Neonatal Hypoglycemia Following Diet-Controlled and Insulin-Treated Gestational Diabetes Mellitus

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OBJECTIVE

To assess the risk of neonatal hypoglycemia following diet-controlled and insulin-treated gestational diabetes mellitus (GDM) and how it relates to birth weight.

RESEARCH DESIGN AND METHODS

Prospective cohort study included term neonates born after GDM from January 2013 through December 2015 at the University Medical Center Utrecht (Utrecht, the Netherlands). Routine screening of neonatal blood glucose levels was performed at 1, 3, 6, 12, and 24 h after birth. Main outcome measures were neonatal hypoglycemia defined as blood glucose ≤36 mg/dL (severe) and ≤47 mg/dL (mild).

RESULTS

A total of 506 neonates were included, born after pregnancies complicated by GDM treated either with insulin (22.5%) or without insulin (77.5%). The incidence of mild and severe hypoglycemia was similar in the insulin-treated and diet-controlled groups (33 vs. 35%, *P* = 0.66; and 20 vs. 21%, *P* = 0.79). A birth weight >90th centile was seen in 17.2% of all infants. Although children with a birth weight >90th centile had the highest risk for hypoglycemia, the vast majority of hypoglycemia (78.6%) was detected in those with a birth weight <90th centile. Over 95% of all hypoglycemia occurred within 12 h after birth.

CONCLUSIONS

Routine screening for neonatal hypoglycemia following pregnancies complicated by GDM reveals high incidence of both mild and severe hypoglycemia for both diet-controlled and insulin-treated GDM and across the full range of birth weight centiles. We propose routine blood glucose screening for neonatal hypoglycemia within the first 12 h of life in all neonates after GDM, irrespective of maternal insulin use or birth weight.

The incidence of undiagnosed diabetes in pregnancy and gestational diabetes mellitus (GDM) is rising, now complicating up to 10–25% of all pregnancies worldwide (1,2). One of the major problems in infants born following a pregnancy complicated by diabetes is hypoglycemia. Because glucose freely passes through the placenta, maternal hyperglycemia associated with GDM results in elevated glucose levels in the fetus, causing excess fetal insulin production (hyperinsulinism) (3,4). After birth, as maternal glucose supply ceases, elevated neonatal insulin levels persist and may result in hypoglycemia and inhibition of metabolic compensation mechanisms. Timely recognition and treatment of neonatal hypoglycemia is important because of the

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potential for adverse neurodevelopmental outcome. Infants exposed to hypoglycemia show abnormalities on cranial MRI and are at risk for developmental delay at an older age, even in case of mild, transient hypoglycemia. Treatment has been demonstrated to reduce risks for adverse outcomes (5–7). Although clinical relevance is evident, controversy exists concerning definition, screening, and treatment of neonatal hypoglycemia. A generally accepted threshold is 47 mg/dL for mild and 36 mg/dL for severe hypoglycemia, and clinical guidelines advise postpartum glucose screening of infants at risk (8). Nevertheless, guidelines differ on which infants are classified as high risk (8–11). Apart from preexisting maternal diabetes, risk factors for neonatal hypoglycemia are large for gestational age (LGA), small for gestational age (SGA), and prematurity. As to GDM, some guidelines advise to screen all infants from mothers with GDM (8,9,12), whereas others advise screening only those infants born from mothers with insulin-treated GDM (10,11). In order to improve care and plan solid trials on treatment effects, reports on the incidence of neonatal hypoglycemia based on a systematic screening protocol are needed. We assessed the incidence of neonatal hypoglycemia in term infants born from mothers with insulin- and non–insulin-treated GDM, determined by standardized glucose measurements in the first 24 h of life.

RESEARCH DESIGN AND METHODS

Setting and Study Population

We conducted a prospective cohort study including all infants from women diagnosed with GDM from January 2013 through December 2015 at the University Medical Center Utrecht in the Netherlands. Exclusion criteria were prematurity (gestational age <37.0 weeks), stillbirth, or major congenital malformation. Premature infants, already clearly recognized as being prone to hypoglycemia and thus being routinely screened in clinical practice, were excluded from the study. This study was approved by the ethics committee of the University Medical Center Utrecht (file number 16–627/C).

