

Association between neonatal hyperbilirubinemia and hypoglycemia in Chinese women with diabetes in pregnancy and influence factors

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Abstract

This retrospective study aimed to investigate the correlation between neonatal hyperbilirubinemia (NHB) and hypoglycemia (NH) in Chinese women with diabetes in pregnancy (DIP), and the influencing factors. All the data were collected July 1, 2017 and June 30, 2020, and 10,558 Chinese women with DIP and live births were included. Two separate multivariate binary stepwise forward logistic regression analysis calculated OR with 95% CI. The prevalence rates of NHB and NH was respectively 6.47% and 6.42% among women with DIP. The comorbidity of both diseases was 1.15%. NH were 1.73 times (OR 1.73, 1.21-2.47) more likely to have hyperbilirubinemia. NHB is positively correlated with NH (OR 3.61, 2.51-5.20). Increased gestational age has a protective effect on both NH (OR 0.81, 0.77-0.87) and NHB (OR 0.85, 0.76-0.95). Abnormal placental morphology is related to NH (OR 1.47, 1.11-1.95) and NHB (OR 1.41, 1.02-1.98). Regarding neonatal outcomes, congenital heart disease (CHD) (OR 3.00, 2.10-4.29; and OR 7.67, 5.50-10.70) and neonatal anemia (OR 4.90, 2.13-11.26; and OR 6.16, 2.34-16.22) were risk factors of both. NHB and NH were significantly correlated in women with DIP. The offspring of DIP with multiple risk factors have a significantly increased risk of neonatal hyperbilirubinemia.

Introduction

Hyperglycemia during pregnancy is a growing health concern for women and their infants, including pre-gestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM)¹. Diabetes in pregnancy causes short-term and long-term adverse impacts on both pregnant women (e.g., gestational hypertension, abortion, and stillbirth) and neonates (e.g., perinatal death, macrosomia, and infection). Fetuses exposed to maternal hyperglycemia are more likely to have NH and NHB, which significantly threaten the early life of neonates^{2,3}. Fetuses with hyperinsulinemia caused by maternal hyperglycemia in the third trimester of pregnancy are more likely to have NH⁴. NH can also be aggravated by maternal hyperglycemia, poor gluconeogenic response, fetal polycythemia, and neonatal perinatal asphyxia⁵. Hypoglycemia usually occurs in the first few hours after birth. Although hypoglycemia is manifested as a short-term symptom, long-term neurodevelopmental sequelae and other adverse effects should be considered².

Fetal hyperinsulinemia drives catabolism via consuming energy, leading to a depletion of oxygen storage, which in turn accelerates fetal growth and increases oxygen demand⁶. An increased erythropoietin concentration due to fetal chronic hypoxemia, hyperglycemia, and oxidative stress⁵. Increased HbA1c and decreased placental blood flow resulting to decreased placental oxygen supply in pregnant women, further exacerbating the hypoxia problem⁷. The combination of factors contributes to the relative lack of oxygen in the fetus, which is a risk factor for unexplained stillbirth in diabetic pregnancies⁸. Infants of pregnant women with DIP have an increased risk of hyperbilirubinemia compared to normal infants⁵. An increase in red blood cells also leads to an increase in bilirubin. Polycythemia and hyperbilirubinemia are considered as a counter-regulatory mechanism of this relative hypoxic state, which triggers the secretion

of erythropoietin (EPO) and increases the production of red blood cells^{7,9}. It also leads to an increased incidence of hypoxia, such as respiratory distress syndrome and hypoxic-ischemic encephalopathy¹⁰.

As the fetus is in the uterus with hyperglycemia, the physiological and pathological mechanisms of NH and NHB may be correlated, which has rarely been studied. Research evidence shows that there is no correlation was found between NH and NHB in pregnant women with GDM, which may be related to the small sample size¹¹. Based on the physiological mechanism, this study attempted to increase the sample size and collect more comprehensive variables in Chinese diabetic pregnant women to understand the relationship between NH and NHB. We hypothesized an association between NH and NHB in DIP, and further analyzed the influencing factors.

