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Retrospective evaluation of a national guideline to prevent neonatal hypoglycemia

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Key Words
hypoglycemia; neonate; prevention

Background: Hypoglycemia is common in neonates and may cause adverse neurological outcomes. Guidelines should aim to prevent repeated hypoglycemic episodes in risk groups, but they are not usually stratified according to the severity of hypoglycemia risk, which may lead to inappropriate and redundant interventions. We evaluated the effect of a national prevention guideline stratified according to mild, moderate, and severe risks of hypoglycemia.

Methods: From national registers, a population cohort of 22,725 neonates was identified retrospectively before and after implementation of a national guideline. Of these, 1900 had World Health Organization International Classification of Diseases 10 discharge diagnoses of hypoglycemia. Diagnoses indicating hypoglycemia risk [small/large for gestational age (SGA/LGA), asphyxia, prematurity, maternal insulin-treated diabetes mellitus] were recorded. Neonatal ward files were evaluated to validate hypoglycemia diagnoses. Adjusted odds ratios (aORs) were calculated, adjusting for sex, parity, SGA, LGA, preterm birth, and asphyxia, where relevant.

Results: Primiparity and male sex were associated independently with hypoglycemia diagnosis [aORs, 1.29 (1.17–1.42) and 1.14 (1.03–1.26), respectively]. Overall incidence of hypoglycemia at discharge decreased from 9.4% to 5.5% after guideline implementation [aORchange, 0.57 (0.50–0.64)]. Overall incidence of validated hypoglycemia decreased from 2.1% to 1.2% [aOR 0.59 (0.46–0.77), p < 0.001]. By risk group, the hypoglycemia incidence decreased from 30.5% to 18.6% [aOR 0.52 (0.36–0.75)] among SGA neonates, from 25.8% to 16.4% [aOR 0.57 (0.42–0.76)] among preterm infants, and from 27.4% to 16.6% [aOR 0.63 (0.34–0.83)] among those with asphyxia. LGA neonates showed a decreased incidence in obstetric wards only. No significant change was observed for the diabetes group.

Conclusion: Stratification of hypoglycemia risk in a hypoglycemia prevention guideline was followed by decreased estimated hypoglycemia incidence, but no causative conclusion could be
1. Introduction

Glucose is an essential fuel for brain metabolism and, depending on its severity and duration, hypoglycemia may result in adverse neurological outcomes.1–4 The key to hypoglycemia prevention is to identify neonates at risk, as this condition may be difficult to detect clinically.1,5

The threshold for intervention in neonatal hypoglycemia remains controversial.1,9 After the physiological nadir, the mean plasma glucose level in 3–47-hour-old, healthy, nonexclusively breastfed term neonates is 3.5–3.7 mmol/L, with a fifth percentile of 2.2–2.3 mmol/L.10 This value is lower in healthy, exclusively breastfed term neonates,11 but higher ketone bodies provide alternative fuel in this group.9

In risk groups, the clinical cutoff value for treatment of hypoglycemia is usually set around 2.5 mmol/L (45 mg/dL) after the first hours of life. This threshold is used widely in clinical practice, despite differences in the methods and devices used for determination of the glucose concentration,12 and is supported by the recent guideline from The American Academy of Pediatrics.13 Others have stated that asymptomatic neonates at risk should not maintain glucose levels < 2.0 mmol/L after feeding,1,14 and treatment thresholds of 1.8 mmol/L on one occasion and 2.6 mmol/L on multiple occasions have been proposed.15

The incidence of neonatal hypoglycemia ranges from 5% to 15%,1,16,17 possibly reflecting differences in study populations, preventive measures, and hypoglycemia definitions and measuring techniques,18 in addition to normal biological variation.

According to the definition of the Institute of Medicine, clinical guidelines are “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances”,19 and guidelines intend to improve efficiency and quality of care and reduce inappropriate practice.20,21 Hypoglycemia prevention protocols should be individualized according to risk stratification,22 and evidence-based guidelines can improve the standard of care for neonates with hypoglycemia.23 Although guidelines have the potential to have harmful effects as well as benefits if not evaluated,20,21 the consequences of guideline implementation have not been well studied. We are not aware of any previous study evaluating the effects of the implementation of a systematic, stratified guideline on the prevention and treatment of neonatal hypoglycemia.

