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Authors: Dandan Xia, Huiyan Wang, Yuqi Yang, Wenli Wang

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Effects of gestational diabetes mellitus with different birth weight on genetic metabolism of newborns. A retrospective cohort study

Dandan Xia[1], Huiyan Wang[1], Yuqi Yang[2], Wenli Wang[1]

[1]Department of Obstetrics and Gynecology, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Changzhou, China
[2]Department of Medical Genetics, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Changzhou, China

Corresponding author:
Wenli Wang
Department of Obstetrics and Gynecology, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Ding Xiang 16, Zhong Lou District, 213000 Changzhou, China
e-mail: wangwenli750@163.com

ABSTRACT

Objectives: To investigate the effects of gestational diabetes mellitus (GDM) with different birth weights on neonatal genetic metabolism.

Material and methods: 1252 patients with GDM diagnosed at Changzhou Maternal and Child Health Care Hospital from 2017 to 2021 were categorized into three groups: fetal growth restriction (G1), normal birth weight (G2), and macrosomia (G3). The levels of amino acids, free carnitine (CO) and acylcarnitine in neonates were detected using tandem mass spectrometry.

Results: There were no differences in age, height, predelivery weight or gravida across groups. G3 had the highest parity and fasting blood glucose levels ($p < 0.0001$). G1 exhibited the highest rates of cesarean section, neonatal asphyxia, and insulin utilization (p

< 0.0001). Neonatal genetic metabolism analysis revealed that in G1 citrulline levels were the highest, with significantly elevated levels of leucineornithine and valine ($p < 0.001$). CO was also the highest ($p < 0.001$). The levels of isovalerylcarnitine, octanoylcarnitine and 18-carbodienoylcarnitine increased, while malonylcarnitine/3-hydroxy-butyrylcarnitine, hexadecanoylcarnitine, hexadecenoylcarnitine, 3-hydroxy-hexadecenoylcarnitine and 3-hydroxy-hexadecanoylcarnitine decreased ($p < 0.05$). In G2, methionine levels decreased ($p < 0.001$), whereas decenoylcarnitine, dodecanoylcarnitine, dodecenoylcarnitine and myristoylcarnitine levels increased ($p < 0.001$). In G3, proline decreased significantly ($p < 0.001$), and CO was the lowest ($p < 0.001$). Propionylcarnitine and octenoylcarnitine levels increased, whereas butyrylcarnitine decreased ($p < 0.05$).

Conclusions: Gestational diabetes mellitus with different birth weights influences neonatal genetic metabolism in distinct ways. Therefore, neonatal screening for inherited metabolic disorders provides insights into the metabolic levels of offspring of patients with GDM in early life.

Keywords: gestational diabetes mellitus; macrosomia; fetal growth restriction; neonatal disease screening

INTRODUCTION

Gestational diabetes mellitus (GDM) refers to glucose intolerance first discovered or occurring during pregnancy [1]. Nutrients in the fetus depend on the mother [2] and newborns with different birth weights may be affected by GDM to varying degrees. Understanding the metabolic characteristics of infants born to mothers with GDM can aid in correcting metabolic disorders, and in providing appropriate nutritional support, which is crucial for the prognosis of pregnancy outcomes and the diagnosis of genetic metabolic disorders associated with GDM.

Neonatal screening for genetic metabolic disorders is an effective method for the early detection of certain congenital or genetic metabolic diseases [3]. Tandem mass spectrometry, a major advancement in the field of neonatal screening, allows for the measurements of amino acid contents, free carnitine, and acylcarnitine in target samples to

understand the basic metabolism of newborns with different pregnancy outcomes, and to guide the optimal nutritional management of GDM during pregnancy.

Regardless of the birth weight of the newborn, screening for genetic metabolic diseases is necessary when the mother has GDM. There are few comprehensive studies on whether the final outcome of GDM macrosomia or fetal growth restriction (FGR) is, and limited studies have explored the influence of different fetal birth weights on perinatal genetic metabolism. Therefore, this study retrospectively analyzed the genetic screening levels of newborns of different weights delivered by mothers with GDM to explore the effects of GDM on the genetic metabolism of newborns with different delivery outcomes.

