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ORIGINAL RESEARCH

Association Between Maternal Glucose/Lipid Metabolism Parameters and Abnormal Newborn Birth Weight in Gestational Diabetes Complicated by Preeclampsia: A Retrospective Analysis of 248 Cases

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ABSTRACT

Introduction: Women with gestational diabetes mellitus (GDM) with co-existent preeclampsia (GCP) are at increased risk of giving birth to a baby with an abnormal birth weight. We have analyzed the risk factors for abnormal newborn birth weight (NBW) in women with co-presence of GDM and GCP, focusing on maternal glucose/lipid metabolism, with the aim to optimize the clinical intervention strategy.

Methods: The clinical data of 248 pregnant women with GCP and their infants were retrospectively analyzed through a comprehensive review of the electronic medical records of Women and Children's Hospital, Xiamen University (Xiamen, China). These women had received prenatal care and had their baby delivered in the hospital between January 2016 and November 2018. Major characteristics assessed were large for gestational age (LGA), small for gestational age (SGA), severe preeclampsia (S-PE), and maternal plasma glucose/lipid profile in late pregnancy. Secondary characteristics were maternal age, height, body mass index (BMI), gestational weight gain (GWG), abortion history, education level, primipara or not, preterm or not, and fetal gender. Regression analysis was used to analyze the association between maternal glucose/lipid metabolism parameters and LGA or SGA.

Results: There was no difference in the ratio of advanced maternal age, primipara, abortion history, preterm delivery, and newborn sex between the control group and the LGA or SGA group. Logistic regression analysis, with such factors as maternal stature, BMI, among others, was applied. Multivariate analysis of SGA infants revealed the following associations: S-PE (odds ratio [OR] 3.226, 95% confidence interval [CI] 1.385–7.515; adjusted OR [AOR] 3.675, 95% CI 1.467–9.207; $p < 0.05$); high levels of glycated hemoglobin (HbA1c > 6.5%) (OR 0.436, 95% CI 0.187–1.017; AOR 0.459, 95% CI 0.179–1.173; $p > 0.05$); low levels of high-density lipoprotein cholesterol (HDL-C < 1.0 mmol/L) (OR 0.625, 95% CI 0.287–1.361; AOR 0.637, 95% CI 0.267–1.520; $p > 0.05$). Multivariate analysis of LGA revealed the following associations: S-PE (OR 30.885, 95% CI 0.398–2.013; AOR 0.974, 95% CI 0.400–2.371; $p > 0.05$); high levels of HbA1c (OR 4.542, 95% CI 0.187–11.824; AOR 3.997, 95% CI 1.452–10.998; $p < 0.05$); low

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levels of HDL (OR 3.393, 95% CI 1.362–8.453; AOR 2.900, 95% CI 1.100–7.647; $p < 0.05$).
Conclusions: The results of our analysis revealed that severity of preeclampsia was associated with SGA. The high HbA1c and low HDL-C values found in our analysis were independent risk factors for LGA in women with GCP, while other lipoproteins were not associated with abnormal NBW. These findings suggest that there are differences in the effects of various maternal lipid parameters on NBW.

Keywords: Gestational diabetes mellitus; Glucose/lipid metabolism; HbA1c; HDL-C; Preeclampsia

Key Summary Points

Why carry out this study?

It is essential to identify the risk factors for abnormal newborn birth weight (NBW) to improve the clinical management of gestational diabetes mellitus complicated by preeclampsia (GCP). Previous studies on GCP have tended to be undermotivated.

The purpose of this study was to investigate the association between maternal glycolipid metabolism parameters and the abnormal NBW in women with GCP.

What was learned from this study?

The severity of preeclampsia was found to be associated with small for gestational age newborns. High glycated hemoglobin A1c and low high-density lipoprotein cholesterol values were independent risk factors for large for gestational age infants in women with GCP, while other lipoproteins were not associated with abnormal NBW.