In Denmark, a national guideline for the prevention of neonatal hypoglycemia was introduced in 2010 (Table S1). In brief, infants were classified into no-, low-, moderate-, and high-risk groups at birth, depending on the risk factors present. Prevention measures ranged from breast contact to intravenous glucose administration within the first 30 minutes of life. If the first two glucose measurements were ≥ 2.5 mmol/L, no further glucose determination was required.
2.3. Time periods

The preguideline period extended from August 1, 2006 to July 31, 2008; the postguideline period extended from January 1, 2011 to December 31, 2011, or from July 1, 2012 to December 31, 2012 (for Lillebaelt Hospital, Kolding). Data collected between these periods were not included due to use of pilot versions of the guideline, and the difference in the postguideline period is due to a delay in guideline implementation at Lillebaelt Hospital, Kolding.

2.4. Risk groups

The risk groups were defined retrospectively according to small for gestational age (SGA) or large for gestational age (LGA) status [birth weight exceeding ±2 standard deviations (SDs) of the reference value], prematurity (GA < 37 + 0 weeks), asphyxia (umbilical cord pH < 7.1 and/or base excess ≤ 10), and mIDM. Neonates with ICD10 diagnoses of hypoglycemia (P70.0–70.9) were identified. Mothers with mIDM attending the neonatal ward of OUH could be identified, but maternal ICD10 diabetes diagnosis codes were generally not available in the national registries used for the present study. Neonates with more than one hypoglycemia risk factor were assigned to more than one risk group.

2.5. Blood glucose measurement

Glucose concentrations were measured using different devices. In the neonatal ward of OUH, capillary blood glucose was tested using the HemoCue 201/201 point-of-care testing (POCT) device until mid-April 2011, where after the HemoCue 201 DM RT and 201 DM were used (HemoCue denmark, Åkandevej 21, DK-2700 Brønshøj, Denmark). The Roche Accu-Chek Inform II system was used in the neonatal ward of Lillebaelt Hospital, Kolding, and Radiometer ABL 800 flex analyzers were used in the obstetric departments throughout the study period.

All HemoCue devices measured glucose concentrations in whole blood, but the HemoCue 201 RT/201 DM device automatically presented calculated plasma glucose values after multiplying by 1.11.

2.6. Populations and outcome measures

We studied the incidence proportions of neonatal hypoglycemia in the uptake area of the hospitals for each of the two time periods in four different patient populations, overall and separately for risk groups (SGA, LGA, preterm, asphyxia, and mIDM). For national registry data, the denominator was the total birth count extracted from the DNPR/DMBR for the uptake area, and the numerator (count of neonates with hypoglycemia within the denominator group) was based on ICD10 diagnoses of hypoglycemia (P70.0–70.9) from the DNPR/DMBR in the neonatal period. For obstetric ward neonatal data, the denominator consisted of all neonates discharged from one of the three obstetric wards to home, and the numerator was based on recording of P70.0–70.9 diagnoses in the medical records. Bedside blood glucose values were not recorded systematically in the medical records of the obstetric departments, disallowing blood-sample-based validation of neonatal hypoglycemia diagnoses in this population. For neonatal ward data, the denominator consisted of all neonates referred to one of the two neonatal wards. The numerator was based on recording of P70.0–70.9 diagnoses in the medical records. For neonatal ward data on validated hypoglycemia, the denominator was the same and the numerator was based on recording of P70.0–70.9 diagnoses in the medical records in cases for which data on blood glucose level and age (in hours) at the time of blood glucose determination were also available. These data were analyzed to validate diagnoses of hypoglycemia. Hypoglycemia was defined as glucose value < 1.7 mmol/L at 0–2 hours of life and < 2.5 mmol/L after 2 hours of life.

2.7. Methodological bias (sensitivity analysis)

We reviewed a random sample of data from 400 neonates without ICD10 hypoglycemia diagnoses in the neonatal ward of OUH within the asphyxia and SGA hypoglycemia risk factor groups. Hypoglycemic neonates identified by this search, but not identified through the original registry data search, were not included in the incidence estimates.

2.8. Statistical analysis

First, odds ratios (ORs) for hypoglycemia diagnosis with 95% confidence intervals (CIs) were calculated based on logistic regression models for the following risk factors: SGA, LGA, preterm birth, asphyxia, and mIDM (where relevant), as well as parity and sex. This analysis was conducted for the overall patient population, across both time periods. Second, neonatal characteristics were compared between neonates with and without hypoglycemia diagnoses for each time period using the Mann–Whitney U, Student t, and χ² tests, where appropriate. Third, incidence proportions of hypoglycemia with 95% CIs were calculated for five patient populations (overall and separately according to risk groups). In addition, ORs for change with 95% CIs were calculated based on logistic regression models (univariate and adjusted for sex, parity, SGA, LGA, preterm birth, and asphyxia, where relevant). No adjustment for multiple testing was performed. Data were analyzed using Stata software (StataCorp, College Station, TX, USA).

