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Early blood glucose screening in asymptomatic high-risk neonates

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Abstract

Objectives: Detecting and treating severe hypoglycemia promptly after birth is crucial due to its association with adverse long-term neurodevelopmental outcomes. However, limited data are available on the optimal timing of glucose screening in asymptomatic high-risk neonates prone to hypoglycemia. Risk factors associated with asymptomatic high-risk neonates include late prematurity ≥35 and <37 weeks gestation (LPT), small-for-gestational-age (SGA), large-for-gestational-age (LGA), and infant-of-a-diabetic mother (IDM). This study aims to determine the incidence and the impact of individual risk factors on early hypoglycemia (defined as blood glucose ≤25 mg/dL in the initial hour after birth) in asymptomatic high-risk neonates.

Methods: All asymptomatic high-risk neonates ≥35 weeks gestation underwent early blood glucose screening within the first hour after birth (n=1,690). A 2-year retrospective analysis was conducted to assess the incidence of early neonatal hypoglycemia in this cohort and its association with hypoglycemia risk factors.

Results: Out of the 9,919 births, 1,690 neonates (17 %) had risk factors for neonatal hypoglycemia, prompting screening within the first hour after birth. Incidence rates for blood glucose ≤25 mg/dL and ≤15 mg/dL were 3.1 and 0.89 %, respectively. Of concern, approximately 0.5 % of all asymptomatic at-risk neonates had a blood glucose value of ≤10 mg/dL. LPT and LGA were the risk factors significantly associated with early neonatal hypoglycemia.

Conclusions: Asymptomatic high-risk neonates, particularly LPT and LGA neonates, may develop early severe neonatal hypoglycemia identified by blood glucose screening in the first hour of life. Additional investigation is necessary to establish protocols for screening and managing asymptomatic high-risk neonates.

Keywords: early hypoglycemia; screening; asymptomatic hypoglycemia; high-risk neonates; hypoglycemia risk factors

Introduction

Glucose is the primary source of energy for the fetus and newborn [1, 2]. The newborn brain utilizes most of the glucose produced in the body, making it a highly dependent substrate [3]. The normal postnatal adaptation of glucose homeostasis involves a decrease in glucose concentration in the newborn in the first few hours of life. Counter-regulatory hormones such as glucagon and catecholamines stimulate the processes of gluconeogenesis and glycolysis, resulting in a gradual increase in plasma glucose. Any disturbance in this homeostasis results in neonatal hypoglycemia [4]. Alternate fuels, such as ketones and lactate, help to sustain cellular metabolism during hypoglycemia [5]. However, the levels of these substrates are low in the first few hours of life and are unlikely to provide neuroprotection during early and severe hypoglycemia [6]. About 15 % of newborns have low blood glucose (BG) levels, defined as a BG ≤47 mg/dL, in the first few days after birth [7]. However, this incidence is higher in neonates with specific risk factors for neonatal hypoglycemia, such as late-preterm (LPT) neonates, small-for-gestational-age (SGA) neonates, large-for-gestational-age (LGA) neonates, and neonates of diabetic mothers (IDM) [8]. In this manuscript, we are designating a collective term, “asymptomatic high-risk neonates prone to hypoglycemia” as AH neonates.

Neonatal hypoglycemia has been associated with poor neurodevelopmental outcomes and long-term brain injury, making it essential to detect and treat this problem promptly [9–13]. The definition of neonatal hypoglycemia can be controversial as there is no universal threshold for a safe BG.
concentration, especially in the first few hours of life [12]. However, the risk of neurological damage increases with decreasing BG levels regardless of the presence or absence of signs and symptoms for neonatal hypoglycemia [9]. It was recommended to initiate glucose monitoring as soon as possible after birth and before feeding in neonates known to be at risk for hypoglycemia [12]. If the plasma glucose concentration is <36 mg/dL (2.0 mmol/L), close surveillance should be maintained, and intervention is recommended [12].

