# 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.**

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***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 (HDL-C) 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

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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.[10,17-20] Studies[14-16] 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 ($HbA_{1c}$). Therefore, the present study aimed to determine the effect of the levels of maternal lipids, C-peptide, insulin and $HbA_{1c}$ 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. Inclusion 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, $HbA_{1c}$, 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 $HBA_{1c}$ measurement. ApoA1 and $HbA_{1c}$ levels were measured with an immunoturbidimetry method,[21] with reference values (from nonpregnant individuals) of 1.00-2.25 g/L and 4.0%-6.3%, respectively. C-peptide and insulin levels were measured using an electrochemiluminescence method,[22,23] 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*.[24]

Body mass index (BMI) ($kg/m^2$) was calculated by pre-pregnancy weight/height$^2$ based on pre-pregnancy weight and maternal height. The levels of maternal ApoA1, C-peptide, insulin, and $HbA_{1c}$ 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.[25] 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

regression analysis was made to determine the independent risk factors for LGA newborns at term. In the model, maternal age, pre-pregnancy BMI, education level, smoking, annual household income, amniotic fluid volume, gestational hypertension, newborn sex, and gestational age at blood collection were used as confounding variables. SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P<0.05$ was considered statistically significant.

## Results

Maternal and neonatal demographic characteristics are shown in Table 1. There were 2236 (80.1%) AGA and 554 (19.9%) LGA newborns. The median maternal age was 26 years and pre-pregnancy BMI was 19.93 kg/m$^2$. The median gestational age at blood collection and delivery was 34 and 39 weeks, respectively. The median birth weight of the neonates was 3350 g. There were no significant differences in gestational age at blood collection, maternal age, maternal smoking, maternal education, annual household income, or gestational hypertension between the LGA and AGA groups. Pre-pregnancy BMI in the LGA group was significantly higher than that in the AGA group ($P<0.05$). The occurrence of LGA was significantly higher in boys than in girls ($P<0.05$). There was significant difference in amniotic fluid volume between the two groups ($P<0.05$).

Data on the levels of fasting maternal lipids, C-peptide, $HBA_{1c}$, and insulin are shown in Table 2. There were significantly higher levels of maternal C-peptide, $HbA_{1c}$, insulin and TG in the LGA group than in the AGA group ($P<0.05$). The levels of maternal HDL-C, LDL-C and TC were significantly lower in the LGA group than in the AGA group ($P<0.05$). However, there was no significant difference in ApoA1 levels between the two groups.

After controlling maternal age, pre-pregnancy BMI, education, smoking, annual household income, amniotic fluid volume, gestational hypertension, gestational age at blood collection and newborn sex, maternal TG levels remained significantly associated with LGA newborns (Table 3). Women with TG ≥1.70 mmol/L during late pregnancy experienced an approximately 3.0-fold



**Table 1.** Maternal and neonatal characteristics

| Variables | Total ($n$=2790) | AGA ($n$=2236) | LGA ($n$=554) | $P$ |
|---|---|---|---|---|
| Maternal characteristics | | | | |
| Maternal age (y) | 26 (24-29) | 26 (24-28) | 27 (24-29) | 0.004* |
| Pre-pregnancy BMI (kg/m$^2$) | 19.93 (18.55-21.63) | 19.83 (18.49-21.48) | 20.32 (18.83-22.23) | 0.000* |
| Gestational age at screening (wk) | 34 (32-35) | 34 (32-35) | 34 (32-36) | 0.735 |
| Maternal smoking ($n$, %) | | | | 0.120 |
| Current smoking or quitting time <1 y | 17 (0.6) | 13 (0.6) | 4 (0.7) | |
| Quitting time ≥1 y | 40 (1.4) | 27 (1.2) | 13 (2.3) | |
| Never or total <100 cigarettes | 2733 (98.0) | 2196 (98.2) | 537 (96.9) | |
| Maternal education ($n$, %) | | | | 0.448 |
| Junior high school or lower | 732 (26.2) | 576 (25.8) | 156 (28.1) | |
| Senior high school | 748 (26.8) | 608 (27.2) | 140 (25.3) | |
| Undergraduate or higher | 1310 (47.0) | 1052 (47.0) | 258 (46.6) | |
| Annual household income ($n$, %) | | | | 0.936 |
| ≤¥50 000 | 1135 (40.7) | 911 (40.7) | 224 (40.4) | |
| ¥50 000-¥100 000 | 1091 (39.1) | 873 (39.0) | 218 (39.4) | |
| ¥100 000-¥200 000 | 421 (15.1) | 340 (15.2) | 81 (14.6) | |
| >¥200 000 | 143 (5.1) | 112 (5.0) | 31 (5.6) | |
| Gestational hypertension ($n$, %) | | | | 0.779 |
| Yes | 44 (1.6) | 36 (1.6) | 8 (1.4) | |
| No | 2746 (98.4) | 2200 (98.4) | 546 (98.6) | |
| Amnioticfluid ($n$, %) | | | | 0.000* |
| Normal | 2563 (91.9) | 2046 (91.5) | 517 (93.3) | |
| Oligohydramnios | 187 (6.7) | 165 (7.4) | 22 (4.0) | |
| Polyhydramnios | 40 (1.4) | 25 (1.1) | 15 (2.7) | |
| Neonatal characteristics | | | | |
| Gestational age at delivery (wk) | 39 (38-40) | 39 (38-40) | 39 (39-40) | |
| Gender ($n$, %) | | | | 0.000* |
| Male | 1546 (55.4) | 1175 (52.5) | 371 (67.0) | |
| Female | 1244 (44.6) | 1061 (47.5 ) | 183 (33.0) | |
| Birth weight (g) | 3350 (3114-3600) | 3270 (3060-3450) | 3850 (3750-4000) | |

