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ORIGINAL ARTICLE

A Feasibility Study to Detect Neonatal Hypoglycemia in Infants of Diabetic Mothers Using Real-Time Continuous Glucose Monitoring

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Abstract

Background: Infants born to mothers with diabetes commonly experience asymptomatic hypoglycemia after birth. Continuous glucose monitors (CGM) can detect asymptomatic hypoglycemia in this population without the need for painful glucose checks.

Methods: Infants born after 34 weeks of gestation to mothers with diabetes had a CGM placed after birth. One group of infants was remotely monitored in real-time by research staff during the hospitalization, whereas another group wore a blinded CGM. In both groups, hospital standard-of-care (SOC) glucose checks were performed. Clinical staff and families were blinded to CGM data. For CGM readings <45 mg/dL, research staff requested a verification blood glucose (BG) using the point-of-care glucometer.

Results: Sixteen infants were studied; 4 with a blinded CGM and 12 with remote monitoring (RM). When there were confirmatory hospital glucometer readings, the sensitivity of the CGM to detect hypoglycemia was 86% and the specificity was 91%. The positive predictive value was 55% and the negative predictive value was 98%. In the full cohort, hypoglycemia (<45 mg/dL) was confirmed in 12 of 16 infants with 30 events at <12 hours of life (HOL), 3 events between 12 and 24 HOL, and 1 event at >48 HOL. In the RM group, CGM detected hypoglycemia five times when the infant was not due for a BG check based on the SOC. Overall, the CGM detected five false-positive alerts and six true-positive alerts for hypoglycemia. Only one hypoglycemic episode was missed by CGM in the RM group. Barriers to recruitment included fear of pain with glucose checks, concerns with CGM use, satisfaction with the hospital SOC, personal reasons independent of the study, and lack of interest in participating in research.

Conclusions: Although there were barriers to recruitment and retention in the study, we conclude that CGM can provide added benefit for detecting hypoglycemia when used early after birth.

Keywords: Neonatal hypoglycemia, Continuous glucose monitor (CGM), Low blood sugar, Infant diabetic mother.

Background

Hypoglycemia is the most common metabolic problem in the neonatal period and infants of diabetic mothers are at high risk of hypoglycemia (<47 mg/dL) after birth with rates approaching 50% in the first 48 hours of life (HOL).[1] However, the long-term outcomes of infants who experience hypoglycemia in the neonatal period are unclear. Most studies looking at long-term outcomes in infants who have experienced hypoglycemia are based on intermittent point-of-care glucose testing,[2–4] potentially missing hypoglycemic episodes and important information about the duration and severity of hypoglycemia. Previous studies have suggested that the neonatal hypoglycemia may be linked to declines in neurodevelopmental outcomes.[5–8] Specifically, some studies have suggested that diabetes during pregnancy relates to poorer attention and motor skills in school-age children.[9,10]

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To carefully monitor neonatal hypoglycemia, continuous glucose monitoring (CGM) is needed. Asymptomatic hypoglycemic episodes in the hospital setting might be missed with intermittent standard-of-care (SOC) measurements. CGM devices have the potential to reduce or eliminate painful glucose testing, reduce nursing workload, and improve patient safety by alerting providers about hypoglycemia early, thus giving them the opportunity to prevent or quickly treat hypoglycemia.

Methods

Study design and participants

The study was approved by the Stanford University Institutional Review Board and registered on the National Institutes of Health ClinicalTrials.gov website (NCT03032523). A total of 119 mothers of potential participants were approached during obstetrics visits at Stanford University between August 1, 2016 and March 31, 2018. Nineteen infants were enrolled and 16 completed the study. Eligible infants were those born to mothers with a diagnosis of diabetes during pregnancy, including type A1 (diet-controlled gestational diabetes), type A2 (medication-controlled gestational diabetes), type 1 diabetes, or type 2 diabetes.[11] Exclusion criteria included birth before 34 weeks of gestation, weight <2000 g, or if the infant received a medication known to affect sensor values (i.e., acetaminophen).

All infants followed the SOC glucose monitoring protocol, involving at least four glucose checks after birth (Supplementary Fig. S1). The SOC protocol recommends an initial blood glucose (BG) check be performed 30 min after the infant's first feed, which should occur within the first HOL. Thereafter, BG checks are performed every 2–3 h before feeds until at least three consecutive BG levels are greater than 45 mg/dL, at which point the SOC BG checks are complete.