The AAP recommends BG screening and management of postnatal glucose homeostasis in those high-risk neonates between 0 and 4 h of life, with a target glucose screen of ≥40 mg/dL after the first feeding, with immediate intervention (feeding/IV glucose) if BG is <25 mg/dL [14]. The Pediatric Endocrine Society recommends maintaining a plasma glucose value of >50 mg/dL (2.77 mmol/L) in the first 48 h after birth [15]. The Royal College of Paediatrics and Child Health defines neonatal hypoglycemia in a full-term neonate as <36 mg/dL (2 mmol/L) and in a late-preterm neonate as <45 mg/dL (2.5 mmol/L) and recommend intervention to raise blood glucose levels if blood glucose value was <36 mg/dL (2 mmol/L) in asymptomatic neonates with risk factors for hypoglycemia [16, 17].

This study aims to investigate the incidence of early neonatal hypoglycemia (defined as a BG level ≤25 mg/dL or 1.38 mmol/L) [18] and critical neonatal hypoglycemia (defined as a BG level ≤10 mg/dL or 0.55 mmol/L) within the first hour of life in AH neonates. Furthermore, we investigated the relative impact of each risk factor on the development of early hypoglycemia in AH neonates.

Materials and methods

Study design

The study included all asymptomatic neonates at risk of hypoglycemia born at ≥35 weeks gestation admitted to the normal newborn nursery at a single tertiary care center. Neonates at-risk for hypoglycemia included the following groups: (1) SGA neonates, defined as a birth weight <10th percentile for age on the Fenton growth chart; (2) LGA neonates, defined as a birth weight >90th percentile for age on the Fenton growth chart; (3) IDM, defined as gestational diabetes type 2, not requiring insulin; and (4) LPT neonates, defined as those who were born between 35th to 36th weeks gestation and 36th to 37th weeks gestation.

A BG screening protocol was initiated at our institution for AH neonates ≥35 weeks gestation by performing point-of-care BG levels within the first hour of life, with the aim of obtaining BG levels at 30 min of life. All AH neonates who had early hypoglycemia (defined as BG ≤25 mg/dL) in the first hour of life were admitted to the NICU for intravenous (IV) glucose infusion [12, 16]. All AH neonates who didn’t have early hypoglycemia (BG >25 mg/dL) in the first hour of life continued to be screened for hypoglycemia per AAP guidelines, including glucose screening before feeding [14]. Some of these neonates developed hypoglycemia with subsequent screening as per the AAP guidelines (defined as BG <40 mg/dL in the first 4 h or <45 mg/dL between 4 and 24 h after birth) [14]. This group is referred to in this paper as the “delayed hypoglycemia group.” If feeding or dextrose gel failed to reverse hypoglycemia in this group (as defined by the AAP guidelines), those neonates were admitted to the NICU for IV glucose infusion. Only neonates admitted to the NICU solely for hypoglycemia were included in the analysis. Our institution is designated as a Baby-Friendly Facility, so early BG screening in the first hour of life didn’t cause separation from the mother, as the BG check may occur while skin-to-skin is being performed. The initial BG was measured using the StatStrip® Glucose Meter (Nova Biomedical; Waltham, MA, USA) [19]. Abnormal BG values (≤40 mg/dL) were confirmed with a repeat glucometer test per the manufacturer’s recommendations. The StatStrip® Glucose Meter uses the glucose oxidase method for sample analysis and is noted for its high accuracy in neonates, as indicated by several studies [19–21]. Of note, any glucometer reading below 10 mg/dL is displayed as an undetectable BG level. In this study, we are reporting these measures as ≤10 mg/dL.

