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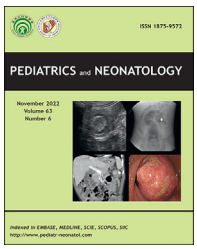

Original Article

Identifying additional risk factors for early asymptomatic neonatal hypoglycemia in term and late preterm babies

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Key Words
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Background: Neonatal hypoglycemia is a common metabolic disorder in newborns, which may present with non-specific symptoms or even be asymptomatic. Current guidelines recommend screening for hypoglycemia in at-risk babies (late preterm, small for gestational age, large for gestational age, and infants of diabetic mothers). Past studies have suggested other potential risk factors, such as maternal obesity, gestational hypertension, cesarean section, etc. In this study, we aim to identify additional prenatal and perinatal maternal/fetal characteristics associated with early asymptomatic hypoglycemia in term and late preterm babies.
Methods: We performed a retrospective review on medical charts of all newborns, born between January, 2017 and December, 2020, in the well-baby newborn nursery of a tertiary medical center. We identified newborns who had received blood glucose concentration monitor after birth. Detailed prenatal and perinatal maternal/newborn information were collected for analysis.
Results: In the study period, 841 newborns had received blood glucose screening after birth. After matching by sex and indication for postnatal blood glucose screen (SGA, LGA, and GDM), 148 newborns were included in the "hypoglycemia group" and 296 newborns were included in the "euglycemia group". In the univariate analysis, parity, insulin treatment for gestational diabetes mellitus (GDM), and cesarean section were associated with an increased

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risk for neonatal hypoglycemia. Factors associated with decreased risk included higher gestational age, longer duration of skin-to-skin contact, neonatal hyperthermia, higher maternal labor pain score, and epidural anesthesia administration. By multivariable analysis, insulin treatment for GDM was identified as an independent factor associated with increased risk for neonatal hypoglycemia.

Conclusion: Our study showed insulin treatment for GDM to be independently associated with neonatal hypoglycemia. Other risk factors noted in the univariate analysis, such as decreased skin-to-skin contact duration, hypothermia, Cesarean section, and preterm delivery, would require further investigation to confirm the findings.

1. Introduction

Neonatal hypoglycemia is a common metabolic disorder that occurs shortly after the birth of a newborn baby.[1] During gestation, the fetus receives energy substrates, such as glucose, ketones, free fatty acids, and amino acids through placental transfer to meet its metabolic demands.[2] After birth, this energy source is cut off and an abrupt decrease in blood glucose concentration results. The nadir of blood glucose concentration occurs around 1 h after birth, which can be as low as 20–25 mg/dL (1.1–1.4 mmol/L).[3] This drop in blood glucose concentration, also known as transitional neonatal hypoglycemia, leads to an important question, "How low is too low?"

The definition for neonatal hypoglycemia remains controversial. The "numerical" level below which adverse neurological or developmental outcome may result is still unclear.[2] A widespread accepted definition for neonatal hypoglycemia is $<$ 47 mg/dL ($<$2.6 mmol/L), which was suggested by Lucas et al. in a 1988 multicenter nutritional study.[4] In this study of 661 preterm infants with a birth weight $<$1850 g, the number of days that blood glucose concentration was below 47 mg/dL correlated with lower motor and mental development scores when evaluating with the Bayley Scales of Infant Development at the corrected age of 18 months old.[1,4]

Clinically, babies experiencing neonatal hypoglycemia can present with non-specific symptoms or they may even be asymptomatic.[4,5] Due to concern about the potential harm of neonatal hypoglycemia, it is a common practice to screen for babies at risk (late preterm infants, small for gestational age, large for gestational age, and infants of diabetic mothers) for neonatal hypoglycemia.[5,6]