Initially, infants were randomized 1:1 to a blinded CGM or remote monitoring (RM) group to compare the number of detected hypoglycemic events between the two groups. The blinded CGM group wore a blinded sensor that collected BG information and followed the SOC procedures. The RM group had a blinded CGM at bedside, but CGM values were monitored remotely by research staff. Many families were hesitant to participate in the study because they did not want their infant to wear a blinded CGM, thus the study was later modified to remotely monitor all infants. The Dexcom G4 Platinum CGM sensor (Dexcom, Inc., San Diego, CA) was placed on the anterior or lateral thigh within 8 h of birth according to manufacturer guidelines for pediatric users.[12] No anesthetic was administered. After a 2-h warm-up period, the sensor was calibrated with two glucose values using the Contour Next Glucometer (Ascensia Diabetes Care, Parsippany, NJ). Hospital staff and family members were blinded to the CGM data. The CGM recorded glucose values every 5 min in the range of 40–400 mg/dL. For values <40 mg/dL, the CGM recorded a ''low'' value. Calibrations were performed at least every 12 h based on the manufacturer's protocol and coordinated with the SOC glucose checks to minimize additional BG checks.[12] Research staff evaluated sensor sites at least every 12 h and any changes to the skin associated with CGM use were documented. Detailed daily chart reviews were performed. Infants remained in the study for up to 7 days while they were hospitalized.

Remote monitoring

In those infants remotely monitored, real-time CGM values were transmitted to the research staff using the Dexcom Follow Application.[18] Hypoglycemia was defined as a BG level of <45 mg/dL.[13] When the CGM glucose value decreased to <45 mg/dL for at least 15 min, the research staff received an alert through the Dexcom Follow Application, and the nurse was contacted to verify the glucose reading using the hospital glucometer, the Precision Xceed Pro Glucose Monitoring System (Abbott Laboratories, Abbott Park, IL). Hospital glucometer values were used to determine treatment according to the SOC nursery guidelines (Supplementary Fig. S1).

Data collection

Maternal data, including mother's age, pregnancy history, type of diabetes, and treatment of diabetes during pregnancy were collected. Neonatal characteristics collected included sex, race, ethnicity, gestational age, birth weight, type of delivery, and other risk factors for hypoglycemia. Perinatal stressors were defined as an Apgar score <7, admission to NICU, or treatment of the infant beyond the usual suctioning and stimulating that routinely occurs after birth.[14] Prematurity was defined as birth at <37 weeks gestation. Small for gestational age (SGA) infants weighed less than the 10th percentile for gestational age, whereas large for gestational age (LGA) infants weighed greater than the 90th percentile for gestational age.

Power calculation

Using an older retrospective CGM device in a similar cohort of at-risk infants, Harris found that using similar SOC intermittent heel-stick glucose monitoring, 32% of infants had glucose levels <47 mg/dL.[15] We estimated that in our cohort, the SOC would find 32% of these high-risk infants with glucose levels <47 mg/dL. We estimated that with a sample size of 40, we should be able to detect a higher CGM rate of hypoglycemia of $\sim$57% (80% power, alpha = 0.05, one sided). However, because we were unable to recruit 40 infants during the time frame of the randomized trial, we modified the study design; instead, our goal was to determine if there was additional benefit of using CGM monitoring to detect hypoglycemia missed by SOC testing and to determine the false-positive rate of CGM alerts for hypoglycemia.

Outcome measures

Hypoglycemia was defined as a glucose concentration of <45 mg/dL in order to correspond with the hospital's SOC protocol. Primary outcome measures were the number of hypoglycemic events detected by the sensor that were not detected by the hospital SOC. Secondary outcome measures were sensitivity, specificity, and positive predictive value of the device to detect hypoglycemia. When evaluating number of hypoglycemic episodes that occurred with each infant, the start of each hypoglycemic episode needed to be at least 60 minutes from the last episode to allow for treatment and resolution of hypoglycemia. A duration of 60 minutes was used to allow time for breast feeding in accordance with the nursery's SOC procedures (Supplementary Fig. S1). The CGM data were reviewed post hoc using Dexcom Studio Software.

