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Cord Blood C-peptide, Insulin, HbA1c, and Lipids Levels in Small- and Large-for-Gestational-Age Newborns

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Data Interpretation D
Manuscript Preparation E
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Background: Small- and large-for-gestational-age (SGA, LGA) newborns are associated with metabolic syndrome in their later life. Cord blood C-peptide, insulin, glycosylated hemoglobin (HbA1c), and lipids levels may be altered in SGA and LGA newborns; however, the results are conflicting. Therefore, this study aimed to determine the effect of cord blood markers on SGA and LGA newborns.

Material/Methods: This was a prospective cohort study and included 2873 term newborns of non-diabetic women. Among these newborns, 83 (2.9%) were SGA, 2236 (77.8%) were appropriate-for-gestational-age (AGA), and 554 (19.3%) were LGA newborns. Cord blood C-peptide, insulin, HbA1c, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured. The chi-square, Kruskal-Wallis, and Mann-Whitney tests were used to analyze categorical variables and continuous variables, respectively. Multinomial logistic regression analysis was used to determine the independent effect of these variables on SGA and LGA newborns.

Results: Cord serum TG level was significantly higher in the SGA group than in AGA and LGA groups ($p<0.05$). The LGA group had significantly higher cord serum insulin level than AGA and SGA groups ($p<0.05$). After adjustment for confounding variables, including maternal age, parity, pre-pregnancy body mass index (BMI), education, annual household income, pregnancy-induced hypertension (PIH), mode of delivery, and newborn sex, high TG and insulin levels remained significantly associated with SGA and LGA newborns, respectively ($p<0.05$).

Conclusions: High cord serum TG and insulin levels are independently associated with SGA and LGA newborns, respectively.

MeSH Keywords: Lipids • Insulin • Small-For-Gestational Age Newborns • Large-For-Gestational Age Newborns

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Background

Fetal growth and development is a complex process determined by genetic and environmental factors [1]. Environmental factors mainly include maternal metabolic conditions and nutrients, such as glucose, lipids, and amino acids [1]. Intrauterine growth retardation (IUGR) is well known as a major contributor to perinatal morbidity and mortality [2]. Intrauterine growth dysplasia may affect their metabolism in later life and adult health [3]. Newborns with IUGR are associated with an increased risk of cardiovascular disease, insulin resistance, hypertension, hyperlipidemia, and diabetes mellitus [4–7]. Similarly, large-for-gestational-age (LGA) newborns are also prone to developing obesity, insulin resistance, and cardiovascular diseases in later life [8–10]. Therefore, it is very important to confirm the possible risk factors for the occurrence of SGA and LGA newborns.

As the main component of the maternal metabolic environment, cord blood C-peptide and insulin levels are significantly positively correlated with birth weight [11]. The levels of cord blood lipids can change in women whose pregnancies are complicated by preeclampsia and gestational diabetes mellitus (GDM), and they are also associated with birth weight, which has been investigated in previous studies [12–14]. However, the association between SGA, LGA, and cord blood lipids is not yet well understood and the results of previous studies are controversial [12,14–16]. Therefore, the purpose of this study was to determine the relationship between cord blood C-peptide, insulin, glycosylated hemoglobin (HbA1c), and lipids levels, and SGA and LGA newborns. In this study, we included maternal nutritional status and socioeconomic status, and also excluded women whose pregnancies were complicated by diabetes or GDM.

