity method, with reference values (from nonpregnant individuals) of 0.370-1.470 nmol/L and 4.50-16.15 mIU/L, respectively. TC, HDL-C, and LDL-C levels were measured by enzymatic colorimetric assay, with reference values (from nonpregnant individuals) of 3.10-6.00 mmol/L, 0.80-1.80 mmol/L and 1.40-4.90 mmol/L, respectively. TG levels were measured by the colorimetric assay, with reference values (from nonpregnant individuals) of 0.56-1.70 mmol/L.

Definitions
Newborns were defined as LGA when their birth weights were above the 90th percentile for gestational age. Newborns were defined as AGA when their birth weights were at or above the 10th percentile, but below the 90th percentile for gestational age in accordance with Neonatal Birth Weight for Gestational Age and Percentile in 15 Cities in China. Body mass index (BMI) (kg/m²) was calculated by pre-pregnancy weight/height² based on pre-pregnancy weight and maternal height. The levels of maternal ApoA1, C-peptide, insulin, and HbA1c were classified according to references from the protocols. Classification of maternal serum lipids was based on the Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults. Maternal smoking was classified as current smoking or quitting time <1 year, quitting time ≥1 year, never smoking, or <100 cigarettes consumed. Polyhydramnios was defined as the maximum depth of amniotic fluid ≥8.0 cm or an amniotic fluid index of ≥20 cm. Oligohydramnios was defined as the maximum depth of the amniotic fluid ≤3.0 cm or amniotic fluid index of ≤5.0 cm.

Statistical analysis
Data were presented as median (interquartile range, IQR) or n (%). The Chi-square test was used to evaluate mean differences in categorical variables between the AGA and LGA groups. The Mann-Whitney U test was used to evaluate mean differences in continuous variables between the two groups. Binary logistic