Currently, two different operational thresholds are provided by the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES).[6,7] The AAP guideline takes into consideration of the lower glucose concentration in asymptomatic infants and focuses on the clinical condition of the newborn.[3,6] It recommends intervention when blood glucose concentration is $<$ 40 mg/dL in the first 4 h after birth and $<$45 mg/dL afterwards.[6] The PES, on the other hand, takes into consideration of the 55–65 mg/dL blood glucose concentration threshold for neurogenic symptoms in older children and adults and the relative lack of alternative fuel in the newborn period.[3,7] Therefore, the PES recommended the safety threshold of 50 mg/dL (2.8 mmol/L) within the first 48 h of life.[7]

In addition to the established risk factors for neonatal hypoglycemia (late preterm infants, small for gestational age, large for gestational age, and infants of diabetic mothers), several studies have tried to identify other risk factors. One frequently mentioned risk factor is maternal obesity, which has been shown to be associated with a higher neonatal hypoglycemia rate.[8–10] Several studies also focus on the premature population. In premature babies born $<$33 weeks' gestation, maternal hypertension was shown to be a risk factor for neonatal hypoglycemia, while being in labor at the time of delivery and antenatal magnesium sulfate administration were shown to offer protective effects.[11] Antenatal steroid administration has also been suggested as another risk factor for neonatal hypoglycemia in premature babies born $\leqq$ 32 weeks' gestation.[12]

The abovementioned risk factors were identified mainly in non-Asian study populations, and many were performed on premature babies. Premature babies often received more intensive care after birth, including blood glucose concentration monitoring, compared to healthy babies in the well newborn nursery. Therefore, it may be even more crucial to identify risk factors for neonatal hypoglycemia in the well newborn nursery. In this study, we aim to identify additional prenatal and perinatal maternal/fetal characteristics associated with early asymptomatic hypoglycemia in term and late preterm babies admitted to the well newborn nursery.

2. Methods

We performed a retrospective review on medical charts of all newborns, born between January, 2017 and December 2020, in the well-baby newborn nursery (Level I nursery) of Chi Mei Medical Center, Tainan, Taiwan. Approval was obtained from the Institutional Review Board of the hospital before data collection (IRB No.: 11001-006).

Our well newborn nursery admits newborns with gestational age of more than 35 weeks, who are healthy-appearing after birth. Our protocol is as the PES guideline.[7] Blood glucose concentration monitors were provided for newborns small for gestational age, large for gestational age, or born to diabetic mothers. The measurement of

blood glucose concentration was performed by point-of-care-testing on capillary blood samples obtained by heel-prick lance. An operational threshold of <50 mg/dL (2.8 mmol/L) was used for defining neonatal hypoglycemia. The safe target for blood glucose concentration is set at > 50 mg/dL (2.8 mmol/L) within 48 h after birth. Increased feeding with breast milk or D10W would be provided when the blood glucose concentration was below the operational threshold. Patients with persistent hypoglycemia or symptomatic hypoglycemia requiring intravenous glucose infusion would be transferred to the specialty care nursery (level 2 nursery) for further care.

2.1. Inclusion and exclusion criteria

By chart review, we identified newborns admitted to the well newborn nursery who were born between January, 2017 and December 2020, and who had received blood glucose concentration monitor by the nursery protocol. These "at-risk" newborns include those born small for gestational age, large for gestational age, and those born to diabetic mothers.

The purpose of this study was to identify additional prenatal and perinatal risk factors for early asymptomatic neonatal hypoglycemia shortly after birth. Postnatal environment factor, breastfeeding establishment, and maternal breast milk amount can be confounding factors. Therefore, we excluded newborns with hypoglycemia episodes that occurred after 4 h (240 min) of life. Patients with medical records containing missing values and incomplete data were also excluded for accurate analysis.