Procedures and Measurements

Diagnosis and Treatment of GDM

According to the national Dutch guidelines, women were either screened based on the presence of defined risk factors (previous GDM, previous child with birth weight >95th centile, maternal BMI >30, maternal polycystic ovary syndrome, first-degree family member with diabetes, or previous unexplained fetal death) at 24–28 weeks of pregnancy or tested because of clinical findings suggesting GDM (i.e., hydramnios or fetal growth >90th centile) (13). A 75-g oral glucose tolerance test (OGTT) was used, and GDM was diagnosed in case of a fasting plasma blood glucose level >126 mg/dL or a 2-h plasma blood glucose level >141 mg/dL. Women with GDM were taught self-monitoring of blood glucose levels, received medical nutritional therapy, and were intensively followed at the outpatient clinic by a team comprising a gynecologist, endocrinologist, dietitian, and nurse specializing in diabetes. Target blood glucose levels were 96–126 mg/dL (fasting and 1.5 h after meals). In case of insufficient glycemic control, insulin treatment was initiated. Glycemic control was evaluated by the most recent four-point blood glucose profile prior to delivery for both fasting and average postprandial glucose values. Overall, the median number of days prior to delivery in which the blood glucose profile was taken was 15 days (range 9–25 days).

Neonatal Care

All neonates were admitted for at least 24 h after birth. Blood glucose levels were measured using heel-stick sampling at 1, 3, 6, 12, and 24 h after birth before a feeding. We used point-of-care testing by means of the glucose oxidase method (i-STAT; Abbott Laboratories, Princeton, NJ). In case of clinical symptoms, additional blood glucose measurements were performed. Blood glucose concentrations and measurement date and time were retrieved from the electronic patient records. Maternal characteristics such as age, BMI, GDM treatment, OGTT results, and delivery and neonatal characteristics such as sex, gestational age at birth, and birth weight were also obtained from the electronic patient records.

Mild neonatal hypoglycemia was defined as glucose level ≤47 mg/dL and severe hypoglycemia as ≤36 mg/dL according to the consensus paper on operational thresholds by Cornblath et al. (14). Glucose readings were not blinded, and subsequent management followed any hypoglycemia. As initial treatment, additional breast milk or formula feeds were administered, and in case of persistent hypoglycemia, i.v. glucose treatment was administered to maintain blood glucose levels preferably >54 mg/dL. Glucose was

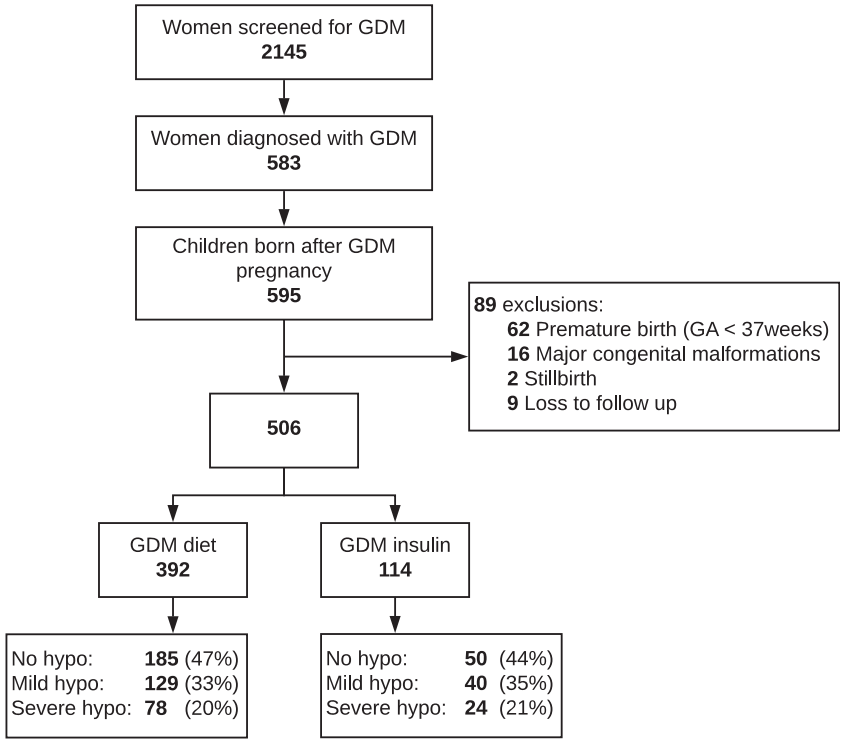

Figure 1—Study profile. GA, gestational age; hypo, hypoglycemia.