Material and Methods

Study population

The study enrolled late-pregnancy (28–37 gestational weeks) women who attended regular prenatal examinations in Yongkang, Huzhou, Cixi, Ninghai, Shaoxing, Yiwu, Dongyang, and Wenling maternal and children health hospitals in Zhejiang province, China, from 1 January 2010 to 30 June 2011. We established the study cohort according to inclusion and exclusion criteria. All participants' provided written informed consent before enrollment. However, we did not account for the population who declined to take part in this study. Pregnant women were asked to complete a questionnaire including information on maternal age, parity height, pre-pregnancy weight, education, and annual household income. Information on diabetes, GDM, and pregnancy-induced hypertension (PIH) was collected from their medical records. Data on mode of delivery gestational age, Apgar score, newborn sex, and birth weight were recorded by the doctor upon delivery. Inclusion criteria of pregnant women were: conceived naturally, clear gestational age, 28–37 weeks gestational age, singleton pregnancy, and cooperation with blood collection for measurement. Exclusion criteria of pregnant women were: diabetes, GDM, chromosomal abnormality, inherited metabolic diseases, and thyroid disease. Inclusion criteria of newborns: full-term birth and cord blood collected for measurement. Exclusion criteria of newborns were inherited metabolic diseases, congenital abnormalities, and congenital heart diseases. In all, 3394 subjects were enrolled, including 432 pregnant women with incomplete information who were excluded from the study, and 2962 women were included. Of the 2962 newborns, there were 2873 full-term (including 83 SGA, 2236 AGA, and 554 LGA), 82 pre-term, and 7 post-term newborns. Pre-term and post-term newborns were also excluded based on the criteria above. Finally, 2873 full-term newborns were included in the study. Ethics approval was obtained from the hospital's Ethics Committee.

Reduction of bias

We took some measures to reduce bias. Firstly, the subjects were randomly selected, and every obstetrician received consistent training, which included how to guide the participants in completing the questionnaires, collection of cord blood, and its subsequent processing (centrifugation and storage). Secondly, all of the cord blood parameters were determined in the same medical laboratory, which might reduce the chance of error.

Definitions

Newborns were defined as SGA when their birth weights were below the 10th percentile for gestational age and as LGA when their birth weights were above the 90th percentile for gestational age. Appropriate-for-gestational-age (AGA) newborns were defined as birth weights at or above the 10th percentile and at or below the 90th percentile for gestational age, in accordance with the Neonatal Birth Weight for Gestational Age and Percentile in 15 Cities in China [17]. This standard does not take into account the difference between boys and girls.

Body mass index (BMI) (kg/m^2) was calculated by pre-pregnancy weight/height^2 based on pre-pregnancy weight and maternal height. According to the World Health Organization BMI categorization, maternal pre-pregnancy BMI was divided into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥30 kg/m^2) groups. We combined maternal overweight and obesity groups together because the population of obese women in our study was small. Cord blood C-peptide, insulin, HbA1c, and lipids levels were classified according to their quartiles.

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Diabetes and GDM were diagnosed on the basis of the Recommendations from the American Diabetes Association (ADA) and the International Association of Diabetes and the Pregnancy Study Groups (IADPSG) [18,19]. The definition of diabetes in pregnancy was: (1) FPG ≥7.0 mmol/L.; (2) HbA1c ≥6.5% (NGSP certified and standardized to the DCCT assay); (3) 2-hour plasma glucose level ≥11.1 mmol/L during a 75 g oral glucose tolerance test (OGTT); and (4) Subjects with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥11.1 mmol/L. Subjects were diagnosed with diabetes if they fulfilled any 1 of the above 4 criteria. The diagnostic standards of GDM were: before an OGTT, a 50-g glucose challenge test was ordered for each participant and plasma glucose level was measured 1 h later. The subjects with test results at or higher than 7.8 mmol/L were required to undergo 75-g OGTT tests, and plasma glucose levels were measured at 0, 1, 2 h, respectively. Normal values were <5.1, <10.0, <8.5 mmol/L at each time point, respectively. One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM.

Criteria for diagnosis of PIH were: (1) systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg appeared for the first time during pregnancy and returned to normal at 12 weeks postpartum; or (2) systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation and new onset proteinuria, with or without convulsions [20]. Subjects were diagnosed PIH if they met any 1 of the 2 criteria.