Results

The results of baseline maternal characteristics of Chinese women with DIP were shown in Table 1. The mean age, height, pregestational BMI, gestational age at delivery, gravidae, and parity was 31.24 (\pm 4.37) years, 1.58.53 (\pm 5.02) cm, 22.37 (\pm 3.17) kg/m², 38.36 (1.52) weeks, 2.49 (\pm 1.56) times and 0.48 (\pm 0.58) times, respectively. The incidence of NH among Chinese women with DIP was 6.47% and NHB was 6.42%, with a 1.15% combined incidence of both.

Table 1

Characteristics of participants and delivery information(n=8504)

Characteristic	Classification	No. (%)
Age, years	≥18	1 (0.01)
	18-24	343 (4.03)
	25-29	2872 (33.77)
	30-34	3383 (39.78)
	35-39	1547 (18.19)
	40-44	329 (3.87)
	≥45	29 (0.34)
Height, cm	≥155	1529 (17.98)
	155-159	3232 (38.01)
	160-164	2652 (31.19)
	165-169	919 (10.81)
	≥170	151 (1.78)
	Unknown	21 (0.25)
Pregestational BMI, kg/m ²	≥18.5	664 (7.81)
	18.5-24.9	6043 (71.06)
	25.0-29.9	1425 (16.76)
	≥30.0	175 (2.06)
	Unknown	197 (2.32)
Gestational age at delivery, weeks	≥30	15 (0.18)
	30-31	29 (0.34)
	32-34	195 (2.29)
	35-36	449 (5.28)
	37-40	7752 (91.16)
	≥40	64 (0.75)
	Unknown	21 (0.25)
Gravidae	1	2803 (32.96)
	2	2226 (26.18)
	3	1561 (18.36)
	4	1008 (11.85)

	≥5	897 (10.55)
	Unknown	9 (0.11)
Parity	0	4772 (56.11)
	1	3408 (40.08)
	2	296 (3.48)
	3	18 (0.21)
	≥4	1 (0.01)
	Unknown	9 (0.11)
Delivery mode	Spontaneous delivery	3715 (43.69)
	Cesarean operation	4789 (56.31)

Univariate analysis of maternal demographic information showed that pregnant women who were older, more gravidae, heavier pre-pregnancy weight, larger pre-pregnancy BMI, and BMI more than 30kg/m² were more likely to have NH. In clinical variables, the risk of NH can also be aggravated by more weight gain during pregnancy, insulin use, gestational hypertension, pre-eclampsia, higher OGTT 1-h glucose, higher OGTT 2-h glucose, smaller gestational age, and preterm delivery. Among the obstetric factors, cesarean section, pregnancy with scar uterus, placenta previa, threatened premature labor (TPTL), fetal distress, abnormal placental morphology, chorioamnionitis, and postpartum hemorrhage were more likely to lead to NH. In neonatal outcomes, the birth length, Apgar 1min ≤7, Apgar 5min ≤7, gender (female), macrosomia, neonatal asphyxia, neonatal respiratory distress (NRDS), pneumonia, hypoxic ischemic encephalopathy (HIE), CHD, anemia, and hyperbilirubinemia were more likely to develop hypoglycemia in neonates. Data with statistical differences were shown in Table 2.

In the maternal factor, height, parity, age > 35 years, family history of diabetes, and OGTT fasting glucose had no significant effect on NH. Other complications during pregnancy (ICP, thalassemia in pregnancy, hysterosmyoma, anemia in pregnancy, hypothyroidism during pregnancy, viral hepatitis type B, thrombocytopenia in pregnancy, Group B Streptococcus (GBS) infection) had no significant effect on neonatal hypoglycemia. Among the obstetric factors and neonatal outcome, premature rupture of membranes (PROM), oligohydramnios, polyhydramnios, placental abruption, umbilical cord around neck, neonatal weight, head circumference, Apgar 10min ≤7, and FGR had no significant difference in the influence of NH (Table S1).

