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Retrospective Study

Early neonatal complications in pregnant women with gestational diabetes mellitus and the effects of glycemic control on neonatal infection

INTRODUCTION

Gestational diabetes mellitus (GDM) is a glucose metabolism disorder during pregnancy. Studies have indicated that GDM tends to cause diabetes mellitus and cardiovascular disease in neonates after delivery by pregnant women with GDM[1]. Recently, studies reported that GDM incidence has shown a significant increasing trend worldwide[2] and has become a global health concern. Previous studies[3,4] have shown that GDM is considered to be one of the major risk factors for maternal and child complications in the perinatal phase and the incidence of cesarean section, polyhydramnios, premature birth, fetal deformities, neonatal infection, hyperbilirubinemia, fetal macrosomia, and neonatal hypoglycemia is higher in pregnant women with GDM who have abnormal glucose metabolism for a long period. Rational diet control, exercise, and glucose-lowering treatments have achieved good results in terms of glycemic control in pregnant women with GDM. However, 30% of pregnant women with GDM were reported to be affected by multiple factors, including irregular diet, lack of exercise, hormone secretion disorder, *etc*[5]. In addition, glycemic control was poor. This ultimately affected maternal and child health, and increased the risk of neonatal complications. A study found that the immune function of neonates may be significantly affected by GDM, and the effectiveness of glycemic control is strongly associated with adverse pregnancy outcomes and neonatal complications[6]. Early detection of abnormal glucose metabolism and achieving good glycemic control during

pregnancy can effectively prevent adverse maternal and child outcomes in the perinatal stage of GDM patients[7]. However, there is still unclear whether glycemic control that does not conform to the standards in pregnant women with GDM decreases immune function in neonates and increases the incidence of neonatal infections.

In this study, we investigated the differences in neonatal complications between pregnant women with GDM and healthy controls to examine the effects of GDM on neonatal prognosis. We then divided the pregnant women with GDM into two groups based on whether glycemic control conformed to standards. Subsequently, we compared the blood glucose levels in pregnant women with GDM, immune function, infection-related marker levels, and the incidence of infection in neonates of the pregnant women with GDM in these two groups. The purpose of this study was to analyze the effects of glycemic control in GDM pregnant women on neonatal immune function and infection.

MATERIALS AND METHODS
Patient characteristics
The newborns delivered by 236 pregnant women with GDM in Taizhou People's Hospital of Jiangsu Province from March 2020 to December 2021 were retrospectively included in the GDM group. The neonates of 240 healthy pregnant women during the same period were selected as the control group. The patients were divided into the conforming glycemic control group (CGC group) and the non-conforming glycemic control group (NCGC group) based on whether glycemic control in pregnant women with GDM conformed to standards.

Inclusion criteria: (1) Natural singleton pregnancy; (2) age 20–40 years; and (3) for the GDM group, blood glucose measurement at week 24–28 of pregnancy conformed to the diagnostic criteria for GDM formulated by the American Diabetes Association in 2013[8]: 75 g oral glucose tolerance test result showed fasting plasma glucose (FPG) ≥ 5.1

mmol/L, blood glucose 1 h after test ≥ 10.0 mmol/L or blood glucose 2 h after test ≥ 8.5 mmol/L; the GDM group received diet and/or glucose-lowering treatment.

Exclusion criteria: (1) Comorbid hypertension, anemia, polyhydramnios, and other underlying diseases or pregnancy complications; (2) past history of adverse pregnancy outcomes; (3) gestational age at delivery < 28 wk; and (4) presence of heart, brain, lung, liver, and other organ diseases.

The screening process is shown in Figure 1. The study was reviewed and approved by the Taizhou People's Hospital of Jiangsu Province Institutional Review Board.

Treatment methods

Dietary control and/or insulin treatment was carried out in all pregnant women with GDM, which was specified as follows: total daily caloric intake was calculated based on 130 J/kg-145 J/kg, and the proportions of carbohydrates, proteins, and fats were 55%–65%, 20%–25%, and 15%–25%, respectively. A routine diet complied with the principle of eating less in more meals and 4–6 meals were consumed each day. Insulin treatment of 0.6 U/kg–0.8 U/kg was administered every day, blood glucose level was closely monitored, and insulin dose was promptly adjusted in pregnant women with GDM with abnormal blood glucose after comprehensive dietary intervention. Follow-up was carried out every 2 wk in the form of hospital visits. Glycemic control criteria[9] were FPG ≤ 5.6 mmol/L, 2 h postprandial blood glucose (P2h-PG) ≤ 6.7 mmol/L, and glycated hemoglobin (HbA1$_C$) < 6%. All three criteria must be met to conform to glycemic control standards. Otherwise, the patient was considered not to conform to glycemic control standards.