Table 1—Patient characteristics

Characteristic	Neonates born after GDM (n = 506)			
	No hypoglycemia (n = 235)	Mild hypoglycemia (n = 169)	Severe hypoglycemia (n = 102)	P value
Maternal				
Insulin treatment	50 (21.3)	40 (23.7)	24 (23.5)	0.82
Age (years)	32.6 ± 4.7	32.9 ± 5.2	33.2 ± 5.2	0.65
Ethnicity				0.89
Caucasian	110 (46.8)	87 (51.5)	50 (49)	
Mediterranean	97 (41.3)	57 (33.7)	37 (36.3)	
Asian	10 (4.3)	9 (5.3)	5 (4.9)	
Black	6 (2.6)	8 (4.7)	3 (2.9)	
Other	12 (5.1)	8 (4.8)	7 (6.8)	
BMI (kg/m^2)	26.5 (23.2–32.0)	26.9 (23.9–31.1)	26.7 (23.1–30.7)	0.77
Primiparous	90 (38.3)	61 (36.1)	30 (29.4)	0.29
OGTT fasting plasma glucose level (mg/dL)	90 (83–99)	90 (85–99)	92 (86–104)	0.14
OGTT 2-h postload plasma glucose level (mg/dL)	153 (144–167)	153 (146–167)	153 (144–170)	0.76
GA at GDM diagnosis (days)	191 (175–215)	190 (173–216)	192 (169–212)	0.59
Capillary fasting glucose prior to delivery (mg/dL)	79.2 (73.8–90.0)	82.8 (74.3–88.2)	82.8 (77.4–90.9)	0.40
Capillary postprandial glucose prior to delivery (mg/dL)	106.8 (99.6–114.6)	109.8 (100.8–117.6)	109.5 (100.8–115.2)	0.21
Induction of labor	87 (37.0)	67 (39.6)	44 (43.1)	0.57
Primary cesarean section	27 (11.5)	26 (15.4)	17 (16.7)	0.35
Emergency cesarean section	23 (9.8)	21 (12.4)	17 (16.7)	0.20
Instrumental delivery	17 (7.2)	7 (4.1)	3 (2.9)	0.19
Neonatal				
N of blood glucose measurements	5 (5–5)	5 (5–6)	6 (5–7)	<0.001[abc]
GA at birth (days)	279 (272–285)	275 (270–282)	274 (267–279)	<0.001[bc]
Male	127 (54.0)	91 (53.8)	56 (54.9)	0.99
Twins (number of children)	8 (3.4)	11 (6.5)	5 (4.9)	0.35
Birth weight (g)	3,471 ± 503	3,554 ± 561	3,525 ± 490	0.28
Birth weight centile	49.6 (22.1–75.2)	52.4 (28.8–86.7)	62.2 (35.3–88.0)	0.01[b]
AGA	187 (79.6)	122 (72.2)	73 (71.5)	0.14
SGA (<10th centile)	19 (8.1)	11 (6.5)	7 (6.9)	0.82
LGA (>90th centile)	29 (12.3)	36 (21.3)	22 (21.6)	0.03[ab]
Extremely LGA (>97th centile)	10 (4.3)	17 (10.1)	8 (7.8)	0.07
Shoulder dystocia	8 (3.4)	3 (1.8)	4 (3.9)	0.52
Admission to neonatal ward	27 (11.5)	17 (10.1)	25 (24.5)	0.002[bc]
Admission to NICU	6 (2.6)	1 (0.6)	0	0.10
Low Apgar score (≤7 at 5 min)	14 (6.0)	6 (3.6)	0	0.03[a]
Requiring glucose i.v.	2 (0.9)	4 (2.4)	11 (10.8)	<0.001[bc]

Data are n (%), mean ± SD, or median (interquartile range). GA, gestational age. [a]No hypoglycemia vs. mild hypoglycemia. [b]No hypoglycemia vs. severe hypoglycemia. [c]Mild hypoglycemia vs. severe hypoglycemia.

remeasured 1 h after intervention to check whether hypoglycemia had resolved.