MATERIALS AND METHODS

Research objects and groups

This population-based retrospective cohort study included all patients with GDM diagnosed at Changzhou Maternal and Child Health Care Hospital between January 2017 and December 2021, according to the diagnostic criteria for GDM [4]. Patients were grouped according to fetal birth weight: GDM combined with FGR (G1 group), GDM with normal birth weight (G2 group), and GDM with macrosomia (G3 group). FGR was defined as a birth weight of less than 2500 g after 37 weeks of gestation, or two standard deviations below the average weight for the gestational age, or below the 10^{th} percentile of normal weight for the gestational age. Macrosomia was defined as a birth weight of 4000 g or more. Patient selection and exclusion criteria are shown in Figure 1. This study was approved by the Ethics Committee of Nanjing Medical University [IRB No. (2023) 367] on March 2, 2023. The study was conducted according to the principles of the Declaration of Helsinki and its amendments.

Sample collection and testing

In accordance with the Technical Guidelines for Neonatal Disease Screening, we collected four blood spots from the heel of the newborn 72 h after birth, following six full breastfeedings (filter paper used was by Schleicher & Schuell 903). For low-birth-weight infants, blood collection was delayed until the infant weighed 2500 g or 20 days after birth.

The blood spots were then air-dried naturally to a dark brown color. Next, they were sealed in plastic bags and sent to the neonatal disease screening center laboratory within the specified time. The samples were stored at 4℃ for further testing. For screening and testing, we used Waters AcquityTM TQD tandem mass spectrometer, Waters 2777C automatic sampler, Waters 1525μ HPLC pump, non-derivatized multiple amino acids, carnitine, and succinyl acetone assay kit (neo base non-derivatized MSMS Kit, Perkin Elmer, USA).

Detection indicators

We detected the levels of 11 amino acids, including alanine (ALA), arginine (ARG), citrulline (CIT), glycine (GLY), leucine (LEU + ILE + PRO–OH), methionine (MET), ornithine (ORN), phenylalanine (PHE), proline (PRO), tyrosine (TYR), and valine (VAL). Additionally, 31 carnitines were measured, including free carnitine (CO), acetylcarnitine (C2), propionylcarnitine (C3), 3-hydroxy-butyrylcarnitine (C3DC + C4OH), butyrylcarnitine (C4), crotonobetaine/3-hydroxyvalerylcarnitine (C4DC + C5OH), isovalerylcarnitine (C5), pentanoylcarnitine (C5:1), glutarylcarnitine/3-hydroxyhexanoylcarnitine (C5DC + C6OH), hexanoylcarnitine (C6), suberylcarnitine (C6DC), octanoylcarnitine (C8), octenoylcarnitine (C8:1), decanoylcarnitine (C10), decenoylcarnitine (C10:1), 10-decenoylcarnitine (C10:2), dodecanoylcarnitine (C12), dodecenoylcarnitine (C12:1), tetradecanoylcarnitine (C14), myristoylcarnitine (C14:1), 9,12-tetradecadienoylcarnitine (C14:2), 3-hydroxytetradecanoylcarnitine (C14OH), hexadecanoylcarnitine (C16), hexadecenoylcarnitine (C16:1), hexadecenoylcarnitine (C16:1OH), 3-hydroxy-hexadecanoylcarnitine (C16OH), octadecanoylcarnitine (C18), octadecenoylcarnitine (C18:1), 3-hydroxyoctadecenoylcarnitine (C18:1OH), 18-carbodienoylcarnitine (C18:2), and 3-hydroxyoctadecanoylcarnitine (C18OH).

Statistical methods

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 24.0. Quantitative data are expressed as mean ± standard deviation (SD), with inter-group comparisons conducted using one-way analysis of variance. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 67 cases (5.4%) were in the G1 group, 750 cases (59.9%) in the G2 group, and 435 cases (34.7%) in the G3 group. There was no difference in age, height, predelivery weight, or gravida among the groups ($p > 0.05$). Parity was highest in G3 ($p < 0.001$). The rates of cesarean section, neonatal asphyxia and insulin use were highest in G1, with greater differences compared to G2 ($p < 0.001$). In terms of glucose tolerance, both the G1 and G2 groups had abnormal blood glucose levels at 1 and 2 h after meals. All three indexes were abnormal in G3, with the fasting blood glucose levels being the highest ($p < 0.0001$) (Tab. 1).