Using the Dexcom Studio Software to calculate the average CGM glucose level for each infant, a value of 39 mg/dL

was used for all values that were reported as ''low.'' All values reported by the CGM as ''low'' were excluded from the accuracy analysis. The mean absolute relative difference (MARD) was calculated by taking the absolute value of the difference between the CGM and hospital glucometer values and dividing by the hospital glucometer value individually, and then taking the mean of these values,[16]

$$MARD = \frac{1}{N} x \sum_{i=1}^{N} \frac{|CGM - SOC|}{SOC}$$

where N represents the number of values. In this study, compression artifacts were defined when sensor tracings met the following three criteria: (1) evidence of sensor compression on examination, (2) concurrent hypoglycemia or signal loss, and (3) resolution of hypoglycemia or signal loss after repositioning the infant.

Additional outcome measures included CGM feasibility in the hospital setting. During the recruitment process and throughout the study, we asked caregivers for feedback about satisfaction with the CGM device. If any devices were removed before the end of the study period, we requested feedback from the families as well.

Results

Maternal factors

The charts of mothers attending the obstetrics clinic at Stanford were reviewed and 119 expecting mothers were approached to participate in the study, which resulted in 19 infants enrolled in the study and data were collected on 16 infants (Fig. 1). Of the 66 families that declined the study, 26% gave no reason for declining. However, the remainder reported fear of pain with glucose checks (27%), concerns about using the CGM on an infant (24%), satisfaction with the hospital SOC (5%), personal reasons independent of the study (12%), and lack of interest in participating in research (6%). Three infants were unable to complete the study because of sensor failures after placement.

Maternal characteristics

Maternal characteristics are listed in Table 1. The average age of the mothers was 34 years. The average hemoglobin A1c was 6.5% in the first trimester, 5.6% in the third trimester, and

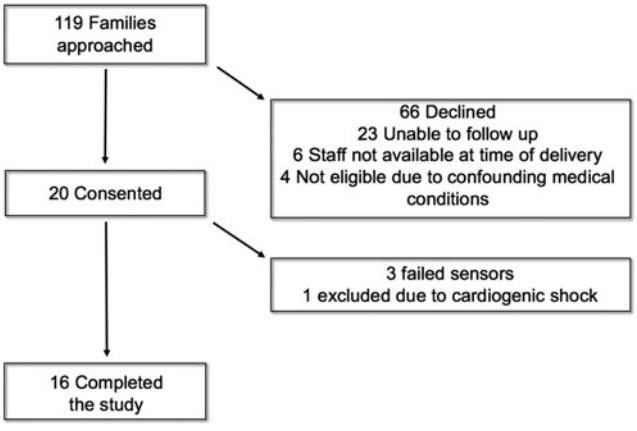

FIG. 1. Cohort of infants completing the study.

TABLE 1. MATERNAL CHARACTERISTICS

Maternal characteristics	*Overall* (n = *16*)
Maternal age (years)	34.4 ± 4.4 (22–40)
Insurance type	
Public	50% (8)
Private	50% (8)
Diabetes type	
Type A1 gestational DM	12% (2)
Type A2 gestational DM	44% (7)
Type 1 DM	19% (3)
Type 2 DM	25% (4)
Insulin during pregnancy	81% (13)
HbA1c first trimester (%)	6.5 ± 1.7 (4.8–10)
HbA1c third trimester (%)	5.6 ± 0.7 (4.7–6.8)
Mode of delivery	
Vaginal	56% (9)
C-section	44% (7)

Values are reported as mean ± SD (range).
HbA1c, hemoglobin A1c; DM, diabetes mellitus; type A1, diet-controlled gestational diabetes mellitus; type A2, medication-controlled gestational diabetes mellitus.

