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Meta-analysis of Clinical High-risk Factors for the Development of Neonatal Hypoglycemia

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Abstract: GDM is a common clinical complication of pregnancy, the incidence rate has been increasing in recent years and the risk of neonatal development of neonatal hypoglycemia (NH) has significantly increased. Studies have shown that the incidence of NH in GDM-delivered newborns is up to 27%. Severe hypoglycemia can cause irreversible brain injury and neurological sequelae in newborns, NH is one of the most common metabolic diseases in neonatal intensive care units. However, many scholars have discussed the related risk factors of neonatal hypoglycemia, but the risk factors and research results are different among the studies and there are some controversies. Therefore, this study aims to conduct a Meta-analysis through the domestic and foreign published studies on the risk factors for neonatal hypoglycemia, to identify the main risk factors for neonatal hypoglycemia, and to provide a basis for early clinical prevention and timely development of scientific and effective interventions. Through health and interest Engineering, the computer conducted a literature search in the medical databases of Wanfang Medical, PubMed database, domestic medical research journals, and biomedical medical literature, and conducted a Meta-analysis using Rev Man 5.2 software based on the clinical risk factors of neonatal hypoglycemia. The retrieved literature was screened according to the criteria of study subjects, methods, disease type, and so on, and a total of 9 documents meeting the criteria were finally included, with low bias. The results of the Meta-analysis showed statistical differences in the incidence of pregnant and maternal gestational diabetes, neonatal asphyxia and low birth weight infants in the hypoglycaemic and non-hypoglycaemic neonatal groups, Moreover, the incidence of pregnant and maternal gestational diabetes, neonatal asphyxia, and low birth weight infants was significantly lower in the hypoglycemic neonatal group($P<0.05$); Studies evaluated maternal gestational diabetes, neonatal asphyxia and low birth weight infants with neonatal hypoglycemia, The results showed that maternal gestational diabetes, neonatal asphyxia, and low birth weight infants all increase the risk of neonatal hypoglycemia($P<0.001$). Therefore, for children with neonatal hypoglycemia, pregnant mothers and gestational diabetes, neonatal asphyxia, and low-weight children are all high-risk factors for hypoglycemia, clinicians should do a good job in prevention and control, and intervention to reduce the incidence of neonatal hypoglycemia.

Keywords: Newborn; Hypoglycemia; Asphyxia; Gestational Diabetes; Risk Factors; Meta-analysis.

1. Introduction

Gestational diabetes mellitus (Gestational diabetes mellitus (GDM) is a common and clinical complication of pregnancy, the incidence has increased in recent years, and the risk of neonatal hypoglycemia (neonatal hypoglycemia, NH) is significantly increased[1]. Studies have shown that the incidence of NH in GDM-delivered newborns is up to 27%. Severe hypoglycemia can cause irreversible brain injury and neurological sequelae in newborns, NH is one of the most common metabolic diseases in neonatal intensive care units[2-3]. The occurrence of NH is associated with childbirth and obstetric factors, such as low birth weight infants, macrosomia, preterm infants, fetal intrauterine distress, neonatal asphyxia, neonatal hemolysis, congenital diseases, perinatal stress and poor maternal blood glucose control during childbirth, GDM, etc[4-5]. Neonatal hypoglycemia is a common disease, frequently-occurring, good in premature term, term infants, infants, hypoxia asphyxia, hard swelling, infection of sepsis, and diabetic mother delivery newborn, if not timely and effective treatment, can lead to irreversible central nervous system damage, survivors often with low intelligence, serious sudden death will occur[6-7]. Studies have shown that various factors such as perinatal maternal and infant physiology and pathology may affect neonatal glucose metabolism, the American Academy of Pediatrics believes that clarifying the high-risk factors of neonatal hypoglycemia is the key to preventing severe neurological damage[8-9]. In recent years, although many scholars have explored the related risk factors of neonatal hypoglycemia, the risk factors and research results included in the analysis are different among the studies and there are some controversies[10]. Therefore, this study aims to conduct a Meta-analysis through the domestic and foreign publicly published studies on the risk factors for neonatal hypoglycemia, to identify the main risk factors for neonatal hypoglycemia and to provide a basis for early clinical prevention and timely development of scientific and effective interventions, which is now reported as follows.