As birth weight increased, CIT levels decreased. The levels of ARG and PHE increased in G1 and G3; however, G1 showed a more significant increase ($p < 0.001$). The levels of LEU + ILE + PRO–OH, ORN, and VAL were significantly elevated in G1, with a more significant difference compared to G2 ($p < 0.005$). G2 showed a significant decrease in MET levels ($p < 0.001$). The PRO levels in G3 were significantly reduced, with a more significant difference compared to G1 ($p < 0.001$) , as shown in Table 2.

Table 3 shows that G1 had the highest level of free CO, while G3 had the lowest level ($P < 0.001$).

Compared to G2, G1 and G3 showed a decrease in C10:1, C12, C12:1, and C14:1, with G1 exhibiting a more significant decrease ($p < 0.001$). G3 showed an increase in C3 and C8:1 level and a decrease in C4 levels ($p < 0.05$). There were differences in the levels of C3DC + C4OH, C5, C8, C16, C16:1, C16:1OH, C16OH, and C18:2 between G1 and the other two groups ($p < 0.05$), with increased levels of C5, C8, and C18:2, and decreased levels of C3DC + C4OH, C16, C16:1, C16:1OH, and C16OH (Tab. 4).

DISCUSSION

GDM is the most common endocrine disorder in pregnant women, and its prevalence continues to increase annually [5]. GDM considerably contributes to many adverse outcomes, including abortion, fetal malformation, preeclampsia, FGR, macrosomia,

neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome and may increase the risk of obesity, hypertension and type 2 diabetes in future generations.

Differences in gestational nutrition and blood glucose control in GDM can lead to varing pregnancy outcomes for newborns, primarily manifesting as different birth weights. The incidence of GDM with macrosomia is 25–42% [6]. The increased transport of placental glucose, amino acids, and fatty acids in patients with GDM stimulates the production of endogenous insulin and insulin-like growth factor-1 (IGF-1) in the fetus [7], increasing the long-term risk of metabolic diseases. The incidence of GDM with FGR is 21%. Poor glucose control is a major risk factor for FGR, which is closely related to abnormal changes in endocrine metabolism levels [8]. FGR also increases the risk of perinatal complications such as fetal distress, fetal malformations, and neonatal asphyxia and is correlated with the physical and intellectual development of children and adolescents at various stages. We found that the incidence of GDM combined with macrosomia within 5 years was 34.7%, while it was only 5.4% in FGR. This disparity may be related to standardized prenatal checkups, changes in nutritional structure, improvements in prenatal diagnostic technology for fetal medicine, and changes in maternal attitudes. The relatively small sample size in the FGR group is a potential limitation that may have affected the statistical power of the findings. Future studies involving larger and more diverse populations are required to validate these findings. The three indicators of glucose tolerance in the GDM combined with macrosomia group were all abnormal, with 2 h postprandial blood glucose showing the most significant abnormality. However, the FGR group demonstrated a higher use of insulin, which may indicate that poor blood glucose control in this group necessitates insulin treatment and is associated with increased complications. However, considering the small number of FGR cases, the results should be interpreted with caution, and gestational blood glucose control should also be considered. Furthermore, cesarean section and neonatal asphyxia rates were higher in the FGR group. This finding is consistent with previous studies, which have shown that GDM complicated by FGR increases the risk of neonatal complications. Therefore, strengthening gestational blood glucose management in GDM and monitoring fetal growth and development are

crucial for reducing adverse pregnancy outcomes.

GDM can lead to abnormal metabolism of sugar, fat and amino acids in pregnant women [9]. Nutrients such as sugar, fat, and amino acids in the fetus depend on the mother; however, whether GDM has an impact on the genetic metabolism level of the newborn is rarely reported. Neonatal screening, which includes screening for genetic metabolic diseases and congenital endocrine abnormalities [10], has a profound significance in improving population quality and reducing intellectual disabilities in children. Recently, tandem mass spectrometry has become one of the most significant advancements in neonatal screening.