Biochemical analyses

The umbilical cord was double-clamped immediately after delivery, and then cord venous blood was collected and placed into a separation tube and a sodium fluoride anticoagulant tube. The blood sample in the separation tube was allowed to clot for 30 min before centrifugation for 5 min at 3000 rpm. The serum was collected and assayed immediately for C-peptide, insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) levels. The blood placed in the sodium fluoride anticoagulant tube was immediately used for HbA1c measurement. If a pregnant woman delivered at night, the serum was stored at –20°C and sodium fluoride anticoagulant blood was stored at 4°C, which were measured as soon as possible the next day. All these measurements were performed in Hangzhou Dean Medical Laboratory Centre in Zhejiang province, China. HbA1c levels were measured by immunoturbidimetry method [21], which was performed on an automatic analyser (Roche-Cobase-C501, Roche Diagnostics, Germany) with a HbA1c detection kit (Roche Diagnostics) (the inter- and intra-assay coefficient of variation were <2.0%, 1.6%, respectively). C-peptide and insulin levels were determined with electrochemiluminescence method [22,23] on an automatic analyser (Roche-Cobase-E601, Roche Diagnostics, Germany) with a C-peptide detection kit (Roche Diagnostics) (the inter- and intra-assay coefficient of variation were <2.3% and 1.5%, respectively) and an insulin detection kit (Roche Diagnostics) (the inter- and intra-assay coefficients of variation were <2.8% and 1.5%, respectively). TC, HDL-C, and LDL-C levels were measured using an enzymatic colorimetric assay and TG levels were measured by colorimetric assay [24] on an automatic analyser (Roche-Cobase-C8000, Roche Diagnostics, Germany) with TC, HDL-C, LDL-C, and TG detection kits (Roche Diagnostics) (the inter- and intra-assay coefficients of variation were <1.9%, 0.81%; <1.9%, 1.5%; <0.9%, 0.7%; <1.9%, and 1.6%, respectively).

Statistical analysis

Data are presented as median (interquartile range) or N (%). The chi-square test was used to analyze categorical variables. Because the continuous variables were not normally distributed, they were analyzed by the Kruskal-Wallis or Mann-Whitney test. Multinomial logistic regression analysis was used to determine the independent effect of cord blood C-peptide, insulin, HbA1c, and lipids levels on SGA and LGA newborns at term. In the model, maternal age, parity, pre-pregnancy BMI, education, annual household income, PIH, mode of delivery, and newborn sex were used as confounding variables. SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. P value <0.05 was considered statistical significance.

Results

A total of 2873 newborns were recruited for the study. Maternal and neonatal characteristics are shown in Table 1. This study population consisted of 1576 (54.9%) boys and 1297 (45.1%) girls. Of these newborns, 83 (2.9%) were SGA, 2236 (77.8%) were AGA, and 554 (19.3%) were LGA newborns. In the LGA group, pregnant women were older than those in the SGA and AGA groups ($p<0.05$), and the ratio of cesarean section was also significantly higher than in the other 2 groups ($p<0.05$). Compared with pregnant women in the SGA and AGA groups, women's pre-pregnancy BMI was significantly higher in the LGA group ($p<0.05$). Compared with girls, the occurrence of LGA newborns was significantly higher in boys ($p<0.05$). However, the distribution of parity, maternal education, and annual household income was not significantly different among SGA, AGA, and LGA groups ($p>0.05$). The proportion of PIH was not significantly different among the 3 groups ($p>0.05$).

Data about cord blood C-peptide, HbA1c, insulin and lipids levels are shown in Table 2. The LGA group had significantly higher cord serum C-peptide and insulin levels than in the SGA and AGA groups ($p<0.05$). Cord serum TG levels in the SGA group were significantly higher than in the AGA

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Table 1. Maternal and neonatal characteristics.