2. Data and Methods

2.1. Literature Search

2.1.1. Literature Search

Neonates hypoglycemia; asphyxia; gestational diabetes; high-risk factors neonatal; hypoglycemia; asphyxia; gestational diabetes; risk factors, etc. Relevant literature on the meta-analysis of clinical risk factors for the occurrence of neonatal hypoglycemia in nearly 20 years can be collected by computer in domestic biological and medical research journals, Wanfang database, PubMed, and other medical journal databases, which can also be contacted with experts

and pharmaceutical factories in relevant fields to obtain information. Contact the original author for acquisition when the literature is missing or roughly reported. Through the summary of the literature: the newborn hypoglycemia; asphyxia; gestational diabetes; risk factors. The study must be approved by the relevant institutions. There is no error in the operation steps of the study. At the same time, the literature with repeated contents, inconsistent research methods, and lax operation will be excluded, the literature that meets the requirements will be used by Meta for data analysis.

2.2. Literature Selection Criteria

1) inclusion criteria: The study children were newborn or hypoglycaemic newborns; each study covered any of the following neonatal hypoglycemia risk factors: maternal factors (gestational diabetes, gestational hypertension, cesarean delivery, improper feeding), neonatal factors (asphyxia, hypothermia, follow-weight) during follow-up, the study must be approved for nearly 20 years; no errors during the study.

2) exclusion criteria: studies only on specific newborns such as preterm or low birth quality infants; incomplete clinical data; diabetes combined with pregnancy; hypertension during pregnancy; twin pregnancy; animal experiments; unrelated to the study topic; review, meta, case report, conference summary; patients with severe hematological disorders.

2.3. Study Outcome Measures

Gestational diabetes mellitus; neonatal asphyxia; low birth weight; risk factors; gestational diabetes; neonatal asphyxia; low birth weight infants; risk factors.

2.4. Quality Evaluation

The modified Jadad scale was scored from 1 to 7 points, the literature quality was evaluated using this scale, with 3 points classified as low-quality literature and otherwise as high-quality literature.

2.5. Statistical Treatment

RevMan5.2 statistical software was analyzed, the count data in RR as representation, the analysis statistics in SMD, and the effect size as 95% CI. When the heterogeneity of $P<0.1$, I^2 The 50% used random effects model analysis, whereas used fixed model analysis, the difference was statistically significant.

3. Results

3.1. Literature Search Results and the Characteristics of the Included Study

In Chinese and English databases, according to the search strategy search, the total search literature was 342 articles, according to the exclusion criteria for literature screening, eventually into 9 literature, 4 of the English literature and 5 Chinese literature into the basic characteristics of the research literature, the literature quality evaluation results into the literature has 1 low quality, 8 high quality. table 1 is the specific information.

Table 1. Basic characteristics of literature

the first author	The year of publication	sample capacity	Outcome indicators	Quality of literature
Jia Tianming[11]	2018	100/100	1) 2)3)4)5)6)	4
Dunbar D C[12]	2021	46/46	1)2)3)4)5)6)	4
Jin Ye[13]	2019	36/36	1)2)4)5)	2
Huang S[14]	2021	40/40	2)3)5)6)	4
Sgouros D[15]	2015	50/50	1)3)4)6)	6
Wang Min[16]	2017	55/55	2)5)	5
Zhou C[17]	2016	43/42	3)3)5)6)	3
Huang H[18]	2018	50/50	1)4)	6
Chen Yuping[19]	2017	30/30	1)3)4)6)	6

Note: 1) gestational diabetes; 2) neonatal asphyxia; 3) low birth weight children; 4) risk factors for gestational diabetes; 5) newborn asphyxia risk factors; 6) low birth weight child risk factors.