TABLE 2. NEONATAL CHARACTERISTICS AND DURATION OF HYPOGLYCEMIA BASED ON CONTINUOUS GLUCOSE MONITOR READINGS

Infant characteristics	*Overall* (n = *16*)
Sex	
Female	56% (9)
Male	44% (7)
Ethnicity	
Hispanic	38% (6)
Non-Hispanic	62% (10)
Race	
White	44% (7)
Asian	25% (4)
Pacific Islander	6% (1)
Other	25% (4)
Gestational age (weeks)	38.1 ± 1.6 (34–39.4)
Birth weight (kg)	3.3 ± 0.6 (2.3–4.2)
Size	
SGA	2
AGA	9
LGA	5
CGM placed (HOL)	3.6 ± 1.4 (1.5–7.5)
CGM recording started (HOL)	6.8 ± 1.8 (5.0–12.6)
Duration of CGM recording (h)[a]	33 (20, 53)
Average CGM glucose (mg/dL)[b]	63 ± 16
Duration of time CGM <45 mg/dL (h)[a]	3 (0.7–6.8)
% time CGM <45 mg/dL while sensor in place[a]	10 (3–21)

Values are reported as mean ± SD (range) unless otherwise noted.
[a]Results are reported as median (interquartile range).
[b]Average glucose calculated using 39 mg/dL for values reported as ''low'' on CGM.
AGA, appropriate for gestational age; CGM, continuous glucose monitor; HOL, hour of life; LGA, large for gestational age; SGA, small for gestational age.

81% were treated with insulin. Nearly half of the mothers (44%) underwent C-section. Regarding maternal risk factors for neonatal hypoglycemia, 19% of mothers had preeclampsia, 19% had hypertension, and 19% had obesity during pregnancy. In addition, 38% of mothers were qualified as having advanced maternal age (35 years or older). Fifty percent of families had public insurance.

Infant characteristics

Nine female and seven male infants with an average gestational age of 38.1 weeks and an average birth weight of 3.3 kg were studied (Table 2). Two infants were born SGA and five were born LGA. Sensors were placed within 8 h of birth and recorded data with a median duration of 33 h. Participants remained hospitalized for a median of 2.5 days. Each participant had an average of 4.3 glucose checks per day based on the SOC. Timing of calibration glucose checks was coordinated with SOC checks, and the study protocol resulted in an average of 0.7 additional checks per participant per day.

Infant glycemia

Fourteen infants were admitted to the nursery after birth, one was admitted to the intermediate care nursery for hypoglycemia and phototherapy, and one was initially admitted to the neonatal intensive care unit for respiratory distress but transitioned to the intermediate care nursery the following day for hypoglycemia. Two infants required intravenous fluids for hypoglycemia. In the full cohort, hypoglycemia occurred 34 times in 12 of 16 infants (75%). Hypoglycemia verified by the SOC occurred 30 times in the first 12 HOL, 3 times between 12 and 24 HOL, and 1 time at >48 HOL. Four infants had sensors placed without RM, so there were no real-time alerts in these infants (Supplemental Figures S2–S17).

Of those infants remotely monitored, 9 of the 12 infants developed hypoglycemia. Remotely monitored infants had 32 hypoglycemic alerts, of which 21 had no SOC confirmation glucose and were not included in the analysis (Fig. 2). Hypoglycemia was verified in 6 of the remaining 11 events (55%). Five events were detected by CGM during the SOC monitoring period, 3 of which would have been missed by SOC measures. Two events detected by CGM occurred after the SOC monitoring was complete. CGM therefore detected 5 hypoglycemic events that would have been missed by SOC. Furthermore, CGM detected all but one hypoglycemic event that were detected by SOC during the study period. When there were confirmatory hospital glucometer readings, the sensitivity of the CGM to detect hypoglycemia was 86% and the specificity was 91%. The positive predictive value was 55% and the negative predictive value was 98%. The MARD for the CGM at the time of glucose readings taken by the hospital glucometer was 16.3% using 101 paired CGM-hospital glucometer values over a range of glucose values from 30 to 99 mg/dL (Fig. 3). In calculating the MARD, it is important to note that many of these glucose values fell into the low glucose range. Although the hospital glucometer is not as accurate as a laboratory glucose value, it is currently used as the standard for neonatal glucose measurements in the hospital and thus was used as a measure of comparison.