2.2. Data collection

The following information was collected from the patient's medical charts: gestational age, sex, birth body weight, body length, duration of skin-to-skin contact after birth, Apgar score at 1 min after birth, and Apgar score at 5 min after birth. Further information was collected from the medical charts of the neonates' mothers, including maternal age, gravidity, parity, presence of peripartum fever, pain score during labor, presence and management of PIH, presence of and management of GDM, BMI, route of delivery (NSD or C/S), rupture of membrane duration, and presence of amniotic fluid staining. We also collected information on peripartum medication administration, including induction agents (dinoprostone, oxytocin, and hyoscine butylbromide), epidural analgesia during labor, and antibiotics (cefazolin).

2.3. Statistical analysis

Neonates who developed hypoglycemia (hypoglycemia group) and those who did not (euglycemia group) were presented in this study. In consideration of potential confounding factors affecting comparison between the two study groups, the exact matching approach was used to 1:2 match the neonates for sex and indication for postnatal blood glucose screen (SGA, LGA, or GDM). Each hypoglycemia patient had two corresponding euglycemia patients based on the same sex and indication for postnatal blood glucose screen. All categorical variables were presented as frequencies with percentage and Pearson's chi-square test or Fisher's exact test was used to compare the difference between two groups. Mean with standard deviation was used for the continuous variables and the difference between two groups was estimated using t test. To find the potential confounding factors which had association with the hypoglycemia group and euglycemia group, conditional logistic regression analysis was used to calculate the odds ratios (OR) with 95% confidence interval (95% CI) according to the matched case–control data. In addition, to ascertain the major confounding factors, the crude OR from univariate conditional logistic regression analysis was used selecting the variables for which $p < 0.05$ in the multivariable conditional logistic regression model. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The level of significance was set as $p < 0.05$.

3. Results

Between January 2016 and December 2020, 3895 newborns were admitted to the well newborn nursery. As shown in Fig. 1, 841 (21.6%) of all newborns were LGA, SGA, or born to diabetic mothers, and had received blood glucose concentration measurements after birth. Thirteen newborns

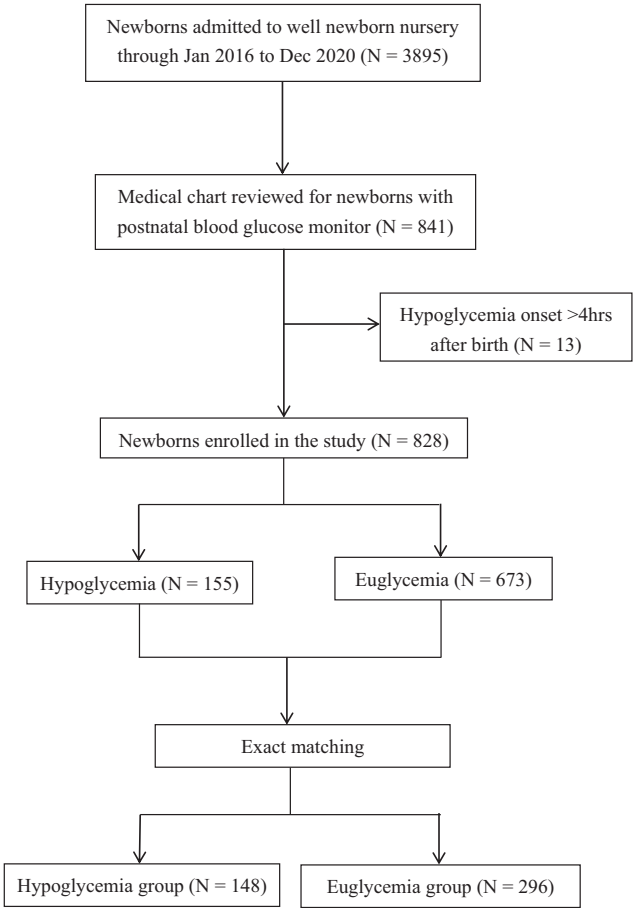

Figure 1 Enrollment of newborns screened for early hypoglycemia after birth.

were excluded due to hypoglycemia onset over 4 h after birth. After matching, 148 newborns were included in the "hypoglycemia group" and 296 newborns were included in the "euglycemia group".