3.2. Results of the Literature Bias Analysis

The final 9 included documents all RCT documents with multi-center characteristics, all gave detailed explanations and the methods were correct. The results of publication bias assessment showed that the risk of bias in the included research literature was low with attached Figures 1 and Figure 2.

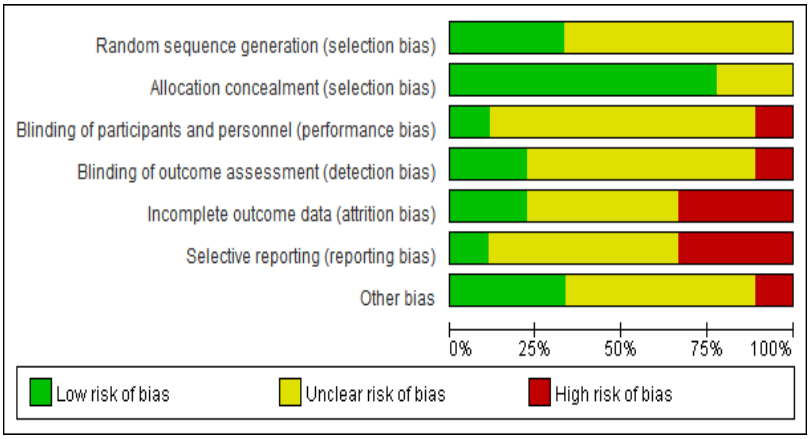

Figure 1. Bias analysis of literature

Figure 2. Bias analysis of literature (2)

3.3. The Meta-analysis Results

3.3.1. Results of the Meta-analysis of Differential Gestational Diabetes Mellitus

A total of 5 articles on gestational diabetes were included, the heterogeneity was not significant (I^2=0%, P=0.69). Fixed-effect model analysis showed a statistical difference in the incidence of maternal gestational diabetes in the hypoglycemic and non-hypoglycemic neonatal groups, it was significantly higher in the hypoglycaemic neonatal group [P<0.00001] as shown in Figures 3–4.

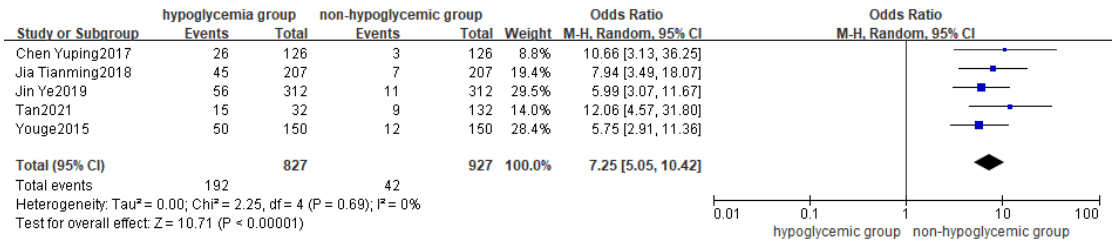

Figure 3. Forest plot of the Meta-analysis results of differences in gestational diabetes

3.3.2. Results of the Meta-analysis of Neonatal Asphyxia Differences

A total of 6 articles on neonatal asphyxia were included, with significant heterogeneity (I^2=66%, P=0.01). Fixed-effect model analysis showed a statistical difference in the incidence of asphyxia in hypoglycemic and non-hypoglycemic newborns and was significantly higher in hypoglycemia newborns[P<0.00001] as shown in Figures 5-6.