In this study, the genetic metabolic profile of newborns was detected using tandem mass spectrometry. The GDM combined with FGR group showed the following characteristics: (1) the highest level of CIT and elevated levels of ARG, PHE, LEU + ILE + PRO-OH, ORN, and VAL, (2) the highest level of free CO, and (3) increased levels of C5, C8, and C18:2 and decreased levels of C3DC + C4OH, C16, C16:1, C16:1OH, and C16OH. The GDM combined with macrosomia group showed the following characteristics: (1) a significant decrease in PRO and a high level of CIT, (2) the lowest level of free CO, and (3) increased C3 and C8:1 levels, with a decrease in C4 levels. The GDM combined with normal weight group showed the following characteristics: (1) a significant decrease in MET levels, and (2) elevated levels of C10:1, C12, C12:1, and C14:1. These findings suggest that the GDM combined with FGR group demonstrated more pronounced metabolic abnormalities. Even with normal birth weight, changes in the metabolites were observed, which confirms that GDM may affect the metabolic environment of the fetus.

Previous studies have found that gestational age and weight are important factors affecting amino acid levels in premature infants and newborns. As gestational age and birth weight increase, the amino acid levels of premature infants tend to approach that of healthy full-term newborns [11]. In our study, the levels of four amino acids — CIT, LEU + ILE + PRO-OH, PHE, and TYR— significantly increased in the blood of premature infants, while levels of ALA, GLY, MET, and PRO significantly decreased. GDM can affect offspring

development through various mechanisms such as placental mediation and epigenetics [12], which is consistent with our findings that the FGR group, which had a small gestational age and low birth weight, , exhibited elevated levels of CIT, ARG, PHE, LEU + ILE + PRO-OH, ORN, and VAL. However, we observed a significant decrease in PRO levels in the macrosomia group. PRO has a regulatory effect on glucose in the liver and hypothalamic astrocytes [13], and is believed to protect against the occurrence of GDM. There was a negative correlation between serum proline levels in early pregnancy and glucose metabolism indicators in mid-pregnancy in pregnant women with GDM. PRO also improves the body's antioxidant function, inhibits oxidative stress, and protects and repairs pancreatic islets β cellular damage [14]. These findings suggest that early monitoring of PRO levels in the GDM with macrosomia group or using medication to regulate PRO levels has certain research value in controlling neonatal weight.

We also found that the FGR group had the highest CO level, while the macrosomia group had the lowest. This finding is consistent with that of previous studies showing that premature infants have higher levels of CO than normal infants, and the difference increases when combined with low body weight. According to gestational age statistics, plasma CO levels gradually decrease with increasing gestational age in premature infants [15]. The FGR group had a low birth weight and high preterm birth rate and had not yet completed the process of transferring free CO from the body to the tissue, resulting in a decrease in plasma CO levels. Thus, in addition to improving amino acid intake during pregnancy, CO may also need to be considered to improve neonatal organic acid metabolism in GDM cases with FGR.

Acylcarnitines are a class of ester substances that bind to amino acids or fatty acid metabolites. Studies have found that most short- and medium-chain acylcarnitine indicators in premature infants are higher than those in the normal infants, while the vast majority of long-chain acylcarnitine indicators are lower [16]. In our study, we observed multiple differences in acylcarnitine metabolism among the three groups. The FGR group showed more differences in medium- and long-chain acylcarnitine levels, while the normal-weight group and macrosomia groups showed differences in short-chain acylcarnitine levels.

Short-chain acylcarnitine plays a vital role in cellular energy metabolism, preventing oxidative stress, reducing oxidative damage, and increasing the production of nerve growth factors. Additionally, it promotes nerve regeneration and improves the recovery of normal blood flow and revascularization after ischemia. Conversely, long-chain acylcarnitines interfere with signal transduction pathways by destroying cell membranes and affecting the activity of membrane-related transporters, proteins involved in neuronal development, neurotransmission, and signal transduction for cell growth and differentiation [17]. Our study aligns with many literature reports both domestically and internationally; however, there are differences in some indicators, which may be attributed to differences in population, race, and region, as well as differences in analytical techniques and methodologies.