The demographics of the two groups of patients are presented in Table 1. Sex and indication for postnatal blood glucose screen were matched in the same distribution. There was no difference in birth body weight, body length, Ponderal Index, amniotic fluid staining, amniotic membrane rupture duration, 1-min Apgar score, or 5-min Apgar score. The maternal demographics in the hypoglycemia and euglycemia groups are presented in Table 2. There was no significant difference in age, WBC, peripartum fever (no mother in this study developed fever), gestational diabetes frequency, pregnancy induced hypertension frequency, or BMI.

For neonatal factors, the hypoglycemic group had lower gestational age, lower body temperature at admission, and lower skin-to-skin contact duration. In maternal factors, higher parity, higher frequency of insulin treatment for GDM, and higher frequency of cesarean section were found in the hypoglycemic group. The hypoglycemic group also had lower maternal pain score and lower frequency of epidural anesthesia during labor.

In the univariate analysis (Table 3), parity (OR 1.49, 95% CI 1.12—2.00), insulin treatment for GDM (OR 5.75, 95% CI 1.51—21.91), and cesarean section (OR 2.38, 95% CI 1.56—3.65) were associated with an increased risk for neonatal hypoglycemia. Factors associated with decreased risk of neonatal hypoglycemia included higher gestational age (OR 0.76, 95% CI 0.64—0.90), longer duration of skin-to-skin contact (OR 0.97, 95% CI 0.95—0.99), neonatal hyperthermia (OR 0.23, 95% CI 0.07—0.79), higher maternal labor pain score (OR 0.90, 95% CI 0.84—0.97), and epidural anesthesia administration in labor (OR 0.44, 95% CI 0.27—0.70).

In the multivariable analysis (Table 3), maternal insulin treatment for GDM was identified solely as an independent factor associated with increased risk for neonatal hypoglycemia (OR 6.65, 95% CI 1.54—28.82).

4. Discussion

The strength of this study is that many detailed factors were taken into consideration. In addition to maternal and neonatal basic characteristics, we also included maternal factors such as pain score during labor, medication administration such as induction agents and epidural anesthesia, and even management after delivery such as skin-to-skin contact.

In our study, significantly lower gestational age was observed in the hypoglycemic group, when compared to the

Table 1 Demographics of newborns in the hypoglycemia and euglycemia groups.

	Hypoglycemia (n = 148)	Euglycemia (n = 296)	P-value
Indication for postnatal blood glucose screening			>0.99
SGA	79 (53.38%)	158 (53.38%)	
LGA	26 (17.57%)	52 (17.57%)	
Maternal GDM	43 (29.05%)	86 (29.05%)	
Sex			>0.99
Male	69 (46.62%)	138 (46.62%)	
female	79 (53.38%)	158 (53.38%)	
GA	38.23 ± 1.24	38.63 ± 1.22	0.001*
Term	129 (87.16%)	268 (90.54%)	0.326
Preterm (≤36 + 6)	19 (12.84%)	28 (9.46%)	0.326
Gravida	2.09 ± 0.98	1.92 ± 1.17	0.096
Para	1.68 ± 0.67	1.48 ± 0.73	0.005*
BBW	2993.30 ± 707.90	2918.3 ± 599.20	0.270
Body length	49.69 ± 3.00	49.6 ± 2.77	0.755
Ponderal index	2.41 ± 0.28	2.37 ± 0.24	0.143
Apgar Score			
1 min	7.99 ± 0.12	7.97 ± 0.19	0.248
5 min	9.00 ± 0.00	9.00 ± 0.00	—
BT at admission	37.16 ± 0.54	37.33 ± 0.56	0.003*
BT > 37.5	35 (23.65%)	112 (37.84%)	0.003*
BT > 38	3 (2.03%)	23 (7.77%)	0.017*
BT < 36.5	38 (25.68%)	50 (16.89%)	0.029*
ROM time (min) (mean ± SD)	102.70 ± 226.00	149.60 ± 246.10	0.053
AF staining	9 (6.08%)	16 (5.41%)	0.828
Delivery			<0.001*
NSD	59 (39.86%)	177 (59.80%)	
C/S	89 (60.14%)	119 (40.20%)	
Skin-to-skin contact duration (min)	13.09 ± 9.66	16.26 ± 9.96	0.002*