	SGA (83)	AGA (2236)	LGA (554)	P
Maternal characteristics				
Maternal age (y)	26 (24–29)	26 (24–28)	27 (24–29)	0.008**
20–35	80 (96.4)	2156 (96.4)	518 (93.5)	
>35	3 (3.6)	80 (3.6)	36 (6.5)	
Pre-pregnancy BMI (kg/m²)	18.43 (17.58–20.08)	19.83 (18.49–21.48)	20.31 (18.83–22.23)	0.000**
<18.5	42 (50.6)	569 (25.4)	107 (19.3)	
18.5~25	40 (48.2)	1571 (70.3)	405 (73.1)	
≥25	1 (1.2)	96 (4.3)	42 (7.6)	
Maternal education (N, %)				**0.459**
≤ Junior high school	27 (32.5)	576 (25.8)	156 (28.2)	
Senior high school	18 (21.7)	608 (27.2)	140 (25.3)	
≥ Undergraduate	38 (45.8)	1052 (47.0)	258 (46.6)	
Annual household income (N, %)				**0.866**
≤50000 ¥	34 (41.0)	911 (40.7)	224 (40.4)	
50000–100000 ¥	36 (43.4)	873 (39.0)	218 (39.4)	
100000–200000 ¥	8 (9.6)	340 (15.2)	81 (14.6)	
>200000 ¥	5 (6.0)	112 (5.0)	31 (5.6)	
Pregnancy induced hypertension (N, %)				**0.806**
Yes	2 (2.4)	36 (1.6)	8 (1.4)	
No	81 (97.6)	2200 (98.4)	546 (98.6)	
Parity (N, %)				**0.090**
Primipara	73 (88.0)	2005 (89.7)	479 (86.5)	
Multipara	10 (12.0)	231 (10.3)	75 (13.5)	
Mode of delivery (N, %)				
Vaginal delivery	44 (53.0)	1139 (50.9)	198 (35.7)	0.000**
Cesarean section	39 (47.0)	1097 (49.1)	356 (64.3)	
Neonatal characteristics				
Gestational age at delivery (wk)	39 (39–40)	39 (38–40)	39 (39–40)	
Gender (N, %)				0.000**
Male	30 (36.1)	1175 (52.5)	371 (67.0)	
Female	53 (63.9)	1061 (47.5)	183 (33.0)	
Birth weight (g)	2600 (2450–2700)	3270 (3060–3450)	3850 (3750–4000)	

Values were median (IQR) or N (%). The chi-square test was made to analyze categorical variables. ** P<0.01.

and LGA groups (p<0.05). However, there were no significant differences in HbA1c, HDL-C, LDL-C, or TC levels among the 3 groups (p>0.05). Data on the impact of mode of delivery on cord blood parameters are shown in Table 3. Compared with

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Table 2. Metabolic parameters of cord blood.

	SGA (83)	AGA (2236)	LGA (554)	P
C-Peptide (nmol/L)	0.28 (0.18–0.34)	0.31 (0.23–0.42)	0.36 (0.27–0.49)	0.000**
HbA1c (%)	2.8 (2.6–3.1)	2.8 (2.6–3.1)	2.9 (2.6–3.1)	0.570
Insulin (mIU/L)	2.81 (1.26–5.22)	4.31 (2.32–7.13)	6.05 (3.42–9.71)	0.000**
HDL-C (mmol/L)	0.78 (0.56–1.00)	0.80 (0.66–0.98)	0.80 (0.66–0.96)	0.170
LDL-C (mmol/L)	0.67 (0.51–0.81)	0.68 (0.56–0.83)	0.67 (0.55–0.83)	0.343
TG (mmol/L)	0.38 (0.26–0.51)	0.29 (0.23–0.37)	0.27 (0.21–0.34)	0.000**
TC (mmol/L)	1.59 (1.26–1.91)	1.64 (1.41–1.92)	1.61 (1.38–1.88)	0.147

Values were median(IQR). Statistical analysis was performed using Kruska-Wallis Test. ** P<0.01.

Table 3. The impact of mode of delivery on the cord blood markers.