The study highlights the importance of carrying out timely risk monitoring and identifying the early warning signs, with the aim to improve infant health.

INTRODUCTION

Newborn birth weight (NBW), which refers to the weight of a newborn measured within 1 h after birth, is a good indicator of intrauterine fetal development and maternal nutrition. There are two types of NBW abnormalities according to the gestational age and sex-specific INTERGROWTH-21st curves: small for gestational age (SGA; birth weight < 10th percentile) and large for gestational age (LGA; birth weight > 90th percentile) [1]. SGA is associated with increased newborn morbidity and mortality and an increased risk of developmental dysfunction and metabolic disease in later life [2]. LGA may lead to fetal brachial plexus injury, intracranial hemorrhage, and shoulder dystocia during delivery. It is also associated with long-term complications, such as various metabolic diseases and cardiovascular diseases [3].

NBW is closely related to the health status of the mother during pregnancy. It has been reported that women with gestational diabetes mellitus (GDM) or preeclampsia have an increased risk of an abnormal NBW. GDM is defined as hyperglycemia that is recognized for the first time during pregnancy, excluding cases of overt diabetes prior to gestation. The main manifestation of preeclampsia is apparent hypertension after 20 weeks of pregnancy, which may be accompanied by proteinuria, edema, and other symptoms [4]. In recent years, the incidence of GDM has increased gradually, reaching 17.5% in China [5]. Sun et al. reported that the incidence of preeclampsia in GDM patients was 8.7% [6]. Some researchers have also reported that patients with preeclampsia also have an increased the risk for developing GDM [7]. Women with co-presence of these two diseases present a challenge for good clinical managment and have a significantly increased risk of an adverse pregnancy outcome.

The poor intrauterine environment caused by GDM and preeclampsia induces changes in fetal DNA methylation patterns related to fat synthesis, leading to abnormal NBW [8]. Dyslipidemia is an important risk factor affecting the growth and development of the fetus and may also be the critical pathogenesis of GDM

with co-existent preeclampsia (GCP) [9, 10]. Disturbances in lipid metabolism are a common cause of GDM and preeclampsia. Lipid levels are the result of the dynamic balance of synthesis and decomposition and are closely related to insulin sensitivity and insulin resistance [11]. Insulin resistance in pregnant women with GDM will lead to dyslipidemia, which damages the vascular function and further develops into preeclampsia.

To date, there has been a relative lack of research on the risk factors of abnormal NBW in women with GCP. In this study, we focused on the association between maternal glucose/lipid metabolism parameters and LGA or SGA.

METHODS

Study Population and Eligibility Criteria

All data used is this study were retrieved the electronic medical records (EMR) system of Women and Children's Hospital, Xiamen University (Xiamen, China), which is a tertiary care public hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards ethics committee of Women and Children's Hospital, Xiamen University (ky-2019-006), and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants.

This study is a retrospective observational study. All personal identification information was replaced by a digital number to protect the privacy of the participants. All pregnant women who had received prenatal care and delivered their baby in Women and Children's Hospital, Xiamen University, between January 2016 and November 2018 were eligible to participate.

Inclusion and Exclusion Criteria

The inclusion criteria were: pregnant women with GCP who gave birth to a singleton without chromosomal abnormality and developmental malformation; both parents with no congenital defects or genetic diseases.

GDM diagnosis was made when glucose values exceeded the standard cutoff levels (fasting, 5.1 mmol/L; 1 h, 10.0 mmol/L; and 2 h, 8.50 mmol/L) in a 75 g oral glucose tolerance test performed between 24 and 28 weeks of pregnancy [12]. Preeclampsia was diagnosed on the basis of systolic blood pressure (SBP) of $\geq$ 140 mmHg) and/or diastolic blood pressure (DBP) of $\geq$ 90 mmHg after 20 weeks of gestation, proteinuria $\geq$ 0.3 g/24 h, or positive random urinary protein test, as well as upper abdominal discomfort, headache, and other known symptoms [13].