2.9. Ethics

The Regional Ethics Committee approved the study (protocol no. S-20120119).

3. Results

Overall, the study population included 22,725 neonates (48.4% girls, 51.6% boys). The mean (±SD) birth weights were 3400 (±600) g for girls and 3506 (±644) g for boys. The mean GA was 39 (±2.2) weeks. Prematurity was seen in 1693 (7.4%), asphyxia in 902 (3.9%), SGA in 848 (3.7%), LGA in 822 (3.6%), and mIDM in 245 (1.1%) neonates. In total,
3949 (17.3%) neonates fell into risk groups, of which 406 (10.3%) had more than one risk factor. In univariate and adjusted analyses, SGA, LGA, preterm birth, and asphyxia were associated strongly with increased odds of hypoglycemia diagnosis (Table 1). Surprisingly, primiparity status and male sex were also associated strongly with increased adjusted ORs (aORs) for hypoglycemia. Neonates belonging to the risk groups defined in this study accounted for 1289/1900 (67.8%) of all neonates with hypoglycemia diagnoses. Accordingly, almost one-third of neonates with such diagnoses could not be assigned to any risk group.

The baseline characteristics of all neonates and those with hypoglycemia, defined by discharge diagnoses, in the two study periods are shown in Figure 1.

The estimated incidence proportion of hypoglycemia by discharge diagnosis was 8.4% (Table 2).

National registry data showed that the incidence of hypoglycemia diagnoses in the SGA, LGA, preterm, and asphyxia risk groups was 26.2% (22.7–27.0%), with no significant difference among risk group estimates. In the neonatal ward, the incidence of validated hypoglycemia ranged from 5.5% to 10.5% among risk groups, but was much higher (32.2%) in the mIDM group.

The implementation of the hypoglycemia guideline was associated with a highly significant decrease in the incidence proportion of this condition in the overall population in all analyses (Table 2).

For neonates in the neonatal ward, the incidence of validated hypoglycemia also decreased, from 2.1% to 1.2% [crude OR for change, 0.55 (0.43–0.71), p < 0.001; aOR, 0.59 (0.46–0.77)].

All analyses showed decreased incidence proportions in the SGA and preterm birth groups. For the asphyxia group, a highly significant decrease was seen in the national registry and in the obstetric wards, but no change was observed in the neonatal wards. For the mIDM and LGA risk groups, no significant change was observed in any analysis.

The change in glucose measurement technique during the study period could theoretically have affected the incidence of mild hypoglycemia (2.3–2.4 mmol/L) diagnoses within the postimplementation period. To compensate for this bias, we conducted a subanalysis including only OUV neonatal ward patients with validated hypoglycemia (< 2.3 mmol/L) to April 15, 2011. This methodological bias correction did not change the incidence estimates.

In the review of 400 neonatal ward files with ICD10 codes for asphyxia and SGA, without discharge diagnosis codes for hypoglycemia, we identified unreported hypoglycemia in 16.5% of neonates. Under-reporting showed a decreasing trend between the pre- and postimplementation periods, especially for SGA (overall, from 20% to 13%, p = 0.18; asphyxia, from 16% to 12%, p = 0.42; SGA, from 24% to 14%, p = 0.07).

### 4. Discussion

In Danish neonatal departments, various initiatives to prevent and treat neonatal hypoglycemia have existed for decades. Until the introduction of the national guideline, however, practices were heterogeneous, differing within as well as between departments. The implementation of the national guideline instituted a homogenous, consistent, and systematic approach, and the current study was conducted to evaluate its effect on the risk of hypoglycemia. The retrospective design of our study and methodological constraints, including the lack of a uniform blood glucose recording protocol and the quality dependence of discharge diagnoses, except for the validation substudy that was conducted using data from the neonatal ward, do not allow the calculation of exact incidence estimates or drawing of definitive conclusions on the causes of changes. However, the estimated overall hypoglycemia incidence fell significantly between the two study periods; this effect was most pronounced in the obstetric wards, but was also seen in neonatal wards among cases of validated hypoglycemia diagnosis. No evidence of an increase in hypoglycemia was observed after the guideline introduction, suggesting that the uniform incidence decrease was not due to methodological bias.