This study has some limitations that warrant further investigation. First, maternal age, pre-pregnancy BMI, weight gain during pregnancy, and other factors can also affect neonatal metabolism. Further analysis adjusting for these confounding factors will help to isolate the specific effects of GDM and birth weight on neonatal metabolism. Second, while this study provided descriptive data on the differences in metabolic profiles, it did not investigate the underlying biological mechanisms responsible for these differences, which may be a focus of future studies. Third, this study was conducted at a single center, and the results need to be validated in other populations and settings to improve the generalizability of the study.

CONCLUSIONS

Screening for genetic metabolic diseases in newborns should be emphasized in mothers with GDM. Additionally, nutritional interventions are essential in GDM pregnancies, including balanced nutrition and adjusting the intake of nutrients to improve the metabolic levels of amino acids, organic acids, and fatty acids in the early life of offspring. Such interventions could reduce the risk of long-term metabolic diseases.

Article information and declarations

Author contributions

Dandan Xia contributed to the data collection, analysis, and manuscript writing. Huiyan Wang analyzed the data and revised the manuscript. Yuqi Yang was responsible for testing and analyzing the newborn genetic screening data. Wenli Wang designed the study, revised the manuscript, and approved the final version.

Ethics statement

This study was approved by the Ethics Committee of Nanjing Medical University [IRB No. (2023) 367] on March 2, 2023.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author, Wenli Wang, upon reasonable request.

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Conflict of interest

The authors have no conflicts of interest.

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018; 138: 271–281, doi: 10.1016/j.diabres.2018.02.023, indexed in Pubmed: 29496507.
2. Gorban de Lapertosa S, Alvariñas J, Elgart JF, et al. EduGest group. The triad macrosomia, obesity, and hypertriglyceridemia in gestational diabetes. Diabetes Metab Res Rev. 2020; 36(5): e3302, doi: 10.1002/dmrr.3302, indexed in Pubmed: 32068345.

3. El-Hattab AW, Almannai M, Sutton VR. Newborn Screening: History, Current Status, and Future Directions. Pediatr Clin North Am. 2018; 65(2): 389–405, doi: 10.1016/j.pcl.2017.11.013, indexed in Pubmed: 29502920.
4. Sweeting A, Wong J, Murphy HR, et al. A Clinical Update on Gestational Diabetes Mellitus. Endocr Rev. 2022; 43(5): 763–793, doi: 10.1210/endrev/bnac003, indexed in Pubmed: 35041752.
5. Poon LC, McIntyre HD, Hyett JA, et al. FIGO Pregnancy and NCD Committee. The first-trimester of pregnancy - A window of opportunity for prediction and prevention of pregnancy complications and future life. Diabetes Res Clin Pract. 2018; 145: 20–30, doi: 10.1016/j.diabres.2018.05.002, indexed in Pubmed: 29852233.
6. Sun YY, Juan J, Xu QQ, et al. Increasing insulin resistance predicts adverse pregnancy outcomes in women with gestational diabetes mellitus. J Diabetes. 2020; 12(6): 438–446, doi: 10.1111/1753-0407.13013, indexed in Pubmed: 31808991.
7. Rosinha PM, Dantas RA, Alves MI, et al. Body mass index and gestational weight gain: relevance in gestational diabetes and outcomes - A retrospective cohort study. Arch Endocrinol Metab. 2022; 66(2): 261–268, doi: 10.20945/2359-3997000000463, indexed in Pubmed: 35420269.
8. Soares MJ, Iqbal K, Kozai K. Hypoxia and Placental Development. Birth Defects Res. 2017; 109(17): 1309–1329, doi: 10.1002/bdr2.1135, indexed in Pubmed: 29105383.
9. Scholtens DM, Bain JR, Reisetter AC, et al. HAPO Study Cooperative Research Group. Metabolic Networks and Metabolites Underlie Associations Between Maternal Glucose During Pregnancy and Newborn Size at Birth. Diabetes. 2016; 65(7): 2039–2050, doi: 10.2337/db15-1748, indexed in Pubmed: 27207545.
10. Fabie NA, Pappas KB, Feldman GL. The Current State of Newborn Screening in the United States. Pediatr Clin North Am. 2019; 66(2): 369–386, doi: 10.1016/j.pcl.2018.12.007, indexed in Pubmed: 30819343.