Larger gestational weeks (OR 0.81, 95%CI 0.77-0.87), elevated OGTT 2-h glucose (OR 1.32, 95%CI 1.20-1.45), pre-eclampsia (OR 1.49, 95%CI 1.00-2.22), cesarean section (OR 2.34, 95%CI 1.87-2.94), placenta previa (OR 1.61, 95%CI 1.04-2.22), TPTL (OR 1.58, 95%CI 1.16-2.15), fetal distress (OR 1.46, 95%CI 1.11-1.95), abnormal placental morphology (OR 1.47, 95%CI 1.11-1.91), neonatal gender(female) (OR 1.38, 95%CI 1.05-1.80), septicemia (OR 2.46, 95%CI 1.26-4.82), HIE (OR 6.70, 95%CI 2.60-17.27), CHD (OR 3.00, 95%CI 2.10-4.29), anemia (OR 4.90, 95%CI 2.13-11.26), and hyperbilirubinemia were statistically

significant and associated with NH in multivariate analysis. These factors increased the risk of NH (Fig. 2). Postpartum hemorrhage (OR 1.00, 95%CI 1.00-1.00) had little effect on the occurrence of hypoglycemia.

Univariate analysis of the independent variables that we included, parity, GWG, and BMI > 30kg/m², were associated with NHB. In addition, having gestational hypertension, higher OGTT fasting glucose, higher OGTT 1-h glucose, and higher OGTT 2-h glucose were more likely to develop NHB. We conducted continuous variable analysis for gestational age and classified variable analysis for preterm delivery, and there were differences in the incidence of NHB between the both ($P < 0.05$).

NHB is at higher risk through cesarean section, PROM, scar uterus, placenta previa, TPTL, fetal distress, oligohydramnios, placental abruption, abnormal placental morphology, chorioamnionitis, umbilical cord around neck, and postpartum hemorrhage effects.

In neonatal outcomes, the lower neonatal weight, shorter birth length, Apgar 1min ≤ 7 , Apgar 5min ≤ 7 , and Apgar 10min ≤ 7 had an impact on the development of NHB. Neonates with FGR, asphyxia, NRDS, septicemia, pneumonia, HIE, CHD, anemia, or hypoglycemia were more likely to develop NHB. All significant data results were presented in Table 2 and Table S1.

A new risk assessment regression model for NHB was established. Our results showed that premature delivery (OR 2.98, 95%CI 1.87-4.47), PROM (OR 1.80, 95%CI 1.42-2.30), abnormal placental morphology (OR 1.41, 95%CI 1.02-1.98), FGR (OR 2.79, 95%CI 1.51-5.17), neonatal pneumonia (OR 4.45, 95%CI 2.88-6.86), CHD (OR 7.76, 95%CI 5.50-10.70), anemia (OR 6.16, 95%CI 2.34-16.22), and hypoglycemia (OR 1.73, 95%CI 1.21-2.47) increased the risk of NHB. Larger gestational weeks (OR 0.85, 95%CI 0.76-0.95) and increased parities (OR 0.73, 95%CI 0.58-0.91) decreased the incidence of bilirubinemia in the newborn (Fig. 3).

Discussion

Our results showed that the incidence of hyperbilirubinemia in neonates with hypoglycemia is 1.73 times higher than that in neonatal non-hypoglycemia, and that NH is an important independent risk factor for NHB. Moreover, increased gestational age has a protective effect on NH and NHB, but abnormal placental morphology is related to the risk factors. In neonatal outcomes, CHD and neonatal anemia were risk factors for NH and NHB, respectively.