Categorical variables are presented as frequencies with percentage, n (%). Continuous variables were presented as mean with standard deviation (mean ± SD). *p < 0.05.

Table 2 Maternal demographics in the hypoglycemia and euglycemia groups.

	Hypoglycemia (n = 148)	Euglycemia (n = 296)	P-value
Maternal characteristics			
Maternal Age	33.48 ± 4.98	32.76 ± 5.21	0.165
Maternal Fever	0 (0%)	0 (0%)	–
Highest pain score	1.22 ± 2.59	2.08 ± 3.15	0.002*
Maternal Weight	70.22 ± 13.85	68.21 ± 12.24	0.120
Maternal Height	159.60 ± 6.08	159.30 ± 5.58	0.603
Maternal BMI	27.66 ± 5.67	26.85 ± 4.38	0.130
<20	2 (1.35%)	4 (1.35%)	0.607
20–25	49 (33.11%)	105 (35.47%)	
25–30	60 (40.54%)	129 (43.58%)	
≧30	37 (25.00%)	58 (19.59%)	
PIH	17 (11.49%)	25 (8.45%)	0.302
Pre-eclampsia	11 (7.43%)	15 (5.07%)	0.391
GDM	43 (29.05%)	86 (29.05%)	>0.99
Maternal WBC	9.49 ± 2.54	9.6 ± 2.82	0.688
Maternal medication administration			
PIH/Preeclampsia treatment	14 (9.46%)	20 (6.76%)	0.313
GDM treatment			0.019*
No	123 (83.11%)	256 (86.49%)	
Metformin	15 (10.14%)	35 (11.82%)	
Insulin	10 (6.76%)	5 (1.69%)	
Cefazolin	26 (17.57%)	60 (20.27%)	0.497
Dinoprostone	10 (6.76%)	30 (10.14%)	0.241
Oxytocin	34 (22.97%)	92 (31.08%)	0.074
Hyoscine butylbromide	2 (1.35%)	8 (2.70%)	0.507
PCA (Epidural anesthesia)	30 (20.27%)	108 (36.49%)	<0.001*

Categorical variables are presented as frequencies and percentage, n(%). Continuous variables are presented as mean with standard deviation (mean ± SD). *$p < 0.05$.

euglycemic group. Decreased gestational age has been suggested as an independent risk factor for neonatal hypoglycemia.[21] Preterm babies may have less glycogen and fat stores, immature gluconeogenesis pathways, and inadequate counter-regulatory response to hypoglycemia.[13] Therefore, late preterm babies have been considered as at-risk and should be screened for development of neonatal hypoglycemia.[6,7]

Significantly lower skin-to-skin contact duration was noted in the hypoglycemic group. This is consistent with the literature that suggested a protective effect of skin-to-skin contact against neonatal hypoglycemia.[14,15] A recent systemic review also showed healthy infants with early skin-to-skin contact had a mean blood glucose concentration 10.49 mg/dL higher than healthy infants with usual hospital care, when measured at 75–180 min after birth.[16] Other studies have suggested that skin-to-skin care is helpful for body temperature regulation. This may prevent depletion of glycogen stores and aid in stabilizing the blood glucose concentration.[15,18]