Observation markers

Baseline data and blood glucose in pregnant women and immune function, infection-related markers, and infection rate in neonates were observed and compared. (1) Blood glucose: This was measured 24 h before delivery. Venous whole blood was

collected from pregnant women, and a low-speed centrifuge was used to extract serum samples at 3000 r/min for 10 min. A Mindray glucose assay kit (glucose oxidase assay) was used to measure FPG and P2h-PG in serum samples. Heparin anticoagulant tubes were used to collect venous whole blood from pregnant women. Ion exchange chromatography and gradient elution were used to measure $HbA1_C$ after hemolysis of blood samples using hemolysin; (2) Immune function: 5 mL of umbilical vein blood was collected from neonates after delivery. Blood samples were mixed with allophycocyanin (APC)/cyanine dye 7 (Cy7) fluorescently labeled mouse anti-human CD3 antibody, phycoerythrin/Cy7 mouse anti-human CD4 antibody, and APC/Cy7 mouse anti-human CD8, and incubated at room temperature for 15 min. BD FACS™ lysis solution (BD Inc., USA) was added and incubated in the dark for 15 min. A BD FACSCanto II flow cytometer (BD Inc., USA) was used to measure the proportions of CD3+ T cells, CD4+T cells, and CD8+ T cells with different fluorescent labels in peripheral blood. The CD4/CD8 ratio was then calculated; (3) The levels of immunoglobulin G (IgG), IgA, and IgM in the peripheral blood of newborns in both groups were measured by immunoturbidimetry; (4) A Roche Cobas 8000 fully automatic biochemical analyzer was used to measure the white blood cell (WBC) count in the umbilical vein blood in neonates; (5) Enzyme-linked immunosorbent assay (ELISA) was used to measure procalcitonin (PCT) and C-reactive protein (CRP) levels. ELISA kits were purchased from Beyotime Biotechnology Co., Ltd; and (6) Neonatal infections were observed and recorded, including upper respiratory tract infection, lower respiratory tract infection, skin infection, intestinal infection, and sepsis.

Statistical analysis

Statistical data were processed using SPSS 20.0 software, and quantitative data were tested for normal distribution. Quantitative data with normal distribution were expressed as mean ± SD. An independent sample *t*-test was used for inter-group comparisons. Quantitative data with abnormal distribution are represented by median (quartile), and a non-parametric test was used for inter-group comparisons. Qualitative

data were expressed as % and the χ^2 test was used. A P-value < 0.05 was considered statistically significant.

RESULTS

Comparison of baseline data

In the GDM group, the age of pregnant women ranged from 21–39 years and the mean age was 29.98 ± 4.65 years; body mass index (BMI) was 19.7–38.1 kg/m² and mean BMI was (29.75 ± 2.68) kg/m². There were 143 primipara and 93 multipara women. In the control group, the age ranged from 22–40 years and the mean age was 30.26 ± 4.74 years; BMI was 20.3–37.9 kg/m² and mean BMI was 30.01 ± 3.12 kg/m²; there were 159 primipara and 181 multipara women. There were no differences in age, BMI, parity, and gravidity between the two groups and the groups were comparable (P > 0.05). as shown in Table 1.

Comparison of early neonatal complications

The incidence of premature births, fetal macrosomia, hypoglycemia, hypocalcemia, and hyperbilirubinemia in neonates delivered by pregnant women with GDM was significantly higher than that in neonates delivered by women in the control group. These differences were statistically significant (P < 0.05) as shown in Table 2.

Comparison of blood glucose markers

Pregnant women with GDM were divided into the CGC group and the NCGC group based on whether their glycemic control conformed to standards. Blood glucose markers in the NCGC group, such as FPG, P2h-PG, and HbA1$_C$ levels, were significantly higher (P < 0.05) compared with pregnant women with GDM in the CGC group. These results are shown in Table 3.

Comparison of peripheral blood T cell subsets

Results of the flow cytometry analysis of peripheral blood T cell subsets were compared between the two groups of neonates. The ratio of peripheral blood CD3$^+$T cells, CD4$^+$T cells, and CD8$^+$T cells, and the CD4/CD8 ratio in neonates in the NCGC group were all significantly lower than those in the CGC group ($P < 0.05$). These results showed that immune function was significantly decreased in neonates from the NCGC group. These results are shown in Table 4.