Data were expressed as median (interquartile range) or $n$ (%). Statistical analysis between the LGA and AGA groups was performed by the Chi-square test, while maternal age and gestational age at screening and pre-pregnancy BMI were analyzed by the Mann-whitney $U$ Test. LGA: large-for-gestational age; AGA: appropriate-for-gestational age; BMI: body mass index. *: $P<0.01$.

**Table 2.** Metabolic parameters of maternal blood between large-for-gestational age (LGA) and appropriate-for-gestational age (AGA) newborns

| Variables | Total (*n*=2790) | AGA (*n*=2236) | LGA (*n*=554) | *P* |
|---|---|---|---|---|
| ApoA1 (g/L) | 2.18 (1.94-2.42) | 2.18 (1.94-2.42) | 2.14 (1.94-2.39) | 0.145 |
| C-peptide (nmol/L) | 0.66 (0.52-0.82) | 0.65 (0.52-0.81) | 0.70 (0.54-0.87) | 0.000† |
| $HbA_{1c}$ (%) | 5.30 (5.0-5.6) | 5.30 (5.0-5.6) | 5.30 (5.0-5.7) | 0.010* |
| Insulin (mIU/L) | 8.53 (5.95-12.10) | 8.40 (5.88-12.02) | 9.22 (6.26-12.62) | 0.012* |
| HDL-C (mmol/L) | 1.75 (1.51-2.03) | 1.76 (1.52-2.05) | 1.70 (1.48-1.95) | 0.000† |
| LDL-C (mmol/L) | 3.06 (2.44-3.72) | 3.07 (2.47-3.74) | 2.95 (2.30-3.65) | 0.003† |
| TC (mmol/L) | 6.28 (5.59-7.09) | 6.30 (5.62-7.10) | 6.18 (5.49-7.04) | 0.017* |
| TG (mmol/L) | 3.05 (2.50-3.75) | 3.02 (2.48-3.69) | 3.19 (2.61-3.97) | 0.000† |

Data are median (interquartile range). Statistical analysis was performed by the Mann-whitney *U* test for the differences between the LGA and AGA groups. ApoA1: apolipoprotein A1; C-peptide: connecting peptide; $HbA_{1c}$: glycosylated hemoglobin1c; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglyceride; TC: total cholesterol. *: $P<0.05$; †: $P<0.01$.

**Table 3.** Odds ratios and 95% confidence intervals (CIs) of maternal blood markers and characteristics between AGA and LGA newborns