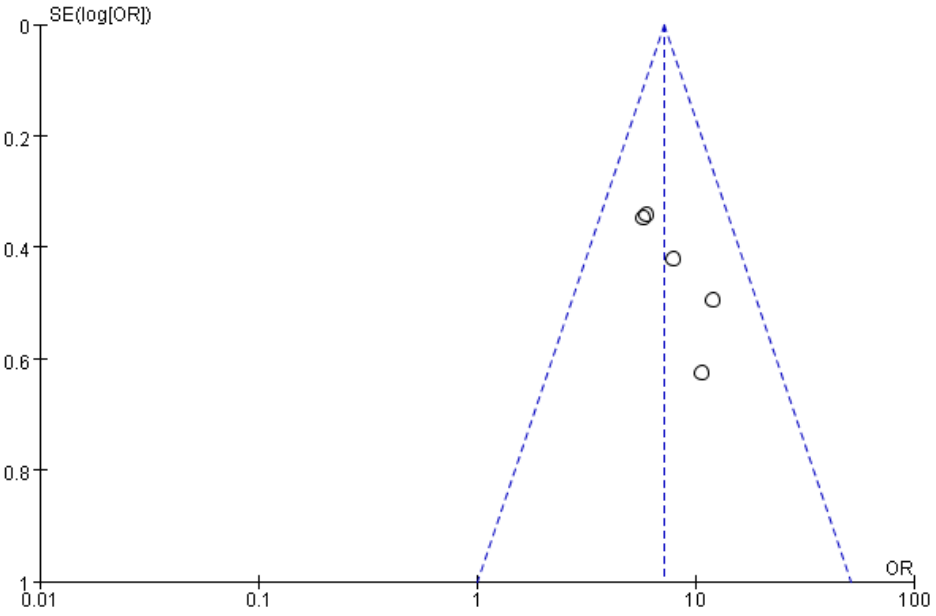

Figure 4. Funnel plot of the Meta-analysis results of the differences in gestational diabetes

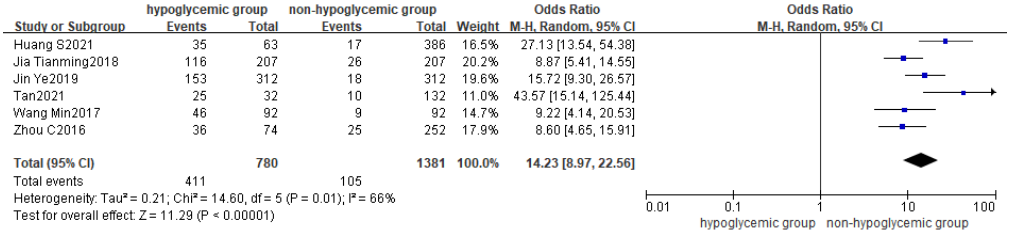

Figure 5. Forest plot of Meta-analysis of neonatal asphyxia

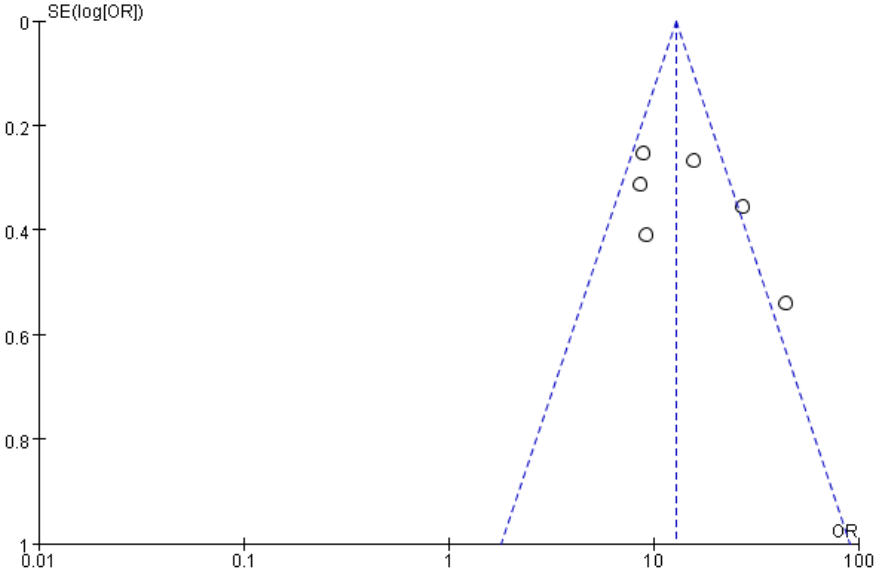

Figure 6. Funnel plot of the Meta-analysis results of neonatal asphyxia differences

3.3.3. Results of the Meta-analysis of Low Birth Weight Infants

A total of 6 articles on low birth weight children were included, the heterogeneity was not significant(I^2=36%, P=0.16). Fixed-effect model analysis showed a statistical difference in the incidence of low birth weight infants in the hypoglycemic and non-hypoglycemic newborn groups, it was significantly higher in the hypoglycemic newborn group[P<0.00001] as shown in Figures 7–8.