Birth weight centiles were calculated based on Dutch population curves corrected for gestational age, sex, and parity (15). SGA was defined as birth weight <10th centile, LGA was defined as birth weight >90th centile, and appropriate for gestational age (AGA) as birth weight between the 10th and 90th centile.

Statistical Analysis

Analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL). Baseline characteristics were compared using χ^2 tests for discrete variables or one-way ANOVA for continuous variables or nonparametric testing in case of nonparametric distribution, and Bonferroni post hoc tests were performed as needed. Results are presented as mean ± SD, median (interquartile range), or number (percentage) where appropriate. A P value <0.05 is defined as the threshold for statistical significance. A prevalence curve was drawn for the detection of neonatal hypoglycemia over time, with neonates not developing hypoglycemia as censored observations.

RESULTS

A total of 2,145 women were screened for GDM at our hospital in the study period, identifying 583 women with GDM. Twelve women carried twins, resulting in a total of 595 neonates born after a GDM pregnancy. Two cases were excluded because of stillbirth, 62 because of premature birth, and 16 were excluded because of major congenital malformations. Nine patients were lost to follow-up (transfer to another hospital or refusal to follow protocol). Thus, 506 neonates were included in the study, of which 392 (77.5%) were born after non–insulin-treated GDM pregnancies and 114 (22.5%) after insulin-treated GDM. A study profile is shown in Fig. 1.

The incidence of mild hypoglycemia was similar between the non–insulin-treated and insulin-treated groups (33 vs. 35%; P = 0.66) (Fig. 1). Also, the incidence of severe hypoglycemia was comparable for both groups (20 vs. 21%; P = 0.79).

Table 1 shows maternal and neonatal characteristics for infants experiencing no, mild, or severe hypoglycemia. Overall, a total of 2,769 blood glucose readings were performed, with a median number

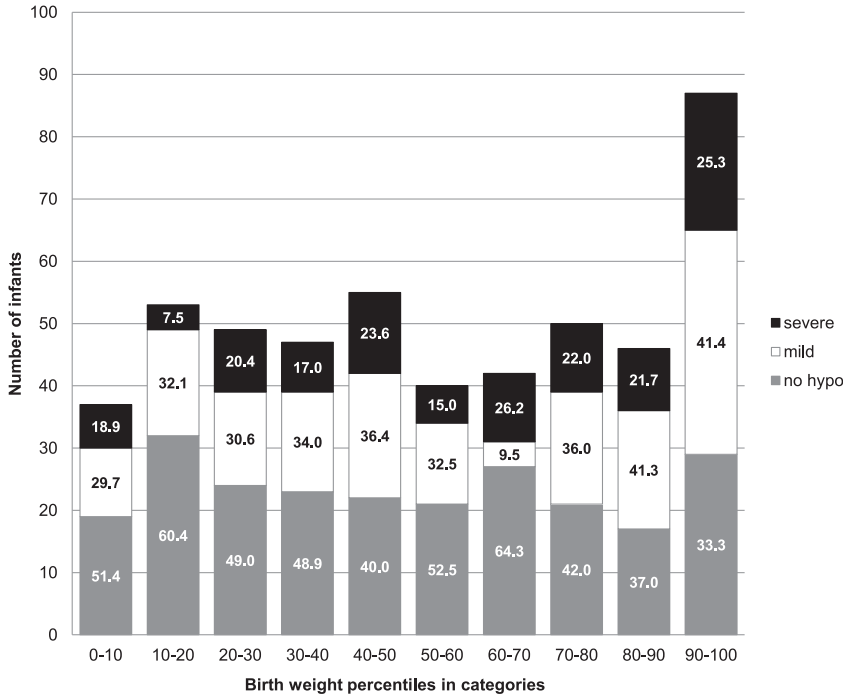

Figure 2—Infants with no, mild, or severe hypoglycemia (hypo) per birth weight percentile (numbers in bars indicate the percentage within the birth weight decile).