	Vaginal delivery (1381)	Cesarean delivery (1492)	P
C-Peptide (nmol/L)	0.30 (0.22–0.41)	0.34 (0.25–0.45)	0.000**
Insulin (mIU/L)	3.38 (1.79–5.92)	5.88 (3.51–8.93)	0.000**
HbA1c (%)	2.9 (2.6–3.1)	2.8 (2.6–3.1)	0.242
TC (mmol/L)	1.67 (1.42–1.95)	1.60 (1.38–1.88)	0.000**
HDL-C (mmol/L)	0.81 (0.67–0.98)	0.79 (0.66–0.96)	0.024*
LDL-C (mmol/L)	0.69 (0.56–0.85)	0.67 (0.55–0.82)	0.014*
TG (mmol/L)	0.32 (0.26–0.40)	0.26 (0.20–0.32)	0.000**

Values were median(IQR). Statistical analysis was performed using Mann-Whitney Test. * P<0.05; ** P<0.01.

vaginal delivery, cord serum C-peptide and insulin levels were significantly higher in cesarean delivery (p<0.05). Cord serum TC, HDL-C, LDL-C, and TG levels were significantly lower in cesarean delivery than in vaginal delivery (p<0.05). However, there was no significant difference in HbA1c level between the 2 groups (p>0.05).

After controlling for maternal age, parity, pre-pregnancy BMI, maternal education, annual household income, PIH, mode of delivery, and newborn sex, only high cord serum TG level remained significantly associated with SGA newborns and high insulin level was significantly associated with LGA newborns (Table 4). Newborns with cord serum insulin level ≥7.63 mIU/L experienced 1.6-fold increased risk of being LGA newborns (p=0.001, adjusted OR=1.628, 95% confidence interval [CI]: 1.221–2.169), with insulin level being at Q1~Q3 (2.45~7.63) mIU/L as reference. Additionally, newborns with cord serum TG level ≥0.37 mmol/L experienced an approximately 3.3-fold increased risk of being SGA newborns (p<0.001, adjusted odds ratio [OR]=3.335, 95% CI: 1.982–5.611), with TG levels at Q1~Q3 (0.22~0.37) mmol/L as reference. Furthermore, older women (≥35 years), women with pre-pregnancy BMI ≥25 kg/m^2, and newborn sex (male) were significantly associated with LGA newborns. Maternal pre-pregnancy BMI <18.5 kg/m^2 was independently significantly associated with both SGA and LGA newborns. Additionally, newborn sex (male) was also independently associated with SGA newborns, and it was an independent protective factor for SGA newborns.

Discussion

Fetal growth and development are known to be impacted by multiple factors. In this study, we mainly investigated the effect of maternal metabolic conditions on SGA and LGA newborns, which mainly included glucose and lipids metabolism. In our study, the ratio of SGA and LGA was 2.9% and 19.3%, respectively. One recent study showed that the total prevalence of macrosomia (birth weight ≥4000g) was 7.3% (range, 4.1–13.4%) in several provinces of China [25]. Our study was conducted in Zhejiang province of China, which is a more economically developed province; hence, the low prevalence of SGA and high prevalence of LGA may be due to more rapid economic growth, improved living conditions, and changed lifestyle. In addition, the ratio of PIH in the study population was low, which is possibly due to the enhanced prevention of PIH and changed lifestyle in Zhejiang province. This study shows that LGA newborns had significantly higher cord

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Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) of cord blood markers and maternal characteristics between SGA and AGA newborns, LGA and AGA newborns, respectively.