3.3.4. Relationship between Pregnant and Maternal Gestational Diabetes Mellitus and Neonatal Hypoglycemia

Six studies evaluated the relationship between maternal gestational diabetes and neonatal hypoglycemia, the heterogeneity test results were statistically significant (I^2=89%) and were analyzed using a random effects model. The results showed that pregnant and maternal gestational diabetes increased the risk of neonatal hypoglycemia, combined with an OR of 1.53(P=0.003) as shown in Figure 9.

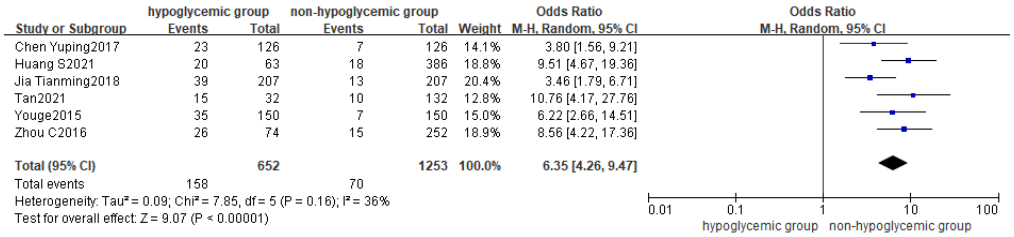

Figure 7. Forest plot of Meta-analysis results for low birth weight infants

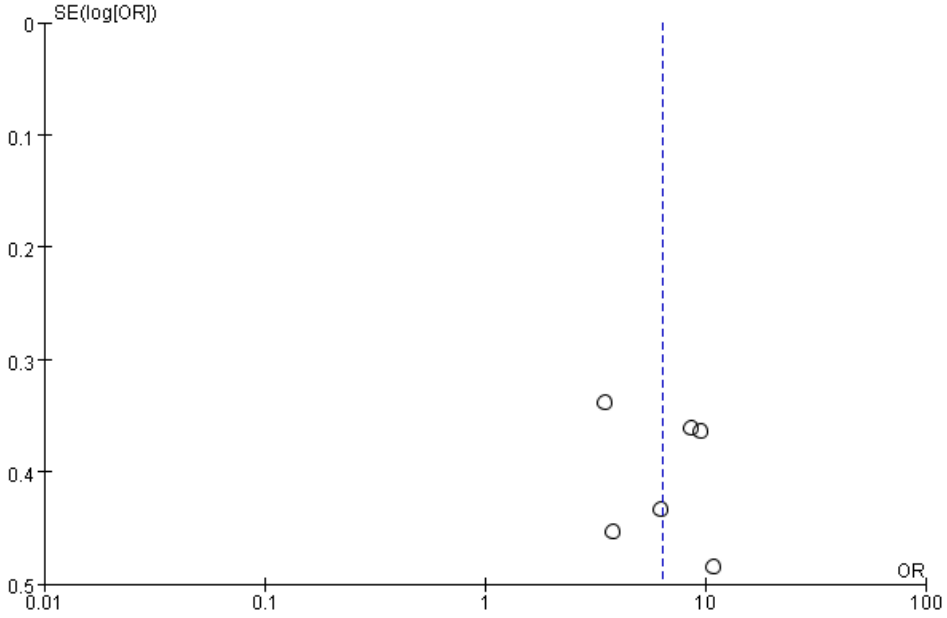

Figure 8. Funnel plot of Meta-analysis results of low birth weight infants

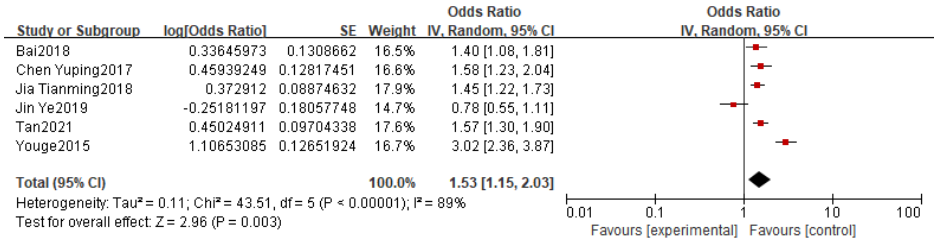

Figure 9. Forest plot of the relationship between gestational diabetes mellitus and neonatal hypoglycemia in pregnant mothers

3.3.5. Relationship between Neonatal Asphyxia and Neonatal Hypoglycemia

Six studies evaluated the relationship between neonatal asphyxia and neonatal hypoglycemia, the heterogeneity test results were statistically significant(I^2=97%) and were analyzed using a random-effect model. The results showed that neonatal asphyxia increased the risk of neonatal hypoglycemia, with a combined OR of 1.36(P<0.00001) as shown in Figure 10.

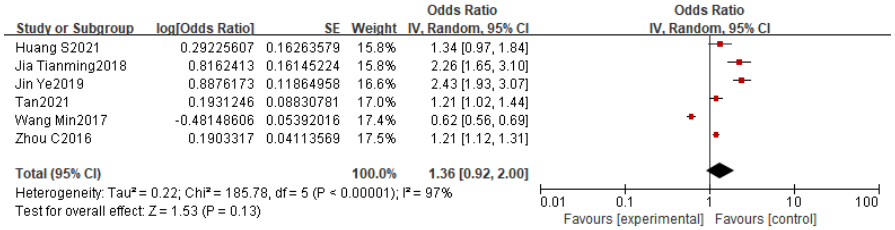

Figure 10. Forest plot of the relationship between neonatal asphyxia and neonatal hypoglycemia

3.3.6. Association between Low Birth Weight Infants and Neonatal Hypoglycemia

