Maternal Low Fasting Plasma Glucose in the Second Trimester is Associated with Neonatal Asphyxia

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Abstract

**Background** Neonatal asphyxia (NA) is associated with neonatal respiratory distress syndrome, cerebral palsy and neonatal death. Risk factors for NA have been identified as maternal hypertension, premature birth and anemia. While the effect of maternal fasting plasm glucose (FPG) in the second trimester of pregnancy on NA remains unclear.

**Method** Retrospective data from 9661 singleton newborns and mothers were analyzed from January 2016 to July 2018 in Tongzhou district, Beijing. Multivariate logistic regression was used to investigate the risk factors of NA, adjusted for gestational hypertension, triglyceride in the second trimester of pregnancy, fetal distress in utero and preterm birth.

**Results** Of the 9,661 newborns, 26 (2.7‰) were diagnosed with neonatal death (Apgar score 1min = 0) and 52 (5.4‰) with varying degrees of asphyxia (Apgar score 1min = 1 to 6). The asphyxia group showed lower FPG [asphyxia group vs non-asphyxia group, 4.5±0.4 vs 4.8±0.5 mmol/L, P<.01], higher triglyceride level (asphyxia group vs non-asphyxia group, 3.0±1.3 vs 2.5±1.9 mmol/L P<.01) in the second trimester, higher rates of gestational hypertension, fetal distress in utero, preterm birth than the non-asphyxia group (P<.05). Multivariate logistic regression revealed that lower FPG in the second trimester was an independent risk factor of NA [adjusted odds ratio (AOR) 0.26; 95% CI 0.08 to 0.80].

**Conclusion** Pregnant women with low fasting glucose in the second trimester of pregnancy are at increased risk of birth asphyxia in their offspring.

Introduction

Neonatal asphyxia (NA) is a burdening pathology with high short-term mortality and severe long-term consequences [1]. Despite the efforts to reduce its incidence and consequences, NA continues to occur globally in about 4 million babies every year [2] and accounts for 23% of all neonatal deaths and 8% of childhood deaths [3, 4]. The incidence has reached as high as 10 cases per 1000 live births in the less developed countries [5]. The risk of NA among infants is closely correlated with neonatal respiratory distress syndrome (RDS), cerebral palsy (CP) [6], epilepsy, neonatal hypoglycemia, neonatal infections, malignancy [7, 8, 9, 10] and neonatal mortality [11, 12].

The pathogenesis of NA has not been fully elucidated and may be related to increased levels of oxidative stress (OS) and reduced antioxidative capacities [13, 14, 15]. Prolonged or severe NA may have harmful effects first and foremost on the fetal brain [16], as well as other organs, like the heart, lungs, or the kidneys [2]. Several prospective and retrospective studies showed that NA is associated with fetal cardiac rhythm disturbances, cord blood acidosis and a low Apgar score [17]. Clinical studies have suggested that the factors for NA were young maternal age (< 20 years), limited maternal literacy, insufficient antenatal care, non-hospital delivery, maternal hypertension [18, 19, 20], peripartum fetal distress [21], and anemia [22].
Some previous studies showed that gestational diabetes mellitus (GDM) was not significantly correlated with NA [17, 23]. While recent research has demonstrated that, a 1% increase (a unit increase) in HbA1c was observed to be associated with 2.99 times higher odds of NA [95%CI 1.31, 3.85] [24]. The association between maternal fasting blood glucose (FPG) with NA has not been well reported. In this retrospective case-control study, NA was defined as cannot spontaneously initiated breathing within the first minute after delivery and Apgar score < 7 [24]. We mainly explored the relationship between maternal FPG and NA in the second trimester of pregnancy. Identification of risk factors and early initiation of therapy thereby can decrease the rate of NA.