Outcomes

A retrospective analysis was conducted for 2 years after implementing the new screening protocol to determine the incidence and the impact of individual risk factors on early hypoglycemia in AH neonates. Demographics and clinical characteristics for the early and delayed hypoglycemia groups were extracted from the electronic health record, including gestational age, sex, birth weight, time of birth, mode of delivery, initial BG value, time the initial BG was taken, and Apgar scores. The neonates were stratified according to their respective risk factors. Data were also analyzed under three different categories of the severity of hypoglycemia: ≤25 mg/dL, ≤15 mg/dL, and ≤10 mg/dL. Data were summarized using descriptive statistics such as median (interquartile range) and frequency (percentage) for different groups. Continuous variables were checked for outliers and assessed for normality using formal statistical tests, histograms, and Q–Q plots. The incidence of hypoglycemia was computed along with a 95% exact confidence interval. The incidence was compared between risk factors using Chi-square or Fisher’s exact test. Univariate logistic
regression models for hypoglycemia were developed using preselected risk factors. Odds ratios, along with 95% confidence intervals, were presented. Models were assessed using the c-statistic. SAS 9.4 was used for all analyses, and a p-value of <0.05 was assumed to be statistically significant. The study was approved by the NYU School of Medicine Institutional Review Board.

Results

There were 9,919 neonates born at gestational age ≥35 weeks at our hospital in the 2-year study period. Among these neonates, 1,690 (17%) had risk factors for hypoglycemia and were screened for hypoglycemia within the first hour after birth (Figure 1).

The figure demonstrates the breakdown of neonates in the low-risk group and the high-risk group prone to hypoglycemia (AH neonates) who were screened for hypoglycemia and their respective BG values. The incidences of hypoglycemia in the AH neonates were as follows: BG ≤25 mg/dL = 3.1% (52/1,690) [95% CI 2.3%, 4.0%]; BG ≤15 mg/dL = 0.89% (15/1,690) [95% CI 0.5%, 1.46%]; BG ≤10 mg/dL = 0.47% (8/1,690) [95% CI 0.2%, 0.93%]. There were 1,638 high-risk neonates with an initial BG value of ≥25 mg/dL. The distribution of neonates with risk factors in this group was as follows: 297 were late preterm (LPT), 244 were large for gestational age (LGA), 495 were infants of diabetic mothers (IDM), 300 were small for gestational age (SGA), and 302 had multiple risk factors. Among these, 116 neonates later developed hypoglycemia, defined as a blood glucose level below 40 mg/dL within the first 4 h or below 45 mg/dL between 4 and 24 h after birth, according to the standard AAP hypoglycemia screening protocol [14]. This group was categorized as the delayed hypoglycemia group. Of the 116 delayed hypoglycemia group, 27 neonates with early BG screening between 26 and 40 mg/dL and 34 neonates with early BG screening >40 mg/dL required NICU admission and IV glucose infusion (Figure 1). The average times from birth to NICU admission were 8 and 14 h, respectively. For the neonates admitted to the NICU for intravenous glucose infusion, the length of stay (LOS) differed across various groups. Specifically, for those in the early hypoglycemia group (initial BG <25 mg/dL), the LOS correlated with the severity of the initial early BG screening results. Of note, our NICU admissions rate for hypoglycemia in the AH neonates during the study period was approximately 10% compared to 10–12% in previous years, indicating that the NICU admission rate has not increased since instituting early BG screening.

Table 1 demonstrates the demographics and clinical characteristics of neonates with early hypoglycemia (n=52) and the delayed hypoglycemia group (n=116). The median time for the initial BG value measurement was 36 min (0.6 h) after birth. Table 2 shows the prevalence of various risk factors in the 52 neonates with a BG ≤25 mg/dL detected during early screening. There were 17 neonates who had multiple risk factors (2 or 3 risk factors). Since a single newborn can have more than one risk factor, the parentheses in the table indicate the number of neonates with multiple risk factors, including that specific risk factor. For example, out of 52 neonates with early hypoglycemia, there were 31 LPT neonates. However, 18 neonates had LPT as the only risk