In addition, neonates with hyperbilirubinemia were 3.5 times more likely to have hypoglycemia than those without hyperbilirubinemia. NH mainly occurs in the first few hours after birth, but this result illustrates the correlation between NHB and the physiological and pathological mechanism of hypoglycemia⁵. Theoretically, fetal hyperinsulinemia caused by maternal hyperglycemia is the core of NH and increased oxygen demand¹². At the same time, the influence of hyperglycemia on the placenta blood glucose increases neonatal hypoxia^{7,13}.

The relationship between NH and NHB may be mutually influencing, and we conducted two regression analyses of its possible influencing factors. In our model, OGTT 2-h glucose had an effect on NH. Abnormal postprandial glucose levels suggested impaired glucose tolerance and β cell dysfunction on a physiological basis¹⁴. Maternal postprandial hyperglycemia affects the fetus through the placenta, leading to fetal and neonatal hyperinsulinemia, which was one of the main causes of NH¹⁵. Therefore, it is necessary to manage the blood glucose during pregnancy for neonatal outcomes.

Chinese women with DIP are at increased risk for hypertensive disorders during pregnancy or pre-eclampsia, further exacerbating insulin resistance, and are more likely to have adverse pregnancy outcomes¹⁶. In our study, the probability of hypoglycemia was 1.54 times higher in the neonates of mothers with diabetes complicated with pre-eclampsia than in the neonates of pregnant women with diabetes and non-preeclampsia. The rate of cesarean section, macrosomia, and fetal distress in Chinese women with DIP was increased by obstetric screening techniques. Neonates delivered by cesarean section are more likely to develop hypoglycemia¹⁷. Our study also showed that cesarean section was an independent risk factor for NH, and the probability of hypoglycemia was 2.39 times that of neonates delivered by non-cesarean section.

In our study, placenta previa, abnormal placental morphology, fetal distress, and TPTL were risk factors for NH. Placenta previa is prone to premature rupture of the placenta and repeated bleeding, resulting in fetal distress and premature delivery¹⁸. Abnormal placental morphology is prone to intrauterine growth restriction and fetal distress. While the probability of hypoglycemia increased in the fetuses with diabetic mothers due to glucose stimulation of placental blood vessels, to date there is little research on the correlation of abnormal placental morphology and DIP and further exploration is needed. In the hypoglycemia regression model, we also found a positive correlation between neonatal gender, with male neonates being 1.38 times more likely to have hypoglycemia than female neonates.

In NHB, there was a negative correlation for gestational age and a positive correlation for premature delivery, which is consistent with previous studies¹⁹. Previous studies have shown that multiparity are more prone to abnormal blood glucose of pregnant women due to age and other factors^{20,21}. In our study, there was a negative correlation between parity and NHB, the mechanism of which is unknown. The reason that parity is a protective factor for neonatal hyperbilirubinemia may be due to less use of oxytocin and fetal head aspirators in the second fetus, thereby reducing complications²². Among obstetric factors, premature rupture of membranes is prone to fetal infection and hypoxia, resulting in increased erythrocytosis and destruction²³. Hyperglycemia stimulation in DIP leads to decreased placental function and vascular lesions, which aggravated the risk of fetal hypoxia²⁴.

In the physiological and pathological mechanisms, NHB may be a sign of potential intrauterine hypoxia, and the occurrence of neonatal sepsis, ischemia, hypoxia, and anemia is significantly positively correlated with NH²⁵. The lack of detection of neonatal erythrocytes as a direct predictor of NHB in our study only showed a possible correlation with adverse neonatal outcomes in the regression model.

Previously studies have reported that neonates of mothers with diabetes have a higher risk of cardiovascular system abnormalities⁶, and we also observed a positive correlation between congenital heart disease and NH. Neonatal anemia was positively associated with both NH and NHB. It is necessary to strengthen the nursing of neonatal anemia, timely find the risk of adverse outcomes, and give corresponding countermeasures. These findings highlight the correlation between NH and NHB, suggesting that there are physiological and pathological links.