Methods

Study population and data sources

This retrospective case-control study based on live singleton neonates delivered in Beijing between January 1, 2016 and December 31, 2018. Inclusion criteria were: All infants with Apgar score of the first minute after delivery was 1 to 6 at the labor ward during the study period were selected as cases. Exclusion criteria were: multiple pregnancy, embryo transplantation, perinatal fetal death, severe fetal malformation, stillbirths. Newborns with Apgar score of 0 in 1 minute after birth will be excluded in order to avoid the interference of fetal death to NA. Newborns delivered with Apgar score of 10 in 1 minute after delivery were selected and served as control. Cases and controls were matched for maternal age and pre-pregnancy body mass index (BMI).

Oral glucose tolerance test (OGTT) and other serological tests were performed in the morning after an overnight fasting of at least 8 hours. This database contains information on antenatal, obstetrical, and neonatal care that is recorded on Perinatal Health Care System. Clinical information, including variables related to maternal demographics, previous medical and obstetric history, and clinical outcomes of newborns were retrospectively reviewed from medical records. Maternal factors include age, Body Mass Index (BMI), smoking history, family history of diabetes and hypertension in first-degree relatives, hypothyroidism, polycystic ovary syndrome, anemia (defined as third-trimester hemoglobin value less than 10.9 g/dL, or anemia of unspecified severity with diagnosis made before delivery), preeclampsia (defined as systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg on two or more occasions at least 6 h apart and proteinuria $\geq$ 1 + on dipstick or $\geq$ 300 mg on 24-h urine collection), GDM (diagnosed according to IADPSG (The International Association of Diabetes and Pregnancy Study Groups) criteria [25], scar uterine pregnancy, uterine weakness, gestational week of delivery, preterm delivery (delivered prior to 37 weeks gestation), shoulder dystocia, threatened abortion, fetal distress, intrauterine growth restriction and the mode of delivery (natural delivery and cesarean section, use of forceps). Neonatal factors include fetal sex, body length, weight and gestational age. Neonatal outcomes included large for gestational age (LGA, defined as birthweight $>$ 90th percentile for gestational age and sex), small for gestational age (SGA, defined as birthweight $<$ 10th percentile for gestational age and sex), macrosomia (defined as birthweight $\geq$ 4000 g), neonatal asphyxia (defined as cannot spontaneously
initiated breathing and Apgar score = 1 to 7) within the first minute after delivery. Fetal distress in utero was defined by late-decelerations in fetal heart rate [26].

The protocol of this study was approved by Medical Ethics Committee of Beijing Luhe Hospital affiliated to Capital Medical University. And all pregnant women who participated in the study provided written informed consent.

**Statistical analysis**

All data were analyzed using JMP Pro 13.0. Continuous and normally distributed variables were described as means and SDs, and analyzed by independent sample t-test. Categorical variables were described as proportions and examined with Chi-square. Multiple logistic regression model was used to explore the association of FPG in the second trimester of pregnancy and the risk of NA. Potential confounders were retained in the final model if they were preferentially considered important (maternal hypertension, intrapartum hemorrhage, triglyceride in the second trimester, fetal distress in utero and preterm birth). Unadjusted odds ratios (UOR) and adjusted odds ratios (AOR) are reported along with their 95% confidence intervals [CI] and statistical significance was defined at the two-sided level of 0.05.

**Results**

Among the 9661 neonates, 26 (2.7‰) were delivered with perinatal death (Apgar score 1 min = 0), 52 (5.4‰) with NA (Apgar score 1 min = 1 to 6) and 9583 (99.5%) without NA (Apgar score 1 min = 10), as is shown in Fig. 1. Among the asphyxiated newborns, 40 (76.9%) can return to normal Apgar score (Apgar score = 10) within 5 min and 4 (7.7%) within 10 min. We selected 104 newborns with normal Apgar score in a 1:2 case-control ratio from the neonates without NA based on the mother's age and pre-pregnancy BMI as controls.