| Variables | B | Wald | Sig. | Exp (B) | 95.0% CI for EXP (B) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Maternal age | 0.026 | 3.533 | 0.06 | 1.026 | 0.999 | 1.054 |
| Pre-pregnancy BMI | 0.077 | 16.053 | 0.000† | 1.081 | 1.04 | 1.122 |
| Smoking | | 5.426 | 0.066 | | | |
| 1 | 0.309 | 0.275 | 0.600 | 1.363 | 0.428 | 4.334 |
| 2 | 0.804 | 5.187 | 0.023* | 2.235 | 1.119 | 4.465 |
| Amniotic fluid | | 14.635 | 0.001† | | | |
| Oligohydramnios | -0.707 | 8.967 | 0.003† | 0.493 | 0.31 | 0.784 |
| Polyhydramnios | 0.775 | 5.202 | 0.023* | 2.171 | 1.115 | 4.227 |
| Gender | 0.625 | 37.689 | 0.000† | 1.868 | 1.53 | 2.281 |
| ApoA1 (1-2.25) | | | | | | |
| >2.25 | -0.138 | 1.421 | 0.233 | 0.871 | 0.694 | 1.093 |
| C-peptide (0.37-1.47) | | 2.97 | 0.226 | | | |
| <0.37 | -0.437 | 2.424 | 0.12 | 0.646 | 0.373 | 1.12 |
| >1.47 | 0.328 | 0.56 | 0.454 | 1.389 | 0.587 | 3.282 |
| Insulin (4.50-16.15) | | 0.515 | 0.773 | | | |
| <4.50 | 0.036 | 0.042 | 0.838 | 1.037 | 0.735 | 1.463 |
| >16.15 | 0.117 | 0.493 | 0.483 | 1. 124 | 0.811 | 1.558 |
| $HbA_{1c}$ (4.0-6.3) | | 2.697 | 0.260 | | | |
| <4.0 | -0.333 | 0.947 | 0.331 | 0.717 | 0.367 | 1.401 |
| >6.3 | 0.256 | 1.653 | 0.198 | 1.292 | 0.874 | 1.909 |
| HDL-C (1.04-1.55 ) | | 4.942 | 0.085 | | | |
| <1.04 | -1.601 | 2.35 | 0.125 | 0.202 | 0.026 | 1.562 |
| ≥1.55 | -0.209 | 2.816 | 0.093 | 0.812 | 0.636 | 1.036 |
| LDL-C (<3.37) | | 2.582 | 0.275 | | | |
| 3.37-4.14 | -0.242 | 2.455 | 0.117 | 0.785 | 0.58 | 1.063 |
| ≥4.14 | -0.188 | 1.126 | 0.289 | 0.829 | 0.585 | 1.173 |
| TC (<5.18) | | 0.654 | 0.721 | | | |
| 5.18-6.22 | -0.034 | 0.047 | 0.827 | 0.967 | 0.712 | 1.313 |
| ≥6.22 | 0.081 | 0.192 | 0.661 | 1.084 | 0.754 | 1.559 |
| TG (<1.70) | | 5.329 | 0.070 | | | |
| 1.70-2.25 | 1.111 | 4.235 | 0.04* | 3.037 | 1.054 | 8.747 |
| ≥2.26 | 1.195 | 5.152 | 0.023* | 3.303 | 1.177 | 9.27 |

Adjusted for maternal age, pre-pregnancy BMI, education, smoking, annual household income, amniotic fluid state, gestational hypertension, newborn gender and gestational age at sample collection. Reference of maternal ApoA1, C-peptide, insulin, $HbA_{1c}$ and lipids was 1-2.25, 0.37-1.47, 4.50-16.15, 4.0-6.3, 1.04-1.55, <3.37, <5.18 and <1.70, as shown above. Reference of maternal smoking, amniotic fluid and gender were never or total <100 cigarettes, normal and female, respectively. Smoking: 1: current smoking or quitting time<1 year; 2: quitting time≥1 year. LGA: large-for-gestational age; AGA: appropriate-for-gestational age; BMI: body mass index; ApoA1: apolipoprotein A1; C-peptide: connecting peptide; $HbA_{1c}$: glycosylated hemoglobin1c; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglyceride; TC: total cholesterol. *: $P<0.05$; †: $P<0.01$.

increase of risk of having an LGA newborn [$P$=0.04, adjusted odds ratio (OR)=3.037, 95% confidence interval (CI): 1.054-8.747], with TG <1.70 mmol/L as reference. In addition, women with TG ≥2.26 mmol/L experienced a 3.3-fold increase of risk of having an LGA newborn ($P$=0.022, adjusted OR=3.303, 95% CI: 1.177-9.27), with TG <1.70 mmol/L as reference.