Twenty-one hypoglycemic events occurred without a confirmatory hospital glucometer check: 7 events resolved before the check being performed by nursing and thus were deferred, 5 events met our definition of compression artifacts, 5 did not have a confirmed glucometer check because the

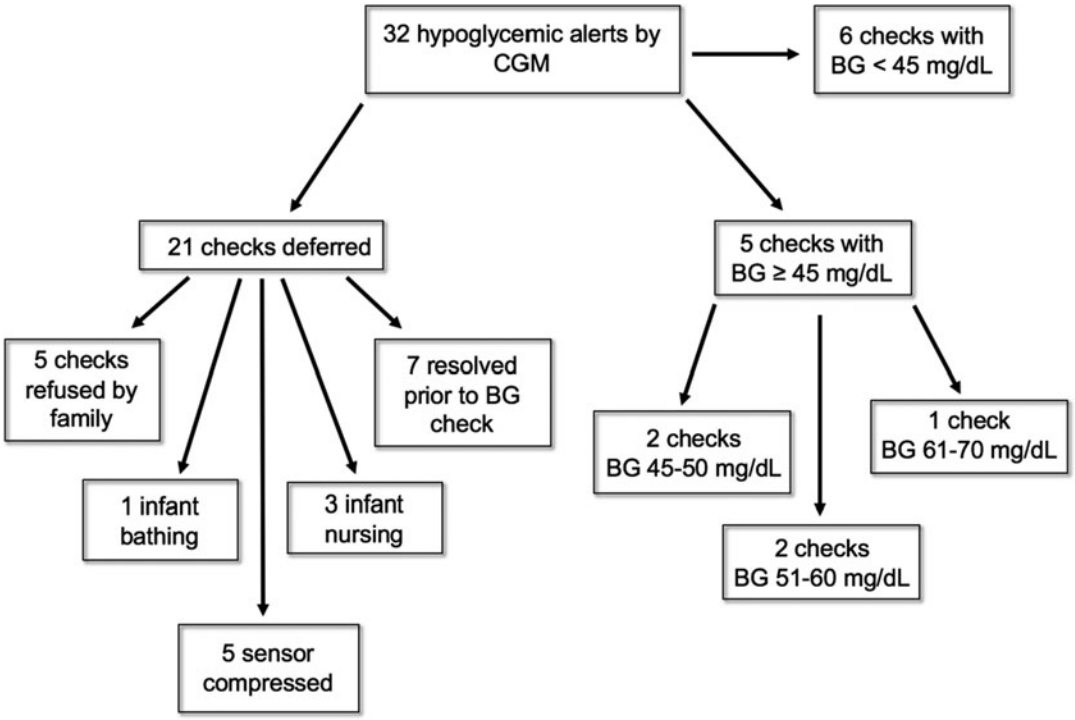

FIG. 2. CGM reported hypoglycemic alerts 32 times in the remote monitoring group. The events and outcomes are shown. Fifty-five percent of the hypoglycemic events verified glucose of <45 mg/dL. BG, blood glucose; CGM, continuous glucose monitor.

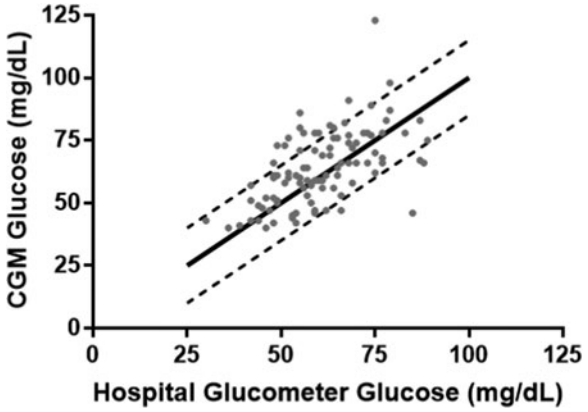

FIG. 3. Comparison of CGM glucose values with the standard-of-care hospital glucometer values ($n = 102$). Solid line represents line of identity. Dotted lines represent 15 mg/dL above and below the line of identity, as recommended by ISO Guidelines.[28]

guardian refused the check, and 4 occurred when an infant was feeding or bathing (Fig. 2). Compression artifacts were defined when the following three criteria were met: (1) evidence of sensor compression on examination, (2) concurrent hypoglycemia or signal loss, and (3) resolution of hypoglycemia or signal loss after repositioning of the infant. Although there were multiple BG check refusals, only two families refused checks, and refused them multiple number of times. These families reported fear of pain for the infant with additional heel sticks. If all the unconfirmed hypoglycemic CGM readings had been confirmed with a BG check, there would have been an additional 21 heel sticks.