A total of 156 newborns and mothers were included in the analysis. As is shown in Table 1, the maternal age and pre-pregnancy BMI of the women in different groups were similar, which was 31.3 ± 3.5 years and 23.5 ± 4.6 kg/m² in non-asphyxia group and 31.9 ± 5.04 years and 24.5 ± 4.9 kg/m² in the asphyxia group (P > .05). There were no significant difference in the gestational age during which an obstetric examination performed in the first trimester (4–12 weeks) and second trimester (13–24 weeks) of pregnancy. FPG in the second trimester of pregnancy in the asphyxia group was lower than the non-asphyxia group (asphyxia group vs non-asphyxia group, 4.5 ± 0.4 vs 4.8 ± 0.5 mmol/L, P < .01), while triglyceride and uric acid level were higher than the non-asphyxia group (asphyxia group vs non-asphyxia group, triglyceride 3.0 ± 1.3 vs 2.5 ± 1.9 mmol/L P < .01; uric acid 246.8 ± 58.0 vs 229.3 ± 44.3 umol/L P < .05). In the analysis of categorical variables, the rates of preconception hypertension, gestational hypertension, fetal distress in utero, placental abruption, multigravida, preterm birth, SGA in the asphyxia group tend to be higher than those in the non-asphyxia group (P < .05).
Table 1
Clinical characteristics of maternal and infants of non-asphyxia and asphyxia group.

|                                | Non-asphyxia group (n = 105) | Asphyxia group (n = 53) | P values |
|--------------------------------|------------------------------|-------------------------|----------|
| Maternal age, years            | 31.3 ± 4.5                   | 31.9 ± 5.04             | 0.476    |
| Pre-pregnancy BMI, kg/m²       | 23.5 ± 4.6                   | 24.5 ± 4.9              | 0.200    |
| Overweight or obesity BMI ≥ 25, n (%) | 29(27.6%)                | 22(41.5%)               | 0.063    |
| Standard weight 18.5 ≤ BMI < 25, n (%) | 68(64.8%)                | 24(45.3%)               |          |
| Underweight BMI ≤ 18.5, n (%)  | 8(7.6%)                      | 7(13.2%)                |          |
| Gestational week of first trimester, weeks | 12.3 ± 1.8             | 12.9 ± 2.6              | 0.266    |
| FPG, mmol/L                    | 4.9 ± 0.4                    | 4.9 ± 0.5               | 0.873    |
| UA, umol/L                     | 209.5 ± 47.6                | 226.3 ± 61.3            | 0.083    |
| Creatinine, umol/L             | 50.7 ± 7.1                   | 51.2 ± 6.7              | 0.680    |
| TC, mmol/L                     | 4.6 ± 0.7                    | 4.5 ± 0.8               | 0.560    |
| TG, mmol/L                     | 1.4 ± 0.5                    | 1.5 ± 0.6               | 0.096    |
| LDL, mmol/L                    | 2.5 ± 0.6                    | 2.4 ± 0.6               | 0.424    |
| HDL, mmol/L                    | 1.7 ± 0.3                    | 1.6 ± 0.3               | 0.601    |
| Gestational week of second trimester, weeks | 24.1 ± 1.7             | 24.3 ± 1.6              | 0.544    |
| FPG, mmol/L                    | 4.8 ± 0.5                    | 4.5 ± 0.4               | 0.004    |
| UA, umol/L                     | 229.3 ± 44.3                 | 246.8 ± 58.0            | 0.041    |
| Creatinine, umol/L             | 51.0 ± 6.4                   | 51.0 ± 6.6              | 0.717    |
| TC, mmol/L                     | 6.0 ± 1.1                    | 5.9 ± 1.1               | 0.567    |
| TG, mmol/L                     | 2.5 ± 0.9                    | 3.0 ± 1.3               | 0.005    |
| LDL, mmol/L                    | 3.3 ± 0.9                    | 3.2 ± 0.8               | 0.399    |
| HDL, mmol/L                    | 2.9 ± 0.3                    | 1.9 ± 0.4               | 0.681    |