The overall population incidence of neonatal hypoglycemia, according to discharge diagnosis, was 8.4%, which was within previously reported incidences of 5–15%. Our estimate had the advantage of being based on a large population birth cohort, but the disadvantage of being based predominantly on discharge diagnoses and glucose measurements obtained with different methods. Validation exercises for these diagnoses showed both over- and under-reporting of hypoglycemia compared with medical records reviews.

### Table 1  Factors associated with hypoglycemia diagnosis (ICD10 discharge diagnosis).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Crude OR (95% CI)</th>
<th>p value</th>
<th>Adjusted p value</th>
<th>Adjusted OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA vs. AGA</td>
<td>4.88 (4.15–5.72)</td>
<td>&lt; 0.001</td>
<td>3.39 (2.86–4.03)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>LGA vs. AGA</td>
<td>3.88 (3.27–4.61)</td>
<td>&lt; 0.001</td>
<td>4.10 (3.43–4.90)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>4.12 (3.54–4.54)</td>
<td>&lt; 0.001</td>
<td>3.41 (3.04–3.96)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Asphyxia</td>
<td>4.10 (3.50–4.81)</td>
<td>&lt; 0.001</td>
<td>4.20 (3.56–4.95)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Parity 1 vs. &gt;1</td>
<td>1.47 (1.34–1.62)</td>
<td>&lt; 0.001</td>
<td>1.29 (1.17–1.42)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Male vs. female</td>
<td>1.17 (1.06–1.28)</td>
<td>0.001</td>
<td>1.14 (1.03–1.26)</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

ORs with 95% CIs based on logistic regression analysis of 22,725 neonates in the national registry database are presented. Both time periods are included.

AGA = appropriate for gestational age; CI = confidence interval; ICD = International Classification of Diseases; LGA = large for gestational age; OR = odds ratio; SGA = small for gestational age.

* OR adjusted for sex, parity, and SGA, LGA, preterm birth, and asphyxia, where relevant.
In a multivariable analysis, we identified SGA, LGA, preterm birth, and asphyxia as independent risk factors for hypoglycemia. These risk groups, as well as the risk faced by infants of diabetic mothers, are well known. Almost one-third of our neonates with hypoglycemia diagnoses were not assigned to a risk group. One explanation for this finding could be missing discharge diagnoses of gestational diabetes, which in the absence of hypoglycemia could have been reported in the mothers’ hospital records only, and hence not included in the current study. Surprisingly, the analysis based on the identified risk groups showed that primiparity and male sex were independent risk factors for hypoglycemia. Explanatory factors may include delayed onset of lactogenesis in breastfeeding primipara and increased male representation in neonates below the LGA cutoffs, but >4000 g, above which the risk of hypoglycemia also may be increased.

The overall incidence of hypoglycemia according to discharge diagnosis among the risk groups of SGA, LGA, preterm birth, and asphyxia was 26.2%. Others have reported hypoglycemia incidences among at-risk neonates of 11.7–51%. In the analysis restricted to neonatal ward data for newborns with validated hypoglycemia, the incidence was at the lower end of this reported range (12.4%).

The estimated incidence of hypoglycemia diagnosis fell significantly after the implementation of the prevention guideline. This change may be attributed to a preventive effect of the guideline, but the contribution of methodological bias, including errors in discharge diagnoses and variations in blood glucose measurement counts and methods, cannot be
Table 2 Incidence proportions of hypoglycemia before and after national guideline implementation, and ORs for change.

