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Predicting resolution of hypoglycemia with and without dextrose infusion in newborn infant of gestational diabetic mothers

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Introduction: Neonatal hypoglycemia (NH) may lead to significant neurological impairment if left untreated. Infants of gestational diabetic mothers (IGDM) are at increased risk of early NH and need to be screened. However, it is challenging to predict management with or without intravenous dextrose once hypoglycemia is identified. We evaluated the association between hypoglycemia risk scores at 1-hour of life and the need for intravenous dextrose for hypoglycemia resolution in IGDM.

Methods: This was a retrospective cohort study of IGDM born at a gestational age \geq 35 weeks from January 2015 to December 2017. NH was the disease of interest. The outcomes were the association of hypoglycemia risk score (HRS) with and without intravenous dextrose for hypoglycemia resolution. Each infant's hypoglycemia risk score (HRS) was calculated using data extracted from the maternal and neonatal electronic medical records. Resolution of hypoglycemia with and without intravenous dextrose was compared between the low HRS (0–1) group and the high HRS (2–5) group.

Results: Sixty-five infants were included in the study with a mean gestational age of 38.2 ± 1 weeks for low HRS and 38.0 ± 2 weeks for high HRS. While more children with high HRS were delivered by cesarean section (p = 0.04), hypoglycemia resolved more frequently without intravenous dextrose in infants with low HRS (p = 0.03).

Conclusion: IGDM is at increased risk of NH. The resolution of hypoglycemia without dextrose infusion is frequently associated with low HRS at 1-hour of life. Early identification using HRS of IGDM whose hypoglycemia will resolve with or without intravenous dextrose may help clinicians triage newborns to either stay in the nursery or transfer for more invasive care.

KEYWORDS

neonatal hypoglycemia, infant of gestational diabetic mothers, intravenous dextrose infusion, score system, term infants

Introduction

NH is a common diagnosis in newborns, and infants of diabetic mothers are at higher risk than infants of nondiabetic mothers. It occurs in 15%–25% of IGDM despite advancements in the perinatal management of diabetic mothers (1). This increased risk of NH in the IGDM is severe in infants of mothers with poorly controlled diabetes due to the relative fetal hyperinsulinemia developed in response to high maternal glucose levels (2, 3). The glucose level of 47 mg/dl (2.6 mmol/L) is usually considered a clinical threshold for the definition of hypoglycemia because levels <47 mg/dl (2.6 mmol/L) trigger concern for permanent neurological sequelae (4–7). This safety concern for infants at risk for NH led to the generation of guidelines by the American Academy of Pediatrics (AAP) to manage NH.

The AAP focuses on at-risk infants or infants with symptomatic hypoglycemia in the first 24 h of life. For all asymptomatic IGDM, AAP recommends starting glucose screening within an hour of life. Glucose levels <25 mg/dl (1.4 mmol/L) within 4 h of age despite initiating enteral feed indicate the need for intravenous dextrose. After the first 4 h of life, the hourly screening goal is to maintain pre-prandial glucose levels <35 mg/dl (2.5 mmol/L) for up to 12 h. While glucose levels <35 mg/dl (1.9 mmol/L) indicate the need for intravenous dextrose, borderline levels between 35 and 45 mg/dl (1.9–2.5 mmol/L) trigger continuing glucose monitoring (8). These continuous monitoring results from the inability to predict which infants will still have NH that will require intravenous dextrose for resolution.

Given the need for recurrent glucose monitoring in IGDM until 12 h of age, we aimed to evaluate the association between the HRS (9) at an hour of life in IGDM born at \geq 35 weeks gestational age and the resolution of NH with or without intravenous dextrose.

Materials and methods

A retrospective chart review was undertaken of all hypoglycemic IGDMs born at \geq 35 weeks gestational age in our institution for 2 years (January 2015 and December 2017). We excluded infants with conditions that affected glucose levels like prenatal exposure to beta-agonists, known metabolic disorders, or congenital malformations.

As part of our routine care, newborn IGDM were admitted to the NBN if born at \geq 36 weeks' gestation, tolerated oral feed, and had a glucose level of \geq 25 mg/dl (1.4 mmol/L) within an hour of life. All neonates <36 weeks' gestation or those with glucose levels <25 mg/dl (1.4 mmol/L) were admitted to the NICU. All POC glucose was done at the bedside with the Stat strip^{*} glucometer (Nova Biomedical, Waltham, MA, USA). POC glucose <2.2 mmol/L was redrawn from plasma glucose and measured in the central biochemistry laboratory with a Hexokinase-mediated reaction Roche Cobas C501 chemistry analyzer.

Furthermore, as part of our institution routine in the NICU, the growth size of all patients enrolled in this study was evaluated with the Fenton growth curve.