of 5 per neonate. The overall incidence of mild and severe hypoglycemia was 33.4 and 20.2%, respectively. Maternal characteristics, including age, ethnicity, BMI, and primiparity, did not differ between the groups. The mean OGTT values and gestational age at the time of GDM diagnosis were also similar. Admission to the neonatal ward was seen in 24.5, 10.1, and 11.5% of the severe, mild, and no hypoglycemia groups, respectively. Admission to a level III neonatal intensive care unit (NICU) occurred for none of the severe, 0.6% of the mild, and 2.6% of the nonhypoglycemic infants. Reasons for NICU admission were respiratory problems (n = 3), perinatal asphyxia (n = 3), and maternal medication use (n = 1). Two infants without hypoglycemia did receive glucose i.v. Both cases involved infants with birth weight far below the 2.3rd percentile and insufficient oral intake. None of the infants developed seizures. Of all of the hypoglycemic neonates, 65.3% did not have a second episode after intervention, and the mean total number of hypoglycemic episodes measured per hypoglycemic infant was 1.58.

Birth Weight

The distribution of neonatal hypoglycemia among birth weight deciles is visualized in Fig. 2. Mild hypoglycemia occurred in 41.4% of all LGA children and severe hypoglycemia in 25.3%. LGA infants had a significantly higher risk for hypoglycemia (odds ratio 1.93 [95% CI 1.19–3.14]) compared with AGA infants. However, both mild and severe hypoglycemia were seen across the full range of birth weight centiles. Of all infants with mild hypoglycemia, 72.2% were AGA, and 71.6% of all infants suffering from severe hypoglycemia were AGA (Table 1).

Time Course

A prevalence curve was drawn for time to the first detected neonatal hypoglycemia; neonates who did not develop hypoglycemia were censored. Severe and mild hypoglycemia are individually represented (Fig. 3). Most hypoglycemic events occurred during the first few hours after birth. At the first blood glucose measurement 1 h after birth, 66.3% of mild and 81.4% of severe hypoglycemia cases were already detected. After 6 h, newly detected severe hypoglycemia was limited, and the curves show that a plateau is reached at ~12 h after birth. After 12 h of monitoring, 96.5% of all first mild hypoglycemia and 98% of all first severe hypoglycemia cases were detected. Thereafter, six new cases of mild and two new cases of severe hypoglycemia occurred.

CONCLUSIONS

In this large prospective cohort study, we found a similar and high incidence of mild and severe neonatal hypoglycemia in infants born after insulin- and non–insulin-treated GDM pregnancies. Infants born LGA had the highest risk for neonatal hypoglycemia, but nonetheless, 72% of all neonatal hypoglycemia occurred in AGA children.

Clinical guidelines differ on whether infants from GDM pregnancies should be screened for neonatal hypoglycemia, especially when AGA or in cases of diet-controlled mothers. We demonstrate hypoglycemia risks for all GDM infants to be comparable to infants with conventional risk factors such as SGA, LGA, prematurity, and preexisting maternal diabetes. Reports on incidences of neonatal hypoglycemia in relation to different risk factors vary widely depending on definitions, screening methods, and specific patient groups. However, two large prospective cohort studies used currently advised definitions and blood glucose monitoring. Harris et al. (16) investigated the incidence of neonatal hypoglycemia in 514 babies identified as high risk (late preterm, SGA, LGA, and infant of a mother with diabetes). Blood glucose concentrations were measured at 1 h after birth and every 3 to 4 h in the first 24 h and every 3–8 h in the next 24 h. Mild and severe hypoglycemia were defined similar to our protocol. They reported hypoglycemia in 51% of the neonates and severe hypoglycemia in 19%, with no difference among different risk groups (16). McKinlay et al. (5) also applied a comparable intensive screening approach in their prospective cohort study including 404 high-risk late preterm and term neonates. Similar definitions were used; mild hypoglycemia was reported in 53% of the infants and severe hypoglycemia in 16% (5). Unfortunately, both studies do not further specify maternal diabetes. Our findings correspond to their numbers, affirming infants from mothers with GDM being equally prone to hypoglycemia as neonates currently recommended for routine screening.