Figure 1: Glucose screening protocol for asymptomatic high-risk neonates prone to hypoglycemia (AH). N, number of neonates; BG, blood glucose level; LOS, average length of stay after NICU admission; TA, time to admission (defined as the average time from delivery to NICU admission); NICU ADMISSION, NICU admission related to hypoglycemia requiring intravenous fluid; DELAYED HYPOGLYCEMIA, failed AAP screening protocol in subsequent glucometer testing (defined as BG <40 mg/dL in the first 4 h or <45 mg/dL between 4 and 24 h of life); *incidence, the number of babies in each group divided by the number of babies in the high-risk group (n=1,690).
Table 1: Demographics and clinical characteristics of at-risk neonates with early BG <25 mg/dL (early hypoglycemia group) and neonates with early BG ≥25 mg/dL but later developed hypoglycemia using the traditional AAP hypoglycemia screening protocol (delayed hypoglycemia group).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Early hypoglycemia (n=52)</th>
<th>Delayed hypoglycemia (n=116)</th>
<th>p-Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>29 (55.8 %)</td>
<td>45 (38.8 %)</td>
<td>0.041</td>
</tr>
<tr>
<td>Birth weight, grams</td>
<td>3,021 (2,548–4,133)</td>
<td>2,964 (2,470–3,780)</td>
<td>0.238</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>36.4 (36.0–38.3)</td>
<td>37.2 (36.1–39.0)</td>
<td>0.117</td>
</tr>
<tr>
<td>Time to first BG, mins</td>
<td>36 (30–42)</td>
<td>30 (30–36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apgar score, 1 min</td>
<td>9.0 (9.0–9.0)</td>
<td>9.0 (9.0–9.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Apgar score, 5 min</td>
<td>9.0 (9.0–9.0)</td>
<td>9.0 (9.0–9.0)</td>
<td>0.448</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>34 (65.4 %)</td>
<td>68 (58.6 %)</td>
<td>0.408</td>
</tr>
<tr>
<td>LPT (35&lt;sup&gt;th&lt;/sup&gt;–36&lt;sup&gt;th&lt;/sup&gt; weeks)</td>
<td>31 (59.6 %)</td>
<td>53 (45.7 %)</td>
<td>0.095</td>
</tr>
<tr>
<td>AGA</td>
<td>27 (51.9 %)</td>
<td>69 (59.5 %)</td>
<td>0.361</td>
</tr>
<tr>
<td>SGA</td>
<td>4 (7.7 %)</td>
<td>15 (12.9 %)</td>
<td>0.323</td>
</tr>
<tr>
<td>LGA</td>
<td>21 (40.4 %)</td>
<td>32 (27.6 %)</td>
<td>0.1</td>
</tr>
<tr>
<td>IDM</td>
<td>18 (34.6 %)</td>
<td>42 (36.2 %)</td>
<td>0.843</td>
</tr>
</tbody>
</table>

aP-values from Wilcoxon rank sum test for continuous and Chi-square test for categorical variables. Data are presented as median (25th–75th percentile) or frequency (percentage). BG, blood glucose; LPT, late preterm; AGA, appropriate-for-gestational-age; SGA, small-for-gestational-age; LGA, large-for-gestational-age; IDM, infant of a gestational diabetic mother. p-Value < 0.05 was considered significant and highlighted in bold.

Table 2: The various risk factors associated with early neonatal hypoglycemia.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>BG&lt;25 mg/dL (n=52 neonates)</th>
<th>BG&lt;15 mg/dL (n=15 neonates)</th>
<th>BG&lt;10 mg/dL (n=8 neonates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPT</td>
<td>31 (13)</td>
<td>10 (6)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>LGA</td>
<td>21 (12)</td>
<td>9 (6)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>IDM</td>
<td>18 (12)</td>
<td>5 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>SGA</td>
<td>4 (2)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Risk factors (1)</td>
<td>17</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

The data demonstrate the prevalence of various risk factors in 52 neonates with a BG<25 mg/dL, 15 neonates with a BG<15 mg/dL, and 8 neonates with a BG<10 mg/dL. 17 neonates had more than one risk factor. The parentheses indicate the number of neonates with multiple risk factors (2 or more), including that specific risk factor. BG, blood glucose; LPT, late preterm; AGA, appropriate-for-gestational-age; SGA, small-for-gestational-age; LGA, large-for-gestational-age; IDM, infant of a gestational diabetic mother.