We used the plasma glucose level <47 mg/dl (2.6 mmol/L) as the operational definition of hypoglycemia (10, 11). We followed the AAP guidelines (8) for post-delivery glucose screening of IGDM during the study period. None of the subjects in this study received glucose gel, as it had not become the standard of care in our institution at the time. All POC glucose levels <2.2 mmol/L were redrawn within 1–2 min of obtaining the POC glucose for laboratory confirmation with plasma glucose.

The following information was extracted from the maternal hospital's electronic medical records: age, delivery method (vaginal or cesarean), body mass index (BMI), and predelivery glucose. We calculated the HRS for all the subjects at an hour of life using maternal age, maternal pre-delivery glucose, neonatal weight for age, and neonatal blood glucose levels. We considered a HRS of 0–1 as low and a score ≥ 2 as high, as shown in Table 1.

A power analysis determined that a sample size of 65 IGDM was necessary to identify infants whose hypoglycemia would resolve without intravenous dextrose with a sensitivity of 95% and a specificity of \geq 80%. We used the Chi-square and t-test to compare the demographic variables between infants with HRS 0–1 vs. HRS 2–5. A multiple logistic regression model was used to evaluate the relationship between the HRS (0–1 vs. 2–5) and the gestational age, gender, birth weight, mode of delivery, maternal age, maternal pre-delivery glucose, and maternal BMI.

This research was approved by the SUNY Stony Brook Institution Review Board approved the study. The data were analyzed using the SAS v9.4 (SAS Institute, Cary, NC) for statistical analysis, and we considered differences at p values <0.05 as statistically significant.

TABLE 1 Hypoglycemia risk score (HRS).

Independent Factors	0 point	1 point	2 points
Maternal Age	<35 years	≥35 years	n/a
Maternal pre-delivery glucose level (mmol/L)	<6.66	≥6.66	n/a
Neonatal weight for age	AGA	SGA, LGA	n/a
Neonatal glucose (mmol/L)	≥2.22 or <6.66	n/a	<2.22 or ≥6.66

Hypoglycemia Risk Score (HRS) components. AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age.

Results

We assessed 100 newborn IGDM for eligibility during the study period. Of the 100 infants, we excluded 35 infants because they did not have hypoglycemia. We, therefore, included 65 participants in the study. Twenty-four infants had a low HRS, and forty-one infants had a high HRS. The flow chart of all the IGDM reviewed during the study period is displayed in Figure 1.

Demographics

The diagnosis of NH was made in 65 IGDM admitted during the study period. Of the 65 infants, 33 were females. Seven infants were Asian, 4 were black, 17 were Hispanic, and 37 were Caucasian. Using Fenton's growth curve (12), 77% were appropriate for gestational age, 12% were large, and 11% were small. Cesarean section was the method of delivery in 62% of the infants.

Of the 65 mothers with gestational diabetes, 68% were <35 years of age at delivery, 71% had a BMI > 30 Kg/m², and 52% had drug-controlled gestational diabetes (GDMA2).

After evaluating baseline characteristics, we found no significant effect of gender, gestational age, race, size, maternal age, maternal BMI, or type of maternal gestational diabetes in the HRS groups. However, delivery by cesarean section was significantly higher in infants with high HRS than in infants with low HRS (p = 0.04). All the demographics is presented in **Table 2**.

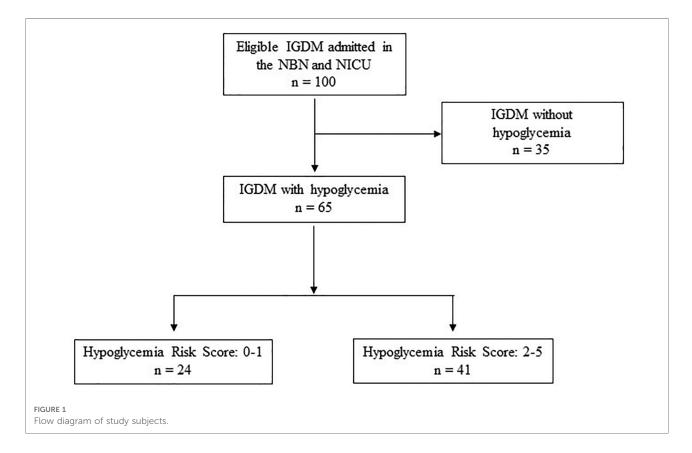
Multiple logistic regression analysis

We found a relationship between gender and maternal predelivery glucose level on the HRS as seen in **Table 3**. Females are 5 times more likely to have an HRS ≥ 2 compared to males. In addition, each maternal pre-delivery glucose level increase by 1 mg/dl increases the likelihood of scoring ≥ 2 in HRS by 6%. However, the relationship between the mode of delivery and HRS is not statistically significant (p = 0.06).