11. Yang Y, Yu B, Long W, et al. Investigating the changes in amino acid values in premature infants: a pilot study. J Pediatr Endocrinol Metab. 2018; 31(4): 435–441, doi: 10.1515/jpem-2017-0372, indexed in Pubmed: 29470177.
12. Pakula MM, Maier TJ, Vorup-Jensen T. Insight on the impacts of free amino acids and their metabolites on the immune system from a perspective of inborn errors of amino acid metabolism. Expert Opin Ther Targets. 2017; 21(6): 611–626, doi: 10.1080/14728222.2017.1323879, indexed in Pubmed: 28441889.
13. Zhao H, Li H, Chung AC, et al. Large-Scale Longitudinal Metabolomics Study Reveals Different Trimester-Specific Alterations of Metabolites in Relation to Gestational Diabetes Mellitus. J Proteome Res. 2019; 18(1): 292–300, doi: 10.1021/acs.jproteome.8b00602, indexed in Pubmed: 30488697.
14. Chen Y, Wang Na, Dong X, et al. Associations between serum amino acids and incident type 2 diabetes in Chinese rural adults. Nutr Metab Cardiovasc Dis. 2021; 31(8): 2416–2425, doi: 10.1016/j.numecd.2021.05.004, indexed in Pubmed: 34158241.
15. Lin Y, Lin B, Chen Y, et al. Biochemical and genetic characteristics of patients with primary carnitine deficiency identified through newborn screening. Orphanet J Rare Dis. 2021; 16(1): 503, doi: 10.1186/s13023-021-02126-3, indexed in Pubmed: 34863234.
16. Schupper A, Almashanu S, Coster D, et al. Metabolic biomarkers of small and large for gestational age newborns. Early Hum Dev. 2021; 160: 105422, doi: 10.1016/j.earlhumdev.2021.105422, indexed in Pubmed: 34271419.
17. Almannai M, Alfadhel M, El-Hattab AW. Carnitine Inborn Errors of Metabolism. Molecules. 2019; 24(18), doi: 10.3390/molecules24183251, indexed in Pubmed: 31500110.

Table 1. The results of clinical data analysis in each groups

	G1	G2	G3	p
number	67	750	435	
Age [years]	32.84 ± 0.62	32.08 ± 0.16	32.18 ± 0.21	0.4172

height [cm]	158.1 ± 0.62	160.9 ± 0.18	162.7 ± 0.23	0.05
predelivery weight [kg]	67.37 ± 1.37	73.83 ± 4.67	80.93 ± 0.51	0.3133
gravida	2.15 ± 0.17	2.10 ± 0.04	2.26 ± 0.06	0.1647
parity	0.51 ± 0.09	0.70 ± 0.03$^{\#}$	1.06 ± 0.04$^{*,\&}$	< 0.0001
OGTT-FBG [mmol/L]	4.81 ± 0.09	4.89 ± 0.02	5.10 ± 0.02$^{*,\&}$	< 0.0001
OGTT-1h [mmol/L]	9.87 ± 0.17	9.83 ± 0.05	10.02 ± 0.08	0.1118
OGTT-2h [mmol/L]	8.63 ± 0.14	8.50 ± 0.05	10.25 ± 1.77	0.404
FW[g]	2042 ± 58.75	3192 ± 7.26$^{\#}$	4254 ± 12.33$^{*,\&}$	< 0.0001
neonatal asphyxia [%]	8.96	0.13$^{\#}$	2.06$^{*,\&}$	< 0.0001
cesarean section rate [%]	76.12	45.74$^{\#}$	61.74$^{*,\&}$	< 0.0001
insulin utilization rate [%]	11.94	2.52$^{\#}$	3.67$^{\&}$	< 0.0001
Gestation days	251.6 ± 2.098	271.6 ± 0.4895$^{\#}$	272.5 ± 1.443$^{\&}$	< 0.0001