	SGA				LGA			
	B	Sig.	95.0% C.I.for EXP(B)		B	Sig.	95.0% C.I.for EXP(B)	
Maternal age	0.191	0.774	1.21	(0.33–4.432)	0.461	0.042*	1.586	(1.017–2.474)
Pre-pregnancy BMI (18.5–24.9)								
<18.5	1.185	0.000**	3.271	(2.06–5.192)	–0.265	0.031*	0.767	(0.603–0.976)
≥25	–1.072	0.298	0.342	(0.045–2.58)	0.425	0.035*	1.53	(1.029–2.274)
Newborn sex	–1.02	0.000**	0.361	(0.22–0.592)	0.682	0.000**	1.977	(1.607–2.432)
C-Peptide (Q1~Q3: 0.23~0.43)								
<Q1 (0.23)	–0.005	0.988	0.995	(0.536–1.849)	–0.242	0.139	0.785	(0.569–1.082)
≥Q3 (0.43)	–0.84	0.068	0.432	(0.175–1.065)	0.067	0.641	1.07	(0.806–1.419)
Insulin (Q1~Q3: 2.45~7.63)								
<Q1 (2.45)	0.336	0.298	1.399	(0.743–2.634)	–0.169	0.312	0.845	(0.609–1.172)
≥Q3 (7.63)	0.207	0.638	1.23	(0.519–2.916)	0.487	0.001**	1.628	(1.221–2.169)
HbA_{1c} (Q1~Q3: 2.6~3.1)								
<Q1 (2.6)	0.374	0.229	1.453	(0.79–2.673)	0.029	0.837	1.03	(0.78–1.358)
≥Q3 (3.1)	–0.329	0.238	0.719	(0.416–1.243)	0.052	0.641	1.054	(0.846–1.312)
HDL-C (Q1~Q3: 0.66~0.97)								
<Q1 (0.66)	0.351	0.33	1.421	(0.701–2.881)	–0.079	0.6	0.924	(0.689–1.24)
≥Q3 (0.97)	0.43	0.259	1.537	(0.728–3.242)	0.088	0.571	1.092	(0.806–1.478)
LDL-C (Q1~Q3: 0.55~0.83)								
<Q1 (0.55)	0.086	0.8	1.09	(0.562–2.112)	–0.047	0.748	0.954	(0.715–1.272)
≥Q3 (0.83)	–0.32	0.399	0.726	(0.345–1.528)	0.218	0.15	1.243	(0.924–1.673)
TC (Q1~Q3: 1.4~1.91)								
<Q1 (1.4)	0.559	0.19	1.749	(0.758–4.034)	0.083	0.637	1.086	(0.771–1.531)
≥Q3 (1.91)	–0.208	0.655	0.812	(0.326–2.024)	–0.138	0.469	0.871	(0.6–1.265)
TG (Q1~Q3: 0.22~0.37)								
<Q1 (0.22)	–0.673	0.108	0.51	(0.225–1.159)	0.029	0.814	1.029	(0.81–1.307)
≥Q3 (0.37)	1.204	0.000**	3.335	(1.982–5.611)	–0.025	0.847	0.975	(0.753–1.263)

Adjusted for maternal age, parity, pre-pregnancy BMI, education, annual household income, PIH, mode of delivery and newborn sex. References of C-peptide, insulin, HbA_{1c} and lipids levels were Q1~Q3. The references of maternal age, parity and pre-pregnancy BMI were 20-35 years, primipara and 18.5–24.9kg/m^2, respectively. PIH, mode of delivery and gender's references were non-PIH, vaginal delivery and female respectively. * P<0.05; ** P<0.01.

serum C-peptide and insulin levels than SGA and AGA newborns, which is consistent with previous studies revealing that C-peptide levels in macrosomia were significantly higher than in AGA infants and the LGA group had significantly higher cord serum insulin levels than the AGA and SGA groups [11,26–28]. Insulin can promote fetal anabolism and insulin level and is positively correlated with neonatal birth weight [11,15]. In the current study, after adjustment for confounding variables, insulin level ≥7.63 mmol/L was an independent risk factor for LGA newborns, and high insulin level could lead to

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LGA newborns. In this study, we also found that TG level was significantly higher in the SGA group than in the AGA and LGA groups, which is supported by other studies [12,29]. Our results show that cord serum TG level ≥0.37 mmol/L was independently associated with SGA newborns. It is possible that low birth weight could cause abnormity of lipids metabolism [30], and may increase the risk of cardiovascular diseases in later life. Hence, high cord serum TG level can be regarded as a predictor of SGA newborns and is a risk factor for atherosclerosis in later life.

However, results of previous studies investigating differences in cord serum TC, HDL-C, and LDL-C levels among the 3 groups are conflicting. One study showed that cord serum HDL-C and LDL-C levels in the LGA group were significantly lower than in the AGA group [14], but other studies showed that SGA newborns had significantly lower cord blood TC, HDL-C, and LDL-C levels than in AGA and LGA newborns [16,30]. Still other studies found that cord blood TC, HDL-C, and LDL-C levels were not significantly different between AGA and LGA newborns [12,15], which is in agreement with our results. The controversial differences in TC, HDL-C, and LDL-C levels might be because the grouping of previous studies was distinct from ours, and we did not distinguish between IUGR and SGA. Additionally, cord serum lipids might be affected by maternal nutrition and lifestyle [31], which were not evaluated in this study.