<table>
<thead>
<tr>
<th>National registry</th>
<th>Incidence proportions (95% CI) in relation to guideline implementation, % (range)</th>
<th>OR (95% CI) for change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both periods</td>
<td>Before</td>
</tr>
<tr>
<td>Overall</td>
<td>8.4 (8.0–8.8)</td>
<td>9.4 (9.0–9.9)</td>
</tr>
<tr>
<td>SGA</td>
<td>27.0 (24.0–30.1)</td>
<td>30.5 (26.9–34.5)</td>
</tr>
<tr>
<td>LGA</td>
<td>23.6 (19.9–25.7)</td>
<td>25.3 (19.9–26.7)</td>
</tr>
<tr>
<td>Preterm</td>
<td>23.6 (21.6–25.7)</td>
<td>25.8 (23.4–28.2)</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>25.3 (22.6–28.3)</td>
<td>27.4 (24.2–30.8)</td>
</tr>
<tr>
<td>Obstetric ward neonates</td>
<td>Overall</td>
<td>5.3 (5.0–5.6)</td>
</tr>
<tr>
<td></td>
<td>SGA</td>
<td>13.2 (11.0–15.6)</td>
</tr>
<tr>
<td></td>
<td>LGA</td>
<td>10.3 (8.3–12.6)</td>
</tr>
<tr>
<td></td>
<td>Preterm</td>
<td>11.1 (9.6–12.7)</td>
</tr>
<tr>
<td></td>
<td>Asphyxia</td>
<td>18.2 (15.7–20.8)</td>
</tr>
<tr>
<td>Neatatal ward neonates</td>
<td>Overall</td>
<td>3.0 (2.8–3.3)</td>
</tr>
<tr>
<td></td>
<td>SGA</td>
<td>13.7 (11.5–16.3)</td>
</tr>
<tr>
<td></td>
<td>LGA</td>
<td>12.4 (10.2–14.8)</td>
</tr>
<tr>
<td></td>
<td>Preterm</td>
<td>12.5 (10.9–14.1)</td>
</tr>
<tr>
<td></td>
<td>Asphyxia</td>
<td>7.2 (5.6–9.0)</td>
</tr>
<tr>
<td>Neatatal ward, validated</td>
<td>Overall</td>
<td>1.8 (1.7–2.0)</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>SGA</td>
<td>10.5 (8.5–12.7)</td>
</tr>
<tr>
<td></td>
<td>LGA</td>
<td>6.2 (4.6–8.1)</td>
</tr>
<tr>
<td></td>
<td>Preterm</td>
<td>7.9 (6.7–9.3)</td>
</tr>
<tr>
<td></td>
<td>Asphyxia</td>
<td>5.5 (4.2–7.4)</td>
</tr>
<tr>
<td></td>
<td>Maternal diabetes, insulin-treated</td>
<td>32.2 (26.4–38.4)</td>
</tr>
<tr>
<td>Bias-corrected</td>
<td>Overall</td>
<td>1.8 (1.6–1.9)</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; LGA = large for gestational age; OR = odds ratio; SGA = small for gestational age.

* Adjusted for sex, parity, SGA, LGA, preterm birth, and asphyxia, where relevant.
ruled out. In support of a true decrease in the incidence of hypoglycemia, a decreased incidence was also seen in the validation exercise. Moreover, our subanalysis of neonatal ward cases of glucose values < 2.3 mmol/L also showed a highly significant decrease in the incidence.

Decreases in the estimated incidence of hypoglycemia were seen in the SGA and preterm risk groups, regardless of data source. The decrease in preterm neonates occurred despite a decrease in the mean GA and birth weight, which would tend to increase the risk of hypoglycemia, among all such neonates in the postguideline period.

For neonates with asphyxia, a decrease was seen only in the obstetric ward, suggesting that hypoglycemia prevention in the neonatal wards was effective before guideline implementation, or that detection of hypoglycemia among those with milder asphyxia in the obstetric ward who were not referred to the neonatal ward was more complete after guideline implementation.

The LGA and mIDM risk groups showed no decrease in hypoglycemia, regardless of the data source. The unchanged incidence in the LGA group may reflect the ease of hypoglycemia prevention in this group by early feeding; a prevention strategy which was carried out before guideline implementation. For mIDM, the avoidance of hypoglycemia in this patient group received much attention before guideline implementation.

Ongoing controversy regarding the definition and consequences of hypoglycemia, and the methodological problems associated with POCT device use, raises open questions about the appropriateness of the prevention strategy examined here and elsewhere. At the least, the national prevention program introduced less-intrusive interventions for low-risk neonates without increasing the incidence of hypoglycemia in any risk group.

The strengths of our study included the examination of a large, population-based birth cohort; the inclusion of data from several sources; the validation of hypoglycemia diagnoses; and the adjustment of analyses of incidence changes in risk groups. Limitations included the retrospective design, with the risk of inaccurate discharge diagnoses and medical records; the methodological problems associated with glucose measurement using different POCT devices; the noninclusion of neonates with diet-treated maternal diabetes; and potential undiscovered reporting bias from unidentified changes in practice.

We conclude that the introduction of a standardized, stratified hypoglycemia prevention program was followed by the use of a more systematic and consistent prevention strategy for hypoglycemia. The stratification of risk as mild, moderate, and severe, which enables the implementation of differentiated prevention initiatives, was met not by an increased hypoglycemia incidence, but by strong suggestions of a decrease. These findings encourage the further use of a stratified approach, which should be studied in other settings using a prospective design.

Conflicts of interest

The authors have no conflict of interest relevant to this study.

References


**Appendix A. Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pedneo.2016.12.002.