Six studies evaluated the relationship between low birth weight infants and neonatal hypoglycemia, the heterogeneity test results were statistically significant(I^2=96%) and were analyzed using a random effects model. The results showed that low birth weight infants would increase the risk of neonatal hypoglycemia, with an integrated OR of 1.11(P<0.00001) as shown in Figure 11.

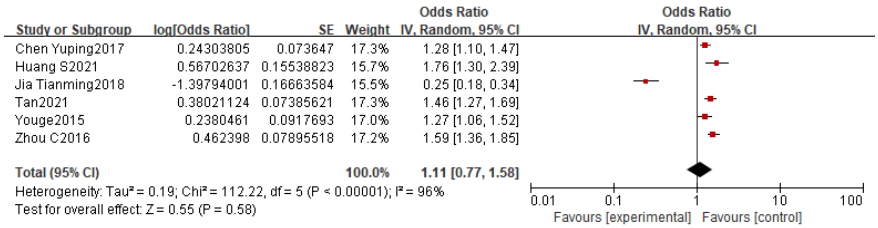

Figure 11. Forest plot of the relationship between low birth weight infants and neonatal hypoglycemia

4. Discussion

With the opening of the two-child policy in China and the improvement of people's living standards in recent years, the advanced age and high-risk women with pregnancy diseases such as GDM have increased year by year[20]. Since 2015, the new time limit of labor has been gradually implemented in China, the blood glucose changes, blood glucose monitoring, and management of GDM patients have become the focus of obstetrics department. Placenta is the main source of energy(glucose)obtained by the fetus from the mother. With the progress of pregnancy, the amount of glucose obtained by the fetus from the mother increases, resulting in the decrease of the plasma glucose level of pregnant women, the increase of the renal plasma flow and glomerular filtration rate during pregnancy, but the sugar reabsorption rate of renal tubules does not increase accordingly[21]; In addition, estrogen and progesterone increase maternal glucose utilization, so the ability to remove glucose when fasting is stronger than during non-pregnancy[22].