## Discussion

Infant development is affected by various factors including maternal BMI, maternal metabolism, gestational weeks at birth. To determine the relationship between maternal blood markers and LGA newborns, we enrolled pregnant women at 28-37 weeks' gestation in the study. We observed the effect of levels of maternal

C-peptide, $HbA_{1c}$, insulin, HDL-C, LDL-C, TG and TC on LGA newborns. Pregnant women who delivered LGA newborns had higher levels of C-peptide, $HbA_{1c}$, insulin, and TG, and lower levels of HDL-C, LDL-C, and TC than those who delivered AGA newborns. The results in our study were consistent with those reported elsewhere,[10,11,13,15,26] showing that high levels of maternal C-peptide and TG are positively correlated with birth weight. The levels of maternal TC and LDL-C were significantly lower in LGA newborns.[27] However, conflicting results indicated that maternal TG level was similar between the LGA and AGA groups,[27] and that there were no significant differences in maternal TC, TG or HDL-C levels during early or late pregnancy.[10,13] This finding might be explained in two aspects: one was the differences in exclusion criteria and the other was that maternal blood was measured during 28-37 weeks' gestation in our study, which was different from others.

In addition, we found that the LGA group had higher pre-pregnancy BMI than the AGA group; this finding is consistent with other report.[13] The finding indicated that women with higher maternal age and pre-pregnancy BMI are more likely to give birth to LGA newborns. In addition, it was revealed that maternal obesity was also associated with inflammation of their children.[28] In the present study, the effect of amniotic fluid volume on LGA was also analyzed. Polyhydramnios resulted in the occurrence of LGA newborns, suggesting that polyhydramnios can lead to fetal overgrowth. However, the effects of maternal education, annual household income and gestational hypertension on LGA infants were not significant. Our findings suggest that boys are more likely to develop LGA than girls.

We regarded gestational age at blood collection as a confounding variable because lipids level increased with gestational age.[1,9] After adjustment for maternal age, pre-pregnancy BMI, education, smoking, annual household income, amniotic fluid volume, gestational hypertension, newborn gender and gestational age at blood collection, TG levels remained significantly different between the LGA and AGA groups. This finding indicated that higher TG level (≥1.7 mmol/L) is an independent risk factor for LGA newborns. Similar results from other studies[13,29] also suggested that maternal fasting serum TG levels could independently predict LGA newborns. Moreover, women with a TG level higher than 2.26 mmol/L had a greater risk for giving birth to LGA newborns than those with a TG level lower than 2.26 mmol/L. Obviously, lipoprotein lipase (LPL) participates in the hydrolysis of maternal TG, and facilitates the transplacental transfer of TG-derived free fatty acid, which is important for the supply of components for fetal development. The increase of TG level may be due to decreased LPL activity and increased concentration of estrogen during late pregnancy.[30,31] The mechanism for the association between maternal TG levels and fetal growth might be enhanced insulin resistance during late pregnancy.[12,13]

However, there was no significant difference in $HbA_{1c}$ levels between the AGA and LGA groups in this study. This finding was not consistent with another study showing that mid-pregnancy $HbA_{1c}$ levels in non-diabetic women may predict neonatal birth weight, with a $HbA_{1c}$ cut-off level of 4.99%.[32] However, another study showed that pregnant women had lower $HbA_{1c}$ levels than non-pregnant women, and the change from the first to second trimester appeared to be important in predicting birth weight.[33]

After adjustment, higher BMI, time of quitting smoking ≥1 year and polyhydramnios remained as independent risk factors for LGA newborns. Women with a duration of quitting smoking ≥1 year were more likely to give birth to LGA newborns than those non-smoking women. However, other studies suggested that maternal smoking can lead to small-for-gestational age newborns and quitting smoking during the first trimester of pregnancy could result in a higher incidence of small-for-gestational age, compared with non-smoker.[34,35] The inconsistency of this finding with others might be due to the following reasons: Pregnant women in our study might obtain more nutrition during gestation, which is difficult to evaluate, and fetal growth was affected by other potential unknown factors. Additionally, oligohydramnios can be regarded as a protective factor for LGA newborns.

The present study has strengths and limitations. The strengths include a large population of non-diabetic women in late pregnancy with comprehensive information, which is useful to determine the independent risk factors for LGA newborns. Besides, the study is a prospective one and the follow-up of the population provided more information about infant development, which is important to detect the mechanism of MS development. The limitation is that some maternal demographic characteristics were self-reported from pregnant women, which may lead to bias. Moreover, although many variables were obtained in our study, we did not include other potential confounding variables (e.g., weight gain during pregnancy), which may affect birth weight.[36-38] Some unknown potential factors that might also affect fetal growth in intrauterine environment were not included in the study. Hence, further study is needed to determine these possibilities.