As far as we know from the search results of the systematic review related to the content of this study, this study is a population-based observational study with a large sample size and relatively comprehensive inclusion of relevant variables. We analyzed the effect of NH on NHB in diabetic mothers, providing evidence for home management of neonatal jaundice. The effects of maternal factors, obstetric factors and neonatal outcomes on NH and NHB respectively, as well as the relationship between the both, were also analyzed.

The limitations of this study should also be considered. First, some of the data of NHB were obtained from EMR in neonatal unit after birth or from obstetrics unit transferred to the neonatal unit. The rest of them were obtained through telephone follow-up, which may have recall bias. Second, obstetricians have some differences in the combination of OGTT results and other examination results of pregnant women who have not found abnormal blood glucose before pregnancy to diagnose GDM or pre-pregnancy diabetes. Third, blood glucose control during pregnancy has an important impact on the outcome of delivery, but we failed to obtain this data. Fourth, pre-pregnancy weight is self-reported, and there may be measurement tool and recall bias.

In conclusion, the blood glucose level of DIP is very important for the outcome of childbirth. These findings highlighted the existence of an association between NH and NHB with common risk factors, suggesting physiological and pathological associations between them. Therefore, it is necessary to strengthen the close monitoring of jaundice in neonates with postnatal hypoglycemia to reduce the adverse effects of high bilirubin on the growth and development of neonates.

Materials And Methods

Study period and participants.

This study retrospectively analyzed 10,558 Chinese women with DIP and the neonatal outcomes by reviewing electronic medical records (EMR) between July 1, 2017 and June 30, 2020 from the Chongqing Health Center for Women and Children in Chongqing, China. Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements. This study was approved by the ethics committee of the Chongqing Health Center for Women and Children (Number: 2020-022), all procedures were performed in accordance with the ethical standards. This study has passed the registration of Chinese Clinical Trial Registry (ChiCTR) with the registration label ChiCTR2000040588. In addition, this study was conducted in accordance with

the strengthening the reporting of observational studies in epidemiology (STROBE) statement²⁶. Infants with a clinical diagnosis of neonatal hemolytic jaundice, congenital malformation, stillbirth, or neonatal death were excluded. In this study, 8,504 cases of pregnant women and neonates met the inclusion criteria (Fig. 1).

Diagnosis and definitions.

Pregnant women who had been diagnosed with diabetes before pregnancy, had a fasting plasma glucose (FPG) during pregnancy ≥ 7.1 mmol, or whose blood glucose after 75-g oral glucose tolerance test (OGTT) (or random blood glucose) ≥ 11.1 mmol were diagnosed with PGDM²⁷. Diagnostic criteria for the 75-g OGTT were that the three blood glucose levels should be respectively lower than 5.1, 10.0, and 8.5 mmol/L before, 1-h, and 2-h after glucose administration²⁷.

The most commonly used clinical threshold for treatment was plasma glucose (P-glucose) below 2.6 mmol/L²⁸. Retest blood glucose > 2.6 mmol/L was given routine care, but again, less than 2.6mmol/L was transferred to neonatology department²⁸. The blood glucose monitoring of neonates was conducted using the GK Dual test instrument produced by On-Call Company in China. Newborns in routine obstetric care were monitored by blood sampling at the end of the heel, and newborns transferred to the neonatal intensive care unit (NICU) were monitored by venous blood sampling. Hyperbilirubinemia was diagnosed when percutaneous bilirubin exceeded the 95th percentile of the Bhurani nomogram monitoring time point during bilirubin monitoring. In this study, phototherapy neonates were grouped into hyperbilirubinemia.