CGM feasibility

If consoled with a pacifier, 80% of infants did not exhibit signs of pain (crying) upon CGM sensor placement. Participants were bathed normally after birth without unintended sensor removal. Fewer compression artifacts were detected when the CGM was placed on the anterior thigh compared with the lateral thigh. However, this varied with respect to how the infant was held when feeding or performing skin-to-skin.

Parental acceptance

Even at times of suspected hypoglycemia, 3 of 16 families expressed that they were displeased with additional BG checks that needed to be performed with the CGM in place. Other families were very willing to have the additional checks carried out and were very concerned about the possibility of hypoglycemia. Five families opted to end the study early, and in one case the sensor was inadvertently removed by nursing during a diaper change and not replaced. Reasons for withdrawing from the study early included avoiding additional glucose checks ($n = 2$), psychosocial stressors unrelated to the study ($n = 1$), prolonged hospital stay for maternal reasons ($n = 1$), or because they were satisfied that their child had normal glucose readings for a period of time ($n = 1$). Of the families that ended the study early, all but one family was satisfied with wearing the sensor, even if they decided to end the study early.

Adverse events

One infant had mild bleeding upon sensor placement that necessitated removal because of a sensor failure error. One infant retained the sensor wire upon removal of the sensor, which is a very rare, but known risk.[17] This infant did not require any medical intervention related to the retained sensor wire. Early in the study, two additional sensors failed the initial warm-up period after insertion and were removed. This was avoided in future participants by repeating the sensor warm-up period and not removing the sensor. Six months after hospital discharge, no infants were readmitted to the hospital for hypoglycemia.

Conclusions

Several studies have been published using CGM on premature and very-low-birth-weight infants,[19–21] but few studies have been performed looking at healthy infants of mothers with diabetes who are born in the late preterm or term period. In addition, few prospective studies on infants in the newborn nursery have evaluated the very early neonatal period with CGM data collected within a few hours of birth.[7,8] Our study provides information on the very early neonatal period among infants at risk for hypoglycemia in real time and allows us to explore important points regarding feasibility of using CGM in this population.

In this study, CGM use increased the number of detectable hypoglycemic episodes in infants born to mothers with diabetes compared with intermittent preprandial glucose checking. In our small study population, CGM use revealed episodes of hypoglycemia occurring outside the first 12 HOL when SOC monitoring is most intense. Reports suggesting similar trends have also been published.[20] In a previous prospective study evaluating long-term outcomes of hypoglycemia using CGM, CGM showed that nearly 25% of infants had low glucose concentrations not detected by intermittent BG monitoring[7] suggesting more frequent hypoglycemia occurrences than were detected in our study (16%). This may have been related to refusal of glucose checks by our families or shorter duration of CGM use.

CGM use in neonates allowed for earlier detection of hypoglycemia compared with the SOC. If infants are at risk of hypoglycemia, it is reasonable to use a CGM device to detect and trend hypoglycemic events over time. In light of the low-positive predictive value, the potential benefits of hypoglycemia detection by CGM must be carefully weighed against the risks of false-positive hypoglycemic events, which could include overtreatment of hypoglycemia, increased caregiver worry, need for increased confirmatory testing, and increased work for nursing staff. However, using CGM highlights the unpredictable and frequent nature of hypoglycemia that deserves further attention and research.

The long-term sequelae of hypoglycemia during the first days of life remain unclear. There has been recent literature to suggest no developmental differences between infants who have experienced hypoglycemia and those who have not; however, these conclusions were based on intermittent glucose tests.[3] Without real-time continuous data, the number and duration of hypoglycemic episodes may not have been fully appreciated. It is possible that infants had hypoglycemia during times when BG levels were not measured; thus, the severity of some episodes was not appreciated. Real-time

CGM can allow better quantification of the duration of hypoglycemia that may be critical in understanding which children are at risk for long-term neurologic sequelae.