Our findings suggest that pre-pregnancy BMI, time of quitting smoking ≥1 year, polyhydramnios and high

maternal TG levels in late pregnancy play a critical role in fetal development. These factors are independently associated with the occurrence of LGA newborns. Some interventional measures should be taken to reduce the adverse effect on fetal growth and development. Therefore, the occurrence of LGA newborns as well as the incidence of adulthood MS can be reduced.

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## References

1 Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115:e290-296.
2 Ong KK, Dunger DB. Birth weight, infant growth and insulin resistance. Eur J Endocrinol 2004;151 suppl 3:U131-139.
3 Wang X, Liang L, Junfen FU, Lizhong DU. Metabolic syndrome in obese children born large for gestational age. Indian J Pediatr 2007;74:561-565.
4 Wang XM. Early life programming and metabolic syndrome. World J Pediatr 2013;9:5-8.
5 Brizzi P, Tonolo G, Esposito F, Puddu L, Dessole S, Maioli M, et al. Lipoprotein metabolism during normal pregnancy. Am J Obstet Gynecol 1999;181;430-434.
6 Ogura K, Miyatake T, Fukui O, Nakamura T, Kameda T, Yoshino G. Low-density lipoprotein particle diameter in normal pregnancy and preeclampsia. J Atheroscler Thromb 2002;9:42-47.
7 Sattar N, Greer IA, Louden J, Lindsay G, McConnell M, Shepherd J, et al. Lipoprotein subfraction changes in normal pregnancy: threshold effect of plasma triglyceride on appearance of small, dense low density lipoprotein. J Clin Endocrinol Metab 1997;82:2483-2491.
8 Misra VK, Trudeau S, Perni U. Maternal serum lipids during pregnancy and infant birth weight: the influence of prepregnancy BMI. Obesity (Silver Spring) 2001;19:1476-1481.
9 Emet T, Ustüner I, Güven SG, Balık G, Ural UM, Tekin YB, et al. Plasma lipids and lipoproteins during pregnancy and related pregnancy outcomes. Arch Gynecol Obstet 2013;288:49-55.
10 Vrijkotte TG, Algera SJ, Brouwer IA, van Eijsden M, Twickler MB. Maternal triglyceride levels during early pregnancy are associated with birth weight and postnatal growth. J Pediatr 2011;159:736-742.
11 Di Cianni G, Miccoli R, Volpe L, Lencioni C, Ghio A, Giovannitti MG, et al. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabet Med 2005;22:21-25.
12 Kitajima M, Oka S, Yasuhi I, Fukuda M, Rii Y, Ishimaru T. Maternal serum triglyceride at 24-32 weeks' gestation and newborn weight in nondiabetic women with positive diabetic screens. Obstet Gynecol 2001;97:776-780.
13 Son GH, Kwon JY, Kim YH, Park YW. Maternal serum triglycerides as predictive factors for large-for-gestational age newborns in women with gestational diabetes mellitus. Acta Obstet Gynecol Scand 2010;89;700-704.
14 Delvaux T, Buekens P, Thoumsin H, Dramaix M, Collette J. Cord C-peptide and insulin-like growth factor-I, birth weight, and placenta weight among North African and Belgian neonates. Am J Obstet Gynecol 2003;189:1779-1784.
15 Akinbi HT, Gerdes JS. Macrosomic infants of nondiabetic mothers and elevated C-peptide levels in cord blood. J Pediatr 1995;127:481-484.
16 Verhaeghe J, Van Bree R, Van Herck E, Laureys J, Bouillon R, Van Assche FA. C-peptide, insulin-like growth factors I and II, and insulin-like growth factor binding protein-1 in umbilical cord serum: correlations with birth weight. Am J Obstet Gynecol 1993;169:89-97.
17 Onal EE, Hirfanoglu IM, Beken S, Altuntas N, Turkyilmaz C, Duyan Camurdan A, et al. Are the neonatal outcomes similar in large-for-gestational age infants delivered by women with or without gestational diabetes mellitus? World J Pediatr 2012;8:136-139
18 Schaefer-Graf UM, Graf K, Kulbacka I, Kjos SL, Dudenhausen J, Vetter K, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care 2008;31:1858-1863.
19 Couch SC, Philipson EH, Bendel RB, Wijendran V, Lammi-Keefe CJ. Maternal and cord plasma lipid and lipoprotein concentrations in women with and without gestational diabetes mellitus. Predictors of birth weight? J Reprod Med 1998;43:816-822.
20 Göbl CS, Handisurya A, Klein K, Bozkurt L, Luger A, Bancher-Todesca D, et al. Changes in serum lipid levels during pregnancy in type 1 and type 2 diabetic subjects. Diabetes Care 2010;33:2071-2073.
21 Weissmann-Brenner A, O'Reilly-Green C, Ferber A, Divon MY. Does the availability of maternal HbA1c results improve the accuracy of sonographic diagnosis of macrosomia? Ultrasound Obstet Gynecol 2004;23:466-471.
22 Boroujeni ZN, Aleyasin A. Insulin producing cells established using non-integrated lentiviral vector harboring PDX1 gene. World J Stem Cells 2013;5:217-228.
23 Li S, Huang S, Mo ZN, Gao Y, Yang XB, Chen XJ, et al. Generating a reference interval for fasting serum insulin in healthy nondiabetic adult Chinese men. Singapore Med J 2012;53:821-825.
24 Jin HZ, Huang DM, Guan XJ. Practical neonatology, 2nd ed. Beijing: People's Health Pub, 1997.
25 Joint Committee for Developing Chinese guidelines on