Table 3: Univariate logistic regression models for early hypoglycemia (BG<25 mg/dL) using selected risk factors.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hypoglycemia incidence related to corresponding risk factor</th>
<th>Hypoglycemia incidence without corresponding risk factor</th>
<th>Unadjusted OR (95 % CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPT</td>
<td>8.6 % (31/360)</td>
<td>1.6 % (21/1,330)</td>
<td>5.87 (3.3–10.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGA</td>
<td>5.7 % (21/370)</td>
<td>2.4 % (31/1,320)</td>
<td>2.50 (1.42–4.41)</td>
<td>0.002</td>
</tr>
<tr>
<td>IDM</td>
<td>3.0 % (18/599)</td>
<td>3.1 % (34/1,091)</td>
<td>0.94 (0.53–1.68)</td>
<td>0.829</td>
</tr>
<tr>
<td>SGA</td>
<td>1.1 % (4/361)</td>
<td>3.6 % (48/1,329)</td>
<td>0.30 (0.11–0.84)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

<sup>b</sup>Estimated via multiple logistic regression model OR, odds ratio; CI, confidence interval. SGA, had a reverse association with early hypoglycemia. BG, blood glucose; LPT, late preterm; AGA, appropriate-for-gestational-age; SGA, small-for-gestational-age; LGA, large-for-gestational-age; IDM, infant of a gestational diabetic mother. p-Value < 0.05 was considered significant and highlighted in bold.

Table 4: Univariate logistic regression models for hypoglycemia (BG<15 mg/dL) using selected risk factors.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hypoglycemia incidence related to corresponding risk factor</th>
<th>Hypoglycemia incidence without corresponding risk factor</th>
<th>Unadjusted OR (95 % CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPT</td>
<td>2.8 % (10/360)</td>
<td>0.4 % (5/1,330)</td>
<td>7.57 (2.57–22.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGA</td>
<td>2.4 % (9/370)</td>
<td>0.5 % (6/1,320)</td>
<td>5.46 (1.93–15.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>IDM</td>
<td>0.8 % (5/599)</td>
<td>0.9 % (10/1,091)</td>
<td>0.89 (0.30–2.61)</td>
<td>0.827</td>
</tr>
<tr>
<td>SGA</td>
<td>0.3 % (1/361)</td>
<td>1.1 % (14/1,329)</td>
<td>0.26 (0.03–1.99)</td>
<td>0.195</td>
</tr>
</tbody>
</table>

<sup>b</sup>Estimated via multiple logistic regression model OR, odds ratio; CI, confidence interval; BG, blood glucose; LPT, late preterm; AGA, appropriate-for-gestational-age; SGA, small-for-gestational-age; LGA, large-for-gestational-age; IDM, infant of a gestational diabetic mother. p-Value < 0.05 was considered significant and highlighted in bold.
developed early hypoglycemia (incidence of 1.6%). The odds ratio and p-value for all individual risk factors are presented in Table 3. LPT and LGA neonates are at a significantly higher risk for developing severe early hypoglycemia compared to neonates with other combined risk factors and contribute the most risk of developing hypoglycemia during early screening. Neonates born to mothers with gestational diabetes had a similar risk of developing early hypoglycemia as neonates with other combined risk factors. Surprisingly, SGA neonates, as a single risk factor, had a significantly lower risk of developing severe early hypoglycemia compared to neonates with other combined risk factors. Similar results were observed for BG ≤ 15 mg/dL (Table 4). Due to the small number of neonates with a BG ≤ 10 mg/dL, univariate logistic regression was not performed for this category.