Comparison of immunoglobulin levels
The levels of IgG, IgM, and IgA, were compared between neonates in the two groups. The results showed that the level of IgG in the CGC group was significantly higher than that in the NCGC group, with a statistically significant difference ($P < 0.05$). There were no significant differences in the levels of IgM and IgA in peripheral blood between the two groups of newborns ($P > 0.05$), as shown in Table 5.

Comparison of infection-related inflammatory markers
Infection-related inflammatory markers, including WBC, serum PCT and CRP levels, were compared between neonates in the two groups. WBC, PCT, and CRP levels in neonates in the NCGC group were significantly higher than those in the CGC group, and these differences were statistically significant ($P < 0.05$), as shown in Table 6.

Comparison of neonatal infections
The incidence of upper respiratory tract infection, lower respiratory tract infection, and skin infection in neonates in the NCGC group was 31.03%, which was significantly higher than neonates in the CGC group (9.35%). These differences were statistically significant ($P < 0.05$) and are shown in Table 7.

DISCUSSION
Glucose metabolism disorders and long-term blood glucose abnormalities in pregnant women with GDM are associated with decreased pancreatic islet function and insulin

resistance[10], and GDM has a major impact on adverse maternal and child outcomes in the perinatal phase compared to the normal diabetic population. Currently, there are 210 million neonates affected by GDM globally, as shown in the 2017 International Diabetes Federation report[11]. Furthermore, GDM has become a major global public health concern. The results of this study show that the incidence of premature births, fetal macrosomia, hypoglycemia, hypocalcemia, hyperbilirubinemia, and infection in neonates delivered by pregnant women with GDM was significantly higher than in neonates delivered by healthy pregnant women. These results demonstrate that the health of neonates is severely affected by blood glucose abnormalities in the mother during pregnancy. The main harm caused by GDM is an increase in maternal and child adverse outcomes and mortality rate during the perinatal phase, resulting in fetal distress, developmental abnormalities, and increases the risk of hypoglycemia, deformities, and infection in neonates[12]. Therefore, it can be seen from these results that stringent glycemic control in pregnant women with GDM is an essential measure to prevent neonatal complications in the perinatal stage. Capobianco *et al*[13] also reported the GDM is an important complication that affects maternal and pregnancy outcomes, and good glycemic control can decrease the risk of pregnancy complications and the cesarean section rate, increase the rate of natural vaginal delivery, and has positive effects in decreasing premature births, fetal macrosomia, hypoglycemia, asphyxiation, and infection.

A recent study[14] found that interleukin (IL)-6 and tumor necrosis factor (TNF)-α levels were significantly increased in the umbilical vein blood from neonates delivered by women with GDM. The neonates also showed varying degrees of immune dysfunction, suggesting that the risk of infection is higher in neonates of GDM patients. Our study results showed that compared with healthy pregnant women, the incidence of neonatal infection was significantly higher in pregnant women with GDM. Blood glucose markers and neonatal infection rates were significantly increased in pregnant women with GDM in the NCGC group compared to those in the CGC group. This suggested that glycemic control has significant effects in decreasing neonatal infection

caused by blood glucose abnormalities in GDM patients. Zarrin *et al*[15] found that the condition of GDM patients worsened as gestational age increased, and glucose metabolism abnormalities during pregnancy may directly affect maternal and fetal immune function. Maternal immune defects and fetal T lymphocyte developmental abnormalities will affect neonatal immune function. Neonatal immune dysfunction is an independent risk factor for infection[16]. T lymphocytes are the most important cell population in the immune system, of which the CD3+ subset represents mature T lymphocytes and immune function[17]. CD4+ T cells mainly regulate humoral immunity while CD8+ T cells are inhibitory/cytotoxic T lymphocytes that mainly regulate cellular immunity and play a critical role in regulating CD3+ and CD4+ functions[18,19]. The CD4+/CD8+ ratio can normally be used to reflect the equilibrium between humoral/cellular immunity. This cell ratio is an important marker for evaluating immune function and a low CD4+/CD8+ ratio usually means that the body is in an immunosuppressed state[20]. Kugler *et al*[21] confirmed that neonatal immune function defects were related to the inheritance of abnormal T lymphocyte development and maternal immune function defects, and were independent risk factors for neonatal infection. We compared the differences in peripheral blood T cell subsets in this study between neonates in the two groups. The results showed that peripheral blood CD3+T cells, CD4+T cells, and CD8+T cells, and the CD4/CD8 ratio of neonates in the NCGC group were all significantly lower than those in the CGC group. These results demonstrated that blood glucose abnormalities in pregnant women with GDM may affect peripheral blood T cell subsets in neonates, resulting in decreased immune function and immune regulation disorders, thus reducing infection resistance.