Exclusion criteria were: incomplete clinical data; drug abuse or alcohol abuse by the pregnant woman and her spouse; a smoking habit of the pregnant women; presence of hemoglobinopathy, tumors, mental disease, severe anemia, or massive blood loss during pregnancy.

Data Collection and Maternal and Newborn Characteristics

The researchers collected information on pregnant women and their newborns from the hospital's EMR system. The major characteristics assessed were LGA, SGA, severe preeclampsia (S-PE), and the maternal plasma glucose/lipid profile in late pregnancy. The secondary characteristics assessed were maternal age, height, body mass index (BMI), gestational weight gain (GWG), abortion history, high education level (college diploma or above) or not, primipara or not, preterm or not, and fetal gender.

Abnormal NBW The newborns were classified as LGA when the NBW was > 90th percentile and as SGA when it was < 10th percentile, according to the gestational age and sex-specific INTERGROWTH-21st curves for China [14]. The remaining babies had a normal birth weight and were considered to be the control group.

Blood glucose control targets The blood glucose targets were a fasting plasma glucose $\leq$ 5.3 mmol/L and 1-h postprandial glucose

< 7.8 mmol/L, as well as glycated hemoglobin (HbA1c) ≤ 6.5%, according to American Diabetes Association (ADA) recommendation in 2020 [15]. High plasma glucose or high HbA1c refers to failure to achieve the above goals.

Hyperlipidemia Hyperlipidemia was defined as triglyceride (TG) ≥ 2.3 mmol/L, total cholesterol (TC) ≥ 6.2 mmol/L, high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L, and low-density lipoprotein cholesterol (LDL-C) ≥ 4.1 mmol/L, according to the standards in China [16].

Preeclampsia severity S-PE is diagnosed by any of the following adverse conditions in patients with preeclampsia: continuous high blood pressure (SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg); proteinuria ≥ 2.0 g/24 h or random proteinuria (++); serum creatinine ≥ 106 μm/L; platelet < 100,000/mL; elevated blood LDH; elevated blood aspartate transaminase and alanine transaminase levels; persistent headache or other brain or visual impairments; and persistent upper abdominal pain [13].

Height and age classification Short figure was defined as height in the lowest quartile of adult women in China (< 155 cm); high figure was defined as height in the highest quartile of adult women in China (> 161 cm) [17]. Advanced age referred to ≥ 35 years according to the the standard of pregnant women's risk assessment in China [18].

BMI and GWG classification Prepregnancy BMI was calculated as weight (kg) divided by height (m) squared. BMI categories were established according to the Working Group of Obesity in China (thin < 18.5; normal 18.5–23.9; overweight/obese > 23.9 [19]. The GWG is divided into three levels: insufficient, adequate, and excessive, according to the US Institute of Medicine (IOM) Guidelines 2009 [20]. In this study, we calculated four indicators: early insufficient or excessive GWG (before 28 weeks of gestation), and late insufficient or excessive GWG (after 28 weeks of gestation).

Statistical Methods

The SAS statistical package version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. Categorical variables were described by frequency. Comparisons among multiple group categorical variables were based on the Chi-square test for the $R \times C$ table. The Chi-square test for 2×2 table or the Fisher exact test was used for comparisons between categorical variables of two groups. The p value was adjusted for multiple treatments. Logistic regression analysis was used to analyze the risk factors of SGA or LGA. The odds ratio (OR) and 95% confidence intervals (CIs) for the association between glucose/lipid metabolism parameters of patients with GCP and abnormal NBW were determined. Factors for adjustment were maternal stature, prepregnancy BMI, GWG, among others. The significance level (alpha value) was set at $p < 0.05$.