Prevention and Treatment of Dyslipidemia in Adults. Chinese guidelines on prevention and treatment of dyslipidemia in adults. Zhonghua Xin Xue Guan Bing Za Zhi 2007;35:390-419. [in Chinese]
26 Kelishadi R, Badiee Z, Adeli K. Cord blood lipid profile and associated factors: baseline data of a birth cohort study. Paediatr Perinat Epidemiol 2007;21:518-524.
27 Parlakgumus HA, Aytac PC, Kalaycı H, Tarim E. First trimester maternal lipid levels and serum markers of small- and large-for-gestational age infants. J Matern Fetal Neonatal Med 2014;27:48-51.
28 Leibowitz KL, Moore RH, Ahima RS, Stunkard AJ, Stallings VA, Berkowitz RI, et al. Maternal obesity associated with inflammation in their children. World J Pediatr 2012; 8:76-79.
29 Vrijkotte TG, Krukziener N, Hutten BA, Vollebregt KC, van Eijsden M, Twickler MB. Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: ABCD study. J Clin Endocrinol Metab 2012;97:3917-3925.
30 Alvarez JJ, Montelongo A, Iglesias A, Lasunción MA, Herrera E. Longitudinal study on lipoprotein profile, high density lipoprotein subclass, and post heparin lipases during gestation in women. J Lipid Res 1996;37:299-308.
31 Knopp RH, Warth MR, Charles D, Childs M, Li JR, Mabuchi H, et al. Lipoprotein metabolism in pregnancy, fat transport to the fetus, and the effects of diabetes. Biol Neonate 1986;50:297-317.
32 Karcaaltincaba D, Yalvac S, Kandemir O, Altun S. Glycosylated hemoglobin level in the second trimester predicts birth weight and amniotic fluid volume in non-diabetic pregnancies with abnormal screening test. J Matern Fetal Neonatal Med 2010;23:1193-1199.
33 Versantvoort AR, van Roosmalen J, Radder JK. Course of Hba1c in non-diabetic pregnancy related to birth weight. Neth J Med 2013;71:22-25.
34 Polakowski LL, Akinbami LJ, Mendola P. Prenatal smoking cessation and the risk of delivering preterm and small-for-gestational-age newborns. Obstet Gynecol 2009;114:318-325.
35 Räisänen S, Gissler M, Sankilampi U, Saari J, Kramer MR, Heinonen S. Contribution of socioeconomic status to the risk of small for gestational age infants-a population-based study of 1 390 165 singleton live births in Finland. Int J Equity Health 2013;12:28.
36 Dietz PM, Callaghan WM, Sharma AJ. High pregnancy weight gain and risk of excessive fetal growth. Am J Obstet Gynecol 2009;201:51.e1-6.
37 Liu Y, Dai W, Dai X, Li Z. Pre pregnancy body mass index and gestational weight gain with the outcome of pregnancy: a 13-year study of 292,568 cases in China. Arch Gynecol Obstet 2012;286:905-911.
38 Jariyapitaksakul C, Tannirandorn Y. The occurrence of small for gestational age infants and perinatal and maternal outcomes in normal and poor maternal weight gain singleton pregnancies. J Med Assoc Thai 2013;96:259-265.

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