In maternal demographic data, pre-pregnancy body mass index (BMI) is calculated as weight recalled from the first obstetric examination. Gestational weight gain (GWG) is calculated as the difference between maternal weight at delivery and pre-pregnancy weight (kg). Scar uterus is defined as having a history of cesarean delivery. Gestational hypertension is defined as the first appearance during pregnancy of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg measured on at least two occasions in the same arm. Pre-eclampsia is an increase in blood pressure and proteinuria that occurs after 20 weeks of gestation. Hypothyroidism is present before pregnancy or detected at the first obstetric examination. Intrahepatic cholestasis of pregnancy (ICP) is diagnosed in women with elevated serum total bile acid (TBA ≥ 10 μ mol/L), the main symptom is pruritus, and other causes of liver dysfunction were excluded²⁹. Polyhydramnios refers to amniotic fluid volume (AFV) ≥ 8 cm or amniotic fluid index (AFI) ≥ 25 cm. Oligohydramnios refers to AFV ≤ 2 cm or AFI ≤ 5 cm.

In obstetric data, abnormal placental morphology included wheel placenta, sail placenta, racket placenta, and accessory placenta. Postpartum hemorrhage is defined as blood loss ≥ 500 ml within 24-h after delivery. Fetal growth restriction (FGR) is defined as a fetus whose birth weight was two standard deviations below the average weight for the same gestational age, or below the 10th percentile of normal weight for the same age. A macrosomia is a newborn with a birth weight greater than 4000g.

Statistical analysis.

Data were collected through double entry (JH and JS) into Excel database. Data was imported and analyzed using SPSS, version 23. Descriptive information was generated, the frequency and percentage of categorical variables and the mean and standard deviation or median (IQR) of continuous variables were calculated. If the variables were continuous (normally or non-normally distributed), an unpaired Student *t* test or Mann-Whitney *U* test was used to compare the differences between the groups. *Chi-squared* tests were used to compare percentages. The missing data of all variables were within 10% without any addressed.

Chinese women with DIP were divided into groups based on neonatal hypoglycemia, non-hypoglycemia, neonatal hyperbilirubinemia, and non-hyperbilirubinemia. For univariate variables, Student *t* test and *Chi-squared* tests were used to compare differences, and $P < 0.05$ was considered statistically significant. Variables with univariate differences were used for multivariate binary stepwise forward logistic regression analysis to produce OR and 95%CI, and parameters of statistical significance ($P < 0.05$) were determined. We compared ignoring missing values within 10% with multiple interpolation methods to evaluate the impact of missing values. The Apgar score was a continuous variable, but there were very few newborns with abnormalities. We converted the Apgar score to ≤ 7 or > 7 for analysis.

Declarations

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Data availability

Data sets generated during the current study have been shared in the research manager (ResMan) repository, (<http://www.medresman.org.cn/login.aspx>). The datasets generated during the current study are not publicly available due to the research data is still being analyzed, but are available from the corresponding author on reasonable request.

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Author contributions

J.H, J.S, X.F, R.T, J.X, Z.Z, Y.Y, Z.C, X.C, and Y.L contributed to the concept and design of the study. J.H. drafted the manuscript. Z.Z, J.S, X.F, R.T, J.X, Y.Y, Z.C have contributed to the acquisition, analysis, or interpretation of data. J.H and J.S completed the statistical analysis. J.B, X.C, and Y.L critically modified the content of the manuscript. Z.C, and X.C provided research supervision. Y.L obtained funding. Z.C, X.C, and Y.L were the guarantors of this study. They have complete access to all the data of the study, and the patients are responsible for the integrity of the data and the accuracy of the data analysis.

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Table

Table 2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Flow chart for study population

Figure 2

Maternal factors and neonatal outcomes associated with neonatal hypoglycemia

Variables	OR (95% CI)	OR (95% CI)	P-value
Gestational weeks		0.85 (0.76, 0.95)	0.004
Premature delivery		2.98 (1.87, 4.74)	<0.001
Parity		0.73 (0.58, 0.91)	0.006
PROM		1.80 (1.42, 2.30)	<0.001
		1.11 (1.02, 1.20)	<0.001

Figure 3

Supplementary Files

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