Our study has several strengths. It is a large prospective cohort study. We deployed a standardized screening strategy and applied commonly used thresholds for hypoglycemia. Furthermore, we only had 1.5% loss to follow-up, minimizing

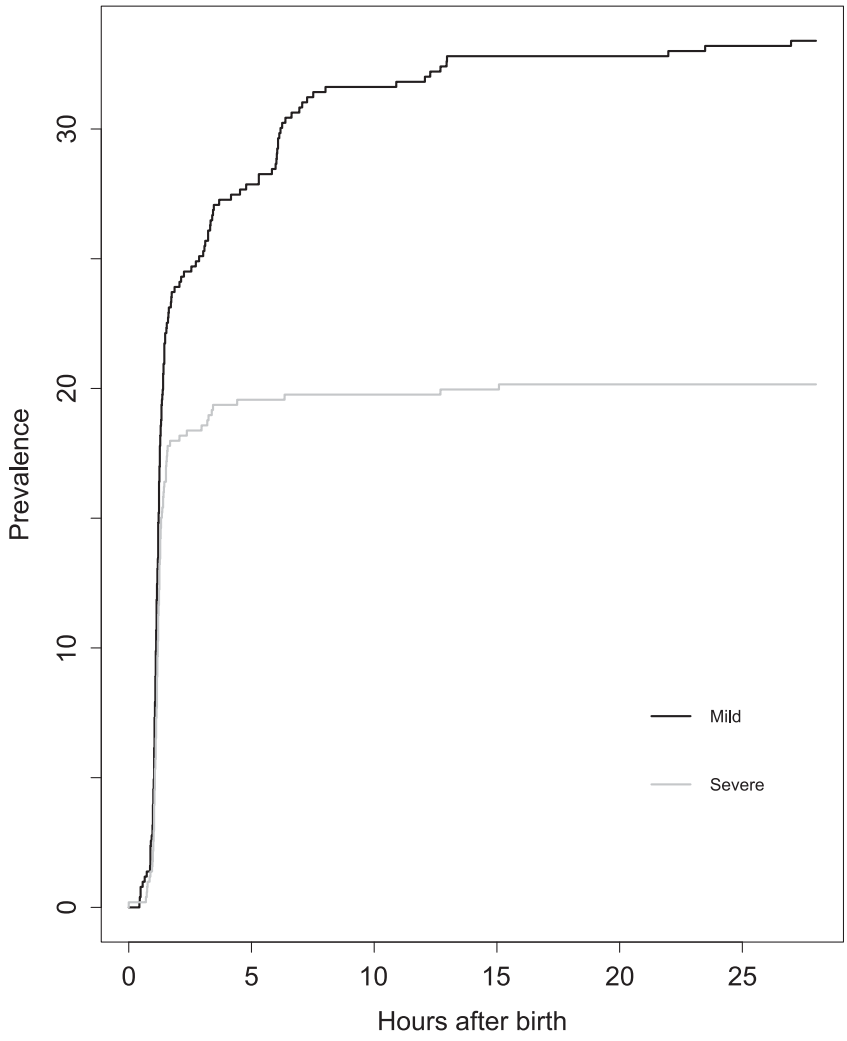

Figure 3—Prevalence curve representing the cumulative detection of mild and severe hypoglycemia in time. The *y*-axis represents the cumulative detection of new cases of hypoglycemia.

selection bias. The median number of glucose measurements was five per infant, indicating good protocol adherence. A limitation of our study is that it does not permit determination of the optimal blood glucose level for treatment or prevention of complications and the lack of a healthy reference group. Furthermore, the exact glucose intake of the infants could not be calculated.