Discussion

Our results confirm that early hypoglycemia can occur among asymptomatic neonates at risk of hypoglycemia, showing an incidence of 3.1% for a BG of ≤ 25 mg/dL and an incidence of approximately 0.5% for a critical BG value of ≤ 10 mg/dL. The severity of early hypoglycemia correlated with increased LOS. Although risk factors for neonatal hypoglycemia are well established, our results suggest that LPT and LGA neonates have a significantly increased risk of severe hypoglycemia in the first hour after birth. Interestingly, SGA and IDM were not significant risk factors contributing to early hypoglycemia in AH neonates.

Many studies have sought to define neonatal hypoglycemia and to determine its incidence in those considered AH neonates [8, 18]. However, defining hypoglycemia in the first hour after birth in asymptomatic high-risk neonates is not established since very few studies define a physiologic nadir [22]. Currently, the AAP guideline recommends maintaining a BG > 40 in the first 4 h after birth and > 45 mg/dL 4–24 h after birth [14]. In most healthy newborns, low blood glucose levels in the first few hours after birth are a common and nonproblematic part of adapting to extrauterine life. However, when these low levels are significantly low, prolonged, or recurrent, they can lead to neurological complications [9–12, 23–25]. Edwards et al. found that neonates with hypoglycemia had a higher likelihood of neurosensory impairment at 2 years compared to normoglycemic infants, especially after severe episodes [9]. Hypoglycemia was defined as BG < 47 mg/dL, with < 36 mg/dL considered severe. Another study on neurodevelopmental outcomes at 4.5 years indicated that hypoglycemia increased the risk of poor executive and visual motor function, particularly in cases of severe, recurrent, or asymptomatic hypoglycemia [26]. Of concern, our results suggest that 0.5% of asymptomatic at-risk neonates had a BG value of ≤ 10 mg/dL. Most clinicians will consider it to be a critical level needing immediate intervention.

There is limited data on the optimal timing and intervals for glucose screening in a newborn. The AAP recommends feeding the newborn within 1 h of birth and performing a screening BG level 30 min after this initial feeding [14]. A study auditing the effect of the 2011 AAP guideline for neonatal hypoglycemia reported that the median first feeding time was 55 min after birth in AH neonates, and the time between the first feed and BG measurement was an additional 30 min [18]. This time frame for the first BG measurement estimation will substantially increase with exclusive breastfeeding, especially after a cesarean section. The AAP recognizes that neonatal BG concentrations will decrease to as low as 30 mg/dL during the first 1–2 h after birth and then increase to higher levels [14]. However, the incidence of BG levels < 30 mg/dL in the first hour after birth and its possible sequelae is unknown, especially in AH neonates. Recommendations from the Committee on Fetus and Newborn suggest that at-risk term neonates should receive immediate intervention if their levels fall below 25 mg/dL in the first 2 h after birth [14]. Other experts in this field have suggested that glucose monitoring can be initiated for high-risk neonates as soon as possible after birth and within 2–3 h after birth and before feeding, or at any time there are abnormal signs [12]. In our study, 47 neonates had initial BG levels between 26 and 40 mg/dL, which did not meet the study’s treatment criteria. However, subsequent glucometer testing revealed that 27 of these neonates did not pass the AAP recommended screening protocol (defined as BG < 40 mg/dL within the first 4 h or < 45 mg/dL between 4 and 24 h of life), necessitating NICU admission and intravenous glucose infusion. The average time to admission was 8 h, and the length of stay in the NICU was 6 days. Further research is required to identify effective strategies for optimal screening times and to define the threshold of early neonatal hypoglycemia [27, 28].