Duration of hypoglycemia and treatment with or without intravenous dextrose

Of the 65 hypoglycemic IGDM included in the study, 23 (35%) required intravenous dextrose. More infants in the group who scored 2–5 on HRS required intravenous dextrose than those who scored 0–1 (20 vs. 3; p = 0.03).

Three IGDM that scored 0-1 on the HRS required intravenous dextrose: two infants had respiratory distress



Variable	Level	Ν	Score 0-1	Score 2-5	<i>P</i> value
Gender	F	33	36%	64%	0.92
	М	32	38%	62%	
Gestational age	≥35weeks	65	38.2 ± 1	38.0 ± 2	0.4
(Mean ± SD)	(wks.)				
Race	Asian	7	29%	71%	0.68
	Black	4	25%	75%	
	Hispanic	17	29%	71%	
	Caucasian	37	43%	57%	
Size for dates	AGA	50	38%	62%	0.62
	LGA	8	25%	75%	
	SGA	7	43%	57%	
Delivery mode	Vaginal	25	52%	48%	0.04
	C-section	40	28%	73%	
Maternal age	<35 y	44	28.4 ± 3.6	28.8 ± 4.2	0.72
(Mean \pm SD)	≥35 y	21	41.3 ± 3.9	38.2 ± 2.1	0.09
Maternal BMI	<30 Kg/m ²	19	27.3 ± 1.8	27.6 ± 1.8	0.76
(Mean \pm SD)	>30 Kg/m ²	46	36.5 ± 8.5	38 ± 7.4	0.57
Maternal diabetic control	Diet- controlled	31	39%	50%	0.36
	Drug- controlled	34	61%	50%	

TABLE 2 Demographic characteristics of study infants and mothers (n = 65).

TABLE 3 The influence of the independent variable on the hypoglycemia risk.

Factors	Odd Ratio	Confi	5% dence erval	P value
Gestational age (weeks)	0.776	0.421	1.432	0.417
Gender (Female vs. male)	5.094	1.147	22.611	0.032
Birth weight (g)	1.000	0.999	1.002	0.618
Mode of delivery (C-section vs. vaginal)	3.653	0.953	14.004	0.059
Maternal age	1.081	0.955	1.224	0.220
Maternal pre-delivery glucose	1.062	1.009	1.118	0.021
Maternal BMI	0.948	0.878	1.024	0.173

A multiple logistic regression of the relationship between the Hypoglycemia Risk Scores (HRS) and the variables showed that females have 5.10 times higher likelihood to have a HRS \geq 2 than males (95% Cl 1.15–22.61, p = 0.03), and 1 mg/dl increase in maternal pre-delivery glucose will increase the likelihood of HRS \geq 2 by 6% (95% Cl 1.01–1.12, p = 0.02).

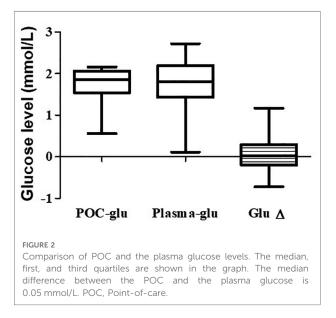
after 1 h of life, and one had persistent low glucose in the NBN. As a result, all three infants were transferred to the NICU. Almost all IGDM who continued on enteral feeds and scored 0–1 on HRS had resolution of their hypoglycemia by 3 h of age (95%). However, hypoglycemia persisted 3-hours after delivery in 10 infants (24.4%) who scored \geq 2 on HRS. The duration of hypoglycemia and treatment are depicted in **Table 4**.

TABLE 4 Intravenous dextrose	requirement and	glucose resolution at
3 h of life in relation to HRS.		-

Hypoglycemia Risk Score (HRS)	IV Dextrose infusion (IDI)	No IV Dextrose infusion	Total	Number of infants with POC glucose ≥2.78 mmol/L by 3 HOL
Score 0–1	3 ^a	21	24	21
Score 2-5	20	21	41	31
Total	23	42	65	52

12.5% of infants that scored 0-1 required intravenous dextrose, and was significantly different from intravenous dextrose requirement by infants that scored 2-5 (p = 0.03).

^a2 out of the 3 had respiratory distress. IV, intravenous; HOL, hours of life; POC, point-of-care.



Point of care glucose vs. plasma glucose levels

Thirty of sixty-five subjects (46%) had their blood redrawn for laboratory plasma glucose levels within 1–2 min of POC glucose levels <40 mg/dl (2.22 mmol/L). We found the median paired difference between the POC glucose and the plasma glucose was 0.05 mmol/L (interquartile ranges, 1.51–2.07; 1.43–2.19 mmol/L respectively, p = 0.81), as shown in **Figure 2**. Nevertheless, 20% (6 of 30) of the subjects with POC glucose <40 mg/dl (2.22 mmol/L) had plasma glucose levels >40 mg/dl (2.22 mmol/L) but <47 mg/dl (2.61 mmol/L), and another 6.7% (2 of 30) had a plasma glucose level of \geq 47 mg/dl (2.61 mmol/L).