A controversial topic remains whether neonatal hypoglycemia must be considered a physiological phenomenon given the relatively high incidence of hypoglycemia after birth in normal infants. Overall, the incidence is estimated to be 5–15% (14). In healthy newborns, the first few hours are characterized by a sharp decline in blood glucose levels to ~50 mg/dL, with a rise after 3 h toward a plateau at ~70 mg/dL (17). This increase is explained by several mechanisms. Counter-regulator hormones such as glucagon, catecholamines, and glucocorticoids drive gluconeogenesis, and also alternative fuels become available for the neonatal brain. Due to hyperinsulinism, infants from mothers with diabetes are therefore prone to more profound and prolonged decline in blood glucose levels. Therefore, it is key to differentiate physiological biochemical low glucose from hypoglycemia with impaired metabolic adaptation, as is the case with neonates born after GDM (18,19).

Studies applying a continuous glucose monitor (CGM) could provide more insight in normal and pathophysiological blood glucose profiles in neonates. Studies with premature neonates in the intensive care unit show that CGM use detects more hypoglycemic episodes than repeated blood glucose measurements (20). However, CGM may currently not yet be the proper tool for screening infants born from mothers with GDM in daily practice due to the limited accuracy, especially in the hypoglycemic range, and the demanding and expensive nature of the technique (21).

The clinical relevance of neonatal hypoglycemia has been well established. Using early cranial MRI, a study on 35 term infants with severe neonatal hypoglycemia (median glucose level 18 mg/dL) showed white matter abnormalities in 94%, cortical abnormalities in 51%, and impairments at 18 months in 65% (6). In addition, milder transient neonatal hypoglycemia has been shown to result in neurological impairments. Kerstjens et al. (7) report a significantly higher risk for developmental delay in 832 moderately preterm-born infants exposed to hypoglycemia (defined as plasma glucose <30 mg/dL at least once within the first 72 h after birth) compared with those who were euglycemic (odds ratio 2.42 [95% CI 1.23–4.77]). At 10 years of age, children who experienced transient neonatal hypoglycemia (defined as glucose levels <35, <40, and <45 mg/dL) had lower achievement test scores (22). In addition, McKinlay et al. (5) recently showed that standardized blood glucose monitoring with consequent treatment of hypoglycemia (defined as blood glucose level <47 mg/dL) in high-risk newborns (34% of study population were infants born to mothers with GDM) prevents neurodevelopmental injury (5). Moreover, they demonstrated an association between neonatal hypoglycemia and an increased risk of low executive function (relative risk 2.32 [95% CI 1.17–4.59]) and visual motor function (relative risk 3.67 [95% CI 1.15–11.69]) at 4.5 years of age. A large prospective cohort was used of 614 neonates at risk for hypoglycemia who were screened and treated in case of low blood glucose. Children at highest risk were those exposed to severe, recurrent, or clinically undetected hypoglycemia (23).

Considering the potential severity of the detrimental effects of neonatal hypoglycemia in light of the relatively simple screening procedure and treatment, screening seems warranted, with a number needed to screen of five neonates from pregnancies complicated by GDM in order to detect one neonate with severe hypoglycemia. Screening during the first 12 h after birth identified 98% of all neonates with severe hypoglycemia and 96.5% of all neonates with mild hypoglycemia.

However, current screening methods require hospital admission, are often painful, and not all point-of-care devices have good precision for the detection of low blood glucose levels (24,25). To facilitate and stimulate routine screening, further development of an accurate, noninvasive, and preferably point-of-care method is imperative.

Summary

Routine screening for neonatal hypoglycemia following pregnancies complicated by GDM reveals high incidence of both mild (32.6%) and severe (21%) hypoglycemia, for both diet-controlled and insulin-treated GDM and across the full range of birth weight centiles. Neonates of GDM pregnancies are as equally prone to hypoglycemia as other acknowledged categories of high-risk infants. We propose routine blood screening for neonatal hypoglycemia within the first 12 h of life in all neonates after GDM pregnancies, irrespective of maternal insulin use or birth weight.

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Author Contributions. D.N.V. and L.d.W. contributed to acquisition, researching, and handling of data; performed the statistical analyses and interpretation of the results; and wrote the manuscript. D.N.V., F.G., and M.L.-d.R. contributed to the study design. B.B.v.R., J.H.D., M.P.H., A.F., F.G., and M.L.-d.R. contributed to interpretation of the results and reviewed and edited the manuscript. D.N.V. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the analyses performed.

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