RESULTS

Maternal and Newborn Clinical Characteristics in 248 Cases of GCP

There was no difference in the ratio of advanced age, primipara, abortion history, and preterm delivery of the pregant women and the composition ratio of newborn sex (male fetus) between the control group and the LGA group or SGA group. The rate of short stature, prepregnancy thin, and early insufficient GWG was higher in the pregnant women in the SGA group than in those in the control group (30.3 vs. 13.8%, $p < 0.05$; 24.2 vs. 7.9%, $p < 0.05$; and 39.4 vs. 21.2%, $p < 0.05$, respectively). The proportion of maternal prepregnancy obesity was lower in the SGA group than in the control group (18.2 vs. 45.5%, $p < 0.05$). The rate of high stature and early excessive GWG was higher in the pregnant women in the LGA group than in those in the control group (46.2 vs. 25.9%, $p < 0.05$ and 55.0 vs. 80.8%, $p < 0.05$, respectively). There was no difference in the constituent ratio of late excessive GWG or late insufficient GWG between the control

Table 1 Maternal and newborn clinical characteristics in the 248 cases of gestational diabetes mellitus and co-existent preeclampsia

Character	SGA (n = 33)	LGA (n = 26)	Control (n = 189)	p
Advanced rate	30.3% (10)	19.2% (5)	35.4% (67	0.241
Primipara rate	72.7% (24)	65.4% (17)	59.8% (113)	0.344
Abortion history rate)	42.4% (14)	57.7% (15)	48.1% (91)	0.503
High education rate	75.8% (25)	61.5% (16)	68.3% (129)	0.498
Preterm rate	21.2% (7)	15.4% (4)	18.0% (34)	0.659
Male fetal rate	48.5% (16)	57.7% (15)	57.7% (109)	0.612
Short figure rate	30.3% (10)*	7.7% (2)	13.8% (26)	0.027
High figure rate	18.2% (6)	46.2% (12)*	25.9% (49)	0.004
Prepregnancy obesity rate	18.2% (6)*	50.0% (15)	45.5% (86)	0.010
Prepregnancy thin rate	24.2 (8)*	0.0% (0)	7.9% (15)	0.003
Early excessive GWG rate	42.4% (14)	80.8% (21)*	5.0% (104)	0.011
Early insufficient GWG rate	39.4% (13)*	3.8% (1) *	21.2% (40)	0.004
Late excessive GWG rate	45.5% (15)	69.2 (18)	56.6% (10)	0.187
Late insufficient GWG rate	30.3% (10)	7.7% (2)	25.9% (49)	0.092

Values in table are given as a percentage, with the number of newborns in that category given in parenthesis
Control Normal newborn birth weight (NBW),*GWG* gestational weight gain, *LGA* large for gestational age (birth weight > 90th percentile), *SGA* small for gestational age (< 10th percentile)
*Statistically significant at $p < 0.05$ compared with the control group

group and the LGA group or SGA group (Table 1).

Maternal Glucose/Lipid Metabolism and Severity of Preeclampsia in 248 Cases of GCP

Maternal glucose/lipid metabolism in the SGA group was associated with higher rates of S-PE compared to the control group (75.8 vs. 49.2%, $p < 0.05$), while maternal glucose/lipid metabolism in the LGA group was associated with higher rates of high HbA1c (76.9 vs. 42.3%, $p < 0.05$) and low HDL-C (73.1 vs. 44.4%, $p < 0.05$) compared to the control. There was no difference in the constituent ratios of high blood glucose, high TG, high TC, and high HDL-C between the control group and the LGA group or SGA group (Table 2).