$^{\#}$Compared with G1, p 0.05; *Compared with G2, p 0.05; $^{\&}$Compared with G1, p 0.05; p value < 0.05 was chosen to be statistically significant; OGTT values were measured between 25 and 28 weeks of pregnancy; data are presented as mean ± standard deviation or n (%); FBG — fasting blood glucose value; FW — Fetal Weight; G1 — fetal growth restriction; G2 — normal birth weight infants; G3 — fetal macrosomia; GDM — gestational diabetes mellitus; OGTT — oral glucose tolerance test

Table 2. Comparison of blood amino acid levels in three groups (μmol/L)

	G1	**G2**	**G3**	**p**
ALA	298.93 ± 85.41	301.75 ± 72.47	300.07 ± 81.34	0.477
ARG	18.26 ±15.83	10.83 ± 7.75$^{\#}$	11.91 ± 8.19$^{*,\&}$	< 0.001
CIT	15.39 ± 4.53	12.46 ± 3.86$^{\#}$	12.05 ± 3.56$^{*,\&}$	< 0.001
GLY	477.04 ± 132.35	476.51 ± 107.86	467.57 ± 115.11*	0.084
LEU + ILE + PRO-OH	161.70 ± 40.06	147.48 ± 32.68$^{\#}$	151.46 ± 34.77$^{\&}$	0.004

MET	25.57 ± 7.32	23.01 ± 6.19[#]	24.38 ± 6.40*	< 0.001
ORN	145.07 ± 48.93	119.94 ± 35.91[#]	119.48 ± 43.27[&]	< 0.001
PHE	60.08 ± 12.53)	54.20 ± 11.10[#]	55.98 ± 11.40*[,&]	< 0.001
PRO	186.37 ± 48.31	178.22 ± 39.25	172.59 ± 35.39*	0.02
TYR	112.34 ± 64.95	103.76 ± 47.13	97.06 ± 34.99*	0.065
VAL	145.96 ± 36.27	131.48 ± 29.13[#]	134.22 ± 31.13[&]	0.004

The levels of amino acids in neonates were detected by tandem mass spectrometry; ALA — alanine; Arg — arginine; CIT — citrulline; GLY — glycine; LEU + ILE + PRO-OH — leucine; MET — methionine; ORN — ornithine; PHE — phenylalanine; PRO — proline; TYR — tyrosine; VAL — valine; p value < 0.05 was chosen to be statistically significant

Table 3. Comparison of blood free carnitine levels in three groups (μmol/L)

	G1	G2	G3	p <
CO	28.80 ± 13.04	21.95 ± 7.42[#]	21.00 ± 7.44*[,&]	0.001

The levels of CO in neonates were detected by tandem mass spectrometry; CO — free carnitine; p value < 0.05 was chosen to be statistically significant

Table 4. Comparison of blood acyl-carnitine levels in three groups (μmol/L)

	G1	G2	G3	p
C2	20.15 ± 7.86	19.86 ± 6.58	20.50 ± 7.20	0.521
C3	1.80 ± 0.84	1.74 ± 0.67	2.08 ± 0.83*[,&]	< 0.001
C3DC + C4OH	0.11 ± 0.06	0.13 ± 0.07[#]	0.12 ± 0.06[&]	0.011
C4	0.24 ± 0.07	0.23 ± 0.08	0.21 ± 0.06*[,&]	< 0.001
C4DC + C5OH	0.20 ± 0.05	0.20 ± 0.06	0.21 ± 0.06	0.407
C5	0.17 ± 0.07	0.10 ± 0.04[#]	0.10 ± 0.04[&]	< 0.001
C5:1	0.01 ± 0.01	0.01 ± 0.00[#]	0.01 ± 0.00[&]	0.001
C5DC + C6OH	0.10 ± 0.03	0.10 ± 0.03	0.10 ± 0.03[&]	0.052
C6	0.04 ± 0.02	0.04 ± 0.01[#]	0.04 ± 0.01[&]	0.006
C6DC	0.10 ± 0.05	0.11 ± 0.05	0.10 ± 0.04	0.014