BMI, body mass index (kg/m²); FPG, fasting plasma glucose; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; OGTT, oral glucose tolerance test; 1hPG, one-hour postprandial glucose; 2hPG, two-hour postprandial glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; LGA, large for gestational age; SGA, small for gestational age. Continuous and normally distributed variables were described as means and SDs, and analyzed by independent sample t-test. Categorical variables were described as proportions and examined with Chi-square or Fisher test.
|                        | Non-asphyxia group (n = 105) | Asphyxia group (n = 53) | P values |
|------------------------|-----------------------------|-------------------------|----------|
| **OGTT for GDM screening** |                             |                         |          |
| FPG, mmol/L            | 4.8 ± 0.5                   | 4.6 ± 0.4               | 0.079    |
| 1hPG, mmol/L           | 8.4 ± 1.9                   | 8.4 ± 1.9               | 0.952    |
| 2hPG, mmol/L           | 7.0 ± 1.56                  | 7.0 ± 1.4               | 0.955    |
| Intrapartum hemorrhage, mL | 340.34 ± 132.7              | 429.8 ± 299.5           | 0.010    |
| SBP, mmHg              | 117.7 ± 11.0                | 124.3 ± 19.5            | 0.007    |
| DBP, mmHg              | 76.0 ± 8.8                  | 79.3 ± 13.7             | 0.067    |
| History of spontaneous abortion, n (%) | 26(24.8%)                 | 14(26.4%)               | 0.822    |
| Family history of diabetes, n (%) | 3(2.9%)                    | 1(1.9%)                 | 1.000    |
| Family history of hypertension, n (%) | 5(4.8%)                    | 5(9.4%)                 | 0.268    |
| Insulin therapy, n (%)  | 3(2.9%)                     | 2(3.8%)                 | 1.000    |
| Gestational hypertension, n (%) | 7(6.7%)                    | 16(30.2%)               | 0.000    |
| GDM, n (%)             | 38(36.2%)                   | 15(28.3%)               | 0.318    |
| Scar uterus, n (%)      | 37(35.2%)                   | 14(26.4%)               | 0.263    |
| Fetal distress in utero, n (%) | 8(7.6%)                    | 20(37.7%)               | 0.0001   |
| Premature rupture of membranes, n (%) | 22(21.0%)                 | 13(24.5%)               | 0.0001   |
| Intrauterine growth restriction, n (%) | 0(0%)                      | 1(1.9%)                 | 0.335    |
| Oligohydramnios, n (%)  | 2(1.9%)                     | 3(5.7%)                 | 0.203    |
| Anemia, n (%)           | 37(35.2%)                   | 17(32.1%)               | 0.692    |
| Polycystic ovary syndrome, n (%) | 2(1.9%)                    | 2(3.8%)                 | 0.603    |
| Hypothyroidism, n (%)   | 11(10.5%)                   | 5(9.4%)                 | 0.838    |
| Umbilical cord around the neck, n (%) | 13(12.4%)                 | 2(3.8%)                 | 0.079    |