There are several limitations to CGM use in this population. Current CGMs may over-report hypoglycemia[22–24] because they are based on glucose oxidase that is intrinsically less accurate at low glucose concentrations; less current is generated by the sensor with a low glucose concentration and there is more sensor noise. Some have suggested this may be because of sensor drift.[25] Whether by function or design, increasing the sensitivity of the device to detect hypoglycemia can result in a bias with an increased frequency of false hypoglycemic values; however, fewer episodes of true hypoglycemia will be missed. It was encouraging that when we reviewed the sensor accuracy in this study, we did not see a bias in the sensor readings.

One of the issues with current sensors is that they require a 2-h warm-up period, and therefore glucose information was not available for the first few hours after birth when hypoglycemia can occur. They also tend to be less accurate in the first 24 h of use. Compression artifacts leading to hypoglycemia alerts occurred five times during the study. Sensor placement was tolerated well without significant pain upon sensor insertion, analogous to other studies using CGM on preterm infants.[26]

Family acceptance

Discussing the study with families well in advance of delivery gave them time to think carefully about participation in the study. One of the biggest barriers to recruitment in our study was the perceived pain of additional glucose checks that would be needed for calibration of the CGM or for sensor-detected hypoglycemia. With the development of factory-calibrated CGM systems that do not require glucose sampling for calibration, acceptance by families will likely improve.[27] Of the families that were interested in the study, many were concerned about hypoglycemic events, but declined because they did not want to be randomized to the group wearing a blinded CGM because it would not necessarily benefit their child. Others who declined were fearful of using CGM technology on their newborn. Some expressed no interest in research whatsoever. In fewer cases, families thought that the hospital protocol was sufficient to detect hypoglycemia despite explanations about the potential flaws with intermittent glucose testing. Although there was also concern about pain with sensor placement, this pain was typically minimal and mitigated by pacifier use.

This study did not have a way of alerting study staff when infants were born, leading to late sensor placement in some cases. Developing a system to alert study staff of the infant's birth would have been useful in preventing delays in sensor placement. Including trained nursery staff as study advocates would also improve early sensor placement in future studies, particularly if sensors with factor calibration are used, removing the need for calibration heel sticks. During the study, false-positive hypoglycemic results may have increased anxiety and frustration for families. Once infants were outside the initial newborn period and fewer low glucose readings were detected, families were less worried about hypoglycemia and felt comfortable removing the device. Thus, a few families opted to withdraw from the study early because they wanted to avoid additional BG checks.

Limitations

Study limitations include the small population size and use of a hospital glucometer as the gold standard. The hospital glucometer has been shown to be accurate over a wide range of glucose values, hematocrit levels, and in neonates.[28] However, for the study to be acceptable to families of healthy newborns at risk of hypoglycemia, the hospital glucometer was used as the gold standard instead of laboratory measured values.

Current glucometer accuracy guidelines are set forth by the International Organization for Standardization (ISO) and are based on ranges most frequently encountered by patients with diabetes. These guidelines require that over 95% of the glucometer values be within 15 mg/dL of a reference value if the glucose level is <100 mg/dL,[29] and the glucometer used in our study met these criteria.[30] In a population where any glucose level <45 mg/dL leads to additional glucose checks, multiple additional blood draws may be required when there is a low reading. In addition, the CGM device was limited in quantitating hypoglycemic values because the lower limit of for CGM results was 40 mg/dL. Also, all marketed glucose oxidase sensors are less accurate in the hypoglycemic range.

Future studies

The development of factory calibrated CGM systems that do not require glucose pricks will allow for better acceptance of this technology in newborns.[31–33] In a small sample, confirmed episodes of hypoglycemia suggest that hypoglycemia occurred more often than could be detected by SOC measures. Fewer, more appropriately timed meter readings may be required with a factory calibrated CGM, making its use more acceptable to families and nursery staff. However, there may still be a number of false-positive alerts because of initial inaccuracies of a newly inserted sensor in the first 12 hours when most neonatal hypoglycemia is occurring. During this time, ''hypoglycemic'' values are near the lower limit of values reported by the sensor. We conclude that CGM is safe for use after birth. Further prospective studies using CGM should be performed to help determine long-term outcomes of children who have experienced neonatal hypoglycemia.

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Author Disclosure Statement

Drs. Wilson and Buckingham have received Dexcom devices free or at a reduced cost as support for other research protocols.

Supplementary Material

Supplementary Figs. S1–S17

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