Immunoglobulins are an important class of immune effector molecules, including IgG, IgA, IgM, and so on. IgG in the peripheral blood of newborns is mainly from the mother, accounting for about 75% of the total serum immunoglobulin content, and plays an important role in preventing infection[22]. This study found that IgG in neonates from women with GDM in the NCGC group significantly decreased compared to that in the CGC group, suggesting that poor blood glycemic control in GDM

pregnant women can lead to a decline in neonatal immune function. It is speculated that for patients with GDM, abnormal glucose metabolism itself is an inflammatory reaction, which hinders the production of IgG, thereby reducing the amount of IgG entering the fetus *via* the placenta[23]. However, IgA and IgM cannot pass through the placental barrier, resulting in extremely low levels in the peripheral blood of newborns, leading to insignificant changes in levels.

WBC are the most commonly used marker for early diagnosis and treatment of neonatal infections, and PCT and CRP are important serum markers for diagnosing neonatal infection[24]. This study compared these markers in pregnant women with GDM and neonates from the two groups. The results revealed that WBC, serum PCT and CRP levels in neonates in the NCGC group were significantly greater than those in the CGC group, suggesting that GDM patients who did not meet glycemic control standards have neonates with elevated inflammatory markers and an increased risk of infection. This may be because blood glucose abnormalities during pregnancy can promote the transcription of placental CRP, IL-6, and PCT, which are important mechanisms that directly affect the fetal immune system[25]. Li *et al*[26] found that a hyperglycemic environment activated placental HIF-1a and TLR4/MyD88/NF-kB pathways in pregnant women with GDM, induced IL-6 and IL-8 secretions, promoted placental inflammation and autophagy to disrupt placental homeostasis and cell renewal, and increased the risk of infection in neonates delivered by pregnant women with GDM. From these findings combined with the results from the present study, we believe that poor glycemic control in pregnant women with GDM can result in long-term blood glucose abnormalities, which may stimulate inflammatory responses in the fetal placenta, thereby affecting the fetal immune system and ultimately increase the risk of neonatal infections.

The innovation of this study is that the relationship between the blood glucose control level in pregnant women with GDM and neonatal immune function was analyzed, which opens up a new direction for predicting neonatal infectious pathology. However, a larger multicenter clinical study is needed in the future to validate the

results of this study as this was a single center study with a limited sample size due to the strict screening conditions. In addition, immunoglobulin, as an antibody related to the immune response *in vivo*, can be used as an early diagnostic indicator of infection, and IgG antibodies can also enhance the anti-infection ability of newborns and prevent related infectious diseases. However, this study lacks the assessment of neonatal peripheral blood immunoglobulin level to verify neonatal immune function. Finally, the neonates included in this study were only followed up for a short time. The influence of blood glucose control level in GDM patients on the long-term immune function of neonates still requires further research.

CONCLUSION

In summary, we speculate that glucose metabolism disorders and long-term blood glucose abnormalities in GDM patients with poor glycemic control may be considered a type of inflammatory response which affects the T lymphocyte subsets in neonates, resulting in immune dysfunction, and ultimately decreasing immune function and increasing the risk of infection.

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Figure Legends

Figure 1 Screening, randomization and analysis of populations. OGTT: Oral glucose tolerance test; FPG: Fasting plasma glucose; P1h-PG: 1 h postprandial blood glucose; GDM: Gestational diabetes mellitus.

Table 1 Comparison of baseline data in pregnant women with gestational diabetes mellitus between conforming glycemic control and non-conforming glycemic control groups

Groups	Cases	Age (yr)	BMI (kg/m²)	Type of pregnant woman, n (%)	
				Primipara	Multipara
CGC group	178	30.05 ± 4.46	29.55 ± 2.82	109 (61.24)	69 (38.76)
NCGC group	58	29.47 ± 3.75	30.08 ± 2.57	34 (56.90)	25 (43.10)
t/χ^2 value		0.893	1.270	0.344	
P value		0.373	0.206	0.558	

BMI: Body mass index; CGC: Conforming glycemic control; NCGC: Non-conforming glycemic control.