BMI, body mass index (kg/m^2); FPG, fasting plasma glucose; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; OGTT, oral glucose tolerance test; 1hPG, one-hour postprandial glucose; 2hPG, two-hour postprandial glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; LGA, large for gestational age; SGA, small for gestational age. Continuous and normally distributed variables were described as means and SDs, and analyzed by independent sample t-test. Categorical variables were described as proportions and examined with Chi-square or Fisher test.
|                                | Non-asphyxia group (n = 105) | Asphyxia group (n = 53) | P values |
|--------------------------------|------------------------------|-------------------------|----------|
| Uterine inertia, n (%)         | 22(21.0%)                    | 8(15.1%)                | 0.375    |
| Abnormal position of fetus, n (%) | 2(1.9%)                   | 4(7.5%)                | 0.098    |
| Primigravida, n (%)            | 41(39.0%)                    | 25(47.2%)               | 0.329    |
| Multigravida, n (%)            | 64(61.0%)                    | 28(52.8%)               | 0.006    |
| Cesarean delivery, n (%)       | 64(61.0%)                    | 30(56.6%)               | 0.599    |
| Male sex of infants, n (%)     | 49(46.7%)                    | 29(54.7%)               | 0.398    |
| Gestational age, weeks         | 38.91 ± 1.7                  | 36.04 ± 4.3             | 0.0001   |
| Preterm birth, n (%)           | 5(4.8%)                      | 23(43.4%)               | 0.0001   |
| Full-term delivery, n (%)      | 97(92.4%)                    | 29(54.7%)               |          |
| Postdates pregnancy, n (%)     | 3(2.9%)                      | 1(1.9%)                 |          |
| Birth height, cm              | 50.0 ± 1.0                   | 46.9 ± 4.8              | 0.0001   |
| Birth weight, grams           | 3431.7 ± 477.7               | 2681.8 ± 1005.6         | 0.0001   |
| Macrosomia, n (%)             | 10(9.5%)                     | 3(5.7%)                 | 0.0001   |
| Normal birth weight, n (%)     | 94(89.5%)                    | 28(52.8%)               |          |
| Low birth weight, n (%)        | 1(1.0%)                      | 22(41.5%)               |          |
| LGA, n (%)                     | 11(10.5%)                    | 4(7.5%)                 | 0.546    |
| SGA, n (%)                     | 3(2.9%)                      | 24(45.3%)               | 0.0001   |

BMI, body mass index (kg/m²); FPG, fasting plasma glucose; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; OGTT, oral glucose tolerance test; 1hPG, one-hour postprandial glucose; 2hPG, two-hour postprandial glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; LGA, large for gestational age; SGA, small for gestational age. Continuous and normally distributed variables were described as means and SDs, and analyzed by independent sample t-test. Categorical variables were described as proportions and examined with Chi-square or Fisher test.

Multivariate logistic regression analysis shows that maternal FPG and triglyceride in the second trimester of pregnancy, fetal distress in utero, preterm delivery were independent risk factors of NA. As is shown in Table 2, in unadjusted model analysis, there were significant associations between FPG [UOR 0.34, 95% CI 0.14, 0.73], triglyceride [UOR 1.58 95% CI 1.14, 2.27] in the second trimester of pregnancy, fetal distress in utero [UOR 7.35, 95% CI 2.96, 18.26], preterm delivery [UOR 15.33, 95% CI 5.76, 48.84] and NA. After adjusting the confounding factors, the correlation of the above variables is still significant. Results from multivariate logistic regression model showed that a 1% (1 mmol/L) increase in triglyceride in the second trimester of pregnancy, 1.87 times higher odds of NA [AOR 1.87, 95% CI 1.21, 2.88], fetal distress and
Table 2
Associations between independent risk factors and neonatal asphyxia.

| Index                        | UOR value | 95%CI          | P value | AOR value | 95%CI          | P value |
|------------------------------|-----------|----------------|---------|-----------|----------------|---------|
| FPG in second trimester      | 0.34      | 0.14–0.73      | 0.0090  | 0.26      | 0.08–0.80      | 0.0184  |
| TG in second trimester       | 1.58      | 1.14–2.27      | 0.0093  | 1.87      | 1.21–2.88      | 0.0047  |
| Fetal distress in utero      | 7.35      | 2.96–18.26     | 0.0001  | 9.17      | 2.82–29.90     | 0.0001  |
| Preterm birth                | 15.33     | 5.76–48.84     | 0.0001  | 30.57     | 7.26–128.71    | 0.0001  |

FPG, fasting plasma glucose; TG, triglyceride; UOR, unadjusted odds ratio; CI, confidence interval; AOR, adjusted odds ratio.