Discussion

In a retrospective study of 65 hypoglycemic IGDMs born at \geq 35 weeks gestational age, we found a strong association between low HRS at an hour of life and resolution of hypoglycemia without intravenous dextrose. In contrast, half of the neonates with high HRS required intravenous dextrose to resolve their hypoglycemia. These findings suggest that low HRS within an hour of life in IGDM may help identify infants who stay with their mothers and feed in the newborn nursery.

Although there was no significant effect of gender, gestational age, race, size, maternal age, maternal BMI, or type of maternal gestational diabetes on the HRS, we found in a univariate analysis that more infants with high HRS were born by C-section (p = 0.04). Notably, infants with high HRS were more likely to require intravenous dextrose for hypoglycemia treatment than infants with low HRS. This finding is consistent with the report by Turner et al. (13), who found that infants born via C-section had higher odds of requiring intravenous dextrose to treat NH when compared with infants born vaginally. Nevertheless, the relationship between C-sections and increased odds of intravenous dextrose for NH has yet to be thoroughly evaluated. This finding therefore, underscores the need for future studies to understand the factors that connect C-sections to intravenous dextrose requirements.

Our result showed that females in a multiple logistic regression have approximately 5% higher likelihood of scoring ≥ 2 in HRS than males (95% CI 1.15–22.61, p = 0.03). Although the reason for this relationship is unclear, females may be more sensitive to in-utero exposure to increased glucose levels than males (14, 15). Our observation is consistent with Ahel et al., who found in a recent study that the chances of developing hypoglycemia are increased three times by females compared to males gender (16).

Our observation that almost all IGDM who tolerated enteral feed and scored 0–1 on HRS had resolution of their hypoglycemia by 3 h of age was consistent with what was described by Agrawal et al. (17), who reported no hypoglycemia in IGDM after 2 h of life. Therefore, these findings suggest that frequent blood glucose monitoring beyond 3 h of life in IGDM who scored low on HRS may not be necessary.

In infants whose POC glucose levels were <40 mg/dl (2.22 mmol/L), we found no statistical difference between the POC and laboratory plasma glucose levels (p = 0.81). Our findings agree with Nuntnarumit et al., who showed no statistical difference between the Stat strip^{*} POC glucose and plasma glucose levels (18). However, the Stat strip^{*} POC glucose underestimated the glucose levels in 26.7% (8 of 30) of the patients. Our study, therefore, underscores the

importance of confirming POC glucose <40 mg/dl (2.22 mmol/L) with laboratory plasma glucose.

We recognize various limitations and pitfalls with our present study. Thus, primary caregivers should consider these limitations when applying the findings to clinical practice. First, the research is limited to hypoglycemia in infants of gestational diabetic mothers. Therefore, we did not account for other conditions that increase the risk of hypoglycemia in newborns. We believe future studies should include large for gestational age infants regardless of maternal diabetic status.

The retrospective nature of this study represents a second limitation. There may be inaccuracies and data loss from the perinatal database completed by clinical staff. However, the glucose monitoring and assessment protocol are per the AAP's recommendation.

The use of a capillary sample for glucose monitoring is the third limitation. Glucose values obtained from capillary sampling can be unreliable if peripheral blood flow is not free-flowing (19). In addition, elevated hematocrit levels seen in neonates can interfere with blood glucose values (20). However, POC glucose using Stat strip^{*} has a narrow margin of error and is not affected by hematocrit levels (18).

Finally, we conducted this single-centered study before our institution's routine use of glucose gel in managing early hypoglycemia. Although Weston PJ et al. (21) showed that dextrose gel did not alter the need for intravenous dextrose in treating hypoglycemia, our findings may still not apply to hypoglycemic IGDM receiving glucose gel. Therefore, a prospective multicenter study is required to assess the impact of oral dextrose gel on the HRS.

Conclusion

Glucose screening is clinically crucial in infants of gestational diabetic mothers for timely recognition and treatment of hypoglycemia. However, early identifying IGDM whose hypoglycemia will or will not require intravenous dextrose for resolution is essential. Our results suggest that HRS discriminated between IGDM requiring intravenous dextrose and those not requiring intravenous dextrose to resolve hypoglycemia. The implementation of HRS, if replicated in a multicenter randomized trial, may facilitate early recognition of IGDM that will be triaged to either a newborn nursery for enteral feeds only or transfer for more invasive care.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Stony Brook University IRB. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

This is a useful scoring system to help identify a high risk population for neonatal hypoglycemia who will likely resolve without intravenous dextrose. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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