Table 2 Comparison of early neonatal complications between the gestational diabetes mellitus and control groups, n (%)

Complications	GDM group (n=236)	Control group (n=240)	χ^2 value	P value
Premature birth	45 (19.07)	12 (5.00)	22.341	< 0.001
Fetal macrosomia	57 (24.15)	23 (9.58)	18.064	< 0.001
Hypoglycemia	42 (17.80)	7 (2.92)	28.53	< 0.001
Hypocalcemia	22 (9.32)	5 (2.08)	11.653	< 0.001
Hyperbilirubinemia	29 (12.29)	13 (5.42)	6.984	0.008
Polycythemia	38 (16.10)	22 (9.17)	5.195	0.023
Hyaline membrane disease	13 (5.51)	2 (0.83)	8.522	0.004
Fetal distress	34 (14.41)	6 (2.50)	21.917	< 0.001
Congenital malformation	11 (4.66)	1 (0.42)	8.723	0.003
Neonatal asphyxia	21 (8.90)	6 (2.50)	9.104	0.003
Neonatal infection	35 (14.83)	11 (4.58)	14.312	< 0.001

GDM: Gestational diabetes mellitus.

Table 3 Comparison of blood glucose markers in pregnant women with gestational diabetes mellitus between conforming glycemic control and non-conforming glycemic control groups

Groups	Cases	FPG (mmol/L)	P2h-PG (mmol/L)	HbA1c (%)
CGC group	178	4.68 ± 0.60	5.51 ± 0.85	5.11 ± 0.45
NCGC group	58	5.96 ± 0.68	7.14 ± 1.04	6.38 ± 0.74
t/χ^2 value		13.645	11.979	15.691
P value		< 0.001	< 0.001	< 0.001

CGC: Conforming glycemic control; NCGC: Non-conforming glycemic control; FPG: Fasting plasma glucose; P2h-PG: 2 h postprandial blood glucose; HbA1c: Hemoglobin.

Table 4 Comparison of CD3+, CD4+, CD8+ and CD4+/CD8+ ratio between the two groups of neonates (mean ± SD, n)

Groups	Cases	CD3+ (%)	CD4+ (%)	CD8+ (%)	CD4/CD8
CGC group	178	52.01 ± 10.78	39.21 ± 7.80	25.69 ± 5.47	1.61 ± 0.54
NCGC group	58	45.25 ± 7.33	22.46 ± 5.48	19.42 ± 2.95	1.17 ± 0.33
t value		4.449	15.170	8.335	5.854
P value		< 0.001	< 0.001	< 0.001	< 0.001

CGC: Conforming glycemic control; NCGC: Non-conforming glycemic control.

Table 5 Comparison of immunoglobulin G, immunoglobulin M and immunoglobulin A levels between the two groups of neonates (mean ± SD, n)

Groups	Cases	IgG (g/L)	IgM (g/L)	IgA (g/L)
CGC group	178	9.78 ± 1.38	0.181 ± 0.043	0.31 ± 0.08
NCGC group	58	7.21 ± 1.32	0.173 ± 0.040	0.29 ± 0.07
t value		12.447	1.251	1.688
P value		< 0.001	0.212	0.093

IG: Immunoglobulin; CGC: Conforming glycemic control; NCGC: Non-conforming glycemic control.

Table 6 Comparison of white blood cell, procalcitonin and C-reactive protein levels between the two groups of neonates (mean ± SD, n)

Groups	Cases	WBC (×10^9/L)	PCT (µg/L)	CRP (mg/L)
CGC group	178	15.56 ± 5.47	0.43 ± 0.12	7.22 ± 2.07
NCGC group	58	25.80 ± 8.61	0.81 ± 0.24	12.38 ± 3.22
t value		10.618	15.920	14.212
P value		< 0.001	< 0.001	< 0.001

WBC: white blood cell; PCT: procalcitonin; CRP: C-reactive protein; CGC: Conforming glycemic control; NCGC: Non-conforming glycemic control.

Table 7 Comparison of neonatal infections between the two groups, n (%)

Groups	Cases	Upper respiratory tract infection	Lower respiratory tract infection	Skin infection	Intestinal infection	Sepsis	Total
CGC group	178	10 (5.62)	4 (2.25)	1 (0.56)	2 (1.12)	0 (0.00)	17 (9.55)
NCGC group	58	7 (12.07)	3 (5.17)	2 (3.45)	5 (8.62)	1 (1.72)	18 (31.03)
χ^2 value							15.985
P value							< 0.001

CGC: Conforming glycemic control; NCGC: Non-conforming glycemic control.

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