Discussion
Neonatal asphyxia is related to many risk factors, among which the correlation between blood glucose parameters and NA has been controversial. Our research mainly explored the relationship between maternal FPG in the second trimester of pregnancy and NA. After adjusting for risk factors such as gestational hypertension, triglyceride, fetal distress in utero and premature delivery, multivariate logistic regression revealed that maternal FBG level in the second trimester of pregnancy was associated with a decreased risk of NA [(AOR 0.26; 95% CI 0.08 to 0.80) per mmol/L increase in FBG level in the second trimester of pregnancy], which was unreported in previous studies. The results from a study evaluating hypoglycemia and adverse pregnancy outcomes in women with type 1 diabetes, impaired awareness of hypoglycemia (IAH) was associated with an increased risk of neonatal respiratory distress (AOR 11.24, 95% CI 1.01–124.9) [27], were similar to our findings. Additionally, maternal FPG in the third trimester was not significantly associated with asphyxia in our study. Studies have showed that maternal FPG at 24–28 weeks had no significant correlation with NA after adjusting for confounders such as maternal age, parity, pre-pregnancy BMI, blood pressure [24], but before 20 weeks of gestation, the risk of NA increased with the increase of FPG, which was consistent with our study [28]. Additionally, a prospective study showed that an increase in glycated hemoglobin A1c (HbA1c) level at 24–28 weeks of pregnancy will lead to an increased risk of NA [24], which was incompletely consistent with our study. One possible explanation is that, HbA1c reflects average daily glucose levels over an interval of several preceding weeks, so we speculate that blood glucose in the second trimester is possibly related to NA. We even speculate that the association between blood glucose and NA in the second trimester of pregnancy may be a U-shaped
relationship, that is, a certain range of blood glucose does not increase the risk of NA, while too low or too high blood glucose will increase the risk of NA. Due to the limitation of the study size, the FPG level in the second trimester of pregnancy in the study population is between 3.35 mmol/L and 6.92 mmol/L, which may not be enough to cover both ends of the U-shaped curve. The potential mechanism is that elevated oxidative stress and reduced antioxidant capacity caused by hyperglycemia may be related to the pathogenesis of NA [13], while hypoglycemia associated inflammation could lead to impaired fetal lung development, which has been described in animal models induced by hyperglycemia [28, 29].

Dyslipidaemia during pregnancy could also adversely affect the intrauterine environment, leading to short and long-term health issues for both mothers and their offspring. Our study confirmed that the incidence of NA tended to increase with the increase of triglyceride level in the second trimester of pregnancy [AOR 1.87, 95% CI 1.21, 2.88], and previous studies showed that the risk of NA increased with the increase of triglyceride, which was consistent with our results [28]. In addition, we also found that fetal distress and premature delivery were independent risk factors for NA, which was consistent with previous research results [28].

The main research highlight of our research was that we explored the relationship between maternal lower limit of blood glucose and NA, which had previously received little attention. Nonetheless, our study also has some limitations. First, the sample size was relatively small. As this is a retrospective study, we were unable to ascertain the real predicting value of FBG for adverse pregnancy outcomes. Second, data on blood glucose status are derived only from fasting blood glucose, and glycemic spectrum assessment through continuous blood glucose monitoring may help to obtain more accurate data to determine whether the asphyxia group has a higher number of asymptomatic hypoglycemia.

In a word, our study showed that neonates in the asphyxia group showed a trend towards lower fasting glucose in the second trimester than those in the non-asphyxia group. After accounting for important confounders, women with excessively low blood glucose appeared to be more susceptible to neonatal asphyxia. According to our findings, we suggest that the level of blood glucose control in the second trimester of pregnancy should not be too low to avoid adverse pregnancy outcomes for women with or without GDM. In summary, this finding may help identify women at increased risk of neonatal asphyxia and guide clinicians to give the appropriate management to these high-risk patients. However, as this was merely a retrospective study, a large-scale prospective cohort study is needed to further explore the relationship between FBG and NA.

**Declarations**

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**Availability of Data and Materials**
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**

Conceived and designed the experiments: SSY, DZ. Analyzed the data: SSY, YXA, YXY, KL. Contributed reagents/materials/analysis tools: JK, DZ. Wrote the paper: SSY, DZ.

**Competing interest**

Authors have nothing to disclose. There are no potential conflicts of interest of a financial or other nature.

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