Significantly lower body temperature at admission was noted in the hypoglycemic group. The frequency of newborn hypothermia at admission (body temperature below 36.5 °C) was significantly higher in the hypoglycemic group. On the contrary, the frequency of newborn hyperthermia at admission (body temperature over 38 °C) was significantly higher in the euglycemic group. Hypothermia is another factor proposed to be associated with neonatal hypoglycemia in the literature. In a recent study, 49.5% of the hypoglycemic neonates in the study had a body temperature below 36.5 °C.[17]

Significantly higher frequency of cesarean section was found in the hypoglycemic group. To date, conflicting results exist for such an association. A small prospective study in 1994, with 60 patients, showed a higher incidence of neonatal hypoglycemia in neonates delivered by cesarean section, when compared to neonates delivered vaginally (43% vs. 37%).[19] However, in a later study, DePuy et al. found no association between the mode of delivery and neonatal hypoglycemia among 116 cases of neonatal hypoglycemia and 232 controls.[20] In 2017, Ogunyemi et al. suggested that delivery by cesarean section was an independent risk factor neonatal hypoglycemia.[21] A more recent study in 2019 by Turner et al. showed a univariate analysis result of neonates born by cesarean section being more likely to develop neonatal hypoglycemia. Similar to our result, this finding turned out to be insignificant after analysis of the multivariable conditional logistics regression model.[10] Talbert et al. demonstrated a higher cord serum cortisol concentration in neonates born by vaginal delivery than cesarean section. The authors proposed this difference might represent a prelabor surge in fetal cortisol production, or a stress response associated with labor.[22] This mechanism is consistent with one recent study

Table 3 The association of selected factors between hypoglycemia group and euglycemic group using univariate and multivariable conditional logistics regression.

	Crude OR (95% CI)	Adjusted OR (95% CI)
Newborn characteristics		
GA	0.76 (0.64–0.90)*	0.94 (0.75–1.19)
G	1.15 (0.97–1.38)	
P	1.49 (1.12–2.00)*	1.29 (0.95–1.76)
Ponderal index	2.38 (0.92–6.15)	
Apgar score (1 min)	2.02 (0.47–8.67)	
Skin-to-skin contact duration (min)	0.97 (0.95–0.99)*	1.00 (0.97–1.03)
BT > 38	0.23 (0.07–0.79)*	0.46 (0.12–1.76)
AF Staining	1.13 (0.49–2.60)	
ROM time (hr)	0.95 (0.90–1.00)	
Maternal characteristics		
BMI		
<25	1.0	
25–30	1.03 (0.64–1.65)	
≧30	1.42 (0.80–2.52)	
Highest pain score	0.90 (0.84–0.97)*	0.99 (0.91–1.09)
PIH	1.45 (0.74–2.86)	
Pre-eclampsia	1.65 (0.67–4.07)	
Maternal WBC	0.99 (0.92–1.06)	
Maternal medication administration		
PIH/preeclampsia Medication	1.47 (0.71–3.07)	
GDM med		
No	1.0	1.0
Metformin	1.00 (0.42–2.41)	0.94 (0.38–2.32)
Insulin	5.75 (1.51–21.91)*	6.65 (1.54–28.82)*
Delivery		
NSD	1.0	1.0
CS	2.38 (1.56–3.65)*	1.94 (0.97–3.88)
Cefa (ref = no)	0.84 (0.50–1.40)	
Dinoprostone (ref = no)	0.58 (0.25–1.34)	
Oxytocin (ref = no)	0.67 (0.43–1.05)	
Hyoscine butylbromide (ref = no)	0.50 (0.11–2.36)	
PCA (Epidural anesthesia) (ref = no)	0.44 (0.27–0.70)*	1.45 (0.63–3.37)

Data are presented as odds ratio with 95% confidence interval for neonatal hypoglycemia. Variables with $p < 0.05$ were entered into multivariable conditional logistical regression. *$p < 0.05$.

conducted in a premature population <33 weeks' gestation, which showed that being in labor at the time of delivery decreased the risk for neonatal hypoglycemia.[11]

Significantly lower maternal pain score and frequency of epidural analgesia administration were found in the hypoglycemic group. One explanation for these findings is that labor pain and epidural analgesia for labor pain are both factors associated with labor itself. As mentioned above, the labor process has been proposed to be associated with a higher cortisol concentration in the neonate, which may thus prevent the occurrence of neonatal hypoglycemia. However, it might also be possible that maternal pain and epidural analgesia are protective against neonatal hypoglycemia by other unknown mechanisms. Future studies are required to confirm this hypothesis.