In general, fetuses in vaginal delivery are prone to undergo more stress than in cesarean section, and cord serum lipids levels can be influenced by the mode of delivery [32]. Our finding showed that there were higher cord serum TC, HDL-C, LDL-C, and TG levels in the vaginal delivery group than in the cesarean section group. It has been reported that compared with cesarean section, cord blood lipids levels were significantly higher in vaginal delivery [32], and recently there has been more evidence that vaginal delivery newborns might suffer more oxidative stress than cesarean section newborns [33,34]. However, another study showed that neonates were exposed to higher oxidative stress during cesarean section delivery than vaginal delivery [35], which conflicts with our results, but the population in their study is small.

Maternal age and pre-pregnancy BMI may also impact fetal growth and development [36,37]. Through the study, we also found LGA group had higher pre-pregnancy BMI than AGA and SGA groups, which is consistent with another study [38]. Pregnant women in LGA group was also significantly older than that in the other two groups, and this finding is supported by previous studies [39,40]. In our study we also found that advanced maternal age (≥35 years) was an independent risk for LGA newborns, and it has been reported that older pregnant women were also associated with an increased risk of their offspring having type 1 diabetes mellitus [41]. However, another study suggested that advanced maternal age (≥40 years) was associated with an increased risk of SGA and low birth weight newborns [37], and it has been reported that the reason might be the insufficient oxygen exchange within the placenta due to placental insufficiency induced by high incidence of hypertension in the older mothers [42]. Therefore, it is possible that older pregnant women are associated with both SGA and LGA newborns. In our study, maternal pre-pregnancy underweight (BMI <18.5 kg/m^2) was independently related to SGA newborns, and it was an independent risk factor for SGA newborns, which is in agreement with other studies [43,44]. We found maternal pre-pregnancy underweight was also an independently protective factor for LGA newborns. Furthermore, we also found pre-pregnancy BMI ≥25 kg/m^2 was an independent risk factor for LGA newborns [44]. Maternal obesity is associated with the obesity of their offspring and can cause their children to develop obesity [45]. Parity may also influence neonatal birth weight, and previous studies demonstrated that multiparous women were significantly associated with LGA infants [46,47]. However, another study reported no significant association between parity and SGA or LGA groups [48]. Our study suggests that there is no significant difference in parity among the 3 groups. Interestingly, our findings also indicated that male fetuses were more likely to develop into LGA newborns than female fetuses, which was also supported by a recent study [25].

A strength of our study is that it is a prospective study based on a large population of newborns of non-diabetic mothers with comprehensive information, which is helpful and important for us to determine the independent association between cord blood C-peptide, insulin, HbA1c, lipids levels, and SGA and LGA newborns. Our study population is being followed up, which can provide more information about the mechanism of MS development. Moreover, there are few similar studies, especially in a Chinese population. However, our study has some limitations. Although we investigated many variables in this study, the factors that may affect SGA and LGA newborns can be varied and complicated, and we might not have included all the potential factors (e.g., weight gain during pregnancy) which may have impacted birth weight [49,50]. On the other hand, we did not distinguish between IUGR and SGA. Therefore, further research should be conducted to explore these possibilities.

Conclusions

Our results suggest that high cord serum insulin and TG levels are independently significantly associated with SGA and LGA newborns, respectively. Maternal pre-pregnancy BMI <18.5 kg/m^2 and BMI ≥25 kg/m^2 play a critical role in fetal growth and development. These factors can independently

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affect the occurrence of SGA and LGA newborns. Based on our findings, women should prepare themselves for gestation and pay more attention to nutritional intake. These precautions are necessary to reduce the occurrence of SGA and LGA newborns, and consequently decrease the incidence of adulthood metabolic syndrome and improve the population's quality of life. Ultimately, we can achieve the goal of relieving the national burden caused by this problem.

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Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

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