We performed multivariate regression analysis of the association between the maternal glucose/lipid metabolism parameters and abnormal NBW in mothers with GCP (Table 3). Multivariate analysis of SGA revealed the following associations: S-PE (OR 3.226, 95% CI 1.385–7.515; adjusted OR [AOR] 3.675, 95% CI 1.467–9.207; $p < 0.05$); high HbA1c (> 6.5%) (OR 0.436, 95% CI 0.187–1.017; AOR 0.459, 95% CI 0.179–1.173; $p > 0.05$); low HDL-C (< 1.0 mmol/L) (OR 0.625, 95% CI 0.287–1.361; AOR 0.637, 95% CI 0.267–1.520; $p > 0.05$). Multivariate analysis of LGA revealed the following associations: S-PE (OR 30.885, 95% CI 0.398–2.013; AOR 0.974, 95% CI 0.400–2.371; $p > 0.05$); high HbA1c (OR 4.542, 95% CI 0.187–11.824; AOR 3.997, 95% CI 1.452–10.998; $p < 0.05$); low HDL (OR 3.393, 95% CI 1.362–8.453; AOR 2.900, 95% CI 1.100–7.647; $p < 0.05$) (Table 3).

Table 2 Maternal glucose/lipid metabolism and the severity of preeclampsia in 248 cases of gestational diabetes mellitus and co-existent preeclampsia

Risk factor	SGA (n = 33)	LGA (n = 26)	Control (n = 189)	p
High HbA1c rate	24.2% (8)	76.9% (20)*	42.3% (80)	0.000
High plasma glucose rate	15.2% (5)	23.1% (6)	31.2% (59)	0.138
S-PE	75.8% (25)*	46.2% (12)	49.2% (93)	0.015
High triglycerides rate	15.2% (5)	42.3% (11)	25.4% (48)	0.059
High total cholesterol rate	21.2% (7)	15.4% (4)	18.0% (34)	0.841
Low HDL rate	33.3% (11)	73.1% (19)*	44.4% (84)	0.007
High LDL rate	18.2% (6)	3.8% (1)	13.8% (26)	0.255

Values in table are given as a percentage, with the number of newborns in that category given in parenthesis
HbA1c Glycated hemoglobin, *HDL* high-density cholesterol, *LDL* low-density cholesterol, *S-PE*
*Statistically significant at $p < 0.05$ compared with the control group

Table 3 Multivariate regression analysis of the association between the maternal glucose/lipid metabolism parameters and the abnormal NBW in GCP

Characteristics[a]	Crude OR	95% CI	Adjusted OR[b]	95% CI
S-PE for SGA	3.226	1.385–7.515	3.675	1.467–9.207*
S-PE for LGA	0.885	0.398–2.013	0.974	0.400–2.371
High HbA1c for SGA	0.436	0.187–1.017	0.459	0.179–1.173
High HbA1c for LGA	4.542	0.187–11.824	3.997	1.452–10.998*
Low HDL for SGA	0.625	0.287–1.361	0.637	0.267–1.520
Low HDL for LGA	3.393	1.362–8.453	2.900	1.100–7.647*

CI Confidence interval, *OR* odds ratio
*Statistically significant compared with normal NBW group, $p < 0.05$
[a] The reference value for all comparisons was that of the normal NBW
[b] The factors for adjustment were rate of short or high figure, prepregnancy obesity or thin, and early insufficient or excessive GWG of mothers

The factors for adjustment: maternal stature, prepregnancy BMI, GWG and others.

DISCUSSION

The exact pathogenesis of GCP is not clear, although compared with pregnant women without GCP, the dysfunction of glucose/lipid metabolism in GCP patients is more severe.

Continuous maternal hyperglycemia results in relatively high levels of glucose entering the fetal circulation through the placenta; in contrast, the insulin produced by the mother cannot pass through the placenta. Hyperglycemia can stimulate the proliferation of fetal islet β cells and thereby the secretion of excessive insulin, increase the synthesis of protein and fat, and eventually lead to LGA [21]. The association of hyperglycemia and SGA needs to be confirmed in large-scale clinical studies. HbA1c is considered to be the most reliable biomarker for monitoring long-term blood glucose control, and its value can reflect the average blood

glucose level in the past 2–3 months [22]. However, the HbA1c value can be affected by many factors, especially hemoglobin synthesis and iron loading. In the third trimester of pregnancy, these factors will change dramatically. Therefore, many researchers question its value as a suitable pregnancy biomarker [23]. However, it has also been reported that the high HbA1c of GDM pregnant women in late pregnancy is related to macrosomia [24]. The clinical analysis of GCP in this study shows that high HbA1c in late pregnancy is an independent risk factor for LGA, while high blood glucose in the same period is not associated with LGA. The reason for this may be that HbA1c reflects the average blood sugar over a relatively long period in the past, while blood glucose reflects the immediate blood glucose levels and is more likely to fluctuate.