NH is a common disease in neonatal intensive care units. Severe NH can cause neonatal brain injury, including cortical neuronal injury, cerebral cortical atrophy, parenchymal hemorrhage and ischemic stroke, parietal and occipital white matter damage, mainly damage to cerebral cortical nerve cells, the occipital and parietal areas are the most seriously involved. Brain injury caused by severe NH shows extensive cortical damage, which can combine with white matter, basal ganglia, and thalamus damage[23]. Studies have shown that the vast majority of treated NH children will not have brain damage, the neural development of NH children at 2 years old is similar to that of normal infants, but there is an obvious gap between the execution force and visual and motor function of NH children at 4 to 5 years old and that of normal infants[24]. Previous studies have generally believed that asymptomatic hypoglycemia has little effect on the neonatal nervous system, but recent studies have shown that transient asymptomatic hypoglycemia can lead to some neurological sequelae. Therefore, effective preventive measures should be taken to prevent NH of NH high-risk children, such as avoiding cold injury, prescribing milk as soon as possible, and timely glucose supplementation. Thus, we can see that clarifying the birth period high-risk factors for NH in GDM patients and actively preventing and treating them will have an important role in improving the long-term prognosis of GDM offspring[25].

The risk of hypoglycemia in mothers with gestational diabetes, gestational hypertension, and selected cesarean section on delivery mode were 4.83, 5.25, and 3.50 times higher in non-hypoglycemic neonates, respectively. Due to gestational diabetes mother blood sugar concentration is higher, and the fetus from the mother glucose will be greatly increased, to stimulate the amount of fetal islet cell proliferation, increasing insulin levels, the fetal hyperinsulinemia, once the fetus delivery from the mother body glucose source will be interrupted, while the fetal body insulin is continuously at high levels, combined with the fetus shortly after birth because of gluconeogenesis function, leading to the occurrence of neonatal hypoglycemia[26]. Studies have shown that the incidence of hypoglycemia in newborns with gestational diabetes mellitus can be as high as 30% to 50%. Due to the decrease of placental blood perfusion, the pregnant mother affects the blood supply and oxygen from the placenta to the fetus, thus hindering the growth and development of the fetus in utero, the activity of glycogen synthase is significantly reduced in the state of ischemia and hypoxia, leading to the disorder of glycogen synthesis in the fetus, which greatly increases the incidence of neonatal hypoglycemia [27].

Neonatal asphyxia is the absence of spontaneous breathing or the failure to establish regular breathing within 1 min after birth. The anaerobic glycolysis in the hypoxic body reduces the utilization rate of glucose, leading to an increase in glycogen consumption, eventually leading to the hypoglycemia of the newborn baby. Studies have reported that asphyxia is the most important risk factor leading to neonatal hypoglycemia and it is easy to cause severe hypoglycemia, which suggests that medical staff should closely monitor blood glucose changes in addition to blood oxygen indicators of asphyxia newborns. Studies have shown that hyperbilirubinemia can affect the gluconeogenesis pathway of the liver and kidney, neonatal infection can increase the catecholamine and other hormones in the blood and increase the body metabolism, thus leading to the occurrence of neonatal hypoglycemia. However, this Meta-analysis did not show the differential results of neonatal hyperbilirubinemia and neonatal infection in neonatal hypoglycemia, which may be related to the small number of literature included in this time, so more high-quality studies are needed.

5. Conclusion

For newborns, pregnant women, maternal gestational diabetes, neonatal asphyxia and low-weight infants are all high-risk factors for hypoglycemia, clinicians should do a good job in prevention, control and intervention to reduce the incidence of neonatal hypoglycemia.

Data Availability

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Acknowledgments

Explore the application of daytime blue light diagnosis and treatment mode in neonatal wards of primary hospitals, Zhuji

City Science and Technology Bureau, Project number: 2023YW091.

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