Different from previous studies, our result showed that insulin treatment for GDM was associated with increased risk for neonatal hypoglycemia. Few studies tried to find an association between insulin treatment and neonatal hypoglycemia. In 2018, Voormolen et al. reported that the incidence for mild and severe neonatal hypoglycemia was similar, regardless of diet control or insulin treatment for maternal GDM.[23] A more recent study by Kole et al. found that neonates had a significantly higher risk of hypoglycemia when glyburide was used for GDM treatment, compared to diet control. Similar to Voormolen et al.'s finding, insulin was not associated with increased risk for hypoglycemia when compared to diet control.[24] Differences in pharmacological recommendations exist between various guidelines.[25] The NICE guidelines support the use of metformin as first-line therapy.[26] The ACOG and ADA recommended insulin as the first-line therapy because metformin and glyburide cross the placenta to the fetus, while insulin does not.[27,28] Clinically, oral hypoglycemic agents are more convenient and easier to administer. Therefore, insulin may be used in mothers who have more severe GDM, which could not be controlled by oral hypoglycemic agents alone. This can explain for the association between insulin

treatment and increased risk of neonatal hypoglycemia which was observed in our study.

Two additional potential risk factors are pregnancy-induced hypertension and maternal obesity. Past studies have identified maternal hypertension as a risk factor for neonatal hypoglycemia.[11,12] Our result, however, showed no difference in either the frequency of pregnancy-induced hypertension or preeclampsia. Maternal obesity, often defined in BMI in the literature, is another commonly mentioned potential risk factor for neonatal hypoglycemia,[8—10] yet this association was not observed in our study population.

There are some study limitations. First of all, the design of the study is retrospective. Potential problems such as missing data or confounding factors may exist. However, the items we collected were included in the routine format of our well newborn nursery medical and nursing recordings. Therefore, missing values were not a problem encountered during data collection. In addition, we also attempted to eliminate potential confounding factors by matching covariates and multivariable conditional logistic regression. Second, only neonates at risk for neonatal hypoglycemia were screened routinely in the well newborn nursery, as suggested by recommendations from the AAP and PES.[6,7] Therefore, the results from this study can only represent additional risk factors for neonatal hypoglycemia in at-risk newborns. To be certain whether these risk factors are shared with the entire healthy newborn population, a prospective study, under the approval from the review board, would be required. Third, our data were collected from a single center in Southern Taiwan. Most of the neonates are of the Han Chinese ethnic group, with only a few neonates born of the southeastern Asian or Japanese ethnic groups. Therefore, the results of this study may not apply to neonates in other regions of Taiwan, or to other populations around the world. Future research to evaluate these potential risk factors is needed to determine whether newborns with these risk factors should also receive blood glucose concentration screening.

In conclusion, our study showed insulin treatment for GDM to be independently associated with increased risk of early asymptomatic neonatal hypoglycemia in at-risk term babies and late preterm babies. In the univariate analysis, decreased gestational age, neonatal hypothermia, cesarean section, and lower maternal pain score during labor were associated with increased risk for neonatal hypoglycemia. On the other hand, administration of epidural anesthesia and skin-to-skin contact were associated with decreased risk for neonatal hypoglycemia. However, these risk factors were not statistically significant in the multivariable analysis, and future investigations are required for further confirmation.

Declaration of competing interest

The authors declare no conflict of interest.

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