The relationship between maternal lipid metabolism and NBW is very complex and controversial. Some researchers have reported that only in obese pregnant women is the HDL-C value in late pregnancy negatively correlated with NBW [25]. Mossayebi et al. reported that TG is a predictor of NBW in nondiabetic and nonobese pregnant women [26]. It has also been reported that the TC and LDL-C values in pregnant women are related to neonatal weight [27]. In our study, the low HDL-C value of pregnant women with GCP was associated with LGA, while other forms of dislipidemia were not related to abnormal NBW. Although the above findings suggest that the metabolic characteristics of lipids in pregnant women may affect fetal birth weight, the mechanism has not yet been elucidated. TG cannot be transported through the placenta, but it can be hydrolyzed to free fatty acids (FFA) by lipoprotein esterase in the placenta. A high level of FFA can result to high levels of fat and glucose being deposited in the fetus due to the passage of FFA through the placenta; this may ultimately lead to LGA infants [26]. The cholesterol of mothers can be transported to the fetus through the placenta and further regulate the synthesis of fetal cholesterol, thereby affecting the size and weight of the fetus [27].

Preeclampsia is a hypertension disease of pregnancy. Placental perfusion decreases in S-PE patients, resulting in acute atherosclerosis of placental blood vessels and decreased placental function, thereby hindering the transport of nutrients and oxygen and ultimately limiting fetal growth [28]. In our study, we found that SGA was positively correlated with the severity of preeclampsia in GCP.

There are a number of limitations to this study. The most important of these is that many risk factors affect NBW, and we included only a limited number of these factors in the study. Factors affecting the pregnant woman include presence of anemia or iron load, lifestyle, diet structure, and psychological state, and these may have an impact on the NBW. Regarding the father, factors such as height, weight, and other potential genetic factors may also be associated with birth weight. As this study is a retrospective analysis, the clinical information analyzed was based on existing data. Therefore, the analysis of many of the factors mentioned above was not included in this study due to the lack of records. Our aim is to carry out a multicenter prospective study in the future that will have an expanded sample size. This will enable us to conduct in-depth research by designing complete case report on patients.

There are some strengths to our study as well as future implications. Although there have been various studies on the factors affecting NBW, observations on pregnant women with GCP are infrequent. Once GCP has developed, the risk of adverse perinatal outcome is much higher than that in other pregnant women [29, 30]. It is necessary to carry out an in-depth exploration of this patient population. Some researchers believe that the role of HbA1c as a biomarker for monitoring pregnancy needs to be carefully evaluated. We found that HbA1c was an independent LGA risk factor in pregnant women with GCP. The relationship between maternal lipid profile and NBW has been the focus of many studies. We reporte here, for the first time, that low HDL-C value in GCP mothers in late pregnancy was an independent predictor of LGA; in contrast, values for other lipoproteins were not associated with abnormal birth weight.

CONCLUSIONS

The critical indicators of GCP affecting the NBW are maternal HbA1c and HDL-C in the late trimester and the severity of preeclampsia. We also found that the height of the mother, prepregnancy BMI, and early GWG are related to the NBW. This study helps optimize the clinical intervention strategy for GCP.

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Authorship Contributions. XZ performed the design of this study. YX collected data and wrote/edited the manuscript.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards ethics committee of Women and Children's Hospital, Xiamen University (ky-2019-006), and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants.

Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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