C8	0.08 ± 0.04	0.06 ± 0.03[#]	0.06 ± 0.03[&]	< 0.001
C8:1	0.11 ± 0.04	0.11 ± 0.04	0.12 ± 0.04[*,&]	0.006
C10	0.08 ± 0.03	0.08 ± 0.04	0.08 ± 0.03[*]	0.02
C10:1	0.05 ± 0.02	0.07 ± 0.03[#]	0.06 ± 0.02[*,&]	< 0.001
C10:2	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00[*]	< 0.001
C12	0.05 ± 0.04	0.08 ± 0.05[#]	0.07 ± 0.04[*,&]	< 0.001
C12:1	0.04 ± 0.03	0.06 ± 0.04[#]	0.05 ± 0.03[*,&]	< 0.001
C14	0.16 ± 0.07	0.18 ± 0.07[#]	0.17 ± 0.06	0.032
C14:1	0.06 ± 0.04	0.09 ± 0.04[#]	0.08 ±0.03[*,&]	< 0.001
C14:2	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01[*,&]	< 0.001
C14OH	0.01 ± 0.01	0.01± 0.01[#]	0.01 ± 0.01[&]	< 0.001
C16	2.28 ± 1.15	3.12 ± 1.14[#]	3.17 ± 1.03[&]	< 0.001
C16:1	0.13 ± 0.08	0.18 ± 0.08[#]	0.18 ± 0.07[&]	< 0.001
C16:1O H	0.03 ± 0.01	0.04 ± 0.01[#]	0.04 ± 0.01[&]	0.002
C16OH	0.01 ± 0.01	0.02 ± 0.01[#]	0.02± 0.01[&]	< 0.001
C18	0.82 ± 0.27	0.88 ± 0.29	0.87 ± 0.28	0.363
C18:1	1.62 ± 0.65	1.57 ± 0.44	1.59 ± 0.47	0.762
C18:1O H	0.02 ± 0.01	0.02 ± 0.01[#]	0.02 ± 0.01[&]	0.032
C18:2	0.50 ± 0.25	0.27 ± 0.12[#]	0.26 ± 0.12[&]	< 0.001
C18OH	0.01 ± 0.01	0.01 ± 0.01[#]	0.01 ± 0.01[&]	< 0.001

The levels of acylcarnitine in neonates were detected by tandem mass spectrometry; C2 — acetylcarnitine; C3 — propionylcarnitine; C3DC + C4OH — 3-hydroxy-butyrylcarnitine; C4 — butyrylcarnitine; C4DC + C5OH — crotonobetaine/3-hydroxyvalerylcarnitine; C5 — isovalerylcarnitine; C5:1 — pentanoylcarnitine; C5DC + C6OH — glutarylcarnitine/3-hydroxyhexanoylcarnitine; C6 — hexanoylcarnitine; C6DC — suberylcarnitine ; C8 — octanoylcarnitine; C8:1 — octenoylcarnitine; C10 — decanoylcarnitine; C10:1 — decenoylcarnitine; C10:2 — 10-decenoylcarnitine; C12 — dodecanoylcarnitine; C12:1 — dodecenoylcarnitine; C14 — tetradecanoylcarnitine; C14:1 — myristoylcarnitine; C14:2 — 9 —12-tetradecadienoylcarnitine; C14OH — 3-hydroxytetradecanoylcarnitine; C16 — hexadecanoylcarnitine; C16:1 — hexadecenoylcarnitine; C16:1OH — hexadecenoylcarnitine; C16OH — 3-hydroxy-hexadecanoylcarnitine; C18 — octadecanoylcarnitine; C18:1 — octadecenoylcarnitine; C18:1OH — 3-hydroxyoctadecenoylcarnitine; C18:2 — 18-carbodienoylcarnitine; C18OH — 3-hydroxyoctadecanoylcarnitine; p value < 0.05 was chosen to be statistically significant.