Several studies have also identified the risk factors associated with developing neonatal hypoglycemia [18, 29]. One of our aims was to determine the risk factors associated with developing early hypoglycemia. Our results indicate that LPT and LGA neonates had the highest risk of early severe hypoglycemia compared to other risk factors. One study found that LPT neonates had the highest risk of hypoglycemia in the early postnatal period, similar to our findings [18]. In this study of 207 high-risk neonates, the incidence of hypoglycemia (defined as < 40 mg/dL) in the first 4 h was 13.5%, and the incidence of severe hypoglycemia (defined as < 25 mg/dL) was 5.3% [18]. Of these, the majority were asymptomatic with no clinical symptoms or signs suggestive of hypoglycemia, supporting our finding of early severe hypoglycemia in clinically asymptomatic AH neonates. Our finding can help identify the subset of newborns at the highest risk of early severe hypoglycemia that may
require more aggressive screening. Surprisingly, our results indicated that SGA neonates (as a single risk factor) did not contribute significantly to severe early hypoglycemia unless combined with other risk factors. Further studies are required to confirm this finding. In our study, neonates born to mothers with gestational diabetes had a similar risk of developing early hypoglycemia as neonates with other combined risk factors. The incidence of hypoglycemia in infants of diabetic mothers in our study may be lower than anticipated due to the exclusion of cases with severe gestational maternal diabetes requiring insulin. In a previous study evaluating the BG levels in neonates of well-controlled diabetic mothers, 38 neonates were enrolled [29]. Approximately 30% (n=11) developed hypoglycemia 30 min after birth with an average glucose of 18 mg/dL (1.04 ± 0.52 mmol/L), prompting NICU admission and intravenous dextrose infusion. All 11 babies had no symptoms or signs suggestive of hypoglycemia 30 min after birth, and hypoglycemia was only detected because of the glucose screening during the study. This study confirms our finding of potential early and asymptomatic hypoglycemia in AH neonates within the first hour after birth.

There were limitations in our study. The main limitation is the lack of long-term follow-up of neonates who were found to have severe or critical hypoglycemia. These data would provide important information on the cause-and-effect relationship between early hypoglycemia and neurodevelopmental impairment. We also did not evaluate the incidence of hypoglycemia in neonates at low risk; however, the ethical justification for testing such a low-risk population is not established. Although our study was not designed to define hypoglycemia thresholds or suggest a treatment strategy, it established the incidence and the relative influence of each risk factor for early severe hypoglycemia in asymptomatic high-risk neonates. We believe that this study helps to bridge some of the knowledge gaps in this field and potentially informs the development of effective screening and management protocols tailored to high-risk neonates.

In conclusion, asymptomatic high-risk neonates for hypoglycemia, particularly LPT, LGA, or neonates with multiple risk factors, may develop early severe neonatal hypoglycemia that will be identified by early BG screening. Randomized controlled trials are crucial in addressing important questions related to optimal timing for initiating blood glucose monitoring, hypoglycemia threshold, and hypoglycemia long-term effects for asymptomatic at-risk neonates.

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**Research ethics:** Institutional Review Board approval was obtained from New York University before initiating the study.

**Informed consent:** Not applicable.

**Author contributions:** Dr. Hanna and Dr. El-Khawam had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Rania El-Khawam conceptualized the study, performed data collection, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dr. Vikramaditya Dumpa performed data collection, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dr. Shahidul Islam carried out the statistical analysis and interpretation of data, drafted a portion of the manuscript, and critically reviewed and revised the manuscript. Dr. Brenda Kohn conceptualized the study and critically reviewed and revised the manuscript. Dr. Nazeem Hanna conceptualized the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

**Competing interests:** The authors have no conflicts of interest relevant to this article to disclose.

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**Data availability:** The data generated or analyzed during this study are included in this published article. Any additional data will be made available to the scientific community. Such research data will be redacted to prevent the disclosure of personal identifiers. For investigators requesting de-identified data, these requests will be considered and accommodated, subject to IRB approval from New York University.

**References**


